HIGH-POWERED MEDICINE

3rd Ed.

EVIDENCE-BASED RECOMMENDATIONS FOR OPTIMIZING PHARMACOTHERAPY

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High-Powered Medicine

Landmark Clinical Trial Reviews
~ 3rd Edition ~

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The author has no financial disclosures or conflicts of interest to note at this time.

"Good doctors use both individual clinical expertise and the best available external evidence, and neither alone is enough."

-David Sackett, MD

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Indexed by disease state and drug class at back of the book

Quick Review of Biostatistics

Please note - this is not meant to be a comprehensive review of biostatistics. It is only meant to serve as a quick reference relevant to this book.

Throughout this book I will be using "significant" in place of "statistically significant" whenever possible in discussing trial results. This was in effort to avoid the redundancy of specifying the *statistical* significance of *statistical* results. Furthermore, **statistical significance does not equal clinical significance** and I did not want to place emphasis on statistical results alone.

Power: the ability of a *trial* to detect a statistically significant difference between groups when a difference truly exists.

- A trial that sets power at 90% (and meets said criteria) means that there is a 90% probability that the observed difference (or lack thereof) between two groups is not due to chance
- It also means there is a 10% chance for showing no difference between groups when a difference truly exists (false negative)
- If power is set but not met and there is no significant difference between treatment groups the results should be considered inconclusive because the trial did not have enough power to confirm that the lack of difference was not due to chance alone
- If power is not met but a statistically significant difference is observed, this is less of a concern because a significant difference between groups was still detected

P-value: the probability that the observed difference between two groups for a *specific outcome* is due to chance only.

Level of significance (aka alpha): the probability the investigator is willing to take that the results occurred due to chance alone.

- Typically, the level of significance is set at 0.05 (5%) which would indicate that the investigators are willing to accept a 5% chance for a false positive result
- If the p-value is less than alpha then the results are considered statistically significant

Confidence interval: range of values in which the true value likely resides.

- A 95% confidence interval means that if a trial is *repeated* several times from the same sample population, then it would be expected that 95% of the confidence intervals would contain the true value for said measure *(and 5% would not)*
- For hazard ratios, if the confidence interval for a measurement includes the value of 1.00 then the difference cannot be considered statistically significant due to a hazards ratio of 1.00 indicating no difference between treatment groups
- The wider the confidence interval the less precise an estimate can be made for the true value of said measure

Non-inferiority trial: designed to assess if the active treatment is no worse than the control treatment by a predetermined margin (aka non-inferiority margin).

- A non-inferiority trial cannot be used to claim superiority without predetermined testing specified in the protocol
- Please note - superiority trials cannot be used to claim non-inferiority

Non-inferiority margin (aka NI margin): the difference allowed between active and control treatments to be considered non-inferior.

- If the NI margin is set at 1.30 then to meet criteria for non-inferiority the confidence interval for said measure must not include 1.30
- If the confidence interval crosses/touches the NI margin then non-inferiority cannot be claimed

Intent to treat population (ITT): the sample of patients that underwent randomization into the trial.

Modified intent to treat population (mITT): the sample of patients that underwent randomization and met one or more qualifying criteria.

- Typically, the qualifying criteria is receiving at least one dose of study medication in order to be included in a safety analysis

Per protocol population (PP): the sample of patients that successfully completed the trial.

Composite endpoints: a combination of outcomes reported for a single measure of effect.

- Example: composite of cardiovascular death, myocardial infarction or stroke
- Each component should ideally occur at similar rates and have similar clinical significance to avoid distortion of the overall composite measure
- A composite endpoint of cardiovascular death or minor bleeding would not be appropriate due to death being much more significant than minor bleeding

Relative risk reduction: the change in event rate of the active group relative to the control group.

- RRR = 1 - (active/control)
- Relative risk reduction is more commonly used when reporting treatment effect
    - However, it is subject to misinterpretation and overestimation of treatment effect
- For example, if the event rate in group A was 10% and group B was 20% this would represent a 50% relative risk reduction but only a true treatment difference of 10%

Absolute risk reduction: the absolute change in event rates between two groups.

- ARR = control event rate - active event rate
- Less commonly reported when reporting treatment effect

Number needed to treat: an estimate of how many patients would need to receive "Treatment A" to prevent one outcome compared to "Treatment B".

- NNT = 1/ARR (absolute risk reduction)
- Please note - that NNT must be reported as a whole integer (rounded up)
- It is important to consider the time frame of the trial when interpreting the NNT
- For example, a trial averaging 3 years with a NNT of 14 should be interpreted as that for *approximately* every 14 patients given "Therapy A" for an *average* of 3 years one clinical outcome would be prevented compared to patients receiving "Therapy B"

Number needed to harm: an estimate of how many patients would need to receive "Treatment A" for one adverse outcome to occur compared to "Treatment B".

- NNH = 1/ARR (absolute risk reduction)
- Please note - that NNH must be reported as a whole integer (rounded down)
- It is important to consider the time frame of the trial when interpreting the NNH
- For example, a trial averaging 3 years with a NNH of 7 should be interpreted as that for *approximately* every 7 patients given "Treatment A" for an *average* of 3 years one adverse clinical outcome would occur compared to patients receiving "Therapy B"

While NNT and NNH are simple to calculate and appear straightforward to use, it is very important to remember that these values are *estimates* based on trial results used to help illustrate the magnitude of treatment effect in terms of patients instead of percentages.

- A NNT value lower than a NNH value indicates that the benefit/risk ratio is favorable, however these calculations are based on average trial results from populations that may differ significantly from a specific patient
- Additionally, the clinical significance of each outcome must be considered (example - cardiovascular death vs hypotension)
- It is only appropriate to report NNT/NNH for statistically significant differences

Level of evidence: the measure of the quality of evidence from a trial.

- Level I - randomized, controlled trial with power set and met
- Level II - randomized, controlled trial with power set but not met
- Levels III, IV or V - observational trials with or without a control group

Grade of recommendation: used to rate the strength of a recommendation.

- The higher the level of evidence the higher the grade of recommendation
  - Level I - Grade A
  - Level II - Grade B
- However, depending on other factors and considerations a higher or lower recommendation may be given for a trial

Additional Information

The following resources were used to form this review:

- Malone PM, Witt BA, Malone MJ, Peterson DM. eds. *Drug Information: A Guide for Pharmacists, Seventh edition*. McGraw-Hill Education; 2022.
- Bryant PJ, Pace HA. *The Pharmacist's Guide to Evidence-Based Medicine for Clinical Decision Making*. American Society of Health-System Pharmacists; 2008.

Please refer to these resources for more thorough and comprehensive information on the subject.

4S

Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet*. 1994;344(8934):1383-1389.

Objective: To determine the effect of simvastatin on morbidity and mortality outcomes in patients with coronary heart disease and elevated cholesterol levels.

Primary Efficacy Measure: All-cause mortality

Secondary Efficacy Measure: Composite of coronary death, non-fatal myocardial infarction, resuscitated cardiac arrest and silent myocardial infarction

Participants: Patients with history of coronary heart disease

- Age ~59 years; ~81% male
- Qualifying event myocardial infarction only ~62%; angina only ~21%; both ~16%
- Total cholesterol ~260 mg/dL; LDL ~188 mg/dL; HDL ~70 mg/dL
- Triglycerides ~133 mg/dL
- Beta-blocker ~57%; aspirin ~37%; nitrate ~32%; CCB ~31%

Inclusion Criteria:

- Age 35-70 years
- History of acute myocardial infarction or angina pectoris
- Total cholesterol 5.5 to 8.0 mmol/L (~212 mg/dL to ~309 mg/dL)
- Triglycerides ≤ 2.5 mmol/L (~221 mg/dL)

Exclusion Criteria:

- Unstable angina
- Myocardial infarction within previous 6 months
- Planned coronary artery surgery or angioplasty
- Antiarrhythmic therapy or persistent atrial fibrillation
- Congestive heart failure requiring digitalis, diuretics or vasodilators
- History of completed stroke

Drug: Simvastatin

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients with serum total cholesterol > 5.5 mmol/L (~212 mg/dL) were given dietary advice and after 8 weeks a second blood draw was performed and a 2-week placebo run-in period was initiated. Patients meeting the cholesterol and triglyceride requirements were randomized to receive either simvastatin 20 mg once daily before evening meal or matching placebo. Dosages could be adjusted at the 12 week and 6-month visits based on prior serum cholesterol values. The goal of simvastatin therapy was to reduce total cholesterol to 3.0-5.2 mmol/L (~116 to ~201 mg/dL). If patients were out of range, then the dosage was increased to 40 mg daily or reduced to 10 mg daily.

Duration: Median follow-up period of 5.4 years

Statistical Analysis: It was determined that 4400 randomized patients and 440 deaths would achieve 95% power (alpha = 0.05). The ITT population was used for all analyses.

Results: A total of 4444 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. The trial was stopped early based on recommendation from the safety and monitoring committee due to interim analysis demonstrating that the pre-specified boundary had been crossed in favor of simvastatin. In the simvastatin group, 37% of patients had their dosage raised to 40 mg daily during the first six months (only 2 patients were reduced to 10 mg daily). After one year, 72% of simvastatin patients were within the target range for total cholesterol. Coronary death accounted for 74% of the total mortality events in this trial.

Placebo (N=2223) Vs Simvastatin (N=2221)

All-Cause Mortality:
256 (11.5%) vs 182 (8.19%); HR 0.70 (95% CI 0.58-0.85)
p=0.0003; ARR 3.32%; NNT ~31

Coronary Death:
189 (8.50%) vs 111 (5.00%); HR 0.58 (95% CI 0.46-0.73)
ARR 3.50%; NNT ~29

Secondary Composite Outcome:
622 (28.0%) vs 431 (19.4%); HR 0.66 (95% CI 0.59-0.75)
p<0.00001; ARR 8.57%; NNT ~12

Limitations:

- External validity - trial conducted entirely in Scandinavia
- Patient population - cannot extrapolate results to patients without history of coronary artery disease

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I recommend the use of simvastatin 20-40 mg once daily to reduce cardiovascular morbidity and mortality in patients with coronary heart disease and elevated cholesterol levels.

Efficacy:

- All-cause mortality was significantly lower in the simvastatin group compared to placebo (driven primarily by reduced rates of coronary death)
- The rate of the secondary composite outcome was also significantly lower in the simvastatin group

Safety:

- There was one case of rhabdomyolysis in simvastatin group (full recovery)
- Rate of AST liver enzyme elevation (3x ULN) was similar between treatment groups
- ALT liver enzyme elevation (3x ULN) occurred more often in the simvastatin group compared to placebo (49 patients vs 33 patients, respectively)

Cost:

- The cost of using simvastatin must be balanced against the cost-savings of reducing cardiovascular morbidity and mortality

Special Considerations/Populations:

- Patient population must be considered - all had history of coronary heart disease and elevated cholesterol levels

Grade of Recommendation: **A**

ACCOMPLISH

Jamerson K, Weber MA, Bakris GL, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med*. 2008;359(23):2417-2428.

Objective: To determine if combination therapy of ACEi plus amlodipine is superior to ACEi plus thiazide diuretic in reducing cardiovascular outcomes in high-risk patients with hypertension.

Primary Efficacy Measure: Composite of fatal and non-fatal cardiovascular events

Secondary Efficacy Measures: (1) Composite of non-fatal myocardial infarction, non-fatal stroke, hospitalization for unstable angina, coronary revascularization and resuscitation after sudden cardiac arrest (2) Composite of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke

Participants: Patients with hypertension at high-risk for cardiovascular events

- Age ~68 years; male ~60%
- BP ~145/80 mmHg
- Lipid-lowering therapy ~68%; antiplatelet ~65%

Inclusion Criteria:

- Age ≥ 60 years
- High-risk for cardiovascular events (defined as history of coronary events, myocardial infarction, revascularization, stroke, impaired renal function, diabetes, peripheral artery disease, left-ventricular hypertrophy)
- SBP ≥ 160 mmHg (or currently on antihypertensive therapy)

Exclusion Criteria:

- Symptoms of angina pectoris within previous 3 months
- Symptomatic heart failure or LVEF < 40%
- Acute cardiovascular event within previous 1-3 months
- Secondary hypertension or resistant/refractory hypertension

Drugs: Benazepril/amlodipine; benazepril/hydrochlorothiazide

Design: Randomized, double-blind, active-comparison trial

Methods: Eligible patients were randomized to either benazepril/amlodipine 20 mg/5 mg or benazepril/HCTZ 20 mg/12.5 mg once daily. After one month of therapy the benazepril dose was increased to 40 mg for all patients. From there on, investigators could double the dose of amlodipine or HCTZ if needed to attain the target blood pressure of <140/90 mmHg (<130/80 mmHg for diabetes/kidney disease patients). The maximum daily dosage allowed for each trial group was benazepril/amlodipine 40 mg/10 mg and benazepril/HCTZ 40 mg/25 mg. The use of additional antihypertensive agents from other drug classes was allowed.

Duration: Mean follow-up period of 36 months

Statistical Analysis: Initially, it was determined that 1642 primary events would be needed to achieve 90% power (alpha = 0.05). However, the trial's power was later reduced to 80% which only required 1199 primary outcomes. The ITT population was used for the primary efficacy analyses.

Results: A total of 11,506 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. The average daily dose for the benazepril/amlodipine group was 36.3/7.7 mg (60.9% at max dose). The average daily dose for the benazepril/HCTZ group was 36.1/19.3 mg (60.3% at max dose). The average blood pressure for the amlodipine and HCTZ groups were 131.6/73.3 mmHg and 132.5/74.4 mmHg ($p<0.001$).

Benazepril/Amlodipine (N=5744) Vs Benazepril/HCTZ (N=5762)

Composite of Fatal & Non-Fatal Cardiovascular Events:
552 (9.61%) vs 679 (11.8%); HR 0.80 (95% CI 0.72-0.90)
p< 0.001; ARR 2.17%; NNT ~46

Cardiovascular Death:
107 (1.86%) vs 134 (2.33%); HR 0.80 (95% CI 0.62-1.03); p=0.08

Fatal & Non-Fatal Myocardial Infarction:
125 (2.18%) vs 159 (2.76%); HR 0.78 (95% CI 0.62-0.99); p=0.04; ARR 0.58%; NNT ~172

Fatal & Non-Fatal Stroke:
112 (1.95%) vs 133 (2.31%); HR 0.84 (95% CI 0.65-1.08); p=0.17

Composite of Non-Fatal Cardiovascular Events:
494 (8.60%) vs 592 (10.3%); HR 0.83 (95% CI 0.73-0.93); p=0.002; ARR 1.67%; NNT ~60

Composite of Cardiovascular Death, Non-Fatal Myocardial Infarction & Non-Fatal Stroke:
288 (5.01%) vs 364 (6.32%); HR 0.79 (95% CI 0.67-0.92); p=0.002; ARR 1.30%; NNT ~77

Limitations:
- Additional blood pressure lowering agents from other classes was allowed to achieve target blood pressure (potential confounding factor)
- Cannot apply results to thiazide-like diuretics, such as chlorthalidone

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I recommend the use of benazepril/amlodipine over benazepril/HCTZ for reducing cardiovascular event rates in high-risk patients with hypertension.

Efficacy:
- Rates of the primary composite outcome (fatal and non-fatal cardiovascular events) was significantly lower in the benazepril/amlodipine group
- Fatal and non-fatal myocardial infarction occurred at significantly lower rates in the benazepril/amlodipine group
- Rates of the secondary composite outcomes were significantly lower in the benazepril/amlodipine group
- There was no significant difference in the rates of cardiovascular death and total stroke

Safety:
- Rates of adverse drug reactions were comparable between treatment groups with the exception of dizziness and peripheral edema
- Dizziness was reported in 20.7% of patients in the amlodipine group and 25.4% of patients in the HCTZ group
- Peripheral edema was reported in 31.2% of patients in the amlodipine group and 13.4% of patients in the HCTZ group

Cost:
- The cost of using benazepril/amlodipine must be balanced against the cost-savings of reduced cardiovascular event rates

Special Considerations/Populations:
- The target blood pressure of <140/90 mmHg (<130/80 mmHg for DM/CKD patients) must be considered when interpreting the results
- The most common baseline risk-factor for cardiovascular event was diabetes (~60%)

Grade of Recommendation: **A**

ACCORD-BG

Jamerson K, Weber MA, Bakris GL, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med*. 2008;359(23):2417-2428.

Objective: To determine the effect of intensive glycemic control compared to standard glycemic control on cardiovascular event rates in patients with type 2 diabetes and cardiovascular disease or risk-factors.

Primary Efficacy Measure: Composite of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke

Secondary Efficacy Measure: All-cause mortality

Participants: Patients with type 2 diabetes and established cardiovascular disease or risk-factors

- Age ~62 years; male ~62%
- HgA1c ~8.3%; fasting blood glucose ~175 mg/dL; previous cardiovascular event ~35%
- Statin ~62%; metformin ~60%; sulfonylurea ~50%; aspirin ~54%

Inclusion Criteria:

- Patients with type 2 diabetes and HgA1c ≥ 7.5% plus one of the following:
    - Age 40-79 with established cardiovascular disease
    - Age 55-79 with anatomical evidence of atherosclerosis, albuminuria, LV hypertrophy, OR ≥ 2 additional risk factors for cardiovascular disease (dyslipidemia, hypertension, current smoker or obesity)

Exclusion Criteria:

- Frequent or recent serious hypoglycemic events
- Unwilling to perform home blood glucose monitoring
- BMI > 45
- SCr > 1.5 mg/dL

Drugs: n/a

Design: Randomized, open-label, active-comparison trial

Methods: Eligible patients were randomized to either intensive therapy (target HgA1c < 6%) or standard therapy (target HgA1c 7.0-7.9%). Patients were provided glucose-lowering medications from the trial formulary, however the use of outside medications to treat hyperglycemia was allowed. Patient medication regimens were determined individually based on treatment group and response to therapy.

Duration: Mean follow-up period of 3.5 years

Statistical Analysis: It was determined that a follow-up period of at least 5.6 years and an event rate ≥ 2.9% for the primary composite outcome would achieve 89% power (alpha = 0.05). The ITT population was used for the primary and secondary efficacy analyses.

Results: A total of 10,521 patients underwent randomization. The trial was stopped early at the recommendation of the safety committee due to data showing increased mortality rates in the intensive therapy group. After one year of follow-up, the median HgA1c for the intensive and standard treatment groups was 6.4% and 7.5%, respectively. These HgA1c levels were maintained throughout the follow-up period. The intensive treatment group had greater exposure to medications (from all classes) as well as significantly higher rates of adverse events (hypoglycemia, weight gain and fluid retention). The occurrence of weight gain greater than 10 kg from baseline was 27.8% in the intensive therapy group and 14.1% in the standard therapy group ($p<0.001$).

Intensive Treatment (N=5128) Vs Standard Treatment (N=5123)

Composite of Cardiovascular Death, Non-Fatal Myocardial Infarction & Non-Fatal Stroke:
352 (6.86%) vs 371 (7.24%); HR 0.90 (95% CI 0.78-1.04); p=0.16

All-Cause Mortality:
257 (5.01%) vs 203 (3.96%); HR 1.22 (95% CI 1.01-1.46)
p=0.04; ARI 1.05%; NNT ~96

Cardiovascular Death:
135 (2.63%) vs 94 (1.83%); HR 1.35 (95% CI 1.04-1.76)
p=0.02; ARI 0.80%; NNH ~126

Non-Fatal Myocardial Infarction:
186 (3.63%) vs 235 (4.59%); HR 0.76 (95% CI 0.62-0.92)
p=0.004; ARR 0.96%; NNT ~105

Non-Fatal Stroke:
67 (1.31%) vs 61 (1.19%); HR 1.06 (95% CI 0.75-1.50); p=0.74

Hypoglycemia Requiring Medical Assistance:
538 (10.5%) vs 179 (3.49%)
p<0.001; ARI 7.01%; NNH ~14

Limitations:

- Power set but not met - trial stopped early (clinical significance likely low)
    - It is possible that the trial duration (~3.5 years) was not sufficient to demonstrate the full cardiovascular benefit of intensive therapy (although it was sufficient to demonstrate several safety concerns)
- Open-label trial design

Level of Evidence: Level II - with major limitations

Recommendation: For these reasons, I do not recommend targeting an HgA1c < 6% over standard blood glucose control to reduce the risk of cardiovascular events in high-risk patients with type 2 diabetes.

Efficacy:

- There was no significant difference between treatment groups regarding the primary composite outcome
- Rates of cardiovascular death and all-cause mortality were significantly higher in the intensive treatment group

Safety:

- Rates of hypoglycemia requiring medical assistance were significantly higher in the intensive therapy group
- Fluid retention and weight gain (> 10 kg) occurred at significantly higher rates in the intensive therapy group

Cost:

- Any potential benefit of intensive glycemic therapy must be balanced against the increased cost of achieving the lower target HgA1c (via increased medication usage) as well as the added costs of monitoring and managing hypoglycemic episodes

Special Considerations/Populations:

- This trial demonstrated greater harm than benefit with intensive therapy
- Results cannot be applied to a younger, less complicated patient population

Grade of Recommendation: **B**

ACCORD-BP

ACCORD Study Group, Cushman WC, Evans GW, et al. Effects of intensive blood-pressure control in type 2 diabetes. *N Engl J Med*. 2010;362(17):1575-1585.

Objective: To determine the effect of intensive blood pressure lowering therapy compared to standard blood pressure lowering therapy on cardiovascular morbidity and mortality in patients with type 2 diabetes.

Primary Efficacy Measure: Composite of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke

Participants: Type 2 diabetes with hypertension and cardiovascular disease or risk- factors

- Age ~62 years; male ~52%
- BP ~139/76 mmHg
- Previous cardiovascular event ~34%

Inclusion Criteria:

- Met inclusion criteria for the ACCORD-BG trial
- SBP between 130-180 mmHg
- ≤ 3 antihypertensive medications

Exclusion Criteria:

- ACCORD-BG exclusion criteria
- Age > 79 years old

Drugs: n/a

Design: Randomized, open-label, active-comparison trial

Methods: Eligible participants from the ACCORD-BG trial were randomized into either intensive blood pressure treatment (SBP <120 mmHg) or standard blood pressure treatment groups (SBP <140 mmHg). The selection of antihypertensive medication(s) was based on a treatment algorithm designed for the trial.

Duration: Mean follow-up period 4.7 years

Statistical Analysis: It was determined that 4200 randomized patients, ≥ 4% annual event rate in the standard therapy group and an average follow-up period of at least 5.6 years would achieve 94% power (alpha = 0.05). The ITT population was used for the efficacy analyses.

Results: A total of 4733 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. The average blood pressure after one year was ~119/64 mmHg in the intensive treatment group and ~133/70 mmHg in the standard therapy group. The intensive treatment group had significantly higher rates of serious adverse drug reactions due to antihypertensive medications compared to the standard treatment group (3.26% vs 1.27%; $p<0.001$). In particular, rates of hypotension, bradycardia/arrhythmia and hyperkalemia were all significantly higher in the intensive treatment group.

Intensive Treatment (N=2363) Vs Standard Treatment (N=2371)

Cardiovascular Death, Non-Fatal Myocardial Infarction & Non-Fatal Stroke:
208 (8.80%) vs 237 (10.0%); HR 0.88 (95% CI 0.73-1.06); p=0.20

Cardiovascular Death:
60 (2.54%) vs 58 (2.45%); HR 1.06 (95% CI 0.74-1.52); p=0.74

Non-Fatal Myocardial Infarction:
126 (5.33%) vs 146 (6.16%); HR 0.87 (95% CI 0.68-1.10); p=0.25

Non-Fatal Stroke:
34 (1.44%) vs 55 (2.32%); HR 0.63 (95% CI 0.41-0.96)
p=0.03; ARR 0.88%; NNT~114

All-Cause Mortality:
150 (6.35%) vs 144 (6.07%); HR 1.07 (95% CI 0.85-1.35); p=0.55

Limitations:

- Power set but not met – lower than expected annual event rates (< 4%)
- Open-label trial design
- External validity - cannot apply results to high-risk patients without type 2 diabetes

Level of Evidence: Level II - with major limitations

Recommendation: For these reasons, I do not recommend targeting a SBP of <120 mmHg over standard blood pressure goals to reduce rates of cardiovascular morbidity and mortality in high-risk patients with type 2 diabetes and hypertension.

Efficacy:

- There was no significant difference in the rates of the primary composite outcome despite notable differences in the average blood pressure after the first year
- Both treatment groups achieved their respective target blood pressure goals
- While the rates of non-fatal stroke were significantly lower in the intensive treatment group, there were no significant differences in the rates of non-fatal myocardial infarction and cardiovascular death

Safety:

- Rates of serious adverse drug reactions were significantly higher in the intensive therapy group (notably hypotension, hyperkalemia and bradycardia/arrhythmia)

Cost:

- Any potential benefit of intensive blood pressure therapy must be balanced against the cost of increased medication usage as well a monitoring for and managing significantly higher rates of serious adverse drug reactions

Special Considerations/Populations:

- Patient population derived from the ACCORD-BG trial
    - All patients had type 2 diabetes at baseline
- Limited external validity - cannot apply results to patients without type 2 diabetes
- Target SBP used in each treatment group must be considered when interpreting trial results

Grade of Recommendation: **B**

ACCORD-LIPID

ACCORD Study Group, Ginsberg HN, Elam MB, et al. Effects of combination lipid therapy in type 2 diabetes. *N Engl J Med*. 2010;362(17):1563-1574.

Objective: To determine the effect of fibrate plus statin therapy compared to statin therapy alone on cardiovascular morbidity and mortality outcomes in patients with type 2 diabetes and established cardiovascular disease or risk factors.

Primary Efficacy Measure: Composite of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke

Participants: Patients with type 2 diabetes and established cardiovascular disease or risk factors

- Age ~62 years; male ~69%
- Previous cardiovascular event ~36%
- Total cholesterol ~175 mg/dL; LDL ~101 mg/dL; HDL ~38 mg/dL
- Triglycerides ~162 mg/dL
- Baseline statin use ~60%

Inclusion Criteria:

- Meet criteria for ACCORD-BG trial
- LDL 60-180 mg/dL
- HDL < 55 mg/dL for women/blacks (< 50 mg/dL for all others)
- Triglycerides < 750 mg/dL (< 400 mg/dL if on lipid-lowering therapy)

Exclusion Criteria:

- Use of medications known to interact with statins/fibrates
- History of pancreatitis, myopathy or gallbladder disease

Drugs: Simvastatin (standard therapy); simvastatin plus fenofibrate (intensive therapy)

Design: Randomized, double-blind, active-comparison trial

Methods: Eligible patients were randomized to receive either statin monotherapy or statin plus fibrate. Statin therapy (simvastatin) began at randomization with the addition of fibrate/placebo therapy beginning one month after. The initial dose of simvastatin was determined by lipid treatment guidelines and were adjusted as necessary throughout the trial. The initial dose of fenofibrate was 160 mg daily but could be adjusted based on changes in eGFR.

Duration: Mean follow-up period of 4.7 years

Statistical Analysis: It was determined that 5800 randomized patients, ≥ 2.4% annual event rate in the standard treatment group and an average follow-up period of at least 5.6 years would achieve 87% power (alpha = 0.05). The ITT population was used for the efficacy analyses.

Results: A total of 5518 participants underwent randomization. Baseline participant characteristics were similar between treatment groups. The average daily dose of simvastatin achieved during the trial was ~22 mg in each treatment group. The annual event rate for the primary outcome was 2.41% in the standard therapy group. There was no noted increase in rates of rhabdomyolysis with fibrate/statin combination therapy compared to statin monotherapy. However, there were more patients receiving a reduced dosage of fenofibrate due to decreases in eGFR in the intensive therapy group (15.9%) compared to the standard therapy group (7.0%).

Intensive Therapy (N=2765) Vs Standard Therapy (N=2753)

Average LDL at Study End:
81.1 mg/dL vs 80.0 mg/dL

Average HDL at Study End:
41.2 mg/dL vs 40.5 mg/dL

Average Triglycerides at Study End:
122 mg/dL vs 144 mg/dL

Cardiovascular Death, Non-Fatal Myocardial Infarction & Non-Fatal Stroke:
291 (10.5%) vs 310 (11.3%); HR 0.92 (95% CI 0.79-1.08); p=0.32

Cardiovascular Death:
99 (3.58%) vs 114 (4.14%); HR 0.86 (95% CI 0.66-1.12); p=0.26

Non-Fatal Myocardial Infarction:
173 (6.26%) vs 186 (6.76%); HR 0.91 (95% CI 0.74-1.12); p=0.39

Non-Fatal Stroke:
47 (1.70%) vs 40 (1.45%); HR 1.17 (95% CI 0.76-1.78); p=0.48

Limitations:

- Power set but not met - failed to randomize enough patients and insufficient trial duration
- External validity - cannot apply results to high-risk patients without type 2 diabetes

Level of Evidence: Level II - with major limitations

Recommendation: For these reasons, I do not recommend the use of statin plus fibrate therapy over standard statin monotherapy to reduce rates of cardiovascular morbidity and mortality in high-risk patients with type 2 diabetes.

Efficacy:

- There was no significant difference between treatment groups in the rates of the primary composite outcome or any of the individual components
- Average levels of LDL and HDL were similar between treatment groups at trial end

Safety:

- A notably higher proportion of the intensive therapy group experienced eGFR decreases warranting lower dosage of fenofibrate compared to the standard therapy group
- There was no difference in rates of rhabdomyolysis between treatment groups

Cost:

- The cost of adding fenofibrate to standard statin therapy must be considered in addition to the cost of more frequent lab monitoring (lipid levels and renal function)

Special Considerations/Populations:

- Patient population derived from ACCORD-BG trial
    - All patients had type 2 diabetes at baseline
- Limited external validity - cannot apply results to patients without type 2 diabetes

Grade of Recommendation: **B**

ACTIVE-A

ACTIVE Investigators, Connolly SJ, Pogue J, et al. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. *N Engl J Med*. 2009;360(20):2066-2078.

Objective: To determine the effect of clopidogrel plus aspirin compared to aspirin alone on vascular event rates in atrial fibrillation patients at increased risk for stroke unable to use vitamin K antagonists.

Primary Efficacy Measure: Any major vascular event (composite of stroke, non-CNS embolism, myocardial infarction or death from vascular causes)

Participants: Patients with atrial fibrillation and one or more additional risk factors for stroke who were not appropriate candidates for vitamin K antagonist therapy

- Age ~71 years; male ~58%
- Permanent AF ~64%; paroxysmal AF ~22%
- $CHADS_2$ score ~2.0

Inclusion Criteria:

- Atrial fibrillation
- One or more of the following risk factors: age ≥ 75, hypertension, previous stroke/TIA/non-CNS embolism, LVEF < 45%, peripheral vascular disease, age 55-74 with diabetes or coronary artery disease

Exclusion Criteria:

- Requirement for vitamin K antagonist or clopidogrel
- Risk factors for hemorrhage: documented peptic ulcer disease within previous 6 months, history of intracerebral hemorrhage, platelet count <50 x 10^9/L, ongoing alcohol abuse

Drugs: Clopidogrel plus aspirin; aspirin alone

Design: Randomized, double-blind, active-comparison trial

Methods: Eligible patients were randomized to receive clopidogrel 75 mg plus aspirin (75-100 mg) once daily or aspirin (75-100 mg) plus matching placebo once daily.

Duration: Median follow-up period of ~3.6 years

Statistical Analysis: It was determined that 7500 randomized patients and 1600 primary events would achieve 88% power. The ITT population was used for all analyses.

Results: A total of 7554 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. While rates of major and minor bleeding were significantly higher in the clopidogrel plus aspirin group compared to the aspirin group, rates of fatal bleeding were not significantly different. The most common type of major bleeding was gastrointestinal in nature.

Clopidogrel Plus Aspirin (N=3772) Vs Aspirin Alone (N=3782)

Stroke, Non-CNS Embolism, Myocardial Infarction or Death from Vascular Causes:
832 (22.1%) vs 924 (24.4%); HR 0.89 (95% CI 0.81-0.98)
p=0.01; ARR 2.37%; NNT ~43

Total Stroke:
296 (7.85%) vs 408 (10.8%); HR 0.72 (95% CI 0.62-0.83)
p<0.001; ARR 2.94%; NNT ~35
Difference largely driven by reduction in ischemic stroke, not hemorrhagic

Non-CNS Embolism:
54 (1.43%) vs 56 (1.48%); HR 0.96 (95% CI 0.66-1.40); p=0.84

Myocardial Infarction:
90 (2.39%) vs 115 (3.04%); HR 0.78 (95% CI 0.59-1.03); p=0.08

Death from Vascular Causes:
600 (15.9%) vs 599 (15.8%); HR 1.00 (95% CI 0.89-1.12); p=0.97

Major Bleeding:
251 (6.65%) vs 162 (4.28%); HR 1.57 (95% CI 1.29-1.92)
p<0.001; ARI 2.37%; NNH ~42

Severe Bleeding:
190 (5.04%) vs 122 (3.23%); HR 1.57 (95% CI 1.25-1.98)
p<0.001; ARI 1.81%; NNH ~55

Fatal Bleeding:
42 (1.11%) vs 27 (0.71%); HR 1.56 (95% CI 0.96-2.53); p=0.07

Limitations:

- Patients undergoing cardioversion could be treated with vitamin K antagonist and resume trial after completion of said therapy - potential confounding factor
- External validity - cannot apply results of trial to patients without atrial fibrillation
- The dose of aspirin used in this trial must be considered (75-100 mg daily)

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I recommend the use of clopidogrel plus aspirin over aspirin alone for prevention of major vascular events (particularly ischemic stroke) in high-risk patients with atrial fibrillation who are not able to use vitamin K antagonists. However, routine assessment of bleeding risk is warranted to help reduce the potential harm to the patient.

Efficacy:

- Clopidogrel plus aspirin demonstrated significantly lower rates of the primary composite outcome compared to aspirin alone
    - This difference was driven largely by a significant reduction in total stroke event rates, specifically ischemic stroke
    - There was no significant difference in rates of hemorrhagic stroke

Safety:

- Rates of total major bleeding and severe bleeding were significantly higher in the clopidogrel plus aspirin group
- There was no significant difference in rates of fatal bleeding between treatment groups

Cost:

- The cost of adding clopidogrel to aspirin therapy must be balanced against the cost-savings of reduced rates of major vascular events, particularly ischemic stroke
- However, the cost of managing bleeding events must also be considered

Special Considerations/Populations:

- This patient population was unable to use a vitamin K antagonist
- The NNT for total stroke was lower than the NNH for major bleeding, suggesting that the risk of a major bleeding event is outweighed by the benefit of preventing one stroke
- The dose of aspirin used in this trial must be considered (75-100 mg daily)

Grade of Recommendation: **A**

ACTIVE-I

ACTIVE I Investigators, Yusuf S, Healey JS, et al. Irbesartan in patients with atrial fibrillation. *N Engl J Med*. 2011;364(10):928-938.

Objective: To determine the effect of irbesartan on cardiovascular outcomes in high-risk atrial fibrillation patients.

Primary Efficacy Measures: (1) Composite of stroke, myocardial infarction and vascular death (2) Composite of stroke, myocardial infarction, vascular death and hospitalization for heart failure

Participants: Patients with atrial fibrillation at high-risk for cardiovascular events

- Age ~70 years; male ~61%
- $CHADS_2$ score ~2.0; BP ~138/82 mmHg
- Baseline ACEi ~60%; beta-blocker ~55%

Inclusion Criteria:

- Met criteria for ACTIVE-A or ACTIVE-W trials
- SBP ≥ 110 mmHg
- Not currently prescribed an ARB

Exclusion Criteria:

- Required clopidogrel or oral anticoagulant
- Documented peptic ulcer disease within previous 6 months
- History of intracerebral hemorrhage
- Thrombocytopenia
- Mitral stenosis

Drug: Irbesartan

Design: Randomized, double-blind, placebo-controlled trial

Methods: All participants included in this trial were originally enrolled in either the ACTIVE-A or ACTIVE-W trial. Participants were randomized to receive irbesartan (150 mg daily for 2 weeks, then 300 mg daily) or placebo. Use of non-study antihypertensive medications was allowed. The trial was initially designed to last 3 years.

Duration: Mean follow-up period of ~4.1 years

Statistical Analysis: It was initially determined that 9000 randomized patients would achieve 89% power for the first co-primary outcome and 92% for the second co-primary outcome. This assumed an annual event rate of 7% and 11% for co-primary outcomes in the control group. However, due to lower than expected event rates the follow-up period was extended and the power was reduced to 80% (alpha = 0.045). The ITT population was used for all analyses.

Results: A total of 9016 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. The average reduction in blood pressure was -6.8/4.5 mmHg in the irbesartan group compared to -3.9/2.6 mmHg in the placebo group. Among the patients that received a baseline electrocardiograph examination, irbesartan did not demonstrate a significant reduction in the recurrence of atrial fibrillation compared to placebo. There was no significant difference in the co-primary outcomes even after extending the trial to allow for more events. Rates of symptomatic hypotension and discontinuation due to renal dysfunction were significantly higher in the irbesartan group.

Irbesartan (N=4518) Vs Placebo (N=4498)

Stroke, Myocardial Infarction and Vascular Death:
963 (21.3%) vs 963 (21.4%); HR 0.99 (95% CI 0.91-1.08); p=0.85

Stroke, Myocardial Infarction, Vascular Death and Heart Failure Hospitalization:
1236 (27.3%) vs 1291 (28.7%); HR 0.94 (95% CI 0.87-1.02); p=0.12

Stroke:
379 (8.39%) vs 411 (9.14%); HR 0.91 (95% CI 0.79-1.05); p=0.20

Myocardial Infarction:
143 (3.17%) vs 135 (3.00%); HR 1.05 (95% CI 0.83-1.33); p=0.67

Vascular Death:
666 (14.7%) vs 646 (14.4%); HR 1.02 (0.92-1.14); p=0.67

Heart Failure Hospitalization:
482 (10.7%) vs 551 (12.2%); HR 0.86 (95% CI 0.76-0.98)
p=0.02; ARR 1.58%; NNT ~64

Discontinuation due to Symptomatic Hypotension:
127 (2.81%) vs 64 (1.42%); p<0.001

Discontinuation due to Renal Dysfunction:
43 (0.95%) vs 24 (0.53%); p=0.02

Limitations:

- External validity - cannot apply results to patients without atrial fibrillation
- Approximately 60% of all patients were receiving baseline ACEi – this may have obscured the treatment benefit of ARB therapy since RAAS inhibition was already occurring

Level of Evidence: Level II - with major limitations

Recommendation: For these reasons, I do not recommend the use of irbesartan for prevention of cardiovascular events in high-risk atrial fibrillation patients.

Efficacy:

- Rates of the co-primary endpoints were not significantly difference between groups
- Of the individual components, only heart failure hospitalization was significantly lower in the irbesartan group
- The recurrence of atrial fibrillation (determined via ECG) was similar between groups

Safety:

- Rates of discontinuation due to symptomatic hypotension or renal dysfunction were significantly higher in the irbesartan group

Cost:

- The cost of irbesartan must be balanced against the cost-savings of any potential benefit
    - However, the added costs of monitoring and managing hypotension and renal dysfunction must also be considered

Special Considerations/Populations:

- The majority of patients (~60%) were receiving baseline ACEi which may have obscured the treatment benefit of ARB therapy since RAAS inhibition was already occurring

Grade of Recommendation: **B**

ACTIVE-W

ACTIVE Writing Group of the ACTIVE Investigators, Connolly S, Pogue J, et al. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomized controlled trial. *Lancet*. 2006;367(9526):1903-1912.

Objective: To determine if clopidogrel plus aspirin is non-inferior to vitamin K antagonists (oral anticoagulation) for prevention of cardiovascular events in high-risk atrial fibrillation patients.

Primary Efficacy Measure: Composite of stroke, non-CNS embolism, myocardial infarction and vascular death

Participants: Patients with atrial fibrillation at increased risk for stroke who are able to use vitamin K antagonists

- Age ~70 years; male ~67%
- Permanent AF ~68%; paroxysmal AF ~18%
- $CHADS_2$ score ~2.0
- Baseline oral anticoagulant usage ~77%

Inclusion Criteria:

- ECG evidence of atrial fibrillation plus one or more of the following: age > 75, receiving treatment for hypertension, previous stroke/TIA/non-CNS embolism, LVEF < 45%, peripheral artery disease, age 55-74 with diabetes/coronary artery disease

Exclusion Criteria:

- Contraindication to using vitamin K antagonist or clopidogrel
- Documented peptic ulcer disease within previous 6 months, history of intracerebral hemorrhage, platelet count < $50x10^9$/L, mitral stenosis

Drugs: Clopidogrel plus aspirin; vitamin K antagonist

Design: Randomized, open-label, active-comparison, non-inferiority trial

Methods: Eligible patients were randomized to either clopidogrel 75 mg plus aspirin (75-100 mg) once daily or vitamin K antagonist (target INR 2.0-3.0). Patients were provided the vitamin K antagonist available in their country. Measurement of INR was performed at least once per month in patients receiving oral anticoagulation.

Duration: Median follow-up period of 1.3 years

Statistical Analysis: It was determined that 6500 randomized patients would achieve 85% power to demonstrate non-inferiority (alpha = 0.025). A non-inferiority margin of 1.186 was used. The ITT population was used for analyses.

Results: A total of 6706 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. The trial was stopped early by the safety committee due to the clearly demonstrated benefit of vitamin K antagonist over clopidogrel plus aspirin. Patients receiving vitamin K antagonist therapy were in the target INR range ~64% of the time. Subgroup analysis demonstrated that the patients that switched to clopidogrel plus aspirin from their baseline oral anticoagulation had worse adherence and more bleeding episodes compared to those who continued anticoagulation therapy.

Clopidogrel Plus Aspirin (N=3335) Vs Vitamin K Antagonist (N=3371)

Stroke, Non-CNS Embolism, Myocardial Infarction & Vascular Death:
234 (7.02%) vs 165 (4.89%); RR 1.44 (95% CI 1.18-1.76)
p=0.0003; ARR 2.12%; NNT ~48

Total Stroke:
100 (3.00%) vs 59 (1.75%); RR 1.72 (95% CI 1.24-2.37)
p=0.001; ARR 1.25%; NNT ~81

Ischemic Stroke:
90 (2.70%) vs 42 (1.25%); RR 2.17 (95% CI 1.51-3.13)
p<0.0001; ARR 1.45%; NNT ~69

Hemorrhagic Stroke:
5 (0.15%) vs 15 (0.44%); RR 0.34 (95% CI 0.12-0.93); p=0.036

Non-CNS Embolism:
18 (0.54%) vs 4 (0.12%); RR 4.66 (95% CI 1.58-13.8)
p=0.005; ARR 0.42%; NNT ~238

Myocardial Infarction:
36 (1.08%) vs 23 (0.68%); RR 1.58 (95% CI 0.94-2.67); p=0.09

Vascular Death:
120 (3.60%) vs 106 (3.14%); RR 1.14 (95% CI 0.88-1.48); p=0.34

Major Bleeding:
101 (3.03%) vs 93 (2.76%); RR 1.10 (95% CI 0.83-1.45); p=0.53
Includes severe and fatal bleeding

Severe Bleeding:
71 (2.13%) vs 66 (1.96%); RR 1.09 (95% CI 0.78-1.52); p=0.62

Fatal Bleeding
7 (0.21%) vs 11 (0.33%); RR 0.64 (95% CI 0.25-1.66); p=0.36

Limitations:

- Open-label trial design
- External validity - cannot apply results to patients without atrial fibrillation

Level of Evidence: Level I -with major limitations

Recommendation: For these reasons, I do not recommend the use of clopidogrel plus aspirin over anticoagulation therapy with vitamin K antagonists for prevention of vascular events in high-risk atrial fibrillation patients.

Efficacy:

- Clopidogrel plus aspirin did not demonstrate non-inferiority to oral anticoagulation with vitamin K antagonists (trial was stopped early due to clear benefit of oral anticoagulation over clopidogrel plus aspirin)
- The vitamin K antagonist group demonstrated significantly lower rates of the primary composite outcome, as well as the individual components of total stroke (specifically ischemic stroke) and non-CNS embolism

Safety:

- There was no significant difference in the rates of major bleeding (severe or fatal) between treatment groups

Cost:

- The cost of managing vitamin K antagonist therapy (labs and INR draws) must be balanced against the cost-savings of preventing cardiovascular events, specifically ischemic stroke

Special Considerations/Populations:

- Trial was not designed to determine superiority – results must be considered exploratory

Grade of Recommendation: **A**

ADAPTABLE

Jones WS, Mulder H, Wruck LM, et al. Comparative Effectiveness of Aspirin Dosing in Cardiovascular Disease. *N Engl J Med*. 2021;384(21):1981-1990.

Objective: To determine the efficacy and safety of aspirin 325 mg compared to aspirin 81 mg for prevention of secondary events in patients with established cardiovascular disease.

Primary Efficacy Measure: Composite of all-cause mortality, hospitalization for myocardial infarction or hospitalization for stroke (time to first event)

Primary Safety Measure: Hospitalization for major bleeding plus blood-product transfusion

Participants: Patients with established atherosclerotic cardiovascular disease

- Age ~68 years; male ~69%
- Prior myocardial infarction ~35%; coronary revascularization ~53%
- Aspirin use prior to trial ~90% (81 mg ~85%)

Inclusion Criteria:

- Age ≥ 18 years
- Established atherosclerotic cardiovascular disease
- Increased risk for major adverse cardiovascular event in the following three years

Exclusion Criteria:

- Hypersensitivity to aspirin
- History of clinically significant GI bleeding within previous 12 months
- Bleeding disorder preventing the use of aspirin
- Current use of anticoagulant
- Pregnancy or breastfeeding

Drug: Aspirin

Design: Randomized, open-label, active-comparator trial

Methods: Eligible patients were randomized to receive aspirin 81 mg or aspirin 325 mg once daily. Follow-up encounters occurred online or by phone every 3-6 months.

Duration: Median follow-up period of 26.2 months

Statistical Analysis: It was determined that 15,000 randomized patients would provide 88% power (alpha=0.05). The ITT population was used for the efficacy analysis.

Results: A total of 15,076 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. A total of 24.2% of all patients reported changing their aspirin dose during the trial (7.1% in the 81 mg group, 41.6% in the 325 mg group). The impact of this on trial results is uncertain.

Aspirin 81 mg (N=7540) Vs Aspirin 325 mg (N=7536)

Primary Composite Outcome:
590 (7.82%) vs 569 (7.55%); HR 1.02 (95% CI 0.91-1.14); p=0.75

All-Cause Mortality:
315 (4.18%) vs 357 (4.74%); HR 0.87 (95% CI 0.75-1.01)

Hospitalization for Myocardial Infarction:
228 (3.02%) vs 213 (2.83%); HR 1.06 (95% CI 0.88-1.27)

Hospitalization for Stroke:
102 (1.35%) vs 92 (1.22%); HR 1.09 (95% CI 0.82-1.45)

Hospitalization for Major Bleeding Plus Blood-Product Transfusion:
53 (0.70%) vs 44 (0.58%); HR 1.18 (95% CI 0.79-1.77); p=0.41

Limitations:

- Open-label trial design
- Patient population – trial results cannot be applied to those without established ASCVD
- Blood pressure, lipid levels and other pharmacological agents were not assessed, which serves as potential confounding factors
- Minor and non-major bleeding events were not assessed

Level of Evidence: Level I – with minor limitations

Recommendation: For these reasons, I recommend the daily use of aspirin 81 mg over aspirin 325 mg for secondary prevention of cardiovascular events in patients with established ASCVD.

Efficacy:

- Rates of the primary composite outcome and the individual components were not significantly different between treatment groups
- Notably more patients in the aspirin 325 mg group reported changing their dose

Safety:

- Rates of hospitalization for major bleeding plus blood-product transfusion occurred at similar rates between treatment groups

Cost:

- The cost difference of using aspirin 81 mg versus 325 mg is likely minimal

Special Considerations/Populations:

- Trial results cannot be applied to those without established ASCVD
- Antiplatelet therapy is only one aspect of secondary prevention
- Based on these trial results there is no apparent difference in the safety and efficacy of aspirin 81 mg and 325 mg, therefore, it is reasonable to use the lowest effective dose of 81 mg

Grade of Recommendation: **A**

ADVANCE-BG

ADVANCE Collaborative Group, Patel A, MacMahon S, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2008;358(24):2560-2572.

Objective: To determine the effects of intensive blood glucose-lowering therapy (HgA1c ≤ 6.5%) compared to standard blood glucose-lowering therapy on major vascular event rates in patients with type 2 diabetes.

Primary Efficacy Measure: Composite of macrovascular events (cardiovascular death, non-fatal myocardial infarction and non-fatal stroke) and microvascular events (new/worsening nephropathy or retinopathy)

Participants: Patients with type 2 diabetes at increased risk for major vascular events

- Age ~66 years; male ~58%
- HgA1c ~7.5%; duration of diabetes ~8.0 years
- Previous macrovascular event ~32%; microvascular event ~10%
- Metformin ~60%; sulfonylurea ~64%

Inclusion Criteria:

- Diagnosed with type 2 diabetes at age 30 years or older
- Age ≥ 55 years old
- History of major macrovascular/microvascular disease or ≥ 1 risk factor for vascular disease

Exclusion Criteria:

- Contraindication to using any of the study medications
- Definite indication for long-term insulin therapy at baseline

Drugs: n/a

Design: Randomized, open-label, active-comparison trial

Methods: This trial arm was part of the ADVANCE Collaborative Group. Eligible patients underwent a run-in period of 6 weeks consisting of normal glucose management. Those who successfully completed the run-in period were randomized into either intensive glucose-lowering therapy (HgA1c ≤ 6.5%) or standard glucose-lowering therapy (target HgA1c based on local guidelines). Patients entering the intensive blood glucose-lowering therapy group were started on gliclazide XR (30-120 mg) and all other sulfonylureas were discontinued. All other medications could be adjusted at the discretion of the investigator, although there was a suggested treatment protocol in place.

Duration: Median follow-up period of 5 years

Statistical Analysis: The trial was originally designed to have 90% power (alpha = 0.05). However, due to lower than expected event rates it was decided to extend the follow-up period by 12 months and to do a joint analysis of both composite outcomes to increase power. The ITT population was used for all analyses.

Results: A total of 11,140 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. After follow-up, average HgA1c was 6.5% in the intensive therapy group and 7.3% in the standard therapy group. There was no significant difference in rates of all-cause mortality or retinopathy between treatment groups.

Intensive Therapy (N=5571) Vs Standard Therapy (N=5569)

Composite of Macrovascular & Microvascular Events:
1009 (18.1%) vs 1116 (20.0%); HR 0.90 (95% CI 0.82-0.98)
p=0.01; ARR 1.93%; NNT ~52

Macrovascular Events:
557 (10.0%) vs 590 (10.6%); HR 0.94 (95% CI 0.84-1.06); p=0.32

Microvascular Events:
526 (9.44%) vs 605 (10.9%); HR 0.86 (95% CI 0.77-0.97)
p=0.01; ARR 1.42%; NNT ~71

New/Worsening Nephropathy:
230 (4.13%) vs 292 (5.24%); HR 0.79 (95% CI 0.66-0.93)
p=0.006; ARR 1.11%; NNT ~90

Serious Hypoglycemia (BG < 50 mg/dL):
150 (2.69%) vs 81 (1.45%); HR 1.86 (95% CI 1.42-2.40)
p<0.001; ARI 1.24%; NNH ~80

Limitations:

- Requirements for meeting power after trial adjustment/extension not mentioned

Level of Evidence: Level II - with major limitations

Recommendation: For these reasons, I do not recommend targeting a lower HgA1c goal (≤ 6.5%) over standard blood glucose goals in high-risk patients with type 2 diabetes.

Efficacy:

- The rates of the primary composite outcome were significantly lower in the intensive therapy group compared to standard therapy
- However, there was no significant difference in rates of macrovascular event rates between treatment groups
- The individual component of microvascular event rates was significantly lower in the intensive therapy group (driven primarily by reduced rates of nephropathy)

Safety:

- There were significantly higher rates of serious hypoglycemia in the intensive therapy group
- There was no significant difference in rates of all-cause mortality between treatment groups

Cost:

- The cost of increased medication usage to target a lower HgA1c must be balanced against the cost-savings of preventing nephropathy
- However, the cost of monitoring and managing hypoglycemia must also be considered

Special Considerations/Populations:

- The NNT for avoiding new/worsening nephropathy is higher than the NNH for serious hypoglycemia, which suggests that the treatment benefit of intensive therapy is not outweighed by the risk of targeting a lower HgA1c
- Trial design – the target HgA1c for the intensive treatment group (≤ 6.5%) must be considered when interpreting trial results

Grade of Recommendation: **B**

ADVANCE-BP

Patel A; ADVANCE Collaborative Group, MacMahon S, et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes: a randomized controlled trial. *Lancet*. 2007;370(9590):829-840.

Objective: To determine the effect of fixed-dose perindopril and indapamide on vascular outcomes in type 2 diabetes with a broad range of initial blood pressure values.

Primary Efficacy Measure: Composite of major macrovascular (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke) and microvascular events (new/worsening nephropathy or retinopathy)

Participants: Patients with type 2 diabetes at increased risk for major vascular events

- Age ~66 years; male ~57%
- Previous macrovascular event ~32%; microvascular event ~10%
- BP ~145/81 mmHg; baseline antihypertensive therapy ~75%

Inclusion Criteria:

- Diagnosed with type 2 diabetes at age 30 years or older
- Age ≥ 55 years old
- One or more of the following risk factors: history of major cardiovascular disease (stroke, myocardial infarction, TIA, unstable angina, coronary/peripheral revascularization or amputation due to vascular disease), history of major microvascular disease, current smoker, total cholesterol > 232 mg/dL, HDL-C < 38 mg/dL, microalbuminuria, type 2 diabetes diagnosis made 10 years or more prior to trial entry, age ≥ 65

Exclusion Criteria:

- Definite indication or contraindication for any study treatments
- Definite indication for long-term insulin therapy

Drugs: Fixed-dose perindopril and indapamide

Design: Randomized, double-blind, active-comparison trial

Methods: This trial arm was part of the ADVANCE Collaborative Group. Eligible patients underwent a 6-week run-in period where all participants received fixed-dosed perindopril 2 mg and indapamide 0.625 mg daily. Those that successfully completed the run-in period were randomized to the same fixed dose perindopril and indapamide or matching placebo. After 3 months, the doses were increased to perindopril 4 mg and indapamide 1.25 mg daily (or matching placebo). All other medications were continued at the discretion of the treating physician (thiazide diuretics were not allowed). Open-label use of perindopril was allowed up to a max dosing of 4 mg daily. No other ACEis were allowed.

Duration: Mean follow-up period of 4.3 years

Statistical Analysis: This trial was originally designed to have 90% power (alpha = 0.05). However, due to lower than expected event rates the trial was extended by 12 months and analysis of macrovascular and microvascular events was to be conducted both jointly and separately. The ITT population was used for all analyses.

Results: A total of 11,140 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. The average blood pressure was significantly lower in the perindopril/indapamide group compared to placebo (-5.6/-2.2 mmHg; $p<0.0001$). At the end of the follow-up period, ~55% of patients in the placebo group were receiving open-label perindopril. While total renal event rates were significantly lower in the perindopril/indapamide group, individual rates of new/worsening nephropathy and retinopathy (components of microvascular event composite) were not significantly different between treatment groups. The observed difference in all-cause mortality was driven by significantly lower rates of cardiovascular death.

Perindopril/Indapamide (N=5569) Vs Placebo (N=5571)

Composite of Macrovascular & Microvascular Events:
861 (15.5%) vs 938 (16.8%); HR 0.91 (0.81-1.00); p=0.041
While p<0.05, the 95% CI includes 1.00 - this indicates lack of treatment difference

Macrovascular Events:
480 (8.62%) vs 520 (9.33%); RR 8% (95% CI -4% to 19%); p=0.16

Microvascular Events:
439 (7.88%) vs 477 (8.56%); RR 9% (95% CI -4% to 20%); p=0.16

All-Cause Mortality:
408 (7.33%) vs 471 (8.45%); HR 0.86 (95% CI 0.75-0.98)
p=0.025; ARR 1.13%; NNT ~89

Cardiovascular Death:
211 (3.79%) vs 257 (4.61%); RR 18% (2% to 32%)
p=0.027; ARR 0.82%; NNT ~122

Limitations:

- Power not discussed post-adjustment (unable to determine if power met)
- Use of open-label perindopril acts as potential confounding factor
    - The true major difference in drug treatments between groups is indapamide

Level of Evidence: Level II - with major limitations

Recommendation: For these reasons, I do not recommend the routine use of fixed-dose perindopril/indapamide for prevention of vascular events in high-risk patients with type 2 diabetes without elevated blood pressure. Instead, I recommend optimizing glycemic lowering therapy and initiating/intensifying blood pressure lowering therapy only if there is a clear indication.

Efficacy:

- Cardiovascular death occurred at significantly lower rates in the active treatment group
- However, although the primary composite event rate was statistically lower (p<0.05) in the perindopril/indapamide group the 95% CI included 1.00, which indicates a lack of difference in treatment effect
- Event rates of the individual components of the primary composite outcome (macrovascular and microvascular outcomes) were not significantly different between treatment groups

Safety:

- Rates of cough and hypotension/dizziness were higher in the perindopril/indapamide group

Cost:

- The cost of using perindopril/indapamide must be balanced against any potential cost-savings due to treatment benefit

Special Considerations/Populations:

- Lack of specific blood pressure inclusion criteria and treatment goals makes applying trial results difficult as it leaves the patient population extremely broad
    - High-risk patients with type 2 diabetes
- ~55% of the placebo group was receiving perindopril at the end of the follow-up period
    - Makes interpreting the trial results more difficult in terms of determining the treatment and/or dosing responsible for said outcomes
    - The demonstrated treatment effect may be due to differences in average blood pressure alone rather than the individual drug properties of perindopril and indapamide

Grade of Recommendation: **B**

ADVOR

Mullens W, Dauw J, Martens P, et al. Acetazolamide in Acute Decompensated Heart Failure with Volume Overload. *N Engl J Med*. 2022;387(13):1185-1195.

Objective: To determine the effect of acetazolamide (in addition to IV loop diuretic therapy) on clinical outcomes in patients with acutely decompensated heart failure.

Primary Efficacy Measure: Successful decongestion (no signs of volume overload) within 3 days after randomization (as determined by a cardiologist)

Secondary Efficacy Measure: Composite of all-cause mortality or heart failure hospitalization during the 3 months of follow-up

Participants: Patients hospitalized for acute decompensated heart failure (receiving IV loop diuretics)

- Age ~78 years; male ~63%
- Loop diuretic equivalent dose ~ 60 mg of furosemide daily
- LVEF ~43%; NT-proBNP ~6173 pg/mL
- NYHA class III ~57%; class IV ~30%
- ACEi/ARB or ARNi ~52%; beta-blocker ~81%; MRA ~41%

Inclusion Criteria:

- Hospitalization for acute decompensated heart failure
- One or more signs of volume overload
- NT-proBNP level > 1000 pg/mL (or BNP > 250 pg/mL)
- Maintenance therapy with oral loop diuretic (≥ furosemide 40 mg daily) for at least 1 month prior to randomization

Exclusion Criteria:

- Maintenance therapy with acetazolamide or other proximal tubule diuretic (e.g. SGLT2i)
- SBP < 90 mmHg
- eGFR < 20 mL/min

Drug: Acetazolamide

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients were randomized to receive acetazolamide 500 mg IV once daily or matching placebo for the following two days (or until complete decongestion occurred). Upon randomization, oral loop diuretics were stopped and changed to IV loop diuretics (at double the oral dose). Use of IV loop diuretics at doses equivalent to greater than furosemide 80 mg were not allowed during the index hospitalization. The treating physicians were encouraged not to adjust the neurohormonal blocking therapies during the trial period.

Duration: 3 months of follow-up

Statistical Analysis: It was determined that 519 randomized patients would provide 80% power (alpha=0.05). The efficacy analyses included all randomized patients that received at least one dose of study drug (mITT).

Results: A total of 519 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. Significantly more patients achieved successful decongestion within 3 days after randomization in the acetazolamide group compared to the placebo group. The treatment benefit of acetazolamide was also demonstrated at the time of discharge. Rates of adverse events (including hypotension, electrolyte disturbances and metabolic acidosis) were similar between groups.

Placebo (N=259) Vs Acetazolamide (N=256)

Successful Decongestion within 3 Days after Randomization:
79 (30.5%) vs 108 (42.2%); RR 1.46 (95% CI 1.17-1.82)
p<0.001; ARR 11.7%; NNT ~9

Successful Decongestion at Discharge:
145/232 (62.5%) vs 190/241 (78.8%); RR 1.27 (95% CI 1.13-1.43)
Among patients still alive

All-Cause Mortality or Heart Failure Hospitalization During 3 Month Follow-Up:
72 (27.8%) vs 76 (29.7%); HR 1.07 (95% CI 0.78-1.48)

Limitations:

- Sample size relatively small
- External validity – can only apply trial results to inpatient use of IV acetazolamide
- Results must be considered in addition to IV loop diuretic therapy
- Patient population – all patients were receiving chronic oral loop diuretic therapy at baseline

Level of Evidence: Level I – with minor limitations

Recommendation: For these reasons, I recommend the use of IV acetazolamide (in addition to IV loop diuretics) to further improve rates of successful decongestion in patients hospitalized for acute heart failure decompensation.

Efficacy:

- Significantly more patients in the acetazolamide treatment group achieved successful decongestion within 3 days of randomization
- Upon discharge, significantly more patients in the acetazolamide group were successfully decongested
- Rates of the composite outcome of all-cause mortality and heart failure hospitalization during the 3 month follow-up period were similar between treatment groups

Safety:

- Rates of adverse events were similar between treatment groups

Cost:

- The cost of using IV acetazolamide must be balanced against the cost-savings from achieving greater rates of successful decongestion and preventing complications from prolonged fluid overload

Special Considerations/Populations:

- Acetazolamide inhibits carbonic anhydrase in the proximal tubule of the kidney causing decreased sodium reabsorption
- Patients were receiving oral loop diuretic therapy at baseline prior to randomization and IV diuretic therapy during the trial period (IV route at double their maintenance dose)
- Trial results may not be applicable to patients hospitalized for newly diagnosed heart failure

Grade of Recommendation: **A**

AF-CHF

Roy D, Talajic M, Nattel S, et al. Rhythm control versus rate control for atrial fibrillation and heart failure. *N Engl J Med*. 2008;358(25):2667-2677.

Objective: To compare the efficacy and safety of rhythm control to rate control in heart failure patients with atrial fibrillation.

Primary Efficacy Measure: Cardiovascular death

Participants: Patients with heart failure reduced ejection fraction and atrial fibrillation

- Age ~67 years; ~82% male
- LVEF ~27%; persistent AF ~68%; paroxysmal AF ~32%
- Oral anticoagulant ~88%; ACEi ~86%; beta-blocker ~79%; digoxin ~64%

Inclusion Criteria:

- LVEF ≤ 35%
- History of congestive heart failure (NYHA class II or IV within previous 6 months; LVEF ≤ 25%; heart failure hospitalization within previous 6 months)
- History of atrial fibrillation documented by ECG

Exclusion Criteria:

- Persistent atrial fibrillation for more than 12 months
- Reversible atrial fibrillation or heart failure
- Decompensated heart failure within 48 hours prior to randomization
- Second or third degree AV block (HR < 50 bpm)
- Previous AV node ablation

Drugs: Amiodarone (rhythm control); beta blockers & digoxin (rate control)

Design: Randomized, open-label, active-comparison trial

Methods: Eligible patients were randomized to either rhythm control or rate control therapy. Patients in the rhythm control group that did not achieve sinus rhythm were recommended to receive electrical cardioversion. The drug of choice in the rhythm group was amiodarone (sotalol or dofetilide were used if needed). In the rate control group beta-blockers and digoxin were dose adjusted to achieve ventricular rates of < 80 bpm at rest and < 110 bpm during walking tests. Patients that failed rate control were recommended for AV node ablation and pacemaker therapy. Heart failure therapy of ACEi/ARB plus max tolerated beta-blocker was used in all patients. Anticoagulation was recommended for all patients.

Duration: Mean follow-up period 37 months (~3 years)

Statistical Analysis: It was determined that 1374 randomized patients would be needed to achieve 80% power (alpha = 0.05). The ITT population was used for analyses.

Results: A total of 1376 patients underwent randomization. Baseline patient characteristics were generally well-matched. During the study ~21% of the rhythm control group crossed over to the rate control group for the primary reason of failure to maintain sinus rhythm. This is compared to ~10% of patients in the rate control group that crossed over into the rhythm control group for the primary reason of worsening heart failure. In the rate control group, the target heart rates were achieved in 82-88% of patients during the first three years of follow-up. Atrial fibrillation prevalence dropped in the rhythm control group from 54% at baseline (via ECG) to 27% at four years.

Rhythm Control (N=682) Vs Rate Control (N=694)

Cardiovascular Death:
182 (26.7%) vs 175 (25.2%); HR 1.05 (95% CI 0.85-1.29); p=0.67

All-Cause Mortality:
217 (31.8%) vs 228 (32.9%); HR 0.80 (95% CI 0.80-1.17); p=0.73

First Hospitalization:
436 (63.9%) vs 409 (58.9%); p=0.06

Total All-Cause Hospitalizations:
936 vs 895

Total Hospitalizations for Atrial Fibrillation:
133 (14.2%) vs 80 (8.94%); p<0.001; ARI 5.27%; NNH ~19

Total Hospitalizations for Bradyarrhythmia:
52 (5.56%) vs 30 (3.35%); p=0.023; ARI 2.20%; NNH ~45

Total Hospitalizations for Heart Failure:
270 (28.8%) vs 280 (31.3%%); p=0.26

Electrical Cardioversion:
268 (39.3%) vs 52 (7.49%); p<0.001; ARI 31.8%; NNH ~3

Limitations:

- Open-label trial design
- External validity - cannot apply results to patients with preserved ejection fraction
- All patients were receiving maximally tolerated beta-blocker which is a potential confounding factor when comparing the rhythm control and rate control groups

Level of Evidence: Level I - with major limitations

Recommendation: For these reasons, I recommend the use of rate control therapy over rhythm control therapy to manage atrial fibrillation in patients with heart failure and reduced ejection fraction.

Efficacy:

- There was no significant difference in the rates of cardiovascular death or all-cause mortality between rhythm and rate control groups

Safety:

- Rates of overall patient hospitalizations were similar between treatment groups
- However, the number of total hospitalizations for atrial fibrillation and bradyarrhythmia was significantly higher in the rhythm group
- The number of cardioversions was significantly higher in the rhythm control group

Cost:

- The cost of rate control should be balanced against the cost-savings from reduced hospitalizations due to atrial fibrillation and bradyarrhythmia

Special Considerations/Populations:

- All patients were treated for heart failure with ACEi/ARB plus max tolerated beta-blocker
- Oral anticoagulation was recommended for all patients

Grade of Recommendation: **A**

AFFIRM

Wyse DG, Waldo AL, DiMarco JP, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med*. 2002;347(23):1825-1833.

Objective: To compare the efficacy and safety of rate control and rhythm control therapy in atrial fibrillation patients.

Primary Efficacy Measure: All-cause mortality

Participants: Atrial fibrillation patients at increased risk for stroke or death
- Age ~70 years; male ~60%

Inclusion Criteria:
- Recurrent atrial fibrillation
- Age ≥ 65 or additional risk factors for stroke/death

Exclusion Criteria:
- Contraindication for anticoagulation therapy

Drugs: Antiarrhythmic medications (rhythm control); beta-blockers, digoxin, verapamil, diltiazem (rate control)

Design: Randomized, open-label, active-comparison trial

Methods: Eligible patients were randomized to either rate control or rhythm control therapy. In the rhythm control group, the antiarrhythmic drug(s) were chosen by the treating physician (cardioversion was allowed in this treatment group). In the rate control group, a heart rate of < 80 bpm at rest and < 110 bpm when active (during a 6-minute walking test) was targeted using beta-blockers, digoxin, verapamil and diltiazem. Anticoagulation with warfarin was encouraged in the rhythm control group but could be stopped at the physician's discretion if sinus rhythm was maintained for 4 consecutive weeks. In the rate control group, the use of continuous anticoagulation therapy was required by protocol. A target INR range of 2.0 to 3.0 was used.

Duration: Mean follow-up period of 3.5 years

Statistical Analysis: It was determined that 5300 randomized patients would achieve 90% power (alpha=0.05). The ITT population was used for the primary efficacy analyses.

Results: A total of 4060 participants underwent randomization. Baseline patient characteristics were similar between treatment groups. More than 85% participants were receiving anticoagulation therapy in the rate control group. Overall, ~70% of participants in the rhythm control group remained on anticoagulation therapy. Approximately 62% of all measured INR values were within range. Amiodarone (followed by sotalol) was the most common drug used for rhythm control. Digoxin (followed closely by beta-blockers) was the most common drug used for rate control.

Rate Control (N=2027) Vs Rhythm Control (N=2033)

All-Cause Mortality:
310 (15.3%) vs 356 (17.5%); HR 1.15 (95% CI 0.99-1.34); p=0.08

Ischemic Stroke:
77 (3.80%) vs 80 (3.94%); p =0.79

First Hospitalization:
1220 (60.2%) vs 1374 (67.6%); p<0.001; ARR 7.40%; NNT ~14

Torsades de Pointes:
2 (0.10%) vs 12 (0.59%); p=0.007; ARR 0.49%; NNT ~204

Adverse Events Leading to Discontinuation of Medication:

Bradycardia:
64 (3.16%) vs 105 (5.16%); p=0.001; ARR 2.00%; NNT ~50

QTc Prolongation (>520 msec):
4 (0.20%) vs 31 (1.52%); p<0.001; ARR 1.33%; NNT ~76

Limitations:
- Power set but not met - failed to randomize enough patients
- Open-label trial design

Level of Evidence: Level II - with major limitations

Recommendation: For these reasons, I recommend the use of rate control over rhythm control therapy for managing atrial fibrillation patients primarily due to improved safety and tolerability.

Efficacy:
- Rates of all-cause mortality were not significantly different between treatment groups
- Ischemic stroke rates were not significantly different between treatment groups
- Hospitalization rates were significantly higher in the rhythm control group

Safety:
- Adverse events causing discontinuation, specifically bradycardia and QTc prolongation, were significantly higher in the rhythm control group

Cost:
- The cost of using rate control must be balanced against the cost-savings of avoiding increased hospitalization and adverse drug reactions associated with rhythm control therapy

Special Considerations/Populations:
- The main medications used for rate control were digoxin and beta-blockers
- The main medications used for rhythm control were amiodarone and sotalol
- The use of anticoagulation therapy in the majority of these patients must also be considered when interpreting trial results

Grade of Recommendation: **B**

A-HEFT

Taylor AL, Ziesche S, Yancy C, et al. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. *N Engl J Med*. 2004;351(20):2049-2057.

Objective: To determine the efficacy of fixed dose isosorbide dinitrate plus hydralazine in black patients with heart failure (NYHA class III-IV) receiving neurohormonal inhibitors

Primary Efficacy Measure: Composite of all-cause mortality, first heart failure hospitalization and quality of life change at 6 months

Participants: Black patients with NYHA class III-IV heart failure on standard therapy

- Age ~57 years; male ~60%
- NYHA class III ~96%
- LVEF ~24%
- Baseline ACEi ~69%; beta-blocker ~74%; digoxin ~60%; MRA ~39%

Inclusion Criteria:

- Heart failure patients ≥ 18 years old self-identified as black
- NYHA class III-IV for ≥ 3 months
- Receiving standard heart failure therapy for ≥ 3 months
- LVEF ≤ 35% within previous 6 months

Exclusion Criteria:

- Acute myocardial infarction, acute coronary syndrome or stroke within previous 3 months
- Cardiac surgery or PCI within previous 3 months
- Clinically significant valvular heart disease
- Hypertrophic cardiomyopathy or myocarditis
- Uncontrolled hypertension
- History of cardiac arrest or life-threatening arrhythmia within previous 3 months

Drug: Isosorbide dinitrate plus hydralazine

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients were required to be on stable heart failure therapy and have body weight variation of < 2.5% within the 2 weeks prior to randomization. Patients were then randomized to receive fixed dose isosorbide dinitrate plus hydralazine (20 mg/37.5 mg TID) or matching placebo. The dosage could be increased to the target goal of 2 tablets TID at the discretion of the study investigator.

Duration: Mean follow-up period of 10 months

Statistical Analysis: It was initially estimated that 800 randomized patients would achieve 80% power (alpha = 0.02). However, it was increased to 1100 randomized patients (550 per group) based on pre-specified interim analysis. The ITT population was used for the primary efficacy analyses.

Results: The trial was stopped early on the recommendation from the safety monitoring board due to significantly higher mortality rates in the placebo group. A total of 1050 patients underwent randomization by this point. Baseline patient characteristics were similar between treatment groups with the exception of a higher proportion of males in the placebo group (63.9% vs 55.8%; p=0.008) and a higher proportion of baseline diabetes in the isosorbide/hydralazine group (44.8% vs 37.0%; p=0.01). The target dose (2 tabs TID) was achieved in 68% of patients in the active treatment group. The average blood pressure was statistically lower in the combo therapy group at 6 months (-1.9 mmHg SBP and -2.4 mmHg DBP vs +1.2 mmHg SBP and + 0.8 mmHg DBP; p = 0.02 & < 0.001, respectively).

Isosorbide/Hydralazine (N=518) Vs Placebo (N=532)

Primary Composite Endpoint:
-0.1 +/- 1.9 vs -0.5 +/- 2.0; p=0.01
Scores range from -6 to 2 with higher scores indicating improved clinical outcomes

All-Cause Mortality:
32 (6.18%) vs 54 (10.2%); p=0.02

First Heart Failure Hospitalization:
85 (16.4%) vs 130 (24.4%); p=0.001; ARR 8.03%; NNT ~13

Quality of Life Change at 6 Months:
-5.6 +/- 20.6 vs -2.7 +/- 21.2; p=0.02
Lower scores indicate better quality of life

Safety:

Severe Congestive Heart Failure Exacerbation:
3.1% vs 7.0%; p=0.005; ARR 3.9%; NNT ~26

Headache:
47.5% vs 19.2%; p<0.001; ARI 28.3%; NNH ~3

Dizziness:
29.3% vs 12.3%; p<0.001; ARI 17.0%; NNH ~5

Limitations:

- Power set but not met - failed to randomize 550 patients into each group (significance minimal as trial was stopped early and a significant difference was demonstrated)
- Randomization resulted in a significantly different distribution of males and diabetics

Level of Evidence: Level II - with major limitations

Recommendation: For these reasons, I recommend the addition of isosorbide dinitrate/hydralazine to standard heart failure therapy in black patients with NYHA functional class III-IV and LVEF ≤ 35% to further decrease morbidity and mortality outcomes. However, tolerability of adverse effects and the need for frequent dosing may be challenging for certain patients.

Efficacy:

- The primary composite outcome score was significantly higher in the isosorbide/hydralazine group compared to placebo, indicating better clinical outcomes
- Individual components of all-cause mortality and first heart failure hospitalization were significantly lower in the active treatment group

Safety:

- Occurrence of headache and dizziness was significantly higher in the active treatment group
- Rate of severe congestive heart failure exacerbation was significantly lower in the active treatment group compared to placebo

Cost:

- The cost of adding isosorbide/hydralazine to standard heart failure therapy must be balanced against the cost-savings of preventing heart failure hospitalizations and congestive heart failure exacerbations

Special Considerations/Populations:

- Target dosing of 2 tablets 3 times daily may not be feasible in patients with adherence issues

Grade of Recommendation: **B**

AIM-HIGH

AIM-HIGH Investigators, Boden WE, Probstfield JL, et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med*. 2011;365(24):2255-2267.

Objective: To assess if the addition of niacin ER to statin therapy provides additional morbidity and mortality reduction in patients with established cardiovascular disease and low HDL levels.

Primary Efficacy Measure: Composite of coronary artery disease death, non-fatal myocardial infarction, ischemic stroke and hospitalization > 23 hours secondary to acute coronary syndrome or coronary/cerebral revascularization

Participants: Patients with established cardiovascular disease and low HDL levels

- Age ~64 years; male ~85%
- History of myocardial infarction ~56%; PCI ~62%; CABG ~36%
- Baseline statin ~93%
- HDL ~35 mg/dL; LDL ~74 mg/dL

Inclusion Criteria:

- Age ≥ 45 years
- Established cardiovascular disease (stable coronary artery disease, cerebrovascular or carotid disease, or PAD)
- HDL < 40 mg/dL for men; HDL < 50 mg/dL for women
- Elevated triglyceride levels (150-400 mg/dL)
- LDL < 180 mg/dL (if not on baseline statin)

Exclusion Criteria:

- Acute coronary syndrome/revascularization within previous 4 weeks
- Stroke within previous 8 weeks

Drugs: Niacin extended-release; simvastatin

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients underwent a 4-8 week run-in period where they received simvastatin 40 mg plus niacin 500 mg daily (niacin dose would be increased weekly by 500 mg to max of 2000 mg daily). Prior to the run-in period patients were required to stop all lipid-modifying drugs except statins or ezetimibe for a minimum of 4 weeks. Those who could tolerate niacin 1500 mg daily were then randomly assigned to either placebo or niacin ER treatment groups for the main trial period. The active treatment group received simvastatin 40-80 mg plus niacin ER 1500-2000 mg once daily. The placebo group received simvastatin 40-80 mg daily plus matching placebo (containing niacin IR 50 mg to help prevent unmasking). Both treatment groups could receive ezetimibe 10 mg daily in order to reach the target LDL range of 40-80 mg/dL.

Duration: Trial stopped early after ~36 months

Statistical Analysis: It was determined that a total of 800 primary events would provide 85% power (alpha = 0.025). The ITT population was used for all analyses.

Results: A total of 3414 participants underwent randomization. It is notable that ezetimibe was used significantly more in the placebo group compared to the niacin group (21.5% and 9.5%; $p<0.001$). However, while the use of niacin ER demonstrated notable increases in HDL and decreases in triglycerides there was no difference in terms of the primary composite outcome or the individual values. Additionally, rates of study medication discontinuation were significantly higher in the niacin ER group, mainly due to the adverse effect of flushing ($p<0.001$).

Placebo (N=1696) Vs Niacin ER (N=1718)

Primary Composite Endpoint:
274 (16.2%) vs 282 (16.4%); HR 1.02 (95% CI 0.87-1.21); p=0.80

Coronary Artery Disease Death:
26 (1.53%) vs 20 (1.16%)

Non-Fatal Myocardial Infarction:
80 (4.72%) vs 92 (5.36%)

Ischemic Stroke:
15 (0.88%) vs 27 (1.57%)

Hospitalization Secondary to Acute Coronary Syndrome:
67 (3.95%) vs 63 (3.67%)

Coronary/Cerebral Revascularization:
86 (5.07%) vs 80 (4.66%)

Final Lipids Values:
Values in parentheses are the change from baseline

Mean LDL (mg/dL):
68.3 (-5.7) vs 65.2 (-9.0)

Mean HDL (mg/dL):
39.1 (+4.2) vs 44.1 (+9.6)

Limitations:

- Power set but not met - failed to meet set number of primary events
- The higher proportion of ezetimibe usage in the placebo group acts as a potential confounding factor - however, no treatment difference was demonstrated despite this

Level of Evidence: Level II - with major limitations

Recommendation: For these reasons, I do not recommend the use of niacin ER in addition to statin therapy for added morbidity and mortality reduction in patients with established cardiovascular disease and low HDL levels.

Efficacy:

- There was no significant difference in the rates of the primary composite outcome (or the individual components) between treatment groups, despite favorable increases in HDL and decreases in LDL with the niacin ER group over placebo

Safety:

- Discontinuation rates (mainly due to flushing) were significantly higher in the niacin group

Cost:

- The cost of using niacin ER in addition to standard statin therapy must be considered

Special Considerations/Populations:

- Patient population must be considered - all had baseline cardiovascular disease and almost all were receiving statin therapy at baseline

Grade of Recommendation: **B**

AIRE

Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. *Lancet*. 1993;342(8875):821-828.

Objective: To determine the effect of ramipril on mortality outcomes in patients with evidence of heart failure following a myocardial infarction.

Primary Efficacy Measure: All-cause mortality

Participants: Patients with clinical evidence of HF following hospitalization for myocardial infarction

- Age ~65 years; male ~74%
- Previous heart failure ~8%
- Time from myocardial infarction to trial randomization ~5.4 days
- Baseline aspirin ~78%; beta-blocker ~22%; diuretic ~60%; nitrate ~56%

Inclusion Criteria:

- Age 18 years and older
- Hospitalized for acute myocardial infarction
- Clinical evidence of heart failure following myocardial infarction

Exclusion Criteria:

- Severe heart failure (NYHA class IV)
- Valvular heart failure
- Unstable angina
- Contraindication to receiving ACEi therapy

Drug: Ramipril

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients were randomized to receive ramipril or matching placebo. Treatment was begun between day 3 and 10 of hospitalization at a dose of 2.5 mg twice daily for two days, then 5 mg twice daily thereafter (if tolerated).

Duration: Average follow-up period of 15 months

Statistical Analysis: It was determined that 2000 randomized patients would provide 80% power (alpha=0.05). The ITT population was used for the primary efficacy analysis.

Results: A total of 1986 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. The vast majority of patients in the ramipril group (~86%) were discharged from the hospital on the 5 mg twice daily dosing. Treatment benefits become evident as early as 30 days. Rates of discontinuation and serious adverse events were lower in the ramipril group compared to placebo.

Ramipril (N=1004) Vs Placebo (N=982)

All-Cause Mortality:
170 (16.9%) vs 222 (22.6%); HR 0.73 (95% CI 0.60-0.89)
p=0.002; ARR 5.67%; NNT ~18

Limitations:

- Power set but not met – clinical significance minimal (statistical difference still detected)
- Patient population – clinical evidence of heart failure following hospitalization for myocardial infarction
- Inclusion criteria for 'clinical evidence of heart failure' does not specify an ejection fraction
    - Limits ability to apply results to specific EFs (e.g., preserved vs reduced)

Level of Evidence: Level II – with major limitations

Recommendation: For these reasons, I recommend the use of ramipril to reduce mortality rates in patients with clinical evidence of heart failure following hospitalization for acute myocardial infarction. Ideally, ramipril should be initiated during the hospitalization period.

Efficacy:

- Rates of all-cause mortality were significantly lower in the ramipril treatment group

Safety:

- Overall, rates of discontinuation and serious adverse events were lower in the ramipril group

Cost:

- The cost of using ramipril must be balanced against the cost-savings achieved from reduced mortality

Special Considerations/Populations:

- Treatment was initiated between day 3 and 10 following hospitalization for index event
- Guideline-directed medical therapy has changed significantly since the time this trial was published
    - This must be taken into consideration when interpreting trial results

Grade of Recommendation: **B**

ALLHAT

ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA*. 2002;288(23):2981-2997.

Objective: To determine the effect of CCBs, ACEis and alpha-blockers compared to thiazide-type diuretics on morbidity and mortality in high-risk patients with hypertension.

Primary Efficacy Measure: Composite of fatal coronary heart disease or non-fatal myocardial infarction

Secondary Efficacy Measures: All-cause mortality, fatal/non-fatal stroke, combined coronary heart disease, combined cardiovascular disease

Participants: Patients with stage 1 or 2 hypertension at high-risk for cardiac events

- Age ~67 years; male ~53%
- BP ~146/84 mmHg
- Baseline ASCVD ~52%

Inclusion Criteria:

- Age ≥ 55 years
- Hypertension (stage 1 or 2) plus ≥ 1 risk factor for coronary heart disease (previous myocardial infarction or stroke > 6 months prior, left-ventricular hypertrophy, type 2 diabetes, current cigarette smoker, HDL < 35 mg/dL, documented ASCVD)

Exclusion Criteria:

- History of hospitalization due to heart failure
- Symptomatic heart failure
- LVEF < 35%

Drugs: Chlorthalidone; lisinopril, amlodipine, doxazosin

Design: Randomized, double-blind, active-comparison trial

Methods: Eligible patients were allowed to continue previous medications until they received the study drug, at which point all previous medications were stopped. Study medication was titrated to a target blood pressure of < 140/90 mmHg in all groups (chlorthalidone 12.5 – 25 mg; amlodipine 2.5 – 10 mg; lisinopril 10 – 40 mg). The use of open-label agents was allowed per investigator discretion. Amlodipine represented the CCB arm, lisinopril the ACEi arm and chlorthalidone the diuretic arm. The doxazosin treatment arm was stopped early due to increased rates of heart failure (not included in this analysis). Patients underwent randomization at a ratio of 1.7:1:1 (higher for the diuretic arm to maximize power).

Duration: Mean follow-up period of 4.9 years

Statistical Analysis: It was determined that 40,000 randomized patients would provide ~83% for the primary analysis (alpha = 0.0178). For analysis of secondary outcomes, pre-specified components of combined outcomes and patient subgroups a p-value <0.05 was considered statistically significant. The ITT population was used for analyses.

Results: A total of 42,418 patients underwent randomization (9061 patients randomized to doxazosin group). No significant difference was seen for the primary outcome for either amlodipine or lisinopril compared to chlorthalidone.

There was no significant difference for any secondary outcomes between amlodipine and chlorthalidone, however the pre-specified individual components of the combined secondary outcomes were examined and significant differences were seen for heart failure and heart failure hospitalizations/deaths favoring chlorthalidone. Average SBP at 5 years was significantly lower in the chlorthalidone group compared to amlodipine (133.9 mmHg vs 134.7 mmHg; p=0.03).

Amlodipine (N=9048) Vs Chlorthalidone (N=15,255)

Composite of Fatal Coronary Heart Disease & Non-Fatal Myocardial Infarction:
798 (8.82%) vs 1362 (8.93%); RR 0.98 (95% CI 0.90-1.07); p=0.65
Non-fatal myocardial infarction was ~64-66% of composite outcome

Heart Failure:
706 (7.80%) vs 870 (5.70%); RR 1.38 (95% CI 1.25-1.52)
p<0.001; ARR 2.10%; NNT ~48

Heart Failure Hospitalizations/Heart Failure Death:
578 (6.39%) vs 724 (4.75%); RR 1.35 (95% CI 1.21-1.50)
p<0.001; ARR 1.64%; NNT ~61

There were significant differences for the secondary outcomes of stroke and combined cardiovascular disease between lisinopril and chlorthalidone favoring the thiazide group. For the pre-specified individual components of the combined secondary outcomes, significant differences were seen in heart failure and angina hospitalizations/treatment favoring chlorthalidone. Average SBP at 5 years was significantly lower in the chlorthalidone group (133.9 mmHg vs 135.9 mmHg; p<0.001).

Lisinopril (N=9054) Vs Chlorthalidone (15,255)

Composite of Fatal Coronary Heart Disease & Non-Fatal Myocardial Infarction:
796 (8.79%) vs 1362 (8.93%); RR 0.99 (95% CI 0.91-1.08); p=0.81
Non-fatal myocardial infarction was ~64-66% of composite outcome

Stroke:
457 (5.05%) vs 675 (4.42%); RR 1.15 (95% CI 1.02-1.30)
p=0.02; ARR 0.62%; NNT ~161

Combined Cardiovascular Disease:
2514 (27.8%) vs 3941 (25.8%); RR 1.10 (95% CI 1.05-1.16)
p<0.001; ARR 1.93%; NNT ~52

Heart Failure:
612 (6.76%) vs 870 (5.70%); RR 1.19 (95% CI 1.07-1.31)
p<0.001; ARR 1.06%; NNT ~95

Hospitalized/Treated Angina:
1019 (11.3%) vs 1567 (10.3%); RR 1.11 (95% CI 1.03-1.20)
p=0.01; ARR 0.98%; NNT ~102

Limitations:

- Use of open-label add-on antihypertensive therapy is a potential confounding factor (however, statistical differences still seen between treatment groups for multiple outcomes)

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I recommend the use of chlorthalidone over amlodipine and lisinopril as the preferred first-line therapy for high-risk hypertension patients. However, the selection of initial antihypertensive therapy must be individualized according to patient-specific characteristics.

Efficacy:

- There was no significant difference in the rates of the primary composite outcome of fatal coronary heart disease and non-fatal myocardial infarction between chlorthalidone, amlodipine and lisinopril
- Rates of heart failure and heart failure hospitalizations/death were significantly lower in the chlorthalidone group compared to the amlodipine group
- Rates of stroke, combined cardiovascular disease, heart failure and hospitalized/treated angina were significantly lower in the chlorthalidone group compared to the lisinopril group
- Average SBP at 5 years was significantly lower in the chlorthalidone group compared to the amlodipine and lisinopril groups

Safety:

- There were significantly higher rates of angioedema in the lisinopril group compared to the chlorthalidone group
- Chlorthalidone demonstrated significant biochemical changes (increased cholesterol and fasting glucose levels, decreased potassium levels) compared to lisinopril and amlodipine
    - However, these are known and predictable effects of this medication class that can be monitored
    - Additionally, these biochemical changes did not yield net increases in negative cardiovascular outcomes compared to the other treatment arms

Cost:

- The cost of using chlorthalidone over lisinopril or amlodipine must be balanced against the cost-savings of preventing cardiovascular outcomes (specifically, heart failure events)

Special Considerations/Populations:

- Cannot extrapolate the treatment effect of chlorthalidone to other diuretics such as hydrochlorothiazide (different classes of thiazide with different properties)

Grade of Recommendation: **A**

ALLHAT-LLT

ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). *JAMA*. 2002;288(23):2998-3007.

Objective: To determine the effect of moderate-high LDL reductions compared to usual care on mortality outcomes in patients with hyperlipidemia.

Primary Efficacy Measure: All-cause mortality

Participants: ALLHAT trial participants with primary hyperlipidemia

- Age ~66 years; male ~51%
- Baseline coronary heart disease ~14%; type 2 diabetes ~35%
- LDL (baseline CHD) ~129 mg/dL; LDL (no baseline CHD) ~148 mg/dL

Inclusion Criteria:

- Prior enrollment in ALLHAT
- Fasting LDL-C 120-189 mg/dL (if no CHD) or 100-129 mg/dL (if known CHD)
- Fasting triglycerides < 350 mg/dL

Exclusion Criteria:

- Current use of lipid-lowering therapy
- Use of high dose niacin
- Known statin intolerance
- ALT > 100 IU/L
- SCr > 2.0 mg/dL
- Secondary hyperlipidemia

Drugs: Pravastatin; usual care

Design: Randomized, open-label, active-comparison trial

Methods: Enrollment into the LLT trial took place approximately 88 days after randomization into ALLHAT. Eligible patients were randomized to receive pravastatin 40 mg once daily or usual care. Patients enrolled to the usual care group would be treated for LDL lowering at the investigator's discretion, however intensive lipid-lowering therapy was discouraged. All patients were encouraged to follow the NCEP Step I diet.

Duration: Mean follow-up period of 4.8 years

Statistical Analysis: It was determined that 10,000 randomized patients would provide 84% power (alpha=0.05). The ITT population was used for the primary analyses.

Results: A total of 10,355 patients underwent randomization. Baseline patient characteristics were similar between treatment groups with the exception of coronary heart disease history, which was significantly lower in the pravastatin group compared to usual care (13.4% vs 15.0%; p=0.02). The primary outcome analysis showed no significant difference between treatment groups regarding rates of all-cause mortality, even upon subgroup analysis in patients with baseline coronary heart disease. Additionally, rates of cardiovascular death were similar between treatment groups.

Pravastatin (N=5170) Vs Usual Care (N=5185)

All-Cause Mortality:
631 (12.2%) vs 641 (12.4%); RR 0.99 (95% CI 0.89-1.11); p=0.88

Cardiovascular Death:
295 (5.71%) vs 300 (5.79%); RR 0.99 (95% CI 0.84-1.16); p=0.91

Average Total Cholesterol - Baseline:
223.7 mg/dL vs 223.7 mg/dL

Average Total Cholesterol - Year 6:
177.6 mg/dL vs 196.5 mg/dL

Average LDL Values - Baseline:
145.6 mg/dL vs 145.5 mg/dL

Average LDL Values - Year 6:
104 mg/dL vs 121.2 mg/dL

Limitations:

- Open-label trial design
- Smaller difference than expected in lipid values between treatment groups
- Patient population - low proportion with baseline coronary heart disease
- Details of the usual care therapy regimen were not mentioned

Level of Evidence: Level I - with major limitations

Recommendation: For these reasons, I do not recommend the use of pravastatin 40 mg for mortality reduction in this patient population. However, it is important to note that the vast majority of patients did not have coronary heart disease at baseline and that the difference in lipid levels between treatment groups was notably smaller than seen in other similar trials. Use of a higher intensity statin to achieve clinically beneficial reductions in cholesterol may be preferred.

Efficacy:

- There was no significant difference between treatment groups in the rates of all-cause mortality despite greater reductions in LDL favoring the pravastatin group
- Rates of cardiovascular death were similar between treatment groups

Safety:

- ALT elevations greater than three times the upper limit of normal (150 IU/L) occurred in 0.4% of the pravastatin group (rates in usual care group not reported)

Cost:

- The cost of pravastatin therapy must be considered in addition to the cost of laboratory testing necessary to monitor statin therapy

Special Considerations/Populations:

- All patients were included in the ALLHAT trial - which required primary hypertension plus an additional risk factor for coronary heart disease
- The vast majority of patients did not have established coronary heart disease at baseline
- The differences in cholesterol reduction between treatment groups were smaller than expected, which the investigators theorize is a likely reason for the lack of demonstrated mortality benefit

Grade of Recommendation: **A**

ALTITUDE

Parving HH, Brenner BM, McMurray JJ, et al. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. *N Engl J Med*. 2012;367(23):2204-2213.

Objective: To determine the effect of aliskiren (in addition to baseline ACEi or ARB) on cardiovascular and renal outcomes in patients with type 2 diabetes and chronic kidney disease, cardiovascular disease, or both.

Primary Efficacy Measure: Composite of cardiovascular death, cardiac arrest with resuscitation, non-fatal myocardial infarction, non-fatal stroke, heart failure hospitalization, end-stage renal disease, death due to kidney failure, need for renal-replacement therapy, or doubling of serum creatinine from baseline (and exceeding normal range) for at least one month

Participants: Type 2 diabetics with renal and/or cardiovascular disease receiving ACEi/ARB therapy

- Age ~65 years; male ~69%
- BP ~137/74 mmHg
- HgA1c ~7.8%
- eGFR ~57 mL/min; UACR ~207 mg/g
- Known cardiovascular disease ~42%; chronic kidney disease ~98%
- Baseline ACEi ~44%; ARB ~56%; statin ~65%; antiplatelet ~63%

Inclusion Criteria:

- Age ≥ 35 years with type 2 diabetes
- Receiving ACEi or ARB
- Evidence of macroalbuminuria (UACR ≥ 200 mg/g and eGFR ≥ 30 mL/min), microalbuminuria (UACR ≥ 20 and < 200 mg/g and eGFR ≥ 30 to < 60 mL/min) or cardiovascular disease (history of myocardial infarction, stroke, heart failure or coronary artery disease; plus eGFR ≥ 30 to < 60 mL/min)

Exclusion Criteria:

- Serum potassium > 5.0 mmol/L
- Type 1 diabetes
- Unstable serum creatinine
- Renal artery stenosis

Drug: Aliskiren

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients were randomized to receive aliskiren 150 mg or matching placebo (in addition to baseline ACEi or ARB therapy) once daily. After 4 weeks, the dose of aliskiren was increased to 300 mg once daily.

Duration: Median follow-up period of ~33 months

Statistical Analysis: It was determined that 8600 randomized patients and 1620 primary events would achieve 90% power (alpha = 0.046). The ITT population was used for all analyses.

Results: A total of 8608 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. The trial ended early after the second interim efficacy analysis due to lack of demonstrated benefit with aliskiren (for cardiovascular or renal outcomes) and concerns for harm. The most common safety concern was hyperkalemia, which occurred at significantly higher rates in the aliskiren group.

Aliskiren (N=4274) Vs Placebo (N=4287)

Primary Composite Outcome:
783 (18.3%) vs 732 (17.1%); HR 1.08 (95% CI 0.98-1.20); p=0.12

Cardiovascular Death:
246 (5.76%) vs 215 (5.02%); HR 1.16 (95% CI 0.96-1.39); p=0.12

Cardiac Arrest with Resuscitation:
19 (0.44%) vs 8 (0.19%); HR 2.40 (95% CI 1.05-5.48)
p=0.04; ARI 0.26%; NNH ~387

Total Myocardial Infarction:
147 (3.44%) vs 142 (3.31%); HR 1.04 (95% CI 0.83-1.31); p=0.72

Total Stroke:
147 (3.44%) vs 122 (2.85%); HR 1.22 (95% CI 0.96-1.55); p=0.11

Heart Failure Hospitalization:
205 (4.80%) vs 219 (5.11%); HR 0.95 (95% CI 0.78-1.14); p=0.56

ESRD, Death due to Renal Causes, Loss of Kidney Function:
121 (2.83%) vs 113 (2.64%); HR 1.08 (95% CI 0.84-1.40); p=0.56

Doubling or Serum Creatinine:
210 (4.91%) vs 217 (5.06%); HR 0.97 (95% CI 0.80-1.17); p=0.75

All-Cause Mortality:
376 (8.80%) vs 358 (8.35%); HR 1.06 (95% CI 0.92-1.23); p=0.42

Safety

Aliskiren (N=4272) Vs Placebo (N=4285)

Hyperkalemia:
1670 (39.1%) vs 1244 (29.0%); p<0.001
ARI 10.1%; NNH ~9

Hypotension:
519 (12.1%) vs 357 (8.33%); p<0.001
ARI 3.82%; NNH ~26

Limitations:

- Power set but not met – failed to achieve the specified number of primary events
  - Clinical significance minimal as trial was stopped early due to lack of demonstrated benefit and clearly demonstrated safety concerns
- Patient population must be considered – the vast majority had chronic kidney disease
- Trial results must be considered in addition to baseline ACEi or ARB therapy

Level of Evidence: Level II – with major limitations

Recommendation: For these reasons, I do not recommend the use of aliskiren (in addition to baseline ACEi or ARB therapy) to further reduce rates of cardiovascular or renal outcomes in patients with type 2 diabetes. Instead, I recommend focusing on optimizing glycemic and blood pressure control.

Efficacy:

- There was no significant difference in the rates of the primary composite outcome or the individual components (with the exception of cardiac arrest; more common with aliskiren)
- There was no evidence of treatment benefit with aliskiren for cardiorenal outcomes

Safety:

- Hyperkalemia and hypotension occurred at significantly higher rates in the aliskiren group

Cost:

- The cost of using aliskiren must be considered in addition to the cost of monitoring for and managing episodes of hyperkalemia and hypotension

Special Considerations/Populations:

- Aliskiren is a direct renin inhibitor
- Patients were receiving baseline ACE inhibitor or ARB
- All patients had type 2 diabetes plus cardiovascular disease and/or chronic kidney disease

Grade of Recommendation: **B**

AMPLIFY

Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med*. 2013;369(9):799-808.

Objective: To determine if apixaban is non-inferior to conventional therapy (enoxaparin plus warfarin) for the treatment of venous thromboembolism.

Primary Efficacy Measure: Composite of recurrent venous thromboembolism (includes pulmonary embolism and deep vein thrombosis) or death secondary to venous thromboembolism

Primary Safety Measure: Major bleeding (designated 'major' if bleed yielded a decrease in Hgb ≥ 2 g/dL, required a transfusion of 2 units of blood, occurred at a critical site or contributed to death)

Participants: Patients with recent deep vein thrombosis or pulmonary embolism

- Age ~57 years; male ~59%
- Qualifying event DVT ~65%; PE ~25%

Inclusion Criteria:

- Age ≥ 18 years
- Confirmed proximal deep vein thrombosis or pulmonary embolism

Exclusion Criteria:

- Active bleeding or high risk for bleeding
- Contraindications to treatment with enoxaparin/warfarin
- Pre-existing indication for long-term anticoagulation, dual antiplatelet therapy or aspirin at a dose >165 mg/day
- Treatment with potent inhibitors of CYP3A4
- Hemoglobin < 9 mg/dL; platelet count < 100,000; SCr > 2.5 mg/dL; CrCl < 25 mL/min

Drugs: Apixaban; enoxaparin plus warfarin

Design: Randomized, double-blind, active-comparison, non-inferiority trial

Methods: Eligible patients were randomized into either the apixaban group or the conventional therapy group. Apixaban therapy consisted of 10 mg twice daily for 7 days, followed by 5 mg twice daily for 6 months. Conventional therapy consisted of enoxaparin injections at 1 mg/kg every 12 hours for a minimum of 5 days (INR > 2.0 required prior to starting warfarin), followed by warfarin for 6 months (target INR 2.0-3.0). Matching placebo injections and tablets were utilized to maintain blinding.

Duration: 6 months

Statistical Analysis: It was determined that 5400 randomized patients would achieve 90% power for non-inferiority (alpha = 0.025). For apixaban to achieve non-inferiority, the upper limit of the 95% CI must be less than 1.80 (the NI margin) and the absolute risk difference between groups must be less than 3.5%. If non-inferiority was achieved, then hierarchical testing for superiority would be performed for the following pre-specified outcomes: major bleeding, the primary efficacy outcome, and lastly the composite of major and non-major bleeding. The ITT population was used for all efficacy analyses; however, patients must have documented outcome status at 6 months to be included. The safety analysis population included all patients during the treatment period (mITT).

Results: A total of 5400 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. INR was in the target therapeutic range in the conventional therapy group for 61% of the time. Rates of adverse drug reactions and lab abnormalities were similar between treatment groups. Apixaban demonstrated non-inferiority (but not superiority) to conventional therapy regarding the primary composite outcome. Superiority of apixaban to conventional therapy was demonstrated regarding rates of major bleeding (significantly lower in the apixaban group).

Apixaban (N=2691) Vs Warfarin (N=2704)

Composite of Recurrent VTE & Death Secondary to VTE:
59/2609 (2.26%) vs 71/2635 (2.63%); RR 0.84 (95% CI 0.60-1.18); p<0.001
p-value is for non-inferiority (superiority was not demonstrated)

Major Bleeding:
15/2676 (0.56%) vs 49/2689 (1.82%); RR 0.31 (95% CI 0.17-0.55)
p<0.001; ARR 1.26%; NNT ~80

Limitations:

- Trial parameters must be considered - only evaluated efficacy and safety up to 6 months after qualifying event
- Lack of info on the treatment effect of apixaban in patients with cancer, low body weight or CrCl < 50 mL/min

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I recommend the use of apixaban over conventional therapy (enoxaparin plus warfarin) for the treatment of venous thromboembolism. It is reasonable to use warfarin in certain patients that are not eligible for apixaban therapy, however the increased bleed risk must be considered.

Efficacy:

- Apixaban demonstrated non-inferiority (but not superiority) compared to conventional therapy involving enoxaparin and warfarin regarding the primary composite outcome of venous thromboembolism events

Safety:

- Apixaban demonstrated significantly lower rates of major bleeding compared to conventional therapy, achieving superiority

Cost:

- The cost of using the apixaban must be balanced against the cost-savings of avoiding major bleeding events as well as the need for INR monitoring

Special Considerations/Populations:

- Additional information is required regarding the use of apixaban in patients with cancer, low body weight and/or CrCl < 50 mL/min and thus the results of this trial should not be applied to these populations
- Apixaban offers simplified dosing without the monitoring requirements associated with warfarin therapy
- Trial duration of 6 months

Grade of Recommendation: **A**

ANDROMEDA

Køber L, Torp-Pedersen C, McMurray JJ, et al. Increased mortality after dronedarone therapy for severe heart failure. *N Engl J Med*. 2008;358(25):2678-2687.

Objective: To determine the effect of dronedarone on morbidity and mortality outcomes in symptomatic heart failure patients.

Primary Efficacy Measure: Composite of all-cause mortality or heart failure hospitalization

Participants: Patients with symptomatic heart failure (reduced ejection fraction)

- Age ~71 years; male ~75%
- Wall-motion index ~0.9
- NYHA class II ~40%; class III ~56%
- BP ~121/73 mmHg; HR ~79 bpm

Inclusion Criteria:

- Age ≥ 18 years
- Hospitalized with new or worsening heart failure
- One or more shortness of breath episodes on minimal exertion/at rest (NYHA class III-IV)
- Wall-motion index of ≤ 1.2 (approximates a LVEF of ≤ 35%)

Exclusion Criteria:

- Acute myocardial infarction within 7 days before screening
- Heart rate of less than 50 beats per minute
- PR interval longer than 0.28 seconds
- Sinoatrial block
- Second or third-degree AV block not treated with a pacemaker
- History of Torsades de Pointes
- Corrected QT interval > 500 msec
- Serum potassium < 3.5 mmol/L
- Use of class I or III antiarrhythmic drugs or potent CYP3A4 inhibitors
- Clinically significant obstructive heart disease

Drug: Dronedarone

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients were randomized to receive dronedarone 400 mg twice daily or matching placebo. All patients underwent randomization during their hospital stay, no later than the seventh day.

Duration: Median follow-up period of 2 months

Statistical Analysis: It was determined that 1000 randomized patients would provide 90% power (alpha = 0.05). However, due to the trial being ended early this criterion was not met.

Results: A total of 627 patients underwent randomization and were included in the statistical analyses. Baseline patient characteristics were similar between treatment groups. The trial ended early after ~7 months due to safety concerns demonstrating increased mortality in the dronedarone group. The majority of deaths were cardiovascular in nature for both treatment groups. In the dronedarone group, worsening heart failure was the most common cause. Adverse effects were similar between treatment groups except for serum creatinine increase, which occurred significantly more often in the dronedarone group (8 patients vs 0 patients; p=0.01).

Dronedarone (N=310) Vs Placebo (N=317)

All-Cause Mortality or Heart Failure Hospitalization:
53 (17.1%) vs 40 (12.6%); HR 1.38 (95% CI 0.92-2.09); p=0.12

All-Cause Mortality:
25 (8.06%) vs 12 (3.79%); HR 2.13 (95% CI 1.07-4.25)
p=0.03; ARI 4.28%; NNH ~23

Limitations:

- Power set but not met – due to trial being ended early for safety concerns
    - Clinical significance minimal

Level of Evidence: Level II – with major limitations

Recommendation: For these reasons, I do not recommend the use of dronedarone in symptomatic heart failure patients with reduced ejection fraction.

Efficacy:

- Based on available data after trial termination, there was no significant difference in the rates of the primary composite outcome
    - However, the rates of all-cause mortality were significantly higher in the dronedarone group
    - The cause of death was almost entirely cardiovascular in nature with worsening heart failure and arrhythmia being the most common causes

Safety:

- The trial was terminated entire due to the increased mortality rates in the dronedarone group
- Overall, adverse events were similar between treatment groups with the exception of serum creatinine increase (occurred significantly more often in the dronedarone group)

Cost:

- The cost of using dronedarone must be considered in addition to the costs associated with increased mortality rates

Special Considerations/Populations:

- Dronedarone is a class III antiarrhythmic (similar to amiodarone)
- All patients had symptomatic heart failure with reduced LVEF and were enrolled into the study during a hospitalization for new/worsening heart failure

Grade of Recommendation: **B**

ANTLER

Lewis G, Marston L, Duffy L, et al. Maintenance or Discontinuation of Antidepressants in Primary Care. *N Engl J Med*. 2021;385(14):1257-1267.

Objective: To determine the effects of continuing or discontinuing treatment in patients taking antidepressants for more than 9 months (and felt well enough to consider stopping the medication).

Primary Efficacy Measure: Time to first relapse of depression

- Relapse of depression defined as an affirmative answer to one of the following questions:
  - Have you had a spell of feeling sad, miserable, or depressed?
  - Have you been unable to enjoy or take interest in things as much as you usually do?
- Duration must have lasted 2 or more weeks, plus one or more of the following symptoms:
  - Depressive thoughts, fatigue, loss of concentration or sleep disturbance

Participants: Patients with history of depression on antidepressant therapy for 9 months or greater

- Age ~54 years; male ~27%
- Citalopram ~47%; fluoxetine ~33%; sertraline ~16%; mirtazapine ~3%
- Age of depression onset ~32 years; ≥ 3 previous episodes of depression ~93%
- Continuous antidepressant usage for ≥ 3 years ~71%

Inclusion Criteria:

- Age 18-74 years
- Receiving citalopram 20 mg, sertraline 100 mg, fluoxetine 20 mg or mirtazapine 30 mg daily for a minimum of 9 months
- At least 2 prior episodes of depression (or have been taking antidepressants for >2 years)
- Recovery from most recent episode of depression
- Felt well enough to consider stopping antidepressant therapy

Exclusion Criteria:

- Current depression
- Patients receiving escitalopram (not commonly prescribed in the United Kingdom)
- Use of other antidepressants or dosages not listed above in the inclusion criteria

Drugs: Citalopram; sertraline; fluoxetine; mirtazapine

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients were randomized to the maintenance or discontinuation groups. For the first month of the trial, patients randomized to the discontinuation treatment group received half-doses of their baseline medication. During the second month those same patients received half-doses every other day. And starting on month three, all patients in the discontinuation group received placebo only. Patients in the maintenance treatment group continued their baseline antidepressant at their usual dose.

Duration: 52 weeks

Statistical Analysis: It was determined that 479 randomized patients would provide 90% power (alpha=0.05).

Results: A total of 478 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. Rates of adverse events were similar between treatment groups. More patients in the discontinuation group stopped using the trial medication compared to the maintenance therapy group (48% vs 30%, respectively). Of these patients that stopped their trial medication early, 39% from the discontinuation group restarted antidepressant therapy through their primary provider compared to 20% from the maintenance group.

At 12 weeks, secondary outcomes (patient reported symptoms) generally favored the maintenance group over the discontinuation group. However, at week 52 of the trial there was no significant difference in any of the secondary outcomes between treatment groups. Between week 12 and week 52 the data generally trended toward a non-significant difference for all secondary outcomes.

Maintenance (N=238) Vs Discontinuation (N=240)

First Relapse of Depression:
92 (38.7%) vs 135 (56.3%); HR 2.06 (95% CI 1.56-2.70)
p<0.001; ARR 17.6%; NNT ~6

Limitations:

- Power set but not met – clinical significance minimal (significant difference demonstrated)
- Trial conducted entirely in the United Kingdom – clinical significance likely low considering the medications used and the ubiquitous nature of mental health issues
- Patients included in were primarily taking SSRIs and felt they were ready to stop the medication – cannot extrapolate trial results to other antidepressant classes or patient populations

Level of Evidence: Level II – with major limitations

Recommendation: For these reasons, I recommend continuing maintenance antidepressant therapy over discontinuation to prevent episodes of relapse in this patient population. While patient reported symptoms were not significantly different between groups at the end of the trial, the initial negative impact of discontinuing therapy on quality of life and the overall risks associated with depression relapse must be carefully considered.

Efficacy:

- Patients in the maintenance therapy group experienced significantly lower rates of depression relapse compared to the discontinuation therapy group
- Early stoppage of trial medication occurred at significantly lower rates in the maintenance therapy group
- While these patients felt well enough to stop pharmacotherapy, significantly more in the discontinuation group were restarted on antidepressants through their primary care provider during the trial
- Secondary outcomes (patient reported symptoms) initially favored maintenance therapy (at week 12) but there was no significant difference between treatment groups at week 52

Safety:

- Rates of adverse events were similar between treatment groups

Cost:

- The cost of continuing antidepressant therapy must be balanced against the cost-savings from preventing episodes of relapse

Special Considerations/Populations:

- Antidepressants included in this trial were primarily SSRIs
- Patients included in this trial (primarily female) felt ready to stop antidepressant therapy
    - Majority had been receiving therapy for 3 years or more

Grade of Recommendation: **B**

ARISTOTLE

Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365(11):981-992.

Objective: To determine if apixaban is non-inferior to warfarin for prevention of thromboembolic events in patients with atrial fibrillation at increased risk for stroke.

Primary Efficacy Measure: Composite of stroke (ischemic or hemorrhagic) or systemic embolism

Primary Safety Measure: Major bleeding (defined as overt bleed resulting in a decrease in hemoglobin of 2 g/dL or more, transfusion of 2 units or more of packed red cells, bleed location at a critical site or bleed resulting in death)

Participants: Atrial fibrillation patients at increased risk for stroke

- Age ~70 years; male ~65%
- Persistent/permanent AF ~84%; paroxysmal AF ~15%
- $CHADS_2$ score ~2.1
- Baseline ACEi/ARB ~70%; beta-blocker ~63%; CCB ~30%; amiodarone ~11%

Inclusion Criteria:

- Atrial fibrillation or flutter within prior 12 months to enrollment plus one or more of the following: age ≥ 75 years, previous stroke/TIA/systemic embolism, symptomatic heart failure within 3 previous months, LVEF ≤ 40%; diabetes, hypertension requiring pharmacotherapy

Exclusion Criteria:

- Reversible atrial fibrillation
- Moderate-severe mitral stenosis
- Other condition requiring anticoagulation
- Stroke within 7 previous days
- Use of aspirin > 165 mg daily or aspirin plus clopidogrel
- SCr > 2.5 mg/dL or CrCl < 25 mL/min

Drugs: Apixaban; warfarin

Design: Randomized, double-blind, active-comparison, non-inferiority trial

Methods: Eligible patients were randomized to receive either apixaban 5 mg twice daily or dose-adjusted warfarin (target INR 2.0-3.0) plus matching placebo. Low dose apixaban (2.5 mg twice daily) was used in patients meeting 2 or more of the following criteria: age ≥ 80 years, weight ≤ 60 kg or SCr ≥ 1.5 mg/dL.

Duration: Median follow-up period of 1.8 years

Statistical Analysis: It was determined that 448 patients must experience a primary composite outcome in order to achieve 90% power. A non-inferiority margin of 1.38 was used. If non-inferiority was demonstrated, subsequent testing for superiority would be performed in the following order: primary composite outcome, major bleeding and then all-cause mortality. The ITT population was used for the efficacy analyses. The mITT population (all patients that received at least one dose of a study drug) was used for the safety analyses.

Results: A total of 18,201 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. INR values were in range ~62% of the time on average in the warfarin group. Apixaban demonstrated non-inferiority and subsequent superiority to warfarin for the primary efficacy and safety measures. While all-cause mortality was significantly lower in the apixaban group it is important to note that the rates cardiovascular death and non-cardiovascular death were not significantly different between treatment groups.

Apixaban (N=9120) Vs Warfarin (N=9081)

Composite of Stroke & Systemic Embolism:
212 (2.32%) vs 265 (2.92%); HR 0.79 (95% CI 0.66-0.95)
p=0.01; ARR 0.59%; NNT ~169

Total Stroke:
199 (2.18%) vs 250 (2.75%); HR 0.79 (95% CI 0.65-0.95)
p=0.01; ARR 0.57%; NNT ~176

Ischemic Stroke:
162 (1.77%) vs 175 (1.93%); HR 0.92 (95% CI 0.74-1.13); p=0.42

Hemorrhagic Stroke:
40 (0.44%) vs 78 (0.86%); HR 0.51 (95% CI 0.35-0.75)
p<0.001; ARR 0.42%; NNT ~238

Systemic Embolism:
15 (0.16%) vs 17 (0.18%); HR 0.87 (95% CI 0.44-1.75); p=0.70

All-Cause Mortality:
603 (6.61%) vs 699 (7.70%); HR 0.89 (95% CI 0.80-0.99)
p=0.047; ARR 1.09%; NNT ~93
Individual rates of cardiovascular and non-cardiovascular death were not significantly different between treatment groups

Major Bleeding:
327/9088 (3.60%) vs 462/9052 (5.10%); HR 0.69 (95% CI 0.60-0.80)
p<0.001; ARR 1.50%; NNT ~67

Limitations:
- Patient population must be considered (high-risk atrial fibrillation patients)
- Cannot extrapolate trial results to other oral anticoagulants

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I recommend the use of apixaban over warfarin for prevention of thromboembolic events in high-risk atrial fibrillation patients.

Efficacy:
- Apixaban demonstrated non-inferiority and then superiority to warfarin regarding rates of the primary composite outcome
    - Treatment benefit driven primarily by reduced stroke rates (specifically, hemorrhagic stroke)

Safety:
- Rates of major bleeding were significantly lower with apixaban compared to warfarin

Cost:
- The cost of using apixaban must be balanced against the cost-savings from preventing stroke and major bleeding events
- The cost-savings from avoiding the need for INR monitoring should also be considered

Special Considerations/Populations:
- Apixaban (and other DOACs) cannot be used in patients with mechanical valves, mitral valve stenosis or severe renal impairment

Grade of Recommendation: **A**

ARRIVE

Gaziano JM, Brotons C, Coppolecchia R, et al. Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomized, double-blind, placebo-controlled trial. Lancet. 2018;392(10152):1036-1046.

Objective: To determine the efficacy and safety of aspirin for primary prevention of cardiovascular events in patients at a moderately elevated risk.

Primary Efficacy Measure: Composite of myocardial infarction, stroke, cardiovascular death, unstable angina or transient ischemic attack (time to first event)

Primary Safety Measure: Serious bleeding events

Participants: Patients at moderately elevated risk for a primary cardiovascular event

- Age ~64 years; male ~70%
- Elevated total cholesterol ~58%; elevated LDL ~45%
- SBP ~145 mmHg; receiving antihypertensive medication ~65%
- Framingham 10-year coronary heart disease risk score ~14%
- ACC/AHA 10-year ASCVD risk score ~10%

Inclusion Criteria:

- Males age 55 years and older with 2-4 risk factors
- Females age 60 years and older with 3 or more risk factors
- Risk factors included: total cholesterol > 200 mg/dL or LDL > 130 mg/dL (males), total cholesterol > 240 mg/dL or LDL > 160 mg/dL (females), current cigarette smoker (or within the previous 12 months), HDL < 40 mg/dL, SBP > 140 mmHg, receiving antihypertensive therapy, family history of cardiovascular heart disease

Exclusion Criteria:

- History of stroke, myocardial infarction, coronary artery angioplasty or stenting, CABG, arrhythmia, congestive heart failure or vascular intervention
- Diabetes
- Requirement for antiplatelet or anticoagulant therapy
- High risk for gastrointestinal bleeding
- Frequent use of NSAIDs

Drug: Aspirin (enteric-coated)

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients were randomized to receive either enteric-coated aspirin 100 mg once daily or placebo.

Duration: Median follow-up period of 60 months

Statistical Analysis: It was initially determined that 1488 primary outcome events would provide 91% power (alpha=0.05). However, due to lower than expected event rates the trial actually achieved approximately 80% power. The primary composite outcome was analyzed using both ITT and per-protocol populations. The per-protocol population was defined as all patients with a medication adherence rate of 60% or more during the trial. The safety analysis was performed using the ITT population.

Results: A total of 12,546 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. For both the ITT and per-protocol analysis populations there was no significant difference in the rates of the primary composite outcome between treatment groups. Individual components of the composite outcome occurred at similar rates between treatment groups, with the exception of total myocardial infarction in the per-protocol analysis population. This outcome occurred at a significantly lower rate in the aspirin treatment group and was driven almost entirely by non-fatal events. What this indicates is some evidence of morbidity benefit (but not mortality benefit) in patients who were adherent to their study medication (for at least 60% of the trial duration). Rates of total gastrointestinal bleeding was significantly higher in the aspirin treatment group, driven largely by mild and moderate severity events.

Aspirin (N=6270) Vs Placebo (N=6276)
** ITT population **

Primary Composite Outcome:
269 (4.29%) vs 281 (4.48%); HR 0.96 (95% CI 0.81-1.13); p=0.6038

Total Gastrointestinal Bleed:
61 (0.97%) vs 29 (0.46%); HR 2.11 (95% CI 1.36-3.28)
p=0.007; ARI 0.51%; NNH ~195

Moderate Gastrointestinal Bleed:
15 (0.24%) vs 5 (0.08%)

Mild Gastrointestinal Bleed:
42 (0.67%) vs 22 (0.35%)

Aspirin (N=3790) Vs Placebo (N=3912)
** Per-protocol population **

Primary Composite Outcome:
129 (3.40%) vs 164 (4.19%); HR 0.81 (95% CI 0.64-1.02); p=0.0756

Total Myocardial Infarction:
37 (0.98%) vs 72 (1.84%); HR 0.53 (95% CI 0.36-0.79)
p=0.0014; ARR 0.86%; NNT ~116

Non-Fatal Myocardial Infarction:
32 (0.84%) vs 60 (1.53%); HR 0.55 (95% CI 0.36-0.84)
p=0.0056; ARR 0.69%; NNT ~146

Limitations:

- Power set but not met due to much lower than anticipated event rates
- Patient population – this trial excluded all patients with prior vascular event(s)
- The patients included in the trial had a moderately increased risk a primary cardiovascular event
- Patients with diabetes were excluded from this trial

Level of Evidence: Level II – with major limitations

Recommendation: For these reasons, I do not recommend the routine use of aspirin for primary prevention of cardiovascular events in patients (without diabetes) at a moderately elevated risk. However, patient-specific factors must be carefully considered when assessing the benefit-risk ratio of therapy.

Efficacy:

- The trial failed to achieve power and did not demonstrate a significant difference between treatment groups for the primary efficacy outcome (for the ITT and per-protocol population analyses)
    - This raises concerns for a false negative, since the trial may have lacked sufficient power to detect a difference that truly exists
- Rates of each individual component of the composite outcome occurred at similar rates between groups, with the exception of total myocardial infarction in the per-protocol analysis population
    - Total myocardial infarction occurred at significantly lower rates in the aspirin treatment group, driven primarily by non-fatal events

Safety:

- Rates of gastrointestinal bleeding occurred at significantly higher rates in the aspirin treatment group, driven primarily by mild and moderate severity events (ITT population analysis)

Cost:

- The cost of using aspirin 100 mg daily must be balanced against the cost-savings achieved from reducing rates of non-fatal myocardial infarction
    - However, the cost of treating gastrointestinal bleeds must be considered

Special Considerations/Populations:

- The dose of enteric-coated aspirin used in this trial was 100 mg daily
- Patients with diabetes were excluded from this trial
- While the NNT for myocardial infarction is less than the NNH for gastrointestinal bleeding, it is important to note that the demonstrated treatment benefit with aspirin was only demonstrated in the per-protocol population (largely adherent to study medication)
    - Conversely, the demonstrated treatment risk was demonstrated in the ITT population (regardless of adherence to medication)
- Power was set but not met and there was no significant difference demonstrated between treatment groups for the primary outcome, which raises concerns for a false negative
    - However, based on the available data from this trial the use of aspirin for primary prevention shows no clear treatment benefit and has safety concerns regarding gastrointestinal bleeding

Grade of Recommendation: **B**

ASCEND

ASCEND Study Collaborative Group, Bowman L, Mafham M, et al. Effects of Aspirin for Primary Prevention in Persons with Diabetes. *N Engl J Med*. 2018;379(16):1529-1539.

Objective: To determine the effect of aspirin 100 mg daily on cardiovascular outcomes in diabetic patients without established cardiovascular disease.

Primary Efficacy Measure: Composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke or TIA

Primary Safety Measure: Any major bleeding event (defined as intracranial bleed, sight-threatening bleed in the eye, GI bleed, bleed resulting in hospitalization/transfusion or death)

Participants: Diabetic patients without established cardiovascular disease

- Age ~63 years; ~62% male
- Type 2 diabetes ~94%; duration of diabetes ~7 years
- HgA1c ~7.2%

Inclusion Criteria:

- Diabetes (any type) patients age ≥ 40 years
- No known cardiovascular disease

Exclusion Criteria:

- Clear indication for aspirin therapy
- Conditions that might limit adherence for trial period of 5 years

Drug: Aspirin

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients underwent an 8-10 week placebo run-in period. Those that successfully completed the run-in period were randomized to receive aspirin 100 mg daily or matching placebo. Patients were also randomized to receive either n-3 fatty acid 1000 mg daily or matching placebo for a separate trial.

Duration: Mean follow-up of 7.4 years

Statistical Analysis: It was determined that 15,000 randomized patients would need to be followed for at least 7.5 years to achieve 90% power (alpha = 0.05). The ITT population was used for the primary analyses.

Results: A total of 15,480 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. While the primary composite outcome was significantly lower in the aspirin treatment group, none of the individual components were significantly different from placebo. Additionally, if the TIA component is excluded the composite outcome no longer demonstrates a significant difference between treatment groups.

Aspirin (N=7740) Vs Placebo (N=7740)

Primary Composite Outcome:
658 (8.50%) vs 743 (9.60%); RR 0.88 (95% CI 0.79-0.97)
p=0.01; ARR 1.10%; NNT ~92

Primary Composite - Excluding TIA:
542 (7.00%) vs 587 (7.58%); RR 0.92 (95% CI 0.82-1.03)

Cardiovascular Death:
197 (2.55%) vs 217 (2.80%); RR 0.91 (95% CI 0.75-1.10)

Non-Fatal Myocardial Infarction:
191 (2.47%) vs 195 (2.52%); RR 0.98 (95% CI 0.80-1.19)

Non-Fatal Stroke:
202 (2.61%) vs 229 (2.96%); RR 0.88 (95% CI 0.73-1.06)

TIA:
168 (2.17%) vs 197 (2.55%); RR 0.85 (95% CI 0.69-1.04)

Any Major Bleeding:
314 (4.06%) vs 245 (3.17%); RR 1.29 (95% CI 1.09-1.52)
p=0.003; ARI 0.89%; NNH ~112
Most common event was serious gastrointestinal bleeding

Limitations:

- Power set but not met - mean follow-up period less than 7.5 years (clinical significance minimal as significant differences were still detected for efficacy and safety measures)
- Patients were also randomized to receive n-3 fatty acid as part of a separate clinical trial (potential confounding factor - clinical significance unknown)

Level of Evidence: Level II - with major limitations

Recommendation: For these reasons, I do not recommend the use of aspirin 100 mg daily for prevention of cardiovascular events in diabetic patients without established cardiovascular disease. The use of aspirin for primary prevention may be reasonable in certain high-risk patients but must be carefully justified due to the increased bleeding risk.

Efficacy:

- The aspirin group demonstrated significantly lower rates of the primary composite outcome compared to placebo
- However, none of the individual components were significantly different between groups
- Additionally, if TIA was excluded from the primary composite there is no significant difference between treatment groups (raises further concerns about overall clinical benefit)

Safety:

- Major bleeding rates were significantly higher in the aspirin group, driven primarily by increased rates of serious gastrointestinal bleeds

Cost:

- The cost of using aspirin 100 mg must be balanced against any cost-savings from avoiding a primary event outcome
- However, the cost of treating a major bleeding event must also be considered

Special Considerations/Populations:

- Patient population was almost entirely patients with type 2 diabetes (not type 1)
- This trial assessed the effect of aspirin for primary prevention in patients with diabetes

Grade of Recommendation: **B**

ASPREE

McNeil JJ, Woods RL, Nelson MR, et al. Effect of Aspirin on Disability-free Survival in the Healthy Elderly. *N Engl J Med*. 2018;379(16):1499-1508.

Objective: To determine the efficacy and safety of aspirin on clinical outcomes in elderly patients without prior cardiovascular/cerebrovascular event or established ASCVD.

Primary Efficacy Measure: Composite of death, dementia or persistent physical disability (time to first event)

Primary Safety Measure: Major hemorrhagic event (clinically significant bleeding and hemorrhagic stroke)

Participants: Elderly patients without history of cardiovascular/cerebrovascular event or established ASCVD

- Age ~74 years; male ~44%
- Hypertension ~74%; dyslipidemia ~65%

Inclusion Criteria:

- Age 70 years and older (≥65 years for black and Hispanic patients in the United States)
- Expected remaining lifespan of 5 years or more

Exclusion Criteria:

- History of cardiovascular/cerebrovascular event or established ASCVD
- Use of aspirin for secondary prevention
- Atrial fibrillation
- Dementia
- Physical disability
- High risk for bleeding
- Uncontrolled hypertension (SBP ≥180 mmHg and/or DBP ≥105 mmHg)

Drug: Aspirin

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients underwent a four week placebo run-in period to assess adherence. Those that successfully completed the run-in period were randomized to receive 100 mg of enteric-coated aspirin or matching placebo once daily.

Duration: Median follow-up period of 4.7 years

Statistical Analysis: It was determined that 19,000 randomized patients would be sufficient to identify a 10% reduction of the primary composite outcome in the aspirin group. Alpha was set at 0.05 for safety measures.

Results: A total of 19,114 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. Rates of the primary composite outcome were similar between groups. However, rates of major hemorrhagic events occurred at significantly higher rates in the aspirin group. This was driven primarily by increased rates of clinically significant bleeding (rates of hemorrhagic stroke were comparable).

Aspirin (N=9525) Vs Placebo (N=9589)

Primary Composite Outcome:
921 (9.67%) vs 914 (9.53%); HR 1.01 (95% CI 0.92-1.11); p=0.79

All-Cause Mortality:
558 (5.86%) vs 494 (5.15%); HR 1.14 (95% CI 1.01-1.29)
ARI 0.71%; NNH ~141

Dementia:
283 (2.97%) vs 292 (3.05%); HR 0.98 (95% CI 0.83-1.15)

Persistent Physical Disability:
188 (1.97%) vs 224 (2.34%); HR 0.85 (95% CI 0.70-1.03)

Major Hemorrhagic Event:
361 (3.79%) vs 265 (2.76%); HR 1.38 (95% CI 1.18-1.62)
p<0.001; ARI 1.03%; NNH ~97

Limitations:

- Power not formally mentioned (although the targeted number of patients underwent randomization)
- External validity – large Australian patient population (clinical significance likely low)

Level of Evidence: Level II – with major limitations

Recommendation: For these reasons, I do not recommend the use of aspirin 100 mg for morbidity or mortality reduction in elderly patients without prior cardiovascular/cerebrovascular event or established ASCVD.

Efficacy:

- The primary composite outcome occurred at similar rates between treatment groups
- Individual rates of the composite outcome also occurred at similar rates between groups
- All-cause mortality occurred at significantly higher rates in the aspirin group

Safety:

- Rates of major hemorrhagic events occurred significantly more often in the aspirin group
    - Driven primarily by increased rates of clinically significant bleeding

Cost:

- The cost of using aspirin in this patient population must be considered in addition to the cost of monitoring for and managing increased rates of major hemorrhagic events

Special Considerations/Populations:

- Patient population must be carefully considered when interpreting trial results
    - Elderly patients without prior cardiovascular/cerebrovascular event or established ASCVD

Grade of Recommendation: **B**

ATHENA

Hohnloser SH, Crijns HJ, van Eickels M, et al. Effect of dronedarone on cardiovascular events in atrial fibrillation. *N Engl J Med*. 2009;360(7):668-678.

Objective: To assess the efficacy and safety of dronedarone on morbidity and mortality outcomes in patients with atrial fibrillation.

Primary Efficacy Measure: Composite of first cardiovascular hospitalization or all-cause mortality

Secondary Efficacy Measures: (1) All-cause mortality (2) Cardiovascular death (3) First cardiovascular hospitalization

Participants: Patients with paroxysmal or persistent atrial fibrillation/flutter

- Age ~72 years; male ~55%
- Baseline beta-blocker ~71%; ACEi/ARB ~70%; vitamin K antagonist ~60%

Inclusion Criteria:

- Paroxysmal or persistent atrial fibrillation/flutter
- Age ≥ 75 years OR ≥ 70 years plus one or more of the following: arterial hypertension, diabetes, previous stroke/TIA/systemic embolism, left atrial diameter ≥ 50 mm, LVEF ≤ 40%

Exclusion Criteria:

- Permanent atrial fibrillation
- Unstable hemodynamic condition
- NYHA class IV heart failure
- Acute myocardial infarction
- Heart rate < 50 bpm or PR interval > 0.28 seconds
- Serum potassium level < 3.5 mmol/L

Drug: Dronedarone

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients were randomized to receive dronedarone 400 mg twice daily or matching placebo. Patients underwent enrollment while in sinus rhythm or in atrial fibrillation/flutter (after cardioversion and anticoagulation).

Duration: Mean follow-up period of 21 months

Statistical Analysis: It was determined that 970 primary events would achieve 80% power (alpha=0.05). The ITT population was used for the efficacy analyses.

Results: A total of 4628 patients underwent randomization. Baseline characteristics were similar between treatment groups. The dronedarone treatment group demonstrated significantly lower rates of the primary composite outcome which was heavily influenced by the lower rates of cardiovascular hospitalization. While all-cause mortality was not significantly different between treatment groups, cardiovascular mortality was significantly lower in the dronedarone group. Premature discontinuation of study medication occurred more often in the dronedarone group than placebo (12.7% vs 8.1%; $p<0.001$). Bradycardia, QT-interval prolongation, nausea/diarrhea and serum creatinine increase occurred more often in the dronedarone group ($p<0.001$ for each). Rates of pulmonary and thyroid dysfunction were similar between treatment groups. However, the investigators do note that pulmonary toxicity may take several years to develop.

Dronedarone (N=2301) Vs Placebo (N=2327)

First Cardiovascular Hospitalization or All-Cause Mortality:
734 (31.9%) vs 917 (39.4%); HR 0.76 (95% CI 0.69-0.84)
p<0.001; ARR 7.51%; NNT ~14

First Cardiovascular Hospitalization:
675 (29.3%) vs 859 (36.9%); HR 0.74 (95% CI 0.67-0.82)
p<0.001; ARR 7.58%; NNT ~14

All-Cause Mortality:
116 (5.04%) vs 139 (5.97%); HR 0.84 (95% CI 0.66-1.08); p=0.18

Cardiovascular Mortality:
63 (2.74%) vs 90 (3.87%); HR 0.71 (95% CI 0.51-0.98)
p=0.03; ARR 1.13%; NNT ~89

Limitations:

- Cannot extrapolate trial results to patients without atrial fibrillation/flutter
- Patients with severe heart failure were excluded from this trial
- Permanent atrial fibrillation was an exclusion criterion for this trial

Level of Evidence: Level I – with minor limitations

Recommendation: For these reasons, I recommend the use of dronedarone to reduce cardiovascular morbidity and mortality in patients with paroxysmal or persistent atrial fibrillation/flutter.

Efficacy:

- Rates of the primary composite outcome were significantly lower in the dronedarone group
    - However, only the individual component of first cardiovascular hospitalization occurred at significantly lower rates in the dronedarone group versus placebo
- Rates of all-cause mortality were similar between treatment groups
    - However, cardiovascular mortality was significantly lower with dronedarone

Safety:

- Rates of discontinuation were significantly higher in the dronedarone group
- Bradycardia, QT-interval prolongation, nausea/diarrhea and serum creatinine increase occurred more often in the dronedarone group
- Rates of pulmonary and thyroid dysfunction were similar between treatment groups

Cost:

- The cost of using dronedarone must be balanced against the cost-savings from decreased cardiovascular hospitalization and cardiovascular mortality

Special Considerations/Populations:

- Dronedarone is a class III antiarrhythmic
- Patients with severe heart failure were excluded from this trial
- Baseline medications must be considered when interpreting trial results

Grade of Recommendation: **A**

ATLAS

Packer M, Poole-Wilson PA, Armstrong PW, et al. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. ATLAS Study Group. *Circulation*. 1999;100(23):2312-2318.

Objective: To compare the efficacy and safety of low- and high-dose ACE inhibitors on morbidity and mortality outcomes in patients with heart failure and reduced ejection fraction.

Primary Efficacy Measure: All-cause mortality

Secondary Efficacy Measures: (1) All-cause mortality and all-cause hospitalization (2) cardiovascular mortality (3) cardiovascular hospitalizations (4) all-cause mortality and cardiovascular hospitalizations (5) cardiovascular mortality and cardiovascular hospitalizations (6) total myocardial infarction and hospitalization due to unstable angina

Participants: Patients with heart failure reduced ejection fraction

- Age ~64 years; male ~79%
- NYHA class II ~16%; class III ~77%; class IV ~7%
- LVEF ~23%; SBP ~125 mmHg; HR ~80 bpm
- Prior use of ACE inhibitor ~89%

Inclusion Criteria:

- Patients with NYHA class II-IV symptoms
    - Patients with class II symptoms were required to have heart failure hospitalization or emergency room treatment within the previous 6 months
- LVEF ≤ 30% (despite diuretic treatment for at least two months)

Exclusion Criteria:

- Acute coronary ischemic event or revascularization within previous 2 months
- History of sustained or symptomatic ventricular tachycardia
- Intolerance to ACE inhibitors
- SCr > 2.5 mg/dL
- Non-cardiac condition thought to limit survival

Drug: Lisinopril

Design: Randomized, double-blind, placebo-controlled trial

Methods: All eligible patients underwent a 4 week open-label run-in period with lisinopril to assess drug tolerance. Patients that successfully tolerated lisinopril 12.5-15 mg daily for two or more weeks were then randomized to the low- or high-dose ACE inhibitor group. Patients in the low-dose group received 2.5-5 mg daily. Patients in the high-dose group received 32.5-35 mg daily. The highest tolerated dose of lisinopril was used for each patient. Patients were continued on their other usual medications for heart failure.

Duration: Median follow-up period of ~46 months

Statistical Analysis: It was determined that 3000 randomized patients with an approximate follow-up duration of 3 years would achieve 90% power. For the primary efficacy analysis, a p-value < 0.0394 would be considered statistically significant. For the secondary efficacy analyses, a p-value < 0.05 would be considered statistically significant. The ITT population was used for all analyses.

Results: A total of 3164 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. Target dosing was achieved in ~93% of the low-dose group and ~91% of the high-dose group. Average dosing was ~4.5 mg daily in the low-dose group and ~33.2 mmHg daily in the high-dose group. There was no significant difference in rates of the primary composite outcome of all-cause mortality. Likewise, rates of cardiovascular mortality were similar between groups. Composite outcomes of all-cause mortality or all-cause hospitalization as well as all-cause mortality or cardiovascular hospitalization occurred at significantly lower rates in the high-dose group. The rates of the other secondary efficacy outcomes were not significantly different between treatment groups. Overall, these results indicate a morbidity benefit of high-dose therapy (via reduced rates of hospitalization) rather than a mortality benefit.

While dizziness, hypotension and decreased renal function occurred more often in the high-dose group compared to the low-dose group, rates of discontinuation were similar (17% and 18%, respectively). Additionally, rates of worsening heart failure occurred less frequently in the high-dose group (38% vs 44%, respectively).

Low-Dose (N=1596) Vs High-Dose (N=1568)

All-Cause Mortality:
717 (44.9%) vs 666 (42.5%); HR 0.92 (96.1% CI 0.82-1.03); p=0.128

All-Cause Mortality and All-Cause Hospitalization:
1338 (83.8%) vs 1250 (79.7%); HR 0.88 (95% CI 0.82-0.96)
p=0.002; ARR 4.12%; NNT ~25

Cardiovascular Mortality:
641 (40.2%) vs 583 (37.2%); HR 0.90 (95% CI 0.81-1.01); p=0.073

All-Cause Mortality and Cardiovascular Hospitalization:
1182 (74.0%) vs 1115 (71.1%); HR 0.92 (95% CI 0.84-0.99)
p=0.036; ARR 2.95%; NNT ~34

Cardiovascular Mortality and Cardiovascular Hospitalization:
1161 (72.7%) vs 1088 (69.4%); HR 0.91 (95% CI 0.84-0.99)
p=0.027; ARR 3.36%; NNT ~30

Total Myocardial Infarction and Hospitalization for Unstable Angina:
224 (14.0%) vs 207 (13.2%); HR 0.92 (95% 0.76-1.11); p=0.374

Limitations:

- Patient population – cannot apply trial results to patients with preserved ejection fraction
- The difference in ACEi dosing between groups must be considered when interpreting trial results

Level of Evidence: Level I – with minor limitations

Recommendation: For these reasons, I recommend the use of high-dose ACEi therapy over low-dose ACEi therapy in patients with heart failure and reduced ejection fraction to further reduce rates of adverse clinical outcomes. In patients currently treated with less-than high-dose ACEi therapy, consider increasing the dose in order to maximize treatment benefit. However, patient-specific characteristics and safety/tolerability must be carefully considered when making therapy adjustments.

Efficacy:

- Rates of all-cause mortality and cardiovascular mortality were not significant different between treatment groups
- Composite outcomes of all-cause mortality and all-cause hospitalization as well as all-cause mortality and cardiovascular hospitalization occurred at significantly lower rates in the high-dose group
    - This indicates that the demonstrated treatment benefit of high-dose ACEi therapy is driven primarily by reduced rates of morbidity outcomes (e.g., hospitalization)

Safety:

- While dizziness, hypotension and decreased renal function occurred more often in the high-dose group compared to the low-dose group, rates of discontinuation were remained similar
- Rates of worsening heart failure occurred less frequently in the high-dose group

Cost:

- The cost of using high-dose ACEi therapy over lower dosages must be balanced against the cost-savings achieved from reduced morbidity outcomes

Special Considerations/Populations:

- These trial results cannot be applied to patients with heart failure and preserved ejection fraction

Grade of Recommendation: **A**

AURORA

Fellström BC, Jardine AG, Schmieder RE, et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. *N Engl J Med*. 2009;360(14):1395-1407.

Objective: To determine the effect of rosuvastatin on cardiovascular outcomes in patients on hemodialysis.

Primary Efficacy Measure: Composite of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke (time to first event)

Participants: Adults with end-stage renal disease receiving hemodialysis

- Age ~65 years; male ~62%
- Total cholesterol ~175 mg/dL; LDL ~99 mg/dL; HDL ~45 mg/dL; TGL ~156 mg/dL
- BP ~137/76 mmHg
- Duration of hemodialysis treatment ~3.5 years
- Diabetes ~26%; cardiovascular disease ~40%

Inclusion Criteria:

- Age 50-80 years with end-stage renal disease
- Receiving regular hemodialysis/hemofiltration for 3 months or more

Exclusion Criteria:

- Statin therapy in the previous 6 months
- Expected renal transplant within 12 months
- Serious condition expected to limit lifespan to less than 12 months
- History of malignancy
- Active liver disease
- Uncontrolled hypothyroidism
- Unexplained elevation in CK level to >3 times the upper limit of normal

Drug: Rosuvastatin

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients were randomized to receive rosuvastatin 10 mg or matching placebo once daily.

Duration: Median follow-up period of 3.8 years

Statistical Analysis: It was determined that 805 primary events would achieve 87% power (alpha=0.05). The ITT population was used for the primary efficacy analysis.

Results: A total of 2776 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. At three months, the average LDL reduction was 42.9% in the rosuvastatin group and 1.9% in the placebo group ($p<0.001$). Thereafter, the overall average LDL was roughly 60 mg/dL in the rosuvastatin group and 90-95 mg/dL in the placebo group. Adverse effects occurred at similar rates between treatment groups.

Rosuvastatin (N=1389) Vs Placebo (N=1384)

Primary Composite Outcome:
396 (28.5%) vs 408 (29.5%); HR 0.96 (95% CI 0.84-1.11); p=0.59

Cardiovascular Death:
324 (23.3%) vs 324 (23.4%); HR 1.00 (95% CI 0.85-1.16); p=0.97

Non-Fatal Myocardial Infarction:
91 (6.55%) vs 107 (7.73%); HR 0.84 (95% CI 0.64-1.11); p=0.23

Non-Fatal Stroke:
53 (3.82%) vs 45 (3.25%); HR 1.17 (95% CI 0.79-1.75); p=0.42

Non-Cardiovascular Death:
248 (17.9%) vs 268 (19.4%); HR 0.92 (95% CI 0.77-1.09); p=0.34

Limitations:

- Power set but not met – clinical significance likely low (off by a single primary event occurrence)
- Patient population – cannot apply results to patients with CKD not receiving hemodialysis
- Those with statin therapy within the previous 6 months were excluded from this trial

Level of Evidence: Level II – with major limitations

Recommendation: For these reasons, I do not recommend initiating statin therapy to reduce the risk of cardiovascular outcomes in patients with end-stage renal disease receiving hemodialysis. It is important to note that this recommendation does not apply to patients currently receiving statin therapy for a previous indication.

Efficacy:

- The primary composite outcome occurred at similar rates between groups
- Rates of the individual components of the composite were not significantly different between groups
- Predictably, LDL levels were notably lower in the rosuvastatin group

Safety:

- Rates of adverse events were similar between treatment groups

Cost:

- The cost of using rosuvastatin must be balanced against any potential cost-savings achieved from reduced clinical outcomes (not demonstrated in this trial)

Special Considerations/Populations:

- Patient population – cannot apply results to patients with CKD not receiving hemodialysis
- These trial results cannot be applied to patients currently receiving statin therapy for a previous indication – said patients were excluded from this trial
    - Results can only be applied to those not currently receiving statin therapy (> 6 months)
- Those predicted to receive a renal transplant within 12 months were excluded from this trial

Grade of Recommendation: **B**

AVERROES

Connolly SJ, Eikelboom J, Joyner C, et al. Apixaban in patients with atrial fibrillation. *N Engl J Med*. 2011;364(9):806-817.

Objective: To determine the efficacy and safety of apixaban compared to aspirin alone for stroke prevention in atrial fibrillation patients that cannot tolerate vitamin K antagonist therapy.

Primary Efficacy Measure: Composite of stroke (ischemic or hemorrhagic) or systemic embolism

Primary Safety Measure: Major bleeding (defined as overt bleed resulting in a decrease in hemoglobin of 2 g/dL or more, transfusion of 2 units or more of packed red cells, bleed location at a critical site or bleed resulting in death)

Participants: Atrial fibrillation patients at increased risk for stroke who cannot tolerate vitamin K antagonist therapy

- Age ~70 years; male ~59%
- SBP ~132 mmHg; HR ~74 bpm; $CHADS_2$ score ~2
- Baseline beta-blocker ~55%; digoxin ~28%; verapamil or diltiazem ~9%

Inclusion Criteria:

- Age ≥ 50 years
- Documented atrial fibrillation within previous 6 months
- One or more risk factors for stroke (prior stroke/TIA, age ≥ 75, arterial hypertension, diabetes, heart failure NYHA ≥ class II, LVEF ≤ 35%, documented PAD)
- Not receiving vitamin K antagonist therapy (not tolerated or not suitable)

Exclusion Criteria:

- Indication for long-term anticoagulation (other than atrial fibrillation)
- Valvular disease requiring surgery
- Serious bleed within prior 6 months or high bleed risk
- Current alcohol/drug abuse
- SCr > 2.5 mg/dL or CrCl < 25 mL/min
- Elevated liver enzymes

Drugs: Apixaban; aspirin

Design: Randomized, double-blind, active-comparison trial

Methods: Eligible patients were randomized to receive either apixaban 5 mg twice daily or aspirin (81 mg to 324 mg) daily plus matching placebo. Apixaban 2.5 mg twice daily was used for patients meeting 2 or more of the following criteria: age ≥ 80 years, weight ≤ 60 kg or SCr ≥ 1.5 mg/dL. The dosing for aspirin was determined by the attending physician.

Duration: Mean follow-up period of 1.1 years

Statistical Analysis: It was determined that 5600 randomized patients and 226 primary outcomes would be required to achieve 90% power (alpha = 0.025). The ITT population was used for the primary efficacy and safety analyses.

Results: A total of 5599 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. The trial was stopped early at the recommendation of the safety monitoring committee after meeting pre-specified criteria. The vast majority of patients in the apixaban group received the 5 mg twice daily dosing (~93%). The most common dosing in the aspirin group was 81 mg daily (~65%). There were overall significantly fewer serious adverse drug reactions in the apixaban group compared to aspirin (22% vs 27%; $p<0.001$). This was driven primarily by lower rates of central nervous system vascular disorders.

Apixaban (N=2808) Vs Aspirin (N=2791)

Composite of Stroke & Systemic Embolism:
51 (1.82%) vs 113 (4.05%); HR 0.45 (95% CI 0.32-0.62)
p<0.001; ARR 2.23%; NNT ~45

Ischemic Stroke:
35 (1.25%) vs 93 (3.33%); HR 0.37 (95% CI 0.25-0.55)
p<0.001; ARR 2.09%; NNT ~48

Hemorrhagic Stroke:
6 (0.21%) vs 9 (0.32%); HR 0.67 (95% CI 0.24-1.88); p=0.45

Systemic Embolism:
2 (0.07%) vs 13 (0.47%); HR 0.15 (95% CI 0.03-0.68)
p=0.01; ARR 0.39%; NNT ~254

Major Bleeding:
44 (1.57%) vs 39 (1.40%); HR 1.13 (95% CI 0.74-1.75%); p=0.57

Limitations:

- Power set but not met - due to trial being stopped early (clinical significance minimal)

Level of Evidence: Level II - with major limitations

Recommendation: For these reasons, I recommend the use of apixaban over aspirin for prevention of thromboembolic events in high-risk atrial fibrillation patients unable to receive vitamin K antagonist therapy.

Efficacy:

- Apixaban demonstrated significantly lower rates of the primary composite outcome compared to aspirin alone, driven primarily by reduction in ischemic stroke rates

Safety:

- There was no significant difference in rates of major bleeding between treatment groups
- Overall rates of serious adverse drug reactions were significantly lower with apixaban

Cost:

- The cost of using apixaban must be balanced against the cost-savings of avoiding a primary event outcome, particularly ischemic stroke

Special Considerations/Populations:

- Inclusion criteria must be considered - these patients could not tolerate vitamin K antagonist therapy or were not appropriate candidates

Grade of Recommendation: **B**

BEST

Beta-Blocker Evaluation of Survival Trial Investigators, Eichhorn EJ, Domanski MJ, Krause-Steinrauf H, Bristow MR, Lavori PW. A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. N Engl J Med. 2001;344(22):1659-1667.

Objective: To determine the effect of bucindolol on mortality outcomes in patients with heart failure and reduced ejection fraction.

Primary Efficacy Measure: All-cause mortality

Secondary Efficacy Measures: (1) Cardiovascular death (2) All-cause hospitalization (3) Heart failure hospitalization

Participants: Patients with heart failure and reduced ejection fraction

- Age ~60 years; male ~78%
- LVEF ~23%; BP ~117/72 mmHg; HR ~81 bpm
- NYHA class III ~92%; class IV ~8%
- Baseline ACEi ~91%; digoxin ~92%; diuretic ~94%

Inclusion Criteria:

- Patients with NYHA class III-IV symptoms
- LVEF ≤ 35%
- Optimal medical therapy (including ACEi for at least one month)

Exclusion Criteria:

- Reversible cause of heart failure
- Myocardial infarction within the previous 6 months
- Revascularization procedure within the previous 60 days
- Heart rate < 50 bpm
- Renal disease (SCr > 3.0 mg/dL) or active liver disease (serum bilirubin > 3.0 mg/dL)
- Use of calcium-channel blockers within 1 week of randomization

Drug: Bucindolol

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients were randomized to receive bucindolol or matching placebo. The dosing was initiated at 3 mg twice daily for one week. Thereafter, doses were increased weekly (6.25 mg BID, 12.5 mg BID, 25 mg BID) to an upper limit of 50 mg twice daily (100 mg twice daily for those weighing 75 kg or more).

Duration: Mean follow-up period of 2.0 years

Statistical Analysis: It was determined that 2800 randomized patients would achieve 85% power (alpha=0.05). The ITT population was used for all analyses.

Results: A total of 2708 patients underwent randomization. Baseline patient characteristics were largely similar between groups with the exception of higher rates of smokers in the bucindolol group. This trial was terminated early at the request of the safety monitoring committee due to a lack of treatment benefit with bucindolol. The average dose of bucindolol was 76 mg twice daily. The average change in heart rate from baseline to 12 months was -8.6 bpm in the bucindolol group and -2.1 bpm in the placebo group.

Placebo (N=1354) Vs Bucindolol (N=1354)

All-Cause Mortality:
449 (33.2%) vs 411 (30.4%); HR 0.90 (95% CI 0.78-1.02); p=0.10

Cardiovascular Death:
389 (28.7%) vs 342 (25.3%); HR 0.86 (95% CI 0.74-0.99)
p=0.04; ARR 3.47%; NNT ~29

All-Cause Hospitalization:
875 (64.6%) vs 829 (61.2%); HR 0.92 (95% CI 0.84-1.01); p=0.08

Heart Failure Hospitalization:
569 (42.0%) vs 476 (35.2%); HR 0.78 (95% CI 0.69-0.88)
p<0.001; ARR 6.87%; NNT ~15

Bradycardia:
68 (5.02%) vs 156 (11.5%); p<0.001; ARI 6.50%; NNH ~15

Hyperglycemia:
196 (14.5%) vs 243 (17.9%); p=0.01; ARI 3.47%; NNH ~28

Limitations:

- Power set, but not met – due to failure to achieve 2800 randomized patients
    - Clinical significance is likely low as significant differences were still detected

Level of Evidence: Level II – with major limitations

Recommendation: For these reasons, I do not recommend the routine use of bucindolol in patients with heart failure and reduced ejection fraction. Other beta-blockers with more robust morbidity and mortality benefit are preferred in this patient population.

Efficacy:

- There was no significant difference in the rates of all-cause mortality between groups
    - Rates of cardiovascular death were significantly lower in the bucindolol group
- There were no significance differences in rates of all-cause hospitalizations between groups
    - Rates of heart failure hospitalization were significantly lower in the bucindolol group

Safety:

- Rates of bradycardia and hyperglycemia occurred at significantly higher rates in the bucindolol group compared to the placebo group

Cost:

- The cost of using bucindolol must be balanced against the cost-savings achieved from reduced rates of cardiovascular mortality and heart failure hospitalization

Special Considerations/Populations:

- Bucindolol is a non-specific beta-blocker without intrinsic sympathomimetic activity
- Although bucindolol demonstrates evidence of clinical benefit, other agents with more robust morbidity and mortality benefit are available (e.g., carvedilol, metoprolol succinate)

Grade of Recommendation: **B**

CANVAS Program

Neal B, Perkovic V, Matthews DR. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N Engl J Med*. 2017;377(21):2099.

Objective: To determine the effect of canagliflozin on cardiovascular and renal outcomes in patients with type 2 diabetes.

Primary Efficacy Measure: Composite of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke

Secondary Efficacy Measures: (1) All-cause mortality (2) cardiovascular death (3) albuminuria progression (4) composite of cardiovascular death or heart failure hospitalization

Participants: Patients with type 2 diabetes at increased risk for cardiovascular event

- Age ~63 years; male ~64%
- HgA1c ~8.2%; duration of diabetes ~13 years
- History of ASCVD ~72%

Inclusion Criteria:

- Type 2 diabetes with HgA1c $\geq$ 7.0% and $\leq$ 10.5%
- $\geq$ 30 years old with ASCVD or $\geq$ 50 years old with $\geq$ 2 cardiovascular risk factors
- eGFR > 30 mL/min

Exclusion Criteria:

- History of diabetic ketoacidosis
- Type 1 diabetes
- Beta-cell or pancreas transplant
- Diabetes secondary to pancreatitis/pancreatectomy

Drug: Canagliflozin

Design: Randomized, double-blind, placebo-controlled, non-inferiority trial (joint analysis of CANVAS and CANVAS-R)

Methods: Eligible patients underwent a two-week single-blind, placebo run-in period. CANVAS patients were randomized 1:1:1 to receive canagliflozin 100 mg daily, canagliflozin 300 mg daily or matching placebo. CANVAS-R patients were randomized 1:1 to receive canagliflozin 100 mg daily (increased to 300 mg as tolerated) or matching placebo. The use of additional glucose-lowering agents was allowed.

Duration: Mean follow-up period of ~3.6 years

Statistical Analysis: It was determined that 688 cardiovascular events would provide 90% power (alpha = 0.05). The non-inferiority margin was set at 1.3 for the primary composite outcome with pre-specified criteria for demonstrating superiority if the upper bound of the 95% CI was less than 1.0. Sequential testing for superiority would continue for each secondary outcome (in above order) until a non-statistically significant difference was detected.

Results: A total of 10,141 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. The mean difference in HgA1c was -0.58% favoring the canagliflozin group. While canagliflozin demonstrated decreased rates of hospitalization for heart failure and albuminuria progression these results are considered exploratory due to failure of sequential testing. Rates of lower limb amputation were significantly higher in the canagliflozin group than placebo (6.3 vs 3.4 patients per 1000 years, respectively).

Canagliflozin (N=5795) Vs Placebo (N=4347)

Composite of Cardiovascular Death, Non-Fatal Myocardial Infarction & Non-Fatal Stroke:
26.9 vs 31.5; HR 0.86 (95% CI 0.75-0.97); p=0.02

Cardiovascular Death:
11.6 vs 12.8; HR 0.87 (95% CI 0.72-1.06)

Non-Fatal Myocardial Infarction:
9.7 vs 11.6; HR 0.85 (95% CI 0.69-1.05)

Non-Fatal Stroke:
7.1 vs 8.4; HR 0.90 (95% CI 0.71-1.15)

All-Cause Mortality:
17.3 vs 19.5; HR 0.87 (95% CI 0.74-1.01)

Heart Failure Hospitalization:
5.5 vs 8.7; HR 0.67 (95% CI 0.52-0.87)

Albuminuria Progression (>30% increase plus change in classification):
89.4 vs 128.7; HR 0.73 (95% CI 0.67-0.79)

All above values are number of patients per 1000 patient years

Limitations:

- CANVAS Program was a joint analysis of two separate trials
- Cardiorenal benefit cannot be claimed due to failure of the pre-specified sequential superiority testing at all-cause mortality (results must be considered exploratory)

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I recommend the use of canagliflozin as a safe glucose-lowering therapy in high-risk patients with type 2 diabetes. However, I do not recommend canagliflozin as the SGLT2 inhibitor of choice to reduce the risk of cardiovascular events in this patient population. Instead, I recommend usage of a SGLT2 inhibitor with clearly demonstrated cardiovascular benefit.

Efficacy:

- The canagliflozin group demonstrated significantly lower rates of the primary composite outcome compared to placebo
    - However, none of the individual components of the composite were significantly different between treatment groups
- While canagliflozin did demonstrate significantly lower rates of heart failure hospitalization and albuminuria progress, these results must be considered exploratory

Safety:

- Rates of amputation, volume depletion, male genitalia infection and mycotic genital infections in women were significantly higher in the canagliflozin group
    - Area of amputation was primarily toe or metatarsal (~71%)

Cost:

- The cost of using canagliflozin must be balanced against the cost-savings of preventing a primary event outcome, however the cost of managing mycotic genital infections and volume depletion must also be considered

Special Considerations/Populations:

- This was a combined analysis of two trials - neither individual trial showed significant benefit favoring canagliflozin

Grade of Recommendation: **A**

CAPRICORN

Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomized trial. *Lancet*. 2001;357(9266):1385-1390.

Objective: To determine the effect of carvedilol on morbidity and mortality outcomes in patients with left-ventricular dysfunction/heart failure and recent acute myocardial infarction.

Primary Efficacy Measures: (1) All-cause mortality (2) Composite of all-cause mortality or cardiovascular hospitalizations

Participants: Patients with LV dysfunction/heart failure with recent myocardial infarction

- Age ~63 years; male ~73%
- BP ~121/73 mmHg; HR ~77 bpm
- LVEF ~32%

Inclusion Criteria:

- Age ≥ 18 years
- Definite myocardial infarction within previous 3-21 days
- LVEF ≤ 40% (or wall-motion score of 1.3 or less)
- Treatment with ACEi for 48 hours

Exclusion Criteria:

- Required IV diuretics/inotropes
- Uncontrolled heart failure
- Unstable angina/hypertension/hypotension
- Bradycardia
- Uncontrolled insulin-dependent diabetes
- Indication for beta-blocker other than heart failure
- Requirement for inhaled beta-agonists/steroids

Drug: Carvedilol

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients were randomized to receive either carvedilol 6.25 mg twice daily or matching placebo. Dosing was increased every 3-10 days as tolerated to a maximum dose of 25 mg twice daily.

Duration: Mean follow-up period of 1.3 years

Statistical Analysis: The initial primary endpoint was all-cause mortality but due to lower than expected rates at a masked interim analysis the steering committee adopted co-primary endpoints of all-cause mortality and the composite of all-cause mortality plus cardiovascular hospitalization. It was determined that 1850 randomized patients and 633 deaths or cardiovascular hospitalizations would achieve 90% power (overall alpha=0.05). Alpha was divided into 0.005 for the outcome of all-cause mortality and 0.045 for all-cause mortality plus cardiovascular hospitalization. The ITT population was used for all analyses.

Results: A total of 1959 patients underwent randomization. Baseline characteristics were similar between treatment groups. Approximately 74% of the carvedilol group achieved 25 mg twice daily dosing. Neither of the co-primary endpoints were significantly different between groups (per the adjusted alpha values for the trial).

Carvedilol (N=975) Vs Placebo (N=984)

All-Cause Mortality:
116 (11.9%) vs 151 (15.3%); HR 0.77 (95% CI 0.60-0.98); p=0.031

Composite of All-Cause Mortality or Cardiovascular Hospitalization:
340 (34.9%) vs 367 (37.3%); HR 0.92 (95% CI 0.80-1.07); p=0.296

Heart Failure Hospitalization:
118 (12.1%) vs 138 (14.0%); HR 0.86 (95% CI 0.67-1.09); p=0.215

Limitations:

- While 95% CI for all-cause mortality does not cross 1.00 (demonstrating benefit favoring carvedilol) the p-value was > 0.005 which is why a statistically significant difference cannot be claimed
- External validity - patient population must be considered (left ventricular dysfunction with recent myocardial infarction) when interpreting results

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I recommend the use of carvedilol (in addition to standard therapy) to reduce morbidity and mortality in patients with acute myocardial infarction plus left-ventricular dysfunction. However, due to this being such a high-risk patient population an emphasis on medication optimization and lifestyle modifications is warranted to maximize therapy benefit to the patient.

Efficacy:

- There was no statistically significant difference in rates of all-cause mortality or the composite of all-cause mortality and cardiovascular hospitalization between treatment groups
- However, it is important to note that the ARR for all-cause mortality was 3.4% favoring carvedilol, which would input a NNT of 30 (if statistical significance had been achieved)
- Rates of heart failure hospitalizations were not significantly different between treatment groups

Safety:

- Rates of adverse drug reactions or safety events were not reported

Cost:

- The cost of using carvedilol must be weighed against the cost-savings from reduced mortality rates

Special Considerations/Populations:

- High-risk patient population (acute myocardial infarction plus left-ventricular dysfunction)
- Patients were also on ACEi at time of randomization
- This is an example of where the outcome of all-cause mortality did not demonstrate statistical significance (based on pre-specified criteria) but did demonstrate clinical significance by showing clear mortality benefit with carvedilol

Grade of Recommendation: **A**

CAPRIE

CAPRIE Steering Committee. A randomized, blinded, trial of clopidogrel versus aspirin in patients at risk of ischemic events (CAPRIE). CAPRIE Steering Committee. *Lancet*. 1996;348(9038):1329-1339.

Objective: To compare the efficacy of clopidogrel versus aspirin for prevention of cardiovascular outcomes in high-risk patients.

Primary Efficacy Measure: Composite of ischemic stroke, myocardial infarction or vascular death

Participants: Patients at increased risk for cardiovascular events

- Age ~62 years; male ~72%

Inclusion Criteria (one of the following):

- Ischemic stroke more than 1 week prior but within 6 months of randomization
- Myocardial infarction within 35 days of randomization
- Atherosclerotic peripheral artery disease

Exclusion Criteria:

- Age < 21 years
- Severe cerebral deficit
- Uncontrolled hypertension
- Scheduled for major surgery

Drugs: Clopidogrel; aspirin

Design: Randomized, double-blind, active-comparison trial

Methods: Eligible patients were randomized to receive either clopidogrel 75 mg daily or aspirin 325 mg daily plus matching placebo. Any prior antiplatelet or anticoagulant medications were discontinued prior to trial randomization.

Duration: Mean follow-up period of ~1.9 years

Statistical Analysis: It was determined that 15,000 randomized patients would achieve 90% power (alpha = 0.05). The patient recruitment period was extended to preserve > 35,000 patient years at risk. The ITT population was used for the primary analyses.

Results: A total of 19,185 patients underwent randomization resulting in 36,731 patient-years at trial completion. Baseline patient characteristics were similar between treatment groups. Subgroup analysis of baseline inclusion criteria (stroke, MI or PAD) demonstrated a significant difference favoring clopidogrel for PAD only (215 vs 277; RRR 23.8% [8.9-36.2]; p=0.0028). Testing for heterogeneity was statistically significant (p=0.042) which suggests that treatment effect is not equal across the subgroups. The individual rates of myocardial infarction and stroke were not reported in this trial.

Clopidogrel (N=9599) Vs Aspirin (N=9586)

Composite of Ischemic Stroke, Myocardial Infarction & Vascular Death:
939 (9.78%) vs 1021 (10.7%); RRR 8.7% (95% CI 0.3% to 16.5%)
p=0.043; ARR 0.87%; NNT ~116

Vascular Death:
350 (3.65%) vs 378 (3.94%); RRR 7.6% (95% CI -6.9% to 20.1%); p=0.29

Safety:

Gastrointestinal Hemorrhage:
191 (1.99%) vs 255 (2.66%); p<0.05
ARR 0.67%; NNT ~149

Limitations:

- Dosage of aspirin must be considered (325 mg daily) - cannot apply trial results to other aspirin strengths/dosages

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I recommend the use of clopidogrel 75 mg daily over aspirin 325 mg daily for reduction of cardiovascular events in high-risk patients.

Efficacy:

- Rates of the primary composite outcome were significantly lower in the clopidogrel group compared to aspirin
- There was no significant difference in the rates of vascular death
- Subgroup analysis demonstrated that only patients with baseline PAD had significantly lower rates of the primary composite outcome compared to aspirin (no significant difference in subgroups of stroke or myocardial infarction)

Safety:

- Rates of gastrointestinal hemorrhage were significantly higher in the aspirin group compared to clopidogrel

Cost:

- The cost of using clopidogrel over aspirin must be balanced against the cost-savings of preventing a primary outcome or gastrointestinal bleed

Special Considerations/Populations:

- Aspirin dosage was 325 mg daily (cannot extrapolate results to other dosages)
- Patient population must be considered - recent stroke/myocardial infarction or established peripheral artery disease
- These trial results demonstrate a more favorable efficacy and safety profile for clopidogrel compared to aspirin 325 mg

Grade of Recommendation: **A**

CARDS

Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicenter randomized placebo-controlled trial. Lancet. 2004;364(9435):685-696.

Objective: To assess the efficacy and safety of atorvastatin for primary prevention of cardiovascular disease in patients with type 2 diabetes.

Primary Efficacy Measure: Composite of myocardial infarction, unstable angina, acute coronary heart disease death, resuscitated cardiac arrest, coronary revascularization procedure or stroke

Participants: Patients with type 2 diabetes at increased risk for primary cardiovascular event

- Age ~62 years; male ~68%
- Duration of diabetes ~8 years; HgA1c ~7.8%
- Total cholesterol ~207 mg/dL; LDL ~116 mg/dL

Inclusion Criteria:

- Age 40-75 years with type 2 diabetes (diagnosed at least 6 months prior to randomization)
- LDL ≤ 160 mg/dL
- Triglycerides ≤ 600 mg/dL
- One or more of the following risk factors: hypertension, retinopathy, micro- or macroalbuminuria, current smoker

Exclusion Criteria:

- History of myocardial infarction, angina, coronary vascular surgery, cerebrovascular accident, or severe peripheral vascular disease
- HgA1c > 12%

Drug: Atorvastatin

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients were randomized to receive atorvastatin 10 mg or placebo daily.

Duration: Median follow-up period of 4 years

Statistical Analysis: It was determined that 304 primary endpoints would need to occur for 90% power to be achieved (alpha = 0.05). The modified ITT population (all randomized patients that received at least one dose of study medication) was used for safety and efficacy analyses.

Results: A total of 2838 patients underwent randomization and received at least one dose of study medication. Baseline patient characteristics were similar between groups. The trial was stopped early (~two years prior to expected end) at the recommendation of the data and safety monitoring board after an interim analysis showed significant treatment benefit with atorvastatin over placebo. Overall, rates of adverse reactions were similar between treatment groups. There were no reported cases of rhabdomyolysis. The average difference in LDL was -46 mg/dL, favoring the atorvastatin group ($p<0.001$).

Placebo (N=1410) Vs Atorvastatin (N=1428)

Primary Composite Outcome:
127 (9.01%) vs 83 (5.81%); HR 0.63 (95% CI 0.48-0.83)
p=0.001; ARR 3.19%; NNT ~32

Acute Coronary Events:
77 (5.46%) vs 51 (3.57%); HR 0.64 (95% CI 0.45-0.91)
ARR 1.89%; NNT ~53

Coronary Revascularization:
34 (2.41%) vs 24 (1.68%); HR 0.69 (95% CI 0.41-1.16)

Stroke:
39 (2.77%) vs 21 (1.47%); HR 0.52 (95% CI 0.31-0.89)
ARR 1.30%; NNT ~78

Limitations:

- Power set but not met – clinical significance minimal as the trial was stopped early at the recommendation of the data and safety monitoring board due to clearly demonstrated benefit
- Patient population must be considered – this trial was conducted entirely of patients with type 2 diabetes being treated for primary prevention (cannot extrapolate results for secondary prevention)

Level of Evidence: Level II – with major limitations

Recommendation: For these reasons, I recommend the use of atorvastatin for primary prevention of cardiovascular events in patients with type 2 diabetes at an increased risk.

Efficacy:

- The trial was stopped early due to clearly demonstrated benefit of atorvastatin over placebo
- Rates of the primary composite outcome were significantly lower in the atorvastatin group, driven by significantly lower rates of acute coronary events and stroke
- Predictably, LDL reduction was significantly greater in the atorvastatin group

Safety:

- Overall rates of adverse effects were similar between groups
- There were no reported cases of rhabdomyolysis

Cost:

- The cost of using atorvastatin must be balanced against the cost-savings achieved from preventing primary cardiovascular events in this patient population

Special Considerations/Populations:

- All included patients had type 2 diabetes and no prior cardiovascular event
- Results of this trial can only be applied to primary prevention (not secondary)

Grade of Recommendation: **B**

CARE

Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *N Engl J Med*. 1996;335(14):1001-1009.

Objective: To determine the effect of cholesterol lowering therapy with pravastatin on coronary event rates in patients post-myocardial infarction with average cholesterol values.

Primary Efficacy Measure: Composite of coronary heart disease death (myocardial infarction, sudden death, cardiovascular death or death during coronary intervention) or symptomatic non-fatal myocardial infarction

Participants: Patients with history of myocardial infarction with average cholesterol values

- Age ~59 years; male ~86%
- Time from qualifying event ~10 months
- Total cholesterol ~209 mg/dL; LDL ~139 mg/dL; HDL ~39 mg/dL

Inclusion Criteria:

- Age 21 to 75 years (men and postmenopausal women)
- Acute myocardial infarction 3-20 months prior to randomization
- Total cholesterol < 240 mg/dL
- LDL 115 - 174 mg/dL
- Fasting triglycerides < 350 mg/dL
- Fasting glucose ≤ 220 mg/dL
- LVEF ≥ 25% and no symptomatic heart failure

Exclusion Criteria:

- Overt congestive heart failure despite drug therapy
- Sensitivity to HMG-CoA reductase inhibitors
- Hepatobiliary disease
- Medical condition thought to limit survival

Drug: Pravastatin (with cholestyramine as adjunct therapy if required)

Design: Randomized, double-blind, placebo-controlled trial

Methods: Prior to randomization, eligible patients underwent 4 weeks of treatment with the NCEP Step 1 diet. Then patients were randomized to either pravastatin 40 mg daily or matching placebo. If the patient's LDL level exceeded 175 mg/dL then NCEP Step 2 diet was initiated. If LDL values > 175 mg/dL persisted then cholestyramine therapy was initiated at 8-16 g daily to target an LDL < 175 mg/dL.

Duration: Mean follow-up period ~5.0 years

Statistical Analysis: It was determined that 4000 randomized patients would provide ≥ 80% power (alpha = 0.05). The ITT population was used for all analyses.

Results: A total of 4159 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. The average LDL value in the pravastatin group was maintained at ~98 mg/dL throughout trial duration. In the last year of follow-up 6% of patients in each group were taking cholestyramine. Subgroup analysis of results by pre-treatment LDL showed that those with LDL < 125 mg/dL experienced no significant risk reduction (p=0.85). However, baseline LDL values ranging 125-150 mg/dL and > 150 mg/dL did show significant treatment benefit with pravastatin (p<0.001; p=0.008).

Placebo (N=2078) Vs Pravastatin (N=2081)

Composite of Coronary Heart Disease Death & Non-Fatal Myocardial Infarction:
274 (13.2%) vs 212 (10.2%); RRR 24% (95% CI 9% to 36%)
p=0.003; ARR 2.99%; NNT ~34

Coronary Heart Disease Death:
119 (5.73%) vs 96 (4.61%); RRR 20% (95% CI -5% to 39%); p=0.10

Non-Fatal Myocardial Infarction:
173 (8.33%) vs 135 (6.49%); RRR 23% (95% CI 4% to 39%)
p=0.02; ARR 1.84%; NNT ~55

There was no significant difference in rates of lab value abnormalities. There was a significantly higher rate of breast cancer in the pravastatin group compared to placebo (12 vs 1; p=0.002). All cases of breast cancer in the pravastatin group were non-fatal. Rates of other cancers were not significantly different between groups.

Limitations:

- External validity - patient population must be considered (history of myocardial infarction with average cholesterol levels)

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I recommend the use of pravastatin 40 mg daily to reduce the risk of coronary events in patients post-myocardial infarction with average cholesterol levels.

Efficacy:

- Rates of the primary composite outcome were significantly lower in the pravastatin group compared to placebo
- Non-fatal myocardial infarction occurred at significantly lower rates in the pravastatin group compared to placebo
- Rates of coronary heart disease death were not significantly different between treatment groups
- Subgroup analysis demonstrated that those with baseline LDL < 125 mg/dL did not experience significant treatment benefit over placebo

Safety:

- There was no significant difference in rates of laboratory abnormalities
- Rates of breast cancer were significantly higher in the pravastatin group compared to placebo (however, this trial was not designed or powered to detect such differences)

Cost:

- The cost of using pravastatin must be balanced against the cost-savings of preventing cardiovascular morbidity and mortality

Special Considerations/Populations:

- Patient population must be considered – individuals with history of ASCVD with relatively normal/average cholesterol levels

Grade of Recommendation: **A**

CARES

White WB, Saag KG, Becker MA, et al. Cardiovascular Safety of Febuxostat or Allopurinol in Patients with Gout. *N Engl J Med*. 2018;378(13):1200-1210.

Objective: To compare the effect of febuxostat and allopurinol on cardiovascular event rates in patients with gout and established cardiovascular disease.

Primary Safety Measure: Composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke and urgent revascularization for unstable angina

Participants: Patients with gout and history of major cardiovascular/cerebrovascular disease

- Age ~64 years; male ~84%
- Serum uric acid level ~8.7 mg/dL
- History of myocardial infarction ~39%; coronary revascularization ~37%; hospitalization for unstable angina ~27%; diabetes plus small-vessel disease ~39%

Inclusion Criteria:

- Males age ≥ 50 years or females age ≥ 55 years
- Diagnosis of gout (per American Rheumatism Association standards)
- History of major cardiovascular or cerebrovascular disease (myocardial infarction, stroke, TIA, revascularization procedure, diabetes plus vascular disease etc.)
- Serum uric acid level ≥ 7.0 mg/dL (or ≥ 6.0 mg/dL with inadequately controlled gout)

Exclusion Criteria:

- Secondary hyperuricemia
- eCrCl < 30 mL/min
- Elevated liver enzymes (> 2 times the upper limit of normal)
- Active peptic ulcer disease

Drugs: Allopurinol; febuxostat

Design: Randomized, double-blind, active-controlled, non-inferiority trial

Methods: Eligible patients were randomized to receive allopurinol or febuxostat once daily (plus matching placebo). The dose of allopurinol was based on renal function and was titrated to achieve a serum uric acid level of < 6.0 mg/dL. Patients with an eCrCl ≥ 60 mL/min were started at 300 mg daily (max 600 mg daily). Patients with an eCrCl ≥ 30 mL/min but less than 60 mL/min were started at 200 mg daily (max 400 mg daily). Febuxostat does not require renal dose adjustments. Patients randomized to febuxostat received 40 mg daily initially with the option to increase to 80 mg daily if uric acid levels remain greater than 6.0 mg/dL. All patients received colchicine 0.6 mg daily as acute flare prophylaxis for the first 6 months.

Duration: Median follow-up period of 32 months

Statistical Analysis: It was determined that 624 primary events would provide 90% power for determining non-inferiority. A non-inferiority margin of 1.3 was used for the trial. A level of significance of 0.05 was used for this trial. All patients that underwent randomization and received study medication were included in the primary safety analyses.

Results: A total of 6190 patients underwent randomization and received study medication. Baseline patient characteristics were similar between treatment groups (including cardiovascular medication usage. Rates of acute gout flares were similar between treatment groups. Febuxostat demonstrated non-inferiority to allopurinol regarding the primary composite outcome. However, rates of cardiovascular death and all-cause mortality were significantly higher in the febuxostat group. Usage of cardiovascular medications during the trial was not significantly different between groups.

Febuxostat (N=3098) Vs Allopurinol (N=3092)

Primary Cardiovascular Composite Outcome:
335 (10.8%) vs 321 (10.4%); HR 1.03 (97% CI 0.87-1.23); p=0.66

Cardiovascular Death:
134 (4.25%) vs 100 (3.23%); HR 1.34 (95% CI 1.03-1.73)
p=0.03; ARI 1.09%; NNH ~91

All-Cause Mortality:
243 (7.84%) vs 199 (6.44%); HR 1.22 (95% CI 1.01-1.47)
p=0.04; ARI 1.41%; NNH ~71

Limitations:

- Patient population must be considered – all patients had gout plus a history of major cardiovascular or cerebrovascular disease

Level of Evidence: Level I – with minor limitations

Recommendation: For these reasons, I recommend the use of allopurinol over febuxostat in patients with gout and a history of cardiovascular disease.

Efficacy:

- Rates of acute gout flares were similar between febuxostat and allopurinol treatment groups

Safety:

- Overall, the rates of the primary safety composite outcome were not significantly different between treatment groups
- However, rates of all-cause mortality and cardiovascular death were significantly higher in the febuxostat group

Cost:

- The cost of using febuxostat over allopurinol must be considered in addition to the costs associated with increased mortality

Special Considerations/Populations:

- Generally, patients with chronic gout have an increased risk for cardiovascular events
- Allopurinol and febuxostat are both xanthine oxidase inhibitors, however allopurinol is purine-based while febuxostat is non-purine based

Grade of Recommendation: **A**

CARMELINA

Rosenstock J, Perkovic V, Johansen OE, et al. Effect of Linagliptin vs Placebo on Major Cardiovascular Events in Adults with Type 2 Diabetes and High Cardiovascular and Renal Risk: The CARMELINA Randomized Clinical Trial. *JAMA*. 2019;321(1):69-79.

Objective: To determine the effect of linagliptin compared to standard therapy on cardiorenal outcomes in patients with type 2 diabetes.

Primary Efficacy Measure: Composite of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke

Secondary Efficacy Measure: Composite of ESRD, renal death or 40% decline in eGFR from baseline

Participants: Patients with type 2 diabetes at increased risk for cardiovascular and renal events

- Age ~66 years; male ~62%
- HgA1c ~8.0%; duration of diabetes ~15 years
- Established cardiovascular disease ~57%
- Baseline kidney disease ~74%; eGFR ~55 mL/min; UACR ~162 mg/g

Inclusion Criteria:

- Type 2 diabetes with HgA1c 6.5%-10%
- High cardiovascular and renal risk (high cardiovascular risk - history of CAD, stroke, PAD or albuminuria [UACR ≥ 30 mg/g]; high renal risk - eGFR 45-75 mL/min and UACR ≥ 200 mg/g, or eGFR 15-45 mL/min regardless of albuminuria)

Exclusion Criteria:

- ESRD or eGFR < 15 mL/min

Drug: Linagliptin

Design: Randomized, double-blind, placebo-controlled, non-inferiority trial

Methods: Eligible patients were randomized to receive linagliptin 5 mg daily or matching placebo. Investigators were encouraged to use additional glucose-lowering agents to maintain glycemic control (except DPP-4 inhibitors, GLP-1 receptor agonists and SGLT2 inhibitors).

Duration: Median follow-up period of ~2.2 years

Statistical Analysis: It was determined that 611 primary events would provide 90% power detecting non-inferiority of the primary composite outcome (alpha = 0.025). A non-inferiority margin of 1.3 was used. If non-inferiority was achieved, then sequential testing for superiority would be performed for the primary cardiovascular composite (alpha = 0.05) and secondary renal composite (alpha = 0.02). The mITT population (all patients that received one or more dose of study drug) was used for all analyses.

Results: A total of 6979 patients received study medication following randomization. Baseline patient characteristics were similar between treatment groups. Average overall HgA1c difference was -0.36% in favor of linagliptin over standard care. Linagliptin demonstrated non-inferiority (but not superiority) to placebo for the primary composite outcome. While rates of the renal composite outcome were similar between treatment groups, non-inferiority cannot be claimed due to the trial design.

Linagliptin (N=3493) Vs Placebo (N=3485)

Cardiovascular Composite Outcome:
434 (12.4%) vs 420 (12.1%); HR 1.02 (95% CI 0.89-1.17); p=0.74

Cardiovascular Death:
221 (6.33%) vs 225 (6.46%)

Non-Fatal Myocardial Infarction:
154 (4.41%) vs 132 (3.79%)

Non-Fatal Stroke:
59 (1.69%) vs 63 (1.81%)

Heart Failure Hospitalization:
209 (5.98%) vs 226 (6.48%); HR 0.90 (95% CI 0.74-1.08); p=0.26

Renal Composite Outcome:
327 (9.36%) vs 306 (8.78%); HR 1.04 (95% CI 0.89-1.22); p=0.62

ESRD:
63 (1.80%) vs 64 (1.84%)

Renal Death:
1 (0.02%) vs 1 (0.02%)

40% Decline in eGFR from Baseline:
263 (7.53%) vs 241 (6.92%)

Limitations:
- Patient population must be considered – type 2 diabetes at high risk for cardiorenal events

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I recommend the use of linagliptin 5 mg daily as a safe glucose-lowering therapy in patients with type 2 diabetes at high-risk for cardiovascular and renal events. It would be reasonable to prefer linagliptin over other DPP-4 inhibitors for this patient population.

Efficacy:
- Linagliptin demonstrated non-inferiority (but not superiority) to placebo regarding the primary cardiovascular composite outcome
- Rates of the renal composite outcome were similar between treatment groups
- There was no significant difference in rates of heart failure hospitalization between treatment groups

Safety:
- Overall rates of adverse drug reactions were similar between treatment groups

Cost:
- The cost of using linagliptin must be balanced against any potential cost-savings from preventing adverse clinical outcomes (via use of safe glucose-lowering therapy)
    - This trial did not demonstrate any significant difference in clinical outcomes with use of linagliptin compared to placebo

Special Considerations/Populations:
- High-risk patient population (increased risk for cardiovascular and renal events)

Grade of Recommendation: **A**

CAROLINA

Rosenstock J, Kahn SE, Johansen OE, et al. Effect of Linagliptin vs Glimepiride on Major Adverse Cardiovascular Outcomes in Patients with Type 2 Diabetes: The CAROLINA Randomized Clinical Trial [correction appears in JAMA. 2019 Dec 3;322(21):2138]. *JAMA*. 2019;322(12):1155-1166.

Objective: To determine the effect of linagliptin compared to glimepiride on cardiovascular outcomes in patients with type 2 diabetes and established cardiovascular disease or risk-factors.

Primary Efficacy Measure: Composite of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke

Participants: Patients with type 2 diabetes at increased risk for cardiovascular events

- Age ~64 years; male ~60%; baseline cardiovascular disease ~42%
- HgA1c ~7.2%; duration of diabetes ~6.2 years
- Baseline metformin ~83%

Inclusion Criteria:

- Type 2 diabetes with HgA1c 6.5%-8.5%
- High cardiovascular risk (established cardiovascular disease, multiple cardiovascular risk factors, age > 70 years, evidence of microvascular complications)

Exclusion Criteria:

- Current insulin therapy
- Previous exposure to DPP-4 inhibitors/GLP-1 receptor agonists/TZDs
- NYHA class III-IV heart failure

Drugs: Linagliptin; glimepiride

Design: Randomized, double-blind, active-comparison, non-inferiority trial

Methods: Eligible patients were randomized to receive either linagliptin 5 mg daily or glimepiride 1-4 mg once daily. Investigators were encouraged to use additional glucose-lowering agents to maintain glycemic control, specifically if HgA1c > 7.5% after the titration period.

Duration: Median follow-up period of ~6.3 years

Statistical Analysis: It was determined that 631 primary events would be required to achieve 90.9% power for detecting non-inferiority (alpha = 0.025). A non-inferiority margin of 1.3 was used. If non-inferiority was determined then testing for superiority would occur. The mITT population (patients that received at least one dose of study medication) was used for all analyses.

Results: A total of 6033 patients received study medication. Baseline patient characteristics were similar between treatment groups. Linagliptin demonstrated non-inferiority (but not superiority) to glimepiride regarding the primary composite outcome. The overall mean dose of glimepiride during the trial period was 2.9 mg daily. Overall, there was no significant difference in HgA1c between treatment groups.

Linagliptin (N=3023) Vs Glimepiride (N=3010)

Primary Composite Outcome:
356 (11.8%) vs 362 (12.0%); HR 0.98 (95% CI 0.84-1.14); p=0.76

Cardiovascular Death:
129 (4.27%) vs 125 (4.15%)

Non-Fatal Myocardial Infarction:
141 (4.66%) vs 138 (4.58%)

Non-Fatal Stroke:
86 (2.84%) vs 101 (3.36%)

Heart Failure Hospitalization:
112 (3.70%) vs 92 (3.06%); HR 1.21 (95% CI 0.92-1.59)

Safety:

Investigator-Reported Hypoglycemic Episode:
320 (10.6%) vs 1132 (37.6%); HR 0.23 (95% CI 0.21-0.26)
p<0.001; ARI 27.0%; NNH ~3

Limitations:

- Upper limit of HgA1c inclusion criteria was 8.5% (relatively low) - consider when interpreting results

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I recommend the use of linagliptin as a safer alternative to glimepiride in high-risk patients with type 2 diabetes, particularly if there are concerns for hypoglycemia.

Efficacy:

- Linagliptin demonstrated non-inferiority (but not superiority) to glimepiride for the primary cardiovascular composite outcome
- There was no significant difference in the rates of heart failure hospitalization between treatment groups
- Overall, the average HgA1c was similar between treatment groups

Safety:

- Significantly higher rates of hypoglycemia occurred in the glimepiride group compared to linagliptin

Cost:

- The cost of using linagliptin over glimepiride must be balanced against the cost-savings from avoiding hypoglycemic episodes

Special Considerations/Populations:

- The majority of patients did not have established cardiovascular disease at baseline

Grade of Recommendation: **A**

CAST

Echt DS, Liebson PR, Mitchell LB, et al. Mortality and morbidity in patients receiving encainide, flecainide, or placebo. The Cardiac Arrhythmia Suppression Trial.
N Engl J Med. 1991;324(12):781-788.

Objective: To determine the effect of antiarrhythmic therapy on morbidity and mortality outcomes in post-myocardial infarction patients with left-ventricular dysfunction and ventricular arrhythmia.

Primary Efficacy Measure: Death or cardiac arrest with resuscitation (either due to arrhythmia)

Participants: Patients with ventricular arrhythmia (and LV dysfunction) post-myocardial infarction

- Age ~61 years; male ~82%
- LVEF ~40%

Inclusion Criteria:

- Myocardial infarction within previous 2 years (but more than 6 days prior)
- Average of 6 or more ventricular premature depolarizations per hour on ECG monitoring
    - No runs of ventricular tachycardia of 15 or more beats at a rate of ≥ 120 bpm
- Ejection fraction ≤ 40% (≤ 55% if MI occurred within previous 90 days)

Exclusion Criteria:

- Ventricular arrhythmia causing severe symptoms, such a syncope
- Failure to meet ECG monitoring criteria

Drugs: Encainide; flecainide

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients underwent an open-label titration period to identify antiarrhythmic agents (and dosing) that provide a minimum of 80% suppression of premature ventricular depolarizations and a minimum of 90% suppression of runs of ventricular tachycardia. Patients that successfully completed the open-label period were randomized to receive an effective agent (encainide, flecainide or moricizine) or matching placebo.

Duration: Average follow-up period of 10 months

Statistical Analysis: It was determined that 4400 randomized patients would provide 85% power (alpha=0.025). The ITT population was used for the primary efficacy analysis. The use of encainide and flecainide was stopped early at the recommendation of the safety monitoring committee due to lack of demonstrated treatment benefit (and evidence of treatment harm). The results in this report are for encainide and flecainide only.

Results: A total of 1498 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. There was no significant difference in rates of non-cardiac deaths between active treatment and placebo. However, rates of cardiac death and arrest with resuscitation were significantly higher with active treatment than placebo. This significant difference was consistent for arrhythmia- and non-arrhythmia related outcomes. Deaths not due to arrhythmia were primarily attributed to acute myocardial infarction and subsequent cardiogenic shock.

Encainide (N=432) Vs Placebo (N=425)

Death or Cardiac Arrest due to Arrhythmia:
29 (6.71%) vs 12 (2.82%)

Flecainide (N=323) Vs Placebo (N=318)

Death or Cardiac Arrest due to Arrhythmia:
14 (4.33%) vs 4 (0.94%)

Total Active (N=755) Vs Total Placebo (N=743)

Death or Cardiac Arrest due to Arrhythmia:
43 (5.70%) vs 16 (2.15%); RR 2.64 (95% CI 1.60-4.36)
p=0.0004; ARI 3.54%; NNH ~28

Cardiovascular Death:
60 (7.95%) vs 21 (2.83%); p<0.0001; ARI 5.12%; NNH ~19

Limitations:

- Power set but not met – significance minimal as trial was stopped early due to safety concerns
- Patient population – post myocardial infarction with ventricular arrhythmia
- Pharmacological agents – cannot apply trial results to other antiarrhythmic medications

Level of Evidence: Level II – with major limitations

Recommendation: For these reasons, I do not recommend the use of encainide or flecainide for treatment of ventricular arrhythmia in patients with left-ventricular dysfunction post-myocardial infarction.

Efficacy:

- The use of encainide and flecainide demonstrated significantly higher cardiovascular mortality rates (arrhythmia- and non-arrhythmia related) compared to placebo

Safety:

- The trial was stopped early at the recommendation of the safety monitoring committee due to a lack of treatment benefit (and evidence of harm)

Cost:

- The cost of using either encainide or flecainide as antiarrhythmic therapy in this patient population must be considered in addition to the costs associated with higher morbidity and mortality outcomes

Special Considerations/Populations:

- Both encainide and flecainide are class IC antiarrhythmics
- This patient population had ventricular arrhythmia (mild-moderate symptoms) and left-ventricular dysfunction post-myocardial infarction

Grade of Recommendation: **B**

CATIE

Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med*. 2005;353(12):1209-1223.

Objective: To compare the efficacy and safety of first-generation and second-generation antipsychotics in patients with schizophrenia.

Primary Efficacy Measure: Discontinuation of treatment for any cause

Secondary Efficacy Measures: Specific reasons for discontinuation of treatment

Participants: Patients with schizophrenia

- Age ~41 years; male ~74%
- Age of first treatment for behavioral/emotional problem ~24 years
- Years since first antipsychotic prescribed ~14
- Exacerbation in the previous 3 months ~28%
- Clinician-rated CGI score ~4.0
    - Ranges 1-7 with higher scores indicating more severe illness

Inclusion Criteria:

- Age 18-65 years
- Diagnosed with schizophrenia
- Able to take oral medications

Exclusion Criteria:

- Schizoaffective disorder
- Cognitive disorder(s)
- Pregnant or breastfeeding
- Serious and unstable medical condition

Drugs: First-generation antipsychotic (perphenazine); second-generation antipsychotics (olanzapine, quetiapine, risperidone, ziprasidone)

Design: Randomized, double-blind, active-controlled trial

Methods: Eligible patients were randomized to receive olanzapine, quetiapine, risperidone, ziprasidone or perphenazine. Antipsychotic dosing ranged widely and was determined by the study physician. While concomitant medications were allowed during this trial the use of additional antipsychotic agents was not.

Duration: 18 months

Statistical Analysis: It was determined that the trial had 85% power to detect differences in rates of discontinuation between two atypical antipsychotics. For comparisons of an atypical antipsychotic to perphenazine or comparisons involving ziprasidone power was determined to be 76% and 58%, respectively. Power for comparisons involving ziprasidone is notably lower due to the inclusion of this agent in the trial after 40% of patients were enrolled. A level of significance (alpha) of 0.017 was used for comparisons of individual treatment groups. The mITT population (all patients that received at least one dose of study medication) were included in the analyses.

Results: A total of 1493 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. The average daily dose per treatment group was 20.1 mg for olanzapine, 543.4 mg for quetiapine, 3.9 mg for risperidone, 112.8 mg for ziprasidone and 20.8 mg for perphenazine. Rates of suicidal ideation and suicide attempts were low and similar across groups.

Efficacy

	Olanzapine (N=330)	Quetiapine (N=329)	Risperidone (N=333)	Perphenazine (N=257)	Ziprasidone (N=183)
Discontinuation of treatment for any cause:	210 (63.6%)	269 (81.8%)	245 (73.6%)	192 (74.7%)	145 (79.2%)
Discontinuation for lack of treatment efficacy:	48 (14.5%)	92 (28.0%)	91 (27.3%)	65 (25.3%)	44 (24.0%)
Discontinuation due to intolerance of treatment:	62 (18.8%)	49 (14.9%)	34 (10.2%)	40 (15.6%)	28 (15.3%)
Patient discontinued treatment:	78 (23.6%)	109 (33.1%)	101 (30.3%)	77 (30.0%)	63 (34.4%)
Median months to discontinuation:	9.2	4.6	4.8	5.6	3.5

The olanzapine group had the lowest rates of discontinuation of all treatment groups. The difference was significant when compared to quetiapine and risperidone ($p<0.017$), but not perphenazine or ziprasidone ($p>0.017$). The olanzapine group also had the lowest rates of discontinuation due to lack of treatment efficacy and discontinuation due to patient choice. However, patients in the olanzapine group experienced the highest rates of discontinuation due to intolerance of treatment. This was primarily due to weight gain or metabolic effects. The average weight gain in the olanzapine group was ~9 lbs.

Safety

	Olanzapine (N=336)	Quetiapine (N=337)	Risperidone (N=341)	Perphenazine (N=261)	Ziprasidone (N=185)
Hospitalization due to schizophrenia exacerbation:	38 (11.3%)	68 (20.2%)	51 (15.0%)	41 (15.7%)	33 (17.8%)

Olanzapine demonstrated the lowest rate of hospitalization due to schizophrenia exacerbation of all treatment groups.

Limitations:

- Criteria for power not mentioned – clinical significance likely low
    - Statistically significant differences still demonstrated
- Cannot extrapolate trial results to other antipsychotic agents or patient populations

Level of Evidence: Level II – with major limitations

Recommendation: For these reasons, I recommend the use of second-generation antipsychotic olanzapine (over the other included trial agents) for treatment of schizophrenia. However, the selection of antipsychotic medication must include consideration of patient-specific factors and treatment goals.

Efficacy:

- The rate of discontinuation for any cause was notably lower in the olanzapine group compared to other treatment groups
    - Discontinuation due to lack of treatment efficacy or due to patient choice was also lowest in the olanzapine group
    - However, discontinuation due to intolerance of treatment was highest in the olanzapine group
        - Primarily due to weight gain or metabolic changes
- The median time to discontinuation was greatest in the olanzapine group

Safety:

- Rates of hospitalization due to schizophrenia exacerbation were lowest with olanzapine

Cost:

- The cost of using olanzapine over the other antipsychotic agents must be balanced against the cost-savings achieved from prevention of acute episodes of schizophrenia (due to continued therapy and reduced hospitalizations)

Special Considerations/Populations:

- First-generation antipsychotics are potent dopamine blockers but are associated with greater rates of extrapyramidal symptoms and tardive dyskinesia
- Second-general antipsychotics are less potent dopamine blockers that bind to additional receptors (e.g. serotonin) and demonstrate lower rates of extrapyramidal symptoms and tardive dyskinesia
    - Additionally, these agents appear to be more effective in treating the negative symptoms of schizophrenia
    - However, second-generation antipsychotics demonstrate concerns for weight gain and changes in lipid and glucose metabolism

Grade of Recommendation: **B**

CHARISMA

Bhatt DL, Fox KA, Hacke W, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med*. 2006;354(16):1706-1717.

Objective: To determine the effect of aspirin plus clopidogrel compared to aspirin alone on cardiovascular outcomes in high-risk patients.

Primary Efficacy Measure: Composite of cardiovascular death, myocardial infarction or stroke

Primary Safety Measure: Severe bleeding (fatal bleeding, intracranial hemorrhage or bleeding requiring intervention)

Participants: Patients at increased risk for cardiovascular event

- Age ~64 years; male ~70%
- Documented vascular disease ~78%

Inclusion Criteria:

- Patients ≥ 45 years old
- Multiple atherothrombotic risk factors, coronary disease, cerebrovascular disease or symptomatic peripheral artery disease

Exclusion Criteria:

- Use of antithrombotic medications or NSAIDs (COX-2 inhibitors allowed)
- Other indication for clopidogrel

Drugs: Clopidogrel; aspirin

Design: Randomized, double-blind, active-comparison trial

Methods: Eligible patients were randomized to receive either clopidogrel 75 mg plus low-dose aspirin (75-162 mg) daily or placebo plus low-dose aspirin. Standard therapy (such as statins and beta-blockers) was also provided as deemed appropriate by treating physicians.

Duration: Median follow-up period of ~28 months

Statistical Analysis: It was determined that 7600 randomized patients per group (15,200 total) and 1040 primary events would achieve 90% power (alpha = 0.05). The ITT population was used for all analyses.

Results: A total of 15,603 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. Pre-specified subgroup analysis of patients with documented vascular disease demonstrates benefit favoring clopidogrel plus aspirin regarding the primary endpoint (6.9% vs 7.9%, HR 0.88 [0.77-0.998]; p=0.046). Subgroup analysis of asymptomatic patients (patients with multiple risk factors without documented cardiovascular disease) demonstrates significantly higher rates of all-cause mortality (5.4% vs 3.8%; p=0.04) and cardiovascular death (3.9% vs 2.2%; p=0.01) in the clopidogrel plus aspirin group (p=0.04 & 0.01, respectively).

Clopidogrel Plus Aspirin (N=7802) Vs Aspirin Alone (N=7801)

Primary Composite Outcome:
534 (6.84%) vs 573 (7.35%); RR 0.93 (95% CI 0.83-1.05); p=0.22

Cardiovascular Death:
238 (3.05%) vs 229 (2.94%); RR 1.04 (95% CI 0.87-1.25); p=0.68

Non-Fatal Myocardial Infarction:
146 (1.87%) vs 155 (1.99%); RR 0.94 (95% CI 0.75-1.18); p=0.59

Non-Fatal Stroke:
150 (1.92%) vs 189 (2.42%); RR 0.79 (95% CI 0.64-0.98); p=0.03; ARR 0.50%; NNT ~200

Severe Bleeding:
130 (1.67%) vs 104 (1.33%); RR 1.25 (0.95% CI 0.97-1.61); p=0.09

Fatal Bleeding:
26 (0.33%) vs 17 (0.22%); RR 1.53 (95% CI 0.83-2.82); p=0.17

Moderate Bleeding:
164 (2.10%) vs 101 (1.29%); RR 1.62 (95% CI 1.27-2.08); p<0.001; ARI 0.81%; NNH ~123

Limitations:
- The majority of patients (>75%) had documented vascular disease at baseline
- Time from qualifying event to trial entry not provided

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I do not recommend the use of clopidogrel plus aspirin over aspirin alone for further reduction of cardiovascular events in high-risk patients with or without documented vascular disease.

Efficacy:
- There was no significant difference in rates of the primary composite outcome
- The individual component of non-fatal stroke was significantly lower in the clopidogrel plus aspirin group
- Subgroup analysis of patients with baseline vascular disease demonstrated significant benefit favoring clopidogrel plus aspirin regarding the primary composite outcome
- Subgroup analysis of asymptomatic patients (those with multiple risk factors but no documented vascular disease) demonstrated significantly higher rates of cardiovascular mortality and all-cause mortality with the clopidogrel plus aspirin group

Safety:
- There was no significant difference in the rates of severe or fatal bleeding between treatment groups, however the rate of moderate bleeding was significantly higher in the clopidogrel plus aspirin group

Cost:
- The cost of using clopidogrel plus aspirin must be considered in addition to the cost of managing a bleeding event

Special Considerations/Populations:
- This trial evaluated the *chronic use* of clopidogrel plus aspirin therapy (no set stop date)
- The majority of patients had documented vascular disease at baseline - benefit of clopidogrel plus aspirin appears to be greatest in this population
- Results of subgroup analyses should be interpreted cautiously

Grade of Recommendation: **A**

CHARM-ADDED

McMurray JJ, Ostergren J, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet*. 2003;362(9386):767-771.

Objective: To determine the effect of using candesartan plus ACEi on clinical outcomes in heart failure patients with reduced left ventricular ejection fraction.

Primary Efficacy Measure: Composite of cardiovascular death or heart failure hospitalization

Participants: Patients with heart failure and reduced ejection fraction receiving ACEi therapy

- Age ~64 years; male ~79%
- LVEF ~28%; NYHA class II ~24%; class III ~73%
- Baseline beta-blocker ~55%; diuretic ~90%; aspirin ~51%

Inclusion Criteria:

- Patients ≥ 18 years old
- LVEF ≤ 40%
- NYHA functional class II-IV
- Treatment with ACEi ≥ 30 days

Exclusion Criteria:

- SCr > 3 mg/dL
- Serum potassium > 5.5 mmol/L
- Bilateral renal artery stenosis
- Symptomatic hypotension
- Myocardial infarction, stroke or cardiac surgery within previous 4 weeks

Drug: Candesartan

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients were randomized to receive candesartan or matching placebo. The starting candesartan dose was 4 mg or 8 mg, which was doubled once every 2 weeks as tolerated as determined by the forced titration protocol to a target dose of 32 mg daily by week 6.

Duration: Median follow-up period ~41 months

Statistical Analysis: It was determined that 2300 randomized patients would provide 80% power (alpha = 0.05). The ITT population was used for the efficacy analyses.

Results: A total of 2548 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. Investigators reported that ~96% of patients were on optimal dosing for ACEi. The mean daily dose for candesartan at 6 months was 24 mg (61% of patients achieved target 32 mg daily). At six months, the average blood pressure was significantly lower in the candesartan treatment group compared to placebo (-4.6 mmHg SBP & -3.0 mmHg DBP; p=0.007 & p=0.004). The candesartan group demonstrated significantly lower rates of the primary composite outcome, including significantly lower rates of both individual components. The reduction of primary composite outcome in the candesartan group was not statistically significant in the subgroup analysis of patients not on baseline beta-blocker or optimal ACEi dosing. The total number of heart failure hospitalizations was notably lower with candesartan compared to placebo (607 vs 836, respectively). However, total heart failure hospitalizations were not specified as a primary or secondary outcome for this trial (interpret this finding cautiously).

Candesartan (N=1276) Vs Placebo (N=1272)

Cardiovascular Death or Heart Failure Hospitalization:
483 (37.9%) vs 583 (45.8%); HR 0.85 (95% CI 0.75-0.96)
p=0.01; ARR 7.98%; NNT ~13

Cardiovascular Death:
302 (23.7%) vs 347 (27.3%); HR 0.83 (95% CI 0.71-0.97)
p=0.021; ARR ~3.61%; NNT ~28

Heart Failure Hospitalization:
309 (24.2%) vs 356 (28.0%); HR 0.83 (95% CI 0.71-0.97)
p=0.018; ARR ~3.77%; NNT ~27

Causes of Permanent Discontinuation:

Hypotension:
58 (4.55%) vs 40 (3.14%); p=0.079

Serum Creatinine Increase:
100 (7.84%) vs 52 (4.09%); p=0.0001; ARI 3.75%; NNH ~26

Hyperkalemia:
44 (3.45%) vs 9 (0.71%); p<0.0001; ARI 2.47%; NNH ~36

Limitations:

- External validity - cannot apply results to patients with preserved ejection fraction

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I recommend the use of candesartan in addition to ACEi to further reduce morbidity and mortality in heart failure patients NYHA class II-IV with reduced ejection fraction. However, due to the safety concerns of using an ACEi and ARB together this combination should be reserved for certain patients already receiving optimal heart failure pharmacotherapy that still experience recurrent hospitalizations. If candesartan is to be used in addition to ACEi therapy, frequent monitoring for adverse effects should be initiated to help minimize the treatment risk to the patient.

Efficacy:

- The candesartan (plus ACEi) group demonstrated significantly reduced rates of the primary composite outcome as well as both individual components of cardiovascular death and heart failure hospitalization
- It is important to note that the benefit seen with the candesartan group was not statistically significant in patients not on baseline beta-blocker or dose-optimized ACEi
- The total number of heart failure hospitalizations was notably lower with candesartan

Safety:

- Overall rates of adverse drug reactions were significantly higher with candesartan, notably SCr increase and hyperkalemia (predictable adverse effects of RAAS inhibition)

Cost:

- The cost of adding candesartan to standard therapy must be balanced against the cost-savings of preventing cardiovascular morbidity and mortality
    - However, the added cost of monitoring for and managing serum creatinine increases and hyperkalemia should also be considered

Special Considerations/Populations:

- All patients had reduced ejection fraction (≤ 40%) and were receiving ACEi therapy

Grade of Recommendation: **A**

CHARM-ALTERNATIVE

Granger CB, McMurray JJ, Yusuf S, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. *Lancet*. 2003;362(9386):772-776.

Objective: To determine the effect of candesartan on clinical outcomes in heart failure patients with reduced ejection fraction and an intolerance to ACE inhibitors.

Primary Efficacy Measure: Composite of cardiovascular death or heart failure hospitalization

Participants: Heart failure patients with reduced ejection fraction and ACEi intolerance

- Age ~66 years; male ~68%
- LVEF ~30%; NYHA class II ~48%; NYHA class III ~49%
- Baseline diuretic ~85%; beta-blocker ~55%; aspirin ~58%
- ACEi intolerance due to cough ~72%

Inclusion Criteria:

- Patients ≥ 18 years old
- NYHA Class II-IV
- LVEF ≤ 40%
- Documented intolerance to ACEis

Exclusion Criteria:

- SCr > 3 mg/dL
- Serum potassium > 5.5 mmol/L
- Bilateral renal artery stenosis
- Symptomatic hypotension
- Myocardial infarction, stroke or cardiac surgery within previous 4 weeks

Drug: Candesartan

Design: Randomized, double-blinded, placebo-controlled trial

Methods: Eligible patients were randomized to placebo or candesartan group. Starting dosing for the candesartan group was 4 mg or 8 mg daily with dose doubling every 2 weeks to a target of 32 mg daily, as tolerated.

Duration: Median follow-up period of ~34 months

Statistical Analysis: It was determined that 2000 randomized patients would provide 80% power (alpha=0.05). The ITT population was used for the efficacy analyses.

Results: A total of 2028 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. The average candesartan dose at six months was 23 mg daily (59% achieved target of 32 mg daily). The average blood pressure at 6 months was significantly lower in the candesartan treatment group compared to placebo (SBP -4.4 mmHg and DBP -3.9 mmHg; $p<0.0001$). The number of total heart failure hospitalizations was notably lower in the candesartan group compared to placebo (445 vs 608, respectively). However, total heart failure hospitalizations were not specified as a primary or secondary outcome for this trial (interpret this finding cautiously).

Candesartan (N=1013) Vs Placebo (N=1015)

Cardiovascular Death & Heart Failure Hospitalization:
334 (33.0%) vs 406 (40.0%); HR 0.70 (95% CI 0.60-0.81)
p<0.0001; ARR 7.03%; NNT ~15

Cardiovascular Death:
219 (21.6%) vs 252 (24.8%); HR 0.80 (95% CI 0.66-0.96)
p=0.02; ARR 3.21%; NNT ~32

Heart Failure Hospitalization:
207 (20.4%) vs 286 (28.2%); HR 0.61 (95% CI 0.51-0.73)
p<0.0001; ARR 7.74%; NNT ~13

Causes of Permanent Discontinuation:

Hypotension:
37 (3.65%) vs 9 (0.89%); p<0.0001; ARI 2.77%; NNH ~36

Serum Creatinine Increase:
62 (6.12%) vs 27 (2.66%); p<0.0001; ARI 3.46%; NNH ~28

Hyperkalemia:
19 (1.88%) vs 3 (0.30%); p=0.0005; ARI 1.58%; NNH ~63

Limitations:

- External validity - cannot apply results to patients with preserved ejection fraction

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I recommend the use of candesartan as an alternative to ACEis for reduction of morbidity and mortality in heart failure patients with reduced ejection fraction.

Efficacy:

- Rates of the primary composite outcome were significantly lower in the candesartan group compared to placebo
- The individual components of cardiovascular death and heart failure hospitalization occurred at significantly lower rates in the candesartan group
- Total heart failure hospitalizations were notably lower in the candesartan group

Safety:

- Rates of hypotension, serum creatinine increase and hyperkalemia were significantly higher in the candesartan group (predictable adverse effects of RAAS inhibition)

Cost:

- The cost of addition candesartan to standard therapy must be balanced against the cost-savings of preventing cardiovascular morbidity and mortality
    - However, the added cost of monitoring for and managing serum creatinine increases and hyperkalemia should also be considered

Special Considerations/Populations:

- These results cannot be applied to patients with preserved ejection fraction
- This patient population was unable to tolerate ACE inhibitor therapy, primarily due to the associated dry cough

Grade of Recommendation: **A**

CHARM-PRESERVED

Yusuf S, Pfeffer MA, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. *Lancet*. 2003;362(9386):777-781.

Objective: To determine the effect of candesartan on cardiovascular outcomes in heart failure patients with preserved ejection fraction.

Primary Efficacy Measure: Composite of cardiovascular death and heart failure hospitalization

Participants: Heart failure patients with preserved ejection fraction (> 40%)

- Age ~67 years; male ~60%
- LVEF ~54%; NYHA class II ~60%; class III ~37%
- Baseline diuretic ~74%; beta-blocker ~55%; aspirin ~58%; ACEi ~19%

Inclusion Criteria:

- Patients ≥ 18 years
- NYHA class II-IV
- History of cardiovascular hospitalization
- LVEF > 40%

Exclusion Criteria:

- SCr > 3 mg/dL
- Serum potassium > 5.5 mmol/L
- Bilateral renal artery stenosis
- Symptomatic hypotension
- Myocardial infarction, stroke or cardiac surgery within previous 4 weeks

Drug: Candesartan

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients were randomized to receive either candesartan or matching placebo. Candesartan was started at 4 mg or 8 mg daily and was to be doubled every 2 weeks (as tolerated) to target dose of 32 mg daily from 6 weeks on. Initially, study investigators could prescribe all treatments other than ACEis. However, after the HOPE trial results were published the use of ACEis was allowed in certain patients.

Duration: Median follow-up of period ~37 months

Statistical Analysis: It was determined that 2900 randomized patients would provide 80% power (alpha=0.05).

Results: A total of 3023 patients underwent randomization. Baseline patient characteristics were generally similar between groups, although several characteristics associated with worse prognosis were slightly higher in the candesartan group (e.g., prior myocardial infarction, diabetes, hypertension). Additionally, baseline treatments associated with reduced mortality were slightly common in the candesartan group (e.g., lipid-lowering therapy, percutaneous interventions, aspirin). At six months, the average dose of candesartan was 25 mg daily (67% of patients achieved target dose of 32 mg). By the end of the trial, ~20-23% of total patients were receiving an ACEi. While rates of the primary composite outcome and the individual components were not significantly different between treatment groups, the total number of heart failure hospitalizations was notably lower in the candesartan group (402 vs 566, respectively). However, total heart failure hospitalizations were not specified as a primary or secondary outcome for this trial (interpret this finding cautiously).

Candesartan (N=1514) Vs Placebo (N=1509)

Cardiovascular Death or Heart Failure Hospitalization:
333 (22.0%) vs 366 (24.3%); HR 0.86 (95% CI 0.74-1.00); p=0.051
Confidence interval contains 1.00

Cardiovascular Death:
170 (11.2%) vs 170 (11.3%); HR 0.95 (95% CI 0.76-1.18); p=0.635

Heart Failure Hospitalization:
241 (15.9%) vs 276 (18.3%); HR 0.84 (95% CI 0.70-1.00); p=0.047
Confidence interval contains 1.00

Cause of Permanent Discontinuation:

Hypotension:
37 (2.44%) vs 17 (1.13%); p=0.009; ARI 1.32%; NNH ~75

Serum Creatinine Increase:
72 (4.76%) vs 36 (2.39%); p=0.0005; ARI 2.37%; NNH ~42

Hyperkalemia:
22 (1.45%) vs 9 (0.60%); p=0.029; ARI 0.86%; NNH ~116

Limitations:
- External validity - cannot apply results to patients with reduced ejection fraction
- Several baseline characteristics associated with worsened outcomes were more common in the candesartan group - clinical significance uncertain
- The allowance of ACEi therapy acts as a potential confounding factor, however, the majority of patients (>75%) were not receiving an ACEi at trial completion

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I do not recommend the use of candesartan for reduction of morbidity and mortality in heart failure patients with preserved ejection fraction.

Efficacy:
- There was no significant difference in rates of the primary composite outcome between treatment groups
- Neither individual component of the composite outcome was significantly different between treatment groups

Safety:
- Rates of hypotension, serum creatinine increase and hyperkalemia were significantly higher in the candesartan group (predictable adverse effects of RAAS inhibition)

Cost:
- The cost of using candesartan must be balanced against the potential cost-savings of reduced morbidity and mortality outcomes (benefit not clearly demonstrated here)
    - However, the cost of monitoring for and managing adverse drug reactions and lab abnormalities must also be considered

Special Considerations/Populations:
- Cannot extrapolate results to heart failure patients with reduced ejection fraction
- The trial did not demonstrate clear morbidity or mortality benefit in this patient population
    - However, ARB therapy may be reasonable for other indications

Grade of Recommendation: **A**

CIBIS-II

The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomized trial. *Lancet*. 1999;353(9146):9-13.

Objective: To determine the effect of bisoprolol on morbidity and mortality outcomes in heart failure patients with reduced ejection fraction.

Primary Efficacy Measure: All-cause mortality

Secondary Efficacy Measures: All-cause hospitalization, cardiovascular death

Participants: Heart failure patients with reduced ejection fraction on standard medication therapy

- Age ~61 years; male ~80%
- NYHA class III ~83%; class IV ~17%
- LVEF ~27%

Inclusion Criteria:

- Age 18-80 years
- Diagnosis of chronic heart failure
- LVEF ≤ 35%
- NYHA class III-IV
- Clinically stable for ≥ 6 weeks (or ≥ 3 months post-MI or unstable angina)
- Stable cardiovascular therapy for 2 weeks (ACEi plus diuretic)

Exclusion Criteria:

- Uncontrolled hypertension
- Myocardial infarction/unstable angina within previous 3 months
- PCI/CABG within previous 6 months
- Previous/scheduled heart transplant
- AV block 2nd degree or more without pacemaker
- Resting HR < 60 bpm or SBP < 100 mmHg
- Renal failure
- Reversible obstructive lung disease
- Pre-existing/planned beta-blocker therapy
- Use of non-DHP/inotropic agents (except digoxin)
- Use of antiarrhythmic (except amiodarone)

Drug: Bisoprolol

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients were randomized to receive bisoprolol or matching placebo. Bisoprolol dosing started at 1.25 mg daily and was titrated up to 10 mg daily (or max tolerated dose).

Duration: Mean follow-up period of 1.3 years

Statistical Analysis: It was determined that 2500 randomized patients would provide 95% power (alpha=0.05). The ITT population was used for the primary analyses.

Results: A total of 2647 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. The most common dose of bisoprolol was 10 mg daily (~42% of patients). The trial was stopped early after meeting pre-specified criteria for mortality difference.

Placebo (N=1320) Vs Bisoprolol (N=1327)

All-Cause Mortality:
228 (17.3%) vs 156 (11.8%); HR 0.66 (95% CI 0.54-0.81)
p<0.0001; ARR 5.51%; NNT ~19

Cardiovascular Mortality:
161 (12.2%) vs 119 (8.97%); HR 0.71 (95% CI 0.56-0.90)
p=0.0049; ARR 3.23%; NNT ~31

All-Cause Hospitalization:
513 (38.9%) vs 440 (33.2%); HR 0.80 (95% CI 0.71-0.91)
p=0.0006; ARR 5.71%; NNT ~18

Heart Failure Hospitalization:
232 (17.6%) vs 159 (12.0%); HR 0.64 (95% CI 0.53-0.79)
p=0.0001; ARR 5.59%; NNT ~18

Limitations:

- External validity - cannot apply results to patients with preserved ejection fraction
- Patients included in trial were clinically stable

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I recommend the use of bisoprolol (in addition to standard medication therapy) to reduce morbidity and mortality in heart failure patients with reduced ejection fraction.

Efficacy:

- All-cause mortality was significantly lower in the bisoprolol group compared to placebo
- Rates of heart failure hospitalization and cardiovascular mortality were significantly lower in the bisoprolol group

Safety:

- Trial was stopped early due to clear evidence of mortality benefit with bisoprolol
- Rates of discontinuation were not significantly different between treatment groups

Cost:

- The cost of using bisoprolol must be balanced against the cost-savings of preventing heart failure morbidity and mortality

Special Considerations/Populations:

- Heart failure hospitalization was considered an exploratory analysis in this trial - interpret this finding cautiously

Grade of Recommendation: **A**

CLEAR OUTCOMES

Nissen SE, Lincoff AM, Brennan D, et al. Bempedoic acid and cardiovascular outcomes in statin-intolerant patients. *N Engl J Med*. Published online March 4, 2023: NEJMoa2215024.

Objective: To determine the effect of bempedoic acid on cardiovascular outcomes in high-risk patients with a statin intolerance.

Primary Efficacy Measure: Composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke or coronary revascularization

Secondary Efficacy Measures: (1) Composite of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke (2) Total myocardial infarction (3) Coronary revascularization (4) Total stroke (5) Cardiovascular death (6) All-cause mortality

Participants: Patients at high-risk for cardiovascular event with statin intolerance

- Age ~66 years; male ~52%
- Established cardiovascular disease ~70%; high-risk for primary event ~30%
- Total cholesterol ~223 mg/dL; HDL ~50 mg/dL; LDL ~139 mg/dL
- Baseline statin use ~23%; ezetimibe ~12%; fibrate ~5%; PCSK9 inhibitor ~0.6%

Inclusion Criteria:

- Age 18-85 years
- Prior cardiovascular event or high-risk for experiencing a primary event
- Unwilling or unable to tolerate statin therapy at recommended doses
    - Patients able to tolerate lower than recommended doses of statin therapy were included
- LDL-C ≥100 mg/dL while taking stable and optimized lipid-lowering therapy

Exclusion Criteria:

- Fasting triglyceride levels >500 mg/dL
- eGFR <30 mL/min
- NYHA class IV heart failure
- Uncontrolled hypertension (SBP ≥ 180 mmHg and/or DBP ≥ 110 mmHg)
- Liver disease or dysfunction

Drug: Bempedoic acid

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients underwent a run-in period of 4 weeks to assess adherence. Those that successfully completed the run-in period were randomized to receive bempedoic acid 180 mg daily or matching placebo. Use of non-statin lipid-lowering therapies (e.g., ezetimibe, fibrates, PCSK9 inhibitors) were allowed.

Duration: Median follow-up period of 40.6 months (~3.5 years)

Statistical Analysis: It was determined that 12,600 randomized patients and 1620 primary endpoints would provide 90% power (alpha=0.05). Hierarchical testing for the secondary efficacy measures (in the order listed above) was prespecified. The ITT population was used for the efficacy analyses.

Results: A total of 13,970 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. The average difference in LDL between treatment groups over the whole trial duration was -22 mg/dL in favor of the bempedoic acid treatment group. Bempedoic acid demonstrated significantly lower rates of the primary composite outcome and the first three secondary outcomes. Hierarchical testing failed after the outcome of coronary revascularization. Analyses of subsequent outcomes must be considered exploratory.

Rates of muscle related adverse events were similar between groups. There was no significant difference in the rates of new-onset diabetes or worsening hyperglycemia. Renal impairment (11.5% vs 8.6%), liver enzyme elevation (11.5% vs 8.6%), hyperuricemia (10.9% vs 5.6%), gout (3.1% vs 2.1%) and cholelithiasis (2.2 vs 1.2%) occurred at higher rates in the bempedoic acid treatment group compared to placebo.

Bempedoic Acid (N=6992) Vs Placebo (N=6978)

Primary Composite Outcome:
819 (11.7%) vs 927 (13.3%); HR 0.87 (95% CI 0.79-0.96)
p=0.004; ARR 1.57%; NNT ~64

Composite of Cardiovascular Death, Non-Fatal MI or Non-Fatal Stroke:
575 (8.22%) vs 663 (9.50%); HR 0.85 (95% CI 0.76-0.96)
p=0.006; ARR 1.28%; NNT ~79

Fatal & Non-Fatal Myocardial Infarction:
261 (3.73%) vs 334 (4.79%); HR 0.77 (95% CI 0.66-0.91)
p=0.002; ARR 1.05%; NNT ~95

Non-Fatal Myocardial Infarction:
236 (3.38%) vs 317 (4.54%); HR 0.73 (95% CI 0.62-0.87); ARR 1.17%; NNT ~86

Coronary Revascularization:
435 (6.22%) vs 529 (7.58%); HR 0.81 (95% CI 0.72-0.92)
p=0.001; ARR 1.36%; NNT ~74

Fatal & Non-Fatal Stroke:
135 (1.93%) vs 158 (2.26%); HR 0.85 (95% CI 0.67-1.07); p=0.16

Non-Fatal Stroke:
119 (1.70%) vs 144 (2.06%); HR 0.82 (95% CI 0.64-1.05)

Cardiovascular Death:
269 (3.84%) vs 257 (3.68%); HR 1.04 (95% CI 0.88-1.24)

All-Cause Mortality:
434 (6.21%) vs 420 (6.02%); HR 1.03 (95% CI 0.90-1.18)

Limitations:

- Included patients were unable to tolerate statin therapy at recommended doses
    - Cannot apply trial results to patients receiving statin therapy at guideline recommended dosing
- The majority of patients included in this trial had history of cardiovascular disease and were being treated for secondary prevention

Level of Evidence: Level I – with minor limitations

Recommendation: For these reasons, I recommend the use of bempedoic acid as a safe and effective lipid-lowering therapy to reduce the risk for cardiovascular outcomes in patients unable to tolerate statin therapy.

Efficacy:

- Rates of the primary composite outcome were significantly lower in the bempedoic acid group
    - Of the individual components of the composite outcome, non-fatal myocardial infarction and coronary revascularization occurred significantly less often in the bempedoic acid group
    - Rates of non-fatal stroke and cardiovascular death were not significantly difference between treatment groups
- Rates of the secondary composite outcome (cardiovascular death, non-fatal myocardial infarction and non-fatal stroke) occurred at significantly lower rates in the bempedoic acid treatment group
    - However, as with the primary composite outcome this benefit was largely driven by reductions in morbidity rather than mortality
- Rates of all-cause mortality and cardiovascular death were similar between treatment groups

Safety:

- Rates of muscle related adverse reactions were similar between groups
- There was no significant difference in the rates of new-onset diabetes or worsening hyperglycemia
- Renal impairment, liver enzyme elevation, hyperuricemia, gout and cholelithiasis occurred at higher rates in the bempedoic acid treatment group compared to placebo

Cost:

- The cost of using bempedoic acid must be balanced against the cost-savings achieved from reduced rates of cardiovascular morbidity outcomes

Special Considerations/Populations:

- Bempedoic acid inhibits ATP citrate lyase
- Patients included in this trial were unable to tolerate statin therapy at recommended doses

Grade of Recommendation: **A**

COGENT

Bhatt DL, Cryer BL, Contant CF, et al. Clopidogrel with or without omeprazole in coronary artery disease. *N Engl J Med*. 2010;363(20):1909-1917.

Objective: To determine the safety and efficacy of clopidogrel and aspirin plus omeprazole in patients with coronary artery disease.

Primary Safety Measure: Composite of overt gastroduodenal bleed, overt upper gastrointestinal bleed, gastrointestinal bleed with Hgb decrease ≥ 2 g/dL (occult bleed), symptomatic duodenal ulcer, gastrointestinal pain lasting ≥ 3 days plus five or more gastroduodenal ulcers, obstruction or perforation

Primary Efficacy Measure: Composite of cardiovascular death, non-fatal myocardial infarction, coronary revascularization or ischemic stroke

Participants: Patients with history of cardiovascular disease

- Age ~69 years; male ~68%
- History of PCI ~71%; acute coronary syndrome ~42%

Inclusion Criteria:

- Age ≥ 21 years
- Anticipated use of clopidogrel plus aspirin for next 12 months

Exclusion Criteria:

- Hospitalized patients not expected to be discharged within 48 hours
- Need for PPI, H2RA, sucralfate or misoprostol
- Erosive esophagitis, esophageal/gastric variceal disease
- Use of P2Y12 inhibitor for more than 21 days prior to randomization
- Use of anticoagulant therapy that could not be discontinued

Drug: Omeprazole

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients were randomized to receive a fixed-dose combination of clopidogrel 75 mg and omeprazole 20 mg once daily or clopidogrel 75 mg alone. All patients received aspirin 75 mg to 325 mg daily.

Duration: Median follow-up period of 106 days (~3 months)

Statistical Analysis: The trial was designed to be continued until 143 gastrointestinal events had occurred. However, the trial was terminated early when the sponsor pulled funding. Two authors analyzed the data separately and reconciled any discrepancies. All tests were two-sided with a p-value < 0.05 considered statistically significant.

Results: A total of 3873 patients underwent randomization (only 3761 included in final analyses). Baseline patient characteristics were similar between treatment groups. There was no significant difference in overall rates between treatment groups. However, the omeprazole group demonstrated a significantly higher rate of diarrhea (p=0.01).

Omeprazole (N=1876) Vs Placebo (N=1885)

Primary Composite Outcome:
13 (0.69%) vs 38 (2.02%); HR 0.34 (95% CI 0.18-0.63)
p<0.001; ARR 1.32%; NNT ~76

Overt Gastroduodenal Bleed:
1 (0.05%) vs 8 (0.42%); p=0.03

Overt Upper Gastrointestinal Bleed:
1 (0.05%) vs 7 (0.37%); p=0.03

Occult Gastrointestinal Bleed (Hgb decrease ≥ 2 g/dL):
6 (0.32%) vs 11 (0.58%); p=0.21

Cardiovascular Composite Outcome:
55 (2.93%) vs 54 (2.86%); HR 0.99 (95% CI 0.68-1.44); p=0.96
No significant difference demonstrated in the individual components of the composite outcome

Limitations:

- Power set but not met - trial terminated early due to loss of funding (significance uncertain)
- Cannot extrapolate trial results to other PPIs
- Fixed dose combination study drug has different pharmacokinetics than the separate agents (study drug contained core of omeprazole with clopidogrel coating, which separates the release of each drug)

Level of Evidence: Level II - with major limitations

Recommendation: For these reasons, I recommend the use of omeprazole to reduce the risk of gastrointestinal bleeding in patients with coronary artery disease receiving clopidogrel plus aspirin.

Efficacy:

- The addition of omeprazole to clopidogrel and aspirin demonstrated significantly lower rates of the gastrointestinal composite outcome compared to placebo
- The individual components of duodenal bleeding and upper gastrointestinal bleeding were significantly lower in the omeprazole group

Safety:

- There was no significant difference in the rates of cardiovascular outcomes between treatment groups, however as the trial was stopped early this result should be interpreted cautiously (potential for type II error, aka false negative)

Cost:

- The cost of adding omeprazole to dual antiplatelet therapy must be balanced against the cost-savings of preventing gastrointestinal bleeding events

Special Considerations/Populations:

- Clopidogrel and omeprazole are irreversible inhibitors - separation of dosing could minimize any potential drug interaction (decreased efficacy of clopidogrel via 2C19 inhibition) while still providing GI protection (due to short half-life of omeprazole)
- The long-term risks of PPI therapy must be considered and the need for continued PPI therapy evaluated periodically

Grade of Recommendation: **B**

COMET

Poole-Wilson PA, Swedberg K, Cleland JG, et al. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol or Metoprolol European Trial (COMET): randomized controlled trial. *Lancet*. 2003;362(9377):7-13.

Objective: To compare the effects of carvedilol and metoprolol tartrate on morbidity and mortality outcomes in patients with heart failure and reduced ejection fraction.

Primary Efficacy Measures: (1) All-cause mortality (2) Composite of all-cause mortality and all-cause hospitalization

Participants: Patients with heart failure and reduced ejection fraction on stable therapy

- Age ~62 years; male ~79%
- LVEF ~26%
- BP ~126/77 mmHg; HR ~81 bpm
- NYHA class II ~48%; class III ~48%

Inclusion Criteria:

- Symptomatic chronic heart failure (NYHA class II-IV)
- LVEF ≤ 35% within previous 3 months
- One or more cardiovascular hospitalization in previous 2 years
- Receiving stable heart failure treatment with ACEi for ≥ 4 weeks
- Receiving ≥ 40 mg daily of furosemide (or equivalent diuretic)

Exclusion Criteria:

- Recent change in treatment or use of IV inotropic therapy
- Use of non-DHP CCB or amiodarone (>200 mg daily) or other class I antiarrhythmic
- Unstable angina, myocardial infarction, stroke or PCI within previous 2 months
- Uncontrolled hypertension (SBP >170 mmHg or DBP > 105 mmHg)
- Significant valvular disease
- Ventricular arrhythmia within previous 2 months
- Resting HR < 60 bpm or sitting SBP < 85 mmHg
- Sick sinus syndrome or second/third degree AV block

Drugs: Carvedilol; metoprolol tartrate

Design: Randomized, double-blind, active-comparison trial

Methods: Eligible patients were randomized to receive either carvedilol 3.125 mg twice daily or metoprolol tartrate 5 mg twice daily initially and then titrate up every 2 weeks to the target doses of carvedilol 25 mg twice daily and metoprolol 50 mg twice daily (or max tolerated dose).

Duration: Mean follow-up period of 58 months (~5 years)

Statistical Analysis: It was determined that 1020 mortality events would be required to achieve 80% power for the endpoint of all-cause mortality (alpha = 0.04). It was determined that 2400 events would be required to achieve 80% power for the composite endpoint of all-cause mortality and all-cause hospitalization (alpha = 0.01). The ITT population was used for all analyses.

Results: A total of 3029 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. The average carvedilol dose was 41.8 mg daily with 75% of the group achieving 25 mg twice daily. The average metoprolol tartrate dose was 85 mg daily with 78% of the group achieving 50 mg twice daily. The overall rates of adverse events were similar between treatment groups. Bradycardia occurred in 10% of the carvedilol group and 9% in the metoprolol group.

Carvedilol (N=1511) Vs Metoprolol Tartrate (N=1518)

All-Cause Mortality:
512 (33.9%) vs 600 (39.5%); HR 0.83 (95% CI 0.74-0.93)
p=0.002; ARR 5.64%; NNT ~18

Cardiovascular Death:
438 (29.0%) vs 534 (35.2%); HR 0.80 (95% CI 0.70-0.90)
p=0.0004; ARR 6.19%; NNT ~17

All-Cause Mortality & All-Cause Hospitalization:
1116 (73.9%) vs 1160 (76.4%)
HR 0.94 (95% CI 0.86-1.02); p=0.122

Limitations:

- Cannot extrapolate trial results to long-acting formulation of metoprolol (not available at time of trial)
- Very few NYHA class IV patients were included in this trial and thus these results should be interpreted cautiously for this patient population
- Cannot apply trial results to patients with heart failure and preserved ejection fraction

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I recommend the use of carvedilol over metoprolol tartrate to further reduce mortality rates in patients with heart failure and reduced ejection fraction receiving stable medication therapy.

Efficacy:

- There were significantly lower rates of mortality in the carvedilol treatment group compared to metoprolol tartrate, driven primarily by reductions in cardiovascular deaths
- There was no significant difference in rates of the composite outcome, which indicates a lack of significant treatment difference in terms of reduced all-cause hospitalization

Safety:

- Rates of adverse events (including bradycardia) were similar between treatment groups

Cost:

- The cost of using carvedilol over metoprolol tartrate must be balanced against the cost-savings of reduced cardiovascular mortality rates

Special Considerations/Populations:

- The vast majority of patients were NYHA class II-III
- Carvedilol and metoprolol tartrate have different mechanisms of action, which should be considered when selecting therapy

Grade of Recommendation: **A**

COMPASS

Connolly SJ, Eikelboom JW, Bosch J, et al. Rivaroxaban with or without aspirin in patients with stable coronary artery disease: an international, randomized, double-blind, placebo-controlled trial. *Lancet*. 2018;391(10117):205-218.

Objective: To determine the efficacy and safety of rivaroxaban plus aspirin compared to rivaroxaban alone for secondary prevention of cardiac events.

Primary Efficacy Measure: Composite of cardiovascular death, stroke and myocardial infarction

Primary Safety Measure: Major bleeding (fatal bleeding, hospitalization for bleeding, symptomatic bleed of a critical organ and bleeding into a surgical site requiring reoperation)

Participants: Patients with established ASCVD

- Age ~68 years; male ~88%
- Coronary artery disease ~91%; peripheral artery disease ~27%
- Baseline ACEi/ARB ~71%; beta-blocker ~70%; lipid-lowering therapy ~90%

Inclusion Criteria:

- Peripheral arterial disease and/or coronary artery disease
    - Patients with coronary artery disease < 65 years old must have documented atherosclerosis of 2 or more vascular beds (or 2 additional risk factors)

Exclusion Criteria:

- High bleed risk
- Stroke within previous 30 days
- History of hemorrhagic stroke
- Heart failure with LVEF < 30% or NYHA III-IV
- eGFR < 15 mL/min
- Current indication for DAPT, anticoagulant or antiplatelet therapy

Drugs: Rivaroxaban; aspirin

Design: Randomized, double-blind, active-comparison trial

Methods: Eligible patients underwent a run-in period to assess adherence and safety. Those who completed the run-in period were then randomized 1:1:1 to either rivaroxaban 2.5 mg twice daily plus aspirin 100 mg once daily, rivaroxaban 5 mg twice daily plus placebo or aspirin 100 mg once daily plus placebo. Additionally, patients not receiving a proton-pump inhibitor at baseline were randomized to receive pantoprazole 40 mg once daily or matching placebo.

Duration: Mean follow-up period of 23 months

Statistical Analysis: It was determined that 27,400 randomized patients and 2200 primary events would achieve 90% power (alpha=0.05). The ITT population was used for primary efficacy analyses.

Results: A total of 27,395 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. The safety monitoring committee stopped the trial early after pre-specified criteria were met demonstrating superiority of rivaroxaban plus aspirin compared to aspirin alone. The most common site of major bleeding for each treatment group was gastrointestinal.

Rivaroxaban 2.5 mg Plus Aspirin (N=9152) Vs Aspirin Alone (N=9126)

Primary Composite Endpoint:
379 (4.14%) vs 496 (5.44%); HR 0.76 (95% CI 0.66-0.86)
p<0.001; ARR 1.29%; NNT ~74

Cardiovascular Death:
160 (1.75%) vs 203 (2.22%%); HR 0.78 (95% CI 0.64-0.96)
p=0.02; ARR 0.48%; NNT ~210

Stroke:
83 (0.91%) vs 142 (1.56%); HR 0.58 (95% CI 0.44-0.76)
p<0.001; ARR 0.65%; NNT ~155
No significant difference in rates of hemorrhagic stroke

Myocardial Infarction:
178 (1.94%) vs 205 (2.25%); HR 0.86 (95% CI 0.70-1.05); p=0.14

Major Bleeding:
288 (3.15%) vs 170 (1.86%); HR 1.70 (95% CI 1.40-2.05)
p<0.001; ARI 1.28%; NNH ~77
Rates of fatal bleeding were not significantly different between treatment groups

Rivaroxaban 5 mg Alone (N=9117) Vs Aspirin Alone (N=9126)

Primary Composite Endpoint:
448 (4.91%) vs 496 (5.44%); HR 0.90 (95% CI 0.79-1.03); p=0.12

Major Bleeding:
255 (2.80%) vs 170 (1.86%); HR 1.51 (95% CI 1.25-1.84)
p<0.001; ARI 0.93%; NNH ~107
No significant difference in rates of fatal bleeding

Limitations:

- Power set but not met due to failure to randomize the pre-specified number of patients (4 patients short - clinical significance minimal)
- Dosing of rivaroxaban in this trial must be considered
- Trial results must be considered in the context of secondary prevention - all patients had established ASCVD

Level of Evidence: Level II - with major limitations

Recommendation: For these reasons, I recommend the use of rivaroxaban 2.5 mg twice daily plus aspirin 100 mg daily over rivaroxaban 5 mg twice daily alone as well as aspirin 100 mg alone for secondary prevention in patients with established ASCVD. However, the increased rates of major bleeding must be carefully considered. It would be reasonable to reserve this treatment regimen for secondary prevention in very high-risk patients not currently receiving anticoagulation therapy.

Efficacy:

- Rivaroxaban 2.5 mg twice daily plus aspirin 100 mg once daily demonstrated significantly lower rates of the primary composite outcome compared to aspirin alone
    - The individual components of cardiovascular death and stroke occurred at significantly lower rates in the combination therapy group as well
- Rivaroxaban 5 mg twice daily did not demonstrate significantly different rates of the primary composite outcome compared to aspirin 100 mg once daily

Safety:

- Rates of major bleeding occurred at significantly higher rates in both the combination therapy group (rivaroxaban plus aspirin) and rivaroxaban 5 mg twice daily compared to aspirin 100 mg daily alone

Cost:

- The cost of adding rivaroxaban 2.5 mg twice daily to current therapy must be balanced against the cost-savings of preventing a major cardiac event
- The cost of monitoring for and managing major bleeding events must also be considered

Special Considerations/Populations:

- Most patients had coronary artery disease at baseline (~91%)
- The dose of aspirin used in this trial was 100 mg daily
- Comparison of the NNT for the primary efficacy outcome and the NNH for the primary safety outcome estimates a small net benefit (NNT vs NNH; 74 vs 77)

Grade of Recommendation: **B**

CONSENSUS

CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med*. 1987;316(23):1429-1435.

Objective: To determine the effect of enalapril on mortality outcomes in patients with severe congestive heart failure.

Primary Efficacy Measure: All-cause mortality at six months

Participants: Patient with severe congestive heart failure (NYHA class IV) receiving optimal therapy, including digoxin and diuretics

- Age ~70 years; male ~70%
- Coronary artery disease ~73%; prior myocardial infarction ~47%
- Baseline digoxin ~93%; furosemide ~98%; spironolactone ~52%; isosorbide dinitrate ~46%

Inclusion Criteria:

- Clinical diagnosis of heart failure
- NYHA class IV (symptoms at rest)

Exclusion Criteria:

- Use of ACEis
- Acute pulmonary edema
- Aortic/mitral valve stenosis
- Myocardial infarction with previous 2 months
- Unstable angina
- Planned cardiac surgery
- Right-sided heart failure due to pulmonary disease
- SCr > 3.39 mg/dL

Drug: Enalapril

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients were randomized to receive enalapril or matching placebo. Dosing of enalapril was started at 5 mg twice daily and was to be increased weekly as tolerated to a maximum of 20 mg twice daily. Use of additional medications for managing heart failure was allowed at the discretion of the investigating physician (at baseline all patients were receiving digoxin and diuretic therapy).

Duration: Mean follow-up period of 188 days (~6 months)

Statistical Analysis: It was determined that 400 randomized patients would achieve 90% power (alpha=0.05). The ITT population was used for the efficacy analysis.

Results: The trial was terminated early at the recommendation of the ethical review committee due to findings indicating clear benefit of enalapril over placebo. At the time of trial termination, a total of 253 patients had undergone randomization. Baseline patient characteristics were similar between treatment groups. The average dosing of enalapril was 18.4 mg/daily. More patients in the enalapril group saw improvement in their NYHA functional class compared to placebo. Rates of serum creatinine increase and hypotension occurred more frequently in the enalapril group. The most common reason for trial discontinuation was hypotension.

Placebo (N=126) Vs Enalapril (N=127)

All-Cause Mortality at 6 Months:
55 (43.7%) vs 33 (26.0%); p=0.002; ARR 17.7%; NNT ~6

Twelve-Month Mortality:
66 (52.4%) vs 46 (36.2%); p=0.001; ARR 16.2%; NNT ~7

Total Mortality:
68 (54.0%) vs 50 (39.4%); p=0.003; ARR 14.6%; NNT ~7

Cause of Death:

Cardiovascular Death:
64 (50.8%) vs 44 (34.6%); p=0.001; ARR 16.1%; NNT ~7

Progression of Heart Failure:
44 (34.9%) vs 22 (17.3%); p=0.001; ARR 17.6%; NNT ~6

Limitations:

- Power set but not met due to failure to randomize 400 patients - however, this was due to early trial termination (clinical significance minimal)
- Only NYHA class IV heart failure patients were included in this trial

Level of Evidence: Level II - with major limitations

Recommendation: For these reasons, I recommend the use of enalapril to reduce mortality rates in patients with severe congestive heart failure.

Efficacy:

- Six-month mortality rate was significantly lower with enalapril
- Twelve-month mortality and overall mortality were significantly lower with enalapril
- Cause of death was primarily due to progression of heart failure, which occurred at significantly lower rates in the enalapril group
- More patients in the enalapril group experienced improvement in NYHA functional class

Safety:

- Rates of hypotension and serum creatinine increase occurred more frequently in the enalapril group

Cost:

- The cost of adding enalapril to standard therapy must be balanced against the cost-savings of reducing the progression of heart failure and overall mortality rates

Special Considerations/Populations:

- Patient population was entirely NYHA class IV heart failure patients (high-risk population)

Grade of Recommendation: **A**

COPERNICUS

Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med*. 2001;344(22):1651-1658.

Objective: To determine the effect of carvedilol on mortality in patients with severe heart failure.

Primary Efficacy Measure: All-cause mortality

Participants: Patients with heart failure and reduced ejection fraction (NYHA class IV)

- Age ~63 years; male ~80%
- LVEF ~20%
- BP ~123/76 mmHg; HR ~83 bpm
- Baseline ACEi/ARB ~97%; diuretic ~99%; digoxin ~65%

Inclusion Criteria:

- Severe chronic heart failure (dyspnea/fatigue at rest)
- LVEF < 25% despite conventional treatment with ACEi/ARB plus diuretic

Exclusion Criteria:

- Heart failure secondary to valvular disease or reversible cardiomyopathy
- Cardiac transplant patient
- Severe pulmonary/renal/hepatic disease
- Revascularization/acute myocardial infarction/cerebral event/serious arrhythmia within previous 2 months
- Use of alpha-blocker, CCB or class I antiarrhythmic within the previous 4 weeks
- SBP < 88 mmHg or HR < 68 bpm or SCr > 2.8 mg/dL
- Serum potassium < 3.5 mmol/L or > 5.2 mmol/L

Drug: Carvedilol

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients were randomized to receive carvedilol or matching placebo. The initial dose of carvedilol was 3.125 mg twice daily and was to be doubled every 14 days (as tolerated) to a target dose of 25 mg twice daily. Medications other than beta-blockers could be started/adjusted as needed throughout the trial.

Duration: Mean follow-up period ~10 months

Statistical Analysis: It was determined that 900 mortality events would provide 90% power (alpha=0.05). The ITT population was used for primary analyses.

Results: A total of 2289 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. The trial was stopped early based on the recommendations of the safety board due to findings demonstrating clear mortality benefit of carvedilol over placebo. At 4 months, ~65% of patients were at target dosing of carvedilol (average dose 37 mg daily). Rates of permanent discontinuation due to adverse effects were significantly lower in the carvedilol group compared to placebo (p=0.02).

Placebo (N=1133) Vs Carvedilol (N=1156)

All-Cause Mortality:
190 (16.8%) vs 130 (11.2%); RRR 35% (95% CI 19% to 48%)
p=0.0014; ARR 5.52%; NNT ~19

Composite of Death & Heart Failure Hospitalization:
507 (44.7%) vs 425 (36.8%); RRR 24% (95% CI 13% to 33%)
p<0.001; ARR 7.98%; NNT ~13

Limitations:

- Power set but not met - due to trial being stopped early (clinical significance minimal)
- Patient population must be considered - entirely NYHA class IV

Level of Evidence: Level II - with major limitations

Recommendation: For these reasons, I recommend the use of carvedilol to further reduce morbidity and mortality in heart failure patients with reduced ejection fraction and NYHA functional class IV.

Efficacy:

- The use of carvedilol resulted in significantly reduced rates of all-cause mortality compared to placebo
- The composite of death and heart failure hospitalization was also significantly lower in the carvedilol group

Safety:

- Rates of permanent discontinuation due to adverse effects were significantly lower in the carvedilol group compared to placebo

Cost:

- The cost of using carvedilol must be balanced against the cost-savings from reducing heart failure morbidity and mortality rates

Special Considerations/Populations:

- Cannot extrapolate trial results to other beta-blockers
- All patients had severe heart failure and experienced symptoms (dyspnea/fatigue) at rest

Grade of Recommendation: **A**

CORONA

Kjekshus J, Apetrei E, Barrios V, et al. Rosuvastatin in older patients with systolic heart failure. *N Engl J Med*. 2007;357(22):2248-2261.

Objective: To determine the effect of rosuvastatin on morbidity and mortality outcomes in patients with heart failure and reduced ejection fraction.

Primary Efficacy Measure: Composite of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke

Participants: Patients with heart failure and reduced ejection fraction

- Age ~73 years; male ~76%
- LVEF ~31%
- BP ~129/76 mmHg; HR ~72 bpm
- Total cholesterol ~207 mg/dL; LDL ~137 mg/dL; HDL ~48 mg/dL
- NYHA class III ~61%; class II ~37%
- ACEi/ARB ~91%; beta-blocker ~75%; loop diuretic ~75%

Inclusion Criteria:

- Age ≥ 60 years with ischemic heart failure
- NYHA III-IV with LVEF ≤ 40% or NYHA II with LVEF ≤ 35%
- Not indicated for cholesterol lowering therapy
- Stable on optimal therapy for 2 weeks or more

Exclusion Criteria:

- Intolerance to statins
- Decompensated heart failure
- Need for inotropic therapy
- Myocardial infarction within previous 6 months
- Unstable angina/stroke within previous 3 months
- PCI/CABG/pacemaker within previous 3 months
- Uncorrected valvular heart disease
- Myocarditis/endocarditis/pericardial disease
- Liver disease/elevated liver enzymes
- Chronic muscle disease
- Elevated SCr levels (> 2.5 mg/dL)

Drug: Rosuvastatin

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients underwent a 2-4 week placebo run-in period to assess compliance. Patients that successfully complete the run-in period were then randomized to receive rosuvastatin 10 mg daily or matching placebo.

Duration: Median follow-up period ~33 months

Statistical Analysis: It was determined that 4950 randomized patients and 1422 events would achieve 90% power (alpha=0.05). The ITT population was used for the efficacy analyses.

Results: A total of 5011 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. The trial continued until a total of 1422 primary events occurred. There was no significant difference between groups in rates of the primary composite outcome. The number of individual patients that experienced a cardiovascular hospitalization was significantly lower in the rosuvastatin group. While the total number of heart failure hospitalizations was significantly lower in the rosuvastatin group, the number of individual patients hospitalized specifically for worsening heart failure was not significantly different between groups.

Placebo (N=2497) Vs Rosuvastatin (N=2514)

Primary Composite Outcome:
732 (29.3%) vs 692 (27.5%); HR 0.92 (95% CI 0.83-1.02); p=0.12

Cardiovascular Death:
487 (19.5%) vs 488 (19.4%)

Non-Fatal Myocardial Infarction:
141 (5.65%) vs 115 (4.57%)

Non-Fatal Stroke:
104 (4.16%) vs 89 (3.54%)

Cardiovascular Hospitalization:
1164 (46.6%) vs 1104 (43.9%); HR 0.92 (95% CI 0.85-0.99)
p=0.04; ARR 2.70%; NNT ~37

Worsening Heart Failure Hospitalization:
669 (26.8%) vs 622 (24.7%); HR 0.91 (95% CI 0.82-1.02); p=0.11

Lipid Values:
Mean values at baseline to month 3

LDL: 136 mg/dL to 138 mg/dL vs 137 mg/dL to 76 mg/dL; p<0.001

HDL: 47 mg/dL to 47 mg/dL vs 48 mg/dL to 50 mg/dL; p<0.001

Triglycerides: 176 mg/dL to 178 mg/dL vs 178 mg/dL to 138 mg/dL; p<0.001

Limitations:
- External validity - patients lacked clear indication for statin therapy at baseline
- Trial dosage of rosuvastatin must be considered when interpreting results (10 mg daily)

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I do not recommend the use of rosuvastatin to further reduce morbidity and mortality rates in patients with heart failure and reduced ejection fraction (with no baseline indication for statin therapy).

Efficacy:
- Rates of the primary composite outcome were not significantly different between groups
- The number of individual patients that experienced a cardiovascular hospitalization was significantly lower in the rosuvastatin group
- While the total number of heart failure hospitalizations was significantly lower in the rosuvastatin group, the number of individual patients hospitalized specifically for worsening heart failure was not significantly different between groups

Safety:
- Rates of muscle related symptoms and adverse reactions were similar between groups

Cost:
- The cost of using rosuvastatin must be balanced against the cost-savings of preventing cardiovascular hospitalizations

Special Considerations/Populations:
- This patient population did not have an indication for statin therapy at baseline
- Rosuvastatin therapy provided significant changes in lipid levels compared to placebo

Grade of Recommendation: **A**

CREDENCE

Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. *N Engl J Med*. 2019;380(24):2295-2306.

Objective: To determine the effect of canagliflozin on renal outcomes in type 2 diabetes with chronic kidney disease and albuminuria.

Primary Efficacy Measure: Composite of ESRD (dialysis for 30 days, kidney transplantation, eGFR < 15 mL/min for 30 days), SCr doubling from baseline for 30 day period or death from renal or cardiovascular causes

Secondary Efficacy Measures: (1) Composite of cardiovascular death or heart failure hospitalization (2) Composite of cardiovascular death, myocardial infarction or stroke (3) heart failure hospitalization (4) Composite of ESRD, SCr doubling or renal death (5) Cardiovascular death (6) All-cause mortality (7) Composite of cardiovascular death, myocardial infarction, stroke or hospitalization for heart failure or angina

Participants: Patients with type 2 diabetes plus albuminuric chronic kidney disease receiving stable ACEi/ARB therapy

- Age ~63 years; male ~66%
- HgA1c ~8.5%; eGFR ~56 mL/min; UACR ~927 mg/g
- History of cardiovascular disease ~50%

Inclusion Criteria:

- Age ≥ 30 years with type 2 diabetes
- HgA1c 6.5 - 12%
- eGFR 30 mL/min to less than 90 mL/min
- UACR > 300 to 5000 mg/g
- Stable ACEi/ARB therapy for 4 weeks or more

Exclusion Criteria:

- Combination therapy of the following drug classes: ACEi, ARB, direct renin inhibitor, mineralocorticoid receptor blocker
- Non-diabetic chronic kidney disease
- Type 1 diabetes
- History of dialysis or kidney transplantation

Drug: Canagliflozin

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients underwent a 2-week placebo run-in period to assess adherence. Patients that successfully completed the run-in period were then randomized to receive canagliflozin 100 mg daily or matching placebo. Dual treatment with ACEi/ARB, direct renin inhibitor or mineralocorticoid receptor blocker was not allowed.

Duration: Median follow-up period of ~2.6 years

Statistical Analysis: It was determined that 4200 randomized patients and 844 primary events would provide 90% power (alpha = 0.045). Secondary outcomes were tested sequentially (in the order noted above). Criteria for stopping the trial early were $p<0.01$ for primary outcome and $p<0.025$ for the composite of ESRD and renal/cardiovascular death during the interim analysis. The ITT population was used for all primary and secondary analyses. If the trial was stopped early, the alpha value would be 0.022 for the primary outcome and 0.038 for the secondary outcome.

Results: A total of 4401 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. The trial was stopped early by the steering committee due to meeting the pre-specified criteria. Sequential testing for the secondary outcomes progressed until cardiovascular death (failed to demonstrate a significant difference). The overall mean difference in HgA1c was -0.25% favoring the canagliflozin treatment group. The overall mean change in eGFR was -1.85 mL/min/year in the canagliflozin group compared to -4.59 mL/min/year in the placebo group (mean difference of 2.74 mL/min/year). Rates of renal death were not significantly different between treatment groups (2 deaths in the active group, 5 deaths in the placebo group).

Canagliflozin (N=2202) Vs Placebo (N=2199)

Primary Composite Endpoint:
245 (11.1%) vs 340 (15.5%); HR 0.70 (95% CI 0.59-0.82)
p=0.00001; ARR 4.34%; NNT ~24

End-Stage Renal Disease:
116 (5.27%) vs 165 (7.50%); HR 0.68 (95% CI 0.54-0.86)
p=0.002; ARR 2.23%; NNT ~45

Sustained SCr Doubling from Baseline:
118 (5.36%) vs 188 (8.55%); HR 0.60 (95% CI 0.48-0.76)
p<0.001; ARR 3.19%; NNT ~32

Cardiovascular Death:
110 (5.00%) vs 140 (6.37%); HR 0.78 (95% CI 0.61-1.00); p=0.05

Secondary Efficacy Measures:

Composite of Cardiovascular Death or Heart Failure Hospitalization:
179 (8.13%) vs 253 (11.5%); HR 0.69 (95% CI 0.57-0.83)
p<0.001; ARR 3.38%; NNT ~30

Composite of Cardiovascular Death, Myocardial Infarction or Stroke:
217 (9.85%) vs 269 (12.2%); HR 0.80 (95% CI 0.67-0.95)
p=0.01; ARR 2.38%; NNT ~42

Heart Failure Hospitalization:
89 (4.04%) vs 141 (6.41%); HR 0.61 (95% CI 0.47-0.80)
p<0.0001; ARR 2.37%; NNT ~43

Limitations:

- Power set but not met due to trial being stopped early based on meeting pre-specified criteria (clinical significance likely minimal as significant differences were demonstrated)
- The observed results were seen when canagliflozin was added to ACE/ARB therapy
- The trial excluded patients with eGFR < 30 mL/min at baseline
- Patients with microalbuminuria (UACR < 300 mg/g) were not included in this trial

Level of Evidence: Level II - with major limitations

Recommendation: For these reasons, I recommend the use of canagliflozin 100 mg once daily in addition to ACEi/ARB to further reduce renal disease progression and rates of ESRD in patients with type 2 diabetes with albuminuric chronic kidney disease.

Efficacy:

- Rates of the primary composite outcome were significantly lower in the canagliflozin group compared to placebo
    - The individual components of sustained SCr doubling and ESRD occurred at significantly lower rates in the canagliflozin group
    - The rates of cardiovascular death and renal death were not significantly different between treatment groups
- The secondary composite outcomes of (1) cardiovascular death or heart failure hospitalization and (2) cardiovascular death, myocardial infarction or stroke occurred at significantly lower rates in the canagliflozin group
    - Driven primarily by reductions in cardiovascular morbidity outcomes
- Overall HgA1c difference between treatment groups was not large (-0.25% favoring canagliflozin)

Safety:

- Overall rates of adverse drug reactions were lower in the canagliflozin group
- Rates of amputation, pancreatitis and cancer were similar between treatment groups
- While rates of diabetic ketoacidosis were higher in the canagliflozin group, investigators identified precipitating events for 10 out of 11 of the cases

Cost:

- The cost of using canagliflozin must be balanced against the cost-savings of preventing renal disease progression and ESRD

Special Considerations/Populations:

- Canagliflozin demonstrated cardiorenal benefit in this high-risk patient population
    - Benefit driven primarily by significant reductions in morbidity (not mortality)
- It is important to note that these results were seen when canagliflozin was used in addition to stable ACEi/ARB therapy
- Patient population must be considered when interpreting trial results – type 2 diabetes with diabetic kidney disease plus albuminuria (>300 to 5000 mg/g)
- Dual treatment with ACEi, ARB, direct renin inhibitor or mineralocorticoid receptor blocker was not allowed during this trial

Grade of Recommendation: **B**

CURE

Yusuf S, Zhao F, Mehta SR, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med*. 2001;345(7):494-502.

Objective: To determine the safety and efficacy of long-term dual antiplatelet therapy compared to aspirin alone in patients with acute coronary syndrome without ST-elevation.

Primary Efficacy Measures: (1) Composite of cardiovascular death, non-fatal myocardial infarction and stroke (2) 1st primary composite plus refractory ischemia

Primary Safety Measure: Bleeding complications (life-threatening, major and minor)

Participants: Patients with acute coronary syndrome without ST-segment elevation

- Age ~64 years; male ~61%
- Qualifying event - unstable angina ~75%; suspected myocardial infarction ~25%

Inclusion Criteria:

- Hospitalized within 24 hours of symptom onset without ST-segment elevation

Exclusion Criteria:

- Contraindications for antiplatelet therapy
- High bleed risk
- Severe heart failure
- Current use of anticoagulant
- Coronary revascularization within previous 3 months
- Use of intravenous GPIIb/IIIa inhibitors within previous 3 days

Drugs: Clopidogrel; aspirin

Design: Randomized, double-blind, active-comparison trial

Methods: Eligible patients were randomized to receive clopidogrel plus aspirin or aspirin plus matching placebo. Clopidogrel therapy was initiated with a loading dose of 300 mg followed by 75 mg daily for 3 to 12 months. Aspirin was dosed at 75 - 325 mg daily and was initiated simultaneously with study drugs.

Duration: Mean follow-up period of ~9 months

Statistical Analysis: It was determined that 12,500 randomized patients would provide 90% power for the first primary efficacy outcome (alpha = 0.045) and 90% power for the second primary efficacy outcome (alpha = 0.01). The ITT population was used for all analyses.

Results: A total of 12,562 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. The first primary composite outcome was significantly lower in the clopidogrel group compared to placebo, driven mainly by reduced rates of non-fatal myocardial infarction. While the second primary composite outcome did occur at significantly lower rates in the clopidogrel group, the individual rate of refractory ischemia was not significantly different between treatment groups.

Clopidogrel Plus Aspirin (N=6259) Vs Aspirin Alone (N=6303)

Cardiovascular Death, Non-Fatal Myocardial Infarction & Stroke:
582 (9.30%) vs 719 (11.4%); RR 0.80 (95% CI 0.72-0.90)
p<0.001; ARR 2.11%; NNT ~48

Cardiovascular Death:
318 (5.08%) vs 345 (5.47%); RR 0.93 (95% CI 0.79-1.08)

Non-Fatal Myocardial Infarction:
324 (5.18%) vs 419 (6.65%); RR 0.77 (95% CI 0.67-0.89)
ARR 1.47%; NNT ~68

Stroke:
75 (1.20%) vs 87 (1.38%); RR 0.86 (95% CI 0.63-1.18)

Refractory Ischemia:
544 (8.69%) vs 587 (9.31%); RR 0.93 (95% CI 0.82-1.04)

Total Bleeding:
533 (8.52%) vs 317 (5.03%); RR 1.69 (95% CI 1.48-1.94)
p<0.001; ARI 3.49%; NNH ~28

Major Bleeding:
231 (3.69%) vs 169 (2.68%); RR 1.38 (95% CI 1.13-1.67)
p=0.001; ARI 1.01%; NNH ~99
The primary location of major bleeding events was gastrointestinal

Life-Threatening Bleeding:
135 (2.16%) vs 112 (1.78%); RR 1.21 (95% CI 0.95-1.56); p=0.13
Rates of fatal bleeding were not significantly different between treatment groups

Minor Bleeding:
322 (5.14%) vs 153 (2.43%); RR 2.12 (95% CI 1.75-2.56)
p<0.001; ARI 2.72%; NNH ~36

Limitations:

- External validity - patients did not demonstrate ST-segment elevation at time of enrollment

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I recommend the use of clopidogrel 75 mg plus aspirin (75 mg to 325 mg) daily over aspirin alone to reduce rates of cardiovascular events following an acute coronary syndrome without ST-elevation. However, the increased bleeding risk is notable and periodic evaluation of the need for dual antiplatelet therapy is warranted.

Efficacy:

- Clopidogrel plus aspirin demonstrated significantly lower rates of the primary composite outcome compared to aspirin alone, driven primarily by significant lower rates of non-fatal myocardial infarction
- Rates of cardiovascular death, stroke and refractory ischemia were not significantly different between treatment groups

Safety:

- Rates of total bleeding, major bleeding and minor bleeding were all significantly higher in the clopidogrel plus aspirin group compared to aspirin alone
- However, rates of life-threatening and fatal bleeds were not significantly different between treatment groups

Cost:

- The cost of using clopidogrel plus aspirin therapy must be balanced against the cost-savings of preventing cardiac events, particularly non-fatal myocardial infarction
    - However, the cost of treating bleeding events must be considered as well

Special Considerations/Populations:

- Revascularization was not routinely performed in this patient population at time of study entry (exclusion criteria); however, revascularization could occur during the trial if the clinician deemed it necessary

Grade of Recommendation: **A**

DAPA-CKD

Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in Patients with Chronic Kidney Disease. *N Engl J Med*. 2020;383(15):1436-1446.

Objective: To determine the effect of dapagliflozin on renal outcomes in chronic kidney disease patients with or without type 2 diabetes.

Primary Efficacy Measure: Composite of sustained ≥ 50% decline in eGFR (for at least 28 days), ESRD (dialysis, kidney transplant or eGFR <15 mL/min) or cardiovascular/renal death

Participants: Patients with chronic kidney disease receiving ACEi/ARB therapy

- Age ~62 years; male ~67%
- Type 2 diabetes ~68%; eGFR ~43 mL/min; UACR ~949 mg/g

Inclusion Criteria:

- eGFR 25-75 mL/min
- UACR 200-5000 mg/g
- Stable ACEi/ARB dose for 4 weeks or more

Exclusion Criteria:

- Type 1 diabetes
- Polycystic kidney disease
- Lupus nephritis

Drug: Dapagliflozin

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients were randomized to receive dapagliflozin 10 mg daily or matching placebo.

Duration: Median follow-up period of 2.4 years

Statistical Analysis: It was determined that 681 primary events would achieve 90% power (alpha=0.05). The ITT population was used for the primary efficacy analyses. The safety analyses were performed using all randomized patients that received at least one dose of study medication.

Results: A total of 4094 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. The trial was stopped early at the recommendation of the monitoring committee due to the clearly demonstrated benefit of dapagliflozin over placebo. The treatment effect of dapagliflozin was consistent upon subgroup analysis of patients with and without type 2 diabetes. Average rates of eGFR decline were -2.86 mL/min in the dapagliflozin group and -3.79 mL/min in the placebo group. There was no significant difference in discontinuation rates, amputations, or fractures.

Dapagliflozin (N=2152) Vs Placebo N=2152)

Primary Composite Outcome:
197 (9.15%) vs 312 (14.5%); HR 0.61 (95% CI 0.51-0.72)
p<0.001; ARR 5.34%; NNT ~19

≥ 50% Decline in eGFR:
112 (5.20%) vs 201 (9.34%); HR 0.53 (95% CI 0.42-0.67)
ARR 4.14%; NNT ~25

End-Stage Kidney Disease:
109 (5.07%) vs 161 (7.48%); HR 0.64 (95% CI 0.50-0.82)
ARR 2.42%; NNT ~42

Cardiovascular Death:
65 (3.02%) vs 80 (3.72%); HR 0.81 (95% CI 0.58-1.12)

Renal Death:
2 (0.09%) vs 6 (0.28%)

All-Cause Mortality:
101 (4.69%) vs 146 (6.78%); HR 0.69 (95% CI 0.53-0.88)
p=0.004; ARR 2.09%; NNT ~48

Safety:

Major Hypoglycemia:
14/2149 (0.65%) vs 28/2149 (1.30%); p=0.04; ARR 0.65%; NNT ~154

Volume Depletion:
127/2149 (5.91%) vs 90/2149 (4.19%); p=0.01; ARI 1.72%; NNH ~58

Limitations:

- Power set but not met due to trial being stopped early (clinical significance minimal)
- Trial results must be considered in addition to baseline ACEi/ARB therapy
- Patient population must be considered - chronic kidney disease patients with or without type 2 diabetes

Level of Evidence: Level II - with minor limitations

Recommendation: For these reasons, I recommend the use of dapagliflozin 10 mg daily (in addition to ACEi/ARB) to further slow the progression of chronic kidney disease and occurrence of end-stage renal disease in patients with or without type 2 diabetes.

Efficacy:

- Rates of the primary composite outcome were significantly lower in the dapagliflozin group compared to placebo
- The individual components of ≥ 50% decline in eGFR and ESRD occurred at significantly lower rates in the dapagliflozin group
- All-cause mortality was significantly lower in the dapagliflozin group compared to placebo
    - Rates of cardiovascular death were similar between groups

Safety:

- Rates of discontinuation, amputation, and fractures were not significantly different between treatment groups
- Major hypoglycemia occurred at significantly lower rates in the dapagliflozin group
- However, rates of volume depletion were significantly higher in the dapagliflozin group

Cost:

- The cost of using dapagliflozin must be balanced against the cost-savings of preventing the progression of chronic kidney disease as well as the occurrence of ESRD

Special Considerations/Populations:

- All patients were established on stable dosing with either an ACEi or ARB for 4 weeks prior to enrollment
- This trial allowed for baseline eGFR as low as 25 mL/min
- The majority of patients included in this trial had type 2 diabetes at baseline

Grade of Recommendation: **B**

DAPA-HF

McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med*. 2019;381(21):1995-2008.

Objective: To determine the effect of dapagliflozin on morbidity and mortality outcomes in heart failure patients with reduced ejection fraction with or without type 2 diabetes.

Primary Efficacy Measure: Composite of worsening heart failure (heart failure hospitalization or urgent visit requiring IV treatment for heart failure) and cardiovascular death

Participants: Patients with heart failure and reduced ejection fraction (with or without type 2 diabetes)

- Age ~66 years; male ~77%;
- NYHA class II ~67%; class III ~31%; class IV ~1%
- LVEF ~31%; HR ~72; eGFR ~66 mL/min
- History of type 2 diabetes ~42%
- Baseline ACEi ~56%; ARB ~27%; ARNi ~11%; beta-blocker ~96%; MRA ~71%

Inclusion Criteria:

- Age ≥ 18 years
- LVEF ≤ 40%
- NYHA class II-IV
- NT-proBNP ≥ 600 pg/mL (≥ 400 pg/mL if hospitalized for heart failure within prior year)
- Receiving standard heart failure therapy (ACEi/ARB/ARNi plus beta-blocker)

Exclusion Criteria:

- Type 1 diabetes
- eGFR < 30 mL/min
- Symptoms of hypotension or SBP < 95 mmHg

Drug: Dapagliflozin

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients were randomized to receive either dapagliflozin 10 mg daily or matching placebo. Standard heart failure (and type 2 diabetes) treatment was continued and adjusted if needed.

Duration: Median follow-up period of 18.2 months

Statistical Analysis: It was determined that 844 primary events were required to achieve 90% power (alpha = 0.05). The ITT population was used for all efficacy analyses.

Results: A total of 4744 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. The average HgA1c decreased by a significantly greater amount in the dapagliflozin group compared to placebo (-0.21% vs +0.04%; p<0.001). The treatment effect of dapagliflozin was consistent in patients with and without type 2 diabetes.

Dapagliflozin (N=2373) Vs Placebo (N=2371)

Primary Composite Outcome:
386 (16.3%) vs 502 (21.2%); HR 0.74 (95% CI 0.65-0.85)
p<0.001; ARR 4.91%; NNT ~21

Heart Failure Hospitalization:
231 (9.73%) vs 318 (13.4%); HR 0.70 (95% CI 0.59-0.83)
ARR 3.68%; NNT ~28

Urgent Visit Requiring IV Treatment for Heart Failure:
10 (0.42%) vs 23 (0.97%); HR 0.43 (95% CI 0.20-0.90)
ARR 0.55%; NNT ~183

Cardiovascular Death:
227 (9.57%) vs 273 (11.5%); HR 0.82 (95% CI 0.69-0.98)
ARR 1.95%; NNT ~52

Limitations:

- External validity - cannot extrapolate results to patients with preserved ejection fraction

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I recommend the use of dapagliflozin 10 mg to reduce morbidity and mortality rates in heart failure reduced ejection fraction patients with or without type 2 diabetes. However, it would be reasonable to optimize standard heart failure therapy prior to initiation of dapagliflozin to maximize overall treatment benefit.

Efficacy:

- The dapagliflozin treatment group demonstrated significantly lower rates of the primary composite outcome compared to placebo (both individual components favored dapagliflozin significantly)
- The treatment benefit of dapagliflozin was consistent in patients with and without type 2 diabetes

Safety:

- There were no significant differences in rates of volume depletion, renal adverse events, fractures, amputations, major hypoglycemia, or gangrene
- All and major hypoglycemia events occurred in patients with type 2 diabetes

Cost:

- The cost of using dapagliflozin must be balanced against the cost-savings of preventing worsening heart failure and cardiovascular death

Special Considerations/Populations:

- Results must be considered as dapagliflozin in addition to standard heart failure therapy
- Cannot extrapolate data to patients with heart failure and preserved ejection fraction

Grade of Recommendation: **A**

DAPT

Mauri L, Kereiakes DJ, Yeh RW, et al. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *N Engl J Med*. 2014;371(23):2155-2166.

Objective: To assess the efficacy and safety of extended dual antiplatelet therapy beyond 12 months compared to 12 months only in patients with drug-eluting stents.

Primary Efficacy Measures: (1) Stent thrombosis (2) Composite of cardiovascular death, myocardial infarction or stroke

Primary Safety Measure: Moderate/severe bleeding

Participants: Patients with drug-eluting stent that have completed 12 months of dual antiplatelet therapy with no major issues/events

- Age ~62 years; male ~75%
- Indication for PCI - stable angina ~38%; NSTEMI ~16%; STEMI ~10%
- P2Y12 inhibitor during open-label period - clopidogrel ~65%; prasugrel ~35%

Inclusion Criteria:

- Age ≥ 18 years
- Drug-eluting stent
- Completed 12 months of dual antiplatelet therapy

Exclusion Criteria:

- Stent diameter <2.25 mm or > 4.0 mm
- Pregnancy
- Discontinuation of DAPT for > 14 days within first 30 days
- Life expectancy < 3 years
- Long-term warfarin use
- Use of both bare-metal stent and drug-eluting stent

Drugs: Clopidogrel; prasugrel; aspirin

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients were given open-label aspirin plus P2Y12 inhibitor for 12 months starting within 72 hours of drug-eluting stent placement. Those who did not experience a MACE, cerebrovascular event, repeat revascularization or severe bleeding event were eligible for randomization into the extended treatment trial. Patients were randomized to either continue dual antiplatelet therapy or take aspirin plus placebo for an additional 18-month period. Aspirin was dosed at 75 mg to 162 mg daily and was to be continued indefinitely. At the end of this period, patients were assessed for an additional 3-months to determine the effect of P2Y12 inhibitor discontinuation.

Duration: 18 months

Statistical Analysis: The primary efficacy endpoint was designed for superiority analysis. It was determined that 9800 randomized patients would achieve 85% power (alpha = 0.05). The ITT population was used for the efficacy analyses. The primary safety endpoint was designed for non-inferiority analysis with a non-inferiority margin of 0.8%. For the non-inferiority analysis, it was determined that 9960 randomized patients would achieve 80% power. The non-inferiority analysis was performed on all patients that completed a total of 17 months of follow-up post-randomization or had experienced a moderate-to-severe bleeding event.

Results: A total of 9961 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. The increased rate of all-cause mortality in the dual antiplatelet therapy group was driven mainly by non-cardiovascular deaths of bleeding secondary to fatal trauma and cancer. Rates of cardiovascular death were not significantly different between treatment groups.

Dual Antiplatelet Therapy (N=5020) Vs Aspirin Alone (N=4941)

Stent Thrombosis:
19 (0.38%) vs 65 (1.32%); HR 0.29 (95% CI 0.17-0.48)
p<0.001; ARR 0.94%; NNT ~107

Composite of Death, Myocardial Infarction & Stroke:
211 (4.20%) vs 285 (5.77%); HR 0.71 (95% CI 0.59-0.85)
p<0.001; ARR 1.56%; NNT ~64

All-Cause Mortality:
98 (1.95%) vs 74 (1.50%); HR 1.36 (95% CI 1.00-1.85); p=0.05
95% CI contains 1.00 - cannot be considered significantly different

Cardiac Death:
45 (0.90%) vs 47 (0.95%); HR 1.00 (95% CI 0.66-1.52); p=0.98

Myocardial Infarction:
99 (1.97%) vs 198 (4.01%); HR 0.47 (95% CI 0.37-0.61);
p<0.001; ARR 2.04%; NNT ~50

Stroke:
37 (0.74%) vs 43 (0.87%); HR 0.80 (95% CI 0.51-1.25); p=0.32

Composite of Moderate & Severe Bleeding:
119/4710 (2.53%) vs 73/4649 (1.57%)
p<0.001; ARR 0.96%; NNH ~104
Rates of severe bleeding and fatal bleeding were not significantly different

Limitations:

- Different types of drug-eluting stent were allowed (potential confounding factor)
- Patients included in this extended treatment trial had all already successfully completed 12 months of dual antiplatelet therapy

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I recommend continued dual antiplatelet therapy greater than 12 months for further prevention of thrombosis and cardiac events. However, the increased risk for bleeding events must be carefully considered when deciding whether or not to prolong therapy. If the decision to stop dual antiplatelet therapy is made it is important to continue use of aspirin (75 mg to 162 mg) indefinitely.

Efficacy:

- Rates of stent thrombosis were significantly lower in the dual antiplatelet therapy group compared to aspirin alone
- The cardiovascular composite occurred at significantly lower rates in the dual antiplatelet therapy group, driven primarily by reduced rates of myocardial infarction

Safety:

- Rates of moderate/severe bleeding events were significantly higher in the dual antiplatelet therapy group
- However, there was no significant difference in the rates of severe or fatal bleeds

Cost:

- The cost of extended dual antiplatelet therapy must be balanced against the cost-savings of preventing stent thrombosis and cardiac events
- However, the increased cost of treating bleeding events must also be considered

Special Considerations/Populations:

- The DAPT score can be used to assess the risk/benefit of continued dual antiplatelet therapy
- Management of modifiable risk-factors for cardiac events should also be assessed when considering antiplatelet therapy adjustments
- Cannot extrapolate results of trial to dual antiplatelet therapy > 30 months

Grade of Recommendation: **A**

DECLARE-TIMI 58

Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med*. 2019;380(4):347-357.

Objective: To determine the effect of dapagliflozin on cardiovascular outcomes in type 2 diabetes.

Primary Safety Measure: Composite of cardiovascular death, myocardial infarction and ischemic stroke

Primary Efficacy Measures: (1) Composite of cardiovascular death, myocardial infarction and ischemic stroke (2) Composite of cardiovascular death and heart failure hospitalization

Participants: Patients with type 2 diabetes at increased risk for cardiovascular event

- Age ~64 years; male ~63%
- HgA1c ~8.3%; Established ASCVD ~41%

Inclusion Criteria:

- Type 2 diabetes ≥ 40 years old
- HgA1c 6.5% - 12.0%
- CrCl ≥ 60 mL/min
- Established ASCVD or multiple risk factors for ASCVD

Exclusion Criteria:

- Chronic cystitis/recurrent UTIs
- SBP > 180 mmHg or DBP > 100 mmHg
- Recent cardiovascular event within 8 weeks of randomization
- Previous treatment with SGLT2 inhibitor

Drug: Dapagliflozin

Design: Randomized, double-blind, placebo-controlled, non-inferiority trial

Methods: This trial was originally designed with one primary safety outcome (composite of major adverse cardiovascular events). However, due to results of the EMPA-REG OUTCOME trial it was decided that two primary efficacy outcomes would be included: (1) MACE and (2) composite of cardiovascular death plus heart failure hospitalization. Eligible patients underwent a 4-8 week single-blind placebo run-in. Patients that successfully completed the run-in period were then randomized to receive dapagliflozin 10 mg once daily or matching placebo. The use of other glucose-lowering agents was allowed at the discretion of the treating physician (other SGLT2 inhibitors, pioglitazone or rosiglitazone were not allowed).

Duration: Median follow-up period of ~4.2 years

Statistical Analysis: It was determined that a total of 17,150 randomized patients and 1390 events would achieve 85% power for non-inferiority. A non-inferiority margin of < 1.3 was used (alpha=0.023). If non-inferiority was demonstrated then sequential testing would occur in this order: non-inferiority testing for the two primary efficacy measures (alpha = 0.023) followed by superiority testing (alpha = 0.046). The ITT population was used for the primary safety and efficacy analyses.

Results: A total of 17,160 patients underwent randomization (40.6% had established ASCVD). Baseline patient characteristics were similar between treatment groups. Dapagliflozin demonstrated non-inferiority (but not superiority) compared to placebo for the primary safety outcome. There was a mean HgA1c difference of -0.42% favoring the dapagliflozin group throughout the trial (-0.2% at the end of the trial). There was no significant difference in the rates of amputation between treatment groups. Rates of genital infections were significantly higher in the dapagliflozin group.

Dapagliflozin (N=8582) Vs Placebo (N=8578)

Composite of Cardiovascular Death, Myocardial Infarction & Stroke:
756 (8.81%) vs 803 (9.36%); HR 0.93 (95% CI 0.84-1.03); p=0.17

Composite of Cardiovascular Death & Heart Failure Hospitalization:
417 (4.86%) vs 496 (5.78%); HR 0.83 (95% CI 0.73-0.95)
p=0.005; ARR 0.92%; NNT ~109

Cardiovascular Death:
245 (2.85%) vs 249 (2.90%); HR 0.98 (95% CI 0.82-1.17)

Myocardial Infarction:
393 (4.58%) vs 441 (5.14%); HR 0.89 (95% CI 0.77-1.01)

Ischemic Stroke:
235 (2.74%) vs 231 (2.69%); HR 1.01 (95% CI 0.84-1.21)

Heart Failure Hospitalization:
212 (2.47%) vs 286 (3.33%); HR 0.73 (95% CI 0.61-0.88)
ARR 0.86%; NNT ~116

Safety:

Genital Infection:
76 (0.89%) vs 9 (0.10%); HR 8.36 (95% CI 4.19-16.68)
p<0.001; ARI 0.78%; NNH ~128

Limitations:

- The majority of patients in this trial did not have established ASCVD at baseline, however, results did not differ upon subgroup analysis

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I recommend the use of dapagliflozin as a safe glucose-lowering agent in high-risk patients with type 2 diabetes. I do not recommend the use of dapagliflozin to reduce rates of MACE (cardiovascular death, myocardial infarction and stroke) in this patient population.

Efficacy:

- Dapagliflozin demonstrated non-inferiority (but not superiority) to placebo regarding the cardiovascular composite outcome
- No individual component of the cardiovascular composite was significantly lower in the dapagliflozin group
- Rates of heart failure hospitalization were significantly lower in the dapagliflozin group

Safety:

- Rates of amputations and UTIs were not significantly different between treatment groups
- Genital infections occurred at significantly higher rates in the dapagliflozin group

Cost:

- The cost of using dapagliflozin must be balanced against the cost-savings of avoiding heart failure hospitalizations

Special Considerations/Populations:

- The majority of patients had multiple risk factors at baseline (not established ASCVD)
- While there is clear evidence of benefit in terms of reduces heart failure hospitalizations, the rate of the MACE composite (and individual components) was similar between groups

Grade of Recommendation: **A**

DELIVER

Solomon SD, McMurray JJV, Claggett B, et al. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. *N Engl J Med*. August 27, 2022: NEJMoa2206286.

Objective: To determine the effect of dapagliflozin on morbidity and mortality outcomes in heart failure patients with mildly reduced or preserved ejection fraction (with or without type 2 diabetes).

Primary Efficacy Measure: Composite of worsening heart failure (heart failure hospitalization or urgent care visit) and cardiovascular death

Participants: Heart failure patients with preserved ejection fraction

- Age ~72 years; male ~56%
- LVEF ~54%
- NYHA class II ~75%; class III ~24%
- Baseline type 2 diabetes ~45%

Inclusion Criteria:

- Age ≥ 40 years
- Stabilized heart failure (with or without type 2 diabetes)
- LVEF > 40%
- Evidence of structural heart disease
- Elevated natriuretic peptide level

Exclusion Criteria:

- Type 1 diabetes
- eGFR < 25 mL/min
- Acute coronary syndrome within the prior 12 weeks

Drug: Dapagliflozin

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients were randomized to receive dapagliflozin 10 mg once daily or matching placebo. Usual therapy for heart failure was continued for each patient.

Duration: Median follow-up period of 2.3 years

Statistical Analysis: It was determined that 6100 randomized patients and 1117 primary events would provide 93% power (alpha = 0.024). The ITT population was used for all analyses.

Results: A total of 6263 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. In patients treated with dapagliflozin there were significantly lower rates of the primary composite outcome. This was primarily driven by a significantly lower rate of heart failure hospitalization. Trial results were consistent in patients with and without type 2 diabetes. Likewise, results were consistent in patients with LVEF less than and greater than 60%. This demonstrates a lack of attenuated treatment benefit with higher ejection fractions (however, this is only a subgroup analysis). Rates of adverse effects were similar between treatment groups. There were no documented cases of Fournier's gangrene.

Dapagliflozin (N=3131) Vs Placebo (N=3132)

Cardiovascular Death or Worsening Heart Failure:
512 (16.4%) vs 610 (19.5%); HR 0.82 (95% CI 0.73-0.92)
p<0.001; ARR 3.12%; NNT ~32

Cardiovascular Death:
231 (7.38%) vs 261 (8.33%); HR 0.88 (95% CI 0.74-1.05)

Heart Failure Hospitalization or Urgent Care Visit:
368 (11.8%) vs 455 (14.5%); HR 0.79 (95% CI 0.69-0.91)
ARR 2.77%; NNT ~36

Heart Failure Hospitalization:
329 (10.5%) vs 418 (13.3%); HR 0.77 (95% CI 0.67-0.89)
ARR 2.84%; NNT ~36

Urgent Care Visit (due to heart failure):
60 (1.92%) vs 78 (2.49%); HR 0.76 (95 % CI 0.55-1.07)

Total Worsening Heart Failure Events and Cardiovascular Deaths:
815 vs 1057; HR 0.77 (95 % CI 0.67-0.89); p<0.001

Limitations:
- Patient population – no patient had heart failure with reduced ejection fraction

Level of Evidence: Level I – with minor limitations

Recommendation: For these reasons, I recommend the use of dapagliflozin (in addition to standard heart failure care) to further reduce the risk for worsening heart failure events in patients with preserved ejection fraction (with or without the presence of type 2 diabetes).

Efficacy:
- Treatment with dapagliflozin demonstrated significantly lower rates of the primary composite outcome (cardiovascular death or worsening heart failure) compared to placebo
    - Treatment benefit was primarily due to lower rates of heart failure hospitalizations
    - There was no significant difference in the rate of cardiovascular death
- Trial results were consistent upon subgroup analysis of patients with and without type 2 diabetes as well as those with LVEF less than and greater than 60%

Safety:
- Rates of adverse effects were similar between treatment groups
- There were no cases of Fournier's gangrene

Cost:
- The cost of using dapagliflozin must be balanced against the cost-savings of preventing worsening heart failure events, specifically heart failure hospitalization

Special Considerations/Populations:
- Trial results cannot be applied to patients with reduced ejection fraction

Grade of Recommendation: **A**

DIG

Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med*. 1997;336(8):525-533.

Objective: To determine the long-term effects of digoxin on morbidity and mortality outcomes in patients with heart failure.

Primary Efficacy Measure: All-cause mortality

Secondary Efficacy Measures: Cardiovascular death, heart failure death, heart failure hospitalization

Participants: Patients with heart failure reduced ejection fraction with normal sinus rhythm

- Age ~63 years; male ~78%
- LVEF ~28%
- NYHA class II ~54%; NYHA class III ~30%
- Baseline ACEi ~94%; diuretic ~82%

Inclusion Criteria:

- LVEF ≤ 45%
- Normal sinus rhythm
- Diagnosis of heart failure

Exclusion Criteria:

- Age < 21 years
- Unstable angina 1 month prior
- Myocardial infarction/cardiac surgery/PTCA within previous 4 weeks
- Atrial fibrillation or atrial flutter
- II-III degree AV block without pacemaker
- Serum potassium levels < 3.2 mmol/L or > 5.5 mmol/L
- SCr > 3.0 mg/dL

Drug: Digoxin

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients were randomized to receive digoxin or placebo. The dose of digoxin could be adjusted by investigators based on several factors. The use of ACEis was strongly encouraged. Other therapies for managing heart failure symptoms (such as diuretics) were allowed.

Duration: Mean follow-up period of 37 months (~3 years)

Statistical Analysis: It was determined that 7,000 randomized patients would achieve 90% power (alpha = 0.05). The ITT population was used for analyses.

Results: A total of 6800 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. The initial starting dose for the majority of patients in the digoxin group was 0.25 mg daily. Average digoxin serum level at 12 months was 1.02 nmol/L (standard target range 0.5 to 2.0 nmol/L).

Digoxin (N=3397) Vs Placebo (N=3403)

All-Cause Mortality:
1181 (34.8%) vs 1194 (35.1%); RR 0.99 (95% CI 0.91-1.07); p=0.80

Cardiovascular Death:
1016 (29.9%) vs 1004 (29.5%); RR 1.01 (95% CI 0.93-1.10); p=0.78

Worsening Heart Failure Death:
394 (11.6%) vs 449 (13.2%); RR 0.88 (95% CI 0.77-1.01); p=0.06

Heart Failure Hospitalizations:
910 (26.8%) vs 1180 (34.7%); RR 0.72 (95% CI 0.66-0.79)
p<0.001; ARR 7.89%; NNT ~13

Safety:

Hospitalization due to Suspected Digoxin Toxicity:
67 (1.97%) vs 31 (0.91%); RR 2.17 (95% CI 1.42-3.32)
p<0.001; ARI 1.06%; NNH ~94

Limitations:

- Power set but not met - failed to enroll enough participants (clinical significance likely low)
- Results cannot be applied to patients with heart failure and preserved ejection fraction
- Beta-blockers were not used in this trial

Level of Evidence: Level II - with major limitations

Recommendation: For these reasons, I do not recommend the use of digoxin to reduce mortality rates in patients with heart failure and reduced ejection fraction. However, in patients who do not tolerate beta-blockers the use of digoxin could be justified to reduce the risk of heart failure hospitalization.

Efficacy:

- There was no significant difference in rates of all-cause mortality, cardiovascular death or heart failure death between treatment groups
- Rates of heart failure hospitalization were significantly lower in the digoxin group compared to placebo

Safety:

- Hospitalization due to suspected digoxin toxicity occurred at significantly higher rates in the digoxin treatment group compared to placebo

Cost:

- The cost of using digoxin must be balanced against the cost-savings of preventing heart failure hospitalizations
- However, the cost of monitoring digoxin serum levels must also be considered

Special Considerations/Populations:

- Cannot apply results to patients on beta-blocker therapy (not included in this trial)
- Treatment effect must be considered in addition to ACEi (with or without diuretic therapy)
- Cannot apply results to patients with heart failure and preserved ejection fraction

Grade of Recommendation: **B**

DISCOVER

Mayer KH, Molina JM, Thompson MA, et al. Emtricitabine and tenofovir alafenamide vs emtricitabine and tenofovir disoproxil fumarate for HIV pre-exposure prophylaxis (DISCOVER): primary results from a randomized, double-blind, multicenter, active-controlled, phase 3, non-inferiority trial. *Lancet*. 2020;396(10246):239-254.

Objective: To compare the efficacy and safety of tenofovir alafenamide (TAF) to tenofovir disoproxil fumarate (TDF) when used in combination with emtricitabine (FTC) for prevention of HIV infection in cisgender men who have sex with men (MSM) and transgender women that have sex with men.

Primary Efficacy Measure: Incident HIV infection

Secondary Safety Measures: Percentage changes from baseline to week 48 regarding (1) hip bone mineral density (2) spine bone mineral density (3) urine beta-2 microglobulin to creatinine ratio (4) retinol-binding protein to creatinine ratio (5) changes in the distribution of urine protein to creatinine ratio above 22.6 mg/mmol (6) change in serum creatinine from baseline

Participants: Patients at increased risk for HIV infection

- Age ~34 years
- Cisgender men ~98%; transgender women ~2%
- High-risk sexual behavior ~61%
- eGFR ~122 mL/min

Inclusion Criteria:

- Adult (≥ 18 years) MSM or transgender women who have sex with men
- High-risk of acquiring HIV based on self-reported sexual behavior (within past 12 weeks) or recent history of bacterial STIs (within past 24 weeks)
    - Condomless anal sex with at least two partners
    - Syphilis, rectal gonorrhea or rectal chlamydia
- HIV-negative

Exclusion Criteria:

- Suspected or known serious active infection
- Acute hepatitis infection (A, B or C)
- Chronic hepatitis B infection
- History of osteoporosis or fragility fractures
- Impaired renal function (eGFR < 60 mL/min)

Drugs: Tenofovir disoproxil fumarate; tenofovir alafenamide; emtricitabine

Design: Randomized, double-blind, active-controlled, non-inferiority trial

Methods: Eligible patients were randomized to receive either FTC-TAF 200 mg-25 mg or FTC-TDF 200 mg-300 mg once daily (plus matching placebo). Testing for HIV was performed at follow-up visits every 12 weeks. Screening for gonorrhea, chlamydia and syphilis was also performed at follow-up visits.

Duration: 96 weeks

Statistical Analysis: It was determined that a total of 2500 randomized patients per treatment group would provide 82.5% power for determining non-inferiority. A non-inferiority margin of 1.62 and a level of significance of 0.04997 was used. The per protocol population was used for the primary efficacy analysis. The mITT population (patients that received at least one dose of study medication) was used for the safety analyses. The secondary safety outcomes would be analyzed in sequential order.

Results: A total of 5399 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. A total of 5335 patients were included in the per-protocol population and 5387 patients were included in the mITT population. For the primary efficacy analysis, FTC-TAF demonstrated non-inferiority to FTC-TDF regarding the prevention of HIV infection. FTC-TAF demonstrated superiority regarding all secondary safety outcomes. Adverse event rates were similar between treatment groups. The most common drug-related adverse events were nausea and diarrhea.

FTC-TAF (N=2670) Vs FTC-TDF (N=2665)

Incident HIV Infection:
7 vs 15; IRR 0.47 (95% CI 0.19-1.15);
IRR - incidence rate ratio

Mean Percent Change in Hip BMD:
+0.18% vs -0.99%; p<0.0001

Mean Percent Change in Spine BMD:
+0.50% vs -1.12%; p<0.0001

Mean Percent Change in Serum Creatinine:
-0.88% vs +0.88%; p<0.0001

Mean Percent Change in Creatinine Clearance:
+1.8% vs -2.3%; p<0.0001

Limitations:

- Patient population must be considered when interpreting trial results

Level of Evidence: Level I – with minor limitations

Recommendation: For these reasons, I recommend the use of once daily FTC-TAF over FTC-TDF for the prevention of HIV infection in high-risk individuals.

Efficacy:

- FTC-TAF demonstrated non-inferiority to FTC-TDF regarding incident HIV infection

Safety:

- Adverse event rates were similar between treatment groups
- FTC-TAF demonstrated superiority over FTC-TDF regarding all secondary safety measures
    - Preferable effects on bone mineral density and renal biomarkers

Cost:

- The cost of using FTC-TAF over FTC-TDF must be balanced against the cost-savings from decreased long-term complications associated with kidney damaged and loss of bone mineral density

Special Considerations/Populations:

- TDF and TAF are both prodrugs for tenofovir, however, TAF demonstrates preferable long-term effects on bone density and renal function
    - Due to more rapid uptake of active metabolite (tenofovir diphosphate) with TAF

Grade of Recommendation: **A**

Diuretic Comparison Project

Ishani A, Cushman WC, Leatherman SM, et al. Chlorthalidone vs. Hydrochlorothiazide for Hypertension-Cardiovascular Events. N Engl J Med. 2022;387(26):2401-2410.

Objective: To compare the effects of chlorthalidone and hydrochlorothiazide on cardiovascular outcomes in patients with hypertension.

Primary Efficacy Measure: Composite of non-fatal cardiovascular event or non-cancer-related death

- Non-fatal cardiovascular events were defined as: myocardial infarction, stroke, hospitalization for heart failure or urgent revascularization for unstable angina

Participants: VA Healthcare System patients with hypertension receiving HCTZ

- Age ~72 years; male ~97%
- SBP ~139 mmHg; HCTZ dose 25 mg ~94%
- Receiving only one antihypertensive agent ~16%; two agents ~34%; three agents ~33%

Inclusion Criteria:

- Age ≥ 65 years
- Diagnosis of hypertension
- Systolic blood pressure ≥ 120 mmHg at most recent clinic visit
- Receiving hydrochlorothiazide 25-50 mg daily

Exclusion Criteria:

- Receiving hydrochlorothiazide in combination with another medication (in a single tablet)
- Potassium level < 3.1 mEq/L or sodium level < 130 mEq/L (in the previous 90 days)

Drugs: Chlorthalidone; hydrochlorothiazide

Design: Randomized, open-label, active-controlled trial

Methods: Eligible patients were randomized to continue therapy with hydrochlorothiazide or switch to chlorthalidone. Patients switched to chlorthalidone were given a dose one-half of their previous hydrochlorothiazide dose (e.g., patients previously receiving 25 mg HCTZ would be switched to 12.5 mg chlorthalidone). Patients continuing treatment with hydrochlorothiazide maintained their previous dose. It is important to note that this trial occurred during the context of usual care and did not have trial-specific procedures or visits required. This “pragmatic design” uses a centralized trial integration to recruit patients and collect data through the VA Healthcare System EHR.

Duration: Median follow-up period of 2.4 years

Statistical Analysis: It was determined that 1055 primary events would provide 90% power (two-sided alpha = 0.049). The ITT population was used for all analyses.

Results: A total of 13,523 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. The average daily doses of chlorthalidone and hydrochlorothiazide were 12.3 mg and 23 mg, respectively. Average systolic blood pressure was similar between the two groups for the trial duration (~138-139 mmHg). Rates of the primary composite outcome (and the individual components) were not significantly different between treatment groups. Hypokalemia occurred at higher rates in the chlorthalidone group. Baseline potassium levels were not provided.

Chlorthalidone (N=6756) Vs Hydrochlorothiazide (N=6767)

Primary Composite Outcome:
702 (10.4%) vs 675 (9.97%); HR 1.04 (95% CI 0.94-1.16); p=0.45

Non-Fatal Myocardial Infarction:
142 (2.10%) vs 140 (2.07%); HR 1.02 (95% CI 0.80-1.28)

Non-Fatal Stroke:
83 (1.23%) vs 83 (1.23%); HR 1.00 (95% CI 0.74-1.36)

Hospitalization for Heart Failure:
242 (3.58%) vs 232 (3.43%); HR 1.04 (95% CI 0.87-1.25)

Urgent Revascularization for Unstable Angina:
20 (0.30%) vs 13 (0.19%); HR 1.54 (95% CI 0.77-1.30)

Non-Cancer-Related Death:
359 (5.31%) vs 354 (5.23%); HR 1.01 (95% CI 0.88-1.17)

Safety:

Hypokalemia (K < 3.1 mEq/L):
335 (4.96%) vs 243 (3.59%); HR 1.39 (95% CI 1.18-1.64); ARI 1.37%; NNH ~73

Hospitalization due to Hypokalemia:
98 (1.45%) vs 73 (1.08%); HR 1.35 (95% CI 1.00-1.82)
~ CI contains 1.00 – cannot be considered statistically significant ~

Limitations:

- Lack of blinding – clinical significance likely low due to use of objective outcome measures
    - However, the investigators did note that the open-blinding may have caused patients switched from HCTZ to chlorthalidone to be more likely to revert to their original therapy (clinical significance uncertain)
- Trial design – the objective is comparing the effect of chlorthalidone and HCTZ on cardiovascular outcomes; the inclusion of patients using additional antihypertensive agents is a confounding factor that limits the ability to interpret said trial results reliably
    - To most effectively achieve this objective, a head-to-head comparison of HCTZ and chlorthalidone alone would be more appropriate
        - However, in this trial, only ~16% patients were receiving HCTZ alone at baseline
    - Additionally, the lack of a target blood pressure for the trial combined with the fact that the average systolic blood pressure remained elevated (~138-139 mmHg) may further obscure any differences in treatment effect between the two groups
- External validity – all included patients were from the VA Healthcare System (not representative of the general patient population in the United States)

Level of Evidence: Level I – with major limitations

Recommendation: For these reasons, I do not make a strong recommendation for one treatment agent over the other. Although the primary outcome occurred at similar rates between treatment groups, the trial design limits the ability to make a reliable comparison between chlorthalidone and hydrochlorothiazide regarding their effect on clinical outcomes. A more simplified, head-to-head comparison of these agents is needed prior to claiming non-inferiority or superiority (for either agent).

Efficacy:

- There was no significant difference in the rates of the primary composite outcome (or any individual component) between the chlorthalidone and hydrochlorothiazide groups
    - However, the inclusion of patients receiving multiple antihypertensive agents at baseline severely limits the ability of this trial to effectively compare the two diuretics
    - Additionally, the average systolic blood pressure remained elevated (~138-139 mmHg) for the duration of the trial in both groups which may further obscure any differences in treatment effect

Safety:

- Hypokalemia occurred significantly more often in the chlorthalidone group

Cost:

- The cost of using either agent (chlorthalidone or hydrochlorothiazide) must be considered in addition to the other antihypertensive medications used in the included patients
    - The majority of patients were receiving two or more antihypertensive medications at baseline

Special Considerations/Populations:

- All included patients were receiving hydrochlorothiazide at baseline
- Trial population consisted entirely of VA Healthcare System patients
- Patients were allowed to be on multiple antihypertensive medications (confounding factor)
    - However, these patients remained hypertensive (SBP ~138-140 mmHg) during the trial
- Chlorthalidone has a notably longer half-life and demonstrated evidence of cardiovascular benefit (as seen in the ALLHAT trial), unlike hydrochlorothiazide

Grade of Recommendation: **C**

DPP

Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;346(6):393-403.

Objective: To compare metformin to lifestyle intervention for the prevention of type 2 diabetes in adults.

Primary Efficacy Measure: Diagnosis of diabetes

Participants: Adults with elevated glucose levels (but not diagnostic of diabetes)

- Age ~51 years; male ~32%
- Weight ~94 kg; BMI ~34
- HgA1c ~5.9%; FPG ~107 mg/dL; 2-hour OGTT ~165 mg/dL

Inclusion Criteria:

- Age ≥ 25 years
- BMI ≥ 24
- Fasting plasma glucose 95-125 mg/dL
- Plasma glucose 140-199 mg/dL two hours following a 75 gram dose of glucose

Exclusion Criteria:

- Receiving medication that alters glucose tolerance
- Limited life expectancy

Drug: Metformin

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients were randomized to one of three treatment groups: (1) metformin plus standard lifestyle intervention [metformin group] (2) placebo plus standard lifestyle intervention [placebo group] (3) intensive lifestyle intervention. The dose of metformin (or placebo) was started at 850 mg once daily. After 30 days, the dose was increased to 850 mg twice daily. Standard lifestyle intervention consisted of the NCEP Step 1 diet, increased physical activity and weight loss. Intensive lifestyle intervention consisted of diet and physical activity (≥ 150 minutes/week) to achieve and maintain at least a 7% reduction in total body weight. A diagnosis of diabetes would be made if fasting plasma glucose was ≥ 126 mg/dL or if ≥ 200 mg/dL two hours following a 75 gram dose of glucose. A diagnosis would be confirmed via a repeat test conducted within 6 weeks.

Duration: Average follow-up period of 2.8 years

Statistical Analysis: The trial states that its design provides 90% power (alpha=0.0159). The ITT population was used for the efficacy analysis.

Results: A total of 3234 patients underwent randomization. Baseline patient characteristics were similar between groups. There was an average weight loss of 0.1 kg in the placebo group, 2.1 kg in the metformin group and 5.6 kg in the intensive lifestyle intervention group. At three years, the cumulative incidence rate was 28.9% in the placebo group, 21.7% in the metformin group and 14.4% in the intensive lifestyle intervention group. This estimates a NNT of 7 for the intensive lifestyle intervention group and 14 for the metformin group (when compared to the placebo group). Rates of gastrointestinal symptoms were highest in the metformin group.

Intensive Lifestyle Intervention (N=1079) Vs Placebo (N=1082)

Incidence of Diabetes (cases per 100 patient years):
4.8 vs 11.0; RRR 58% (95% CI 48% to 66%); p<0.001

Metformin (N=1073) Vs Placebo (N=1082)

Incidence of Diabetes (cases per 100 patient years):
7.8 vs 11.0; RRR 31% (95% CI 17% to 43%); p<0.001

Intensive Lifestyle Intervention (N=1079) Vs Metformin (N=1073)

Incidence of Diabetes (cases per 100 patient years):
4.8 vs 7.8; RRR 39%; (95% CI 24% to 51%); p<0.001

Limitations:

- Criteria for meeting power not mentioned – clinical significance uncertain
- Trial duration – it is uncertain how long the treatment benefit is maintained in this population

Level of Evidence: Level II – with major limitations

Recommendation: For these reasons, I recommend the use of intensive lifestyle intervention to lower the risk for developing diabetes in adults with prediabetes. If intensive lifestyle intervention is not feasible or appropriate I recommend the use of metformin (in addition to standard lifestyle intervention).

Efficacy:

- The incidence of diabetes was significantly lower in the intensive lifestyle intervention group when compared to both metformin and placebo groups
    - The metformin group demonstrated a significantly lower incidence rate compared to placebo

Safety:

- Predictably, rates of gastrointestinal symptoms were highest in the metformin group

Cost:

- The cost of intensive lifestyle intervention or use of metformin must be balanced against the cost-savings achieved from lowering the incidence rate of diabetes

Special Considerations/Populations:

- The plasma glucose ranges listed in the inclusion criteria are consistent with pre-diabetes
- Adherence to an effective diet and exercise program must be highly emphasized
- Weight loss was notably greater in the intensive lifestyle intervention group

Grade of Recommendation: **B**

EAGLES

Anthenelli RM, Benowitz NL, West R, et al. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomized, placebo-controlled clinical trial. *Lancet*. 2016;387(10037):2507-2520.

Objective: To compare the efficacy and safety of varenicline and bupropion to nicotine patches and placebo for smoking cessation in patients with and without psychiatric disorders.

Primary Safety Measure: Composite of neuropsychiatric adverse events

Primary Efficacy Measure: Continuous smoking abstinence rate for weeks 9-12

- Based on self-reported abstinence and exhaled carbon monoxide concentration < 10 ppm

Secondary Efficacy Measure: Continuous smoking abstinence rate for weeks 9-24

Participants: Cigarette smokers (with or without psychiatric disorders) motivated to quit

- Age ~47 years; male ~44%
- Average 21 cigarettes per day; previous attempt to quit ~82%
- Unipolar and bipolar mood disorders ~71% (of psychiatric cohort)

Inclusion Criteria:

- Smokers age 18-75 years
- Average cigarette consumption of 10 per day in the previous year
- Exhaled carbon monoxide concentration > 10 parts per million (ppm)
- Motivated to quit smoking

Exclusion Criteria:

- Unstable psychiatric condition
- Schizophreniform or delusional disorder
- High-risk for self-injury or suicidal ideation
- Any substance abuse disorder (other than nicotine)

Drugs: Varenicline; bupropion; nicotine patches

Design: Randomized, double-blind, active- and placebo-controlled trial

Methods: Eligible patients were stratified into psychiatric and non-psychiatric cohorts and randomized to receive varenicline 1 mg twice daily, bupropion SR 150 mg twice daily, nicotine 21 mg patch once daily or placebo for 12 weeks of active treatment followed by 12 weeks of non-treatment. A target quit date was set for 1 week after randomization to allow titration of varenicline and bupropion. Nicotine patch treatment was initiated on the target quit date.

Varenicline was titrated using the following schedule: 0.5 mg daily for 3 days, 0.5 mg twice daily for 4 days, then 1 mg twice daily for 11 weeks. Bupropion was titrated using the following schedule: 150 mg daily for 3 days, then 150 mg twice daily for the remainder of the treatment period. Nicotine patches were used in the following manner: 21 mg patch once daily (starting on target quit date) for 7 weeks, 14 mg patch daily for 2 weeks, then 7 mg patch daily for 2 weeks (11 weeks total).

Duration: 24 weeks

Statistical Analysis: It was determined that 2000 randomized patients per treatment group would achieve sufficient power to estimate a 75% increase in the primary safety outcome. The ITT population was used for the efficacy analyses and the mITT population (all patients treated with study medication) was used for the safety analyses. The primary efficacy comparisons were varenicline and bupropion versus placebo. All other comparisons were considered secondary.

Results: A total of 8144 patients underwent randomization. Baseline patient characteristics were similar between cohort treatment groups.

Safety

Non-psychiatric cohort	Varenicline (N=990)	Bupropion (N=989)	Nicotine patch (N=1006)	Placebo (N=999)
Neuropsychiatric composite outcome	13 (1.31%)	22 (2.22%)	25 (2.49%)	24 (2.40%)

Psychiatric cohort	Varenicline (N=1026)	Bupropion (N=1017)	Nicotine patch (N=1016)	Placebo (N=1015)
Neuropsychiatric composite outcome	67 (6.53%)	68 (6.69%)	53 (5.22%)	50 (4.93%)

Rates of neuropsychiatric events were not increased in varenicline or bupropion groups compared to other treatment groups in the non-psychiatric cohort. In the psychiatric cohort, rates of neuropsychiatric events were higher compared to the non-psychiatric cohort but were not significantly different between treatment groups. Rates of suicidal ideation or behavior were not significantly different across treatment groups. There was one completed suicide in the placebo group of the non-psychiatric cohort. Overall, the most common side effect per treatment group was nausea (varenicline, 25%), insomnia (bupropion, 12%), abnormal dreams (nicotine patch, 12%) and headache (placebo, 10%).

Efficacy

Non-psychiatric cohort	Varenicline (N=1005)	Bupropion (N=1001)	Nicotine patch (N=1013)	Placebo (N=1009)
Continuous abstinence rate at weeks 9-12	38.0%	26.1%	26.4%	13.7%

Psychiatric cohort	Varenicline (N=1032)	Bupropion (N=1033)	Nicotine patch (N=1025)	Placebo (N=1026)
Continuous abstinence rate at weeks 9-12	29.2%	19.3%	20.4%	11.4%

Overall	Varenicline (N=2037)	Bupropion (N=2034)	Nicotine patch (N=2038)	Placebo (N=2035)
Continuous abstinence rate at weeks 9-24	21.8%	16.2%	15.7%	9.4%

Varenicline demonstrated significantly greater abstinence rates for weeks 9-12 and weeks 9-24 compared to other treatment groups ($p<0.01$). Rates of continuous abstinence were not significantly different between the bupropion and nicotine patch treatment groups. These results were consistent in both psychiatric and non-psychiatric cohorts.

Limitations:

- Power not mentioned – clinical significance likely low due to significant differences detected between treatment groups regarding the efficacy outcome
- Psychiatric patients included in this trial were stable and treated or in remission
- Patients included smoked an average of 10 or more cigarettes daily
    - Cannot apply trial results to patients smoking less frequently

Level of Evidence: Level II – with major limitations

Recommendation: For these reasons, I recommend the use of varenicline or bupropion as safe agents for smoking cessation in patients motivated to quit (with or without stable psychiatric disorders). It is reasonable to prefer varenicline over bupropion due to a demonstrated greater efficacy.

Efficacy:

- Varenicline demonstrated the greatest abstinence rates of all treatment groups for weeks 9-12 as well as weeks 9-24
- Bupropion demonstrated similar abstinence rates compared to nicotine patches
- Trial results were consistent for weeks 9-12 and weeks 9-24

Safety:

- Rates of neuropsychiatric events were not significantly different between treatment groups in both cohort groups (including suicidal ideation and behavior)
- Varenicline and bupropion groups did not demonstrate increased rates of neuropsychiatric events compared to nicotine patch or placebo groups for either cohort

Cost:

- The cost of using varenicline over bupropion or nicotine patches must be balanced against the cost-savings from avoiding long-term complications secondary to chronic smoking

Special Considerations/Populations:

- The psychiatric cohort excluded patients with unstable psychotic disorders or substance use disorders
- Patients included in this trial smoked 10 cigarettes daily (on average)

Grade of Recommendation: **B**

ELIXA

Pfeffer MA, Claggett B, Diaz R, et al. Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome. *N Engl J Med*. 2015;373(23):2247-2257.

Objective: To determine the effect of lixisenatide on cardiovascular outcomes in type 2 diabetes.

Primary Efficacy Measure: Composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke or hospitalization for unstable angina

Participants: Patients with type 2 diabetes and prior acute coronary event

- Age ~60 years; male ~70%
- HgA1c ~7.6%
- Qualifying event STEMI ~44%; NSTEMI ~39%; unstable angina ~17%

Inclusion Criteria:

- Type 2 diabetes with HgA1c 5.5%-11%
- Acute coronary event within previous 180 days

Exclusion Criteria:

- Age < 30 years
- PCI within previous 15 days
- CABG as qualifying event
- Planned revascularization within 90 days post-screening
- eGFR < 30 mL/min

Drug: Lixisenatide

Design: Randomized, double-blind, placebo-controlled, non-inferiority trial

Methods: Patients underwent a 1-week run-in period to assess ability to self-administer placebo medication. Eligible patients were then randomized to receive either lixisenatide or matching placebo injections. Lixisenatide was dosed at 10 mcg daily for 2 weeks then increased (at investigator discretion) to a max dose of 20 mcg daily. Additional medications to further control blood sugar were allowed in an attempt to yield similar HgA1c values between groups (incretin-based therapies not allowed).

Duration: Median follow-up period of 25 months (~2 years)

Statistical Analysis: It was determined that 6000 randomized patients and 844 primary event outcomes would achieve 96% power. A non-inferiority margin of 1.3 was used. If non-inferiority was demonstrated then superiority would be tested. The ITT population was used for the primary analysis.

Results: A total of 6068 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. A total of 805 patients experienced a primary event outcome. Lixisenatide demonstrated non-inferiority (but not superiority) to placebo regarding the primary efficacy measure. The HgA1c reduction was significantly greater in the lixisenatide group compared to placebo at week 12 (-0.6% vs -0.2%; $p<0.001$). The vast majority (~85%) of patients in the lixisenatide group achieved the max dose of 20 mcg daily.

Lixisenatide (N=3034) Vs Placebo (N=3034)

Composite of Cardiovascular Death, Myocardial Infarction & Stroke:
406 (13.4%) vs 399 (13.2%); HR 1.02 (95% CI 0.89-1.17); p=0.81

Cardiovascular Death:
88 (2.90%) vs 93 (3.07%)

Non-Fatal Myocardial Infarction:
255 (8.40%) vs 247 (8.14%)

Non-Fatal Stroke:
54 (1.78%) vs 49 (1.62%)

Hospitalization for Unstable Angina:
9 (0.30%) vs 10 (0.33%)

Discontinuation rates were significantly higher in the lixisenatide group (p=0.002). The most common reason for discontinuation was gastrointestinal disturbance. There was no significant difference in rates of pancreatitis or pancreatic cancer between treatment groups.

Limitations:
- Power set but not met – failed to achieve the pre-specified number of events (clinical significance minimal)

Level of Evidence: Level II - with major limitations

Recommendation: For these reasons, I recommend the use of lixisenatide as a safe glucose-lowering agent for patients with type 2 diabetes. However, I do not recommend it for the reduction of cardiovascular outcomes.

Efficacy:
- Lixisenatide demonstrated non-inferiority (but not superiority) to placebo regarding the cardiovascular composite outcome
- Rates of the individual components of the composite outcome were similar between treatment groups

Safety:
- The lixisenatide treatment group demonstrated significantly higher discontinuation rates, primarily due to gastrointestinal symptoms
- There was no significant difference in rates of pancreatitis or pancreatic cancer (however, the trial was not powered to detect such differences)

Cost:
- The cost of using lixisenatide must be balanced against the cost of using a GLP-1 RA with demonstrated cardiovascular benefit

Special Considerations/Populations:
- The baseline HgA1c may have been too low for lixisenatide treatment to affect cardiovascular outcomes (clinical significance uncertain)

Grade of Recommendation: **B**

EMPA-KIDNEY

The EMPA-KIDNEY Collaborative Group, Herrington WG, Staplin N, et al. Empagliflozin in Patients with Chronic Kidney Disease. *N Engl J Med*. 2023;388(2):117-127.

Objective: To determine the effect of empagliflozin on cardiorenal outcomes in patients with chronic kidney disease (with or without diabetes).

Primary Efficacy Measure: Composite of cardiovascular death or kidney disease progression

- Kidney disease progression defined as: ESRD (initiation of dialysis, kidney transplant), sustained decrease in eGFR to < 10 mL/min, sustained eGFR decrease ≥ 40% from baseline or renal death

Participants: Patients with chronic kidney disease (with or without diabetes)

- Age ~64 years; male ~67%
- eGFR ~37 mL/min; UACR ~223 mg/g; HgA1c ~6.3%
- History of cardiovascular disease ~26%; diabetes ~46%; baseline ACEi or ARB ~85%

Inclusion Criteria:

- Evidence of progressive chronic kidney disease:
  - eGFR 20 mL/min to less than 45 mL/min, or
  - eGFR 45 mL/min to less than 90 mL/min, plus UACR ≥ 200 mg/g
- Receiving a clinically appropriate dose of an ACEi or an ARB (unless not appropriate)

Exclusion Criteria:

- Concurrent use of ACEi and ARB
- Polycystic kidney disease or kidney transplant recipient

Drug: Empagliflozin

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients underwent a 15 week placebo run-in period. Patients that successfully completed the run-in period were randomized to receive empagliflozin 10 mg once daily or matching placebo.

Duration: Median follow-up period of 2.0 years

Statistical Analysis: It was determined that 1070 primary outcome events would achieve 90% power (alpha=0.05). The ITT population was used for all analyses.

Results: A total of 6609 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. There was no significant difference in rates of first heart failure hospitalization between treatment groups (88 vs 107; HR 0.80 [95% CI 0.60-1.06]). Likewise, the occurrence of renal death was similar between groups (4 vs 4; HR 0.90 [95% CI 0.22-3.66]). The average annual rate of change in eGFR was 2.16 mL/min in the empagliflozin group and 2.92 mL/min in the placebo group. Treatment effect was consistent upon subgroup analysis, including patients with and without diabetes.

Of the six patient cases of ketoacidosis that occurred in the empagliflozin group, only one patient did not have diabetes at baseline (one case of ketoacidosis occurred in the placebo group). Rates of lower-limb amputation were numerically higher in the empagliflozin group compared to placebo (28 vs 19, respectively). The majority of amputations were of the toe (20 vs 14, respectively [difference not statistically significant]). Rates of serious UTIs were similar between groups. Overall, there was no demonstrated increased risk of serious adverse events with use of empagliflozin.

Empagliflozin (N=3304) Vs Placebo (N=3305)

Composite of Cardiovascular Death or Kidney Disease Progression:
432 (13.1%) vs 558 (16.9%); HR 0.72 (95% CI 0.64-0.82)
p<0.001; ARR 3.81%; NNT ~27

Cardiovascular Death:
59 (1.79%) vs 69 (2.09%); HR 0.84 (95% CI 0.60-1.19)

Kidney Disease Progression:
384 (11.6%) vs 504 (15.2%); HR 0.71 (95% CI 0.62-0.81); ARR 3.63%; NNT ~28

End-Stage Renal Disease:
108 (3.27%) vs 158 (4.78%); HR 0.67 (95% CI 0.52-0.85); ARR 1.51%; NNT ~67

Sustained Decrease in eGFR to <10 mL/min:
116 (3.51%) vs 167 (5.05%); HR 0.69 (95% CI 0.54-0.87); ARR 1.54%; NNT ~65

Sustained eGFR Decrease ≥ 40% from Baseline:
359 (10.9%) vs 474 (14.3%); HR 0.70 (95% CI 0.61-0.81); ARR 3.48; NNT ~29

Limitations:

- Power set but not met – failed to achieve specified number of primary outcome events
    - Clinical significance likely low, due to demonstrated statistically significant differences
- Patient population – cannot apply trial results to patients without chronic kidney disease
- Treatment effect must be considered in addition to baseline ACEi or ARB (~85% of patients)

Level of Evidence: Level II – with major limitations

Recommendation: For these reasons, I recommend the use of empagliflozin 10 mg daily (in addition to baseline ACEi or ARB) to further reduce rates of renal disease progression in patients with chronic kidney disease (with or without diabetes).

Efficacy:

- The primary composite outcome occurred at significantly lower rates in the empagliflozin group
    - However, this was driven primarily by reduced rates of kidney disease progression
    - There was no significant difference in the rate of cardiovascular death between groups

Safety:

- Overall, rates of serious adverse events were not markedly different between groups
- Ketoacidosis occurred infrequently, but is a valid concern (especially for patients with diabetes)
- Rates of lower limb amputations were not statistically different between groups

Cost:

- The cost of using empagliflozin 10 mg daily must be balanced against the cost-savings achieved from reducing the rate of kidney disease progression and subsequent clinical complications

Special Considerations/Populations:

- Treatment benefit driven primarily by a reduction in kidney disease progression, not a reduction in cardiovascular death

Grade of Recommendation: **B**

EMPA-REG OUTCOME

Zinman B, Lachin JM, Inzucchi SE. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med*. 2016;374(11):1094.

Objective: To determine the effect of empagliflozin on cardiovascular outcomes in type 2 diabetes.

Primary Efficacy Measure: Composite of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke

Participants: Patients with type 2 diabetes and established cardiovascular disease

- Age ~63 years; male ~71%
- HgA1c ~8.1%
- Coronary artery disease ~76%; Prior myocardial infarction ~47%

Inclusion Criteria:

- Patients ≥ 18 years old with type 2 diabetes
- Established cardiovascular disease
- BMI ≤ 45
- eGFR ≥ 30 mL/min
- No glucose-lowering treatment in previous 12 weeks and HgA1c 7.0-9.0% or on stable glucose-lowering treatment for 12 weeks and HgA1c 7.0-10.0%

Exclusion Criteria:

- Blood glucose > 240 mg/dL after overnight fasting
- Liver disease
- Cardiac surgery/angioplasty within previous 3 months
- Acute coronary syndrome, stroke or TIA within previous 2 months

Drug: Empagliflozin

Design: Randomized, double-blind, placebo-controlled, non-inferiority trial

Methods: Patients meeting eligibility underwent a two-week, open-label, placebo run-in period during which background therapy was unchanged. Patients were then randomized to receive empagliflozin 10 mg, empagliflozin 25 mg or placebo once daily. Background glucose-lowering therapy was left unchanged for the initial 12 weeks, after which intensification was encouraged to achieve local glycemic targets. Other cardiovascular risk factors were also treated to standards of care.

Duration: Median follow-up period of 3.1 years

Statistical Analysis: The trial was designed to test for non-inferiority with sequential testing to demonstrate superiority. It was determined that 691 events would achieve 90% power (alpha = 0.0498). A non-inferiority margin of 1.3 was used. The mITT population (all patients that received at least one dose of a study drug) was used for analyses.

Results: A total of 7020 patients underwent randomization and received at least 1 dose of study medication. Baseline patient characteristics were similar between treatment groups. Differences in HgA1c between the active and placebo groups at the end of the trial were -0.24% and -0.36%, favoring empagliflozin (10 mg & 25 mg). Subgroup analysis of 10 mg and 25 mg groups demonstrated that the treatment effect was consistent between the two doses.

Empagliflozin (N=4687) Vs Placebo (N=2333)

Composite of Cardiovascular Death, Myocardial Infarction & Stroke:
490 (10.5%) vs 282 (12.1%); HR 0.86 (95% CI 0.74-0.99)
p=0.04; ARR 1.63%; NNT ~62

Cardiovascular Death:
172 (3.67%) vs 137 (5.87%); HR 0.62 (95% CI 0.49-0.77)
p<0.001; ARR 2.20%; NNT ~46

Non-Fatal Myocardial Infarction:
213 (4.54%) vs 121 (5.19%); HR 0.87 (95% CI 0.70-1.09); p=0.22

Non-Fatal Stroke:
150 (3.20%) vs 60 (2.57%); HR 1.24 (95% CI 0.92-1.67); p=0.16

Heart Failure Hospitalization:
126 (2.69%) vs 95 (4.07%); HR 0.65 (95% CI 0.50-0.85)
p=0.002; ARR 1.38%; NNT ~73

Safety:

Female Urinary Tract Infection:
492/1351 (36.4%) vs 265/653 (40.6%); p<0.05; ARI 4.16%; NNT ~24

Genital Infection:
301 (6.42%) vs 42 (1.80%); p<0.001; ARI 4.62%; NNH ~21

Limitations:

- Patient population - all participants had baseline cardiovascular disease

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I recommend the use of empagliflozin (in addition to standard therapy) to further reduce morbidity and mortality in patients with type 2 diabetes and established cardiovascular disease. However, the risk for UTIs and genital infections must be carefully considered.

Efficacy:

- Empagliflozin demonstrated significantly lower rates of the primary cardiovascular composite compared to placebo
- Rates of cardiovascular death were significantly lower with empagliflozin
- There was no significant difference in rates of non-fatal myocardial infarction or non-fatal stroke
- Rates of heart failure hospitalization were significantly lower with empagliflozin

Safety:

- Rates of female (but not male) UTI were significantly lower but genital infections were significantly higher in the empagliflozin group compared to placebo

Cost:

- The cost of using empagliflozin must be balanced against the cost-savings of preventing cardiovascular events, particularly cardiovascular death and heart failure hospitalization
- However, the cost of treating female UTIs and genital infections must also be considered

Special Considerations/Populations:

- All patients included in this trial had baseline cardiovascular disease
- The risk of complications from UTIs or genital infections increases with age and this should be considered when deciding to initiate therapy

Grade of Recommendation: **A**

EMPEROR-Preserved

Anker SD, Butler J, Filippatos G, et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. *N Engl J Med*. 2021;385(16):1451-1461.

Objective: To determine the effect of empagliflozin on morbidity and mortality outcomes in patients with heart failure and preserved ejection fraction (with or without type 2 diabetes).

Primary Efficacy Measure: Composite of cardiovascular death or hospitalization for heart failure (time to 1st event)

Secondary Efficacy Measures: (1) Total heart failure hospitalizations (2) eGFR rate decline

Participants: Chronic heart failure patients with preserved ejection fraction

- Age ~72 years; male ~55%
- NYHA class II ~81%; class III ~18%
- Baseline diabetes ~49%
- LVEF ~54%; SBP ~132 mmHg; HR ~70 bpm; eGFR ~60 mL/min
- RAASi ~81%; BB ~86%; MRA ~37%

Inclusion Criteria:

- Age ≥ 18 years
- NYHA class II-IV heart failure
- LVEF > 40%
- NT-proBNP level > 300 pg/mL

Exclusion Criteria:

- MI, CABG, stroke/TIA within previous 90 days
- Acute decompensated heart failure within 1 week of screening
- History of ketoacidosis
- Severe valvular disease

Drug: Empagliflozin

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients were randomized to receive empagliflozin 10 mg daily or matching placebo (in addition to standard care).

Duration: Median follow-up period of 26.2 months

Statistical Analysis: It was determined that 841 primary events would provide 90% power. The ITT population was used for primary efficacy analysis (alpha = 0.0497). If the difference in the primary outcome was statistically significant then hierarchical testing for the secondary outcomes would occur (total HF hospitalizations, then eGFR rate decline). Safety analyses were performed using the mITT population (patients that received at least one dose of study medication).

Results: A total of 5988 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. Hierarchical testing was performed for secondary outcomes after a statistically significant difference was detected for the primary composite outcome. Overall adverse event rates were similar between treatment groups, however, uncomplicated genital infections, UTIs and hypotension were more common in the empagliflozin group. Ketoacidosis occurred at similar rates between treatment groups.

Empagliflozin (N=2997) Vs Placebo (N=2991)

Primary Composite Outcome:
415 (13.8%) vs 511 (17.1%); HR 0.79 (95% CI 0.69-0.90)
p<0.001; ARR 3.24%; NNT ~31

Cardiovascular Death:
219 (7.31%) vs 244 (8.16%); HR 0.91 (95% CI 0.76-1.09)

1st Heart Failure Hospitalization:
259 (8.64%) vs 352 (11.8%); HR 0.71 (95% CI 0.60-0.83)
ARR 3.13%; NNT ~32

Total Heart Failure Hospitalizations:
407 vs 541; HR 0.73 (95% 0.61-0.88); p<0.001

eGFR Rate Decline Per Year:
-1.25 mL/min vs -2.62 mL/min; HR 1.36 (95% CI 1.06-1.66); p<0.001

Safety

Hypotension:
311/2996 (10.4%) vs 257/2989 (8.60%)

Uncomplicated Genital Infections:
67 (2.24%) vs 22 (0.74%)

Uncomplicated UTIs:
297 (9.91%) vs 243 (8.13%)

Limitations:

- Patient population – cannot apply trial results to patients with reduced ejection fraction
- Dosing of empagliflozin must be considered - 10 mg daily

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I recommend the use of empagliflozin 10 mg daily (in addition to standard therapy) to further reduce morbidity rates in heart failure patients with preserved ejection fraction.

Efficacy:

- Rates of the primary composite outcome were significantly lower in the empagliflozin group
    - However, only the component of heart failure hospitalization was significantly lower than placebo
- Total heart failure hospitalizations and eGFR rate decline occurred significantly less with empagliflozin
- Treatment benefit was consistent in patients with and without diabetes

Safety:

- Rates of hypotension, genital infections and UTIs were more common with empagliflozin
- Rates of ketoacidosis were similar between treatment groups
- There was no significant difference in rates of hypoglycemia

Cost:

- The cost of using empagliflozin must be balanced against the cost-savings of reducing heart failure hospitalization rates

Special Considerations/Populations:

- Treatment benefit must be considered in addition to standard heart failure therapy
- Diabetes was not an inclusion criterion - important to consider when interpreting results

Grade of Recommendation: **A**

EMPEROR-Reduced

Packer M, Anker SD, Butler J, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. *N Engl J Med*. 2020;383(15):1413-1424.

Objective: To determine the effect of empagliflozin on morbidity and mortality outcomes in heart failure patients with reduced ejection fraction (with or without type 2 diabetes).

Primary Efficacy Measure: Composite of cardiovascular death or heart failure hospitalization

Secondary Efficacy Measures: (1) Total heart failure hospitalization (2) Rate of eGFR decline

Participants: Heart failure patients with reduced ejection fraction

- Age ~67 years; male ~76%
- LVEF ~27%; SBP ~122 mmHg; HR ~71 bpm; eGFR ~62 mL/min
- NYHA class II ~75%; class III ~24%
- Type 2 diabetes ~50%
- Baseline RAAS inhibitor ~88%; beta-blocker ~95%; MRA ~71%

Inclusion Criteria:

- Age ≥ 18 years
- Chronic heart failure NYHA functional class II-IV
- LVEF ≤ 40% (plus elevated NT-proBNP or heart failure hospitalization within prior year)
- Receiving standard and stable heart failure pharmacotherapy

Exclusion Criteria:

- Myocardial infarction, stroke/TIA or CABG within previous 90 days
- Use of IV diuretics/inotropes/vasodilators within previous 7 days
- History of ketoacidosis

Drug: Empagliflozin

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients were randomized to receive either empagliflozin 10 mg daily or matching placebo (in addition to their standard heart failure medication).

Duration: Median follow-up period of 16 months

Statistical Analysis: It was determined that 841 primary events would provide 90% power (alpha=0.05). If a significant difference was detected for the primary outcome, then the secondary outcomes would undergo analyses. The ITT population was used for the primary efficacy analyses. The mITT population was used for safety analyses.

Results: A total of 3730 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. The effect of empagliflozin was consistent in patients with and without baseline type 2 diabetes. Overall rates of adverse drug reactions were lower in the empagliflozin group, however UTIs and genital infections were more common than in the placebo group.

Empagliflozin (N=1863) Vs Placebo (N=1867)

Composite of Cardiovascular Death or Heart Failure Hospitalization:
361 (19.4%) vs 462 (24.7%); HR 0.75 (95% CI 0.65-0.86)
p<0.001; ARR 5.37%; NNT ~19

Cardiovascular Death:
187 (10.0%) vs 202 (10.8%); HR 0.92 (95% CI 0.75-1.12)

Heart Failure Hospitalization:
246 (13.2%) vs 342 (18.3%); HR 0.69 (95% CI 0.59-0.81)
ARR 5.11%; NNT ~20

Total Number of Heart Failure Hospitalizations:
388 vs 553; HR 0.70 (95% CI 0.58-0.85); p<0.001

Average eGFR Change:
-0.55 mL/min vs -2.28 mL/min; HR 1.73 (95% CI 1.10-2.37); p<0.001

Safety:

Urinary Tract Infection:
91/1863 (4.88%) vs 83/1863 (4.46%)

Genital Infections:
31/1863 (1.66%) vs 12/1863 (0.64%)

Limitations:

- Power set but not met - failed to achieve 841 primary events (clinical significance low as a significant difference was demonstrated)
- Cannot apply trial results to patients with type 1 diabetes or those with heart failure preserved ejection fraction

Level of Evidence: Level II - with major limitations

Recommendation: For these reasons, I recommend the use of empagliflozin 10 mg (in addition to standard heart failure therapy) to further reduce morbidity rates in heart failure patients with reduced ejection fraction (with or without type 2 diabetes). However, it is reasonable to optimize current heart failure therapy prior to initiating empagliflozin in order to maximize the overall treatment benefit.

Efficacy:

- The empagliflozin treatment group demonstrated significantly lower rates of the primary composite outcome compared to placebo
- However, only the component of first heart failure hospitalization was significantly lower in the empagliflozin treatment group
- Rates of both secondary outcomes (total heart failure hospitalization and average change in eGFR) occurred at significantly lower rates in the empagliflozin treatment group

Safety:

- Overall rates of adverse drug reactions (including serious events) were lower in the empagliflozin group compared to placebo
- However, rates of UTIs and genital infections were more common with empagliflozin

Cost:

- The cost of using empagliflozin 10 mg must be balanced against the cost-savings of preventing heart failure hospitalizations

Special Considerations/Populations:

- All patients had heart failure with reduced ejection fraction (primarily LVEF < 30%)
- Approximately 50% of patients had type 2 diabetes at baseline
- Results must be considered in addition to standard heart failure therapy

Grade of Recommendation: **B**

EMPHASIS-HF

Zannad F, McMurray JJ, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med*. 2011;364(1):11-21.

Objective: To determine the effect of eplerenone on morbidity and mortality outcomes in symptomatic heart failure patients.

Primary Efficacy Measure: Composite of cardiovascular death and heart failure hospitalization

Participants: Heart failure patients with reduced ejection fraction and recent hospitalization

- Age ~69 years; male ~77%
- LVEF ~26%; BP ~124/75 mmHg; HR ~72 bpm
- Baseline ACEi ~77%; diuretic ~85%; beta-blocker ~87%; ACEi or ARB ~93%

Inclusion Criteria:

- Age ≥ 55 years
- LVEF ≤ 30 % with NYHA class II
- Receiving optimal dosing of ACEi and/or beta-blocker
- Cardiovascular hospitalization within prior 6 months (or elevated BNP or pro-BNP levels)

Exclusion Criteria:

- Acute myocardial infarction
- NYHA class III-IV
- Serum potassium level > 5 mmol/L
- eGFR < 30 mL/min
- Need for potassium-sparing diuretic

Drug: Eplerenone

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients were randomized to receive eplerenone or matching placebo. Dosing for eplerenone was started at 25 mg daily and increased to 50 mg daily after 4 weeks if the potassium level was ≤ 5 mmol/L.

Duration: Median follow-up period of 21 months

Statistical Analysis: Initially, it was determined that 2584 randomized patients and 813 primary outcomes would achieve 80% power (alpha = 0.05). However, due to a lower event rate than expected the sample size was increased to 3100 patients (per protocol amendment). The ITT population was used for primary analyses.

Results: The trial was stopped early based on recommendations from the safety committee due to data showing clear benefit favoring eplerenone and pre-specified stopping criteria being met. A total of 2737 patients had undergone randomization at this time. Baseline patient characteristics were similar between treatment groups. At month 5 of the trial, 60.2% of patients were receiving eplerenone 50 mg daily (mean dose 39.1 mg daily). There was no significant difference between treatment groups in the rates of renal failure, hypotension or gynecomastia.

Eplerenone (N=1364) Vs Placebo (N=1373)

Composite of Cardiovascular Death & Heart Failure Hospitalization:
249 (18.3%) vs 356 (25.9%); HR 0.63 (95% CI 0.54-0.74)
p<0.001; ARR 7.67%; NNT ~13

Cardiovascular Death:
147 (10.8%) vs 185 (13.5%); HR 0.76 (95% CI 0.61-0.94)
p=0.01; ARR 2.70%; NNT ~38

Heart Failure Hospitalization:
164 (12.0%) vs 253 (18.4%); HR 0.58 (95% CI 0.47-0.70)
p<0.001; ARR 6.40%; NNT ~16

Safety:

Hyperkalemia:
109/1360 (8.01%) vs 50/1369 (3.65%); p<0.001; ARI 4.36%; NNH ~22

Limitations:

- Power set but not met - due to trial being stopped early (clinical significance minimal)
- Patient population had mild symptoms of heart failure at baseline (NYHA class II)

Level of Evidence: Level II - with major limitations

Recommendation: For these reasons, I recommend the use of eplerenone (in addition to standard heart failure therapy) to further reduce the risk for cardiovascular morbidity and mortality in heart failure patients with reduced ejection fraction. However, the risk of hyperkalemia must be considered when making the decision to initiate therapy.

Efficacy:

- Rates of the primary composite outcome were significantly lower in the eplerenone group compared to placebo
- Individual rates of cardiovascular death and heart failure hospitalization were both significantly lower in the eplerenone group

Safety:

- The rates of hyperkalemia were significantly higher in the eplerenone group (predictable effect for medication class)
- Rates of gynecomastia were not significantly different between treatment groups

Cost:

- The cost of using eplerenone must be balanced against the cost-savings of preventing cardiovascular death and heart failure hospitalizations
- However, the cost of monitoring for and managing hyperkalemia must also be considered

Special Considerations/Populations:

- The vast majority of patients were receiving ACEi/ARB, beta-blocker & diuretic at baseline
- All patients had recent hospitalization (within previous 6 months)
- Patients had mild symptoms of heart failure (NYHA class II) - cannot extrapolate results to more symptomatic patients (NYHA class III-IV)

Grade of Recommendation: **B**

ENGAGE AF-TIMI 48

Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2013;369(22):2093-2104.

Objective: To determine the efficacy and safety of edoxaban compared to warfarin in patients with atrial fibrillation.

Primary Efficacy Measure: Composite of stroke and systemic embolic event

Primary Safety Measure: Major bleeding

Participants: Atrial fibrillation patients requiring anticoagulation

- Age ~72 years; male ~63%
- $CHADS_2$ score ~2.8; ~77% with $CHADS_2$ score ≤ 3

Inclusion Criteria:

- Age ≥ 21 years
- Documented atrial fibrillation via electrical tracing
- $CHADS_2$ score ≥ 2
- Planned anticoagulation therapy for duration of trial

Exclusion Criteria:

- Reversible atrial fibrillation
- eCrCl < 30 mL/min
- High bleed risk
- Dual antiplatelet therapy
- Moderate/severe mitral stenosis
- Acute coronary syndrome/revascularization/stroke within 30 days
- Other need for anticoagulation

Drugs: Edoxaban; warfarin

Design: Randomized, double-blind, active-comparison, non-inferiority trial

Methods: Eligible patients were randomized 1:1:1 to receive warfarin (target INR 2.0-3.0), edoxaban 30 mg or edoxaban 60 mg plus matching placebo. The edoxaban dose was cut in half if at any time the following occurred: eCrCl 30-50 mL/min, weight < 60 kg or use of potent P-gP inhibitor.

Duration: Median follow-up period of 2.8 years

Statistical Analysis: The primary efficacy outcome was analyzed for non-inferiority of either edoxaban group to warfarin therapy. It was determined that 672 primary endpoints would achieve 87% for the non-inferiority analysis. The non-inferiority margin was set at 1.38 with a 97.5% upper CI. All patients that received at least one dose of study medication (mITT population) were included in the non-inferiority analysis. If either edoxaban group met the non-inferiority criteria then testing for superiority using the ITT population would occur (alpha = 0.025). For the primary safety measure the mITT population was used for the analysis.

Results: A total of 21,105 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. Patients in the warfarin group had therapeutic INR (2.0-3.0) ~68% of the time and had readings between 1.8-3.2 ~83% of the time. Both edoxaban groups demonstrated non-inferiority to warfarin regarding the primary efficacy outcome, but not superiority.

Warfarin (N=7036) Vs Edoxaban 60 mg (N=7035)

Composite of Stroke & Systemic Embolic Event:
337 (4.79%) vs 296 (4.21%); HR 0.87 (95% CI 0.73-1.04); p=0.08

Total Stroke:
317 (4.51%) vs 281 (3.99%); HR 0.88 (95% CI 0.75-1.03); p=0.11

Systemic Embolic Event:
23 (0.33%) vs 15 (0.21%); HR 0.65 (95% CI 0.34-1.24); p=0.19

Cardiovascular Death:
611 (8.68%) vs 530 (7.53%); HR 0.86 (95% CI 0.77-0.97); p=0.013

Major Bleeding:
524/7012 (7.47%) vs 418/7012 (5.96%); HR 0.80 (95% CI 0.71-0.91)
p<0.001; ARR 1.51%; NNT ~67

Warfarin (N=7036) Vs Edoxaban 30 mg (N=7034)

Composite of Stroke & Systemic Embolic Event:
337 (4.79%) vs 383 (5.44%); HR 1.13 (95% CI 0.96-1.34); p=0.10

Total Stroke:
317 (4.51%) vs 360 (5.12%); HR 1.13 (95% CI 0.97-1.31); p=0.12

Systemic Embolic Event:
23 (0.33%) vs 29 (0.41%); HR 1.24 (95% CI 0.72-2.15); p=0.43

Cardiovascular Death:
611 (8.68%) vs 527 (7.49%); HR 0.85 (95% CI 0.76-0.96); p=0.008

Major Bleeding:
524/7012 (7.47%) vs 254/7002 (3.63%); HR 0.47 (95% CI 0.41-0.55)
p<0.001; ARR 3.85%; NNT ~26

Limitations:

- Power set but not met for non-inferiority - only 667 primary events occurred out of the specified 672 (clinical significance minimal)
- Although rates of cardiovascular death were significantly lower in the edoxaban groups compared to warfarin, superiority cannot be claimed due to failure of hierarchical testing

Level of Evidence: Level II - with major limitations

Recommendation: For primarily safety reasons, I recommend the use of edoxaban over warfarin in patients with atrial fibrillation requiring anticoagulation. However, it would be reasonable to prefer other DOACs that have demonstrated superiority over warfarin regarding reduction of thromboembolic events.

Efficacy:

- Both edoxaban groups demonstrated non-inferiority (but not superiority) to warfarin regarding the primary efficacy composite outcome
- Rates of cardiovascular death were notably lower in the edoxaban groups compared to warfarin, however superiority cannot be claimed due to failure of hierarchical testing

Safety:

- Rates of major bleeding were significantly lower in both edoxaban groups compared to warfarin

Cost:

- The cost of using edoxaban must be balanced against the cost-savings of avoiding major bleeding events and INR testing

Special Considerations/Populations:

- Results cannot be extrapolated to other DOACs

Grade of Recommendation: **B**

EPHESUS

Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med*. 2003;348(14):1309-1321.

Objective: To determine the effect of eplerenone on cardiovascular outcomes in patients with acute myocardial infarction plus left ventricular dysfunction on optimal medication therapy.

Primary Efficacy Measures: (1) All-cause mortality (2) Composite of cardiovascular death or cardiovascular hospitalization

Participants: Heart failure patients with reduced ejection fraction and recent myocardial infarction

- Age ~64 years; male ~71%
- LVEF ~33%; BP ~119/72 mmHg
- Baseline ACEi/ARB ~86%; beta-blocker ~75%; diuretic ~60%; aspirin ~88%

Inclusion Criteria:

- Documented left-ventricular dysfunction (LVEF ≤ 40%)
- Acute myocardial infarction within previous 3-14 days

Exclusion Criteria:

- Use of potassium-sparing diuretics
- SCr > 2.5 mg/dL
- Serum potassium > 5 mmol/L

Drug: Eplerenone

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients were randomized to receive eplerenone 25 mg daily or matching placebo. After 4 weeks the dose of eplerenone was increased to 50 mg daily. Patients also received optimal therapy, including ACEi/ARB, beta-blockers and diuretics.

Duration: Mean follow-up period of 16 months

Statistical Analysis: It was determined that 6200 randomized patients and 1012 deaths would achieve 88.3% power (overall alpha = 0.05). The alpha level was 0.04 for all-cause mortality and 0.01 for the composite of cardiovascular death or hospitalization. The ITT population was used for the efficacy analyses. The mITT population (patients that received at least one dose of medication) was used for the safety analyses.

Results: A total of 6642 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. The average dose of eplerenone was 42.6 mg daily. Eplerenone demonstrated significantly lower rates of all-cause mortality and the composite outcome of cardiovascular death and cardiovascular hospitalization. While rates of the individual component of cardiovascular hospitalization were not significantly different between groups, rates of heart failure hospitalization were significantly lower in the eplerenone group.

Eplerenone (N=3319) Vs Placebo (N=3313)

All-Cause Mortality:
478 (14.4%) vs 554 (16.7%); RR 0.85 (95% CI 0.75-0.96)
p=0.008; ARR 2.32%; NNT ~44

Composite of Cardiovascular Death & Cardiovascular Hospitalization:
885 (26.7%) vs 993 (30.0%); RR 0.87 (95% CI 0.79-0.95)
p=0.002; ARR 3.31%; NNT ~31

Cardiovascular Death:
407 (12.3%) vs 483 (14.6%); RR 0.83 (95% CI 0.72-0.94)
p=0.005; ARR 2.32%; NNT ~44

Cardiovascular Hospitalization:
606 (18.3%) vs 649 (19.6%); RR 0.91 (95% CI 0.81-1.01); p=0.09

Heart Failure Hospitalization:
345 (10.4%) vs 391 (11.8%); RR 0.85 (95% CI 0.74-0.99)
p=0.03; ARR 1.41%; NNT ~72

Safety:

Hyperkalemia:
113 (3.40%) vs 66 (2.00%); p<0.001; ARI 1.41%; NNH ~70

Serum Potassium ≥ 6 mmol/L:
180 (5.42%) vs 126 (3.80%); p=0.002; ARI 1.63%; NNH ~61

Gynecomastia:
12 (0.36%) vs 14 (0.42%); p=0.70

Limitations:

- Cannot apply trial results to patients with heart failure and preserved ejection fraction

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I recommend the use of eplerenone (in addition to standard heart failure therapy) to further reduce the risk for morbidity and mortality outcomes in heart failure patients with reduced ejection fraction. Careful monitoring of serum potassium levels is warranted.

Efficacy:

- The rate of all-cause mortality was significantly lower in the eplerenone group compared to placebo
- The composite outcome of cardiovascular death and cardiovascular hospitalization was significantly lower in the eplerenone group
    - However, only the individual component of cardiovascular death was significantly lower in the eplerenone group
    - Rates of heart failure hospitalization were significantly lower with eplerenone

Safety:

- Hyperkalemia occurred at significantly higher rates in the eplerenone group (predictable effect of this drug class)
- There was no significant difference between treatment groups in the rate of gynecomastia

Cost:

- The cost of using eplerenone must be balanced against the cost-savings of preventing heart failure morbidity and mortality events
- However, the cost of monitoring for and managing hyperkalemia must be considered as well

Special Considerations/Populations:

- Eplerenone has a higher selectivity for the mineralocorticoid receptors than spironolactone, which also binds androgen and progesterone receptors
- Patients included in this trial had recent myocardial infarction (within 3-14 days)
- Cannot apply treatment results to heart failure patients with preserved ejection fraction

Grade of Recommendation: **A**

EPIC-HR

Hammond J, Leister-Tebbe H, Gardner A, et al. Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with COVID-19. *N Engl J Med*. 2022;386(15):1397-1408.

Objective: To determine the safety and efficacy of nirmatrelvir for treatment of SARS-CoV-2 infections in non-hospitalized adults at high-risk for progression to severe disease.

Primary Efficacy Measure: Composite of COVID-19 hospitalization or death from any cause

Participants: Patients with confirmed SARS-CoV-2 at high-risk for progression to severe disease

- Age ~46 years; male ~51%
- Symptom onset ≤ 3 days ~66%
- Positive serology ~51%; negative serology ~47%

Inclusion Criteria:

- Age ≥ 18 years
- Confirmed SARS-CoV-2 infection
- Symptom onset ≤ 5 days prior to randomization
- One or more characteristics/conditions associated with a high risk of progression to severe disease

Exclusion Criteria:

- Prior receipt of SARS-CoV-2 vaccine or convalescent COVID-19 plasma
- Previous confirmed SARS-CoV-2 infection or COVID-19 hospitalization
- Anticipated need for hospitalization within 48 hours of randomization

Drug: Nirmatrelvir/ritonavir

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients were randomized to receive either nirmatrelvir/ritonavir 300 mg/100 mg every 12 hours for 5 days or matching placebo.

Duration: 28 days

Statistical Analysis: It was determined that 1717 randomized patients (within 3 days of symptom onset) would achieve 90% power (alpha=0.05). The primary efficacy analysis used the modified ITT population which consisted of all patients that began treatment within 3 days after symptom onset.

Results: A total of 2246 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. The most common characteristics/conditions associated with increased risk of progression to severe disease were BMI ≥ 25 (~81%) and hypertension (~33%). Treatment effect was consistent across subgroup analysis. However, patients with positive SARS-CoV-2 serology at baseline demonstrated less robust treatment benefit compared to those with negative serology. The use of nirmatrelvir/ritonavir demonstrated significant reductions in viral load at day 5 compared to placebo, with greater reductions when initiated within 3 days of symptom onset ($p<0.001$). The overall rate of adverse events was similar between treatment groups. Dysgeusia (altered taste) occurred more often in the active treatment group than placebo (5.6% vs 0.3%).

Nirmatrelvir/Ritonavir (N=697) Vs Placebo (N=682)
patients treated within 3 days after symptom onset

Primary Efficacy Outcome:
5 (0.71%) vs 44 (6.45%); -5.81% (95% CI -7.78% to -3.84%)
p<0.001; ARR -5.73%; NNT ~18

COVID-19 Hospitalization:
5 (0.71%) vs 44 (6.45%)

All-Cause Mortality:
0 (0%) vs 9 (1.32%)

Nirmatrelvir/Ritonavir (N=1039) Vs Placebo (N=1046)
patients treated within 5 days after symptom onset

Primary Efficacy Outcome:
8 (0.77%) vs 66 (6.31%); -5.62% (95% CI -7.21% to -4.03%)
p<0.001; ARR -5.54%; NNT ~19

COVID-19 Hospitalization:
8 (0.77%) vs 65 (6.21%)

All-Cause Mortality:
0 (0%) vs 12 (1.15%)

Limitations:

- No patient had been vaccinated against COVID-19
- Power set but not met – failed to achieve 1717 patients randomized within 3 days of symptom onset (clinical significance minimal – statistical differences still detected)
- Although patients with known prior COVID-19 infection were excluded from the trial, roughly 50% of the patients included had a positive serology test for antibodies to SARS-CoV-2 (clinical significance of this finding is low given the nature of a pandemic and trial results demonstrating consistent benefit in this population)

Level of Evidence: Level II – with major limitations

Recommendation: For these reasons, I recommend the use of nirmatrelvir/ritonavir to reduce the risk for COVID-19 hospitalization and mortality in high-risk patients with confirmed SARS-CoV-2 infection. Treatment should be initiated within 5 days of symptom onset (ideally within 3 days).

Efficacy:

- The use of nirmatrelvir/ritonavir demonstrated significantly lower rates of the primary efficacy outcome compared to placebo
- Viral load was significantly lower in the active treatment group at day 5 compared to placebo

Safety:

- Overall adverse event rates were similar between treatment groups, with the exception of altered taste (higher in the active treatment group)
- The risk associated with drug-interactions due to CYP3A4 inhibition must be considered

Cost:

- The cost of using nirmatrelvir/ritonavir must be balanced against the cost-savings from decreased COVID-19 hospitalization and death

Special Considerations/Populations:

- Nirmatrelvir prevents viral replication by directly binding to and inhibiting SARS-CoV-2 main protease (Mpro)
- Ritonavir (CYP3A4 inhibitor) is used to boost circulating levels of nirmatrelvir
- Nirmatrelvir/ritonavir 300mg/100mg twice daily achieves plasma concentrations 5-6 times greater than the 90% effective concentration for SARS-CoV-2 viral inhibition
- The Mpro protease enzyme is conserved across coronaviruses which predicts that nirmatrelvir should retain activity against future variants (however, this is an uncertain extrapolation)
- The use of ritonavir requires careful consideration of serious drug interactions via CYP3A4 inhibition

Grade of Recommendation: **B**

ETHOS

Rabe KF, Martinez FJ, Ferguson GT, et al. Triple Inhaled Therapy at Two Glucocorticoid Doses in Moderate-to-Very-Severe COPD. *N Engl J Med*. 2020;383(1):35-48.

Objective: To compare the effect of triple-inhaled therapy (ICS-LAMA-LABA) to dual-inhaled therapy (ICS-LABA or LAMA-LABA) on morbidity and mortality outcomes in COPD patients.

Primary Efficacy Measure: Annual rate of moderate or severe COPD exacerbations

- Moderate: requiring systemic glucocorticoids, antibiotics or both for at least 3 days
- Severe: causing hospitalization or death

Secondary Efficacy Measure: All-cause mortality

Participants: High-risk COPD patients

- Age ~65 years; male ~60%
- Average number of COPD exacerbations in the previous 12 months ~1.7
- Baseline ICS ~80%

Inclusion Criteria:

- Age 40-80 years with symptomatic COPD (CAT score ≥ 10)
- ≥ 2 inhaled maintenance therapies
- Post-bronchodilator FEV_1 25-65% of predicted normal value
- FEV_1/FVC ratio < 0.7
- Smoking history ≥ 10 pack-years
- Documented history of ≥ 1 moderate-severe COPD exacerbations in the prior year

Exclusion Criteria:

- Asthma or other significant disease (excluding COPD)

Drugs: Budesonide-glycopyrrolate-formoterol inhalation (BGF); glycopyrrolate-formoterol inhalation (GF); budesonide-formoterol inhalation (BF)

Design: Randomized, double-blind, active-controlled trial

Methods: Eligible patients were randomized to receive inhaled BGF 160 mcg/9 mcg/4.8 mcg, inhaled BGF 80 mcg/9 mcg/4.8 mcg, inhaled GF 9 mcg/4.8 mcg or inhaled BF 160 mcg/4.8 mcg. All patients received two doses per day (4 puffs total daily). All inhalers were identical.

Duration: 52 weeks

Statistical Analysis: It was determined that 8400 randomized patients would provide 93% power (alpha = 0.05). The modified ITT population was used for the primary efficacy analyses (only on-treatment data from randomized patients).

Results: A total of 8588 patients underwent randomization with 8509 patients being included in the final efficacy analyses. Baseline characteristics were similar between treatment groups. Rates of annual COPD exacerbation were significantly lower in both triple-therapy groups compared to each of the dual-therapy groups. Exacerbation rates were not significantly different between the two triple-therapy groups. Rates of pneumonia were higher in the treatment groups that contained an inhaled corticosteroid compared to the LAMA-LABA group (3.5-4.5% vs 2.3%, respectively).

BGF 160/9/4.8 mcg (N=2137) Vs GF 9/4.8 mcg (N=2120)

Annual Rate of Moderate or Severe COPD Exacerbation:
1.08 vs 1.42; RR 0.76 (95% CI 0.69-0.83); p<0.001

All-Cause Mortality:
28 (1.31%) vs 49 (2.31%); HR 0.54 (95% CI 0.34-0.87); ARR 1.00%; NNT ~100

BGF 160/9/4.8 mcg (N=2137) Vs BF 9/4.8 mcg (N=2131)

Annual Rate of Moderate or Severe COPD Exacerbation:
1.08 vs 1.24; RR 0.87 (95% CI 0.79-0.95); p=0.003

All-Cause Mortality:
28 (1.31%) vs 34 (1.60%); HR 0.78 (95% CI 0.47-1.30)

BGF 80/9/4.8 mcg (N=2121) Vs GF 9/4.8 mcg (N=2120)

Annual Rate of Moderate or Severe COPD Exacerbation:
1.07 vs 1.42; RR 0.75 (95% CI 0.69-0.83); p<0.001

All-Cause Mortality:
39 (1.84%) vs 49 (2.31%); HR 0.79 (95% CI 0.52-1.20)

BGF 80/9/4.8 mcg (N=2121) Vs BF 9/4.8 mcg (N=2131)

Annual Rate of Moderate or Severe COPD Exacerbation:
1.07 vs 1.24; RR 0.86 (95% CI 0.79-0.95); p=0.002

All-Cause Mortality:
39 (1.84%) vs 34 (1.60%); HR 1.13 (95% CI 0.72-1.80)

Limitations:
- Cannot extrapolate trial results to other respiratory conditions (e.g. asthma)

Level of Evidence: Level I – with minor limitations

Recommendation: For these reasons, I recommend the use of triple-therapy (ICS-LAMA-LABA) over dual-therapy (ICS-LABA or LAMA-LABA) to further reduce morbidity and mortality in COPD patients with documented exacerbation within the previous year.

Efficacy:
- Rates of annual COPD exacerbation were significantly lower in both triple-therapy groups compared to both dual-therapy groups
- All-cause mortality was significantly lower in the BGF 160/9/4.8 mcg group compared to the LAMA-LABA group
- Mortality rates were not significantly different between any other treatment groups

Safety:
- Rates of pneumonia were higher in the steroid-containing therapy groups compared to the LAMA-LABA treatment group

Cost:
- The cost of using triple therapy (ICS-LAMA-LABA) over dual therapy (ICS-LABA or LAMA-LABA) must be balanced against the cost-savings from reduced rates of COPD exacerbations
- However, the increased costs associated with higher rates of pneumonia must be considered

Special Considerations/Populations:
- The majority of patients were receiving an inhaled corticosteroid at baseline
- Asthma patients were excluded from this trial

Grade of Recommendation: **A**

EUCLID

Hiatt WR, Fowkes FG, Heizer G, et al. Ticagrelor versus Clopidogrel in Symptomatic Peripheral Artery Disease. *N Engl J Med*. 2017;376(1):32-40.

Objective: To compare the effects of ticagrelor (reversible P2Y12 inhibitor) to clopidogrel (irreversible P2Y12 inhibitor) on cardiovascular outcomes in patients with symptomatic peripheral artery disease.

Primary Efficacy Measure: Composite of cardiovascular death, myocardial infarction or ischemic stroke

Primary Safety Measure: Major bleeding

Participants: Patients with symptomatic peripheral artery disease

- Age ~66 years; male ~72%
- Prior revascularization ~57%
- Ankle brachial index ~0.71

Inclusion Criteria:

- Age ≥ 50 with symptomatic peripheral artery disease
- Hemodynamic evidence of PAD (ABI ≤ 0.80) and/or revascularization of lower limbs > 30 days prior

Exclusion Criteria:

- Current or planned use of dual antiplatelet therapy or aspirin
- Increased bleed risk
- Treatment with long-term anticoagulant
- Poor CYP2C19 metabolizer

Drugs: Ticagrelor; clopidogrel

Design: Randomized, double-blind, active-comparison trial

Methods: Eligible patients underwent randomization to receive either ticagrelor 90 mg twice daily or clopidogrel 75 mg once daily.

Duration: Median follow-up period of 30 months

Statistical Analysis: It was initially determined that 11,500 randomized patients and 1596 primary endpoints would achieve 90% power, however due to a lower event rate the sample size was increased to 13,500 patients and the number of primary events was decreased to 1364 (resulting in 85% power). The ITT population was used for the primary and secondary analyses. The mITT population (patients that received at least one dose of study medication) was used for the safety analyses.

Results: A total of 13,885 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. Patients in the ticagrelor group discontinued therapy due to adverse drug reactions significantly more often than those in the clopidogrel group (30.1% vs 25.9%; $p<0.001$).

Ticagrelor (N=6930) Vs Clopidogrel (N=6955)

Composite of Cardiovascular Death, Myocardial Infarction or Ischemic Stroke:
751 (10.8%) vs 740 (10.6%); HR 1.02 (95% CI 0.92-1.13); p=0.65

Cardiovascular Death:
363 (5.24%) vs 343 (4.93%); HR 1.07 (95% CI 0.92-1.23); p=0.40

Myocardial Infarction:
349 (5.04%) vs 334 (4.80%); HR 1.06 (95% CI 0.91-1.23); p=0.48

Ischemic Stroke:
131 (1.89%) vs 169 (2.43%); HR 0.78 (95% CI 0.62-0.98)
p=0.03; ARR 0.55%; NNT ~182

Major Bleeding:
113 (1.63%) vs 109 (1.57%); HR 1.10 (95% CI 0.84-1.43); p=0.49

Dyspnea:
330 (4.76%) vs 52 (0.75%); p<0.001; ARI 4.01%; NNH ~24

Total Bleeding:
168 (2.42%) vs 112 (1.61%); p<0.001; ARI 0.81%; NNH ~122

Limitations:
- Patient population - cannot apply results to patients without peripheral artery disease
- The use of aspirin was not allowed in this trial

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I do not recommend the use of ticagrelor over clopidogrel for prevention of cardiovascular outcomes in patients with symptomatic peripheral artery disease. While rates of the primary efficacy outcome and major bleeding were similar between treatment groups the clopidogrel group demonstrated increased tolerability and a more favorable safety profile overall.

Efficacy:
- Rates of the primary composite outcome were not significantly different between groups
- However, the individual component of ischemic stroke occurred at a significantly lower rate in the ticagrelor group compared to the clopidogrel group

Safety:
- Rates of major bleeding were not significantly different between treatment groups
- However, the ticagrelor group demonstrated significantly higher rates of total bleeding compared to clopidogrel
- Dyspnea occurred at significantly higher rates with ticagrelor compared to clopidogrel
- Discontinuation rates due to adverse drug reactions were significantly higher with ticagrelor

Cost:
- The cost of using ticagrelor must be balanced against the cost of using clopidogrel
- The cost of managing bleeding events must also be considered

Special Considerations/Populations:
- The patient population must be considered when interpreting trial results
- The of dyspnea associated with ticagrelor usage is not fully understood but is thought to involve indirect stimulation of pulmonary vagal fibers and/or interactions with P2Y12 receptors on sensory neurons
- The dyspnea reaction with ticagrelor is not associated with changes in oxygen levels

Grade of Recommendation: **A**

EUROPA

Fox KM; EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomized, double-blind, placebo-controlled, multicenter trial (the EUROPA study). *Lancet*. 2003;362(9386):782-788.

Objective: To determine the effect of perindopril on cardiovascular event rates in patients with stable coronary heart disease without heart failure or substantial hypertension.

Primary Efficacy Measure: Composite of cardiovascular death, non-fatal myocardial infarction or cardiac arrest with successful resuscitation

Participants: Patients with stable coronary heart disease without heart failure or substantial hypertension

- Age ~60 years; male ~85%
- Prior myocardial infarction ~65%; angiographic evidence of coronary artery disease ~60%
- Platelet inhibitor ~91%; lipid-lowering therapy ~57%; beta-blocker ~61%
- BP ~137/82 mmHg; HR ~68 bpm

Inclusion Criteria:

- Age > 18 years
- No clinical evidence of heart failure
- Evidence of coronary heart disease (previous myocardial infarction, coronary revascularization, angiographic evidence of 70% narrowing of one or more major coronary arteries, history of chest pain and positive ECG)

Exclusion Criteria:

- Clinical evidence of heart failure
- Planned revascularization
- Hypotension (SBP < 110 mmHg)
- Uncontrolled hypertension (SBP > 180 mmHg)
- Recent use of ACEi/ARB (within previous month)
- Renal insufficiency
- Serum potassium > 5.5 mmol/L

Drug: Perindopril

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients underwent a 4 week run-in period where they received perindopril 4 mg daily for 2 weeks then 8 mg daily for 2 weeks, if tolerated. Patients that successfully completed the run-in period would then be randomized to either perindopril 8 mg daily or placebo for at least 3 years.

Duration: Mean follow-up period of 4.2 years

Statistical Analysis: It was determined that 775 primary events would provide 90% power (alpha=0.05). The ITT population was used for primary efficacy analyses. The significance level for the primary endpoint was adjusted to 0.041 to account for the interim analyses.

Results: A total of 12,218 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. In the perindopril group only ~7% of patients had their dosage decreased to 4 mg daily). Overall discontinuation rates were similar between treatment groups. The most common leading to discontinuation in the perindopril group was cough.

Perindopril (N=6110) Vs Placebo (N=6108)

Composite of Cardiovascular Death, Non-Fatal Myocardial Infarction or Cardiac Arrest with Successful Resuscitation:
488 (7.99%) vs 603 (9.87%); RRR 20% (95% CI 9% to 29%)
p=0.0003; ARR 1.89%; NNT ~53

Cardiovascular Death:
215 (3.52%) vs 249 (4.08%); RRR 14% (95% CI -3% to 28%); p=0.107

Non-Fatal Myocardial Infarction:
295 (4.83%) vs 378 (6.19%); RRR 22% (95% CI 10% to 33%)
p=0.001; ARR 1.36%; NNT ~74

Cardiac Arrest with Successful Resuscitation:
6 (0.10%) vs 11 (0.18%); RRR 46% (95% CI -47% to 80%); p=0.22

Heart Failure Hospitalization:
63 (1.03%) vs 103 (1.69%); RRR 39% (95% CI 17% to 56%)
p=0.002; ARR 0.66%; NNT ~153

Limitations:

- Patient population must be considered - stable coronary heart disease with no heart failure or substantial hypertension

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I recommend the use of perindopril to further reduce the risk for cardiovascular morbidity and mortality outcomes in patients with stable coronary heart disease without heart failure or substantial hypertension.

Efficacy:

- Rates of the primary composite outcome were significantly lower in the perindopril treatment group compared to placebo
- The individual component of non-fatal myocardial infarction occurred at significantly lower rates in the perindopril treatment group (the other components of the composite were not significantly different)
- Heart failure hospitalization rates were significantly lower in the perindopril group

Safety:

- Discontinuation rates due to cough were notably higher in the perindopril group compared to placebo (2.7% vs 0.5%)

Cost:

- The cost of using perindopril must be balanced against the cost-savings of preventing cardiac events, specifically non-fatal myocardial infarction

Special Considerations/Populations:

- Patient population must be considered when interpreting trial results (stable coronary heart disease without substantial hypertension or evidence of heart failure)
    - Relatively lower risk group in terms of secondary prevention

Grade of Recommendation: **A**

EXAMINE

White WB, Cannon CP, Heller SR, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med*. 2013;369(14):1327-1335.

Objective: To determine the effect of alogliptin on cardiovascular outcomes in high-risk patients with type 2 diabetes.

Primary Efficacy Measure: Composite of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke

Participants: Patients with type 2 diabetes and recent acute coronary syndrome

- Age ~61 years; male ~68%
- HgA1c ~8.0%
- Qualifying event: myocardial infarction ~77%

Inclusion Criteria:

- Diagnosis of type 2 diabetes
- HgA1c 6.5%-11% receiving treatment (HgA1c 7-11% if receiving insulin)
- Acute coronary syndrome within previous 15-90 days (acute myocardial infarction or hospitalization due to unstable angina)

Exclusion Criteria:

- Type 1 diabetes
- Unstable cardiac disorders
- Dialysis within 14 days of screening
- Receiving therapy with DPP-4 inhibitor or GLP-1 receptor agonist

Drug: Alogliptin

Design: Randomized, double-blind, placebo-controlled, non-inferiority trial

Methods: Eligible patients were randomized to receive either alogliptin (in addition to standard therapy) or matching placebo. The dosing for alogliptin was adjusted based on renal function. Patients with eGFR $\geq$ 60 mL/min received 25 mg daily, those with eGFR $\geq$ 30 mL/min received 12.5 mg daily and those with eGFR < 30 mL/min received 6.25 mg daily. The use of DPP-4 inhibitors or GLP-1 receptor agonists was not allowed.

Duration: Median follow-up period of 18 months (~1.5 years)

Statistical Analysis: This trial was designed to test for non-inferiority with subsequent testing specified for superiority. It was determined that 5400 randomized patients would achieve 91% power (alpha = 0.025). Non-inferiority would be determined if the upper limit of the 95% CI is < 1.3 and superiority would be determined if the upper limit is < 1.00. It was specified that an interim analysis would be performed after 550 primary events. If non-inferiority was determined but the conditional power for superiority (after 650 events) was $\leq$ 20% then the trial was to be stopped.

Results: A total of 5380 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. The trial was stopped early at the recommendation of the steering committee after non-inferiority (but not superiority) was demonstrated during the interim analysis. The overall average HgA1c difference between treatment groups was -0.36% favoring alogliptin ($p<0.001$). Most patients (~71%) were receiving alogliptin 25 mg daily with only ~26% receiving 12.5 mg daily. There was no significant difference in adverse drug reactions between treatment groups.

Alogliptin (N=2701) Vs Placebo (N=2679)

Cardiovascular Death, Non-Fatal Myocardial Infarction or Non-Fatal Stroke:
305 (11.3%) vs 316 (11.8%); HR 0.96 (95% CI ≤ 1.16); p=0.32

Cardiovascular Death:
89 (3.30%) vs 111 (4.14%); HR 0.79 (95% CI 0.60-1.04); p=0.10

Non-Fatal Myocardial Infarction:
187 (6.92%) vs 173 (6.46%); HR 1.08 (95% CI 0.88-1.33); p=0.47

Non-Fatal Stroke:
29 (1.07%) vs 32 (1.19%); HR 0.91 (95% CI 0.55-1.50); p=0.71

Heart Failure Hospitalization:
85 (3.15%) vs 79 (2.95%); HR 1.07 (95% CI 0.79-1.46); p=0.657

Limitations:
- Power set but not met - failed to randomize 5400 patients (clinical significance minimal)
- Patient population - all patients had recent acute coronary syndrome

Level of Evidence: Level II - with major limitations

Recommendation: For these reasons, I recommend alogliptin as a safe glucose-lowering agent in patients with type 2 diabetes and recent acute coronary syndrome. However, it may be reasonable to utilize other glucose-lowering therapies with demonstrated cardiovascular benefit in patients with established cardiac disease.

Efficacy:
- Alogliptin demonstrated non-inferiority (but superiority) to placebo regarding the rate of the cardiovascular composite outcome
- There was no significant difference in the rates of heart failure hospitalization

Safety:
- The rates of adverse drug reactions were not significantly different between treatment groups

Cost:
- The cost of using alogliptin must be balanced against the cost of other oral glucose-lowering therapies with demonstrated cardiovascular safety/benefit

Special Considerations/Populations:
- All patients had recent acute coronary syndrome (represents a high-risk demographic)

Grade of Recommendation: **B**

EXSCEL

Holman RR, Bethel MA, Mentz RJ, et al. Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med*. 2017;377(13):1228-1239.

Objective: To determine the effect of once-weekly exenatide on cardiovascular outcomes in patients with type 2 diabetes.

Primary Efficacy Measure: Composite of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke

Participants: Patients with type 2 diabetes at increased risk for cardiovascular event

- Age ~62 years; male ~62%
- HgA1c ~8.0%
- Baseline cardiovascular disease ~73%

Inclusion Criteria:

- Adult patients with type 2 diabetes
- HgA1c 6.5-10%
- 70% of patients with previous cardiovascular event
- 30% of patients with no prior cardiovascular event
- Previous glucose-lowering therapy with up to 3 agents

Exclusion Criteria:

- ≥ 2 severe hypoglycemic episodes within previous 12 months
- ESRD or eGFR < 30 mL/min
- Personal/family history of thyroid/pancreatic cancer
- Previous treatment with GLP-1 receptor agonist
- Baseline calcitonin level > 40 ng

Drug: Exenatide ER

Design: Randomized, double-blind, placebo-controlled, non-inferiority trial

Methods: Eligible patients were randomized to receive exenatide ER 2 mg once weekly injections or matching placebo. To minimize confounding factors, the use of open-label agents was encouraged to help patients achieve appropriate HgA1c levels. This included DPP-4 inhibitors but no other GLP-1 receptor agonists.

Duration: Median follow-up period of 3.2 years

Statistical Analysis: It was determined that 1360 patients would need to experience a primary event in order to achieve 85% power (alpha = 0.05). Non-inferiority would be tested first (NI margin of 1.3) with sequential testing for superiority. The ITT population was used for the primary analyses.

Results: A total of 14,752 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. The overall average HgA1c difference was -0.53% favoring exenatide ($p<0.001$). Exenatide demonstrated non-inferiority (but not superiority) over placebo regarding the primary composite. Rates of s, including pancreatitis and pancreatic cancer, were similar between treatment groups.

Exenatide ER (N=7356) Vs Placebo (N=7396)

Composite of Cardiovascular Death, Non-Fatal Myocardial Infarction or Non-Fatal Stroke:
839 (11.4%) vs 905 (12.2%); HR 0.91 (95% CI 0.83-1.00); p=0.06

Cardiovascular Death:
340 (4.62%) vs 383 (5.18%); HR 0.88 (95% CI 0.76-1.02)

Non-Fatal Myocardial Infarction:
455 (6.19%) vs 470 (6.35%); HR 0.95 (95% CI 0.84-1.09)

Stroke:
155 (2.11%) vs 177 (2.39%); HR 0.86 (95% CI 0.70-1.07)

Limitations:

- Patient population - majority had established cardiovascular disease at baseline
- Use of other glucose-lowering agents with known cardiovascular benefit, such as SGLT2 inhibitors, may have blunted the true treatment difference (clinical significance uncertain)

Level of Evidence: Level I - with major limitations

Recommendation: For these reasons, I recommend the use of exenatide ER as a safe glucose-lowering therapy in high-risk patients with type 2 diabetes. However, it would be reasonable to prefer other GLP-1 receptor agonists with demonstrated cardiovascular benefit over exenatide ER.

Efficacy:

- Exenatide ER demonstrated non-inferiority (but not superiority) to placebo regarding the rate of the cardiovascular composite outcome
- No individual component of the composite outcome was significantly different between treatment groups

Safety:

- Rates of adverse drug reactions were similar between treatment groups

Cost:

- The cost of using exenatide ER must be balanced against the cost of other GLP-1 agonists with demonstrated cardiovascular safety/benefit

Special Considerations/Populations:

- Trial allowed for use of DPP-4 inhibitors during trial (combo not recommended by ADA)

Grade of Recommendation: **A**

FIDELIO-DKD

Bakris GL, Agarwal R, Anker SD, et al. Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes. *N Engl J Med*. 2020;383(23):2219-2229.

Objective: To determine the effect of finerenone, a non-steroidal selective mineralocorticoid receptor antagonist, on cardiorenal outcomes in patients with diabetic kidney disease.

Primary Efficacy Measure: Composite of kidney failure (ESRD or eGFR < 15 mL/min), sustained decrease in eGFR ≥ 40% for at least 4 weeks, or death from renal causes

Secondary Efficacy Measure: Composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke or heart failure hospitalization

Participants: Patients with type 2 diabetes and chronic kidney disease

- Age ~66 years; male ~70%
- HgA1c ~7.7%; eGFR ~44 mL/min; UACR ~852 mg/g
- Baseline ACEi ~34%; ARB ~66%

Inclusion Criteria:

- Age ≥ 18 years with type 2 diabetes
- Chronic kidney disease (UACR 30 to <300 mg/g, eGFR 25 to <60 mL/min and history of diabetic retinopathy; or UACR 300-5000 mg/g and eGFR 25 to <75 mL/min)
- Receiving ACEi/ARB at maximally tolerated dose
- Serum potassium ≤ 4.8 mmol/L

Exclusion Criteria:

- Non-albuminuric chronic kidney disease
- Chronic kidney disease not due to type 2 diabetes

Drug: Finerenone

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients were randomized to receive finerenone or placebo. Dosing was adjusted based on renal function. Patients with eGFR ≥ 60 mL/min received finerenone 20 mg daily and patients with eGFR 25 to <60 mL/min received finerenone 10 mg daily. Dosing could be increased to 20 mg daily after one month if the serum potassium level was ≤ 4.8 mmol/L and kidney function was stable.

Duration: Median follow-up period of 2.6 years

Statistical Analysis: It was determined that 1068 primary events would be required to achieve 90% power (alpha=0.05). All randomized patients without critical trial design violations were included in the efficacy analyses. All randomized patients that received at least one dose of study medication were included in the safety analyses.

Results: A total of 5734 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. Rates of overall adverse drug reactions and discontinuations due to adverse drug reactions were similar between treatment groups. Hyperkalemia and discontinuation due to hyperkalemia were significantly higher in the finerenone group compared to placebo.

Finerenone (N=2833) Vs Placebo (N=2841)

Primary Renal Composite Outcome:
504 (17.8%) vs 600 (21.1%); HR 0.82 (95% CI 0.73-0.93)
p=0.001; ARR 3.33%; NNT ~30

Kidney Failure:
208 (7.34%) vs 235 (8.27%); HR 0.87 (95% CI 0.72-1.05)

Sustained Decrease in eGFR ≥ 40%:
479 (16.9%) vs 577 (20.3%); HR 0.81 (95% CI 0.72-0.92)
ARR 3.40%; NNT ~30

Death from Renal Causes:
2 (0.07%) vs 2 (0.07%)

Secondary Cardiovascular Composite Outcome:
367 (13.0%) vs 420 (14.8%); HR 0.86 (95% 0.75-0.99)
p=0.03; ARR 1.83%; NNT ~55

Cardiovascular Death:
128 (4.52%) vs 150 (5.28%); HR 0.86 (95% CI 0.68-1.08)

Non-Fatal Myocardial Infarction:
70 (2.47%) vs 87 (3.06%); HR 0.80 (95% CI 0.58-1.09)

Non-Fatal Stroke:
90 (3.18%) vs 87 (3.06%); HR 1.03 (95% CI 0.76-1.38)

Heart Failure Hospitalization:
139 (4.91%) vs 162 (5.70%); HR 0.86 (95% CI 0.68-1.08)

Safety:

Hyperkalemia:
516/2827 (18.3%) vs 255/2831 (9.01%)

Permanent Discontinuation due to Hyperkalemia:
64/2827 (2.26%) vs 25/2831 (0.88%)

Limitations:

- All patients were on ACEi/ARB at baseline - must be considered when interpreting results
- Cannot extrapolate results to patients without type 2 diabetes and chronic kidney disease

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I recommend the use of finerenone (in addition to ACEi/ARB therapy) to further decrease kidney disease progression in patients with type 2 diabetes and chronic kidney disease. However, I do not recommend finerenone strictly for cardiovascular risk reduction. If finerenone is to be used, careful monitoring of serum potassium is warranted.

Efficacy:

- Rates of the primary renal composite outcome were significantly lower in the finerenone group compared to placebo, however, only the individual component of sustained decreased in eGFR was significantly lower
- Rates of the secondary cardiovascular composite outcome were significantly lower in the finerenone group compared to placebo, although none of the individual components were significantly different between treatment groups
- While the composite outcomes for this trial demonstrate a general cardiorenal benefit of finerenone over placebo, the only individual component that was significantly lower with the finerenone group was sustained decreased in eGFR
    - The illustrates that the most reliable treatment effect is the slowing of kidney disease progression (versus cardiovascular risk reduction)

Safety:

- Overall rates of adverse drug reactions were similar between groups
- Rates of hyperkalemia and discontinuation due to hyperkalemia were notably higher in the finerenone group

Cost:

- The cost of using finerenone (in addition to ACEi/ARB therapy) must be balanced against the cost-savings of preventing kidney disease progression as well as cardiovascular morbidity and mortality
- However, the cost of monitoring for and managing hyperkalemia must also be considered

Special Considerations/Populations:

- Patient population must be considered when interpreting trial results - can only be applied to patients with type 2 diabetes and chronic kidney disease

Grade of Recommendation: **A**

FIGARO-DKD

Pitt B, Filippatos G, Agarwal R, et al. Cardiovascular Events with Finerenone in Kidney Disease and Type 2 Diabetes. *N Engl J Med*. 2021;385(24):2252-2263.

Objective: To determine the efficacy and safety of finerenone for prevention of cardiovascular events in patients with diabetic kidney disease.

Primary Efficacy Measure: Composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke or heart failure hospitalization

Secondary Efficacy Measures: Composite of kidney failure (end-stage kidney disease or eGFR < 15 mL/min), sustained eGFR decrease ≥ 40% from baseline or death from renal causes

Participants: Patients with type 2 diabetes and chronic kidney disease

- Age ~64 years; male ~69%
- HgA1c ~7.7%; eGFR ~68 mL/min; UACR ~308 mg/g
- History of cardiovascular disease ~45%

Inclusion Criteria:

- Age ≥ 18 years with type 2 diabetes
- Chronic kidney disease
    - UACR 30 mg/g to < 300 mg/g and eGFR 25-90 mL/min, or
    - UACR 300-5000 mg/g and eGFR ≥ 60 mL/min
- Receiving ACEi or ARB at max tolerated dose
- Serum potassium level ≤ 4.8 mmol/L

Exclusion Criteria:

- Symptomatic chronic heart failure with reduced ejection fraction
- HgA1c > 12%
- Stroke, TIA, ACS or heart failure hospitalization within previous 30 days
- Non-albuminuric chronic kidney disease
- Chronic kidney disease not due to type 2 diabetes

Drug: Finerenone

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients were randomized to receive finerenone or placebo. Patients with eGFR 25 to <60 mL/min received 10 mg daily initially. Patients with eGFR ≥ 60 mL/min received 20 mg daily initially. The target maintenance dose for finerenone was 20 mg daily, if tolerable.

Duration: Median follow-up period ~3.4 years

Statistical Analysis: It was determined that 976 primary events would achieve 90% power (alpha=0.049674). All randomized patients without critical trial design violations were included in the efficacy analyses. All randomized patients that received at least one dose of study medication were included in the safety analyses.

Results: A total of 7437 patients underwent randomization (7352 included in final analysis). Baseline patient characteristics were similar between treatment groups. The average dose of finerenone was 17.5 mg daily. Finerenone demonstrated significantly lower rates of the primary composite outcome, although only one individual component was statistically lower (heart failure hospitalization. There was no significant difference in rates of the secondary renal composite outcome between treatment groups. Rates of hyperkalemia were significantly higher in the finerenone group.

Finerenone (N=3686) Vs Placebo (N=3666)

Primary Cardiovascular Composite Outcome:
458 (12.4%) vs 519 (14.2%); HR 0.87 (95% CI 0.76-0.98)
p=0.03; ARR ~1.73%; NNT ~58

Cardiovascular Death:
194 (5.26%) vs 214 (5.84%); HR 0.90 (95% CI 0.74-1.09)

Non-fatal Myocardial Infarction:
103 (2.79%) vs 102 (2.78%); HR 0.99 (95% CI 0.76-1.31)

Non-fatal Stroke:
108 (2.93%) vs 111 (3.02%); HR 0.97 (95% CI 0.74-1.26)

Heart Failure Hospitalization:
117 (3.17%) vs 163 (4.44%); HR 0.71 (95% CI 0.56-0.90)
ARR 1.27%; NNT ~79

Secondary Renal Composite Outcome:
350 (9.50%) vs 395 (10.8%); HR 0.87 (95% CI 0.76-1.01)

Safety:

Hyperkalemia:
396/3683 (10.8%) vs 193/3658 (5.28%)
p < 0.0001; ARI 5.48%; NNH ~18

Serum Potassium Level > 5.5 mmol/L:
495/3677 (13.4%) vs 233/3655 (6.37%)
p < 0.0001; ARI 7.09%; NNH ~14

Hyperkalemia Leading to Hospitalization:
21/3683 (0.57%) vs 2/3658 (0.05%)
p=0.0002; ARI ~0.52%; NNH ~194

Limitations:

- All patients were on ACEi/ARB at baseline - must be considered when interpreting results
- Cannot extrapolate results to patients without type 2 diabetes and chronic kidney disease

Level of Evidence: Level I – with minor limitations

Recommendation: For these reasons, I do not recommend the use of finerenone (in addition to max tolerated ACEi or ARB) to reduce the risk of cardiovascular events in patients with type 2 diabetes and chronic kidney disease.

Efficacy:

- Finerenone demonstrated a significantly lower rate of the primary composite outcome, however the only component that was statistically lower than placebo was heart failure hospitalization
    - Demonstrates morbidity benefit (but not mortality benefit)
- There was no significant difference in rates of the secondary renal composite outcome

Safety:

- Rates of hyperkalemia, including hospitalization due to hyperkalemia were significantly higher in the finerenone group compared to placebo

Cost:

- The cost of using finerenone must be balanced against any potential cost-savings of preventing cardiovascular events (specifically heart failure hospitalization)
- However, the cost of monitoring for and managing hyperkalemia must also be considered

Special Considerations/Populations:

- Hyperkalemia is a known risk of MRA therapy; however, it can lead to serious arrhythmia if not monitored and managed appropriately
- The NNT for the primary composite outcome is less than the NNH for hyperkalemia, indicating that the risk of therapy is not outweighed by the benefit
- Finerenone demonstrated notable renal benefit (and limited cardiovascular benefit) in the FIDELIO-DKD trial, however this effect was not seen in the current trial
- Finerenone is a selective non-steroidal mineralocorticoid receptor antagonist
- Patients with kidney disease are at higher risk for cardiovascular events

Grade of Recommendation: **A**

FLAME

Wedzicha JA, Banerji D, Chapman KR, et al. Indacaterol-Glycopyrronium versus Salmeterol-Fluticasone for COPD. *N Engl J Med*. 2016;374(23):2222-2234.

Objective: To determine the efficacy and safety of LABA-LAMA therapy compared to LABA-ICS therapy in COPD patients at increased risk for exacerbations.

Primary Efficacy Measure: Annual rate of COPD exacerbations (mild, moderate or severe)

- Mild: worsening symptoms for > 2 days consecutively
- Moderate: requirement for systemic glucocorticoids, antibiotics or both
- Severe: requiring hospital admission or ER visit for >24 hours (plus systemic glucocorticoids, antibiotics or both)

Participants: COPD patients at increased risk for exacerbation

- Age ~65 years; male ~76%
- Current smoker ~40%
- COPD severity (GOLD 2015) Group D ~75%; Group B ~24%
- FEV_1 ~1.2 L (~44% of predicted value); FEV_1/FVC ratio ~0.44
- Baseline ICS ~56%

Inclusion Criteria:

- Age ≥ 40
- COPD grade ≥ 2 (modified Medical Research Council scale)
- FEV_1 25% to <60% of predicted value (post-bronchodilator)
- FEV_1/FVC ratio < 0.70
- One or more documented COPD exacerbations within previous year (received treatment with systemic glucocorticoids, antibiotics or both)

Exclusion Criteria:

- History of asthma
- History of lung transplant
- Oxygen therapy ≥ 12 hours per day

Drugs: Indacaterol-glycopyrronium (LABA-LAMA); salmeterol-fluticasone (LABA-ICS)

Design: Randomized, double-blind, active-controlled, non-inferiority trial

Methods: Eligible patients were randomized to receive inhaled indacaterol-glycopyrronium 110 mcg-50 mcg once daily (LABA-LAMA) or inhaled salmeterol-fluticasone 50 mcg-500 mcg twice daily (LABA-ICS) following a 4 week run-in period. The use of open-label salbutamol 100 mcg (aka albuterol) was available as a rescue medication.

Duration: 52 weeks

Statistical Analysis: It was determined that 3332 patients would need to undergo randomization to provide 95% power for non-inferiority. The non-inferiority margin was set at 1.15 based on a previous trial. The per-protocol population (patients that completed the trial without major protocol deviations) was used for the primary efficacy analysis. All other efficacy outcomes used the modified ITT population (patients that underwent randomization and received at least one dose of study medication). If non-inferiority was demonstrated (upper limit of 95% CI < 1.15) then testing for superiority (upper limit of 95% CI < 1.00) would be conducted. The level of significance was set at 0.05 for the non-inferiority and subsequent superiority analysis.

Results: A total of 3362 patients underwent randomization. A total of 3354 patients were included in the modified ITT population and 3084 patients were included in the per-protocol population. Baseline patient characteristics were similar between treatment groups. After trial conclusion, the use of LABA-LAMA demonstrated non-inferiority and superiority to LABA-ICS in reducing the rates of annual COPD exacerbations in this patient population. The patients in the LABA-LAMA group had a significantly longer time to first COPD exacerbation compared to the LABA-ICS group (71 days vs 51 days; $p<0.001$). The percentage of patients that achieved a clinically significant improvement in SGRQ-C score (score decrease ≥ 4) was higher in the LABA-LAMA group (49.2% vs 43.7%; $p<0.001$). Additionally, the average FEV_1 difference from baseline was +62 mL in favor of the LABA-LAMA group ($p<0.001$). This is notable because the LABA-LAMA group demonstrated an average FEV_1 improvement of +15 mL the LABA-ICS group demonstrated an average worsening of -48 mL from baseline.

LABA-LAMA (N=1528) Vs LABA-ICS (N=1556)

Annual Rate of COPD Exacerbations:
3.59 vs 4.03; RR 0.89 (95% CI 0.83-0.96); p=0.003

Total Exacerbations:
4943 vs 5438
Primarily mild (3678 vs 3986) and moderate (1056 vs 1211)

Safety:

Incidence of Pneumonia:
53/1678 (3.16%) vs 80/1680 (4.77%); p=0.02; ARI 1.60%; NNH ~62

Limitations:

- Patient population - cannot extrapolate trial results to other respiratory conditions

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I recommend the use of LABA-LAMA therapy over LABA-ICS therapy to reduce the rate of exacerbations in high-risk COPD patients.

Efficacy:

- LABA-LAMA treatment demonstrated non-inferiority and superiority to LABA-ICS treatment regarding the primary efficacy outcome
- Patients in the LABA-LAMA group experienced significantly greater improvements in objective (FEV_1) and subjective (SGRQ-C) measures compared to the LABA-ICS group
- The LABA-LAMA group experienced a significantly longer time to their first exacerbation

Safety:

- Overall adverse effect rates were similar between treatment groups
- Rates of pneumonia were significantly higher in the LABA-ICS group

Cost:

- The cost of using LABA-LAMA therapy versus LABA-ICS therapy must be balanced against the cost-savings of reduced COPD exacerbations
- The cost-savings from lower incidence of pneumonia must also be considered

Special Considerations/Populations:

- COPD exacerbations increase the rate of disease progression
- Long-term use of ICS is associated with increased risk for pneumonia
- SGRQ-C measures patient-perceived well-being and health status
- A 5-10% change in FEV_1 is considered clinically significant

Grade of Recommendation: **A**

FOURIER

Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. *N Engl J Med*. 2017;376(18):1713-1722.

Objective: To determine the safety and efficacy of evolocumab on morbidity and mortality outcomes in patients with established cardiovascular disease receiving statin therapy.

Primary Efficacy Measure: Composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina or coronary revascularization

Secondary Efficacy Measure: Composite of cardiovascular death, myocardial infarction or stroke

Participants: Patients with established ASCVD receiving statin therapy

- Age ~63 years; male ~75%
- Prior myocardial infarction ~81%; non-hemorrhagic stroke ~19%; peripheral artery disease ~13%
- High-intensity statin ~69%; moderate-intensity statin ~30%
- LDL ~92 mg/dL; HDL ~44 mg/dL; total cholesterol ~168 mg/dL

Inclusion Criteria:

- Age 40-85 years
- Clinically evident atherosclerotic cardiovascular disease (history of myocardial infarction, non-hemorrhagic stroke, or symptomatic peripheral artery disease)
- Fasting LDL ≥ 70 mg/dL (or non-HDL ≥ 100 mg/dL) on optimized lipid-lowering therapy
    - Defined as preferably high-intensity statin with or without ezetimibe

Exclusion Criteria:

- Myocardial infarction or stroke within 4 weeks of randomization
- History of hemorrhagic stroke
- Uncontrolled hypertension (SBP >180 mmHg or DBP > 110 mmHg)
- NYHA class III-IV or LVEF < 30%

Drug: Evolocumab

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients were randomized to receive subcutaneous evolocumab or matching placebo. Evolocumab was given subcutaneously as a 140 mg dose every 2 weeks or 420 mg every month.

Duration: Median follow-up period of 26 months

Statistical Analysis: It was determined that 1630 primary events would provide 90% power (alpha=0.05). The ITT population was used for the efficacy analyses. The modified ITT population (all randomized patients that received at least one dose of study medication) was used for the safety analyses. If statistically significant differences were detected for the primary and secondary composite outcomes, then testing for cardiovascular death would occur.

Results: A total of 27,564 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. At 48 weeks, the median LDL in the evolocumab group was 30 mg/dL. This represents an LDL difference of -56 mg/dL compared to the placebo group ($p<0.001$). The LDL lowering effect was maintained throughout the trial. Rates of the primary and secondary composite outcomes occurred at significantly lower rates in the evolocumab treatment group. Treatment effect was consistent upon subgroup analysis. Hierarchical testing failed to demonstrate a significant difference in the rates of cardiovascular death between groups. Therefore, any further statistical analysis of the remaining individual components must be considered exploratory only.

Evolocumab (N=13,784) Vs Placebo (N=13,780)

Primary Composite Outcome:
1344 (9.75%) vs 1563 (11.3%); HR 0.85 (95% CI 0.79-0.92)
p<0.001; ARR 1.59%; NNT ~63

Secondary Composite Outcome:
816 (5.92%) vs 1013 (7.35%); HR 0.80 (95% CI 0.73-0.88)
p<0.001; ARR 2.40%; NNT ~42

Cardiovascular Death:
251 (1.82%) vs 240 (1.74%); HR 1.05 (95% CI 0.88-1.25); p=0.62

Myocardial Infarction:
468 (3.40%) vs 639 (4.64%); HR 0.73 (95% CI 0.65-0.82); p<0.001; ARR 1.24%; NNT ~81

Stroke:
207 (1.50%) vs 262 (1.90%); HR 0.79 (95% CI 0.66-0.95); p=0.01; ARR 0.40%; NNT ~251

Hospitalization for Unstable Angina:
236 (1.71%) vs 239 (1.73%); HR 0.99 (95% CI 0.82-1.18); p=0.89

Coronary Revascularization:
759 (5.51%) vs 965 (7.00%); HR 0.78 (95% CI 0.71-0.86); p<0.001; ARR 1.50%; NNT ~67

Limitations:

- Patient population must be considered – all patients had established ASCVD
- Trial results must be considered in addition to baseline statin

Level of Evidence: Level I – with minor limitations

Recommendation: For these reasons, I recommend the use of evolocumab to further reduce the risk for cardiovascular morbidity outcomes in patients with established ASCVD and LDL levels ≥70 mg/dL despite baseline statin therapy (with or without ezetimibe).

Efficacy:

- LDL reduction was significantly greater in the evolocumab group
- Rates of the primary composite outcome occurred at significantly lower rates with evolocumab
    - This benefit was driven mainly by significant reductions in the frequency of the individual components of myocardial infarction, stroke and coronary revascularization
    - Rates of cardiovascular death and hospitalization for unstable angina were similar between treatment groups

Safety:

- No significant differences in safety events related to study medication were demonstrated

Cost:

- The cost of using evolocumab must be balanced against the cost-savings from reduced cardiovascular morbidity outcomes (myocardial infarction, coronary revascularization, etc.)

Special Considerations/Populations:

- Evolocumab is a PCSK9 inhibitor
- Eligible patients had LDL levels ≥ 70 mg/dL despite baseline statin therapy (with or without ezetimibe)

Grade of Recommendation: **A**

GISSI-HF

Tavazzi L, Maggioni AP, Marchioli R, et al. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomized, double-blind, placebo-controlled trial. *Lancet*. 2008;372(9645):1223-1230.

Objective: To determine the effect of n-3 polyunsaturated fatty acids (n-3 PUFA) on morbidity and mortality outcomes in patients with symptomatic heart failure.

Primary Efficacy Measures: (1) All-cause mortality (2) Composite of all-cause mortality or cardiovascular hospitalization

Participants: Patients with symptomatic heart failure (NYHA functional class II-IV)

- Age ~67 years; male ~78%
- LVEF ~33%
- NYHA class II ~63%; class III ~33%; class IV ~3%

Inclusion Criteria:

- Age ≥ 18 years
- Symptomatic heart failure (any cause)
- NYHA functional class II-IV
- LVEF ≤ 40% or heart failure hospitalization within previous 12 months

Exclusion Criteria:

- Non-cardiac morbidity
- Acute coronary syndrome or revascularization within previous 30 days
- Planned cardiac surgery
- Significant liver disease
- Pregnancy

Drug: n-3 polyunsaturated fatty acid

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients were randomized to receive either n-3 PUFA 1000 mg (EHA & DHA as ethyl esters) or matching placebo. Additionally, patients without contraindications to statins were randomized to receive rosuvastatin 10 mg or matching placebo. Treatments with proven benefit for heart failure patients were also recommended.

Duration: Mean follow-up period of 3.9 years

Statistical Analysis: It was determined that 1252 deaths would be required to achieve 90% power. The overall level of significance was set at 0.05 (all-cause mortality tested at 0.045 and composite tested at 0.01). The per protocol population was used for analysis of the co-primary efficacy outcomes. All other outcomes were analyzed using the ITT population.

Results: A total of 7046 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. It is important to note that the unadjusted HRs for the co-primary endpoints failed to demonstrate a statistically significant difference. For all-cause mortality, HR 0.93 (0.852-1.021); p=0.124. For the composite of all-cause mortality or cardiovascular hospitalization, HR 0.94 (0.869-1.022); p=0.059. Deaths due to worsening heart failure accounted for the largest portion of all-cause mortality. However, there was no significant difference in rates of mortality due to worsening heart failure. There was no significant difference in discontinuation rates or rates between treatment groups.

n-3 PUFA (N=3494) Vs Placebo (N=3481)

All-Cause Mortality:
955 (27.3%) vs 1014 (29.1%); HR 0.91 (0.833-0.998)
p=0.041; ARR 1.80%; NNT ~56

Heart Failure Mortality:
319 (9.13%) vs 332 (9.54%); HR 0.92 (95% CI 0.79-1.07); p=0.275

Composite of All-Cause Mortality or Cardiovascular Hospitalization:
1981 (56.7%) vs 2053 (59.0%); HR 0.92 (95% CI 0.849-0.999)
p=0.009; ARR 2.28%; NNT ~44

Cardiovascular Hospitalization:
1635 (46.8%) vs 1687 (48.5%); HR 0.93 (95% CI 0.87-0.99)
p=0.026; ARR 1.67%; NNT ~60

Heart Failure Hospitalization:
978 (28.0%) vs 995 (28.6%); HR 0.94 (95% CI 0.86-1.02); p=0.147

The above HRs were adjusted for covariates of baseline heart failure admission within previous year, previous use of pacemaker and aortic stenosis ($p<0.1$)

The unadjusted HRs failed to demonstrate a statistically significant difference

Limitations:
- Statistical analyses - adjusting based on variables that were unbalanced at baseline is not a recommended practice (stated directly in article)
- Unadjusted HRs do not demonstrate significant difference between treatment groups for the co-primary efficacy measures
- Data on rosuvastatin usage not provided - potential confounding factor

Level of Evidence: Level I - with major limitations

Recommendation: For these reasons, I do not recommend the use of n-3 PUFA to further reduce the risk for cardiovascular morbidity and mortality outcomes in patients with symptomatic heart failure.

Efficacy:
- After adjustment, the rates of both co-primary efficacy measures were significantly lower in the n-3 PUFA treatment group compared to placebo
    - However, the rates of heart failure mortality and heart failure hospitalization were not significantly different between treatment groups
- It is also important to note that prior to adjustment there was no significant difference demonstrated for either co-primary efficacy measure

Safety:
- There was no noted difference in the rates of adverse drug reactions between groups

Cost:
- The cost of using n-3 PUFA must be balanced against the cost-savings achieved from any potential treatment benefit (not clearly demonstrated in this trial)

Special Considerations/Populations:
- Statistical analysis including non-recommended adjustments
- Use of rosuvastatin creates a potential confounding factor for treatment results
- Patients were primarily NYHA functional class II

Grade of Recommendation: **B**

HARMONY OUTCOMES

Hernandez AF, Green JB, Janmohamed S, et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomized placebo-controlled trial. *Lancet*. 2018;392(10157):1519-1529.

Objective: To determine the effect of albiglutide on cardiovascular outcomes in patients with type 2 diabetes.

Primary Efficacy Measures: Composite of cardiovascular death, myocardial infarction or stroke

Participants: Patients with type 2 diabetes and established cardiovascular disease

- Age ~64 years; male ~70%
- HgA1c ~8.7%
- Coronary artery disease ~70%

Inclusion Criteria:

- Age ≥ 40 years with type 2 diabetes
- Established coronary, cerebrovascular or peripheral artery disease
- HgA1c > 7.0%

Exclusion Criteria:

- eGFR < 30 mL/min
- Severe gastroparesis
- Previous pancreatitis or increased risk
- Personal/family history of thyroid/pancreatic cancer
- Current usage of GLP-1 receptor agonist

Drug: Albiglutide

Design: Randomized, double-blind, placebo-controlled, non-inferiority trial

Methods: Eligible patients were randomized to receive either albiglutide weekly injections or matching placebo. The initial dose of treatment medication was 30 mg once weekly for 5 weeks, which could be increased to 50 mg once weekly if indicated. Other glucose-lowering therapy (other than GLP-1 receptor agonists) could be added to achieve local guideline goals.

Duration: Median follow-up period of 1.6 years

Statistical Analysis: It was determined that 611 primary events would need to occur to achieve 90% power for non-inferiority. Non-inferiority would be tested first (NI margin of 1.3) with sequential testing for superiority. The ITT population was used for primary analyses.

Results: A total of 9,463 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. The average HgA1c difference at 16 months was -0.52% favoring albiglutide over placebo. The maximum dosage of 50 mg weekly was achieved in ~50% of patients. Rates of s, including pancreatitis and pancreatic cancer, were similar between treatment groups.

Albiglutide (N=4731) Vs Placebo (N=4732)

Composite of Cardiovascular Death, Myocardial Infarction or Stroke:
338 (7.14%) vs 428 (9.04%); HR 0.78 (95% CI 0.68-0.90)
p=0.0006; ARR 1.90%; NNT ~53

Cardiovascular Death:
122 (2.58%) vs 130 (2.75%); HR 0.93 (95% CI 0.73-1.19); p=0.578

Myocardial Infarction:
181 (3.83%) vs 240 (5.07%); HR 0.75 (95% CI 0.61-0.90)
p=0.003; ARR 1.25%; NNT ~81

Stroke:
94 (1.99%) vs 108 (2.28%); HR 0.86 (95% CI 0.66-1.14); p=0.3

Limitations:

- Patient population - primarily had established coronary artery disease
- Use of other glucose-lowering agents with known cardiovascular benefit, such as SGLT2 inhibitors, may have blunted the true treatment benefit (clinical significance unknown)

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I recommend the use of albiglutide as a safe glucose-lowering therapy and for reducing cardiovascular events in patients with type 2 diabetes and established cardiovascular disease.

Efficacy:

- Non-inferiority and superiority were demonstrated for albiglutide compared to placebo for the cardiovascular composite outcome
- The individual component of myocardial infarction occurred at significantly lower rates in the albiglutide group

Safety:

- Injection site reactions were significantly higher in the albiglutide group (predictable of injectable GLP-1 agonist therapy)
- Rates of pancreatitis and pancreatic cancer were similar between treatment groups

Cost:

- The cost of using albiglutide must be balanced against the cost-savings achieved from preventing cardiovascular events (specifically, myocardial infarction)

Special Considerations/Populations:

- The majority of patients (~70%) had established coronary artery disease at baseline

Grade of Recommendation: **A**

HOPE

Heart Outcomes Prevention Evaluation Study Investigators, Yusuf S, Sleight P, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med*. 2000;342(3):145-153.

Objective: To determine the effect of ramipril on cardiovascular events in high-risk patients without evidence of heart failure.

Primary Efficacy Measure: Composite of cardiovascular death, myocardial infarction or stroke

Secondary Efficacy Measures: (1) All-cause mortality (2) Revascularization (3) Heart failure hospitalization (4) Hospitalization due to unstable angina (5) Complications due to diabetes

Participants: Patients at high-risk for cardiovascular event without evidence of heart failure or left ventricular dysfunction

- Age ~66 years; male ~74%
- History of coronary artery disease ~80% (myocardial infarction ~52%); peripheral vascular disease ~43%; stroke ~10%
- BP ~139/79 mmHg; HR ~69 bpm

Inclusion Criteria:

- Age ≥ 55 years old
- History of coronary artery disease, stroke, PVD or diabetes plus one additional risk factor (hypertension, elevated total cholesterol, low HDL, smoker or microalbuminuria)

Exclusion Criteria:

- Known heart failure
- LVEF < 40%
- Currently using ACEi or vitamin E
- Uncontrolled hypertension
- Overt nephropathy
- Myocardial infarction or stroke within previous 4 weeks

Drug: Ramipril

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients underwent a run-in period where all received ramipril 2.5 mg daily for 7-10 days, followed by matching placebo for 10-14 days. Those who successfully completed the run-in period were randomized to receive ramipril 10 mg daily (titrated up from 2.5 mg) or matching placebo.

Duration: Mean follow-up period of ~5 years

Statistical Analysis: It was determined that 9000 randomized patients would achieve 90% power (alpha=0.05). The ITT population was used for all efficacy analyses.

Results: A total of 9297 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. The average blood pressure at study conclusion was 136/76 mmHg in the ramipril group and 139/77 mmHg in the placebo group. Overall discontinuation rates were similar between treatment groups, however the most common reason related to side-effects in the ramipril group was cough.

Ramipril (N=4645) Vs Placebo (N=4652)

Composite of Cardiovascular Death, Myocardial Infarction or Stroke:
651 (14.0%) vs 826 (17.8%); RR 0.78 (95% CI 0.70-0.86)
p<0.001; ARR 3.74%; NNT ~27

Cardiovascular Death:
282 (6.07%) vs 377 (8.10%); RR 0.74 (95% CI 0.64-0.87)
p<0.001; ARR 2.03%; NNT ~50

Myocardial Infarction:
459 (9.88%) vs 570 (12.3%); RR 0.80 (95% CI 0.70-0.90)
p<0.001; ARR 2.37%; NNT ~43

Stroke:
156 (3.36%) vs 226 (4.86%); RR 0.68 (95% CI 0.56-0.84)
p<0.001; ARR 1.50%; NNT ~67

All-Cause Mortality:
482 (10.4%); 569 (12.2%); RR 0.84 (95% CI 0.75-0.95)
p=0.005; ARR 1.85%; NNT ~54

Revascularization:
742 (16.0%) vs 852 (18.3%); RR 0.85 (95% CI 0.77-0.94)
p=0.002; ARR 2.34%; NNT ~43

Heart Failure Hospitalization:
141 (3.04%) vs 160 (3.44%); RR 0.88 (95% CI 0.70-1.10); p=0.25

Hospitalization due to Unstable Angina:
554 (11.9%) vs 565 (12.1%); RR 0.98 (95% CI 0.87-1.10); p=0.68

Complications Due to Diabetes:
299 (6.44%) vs 354 (7.61%); RR 0.84 (95% CI 0.72-0.98)
p=0.03; ARR 1.17%; NNT ~86

Limitations:

- Patient population - no evidence of heart failure or left ventricular dysfunction

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I recommend the use of ramipril to reduce morbidity and mortality rates in high-risk patients without heart failure or left ventricular dysfunction.

Efficacy:

- Rates of the primary composite outcome, as well as all individual components, were significantly lower in the ramipril group compared to placebo
- Rates of all-cause mortality, revascularization and complications due to diabetes were all significantly lower in the ramipril group compared to placebo

Safety:

- The most common cause of discontinuation in the ramipril group was cough (known adverse effect of ACEi therapy)

Cost:

- The cost of using ramipril must be balanced against the cost-savings from preventing morbidity and mortality outcomes

Special Considerations/Populations:

- The majority of patients had coronary artery disease at baseline, specifically history of myocardial infarction

Grade of Recommendation: **A**

HPS2-THRIVE

HPS2-THRIVE Collaborative Group, Landray MJ, Haynes R, et al. Effects of extended-release niacin with laropiprant in high-risk patients. *N Engl J Med*. 2014;371(3):203-212.

Objective: To determine the effect of niacin ER (plus laropiprant) on cardiovascular outcomes in patients with established cardiovascular disease receiving statin therapy

Primary Efficacy Measures: Composite of major coronary events (death from coronary causes or non-fatal myocardial infarction), total stroke or revascularization

Participants: Patients with established cardiovascular disease on statin-based therapy

- Age ~65 years; male ~82%
- Coronary artery disease ~78%; cerebrovascular disease ~32%; PAD ~13%
- LDL ~63 mg/dL; HDL ~44 mg/dL; total cholesterol ~128 mg/dL

Inclusion Criteria:

- Age 50-80 years
- History of myocardial infarction, cerebrovascular disease, peripheral artery disease or diabetes plus symptomatic coronary disease

Exclusion Criteria:

- Hepatic/renal/muscle disease
- Receiving LDL-lowering therapy more effective than simvastatin/ezetimibe 40 mg/10 mg

Drugs: Niacin ER plus laropiprant

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients underwent a run-in period involving titrating up to simvastatin 40 mg (with or without ezetimibe 10 mg) daily by week 4, followed by the addition of niacin ER 1000 mg plus laropiprant 20 mg daily for 4 weeks, then increasing to niacin ER 2000 mg plus laropiprant 40 mg daily for 3-6 weeks. Those who successfully completed the run-in period were randomized to receive niacin ER 2000 mg plus laropiprant 40 mg daily or matching placebo in addition to the baseline simvastatin (+/- ezetimibe).

Duration: Median follow-up period of 3.9 years

Statistical Analysis: It was initially determined that 20,000 randomized patients would achieve 95% power (alpha = 0.05). However, due to minimal changes in lipid levels during the run-in period the sample size was increased to 25,000 patients to achieve 80% power (assuming 3,400 major vascular events). The ITT population was used for the primary efficacy analyses.

Results: A total of 25,673 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. The niacin ER group demonstrated the following mean changes in lipid lab values: 10 mg/dL decrease in LDL, 6 mg/dL increase in HDL and 33 mg/dL decrease in triglycerides (as compared to placebo). Rates of all-cause mortality were nominally higher in the niacin ER group compared to placebo. Discontinuation rates were significantly higher in the niacin ER group compared to placebo (25.4% vs 16.6%; p<0.001), driven primarily by medication side effects.

Niacin ER (N=12,838) Vs Placebo (N=12,835)

Composite of Major Coronary Event, Stroke or Revascularization:
1696 (13.2%) vs 1758 (13.7%); RR 0.96 (95% CI 0.90-1.03); p=0.29

Major Coronary Event:
668 (5.20%) vs 694 (5.41%); RR 0.96 (95% CI 0.87-1.07); p=0.51

Death from Coronary Causes:
302 (2.35%) vs 291 (2.27%)

Non-Fatal Myocardial Infarction:
402 (3.13%) vs 431 (3.36%)

Total Stroke:
498 (3.88%) vs 499 (3.89%); RR 1.00 (95% CI 0.88-1.13); p=0.56

Revascularization:
807 (6.29%) vs 897 (6.99%); RR 0.90 (95% CI 0.82-0.99)
p=0.03; ARR 0.70%; NNT ~143

All-Cause Mortality:
798 (6.22%) vs 732 (5.70%); RR 1.09 (95% CI 0.99-1.21); p=0.08

Safety:

Gastrointestinal Event:
620 (4.83%) vs 491 (3.83%); RR 1.28 (95% CI 1.13-1.44)
p<0.001; ARI 1.00%; NNH ~99

Musculoskeletal Event:
481 (3.75%) vs 385 (3.00%); RR 1.26 (95% CI 1.10-1.44)
p<0.001; ARI 0.75%; NNH ~134

Glucose Disturbance in Patients with Diabetes:
460/4134 (11.1%) vs 311/4165 (7.47%); RR 1.55 (95% CI 1.34-1.78)
p<0.001; ARI 3.66%; NNH ~27

New-Onset Diabetes:
494/8704 (5.68%) vs 376/8670 (4.34%); RR 1.32 (95% CI 1.16-1.51)
p<0.001; ARI 1.34%; NNH ~74

Limitations:

- Patient population - all were receiving statin therapy at time of randomization
- The majority of patients had established ASCVD at baseline

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I do not recommend the use of niacin ER plus laropiprant to further reduce the risk for morbidity and mortality outcomes in patients with established cardiovascular disease on statin therapy.

Efficacy:

- The addition of niacin ER plus laropiprant to simvastatin (+/- ezetimibe) failed to demonstrate significantly lower rates of the primary composite outcome
    - The individual component of revascularization occurred at significantly lower rates in the niacin ER group
- All-cause mortality was nominally (but not significantly) higher in the niacin ER group

Safety:

- Rates of discontinuation (due primarily to medication side effects) were significantly higher in the niacin ER group
- It is notable that rates of glucose disturbances in patients with baseline diabetes as well as new-onset diabetes occurred at significantly higher rates in the niacin ER group

Cost:

- The cost of using niacin ER plus laropiprant must be balanced against the potential cost-savings from preventing a clinical outcome (not clearly demonstrated in this trial)
- The cost of monitoring and managing blood sugar disturbances and treating new-onset diabetes must also be considered

Special Considerations/Populations:

- Laropiprant is a prostaglandin antagonist that is used to decrease niacin flushing and improve adherence (however, the niacin ER group still demonstrated higher discontinuation rates compared to placebo)

Grade of Recommendation: **A**

HPTN 083

Landovitz RJ, Donnell D, Clement ME, et al. Cabotegravir for HIV Prevention in Cisgender Men and Transgender Women. *N Engl J Med*. 2021;385(7):595-608.

Objective: To determine the efficacy and safety of injectable cabotegravir compared to tenofovir disoproxil fumarate-emtricitabine for prevention of HIV infection.

Primary Efficacy Measure: Incidence of HIV infection

Participants: Patients at increased risk for HIV infection
- Age ~26 years
- Men who have sex with men ~87%
- Transgender women who have sex with men ~13%

Inclusion Criteria:
- Age ≥ 18 years
- Cisgender men who have sex with men or transgender women who have sex with men
- Negative HIV serologic test at enrollment
- Undetectable HIV RNA viral load within 14 days before trial entry
- CrCl ≥ 60 mL/min

Exclusion Criteria:
- Use of illicit IV drugs within previous 90 days
- Participation in active treatment group of HIV vaccine trial
- Coagulopathy
- Seizure disorder
- QTc > 500 msec
- Positive hepatitis B virus surface antigen test
- Positive hepatitis C virus antibody test

Drugs: Cabotegravir intramuscular injection; tenofovir disoproxil fumarate-emtricitabine (TDF-FTC)

Design: Randomized, double-blind, active-controlled, non-inferiority trial

Methods: Eligible patients were randomized to receive cabotegravir intramuscular injection or TDF-FTC following an oral-tablet lead-in phase. Patients that successfully completed the lead-in phase received either cabotegravir 600 mg injections intramuscularly into the gluteus (two doses 4 weeks apart, then every 8 weeks thereafter) or oral TDF-FTC 300 mg-200 mg once daily (plus matching placebo).

Duration: Median follow-up period ~1.4 years

Statistical Analysis: It was determined that 172 incident HIV infections would need to occur to provide 90% power to detect non-inferiority (alpha = 0.025). The non-inferiority margin was set at 1.23 based on previous placebo-controlled trials. If non-inferiority was demonstrated the trial protocol states that a hazards ratio less than or equal to 0.74 would demonstrate superiority of cabotegravir over TDF-FTC. The modified ITT population (excluded patients found to have HIV infection at enrollment) was used for the primary efficacy analysis. The trial protocol originally included criteria for stopping the trial early upon crossing a superiority boundary, however due to concerns surrounding the COVID-19 pandemic this criterion was modified to crossing the non-inferiority boundary.

Results: A total of 4570 patients underwent randomization of which 4566 went on to receive study medication. Baseline characteristics were similar between treatment groups. A total of 76 patients were excluded from the primary efficacy analysis due to testing positive for HIV prior to enrollment (5 patients) or failure to receive follow-up HIV testing after enrollment (71 patients). The trial was stopped early due to interim analysis demonstrating clear benefit of cabotegravir over TDF-FTC. Adherence was determined to be ~74% in the TDF-FTC group and ~92% in the cabotegravir group. It is important to note that of the total number of HIV infections in the cabotegravir group, only 4 infections occurred in those patients that were adherent to the CAB-LA doses. The rest occurred in patients with no recent exposure to the drug or before the lead-in phase ended.

Cabotegravir (N=2247) Vs TDF-FTC (N=2243)

Incident HIV Infection:
13 (0.41 per 100 person-years) vs 39 (1.22 per 100 person-years)
HR 0.34 (95% CI 0.18-0.62); p<0.001
0.58% vs 1.73%; ARR 1.15%; NNT ~88

There was no significant difference in overall rates of adverse effects between treatment groups. In the cabotegravir group, injection-site reactions were reported in ~81% of patients. Pain and tenderness were the most common reactions, beginning the day after injection and lasting on average 3 days. Approximately 2.4% of patients in the cabotegravir group discontinued treatment permanently due to injection-site reaction.

Limitations:
- Power set but not met - failed to achieve 172 incident infections (clinical significance low)
- Patient population - cisgender MSM and transgender women who have sex with men

Level of Evidence: Level II - with major limitations

Recommendation: For these reasons, I recommend the use of long-acting injectable cabotegravir over oral TDF-FTC for prevention of incident HIV infection in cisgender MSM and transgender women who have sex with men.

Efficacy:
- The cabotegravir group demonstrated non-inferiority and subsequent superiority over TDF-FTC for prevention of incident HIV infection in this patient population
- Adherence was notably higher in the cabotegravir group, likely due to the administration requirements for the long-acting injectable formulation

Safety:
- The rates of overall adverse effects were similar between treatment groups
- Injection site reaction was reported in most patients in the cabotegravir group, however only a small percentage permanent discontinued treatment due to this adverse effect

Cost:
- The cost of using injectable cabotegravir over oral TDF-FTC must be considered
- The cost-savings of preventing incident HIV infection (using cabotegravir) must also be considered

Special Considerations/Populations:
- Use of the long-acting injectable cabotegravir requires intramuscular administration into the gluteus by a trained healthcare worker every 8 weeks (after initial dosing) which may pose a barrier to therapy in patients unable to regularly attend scheduled clinic appointments
- Cabotegravir is an integrase strand inhibitor (different mechanism from TDF-FTC; NRTIs)
- The results included here are from the blinded phase of the trial

Grade of Recommendation: **B**

HYVET

Beckett NS, Peters R, Fletcher AE, et al. Treatment of hypertension in patients 80 years of age or older. *N Engl J Med*. 2008;358(18):1887-1898.

Objective: To determine the efficacy and safety of antihypertensive therapy in patients ≥ 80 years old.

Primary Efficacy Measure: Total stroke (fatal or non-fatal)

Secondary Efficacy Measures: (1) All-cause mortality (2) Cardiovascular death (3) Fatal stroke

Participants: Patients age ≥ 80 with sustained hypertension

- Age ~84; male ~40%
- Seated BP ~173/91 mmHg; HR ~75 bpm
- Baseline cardiovascular disease ~12%

Inclusion Criteria:

- Age ≥ 80 years
- Sustained SBP ≥ 160 mmHg

Exclusion Criteria:

- Accelerated/secondary hypertension
- Hemorrhagic stroke within prior 6 months
- Heart failure requiring antihypertensive medications
- SCr > 1.7 mg/dL
- Serum potassium level < 3.5 mmol/L or > 5.5 mmol/L
- Gout or dementia
- Requirement of nursing care

Drugs: Indapamide SR; perindopril

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients were instructed to stop all previous antihypertensive medications and take only a single placebo tablet once daily for 2 months while having blood pressure monitored in the clinic periodically. If the mean SBP readings were between 160-199 mmHg, then patients were eligible to undergo randomization to receive either indapamide SR 1.5 mg daily or matching placebo. The addition of perindopril 2-4 mg daily (or matching placebo) could be added at the investigator's discretion to achieve target SBP < 150 mmHg and DBP < 80 mmHg. The use of additional BP lowering agents for > 3 months would result in withdrawal from the double-blind follow-up period (option for open follow-up). Patients were also withdrawn from double-blind follow-up if while on max dosing of study medications SBP ≥ 220 mmHg or DBP ≥ 110 mmHg for two consecutive visits at least two weeks apart.

Duration: Mean follow-up period of 1.8 years

Statistical Analysis: It was determined that 10,500 patient-years of follow-up would be required to achieve 90% power (alpha = 0.01). The ITT population was used for primary efficacy analyses.

Results: The trial was stopped early after interim analysis showed a clear benefit of active treatment over placebo. A total of 3845 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. Average seated blood pressure was ~15.0/6.1 mmHg lower in the active treatment group compared to placebo at 2 years. The target blood pressure was achieved in ~48% of the active treatment group and ~20% of placebo patients ($p<0.001$).

After 2 years, 25.8% of patients in the active treatment group were on indapamide alone, 23.9% were on indapamide plus perindopril 2 mg and 49.5% were on indapamide plus perindopril 4 mg daily. Overall rates were significantly lower in the active treatment group (p<0.001). There was no significant difference between treatment groups in potassium, uric acid, glucose or SCr levels.

Active Treatment (N=1933) Vs Placebo (N=1912)

Total Stroke:
51 (2.64%) vs 69 (3.61%); HR 0.70 (95% CI 0.49-1.01); p=0.06

Fatal Stroke:
27 (1.40%) vs 42 (2.20%); HR 0.61 (95% CI 0.38-0.99)
p=0.046; ARR 0.80%; NNT ~125

All-Cause Mortality:
196 (10.1%) vs 235 (12.3%); HR 0.79 (95% CI 0.65-0.95)
p=0.02; ARR 2.15%; NNT ~47

Cardiovascular Death:
99 (5.12%) vs 121 (6.33%); HR 0.77 (95% CI 0.60-1.01); p=0.06

Limitations:

- Power set but not met due to trial being stopped early - clinical significance is uncertain as the primary outcome was not significantly different between treatment groups, although rates of all-cause mortality and fatal stroke were significantly lower in the active group
- Patients had previously been treated with antihypertensive therapy prior to trial initiation
- Patient population - only a small percentage had baseline cardiovascular disease which must be considered when interpreting trial results
- Rates of hypotension were not reported in this trial

Level of Evidence: Level II - with major limitations

Recommendation: For these reasons, I recommend the use of antihypertensive therapy to reduce rates of morbidity and mortality in patients ≥ 80 years old with sustained hypertension. However, the risk for hypotension must be carefully considered when deciding to initiate or adjust therapy.

Efficacy:

- The rate of total stroke was not significantly different between treatment groups
- Rates of fatal stroke were significantly lower in the active group compared to placebo
- All-cause mortality occurred at significantly lower rates in the active treatment group, however rates of cardiovascular death were not significantly different between treatment groups

Safety:

- Overall rates of adverse drug reactions were significantly lower with active treatment
- There was no significant difference in lab values of interest between treatment groups

Cost:

- The cost of using indapamide SR with/without perindopril must be balanced against the cost-savings from preventing cardiovascular morbidity and mortality outcomes

Special Considerations/Populations:

- It is important to note that the target blood pressure in this trial was <150/80 mmHg
- Patient age must be carefully considered when interpreting results
- Few patients had established cardiovascular disease at baseline

Grade of Recommendation: **B**

IDNT

Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med*. 2001;345(12):851-860.

Objective: To compare the effects of irbesartan and amlodipine on kidney disease progression in patients with diabetic nephropathy.

Primary Efficacy Measure: Composite of doubling of serum creatinine, end-stage renal disease (initiation of dialysis, renal transplant, serum creatinine ≥ 6.0 mg/dL) or all-cause mortality

Secondary Efficacy Measure: Composite of cardiovascular death, non-fatal myocardial infarction, heart failure hospitalization, permanent neurological deficit due to cerebrovascular event or lower limb amputation above the ankle

Participants: Patients with diabetic nephropathy

- Age ~59 years; male ~66%
- BP ~159/87 mmHg; SCr ~1.67 mg/dL
- HgA1c ~8.2%; Urinary protein excretion ~2900 mg per 24 hour period

Inclusion Criteria:

- Age 30-70 years with type 2 diabetes
- Hypertension (BP > 135/85 mmHg)
- Proteinuria (≥ 900 mg per 24 hour period)
- SCr 1.0-3.0 mg/dL (females); 1.2-3.0 mg/dL (males)

Exclusion Criteria:

- Type 1 diabetes
- Cardiovascular or cerebrovascular event within the previous 3-6 months

Drugs: Irbesartan; amlodipine

Design: Randomized, double-blind, placebo-controlled trial

Methods: Prior to screening, all ACEis, ARBs and CCBs were discontinued. Eligible patients were randomized to receive irbesartan, amlodipine or matching placebo. Dosing in the irbesartan group was titrated from 75-300 mg daily. Dosing the amlodipine group was titrated from 2.5-10 mg daily. The target blood pressure for all randomized patients was less than 135/85 mmHg (or SBP 10 mmHg lower than baseline if initially greater than 145 mmHg).

Duration: Mean follow-up period of ~2.6 years

Statistical Analysis: It was determined that 550 randomized patients per treatment group would provide 90% power (alpha = 0.05). To account for interim analyses, a level of significance of 0.04 would be used for the primary outcome (0.05 for all other outcomes). All analyses were performed using the ITT population.

Results: A total of 1715 patients underwent randomization. Baseline patient characteristics were similar between treatment groups, with the exception of a slightly lower proportion of female patients in the placebo group (p=0.02). The average blood pressure was 140/77 mmHg in the irbesartan group, 141/77 mmHg in the amlodipine group and 144/80 mmHg in the placebo group. The difference in blood pressure between the two active treatment groups was not significant. However, the difference between the active groups and the placebo group was statistically significant (p=0.001). The average HgA1c was similar between treatment groups for the trial duration. Rates of hyperkalemia were significantly higher (p=0.01) in the irbesartan group compared to the amlodipine and placebo groups (1.9% vs 0.5% and 0.4%, respectively).

Irbesartan (N=579) Vs Placebo (N=569)

Primary Composite Outcome:
189 (32.6%) vs 222 (39.0%); RR 0.81 (95% CI 0.67-0.99)
p=0.03; ARR 6.47%; NNT ~16

Doubling of Serum Creatinine:
98 (16.9%) vs 135 (23.7%); RR 0.71 (95% CI 0.54-0.92); p=0.009; ARR 6.80%; NNT ~15

End-Stage Renal Disease:
82 (14.2%) vs 101 (17.8%); RR 0.83 (95% CI 0.62-1.11); p=0.19

All-Cause Mortality:
87 (15.0%) vs 93 (16.3%); RR 0.94 (95% CI 0.70-1.27); p=0.69

Secondary Composite Outcome:
138 (23.8%) vs 144 (25.3%); RR 0.91 (95% CI 0.72-1.14); p=0.40

Amlodipine (N=567) Vs Placebo (N=569)

Primary Composite Outcome:
233 (41.1%) vs 222 (39.0%); RR 1.07 (95% CI 0.89-1.29); p=0.47

Doubling of Serum Creatinine:
144 (25.4%) vs 135 (23.7%); RR 1.15 (95% CI 0.91-1.46); p=0.24

End-Stage Renal Disease:
104 (18.3%) vs 101 (17.8%); RR 1.09 (95% CI 0.82-1.43); p=0.56

All-Cause Mortality:
83 (14.6%) vs 93 (16.3%); RR 0.90 (95% CI 0.66-1.21); p=0.47

Secondary Composite Outcome:
128 (22.6%) vs 144 (25.3%); RR 0.88 (95% CI 0.69-1.11); p=0.27

Irbesartan (N=579) Vs Amlodipine (N=567)

Primary Composite Outcome:
189 (32.6%) vs 233 (41.1%); RR 0.76 (95% CI 0.63-0.92); p=0.005; ARR 8.45%; NNT ~12

Doubling of Serum Creatinine:
98 (16.9%) vs 144 (25.4%); RR 0.61 (95% CI 0.48-0.79); p<0.001; ARR 8.47%; NNT ~12

End-Stage Renal Disease:
82 (14.2%) vs 104 (18.3%); RR 0.76 (95% CI 0.57-1.02); p=0.06

All-Cause Mortality:
87 (15.0%) vs 83 (14.6%); RR 1.05 (95% CI 0.78-1.42); p=0.75

Secondary Composite Outcome:
138 (23.8%) vs 128 (22.6%); RR 1.03 (95% CI 0.81-1.32); p=0.78

Limitations:

- Patient population – patients with nephropathy due to type 2 diabetes

Level of Evidence: Level I – with minor limitations

Recommendation: For these reasons, I recommend the use of irbesartan over amlodipine for slowing the progression of kidney disease in patients with diabetic nephropathy.

Efficacy:

- The primary composite outcome occurred at significantly lower rates in the irbesartan group when compared to both amlodipine and placebo groups
    - The individual component of serum creatinine doubling occurred at significantly lower rates in the irbesartan when compared to both amlodipine and placebo groups
- Rates of the secondary composite outcome were not significantly different between treatment groups
- Adjusting for blood pressure control did not alter trial results
    - This indicates that the demonstrated benefit of irbesartan over amlodipine and placebo was not due to differences blood pressure control (likely due to inhibition of angiotensin activity)

Safety:

- Hyperkalemia occurred significantly more often in the irbesartan group compared to amlodipine and placebo groups (predictable side effect of drug class)

Cost:

- The cost of using irbesartan over amlodipine must be balanced against the cost-savings from slowing the progression of kidney disease

Special Considerations/Populations:

- Irbesartan (ARB) and amlodipine (CCB) demonstrated similar blood pressure lowering effect, however the different pharmacological properties of each agent are likely a major reason for the demonstrated difference in clinical outcomes
- Patient population must be considered – patients with diabetic kidney disease (e.g. diabetic patients with consequential nephropathy)

Grade of Recommendation: **A**

IMPACT

Lipson DA, Barnhart F, Brealey N, et al. Once-Daily Single-Inhaler Triple Versus Dual Therapy in Patients with COPD. *N Engl J Med*. 2018;378(18):1671-1680.

Objective: To compare the effect of triple-inhaled therapy (ICS-LAMA-LABA) to dual-inhaled therapy (ICS-LABA or LAMA-LABA) on clinical outcomes in COPD patients.

Primary Efficacy Measure: Annual rate of moderate or severe COPD exacerbations

- Moderate: requiring systemic glucocorticoids, antibiotics or both
- Severe: causing hospitalization or death

Participants: High-risk COPD patients

- Age ~65 years; male ~66%
- FEV_1 ~46%; CAT score ~20
- One or more moderate-severe COPD exacerbations in the previous 12 months ~45%
- Two or more moderate-severe COPD exacerbations in the previous 12 months ~43%

Inclusion Criteria:

- Age ≥ 40 years
- Symptomatic COPD (CAT score ≥ 10)
- FEV_1 < 50% of predicted normal value plus one or more moderate-severe COPD exacerbations in the previous year, OR FEV_1 50-80% of the predicted normal value plus two or more moderate (or one or more severe) COPD exacerbations in the previous year

Exclusion Criteria:

- Asthma
- Other significant respiratory disease (excluding COPD)

Drugs: Fluticasone-umeclidinium-vilanterol inhalation (FUV); fluticasone-vilanterol inhalation (FV); umeclidinium-vilanterol inhalation (UV)

Design: Randomized, double-blind, active-controlled trial

Methods: Eligible patients were randomized to receive once daily therapy with inhaled FUV 100 mcg/62.5 mcg/25 mcg, inhaled FV 100 mcg/25 mcg or inhaled UV 62.5 mcg/25 mcg. During the two-week run-in period prior to randomization patients were allowed to continue their baseline medications.

Duration: 52 weeks

Statistical Analysis: It was determined that 10,000 randomized patients would provide 90% power (alpha=0.01). The ITT population was used for the efficacy and safety analyses.

Results: A total of 10,355 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. Rates of moderate or severe COPD exacerbation were significantly lower in the inhaled triple-therapy group (ICS-LAMA-LABA) compared to either inhaled dual-therapy group (ICS-LABA or LAMA-LABA). Pneumonia occurred significantly more often in the triple-therapy group compared to the LAMA-LABA group (8% vs 5%; $p<0.001$). Rates of pneumonia were not significantly different between the triple-therapy and the ICS-LABA group (8% vs 7%).

FUV (N=4151) Vs Fluticasone-Vilanterol (N=4134)

Annual Rate of Moderate to Severe COPD Exacerbations:
0.91 vs 1.07; RR 0.85 (95% CI 0.80-0.90); p<0.001

FUV (N=4151) Vs Umeclidinium-Vilanterol (N=2070)

Annual Rate of Moderate to Severe COPD Exacerbations:
0.91 vs 1.21; RR 0.75 (95% CI 0.70-0.81); p<0.001

Limitations:

- Patient population – cannot extrapolate trial results to other respiratory conditions

Level of Evidence: Level I – with minor limitations

Recommendation: For these reasons, I recommend the use of triple-therapy (ICS-LAMA-LABA) over dual-therapy (ICS-LABA or LAMA-LABA) to further reduce morbidity outcomes in COPD patients.

Efficacy:

- Rates of moderate or severe COPD exacerbation were significantly lower in the triple-therapy group compared to either dual-therapy group

Safety:

- Pneumonia occurred significantly more often in the triple-therapy group compared to the LAMA-LABA group
    - Rates of pneumonia were similar between the triple-therapy and ICS-LABA

Cost:

- The cost of using triple therapy (ICS-LAMA-LABA) over dual therapy must be balanced against the cost-savings from reduced rates of COPD exacerbations
    - However, the increased costs associated with higher rates of pneumonia must be considered

Special Considerations/Populations:

- Asthma patients were excluded from this trial

Grade of Recommendation: **A**

IMPROVE-IT

Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *N Engl J Med*. 2015;372(25):2387-2397.

Objective: To determine the effect of ezetimibe in addition to simvastatin on cardiovascular outcomes in patients with recent acute coronary syndrome.

Primary Efficacy Measures: Composite of cardiovascular death, major coronary event (non-fatal myocardial infarction, hospitalization due to unstable angina, coronary revascularization more than 30 days after randomization) or non-fatal stroke

Participants: Patients with acute coronary syndrome within previous 10 days

- Age ~64; male ~75%
- Qualifying event STEMI ~29%; NSTEMI ~47%; unstable angina ~24%
- LDL ~94 mg/dL
- Baseline aspirin ~97%; beta-blocker ~87%; ACEi/ARB ~75%

Inclusion Criteria:

- Age ≥ 50 years
- Hospitalization for acute coronary syndrome/unstable angina within previous 10 days
- LDL 50 mg-125 mg/dL (max 100 mg/dL if on lipid-lowering therapy)

Exclusion Criteria:

- Planned CABG
- CrCl < 30 mL/min
- Active liver disease
- Statin intensity > simvastatin 40 mg

Drugs: Ezetimibe plus simvastatin; simvastatin

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients were randomized to receive simvastatin 40 mg plus ezetimibe 10 mg daily or simvastatin 40 mg plus matching placebo daily. In cases where LDL > 79 mg/dL for two consecutive lab draws the simvastatin dose was increased to 80 mg in a double-blind manner. However, due to published guidelines recommending limited use of simvastatin 80 mg the patients who had been receiving it for < 1 year were lowered back to 40 mg daily. If LDL on the new therapy became greater than 100 mg/dL then the study drug could be discontinued and more potent therapy initiated.

Duration: Median follow-up period of 6 years

Statistical Analysis: It was determined that 5250 primary events would provide 90% power (alpha=0.05). The ITT population was used for primary efficacy analysis.

Results: A total of 18,144 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. In the simvastatin group the 80 mg dose was used in 27% of patients. In the simvastatin/ezetimibe group the 80 mg dose was used in 6% of patients. After one year, LDL levels were 69.9 mg/dL in the simvastatin group and 53.2 mg/dL in the ezetimibe group ($p<0.001$). The average LDL for the entire trial was 69.5 mg/dL in the simvastatin group and 53.7 mg/dL in the ezetimibe group. There was no significant difference in discontinuation rates or relevant adverse reactions.

Simvastatin/Ezetimibe (N=9067) Vs Simvastatin (N=9077)

Cardiovascular Composite Outcome:
2572 (28.4%) vs 2742 (30.2%); HR 0.936 (95% CI 0.89-0.99)
p=0.016; ARR 1.92%; NNT ~53

Cardiovascular Death:
537 (5.92%) vs 538 (5.93%); HR 1.00 (95% CI 0.89-1.13); p=1.00

Non-Fatal Myocardial Infarction:
945 (10.4%) vs 1083 (11.9%); HR 0.87 (95% CI 0.80-0.95)
p=0.002; ARR 1.51%; NNT ~64

Hospitalization due to Unstable Angina:
156 (1.72%) vs 148 (1.63%); HR 1.06 (95% CI 0.85-1.33); p=0.62

Coronary Revascularization 30 Days After Randomization:
1690 (18.6%) vs 1793 (19.8%); HR 0.95 (95% CI 0.89-1.01); p=0.11

Ischemic Stroke:
236 (2.60%) vs 297 (3.27%); HR 0.79 (95% CI 0.67-0.94)
p=0.008; ARR 0.67%; NNT ~150

Limitations:

- Patient population - all had recent acute coronary syndrome
- Treatment effect of ezetimibe must be considered in addition to simvastatin

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I recommend the use of ezetimibe/simvastatin 10 mg/40 mg over simvastatin 40 mg alone to further reduce rates of cardiovascular morbidity and mortality in patients with recent acute coronary syndrome.

Efficacy:

- Rates of the primary composite outcome were significantly lower in the ezetimibe/simvastatin group
- However, only the individual components of non-fatal myocardial infarction and ischemic stroke were significantly lower
- The ezetimibe/simvastatin group demonstrated significantly greater reductions in LDL

Safety:

- There was no significant difference in discontinuation rates or relevant adverse drug reactions (myopathy, liver enzymes, etc.)

Cost:

- The cost of using ezetimibe/simvastatin must be balanced against the cost-savings of preventing cardiac outcomes, particularly non-fatal myocardial infarction

Special Considerations/Populations:

- All patients had recent acute coronary syndrome (primarily myocardial infarction)
- While simvastatin 40 mg is a moderate-intensity statin, ezetimibe/simvastatin 10 mg/40 mg is considered a high-intensity statin
- Use of other statin agents (e.g. atorvastatin, rosuvastatin) may provide improved LDL reduction compared to simvastatin monotherapy
    - Treatment benefit demonstrated in this trial appears to be due to added LDL reduction rather than specific drug properties

Grade of Recommendation: **A**

inTandem3

Garg SK, Henry RR, Banks P, et al. Effects of Sotagliflozin Added to Insulin in Patients with Type 1 Diabetes. *N Engl J Med*. 2017;377(24):2337-2348.

Objective: To determine the efficacy and safety of sotagliflozin (in addition to insulin therapy) in patients with type 1 diabetes.

Primary Efficacy Measure: HgA1c ≤ 7.0% at week 24 with no episodes of severe hypoglycemia or diabetic ketoacidosis

Participants: Patients with type 1 diabetes receiving insulin therapy

- Age ~43 years; male ~50%
- Duration of diabetes ~20 years; HgA1c ~8.2%
- Total daily dose of insulin ~57 units

Inclusion Criteria:

- Age ≥ 18 years
- Type 1 diabetes
- Basal dose of insulin therapy stable for at least 2 weeks prior
- HgA1c 7.0-11.0%
- BMI ≥ 18.5

Exclusion Criteria:

- Severe hypoglycemia or diabetic ketoacidosis within the prior 30 days
- ≥ 2 episodes of diabetic ketoacidosis within the prior 180 days
- eGFR < 45 mL/min

Drug: Sotagliflozin

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients were randomized to receive sotagliflozin 400 mg once daily (before the first meal of each day) or matching placebo. Background insulin therapy was continued, with the exception of the first day of the trial. On day one of the trial, patients received a 30% lower dose of mealtime insulin for the first meal of the day. Thereafter, insulin doses could be adjusted to achieve target blood glucose goals. Notably, all patients received counseling on how to detect and properly treat ketosis.

Duration: 24 weeks

Statistical Analysis: It was determined that 700 randomized patients per group would provide 90% power (alpha = 0.05). The modified ITT population (randomized patients that received at least one dose of study medication) was used for the efficacy and safety analyses.

Results: A total of 1402 patients underwent randomization and received at least one dose of study medication. Baseline patient characteristics were similar between treatment groups. At the end of the trial the average change in HgA1c was -0.79% in the sotagliflozin group and -0.33% in the placebo group ($p<0.001$). The sotagliflozin group demonstrated a reduced total daily insulin dose of -5.3 units on average compared to placebo. Adverse events were more common in the sotagliflozin treatment group, largely driven by negative gastrointestinal effects (e.g., nausea, diarrhea) and genital mycotic infections. While rates of serious hypoglycemia were comparable between treatment groups, rates of diabetic ketoacidosis were notably higher in the sotagliflozin group.

Sotagliflozin (N=699) Vs Placebo (N=703)

Primary Efficacy Outcome:
200 (28.6%) vs 107 (15.2%); 13.4% (95% CI 9.0% to 17.8%); p<0.001

Serious Hypoglycemia:
21 (3.00%) vs 17 (2.42%)

Diabetic Ketoacidosis:
21 (3.00%) vs 4 (0.57%)

Limitations:
- Patient population – cannot apply trial results to patients with type 2 diabetes
- Trial design must be considered – all patients were receiving baseline insulin therapy

Level of Evidence: Level I – with minor limitations

Recommendation: The short term benefit of achieving an HgA1c ≤ 7.0% may be outweighed by the risk for serious adverse effects, specifically diabetic ketoacidosis. For these reasons, I do not recommend the routine use of sotagliflozin (in addition to baseline insulin therapy) as a glucose-lowering agent in patients with type 1 diabetes.

Efficacy:
- Significantly more patients achieved a HgA1c ≤ 7.0% at week 24 with no episodes of severe hypoglycemia or diabetic ketoacidosis in the sotagliflozin group compared to placebo-controlled

Safety:
- Overall, adverse events were more common in the sotagliflozin group
- Severe hypoglycemia (defined as event that required assistance from another individual or resulted in a loss of consciousness) occurred at similar rates between treatment groups
- Diabetic ketoacidosis occurred notably more often in the sotagliflozin group

Cost:
- The cost of using sotagliflozin in addition to insulin therapy must be balanced against the cost-savings from achieving a lower HgA1c
    - However, the cost of monitoring for and managing episodes of diabetic ketoacidosis must also be considered

Special Considerations/Populations:
- Sotagliflozin is a SGLT1/2 inhibitor
    - SGLT1 inhibition is associated with increased rates of gastrointestinal adverse effects
- This trial only included patients with type 1 diabetes receiving insulin therapy

Grade of Recommendation: **A**

I-PRESERVE

Massie BM, Carson PE, McMurray JJ, et al. Irbesartan in patients with heart failure and preserved ejection fraction. *N Engl J Med*. 2008;359(23):2456-2467.

Objective: To determine the effect of irbesartan on morbidity and mortality outcomes in patients with heart failure and preserved ejection fraction.

Primary Efficacy Measures: Composite of all-cause mortality or cardiovascular hospitalization

Participants: Patients with heart failure and preserved ejection fraction

- Age ~72 years; male ~40%
- LVEF ~60%; BP ~136/79 mmHg; HR ~71 bpm
- NYHA class II ~22%; class III ~76%; class IV ~3%
- Loop diuretic ~52%; beta-blocker ~58%; ACEi ~25%

Inclusion Criteria:

- Age ≥ 60 years
- Symptoms of heart failure
- LVEF ≥ 45%
- Heart failure hospitalization within previous 6 months
- NYHA functional class II-IV

Exclusion Criteria:

- Intolerance to ARBs
- Alternative cause to heart failure symptoms
- Any previous LVEF < 40%
- Acute coronary syndrome/stroke/revascularization in previous 3 months
- SBP < 100 mmHg or > 160 mmHg
- DBP > 95 mmHg
- Substantial laboratory abnormalities

Drug: Irbesartan

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients underwent a 1 to 2 week placebo run-in period prior to being randomized to receive irbesartan or matching placebo. The starting dose of irbesartan was 75 mg daily, which was then doubled every 1-2 weeks (as tolerated) to a max of 300 mg daily. Use of concomitant ACEi was allowed if it was essential for an indication other than hypertension.

Duration: Mean follow-up period of 49.5 months (~4 years)

Statistical Analysis: Originally, it was determined that 3600 randomized patients and 1440 primary events would achieve 90% power. However, due to a lower than expected event rate during a blinded review the sample size was increased to 4100 patients to preserve power (alpha = 0.05). The ITT population was used for the efficacy analyses.

Results: A total of 4563 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. During the study, use of concomitant ACEi rose from ~25% to ~40% in both groups. Approximately 84% of the irbesartan group achieved 300 mg daily by the end of the titration phase (average daily dose 275 mg). Overall, the rates of discontinuation and adverse drug reactions were similar between treatment groups.

Irbesartan (N=2067) Vs Placebo (N=2061)

Composite of All-Cause Mortality or Cardiovascular Hospitalization:
742 (35.9%) vs 763 (37.0%); HR 0.95 (95% CI 0.86-1.05); p=0.35

All-Cause Mortality:
445 (21.5%) vs 436 (21.2%); HR 1.00 (95% CI 0.88-1.14); p=0.98

Cardiovascular Death:
311 (15.0%) vs 302 (14.7%); HR 1.01 (95% CI 0.86-1.18); p=0.92

Cardiovascular Hospitalization:
521 (25.2%) vs 537 (26.1%); HR 0.95 (95% CI 0.85-1.08); p=0.44

Heart Failure Hospitalization:
325 (15.7%) vs 336 (16.3%); HR 0.95 (95% CI 0.81-1.10); p=0.50

Limitations:

- Allowing for concomitant ACEi therapy may have blunted the true treatment effect of irbesartan from being illustrated (potential confounding factor)
- Patient population - all patients had heart failure with preserved ejection fraction

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I do not recommend the use of irbesartan specifically for the reduction of morbidity and mortality outcomes in heart failure patients with preserved ejection fraction. However, the use of a RAAS inhibitor as part of optimal pharmacotherapy to help manage comorbid conditions and to slow disease progression is warranted in many patients.

Efficacy:

- Rates of the primary composite outcome, all-cause mortality, cardiovascular death, cardiovascular hospitalization and heart failure hospitalization were not significantly different between treatment groups

Safety:

- Rates of discontinuation and adverse drug reactions were similar between treatment groups

Cost:

- The cost of using irbesartan must be balanced against the potential cost-savings of preventing a clinical event (not clearly demonstrated in this trial)

Special Considerations/Populations:

- Results cannot be extrapolated to patients with reduced ejection fraction
- Allowance of concurrent ACEis in trial may have confounded the trial results - clinical significance uncertain

Grade of Recommendation: **A**

iPrEx

Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med*. 2010;363(27):2587-2599.

Objective: To determine the efficacy and safety of emtricitabine plus tenofovir disoproxil fumarate for prevention of HIV infection in males and transgender females who have sex with males.

Primary Efficacy Measure: Incident HIV infection

Participants: Males and transgender females at high-risk for HIV infection

- Age ~27 years
- Number of partners in previous 12 weeks ~18
- Unprotected receptive anal intercourse in previous 12 weeks ~60%
- Unprotected anal intercourse with partner with positive/unknown status in previous 6 months ~80%

Inclusion Criteria:

- Age ≥ 18 years and male sex at birth
- HIV negative status
- High-risk for HIV infection

Exclusion Criteria:

- Serious and active illness (e.g. tuberculosis, hepatitis, diabetes, cancer)
- History of bone fracture unrelated to trauma

Drugs: Emtricitabine (FTC); tenofovir disoproxil fumarate (TDF)

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients were randomized to receive once daily FTC-TDF 200 mg/300 mg or placebo.

Duration: Median follow-up period of 1.2 years

Statistical Analysis: It was determined that 85 incident HIV infections would provide 80% power (alpha = 0.05). The modified ITT population (all patients except those with HIV detected during initial enrollment) and the as-treated population (all patients except those determined to fall below a compliance rate of 50%) were used for the efficacy analysis.

Results: A total of 2499 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. Only 3 HIV-infected patients within the FTC-TDF group had detectable drug levels. Subgroup analysis demonstrates greater efficacy with greater adherence rates. Serum creatinine elevations (reversible upon discontinuation) were more common in the FTC-TDF group. Nausea and diarrhea occurred more frequently in the FTC-TDF group compared to placebo.

FTC-TDF (N=1251) Vs Placebo (N=1248)

Incidence HIV Infection:
36 (2.88%) vs 64 (5.13%); RR 44% (95% CI 15% to 63%)
p=0.005; ARR 2.25%; NNT ~45
Modified ITT population

Limitations:

- Poor adherence likely distorted true treatment effect (confounding factor)
    - Only 3 HIV-infected patients in the FTC-TDF group had detectable drug levels
    - Subgroup analysis shows increased adherence correlates with improved protection from HIV infection

Level of Evidence: Level I – with minor limitations

Recommendation: For these reasons, I recommend FTC-TDF as an effective treatment for prevention of HIV infection in high-risk males and transgender females who have sex with males. However, a strong emphasis and counseling for strict adherence is warranted to maximize treatment benefit.

Efficacy:

- The FTC-TDF group demonstrated significantly lower rates of incident HIV infection
    - Adherence positively correlated with treatment efficacy

Safety:

- Reversible increases in serum creatinine were noted in the FTC-TDF group
- Nausea and diarrhea were more commonly reported in the active treatment group

Cost:

- The cost of using FTC-TDF must be balanced against the cost-savings achieved from preventing HIV infection (and the accompanying costs associated with lifelong treatment)

Special Considerations/Populations:

- Adherence is a critical factor for treatment efficacy

Grade of Recommendation: **A**

ISAR-TRIPLE

Fiedler KA, Maeng M, Mehilli J, et al. Duration of Triple Therapy in Patients Requiring Oral Anticoagulation After Drug-Eluting Stent Implantation: The ISAR-TRIPLE Trial. *J Am Coll Cardiol*. 2015;65(16):1619-1629.

Objective: To compare the efficacy and safety of 6 weeks of triple therapy to 6 months of triple therapy in reducing clinical outcomes in patients with drug-eluting stents.

Primary Efficacy Measures: Composite of all-cause mortality, myocardial infarction, definite stent thrombosis, stroke or TIMI major bleeding

Participants: Patients established on oral anticoagulation therapy receiving drug-eluting stent

- Age ~73 years; male ~77%
- Indication for stent: stable angina ~69%; unstable angina ~16%; NSTEMI ~15%
- Indication for oral anticoagulation: atrial fibrillation/flutter ~84%
- Medications at discharge: beta-blocker ~87%; ACEi ~64%; statin ~85%

Inclusion Criteria:

- Use of oral anticoagulant for ≥ 12 months
- Receiving drug-eluting stent for stable angina or acute coronary syndrome

Exclusion Criteria:

- Age ≤ 18 years
- Drug-eluting stent implantation in the left main stem
- Previous stent thrombosis
- Active bleeding
- History of intracranial bleeding

Drugs: Vitamin K antagonist (warfarin or phenprocoumon); clopidogrel; aspirin

Design: Randomized, open-label, active-comparison trial

Methods: After drug-eluting stent implantation, eligible patients were randomized to receive clopidogrel 75 mg daily plus aspirin 75-200 mg daily and vitamin K antagonist (warfarin or phenprocoumon) for either 6 weeks or 6 months. The vitamin K antagonist therapy was dosed to target the lowest recommended INR for the duration of the triple therapy. Final patient analysis occurred at 9 months.

Duration: 9 months

Statistical Analysis: It was determined that 283 randomized patients per treatment group would achieve 80% power (alpha = 0.05). The ITT population was used for the final analyses.

Results: A total of 614 patients underwent randomization. Baseline patient characteristics were similar between treatment groups with the exception of history of CABG (higher in six week group) and indication for oral anticoagulation (imbalanced between groups). The median INR values were 2.2 at 6 weeks, 2.3 at 6 months and 2.3 at 9 months with no statistical difference between treatment groups. Post-hoc analysis of the time period where treatments separated (6 weeks to 9 months) and when they were truly different (6 weeks to 6 months) showed no statistical difference in the primary composite endpoint.

Six Week Therapy (N=307) Vs Six Month Therapy (N=307)

Primary Composite Outcome:
30 (9.77%) vs 27 (8.79%); HR 1.14 (95% CI 0.68-1.91); p=0.63

All-Cause Mortality:
12 (3.91%) vs 16 (5.21%); HR 0.75 (95% CI 0.35-1.59); p=0.45

Myocardial Infarction:
6 (1.95%) vs 0 (0%); p=0.03

Definite Stent Thrombosis:
2 (0.65%) vs 0 (0%); p=0.50

Stroke:
4 (1.30%) vs 6 (1.95%); HR 0.67 (95% CI 0.19-2.35); p=0.53

TIMI Major Bleeding:
16 (5.21%) vs 12 (3.91%); HR 1.35 (95% CI 0.64-2.84); p=0.44

Limitations:

- Open-label trial design
- Trial designed for superiority and thus non-inferiority cannot be claimed
- Sample size relatively small

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I recommend the use of triple therapy (clopidogrel plus vitamin K antagonist and aspirin) for 6 weeks over 6 months in patients after drug-eluting stent implantation. However, each patient must be assessed individually when deciding treatment duration. Certain patients may warrant triple therapy for greater than 6 weeks but the risk of major bleeding must be carefully considered.

Efficacy:

- Rates of the primary composite outcome were not significantly different between treatment groups
- Rates of the individual components of the composite outcome were similar between treatment groups with the exception of myocardial infarction, which was significantly lower in the 6 month therapy group

Safety:

- Rates of TIMI major bleeding and total bleeding were not significantly different between treatment groups

Cost:

- The cost of using triple therapy for greater than 6 weeks must be balanced against the cost-savings of preventing an event outcome
- However, the cost of treating a major bleeding event must also be considered

Special Considerations/Populations:

- Non-inferiority cannot be claimed despite similar efficacy and safety results
- Relatively small trial sample size

Grade of Recommendation: **A**

LEADER

Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med*. 2016;375(4):311-322.

Objective: To determine the effect of liraglutide on cardiovascular outcomes in patients with type 2 diabetes at increased risk for cardiovascular events.

Primary Efficacy Measures: Composite of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke

Participants: Patients with type 2 diabetes at increased risk for cardiovascular event

- Age ~64 years; male ~64%
- HgA1c ~8.7%
- Established cardiovascular disease ~81%

Inclusion Criteria:

- Type 2 diabetes with HgA1c ≥ 7%
- Age ≥ 50 years with established cardiovascular disease/CKD stage III or age ≥ 60 years with one or more cardiovascular risk factors

Exclusion Criteria:

- Type 1 diabetes
- Use of GLP-1 receptor agonist, DPP-4 inhibitor, pramlintide or rapid-acting insulin
- Personal or family history of endocrine neoplasia or thyroid cancer
- Acute coronary/cerebrovascular event within previous 14 days

Drug: Liraglutide

Design: Randomized, double-blind, placebo-controlled, non-inferiority trial

Methods: Eligible patients were randomized to receive liraglutide 1.8 mg subcutaneously daily or matching placebo after completing a two week run-in period to assess adherence. Investigators could use additional medications to achieve the target HgA1c ≤ 7.0%. However, the use of DPP-4 inhibitors and pramlintide were not allowed.

Duration: Median follow-up period of 3.8 years

Statistical Analysis: It was determined that 8754 randomized patients and 611 primary events would achieve 90% power (alpha = 0.025). The trial was designed to test for non-inferiority (NI margin 1.3) with sequential testing for superiority. The ITT population was used for all analyses.

Results: A total of 9340 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. Non-inferiority and then superiority was demonstrated for liraglutide compared to placebo for the primary composite outcome. There was a mean HgA1c difference of -0.4% favoring the liraglutide group at 36 months. Discontinuation rates due to adverse drug reactions (mainly nausea, vomiting and diarrhea) were significantly higher in the liraglutide group compared to placebo (9.51% vs 7.26%; $p<0.001$). Rates of pancreatitis were not significantly different between treatment groups.

Liraglutide (N=4668) Vs Placebo (N=4672)

Cardiovascular Death, Non-Fatal Myocardial Infarction or Non-Fatal Stroke:
608 (13.0%) vs 694 (14.9%); HR 0.87 (95% CI 0.78-0.97)
p=0.01; ARR 1.83%; NNT ~55

Cardiovascular Death:
219 (4.69%) vs 278 (5.95%); HR 0.78 (95% CI 0.66-0.93)
p=0.007; ARR 1.26%; NNT ~80

Non-Fatal Myocardial Infarction:
281 (6.02%) vs 317 (6.79%); HR 0.88 (95% CI 0.75-1.03); p=0.11

Non-Fatal Stroke:
159 (3.41%) vs 177 (3.79%); HR 0.89 (95% CI 0.72-1.11); p=0.30

Limitations:

- Patient population must be considered when interpreting trial results - vast majority had established cardiovascular disease at baseline

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I recommend the use of liraglutide as a safe glucose-lowering therapy with clear cardiovascular benefit in high-risk patients with type 2 diabetes.

Efficacy:

- Rates of the primary composite outcome, as well as the individual component of cardiovascular death, were significantly lower in the liraglutide group compared to placebo
- At 36 months, the HgA1c difference was -0.4% favoring the liraglutide group

Safety:

- Rates of discontinuation due to adverse drug reactions were significantly higher in the liraglutide group
- However, there was no significant difference in the rates of pancreatitis

Cost:

- The cost of using liraglutide must be balanced against the cost-savings of preventing cardiovascular outcomes

Special Considerations/Populations:

- The majority of patients had established cardiovascular disease at baseline

Grade of Recommendation: **A**

LIFE

Dahlöf B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomized trial against atenolol. *Lancet*. 2002;359(9311):995-1003.

Objective: To determine the effect of losartan on cardiovascular outcomes in patients with hypertension and left ventricular hypertrophy.

Primary Efficacy Measure: Composite of cardiovascular death, myocardial infarction or stroke

Participants: Patients with primary hypertension and evidence of left ventricular hypertrophy

- Age ~67 years; male ~46%
- BP ~174/98 mmHg; HR ~74 bpm

Inclusion Criteria:

- Age 55-80 years
- Primary hypertension with ECG signs of left ventricular hypertrophy

Exclusion Criteria:

- Secondary hypertension
- Myocardial infarction or stroke within previous 6 months
- Angina pectoris requiring pharmacotherapy with beta-blockers or CCBs
- Heart failure or LVEF ≤ 40%

Drugs: Losartan; atenolol

Design: Randomized, double-blind, active-controlled trial

Methods: Eligible patients underwent a 1-2 week placebo run-in period if their sitting BP was in the range of 160-200 mmHg systolic and 95-115 mmHg diastolic. After this period patients were randomized to receive either atenolol or losartan plus matching placebo Atenolol was selected due to being considered a first-line agent for hypertension at the time of the trial. Dosing for either medication was titrated to achieve target BP < 140/90 mmHg. Hydrochlorothiazide could be added for additional blood pressure control if needed. Patients were to be followed for at least 4 years.

Duration: Median follow-up period of 4.8 years

Statistical Analysis: It was determined that 1040 primary endpoints would need to occur to achieve 80% power (alpha = 0.05). The ITT population was used for all analyses.

Results: A total of 9222 patients underwent randomization (9193 included in analyses). Baseline patient characteristics were similar between treatment groups. In patients that remained on study medication for the duration of the trial the average doses were losartan 82 mg and atenolol 79 mg daily. The distribution of hydrochlorothiazide and additional antihypertensive medications was similar between groups. At the last visit, the mean blood pressure for the losartan group was 144.1/81.3 mmHg and mean blood pressure for the atenolol group was 145.4/80.9 mmHg. The target blood pressure was achieved in 48% of losartan patients and 45% atenolol patients. Overall, there were significantly higher rates of adverse events in the atenolol group compared to losartan.

Losartan (N=4605) Vs Atenolol (N=4588)

Composite of Cardiovascular Death, Myocardial Infarction or Stroke:
508 (11.0%) vs 588 (12.8%); HR 0.87 (95% CI 0.77-0.98)
p=0.021; ARR 1.78%; NNT ~56

Cardiovascular Death:
204 (4.43%) vs 234 (5.10%); HR 0.89 (95% CI 0.73-1.07); p=0.206

Myocardial Infarction:
198 (4.30%) vs 188 (4.10%); HR 1.07 (95% CI 0.88-1.31); p=0.491

Stroke:
232 (5.04%) vs 309 (6.73%); HR 0.75 (95% CI 0.63-0.89)
p=0.001; ARR 1.70%; NNT ~59

Limitations:

- Patient population must be considered - evidence of left ventricular hypertrophy but no evidence of heart failure
- Use of additional antihypertensive agents acts as potential confounding factor, however, the distribution of additional agents and ending blood pressures were similar between treatment groups in this trial

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I recommend the use of losartan over atenolol for reducing the risk of cardiovascular morbidity and mortality in patients with primary hypertension and left ventricular hypertrophy.

Efficacy:

- Rates of the primary composite endpoint were significantly lower in the losartan group compared to atenolol
    - The individual component of stroke occurred at significantly lower rates in the losartan group
- Blood pressure control and use of addition agents was similar between treatment groups

Safety:

- Overall, losartan was better tolerated and had fewer adverse effects compared to atenolol

Cost:

- The cost of use using losartan must be balanced against the cost of using atenolol and the cost-savings of preventing an adverse cardiovascular outcome

Special Considerations/Populations:

- Cannot extrapolate treatment results to other beta-blockers or ARBs

Grade of Recommendation: **A**

LIPID

Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med*. 1998;339(19):1349-1357.

Objective: To determine the effect of pravastatin on mortality outcomes in patients with coronary heart disease.

Primary Efficacy Measure: Death due to coronary heart disease

Participants: Patients with established coronary heart disease

- Age ~62 years; male ~83%
- Qualifying event: myocardial infarction ~64%; time from event ~1.1 years
- Total cholesterol ~218 mg/dL; LDL ~150 mg/dL; HDL ~36 mg/dL
- Baseline aspirin ~82%; beta-blocker ~47%; ACEi ~16%

Inclusion Criteria:

- Age 31 to 75 years
- Acute myocardial infarction or hospitalization for unstable angina within 3-36 months
- Total cholesterol 155-271 mg/dL
- Triglycerides < 445 mg/dL

Exclusion Criteria:

- Clinically significant medical/surgical event within previous 3 months
- Cardiac failure
- Renal/hepatic disease
- Current use of cholesterol-lowering therapy

Drug: Pravastatin

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients underwent an 8 week placebo run-in period where they received dietary counseling targeting a fat intake <30% of total energy intake. Patients were eligible to enroll in the study if they met the cholesterol and triglyceride requirements 4 weeks prior to randomization. Eligible patients were then randomized to receive pravastatin 40 mg once daily or matching placebo. Dietary counseling was continued in both treatment groups.

Duration: Median follow-up period of 6.1 years

Statistical Analysis: It was determined that 700 deaths due to coronary heart disease would be required to achieve 80% power ($p<0.05$). The ITT population was used for all efficacy analyses.

Results: A total of 9014 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. The trial was ended by the safety monitoring committee once the pre-specified boundary for mortality had been reached. The pravastatin group demonstrated significantly greater decreases in LDL and triglycerides and significant greater increases in HDL compared to the placebo group. The average changes in the pravastatin group are as follows: 39 mg/dL decrease in total cholesterol, 38 mg/dL decrease in LDL, 2 mg/dL increase in HDL and 16 mg/L decrease in triglycerides. There were no significant differences in adverse drug reactions between treatment groups.

Pravastatin (N=4512) Vs Placebo (N=4502)

Coronary Heart Disease Death:
287 (6.36%) vs 373 (8.29%); RRR 24% (95% CI 12% to 35%)
p<0.001; ARR 1.92%; NNT ~52

Cardiovascular Death:
331 (7.34%) vs 433 (9.62%); RRR 25% (95% CI 13% to 35%)
p<0.001; ARR 2.28%; NNT ~44

All-Cause Mortality:
498 (11.0%) vs 633 (14.1%); RRR 22% (95% CI 13% to 31%)
p<0.001; ARR 3.02%; NNT ~34

Total Myocardial Infarction:
336 (7.45%) vs 463 (10.3%); RRR 29% (95% CI 18% to 38%)
p<0.001; ARR 2.84%; NNT ~36

Hospitalization due to Unstable Angina:
1005 (22.3%) vs 1106 (24.6%); RRR 12% (95% CI 4% to 19%)
p=0.005; ARR 2.29%; NNT ~44

Limitations:

- Power set but not met - due to trial being stopped early after reaching a pre-specified mortality threshold (clinical significance minimal)
- Results cannot be applied to patients with acute coronary syndrome (event within previous 3 months) - all patients had stable coronary heart disease

Level of Evidence: Level II - with major limitations

Recommendation: For these reasons, I recommend the use of pravastatin 40 mg daily to reduce morbidity and mortality rates in patients with established and stable coronary heart disease. The use of a different statin of similar LDL lowering intensity is also reasonable.

Efficacy:

- Rates of coronary heart disease death were significantly lower in the pravastatin group compared to placebo
- Cardiovascular death and all-cause mortality were significantly lower with pravastatin
- Total myocardial infarction and hospitalization due to unstable angina were significantly lower in the pravastatin group compared to placebo

Safety:

- There were no significant differences in adverse drug reactions between treatment groups

Cost:

- The cost of using pravastatin must be balanced against the cost-savings achieved from preventing cardiovascular morbidity and mortality outcomes

Special Considerations/Populations:

- Patient population must be considered when interpreting trial results - all patients were enrolled after more than 3 months from their qualifying event (stable CHD patients)

Grade of Recommendation: **A**

LoDoCo2

Nidorf SM, Fiolet ATL, Mosterd A, et al. Colchicine in Patients with Chronic Coronary Disease. *N Engl J Med*. 2020;383(19):1838-1847.

Objective: To determine the safety and efficacy of low-dose colchicine for prevention of cardiovascular events in patients with chronic coronary disease.

Primary Efficacy Measure: Composite of cardiovascular death, myocardial infarction, ischemic stroke or ischemia-driven coronary revascularization

Participants: Patients with established coronary artery disease

- Age ~66 years; male ~85%
- Prior acute coronary syndrome ~84%; prior coronary revascularization ~83%
- Baseline statin ~94%; RAASi ~72%; beta-blocker ~62%; single antiplatelet therapy ~67%

Inclusion Criteria:

- Age 35-82 years old
- Evidence of coronary disease on invasive coronary angiography or computed tomography angiography or coronary-artery calcium score ≥ 400 Agatston units (on coronary-artery calcium scan)
- Clinically stable for ≥ 6 months prior to enrollment

Exclusion Criteria:

- Moderate to severe renal impairment
- Severe heart failure
- Severe valvular heart disease

Drug: Colchicine

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients underwent an open-label run-in phase consisting of colchicine 0.5 mg daily for one month. Patients that successfully completed the run-in phase were randomized to receive either colchicine 0.5 mg daily or matching placebo.

Duration: Median follow-up period of 28.6 months

Statistical Analysis: It was determined that 5447 randomized patients and 331 primary endpoints would provide 90% power (alpha = 0.05). The ITT population was used for the efficacy analyses.

Results: A total of 5522 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. Hierarchical testing continued until failing to achieve a statistically significant difference for the outcome of ischemic stroke. There was only one reported case of rhabdomyolysis (full-recovery) in the colchicine group, indicating a lack of clinically relevant interaction between low-dose colchicine and high-dose statins. While the colchicine group demonstrated significantly lower rates of the primary composite outcome compared to placebo, the increased rate of non-cardiovascular death is notable. The majority of non-cardiovascular deaths in both groups were primarily due to cancer.

Colchicine (N=2762) Vs Placebo (N=2760)

Primary Composite Outcome:
187 (6.77%) vs 264 (9.57%); HR 0.69 (95% CI 0.57-0.83); p<0.001
ARR 2.79%; NNT ~36

Ischemia-Driven Coronary Revascularization:
135 (4.89%) vs 177 (6.41%); HR 0.75 (95% CI 0.60-0.94); p=0.01
ARR 1.53%; NNT ~66

Myocardial Infarction:
83 (3.01%) vs 116 (4.20%); HR 0.70 (95% CI 0.53-0.93); p=0.01
ARR 1.20%; NNT ~84

Ischemic Stroke:
16 (0.72%) vs 24 (0.87%); HR 0.66 (95% CI 0.35-1.25); p=0.20

Cardiovascular Death:
20 (0.72%) vs 25 (0.91%); HR 0.80 (95% CI 0.44-1.44)

Safety:

Non-Cardiovascular Death:
53 (1.92%) vs 35 (1.27%); HR 1.51 (95% CI 0.99-2.31)
does not achieve statistical significance

Death due to Cancer:
26 vs 22

Death due to Respiratory Failure:
9 vs 4

Death due to Dementia:
4 vs 1

All-Cause Mortality:
73 (2.64%) vs 60 (2.17%); HR 1.21 (95% CI 0.86-1.71)

Limitations:

- Low proportion of female patients
- Blood pressure and lipid levels were not collected during this trial
- The vast majority of patients were already receiving proven medications for secondary prevention - trial results must be considered in addition to baseline therapies

Level of Evidence: Level I – with minor limitations

Recommendation: For these reasons, I recommend the use of low-dose colchicine (in addition to standard therapy) to further reduce the risk of cardiovascular events in clinically stable patients with chronic coronary artery disease. However, the overall benefit of colchicine appears to be modest based on these trial results. Therefore, optimization of standard medication therapy prior to initiating colchicine is warranted to maximize the overall treatment benefit.

Efficacy:

- The colchicine group demonstrated significantly lower rates of the primary composite outcome compared to placebo
- This benefit was seen in addition to standard recommended therapy for this patient population
- Rates of ischemic stroke and cardiovascular death were similar between treatment groups

Safety:

- Rates of non-cardiovascular death were notably higher in the colchicine group compared to placebo, however statistical significance was not demonstrated and there was no common cause or rationale apparent based on trial data
- Additionally, rates of all-cause mortality were similar between groups
- Only one event of rhabdomyolysis was reported in the colchicine group (full recovery achieved)

Cost:

- The cost of using once daily colchicine must be balanced against the cost-savings achieved from reduced cardiovascular events

Special Considerations/Populations:

- The most recent acute coronary syndrome for most patients (~57%) was >2 years prior
- The concurrent use of low-dose colchicine and high-intensity statin does not appear to cause a clinically significant increase in myopathy (based on the results of this trial)
- The exact mechanism of benefit of colchicine in coronary artery disease is not fully understood but is thought to be due (in part) to its potent anti-inflammatory properties
- Blood pressure and lipid levels were not measured during this trial, which raises concerns regarding potential confounding factors

Grade of Recommendation: **A**

MANDALA

Papi A, Chipps BE, Beasley R, et al. Albuterol–budesonide fixed-dose combination rescue inhaler for asthma. *N Engl J Med*. 2022;386(22):2071-2083.

Objective: To compare the efficacy and safety of as-needed inhaled albuterol-budesonide to as-needed inhaled albuterol alone in patients with moderate-to-severe asthma.

Primary Efficacy Measure: Time to first severe asthma exacerbation

Participants: Patients with moderate-to-severe asthma

- Age ~49 years; male ~35%
- FEV_1 ~64% of predicted value
- Baseline low-dose ICS-LABA ~31%; medium-dose ~40%; high-dose ~27%
- Number of severe exacerbations in the prior 12 months: one ~79%; two ~17%; three ~4%

Inclusion Criteria:

- Age ≥ 4 years with asthma diagnosis (according to GINA criteria)
- One or more severe asthma exacerbation in the previous 12 months:
    - Three or more consecutive days of treatment with a systemic glucocorticoid
    - Emergency department/urgent care visit < 24 hours where systemic glucocorticoids were given
    - Inpatient hospitalization lasting 24 hours or more
- FEV_1 40% to < 90% of predicted normal value
- Receiving medium-to-high dose inhaled steroid or low-to-high dose of ICS-LABA for at least 3 months with stable dosing for at least 4 weeks before screening

Exclusion Criteria:

- Chronic obstructive pulmonary disease or notable lung disease
- Use of systemic glucocorticoid within 3 months before screening
- Use of biologic treatments within 3 months or for a duration of 5 half-lives before screening

Drugs: Inhaled albuterol-budesonide; inhaled albuterol

Design: Randomized, double-blind, active-controlled trial

Methods: Eligible adults and adolescents were randomized to receive inhaled albuterol-budesonide 180 mcg/160 mcg (high-dose combination), inhaled albuterol-budesonide 180 mcg/80 mcg (low-dose combination) or inhaled albuterol 180 mcg alone. Eligible children (age 4-11 years) were randomized to receive inhaled albuterol-budesonide 180 mcg/80 mcg (low-dose combination) or inhaled albuterol 180 mcg alone. All patients were to use the randomized medication as needed for asthma symptoms (max 6 doses daily). The inhaled medication could be used before exercise. The use of additional fast-acting bronchodilators was not allowed.

Duration: 24 weeks

Statistical Analysis: It was determined that 570 primary events would provide 87% power (alpha=0.05). All patients that underwent randomization and received at least one dose of study medication were included in the efficacy and safety analyses. Additionally, on-treatment analysis was pre-specified. This included data prior to therapy changes or discontinuation of therapy.

Results: A total of 3132 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. Treatment results were similar between ITT and on-treatment analyses. The average daily as-needed usage of study was not significantly different between treatment groups (ranging 1.3-1.4 doses per day). Adverse effects were similar between groups, with the exception of oral candidiasis, which was higher in the combination therapy groups (1.0% and 0.9% compared to 0.5% in the albuterol only group).

Albuterol-Budesonide 180 mcg/160 mcg (N=1013) Vs Albuterol 180 mcg (N=1014)
Adults and adolescents only

Severe Asthma Exacerbation:
345 (34.1%) vs 427 (42.1%); HR 0.74 (95% CI 0.62-0.89)
p=0.001; ARR 8.05%; NNT ~13
ITT analysis

334 (33.0%) vs 413 (40.7%); HR 0.73 (95% CI 0.61-0.88)
On-treatment analysis

Albuterol-Budesonide 180 mcg/80 mcg (N=1054) Vs Albuterol 180 mcg (N=1056)
Adults, adolescents and children

Severe Asthma Exacerbation:
372 (35.3%) vs 441 (41.8%); HR 0.84 (95% CI 0.71-1.00); p=0.052
ITT analysis

354 (33.6%) vs 426 (40.3%); HR 0.83 (95% CI 0.70-0.99)
On-treatment analysis

Limitations:
- Small pediatric population (~97% were 12 years and older)
- Trial duration – minimum period of 24 weeks

Level of Evidence: Level I – with minor limitations

Recommendation: For these reasons, I recommend the as-needed use of fixed-dose inhaled albuterol-budesonide over as-needed inhaled albuterol to reduce the frequency of severe asthma exacerbations in this patient population.

Efficacy:
- Both high-dose and low-dose combination inhalation groups demonstrated lower rates of the primary efficacy measure compared to the albuterol-only inhalation group
    - The difference was statistically significant for both groups when using the on-treatment population for analysis
    - The difference was statistically significant for only the high-dose combination group when using the ITT population
- The average daily use of the as-needed trial medication was similar between groups

Safety:
- Rates of adverse effects were similar between groups with the exception for oral candidiasis, which was higher in the combination therapy groups

Cost:
- The cost of using fixed-dose albuterol-budesonide inhalers over albuterol-only inhalers must be balanced against the cost-savings achieved from reducing the frequency of severe asthma exacerbations

Special Considerations/Populations:
- Patients with COPD were excluded from this trial and the demonstrated results cannot be extrapolated outside of asthma patients

Grade of Recommendation: **A**

MATCH

Diener HC, Bogousslavsky J, Brass LM, et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischemic stroke or transient ischemic attack in high-risk patients (MATCH): randomized, double-blind, placebo-controlled trial. *Lancet*. 2004;364(9431):331-337.

Objective: To determine the efficacy of aspirin plus clopidogrel compared to clopidogrel alone on cardiovascular event rates in high-risk patients with recent ischemic stroke or TIA.

Primary Efficacy Measure: Composite of cardiovascular death, ischemic stroke, myocardial infarction or rehospitalization for acute ischemic event

Primary Safety Measures: (1) Life-threatening bleeding event (2) Major bleeding event

Participants: High-risk patients with history of previous ischemic event

- Age ~66 years; male ~63%
- Qualifying event: ischemic stroke ~79%; TIA ~21%

Inclusion Criteria:

- Ischemic stroke or TIA within previous 3 months
- One or more risk factors within the previous 3 years (previous ischemic stroke, myocardial infarction, angina pectoris, diabetes or symptomatic peripheral artery disease)

Exclusion Criteria:

- Age < 40 years
- Severe comorbid conditions
- Increased bleed risk
- Planned major surgery

Drugs: Clopidogrel; aspirin

Design: Randomized, double-blind, active-controlled trial

Methods: Eligible patients were randomized to receive clopidogrel 75 mg plus aspirin 75 mg once daily or clopidogrel 75 mg plus matching placebo once daily.

Duration: 18 months

Statistical Analysis: It was determined that 7600 randomized patients would achieve 80% power (alpha = 0.05). The ITT population was used for the primary efficacy analyses. The mITT population (patients that received at least one dose of study medication) was used for the safety analyses.

Results: A total of 7599 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. Gastrointestinal bleeds were the most common cause of life-threatening and major bleeding.

Aspirin Plus Clopidogrel (N=3797) Vs Clopidogrel Alone (N=3802)

Primary Composite Outcome:
596 (15.7%) vs 636 (16.7%); RRR 6.4% (95% CI -4.6% to 16.3%); p=0.244

Cardiovascular Death:
69 (1.82%) vs 74 (1.95%)

Ischemic Stroke:
299 (7.87%) vs 319 (8.39%)

Myocardial Infarction:
59 (1.55%) vs 62 (1.63%)

Rehospitalization for Acute Ischemic Event:
169 (4.45%) vs 181 (4.76%)

Safety:

Life-Threatening Bleeding:
96/3759 (2.55%) vs 49/3781 (1.30%); p<0.0001; ARI 1.26%; NNH ~80

Major Bleeding:
73/3759 (1.94%) vs 22/3781 (0.58%); p<0.0001; ARI 1.36%; NNH ~74

Minor Bleeding:
120/3759 (3.19%) vs 39/3781 (1.03%); p<0.0001; ARI 2.16%; NNH ~47

Limitations:

- Power set but not met - failed to randomize 7600 patients (clinical significance minimal)
- At baseline ~80% of patients were receiving aspirin therapy which possibly diminished the true treatment difference between treatment groups (clinical significance uncertain)
- High-risk patient population limits external validity of trial results

Level of Evidence: Level II - with major limitations

Recommendation: For these reasons, I do not recommend the use of aspirin plus clopidogrel over clopidogrel alone for reducing the risk of cardiovascular events in patients with recent ischemic event.

Efficacy:

- Rates of the primary composite outcome were not significantly different between groups

Safety:

- Life-threatening bleeding, major bleeding and minor bleeding all occurred at significantly higher rates in the aspirin plus clopidogrel group compared to clopidogrel alone

Cost:

- The cost of using aspirin plus clopidogrel must be considered in addition to the cost of monitoring for and managing bleeding events

Special Considerations/Populations:

- Patient population must be considered - cannot extrapolate results to other demographics

Grade of Recommendation: **B**

MERIT-HF

Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet*. 1999;353(9169):2001-2007.

Objective: To determine the effect of metoprolol succinate on mortality outcomes in patients with symptomatic heart failure and reduced ejection fraction.

Primary Efficacy Measures: (1) All-cause mortality (2) Composite of all-cause mortality or all-cause hospital admission

Participants: Patients with symptomatic heart failure with reduced ejection fraction

- Age ~64 years; male ~77%
- LVEF ~28%
- NYHA class II ~41%; class III ~56%
- BP ~130/78 mmHg; HR ~83 bpm
- ACEi/ARB ~95%; diuretics ~90%

Inclusion Criteria:

- Men and women age 40-80 years old
- NYHA functional class II-IV for ≥ 3 months
- Receiving ACEi and diuretic for 2 weeks
- Stable clinical condition for 2 weeks
- LVEF ≤ 40% within previous 3 months
- Supine resting HR ≥ 68 bpm

Exclusion Criteria:

- Myocardial infarction/unstable angina within previous 28 days
- Beta-blocker usage within previous 6 weeks
- Implanted cardioversion defibrillator; scheduled/performed heart transplant
- PCI/CABG planned/performed within past 4 months
- Unstable/decompensated heart failure; SBP < 100 mmHg
- Use of non-DHP CCBs; use of amiodarone within previous 6 months

Drug: Metoprolol succinate

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients were randomized to receive either metoprolol succinate or placebo. Dosing for metoprolol succinate was started at either 12.5 mg (NYHA class III-IV) or 25 mg daily (NYHA class II). Dosing would be increased once every 2 weeks to the target dose of 200 mg daily. The pre-specified criteria for stopping the trial early were based on all-cause mortality.

Duration: Mean follow-up period of 1 year

Statistical Analysis: It was determined that 1600 randomized patients per treatment group would achieve 80% power. Alpha was set at 0.04 for all-cause mortality and 0.01 for the composite of all-cause mortality or all-cause hospitalization. Only the results from all-cause mortality analysis are reviewed here. The ITT population was used for the primary analyses.

Results: A total 3991 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. The trial was stopped early on the recommendation of the safety committee. The average dose of metoprolol succinate was 159 mg daily. The average heart rate was 14 bpm lower from baseline in the metoprolol succinate group compared to 3 bpm lower in the placebo group ($p<0.001$). Overall, ~87% of patients achieved ≥ 100 mg daily and ~64% achieved 200 mg daily. Rates of discontinuation in the metoprolol succinate and placebo groups were 13.9% and 15.3%, respectively.

Metoprolol Succinate (N=1990) Vs Placebo (N=2001)

All-Cause Mortality:
145 (7.29%) vs 217 (10.8%); RR 0.66 (95% CI 0.53-0.81)
p=0.0062; ARR 3.56%; NNT ~29

Cardiovascular Death:
128 (6.43%) vs 203 (10.1%); RR 0.62 (95% CI 0.50-0.78)
p=0.00003; ARR 3.71%; NNT ~27

Death due to Aggravated Heart Failure:
30 (1.51%) vs 58 (2.90%); RR 0.51 (95% CI 0.33-0.79)
p=0.0023; ARR 1.39%; NNT ~72

Limitations:

- Patient population - cannot apply trial results to patients with preserved ejection fraction

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I recommend the use of metoprolol succinate (at max tolerated dose) in addition to standard therapy to further decrease mortality rates in patients with symptomatic heart failure and reduced ejection fraction.

Efficacy:

- Rates of all-cause mortality were significantly lower in the metoprolol succinate group compared to placebo
- Rates of cardiovascular death and death due to aggravated heart failure were also significantly lower in the metoprolol succinate group

Safety:

- Overall, rates of discontinuation were lower in the metoprolol succinate group

Cost:

- The cost of using metoprolol succinate must be balanced against the cost-savings of reduced mortality rates

Special Considerations/Populations:

- Cannot apply trial results to metoprolol tartrate
- Trial did not included patients with preserved ejection fraction - cannot extrapolate results to this population

Grade of Recommendation: **A**

MIRACL

Schwartz GG, Olsson AG, Ezekowitz MD, et al. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. *JAMA*. 2001;285(13):1711-1718.

Objective: To determine the effect of atorvastatin 80 mg on morbidity and mortality outcomes in patients post-acute coronary syndrome.

Primary Efficacy Measure: Composite of death, non-fatal acute myocardial infarction, cardiac arrest with resuscitation and recurrent symptomatic myocardial ischemia with objective evidence requiring emergency rehospitalization

Participants: Patients with recent acute coronary syndrome requiring hospitalization

- Age ~65 years; male ~35%
- Qualifying event unstable angina ~46%; myocardial infarction ~54%
- Prior myocardial infarction ~25%
- LDL ~124 mg/dL; HDL ~46 mg/dL; TGL ~184 mg/dL
- Baseline smoker ~28%; hypertension ~55%; diabetes ~23%

Inclusion Criteria:

- Age ≥ 18 years
- Chest pain lasting 15 minutes or more (at rest) within the 24 hours prior to hospitalization
- Diagnosis of unstable angina or non-Q-wave acute myocardial infarction

Exclusion Criteria:

- Total cholesterol > 270 mg/dL
- Planned coronary revascularization
- Evidence of Q-wave acute myocardial infarction within the previous 4 weeks
- CABG within the previous 3 months or PCI within the previous 6 months
- Severe congestive heart failure
- Lipid-lowering therapy (other than niacin 500 mg/daily)
- Renal or hepatic dysfunction
- Pregnancy or lactation

Drug: Atorvastatin

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients were randomized to receive either atorvastatin 80 mg or matching placebo. Randomization took place within 24-96 hours after hospitalization. All patients were instructed to follow the NCEP Step 1 diet.

Duration: 16 weeks

Statistical Analysis: It was determined that 3000 randomized patients would provide 95% power (alpha=0.05). All endpoints were analyzed using the ITT population.

Results: A total of 3086 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. LDL increased to an average of 135 mg/dL in the placebo group and reduced to an average of 72 mg/dL in the atorvastatin group ($p<0.001$). While numerically lower, rates of the primary composite outcome were not significantly different between treatment groups. One of the secondary efficacy endpoints, non-fatal stroke, occurred at significantly lower rates in the atorvastatin group.

Placebo (N=1548) Vs Atorvastatin (N=1538)

Primary Composite Outcome:
269 (17.4%) vs 228 (14.8%); RR 0.84 (95% CI 0.70-1.00); p=0.048
~ CI contains 1.00 – cannot claim statistical significance ~

Death:
68 (4.39%) vs 64 (4.16%); RR 0.94 (95% CI 0.67-1.31)

Non-Fatal Acute Myocardial Infarction:
113 (7.30%) vs 101 (6.57%); RR 0.90 (95% CI 0.69-1.16)

Resuscitated Cardiac Arrest:
10 (0.65%) vs 8 (0.52%); RR 0.82 (95% CI 0.33-0.2.06)

Recurrent Symptomatic Myocardial Ischemia Requiring Emergency Rehospitalization:
130 (8.40%) vs 95 (6.18%); RR 0.74 (95% CI 0.57-0.95); ARR 2.22%; NNT ~45

Non-Fatal Stroke:
22 (1.42%) vs 9 (0.59%); RR 0.84 (95% CI 0.20-0.87); ARR 0.83%; NNT ~120

Abnormal Liver Transaminase Levels (>3 times ULN):
9 (0.58%) vs 38 (2.47%); p<0.001; ARI 1.89%; NNH ~52

Limitations:
- Trial duration – four months may be insufficient time to demonstrate full statin benefit
- Patient population – all included patients had a recent acute coronary syndrome (within prior 4 days)

Level of Evidence: Level I – with minor limitations

Recommendation: For these reasons, I recommend the prompt initiation of atorvastatin 80 mg in patients with recent acute coronary syndrome to reduce the short-term risk for cardiovascular morbidity and mortality.

Efficacy:
- The primary composite outcome occurred at numerically lower rates in the atorvastatin group, but did not achieve a statistically significant difference (95% CI contains null value of 1.00)
- Individual rates of cardiac arrest with resuscitation, recurrent symptomatic myocardial ischemia with objective evidence requiring emergency rehospitalization and non-fatal stroke occurred at significantly lower rates in the atorvastatin group
- Predictable, the LDL reduction at 16 weeks was significantly greater with atorvastatin

Safety:
- Rates of abnormal liver enzyme elevation were significantly more common in the atorvastatin group

Cost:
- The cost of using atorvastatin 80 mg must be balanced against the cost-savings achieved from preventing a recurrent cardiovascular event in the period following shortly after an ACS

Special Considerations/Populations:
- Q-waves indicate permanent damage to the heart muscle from a prior myocardial infarction

Grade of Recommendation: **A**

Novel START

Beasley R, Holliday M, Reddel HK, et al. Controlled Trial of Budesonide-Formoterol as Needed for Mild Asthma. *N Engl J Med*. 2019;380(21):2020-2030.

Objective: To compare the efficacy and safety of as-needed budesonide-formoterol to as-needed albuterol and scheduled budesonide plus as-needed albuterol in adults with mild asthma.

Primary Efficacy Measure: Annual asthma exacerbation rate

- Asthma exacerbation: urgent medical care consult, prescription of systemic glucocorticoids or high beta-agonist use (>16 puffs of albuterol or > 8 puffs of budesonide–formoterol over a 24 hour period)

Participants: Adults with mild asthma (receiving SABA as monotherapy)

- Age ~36 years; male ~46%
- Average SABA use in the previous month: ~7 puffs per week
- FEV_1 ~90% of predicted value

Inclusion Criteria:

- Age 18-75 years with asthma diagnosis
- SABA as monotherapy for previous 3 months

Exclusion Criteria:

- Hospitalization for asthma in the previous 12 months
- More than 20 pack-years of smoking
- 10 pack-years or more of smoking plus the onset of respiratory symptoms after age 40

Drugs: Albuterol; budesonide; budesonide-formoterol

Design: Randomized, open-label, placebo-controlled trial

Methods: Eligible patients were randomized to one of three treatment groups: (1) as-needed albuterol (2) scheduled budesonide plus as-needed albuterol (3) as-needed budesonide-formoterol. Group 1 received two puffs of 100 mcg albuterol as-needed for relief of asthma symptoms. Group 2 received one puff of budesonide 200 mcg twice daily (scheduled) plus two puffs of 100 mcg albuterol for as-needed relief of asthma symptoms. Group 3 received one puff of 200 mcg-6 mcg budesonide-formoterol as-needed for relief of asthma symptoms.

Duration: 52 weeks

Statistical Analysis: It was determined that 225 randomized patients per treatment group would achieve 80% power for comparing the as-needed budesonide-formoterol group to the other two treatment groups (alpha=0.05). The ITT population was used for the efficacy analysis.

Results: A total of 668 patients underwent randomization and were included in the efficacy analysis. Baseline patient characteristics were similar between treatment groups. The average number of daily glucocorticoid-containing puffs was 1.11 in the scheduled budesonide plus as-needed albuterol group and 0.53 in the as-needed budesonide-formoterol group. The average number of daily beta-agonist-containing puffs was 1.01 in the as-needed albuterol group, 0.52 in the scheduled budesonide plus as-needed albuterol group and 0.53 in the as-needed budesonide-formoterol group. The overall rate of adverse events was similar between treatment groups, although the as-needed budesonide-formoterol group had the lowest rate.

As-Needed Albuterol (N=223) Vs As-Needed Budesonide-Formoterol (N=220)

Annual Asthma Exacerbation Rate:
0.400 vs 0.195; RR 0.49 (95% CI 0.33-0.72); p<0.001

Total Number of Exacerbations: 74 vs 37

Number of Severe Exacerbations:
23 (10.3%) vs 9 (4.09%); RR 0.40 (95% CI 0.18-0.86)

Budesonide Plus As-Needed Albuterol (N=225) Vs As-Needed Budesonide-Formoterol (N=220)

Annual Asthma Exacerbation Rate:
0.175 vs 0.195; RR 1.12 (95% CI 0.70-1.79); p=0.65

Total Number of Exacerbations: 32 vs 37

Number of Severe Exacerbations:
21 (9.33%) vs 9 (4.09%); RR 0.44 (95% CI 0.20-0.96)

Limitations:

- Power set but not met – clinical significance likely low (statistical difference still demonstrated)
- Open-label trial design
- Patient population – limited to adults with mild asthma (receiving SABA as monotherapy)

Level of Evidence: Level II – with major limitations

Recommendation: For these reasons, I recommend the use of as-needed budesonide-formoterol over as-needed albuterol to reduce exacerbation rates in adults with mild asthma. Additionally, I recommend the use of as-needed budesonide-formoterol over budesonide plus as-needed albuterol in patients that have difficulty adhering to scheduled medication therapy.
Efficacy:

- The annual rate of asthma exacerbation was significantly lower in the as-needed budesonide-formoterol group compared to the as-needed albuterol group
    - Rates were not significantly different between the as-needed budesonide-formoterol group and the scheduled budesonide plus as-needed albuterol group
- The number of severe asthma exacerbations was significantly lower in the as-needed budesonide-formoterol group compared to the other two treatment groups

Safety:

- The overall rate of adverse events was similar between treatment groups

Cost:

- The cost of using as-needed budesonide-formoterol must be balanced against the cost-savings achieved from a lower rate of asthma exacerbation

Special Considerations/Populations:

- Patient population – limited to adults with mild asthma (receiving SABA as monotherapy)

Grade of Recommendation: **B**

ODYSSEY OUTCOMES

Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. *N Engl J Med*. 2018;379(22):2097-2107.

Objective: To determine the effect of alirocumab on cardiovascular morbidity and mortality outcomes in patients with recent acute coronary syndrome and elevated lipid levels despite max-tolerated statin therapy.

Primary Efficacy Measure: Composite of coronary heart disease death, non-fatal myocardial infarction, fatal or non-fatal ischemic stroke or hospitalization for unstable angina

Participants: Patients with recent acute coronary syndrome with elevated lipid levels on statin therapy

- Age ~59 years; male ~75%
- Qualifying event: STEMI ~34%; NSTEMI ~48%; unstable angina ~17%; PCI/CABG ~72%
- Median time from acute coronary syndrome ~2.6 months
- LDL ~92 mg/dL

Inclusion Criteria:

- Age ≥ 40 years
- Hospitalized for acute coronary syndrome (myocardial infarction or unstable angina) within the previous 1-12 months
- LDL ≥ 70 mg/dL, non-HDL ≥ 100 mg/dL or apolipoprotein B level ≥ 80 mg/dL
- Receiving high-intensity statin therapy for a minimum of 2 weeks
    - Atorvastatin 40-80 mg or rosuvastatin 20-40 mg

Exclusion Criteria:

- Uncontrolled hypertension (SBP > 180 mmHg or DBP > 110 mmHg)
- History of hemorrhagic stroke
- NYHA class III or IV heart failure (or LVEF < 25%)
- Fasting triglycerides greater than 400 mg/dL
- Liver transaminases greater than 3 times the upper limit of normal

Drug: Alirocumab

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients were randomized to receive subcutaneous alirocumab 75 mg injection or matching placebo. All doses of study medication were given once every two weeks. The study protocol targeted an LDL range of 25-50 mg/dL to avoid sustained levels less than 15 mg/dL.

Duration: Median follow-up period of 2.8 years

Statistical Analysis: It was determined that 18,000 randomized patients and 1613 primary events would provide 90% power (alpha = 0.0498). The ITT population was used for the efficacy analyses. Hierarchical testing for each of the individual components of the composite outcome (in the order listed above) was pre-specified if statistical significance was demonstrated.

Results: A total of 18,924 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. After 48 months, the average LDL levels in the alirocumab and placebo groups were 66 mg/dL and 103 mg/dL, respectively. Rates of the primary composite outcome occurred at significantly lower rates in the alirocumab treatment group. Treatment effect was consistent upon subgroup analysis. Hierarchical testing failed to demonstrate a significant difference in the rates of coronary heart disease death between groups. Therefore, any further statistical analysis of the remaining individual components must be considered exploratory only.

Alirocumab (N=9462) Vs Placebo (N=9462)

Primary Composite Outcome:
903 (9.54%) vs 1052 (11.1%); HR 0.85 (95% CI 0.78-0.93)
p<0.001; ARR 1.57%; NNT ~64

Coronary Heart Disease Death:
205 (2.17%) vs 222 (2.35%); HR 0.92 (95% CI 0.76-1.11); p=0.38

Non-Fatal Myocardial Infarction:
626 (6.62%) vs 722 (7.63%); HR 0.86 (95% CI 0.77-0.96)

Fatal or Non-Fatal Ischemic Stroke:
111 (1.17%) vs 152 (1.61%); HR 0.73 (95% CI 0.57-0.93)

Hospitalization for Unstable Angina:
37 (0.39%) vs 60 (0.63%); HR 0.61 (95% CI 0.41-0.92)

Limitations:

- Patient population – all had recent acute coronary syndrome (within 1-12 months)
- Trial design – possibly insufficient duration to see LDL lowering benefit from statin therapy alone with a median time from ACS event of roughly 2.6 months (clinical significance uncertain)
- Demonstrated results must be considered in addition to high-intensity statin therapy

Level of Evidence: Level I – with minor limitations

Recommendation: For these reasons, I recommend the use of alirocumab to further reduce cardiovascular morbidity rates in patients with recent acute coronary syndrome and LDL levels ≥ 70 mg/dL despite high-intensity statin therapy.

Efficacy:

- Rates of the primary composite outcome were significantly lower in the alirocumab treatment group compared to placebo
    - Coronary heart disease death occurred at similar rates between treatment groups
    - Rates of non-fatal myocardial infarction, total ischemic stroke and hospitalization for unstable angina occurred a significantly lower rates in the alirocumab group (however, this must be considered an exploratory finding due to prior failure of hierarchical testing)

Safety:

- No significant differences in safety events related to study medication were demonstrated

Cost:

- The cost of using alirocumab must be balanced against the cost-savings from reduced cardiovascular morbidity outcomes (myocardial infarction, ischemic stroke, etc.)

Special Considerations/Populations:

- Alirocumab is a PCSK9 inhibitor
- Eligible patients had LDL levels ≥ 70 mg/dL despite baseline statin therapy

Grade of Recommendation: **A**

ONTARGET

ONTARGET Investigators, Yusuf S, Teo KK, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med*. 2008;358(15):1547-1559.

Objective: To compare the effects of ramipril, telmisartan, and ramipril plus telmisartan on cardiovascular outcomes in high-risk patients.

Primary Efficacy Measure: Composite of cardiovascular death, myocardial infarction, stroke or heart failure hospitalization

Participants: Patients with established cardiovascular disease or high-risk diabetes

- Age ~66 years; male ~73%
- Coronary artery disease ~74%; myocardial infarction ~49%; diabetes ~37%
- Baseline statin ~62%; beta-blocker ~57%; aspirin ~76%
- BP ~142/82 mmHg

Inclusion Criteria:

- Age ≥ 55 years
- Diabetes, coronary artery disease, peripheral artery disease or cerebrovascular disease

Exclusion Criteria:

- Congestive heart failure
- Planned cardiac surgery within 3 months
- Heart transplant recipient
- Renal artery disease

Drugs: Ramipril; telmisartan

Design: Randomized, double-blind, placebo-controlled, non-inferiority trial

Methods: Eligible patients underwent a run-in period consisting of ramipril 2.5 mg daily for 3 days, then telmisartan 40 mg plus ramipril 2.5 mg daily for 7 days, then telmisartan 40 mg plus ramipril 5 mg daily for 11-18 days. Patients that successfully completed the run-in period were randomized to receive either telmisartan 80 mg daily, ramipril 5 mg daily or both for 2 weeks. After two weeks the dose of ramipril was increased to 10 mg daily.

Duration: Median follow-up period of 56 months (~4.6 years)

Statistical Analysis: This trial was designed to test for non-inferiority (NI margin = 1.13) with subsequent testing for superiority, if applicable. Non-inferiority would be tested for telmisartan compared to ramipril, with subsequent testing for superiority. Additionally, the combination of ramipril plus telmisartan compared to ramipril alone would be tested for superiority. A level of significance (alpha) of 0.025 was selected for this trial. It was determined that 7800 randomized patients per treatment group would achieve 89% power for non-inferiority and 93% power for superiority. The ITT population was used for the primary analyses.

Results: A total of 25,260 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. Overall, blood pressure was lower in the telmisartan and combination therapy groups compared to ramipril (-0.9/0.6 mmHg & -2.4/1.4 mmHg, respectively). Changes in SCr levels were similar between all treatment group comparisons. Potassium level elevations > 5.5 mmol/L were similar between ramipril and telmisartan groups, but significantly higher in the combination therapy group. Permanent medication discontinuation due to symptoms of hypotension occurred notably more often in the combination therapy group compared to the ramipril and telmisartan groups (4.8% vs 1.7% vs 2.7%, respectively).

Ramipril (N=8576) Vs Telmisartan (N=8542)

Primary Composite Outcome:
1412 (16.5%) vs 1423 (16.7%); RR 1.01 (95% CI 0.94-1.09); p=0.83

Cardiovascular Death:
603 (7.03%) vs 598 (7.00%); RR 1.00 (95% CI 0.89-1.12)

Myocardial Infarction:
413 (4.82%) vs 440 (5.15%); RR 1.07 (95% CI 0.94-1.22)

Stroke:
405 (4.72%) vs 369 (4.32%); RR 0.91 (95% CI 0.79-1.05)

Heart Failure Hospitalization:
354 (4.13%) vs 394 (4.61%); RR 1.12 (95% CI 0.97-1.29)

Hyperkalemia (> 5.5 mmol/L):
283 (3.30%) vs 287 (3.36%)

Ramipril (N=8576) Vs Ramipril Plus Telmisartan (N=8502)

Primary Composite Outcome:
1412 (16.5%) vs 1386 (16.3%); RR 0.99 (95% CI 0.92-1.07); p=0.38

Cardiovascular Death:
603 (7.03%) vs 620 (7.29%); RR 1.04 (95% CI 0.93-1.17)

Myocardial Infarction:
413 (4.82%) vs 438 (5.15%); RR 1.08 (95% CI 0.94-1.23)

Stroke:
405 (4.72%) vs 373 (4.39%); RR 0.93 (95% CI 0.81-1.07)

Heart Failure Hospitalization:
354 (4.13%) vs 332 (3.90%); RR 0.95 (95% CI 0.82-1.10)

Hyperkalemia (> 5.5 mmol/L):
283 (3.30%) vs 480 (5.65%); p<0.001; ARI 2.35%; NNH ~42

Limitations:

- External validity - cannot extrapolate results to other high-risk patient populations
- Failure to demonstrate superiority does not equate to demonstrating non-inferiority

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I recommend the use of either ramipril or telmisartan to reduce the rate of cardiovascular morbidity and mortality outcomes in high-risk patients. I do not recommend the concurrent use of ramipril and telmisartan for this purpose due to lack of added benefit and notable safety concerns.

Efficacy:

- Telmisartan demonstrated non-inferiority to ramipril regarding the primary composite outcome
- Ramipril plus telmisartan failed to demonstrated superiority to ramipril alone regarding the primary composite outcome (does not equate to non-inferiority)
- No individual component of the primary composite outcome was notably different between treatment comparisons

Safety:

- Rates of hyperkalemia (> 5.5 mmol/L) were significantly higher in the combination treatment group compared to ramipril alone
- Permanent discontinuation due to symptoms of hypotension occurred most often in the combination therapy group
- There was no significant difference in SCr change between either treatment comparison

Cost:

- The cost of using telmisartan must be balanced against the cost of using ramipril

Special Considerations/Populations:

- Majority of patients had established cardiovascular disease
- Cannot apply trial results to patients with heart failure (excluded from study)

Grade of Recommendation: **A**

ORIGIN n-3

ORIGIN Trial Investigators, Bosch J, Gerstein HC, et al. n-3 fatty acids and cardiovascular outcomes in patients with dysglycemia. *N Engl J Med*. 2012;367(4):309-318.

Objective: To determine the effect of n-3 fatty acid supplementation on cardiovascular outcomes in patients with type 2 diabetes.

Primary Efficacy Measure: Cardiovascular death

Secondary Efficacy Measure: Composite of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke

Participants: Patients with dysglycemia at increased risk for cardiovascular events

- Age ~64 years; male ~65%
- History of myocardial infarction, stroke or revascularization ~59%
- HgA1c ~6.4%; triglycerides ~141 mg/dL
- Total cholesterol ~190 mg/dL; HDL ~46 mg/dL; LDL ~112 mg/dL
- BP ~146/84 mmHg; HR ~70 bpm
- Baseline ACEi/ARB ~69%; beta-blocker ~53%; statin ~54%; aspirin/antiplatelet ~69%

Inclusion Criteria:

- Age ≥ 50 years
- Type 2 diabetes using ≤ 1 glucose-lowering medication, impaired fasting glucose (110-126 mg/dL) or impaired glucose tolerance (≥ 140 mg/dL 2 hours after 75 gm oral glucose load)
- History of myocardial infarction, stroke or revascularization, ischemic angina, UACR >30mg/g, left ventricular hypertrophy, >50% artery stenosis or ABI < 0.9

Exclusion Criteria:

- HgA1c ≥ 9%
- CABG within previous 4 years
- Severe heart failure

Drug: n-3 fatty acid (EPA and DHA)

Design: Randomized, double-blind, placebo-controlled trial

Methods: After a 10 day run-in period, eligible patients were randomized to receive either n-3 fatty acid 1000 mg daily (465 mg EPA and 375 mg DHA) or matching placebo (containing ~1000 mg of olive oil). The use of non-study n-3 fatty acid supplements was discouraged. There were no recommendations made regarding diet.

Duration: Median follow-up period of 6.2 years

Statistical Analysis: It was determined that 12,500 randomized patients followed for 6 years would achieve 90% power (alpha = 0.05). The ITT population was used for all efficacy analyses.

Results: A total of 12,611 patients underwent randomization (12,536 patients included in analyses). Baseline patient characteristics were similar between treatment groups. Overall change in triglyceride levels was significantly greater in the n-3 fatty acid group compared to placebo (-23.5 mg/dL vs -9.0 mg/dL; $p<0.001$). There was no significant difference in discontinuation rates or s.

n-3 Fatty Acid (N=6281) Vs Placebo (N=6255)

Cardiovascular Death:
574 (9.14%) vs 581 (9.29%); HR 0.98 (95% CI 0.87-1.10); p=0.72

Cardiovascular Death, Non-Fatal Myocardial Infarction or Non-Fatal Stroke:
1034 (16.5%) vs 1017 (16.3%); HR 1.01 (95% CI 0.93-1.10); p=0.81

Total Myocardial Infarction:
344 (5.48%) vs 316 (5.05%); HR 1.09 (95% CI 0.93-1.27); p=0.28

Total Stroke:
314 (5.00%) vs 336 (5.37%); HR 0.92 (95% CI 0.79-1.08); p=0.32

Limitations:

- The majority of patients were on standard cardiovascular medication therapy at baseline - trial results should be considered in addition to said medications

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I do not recommend the use of n-3 fatty acids for reduction of cardiovascular morbidity and mortality outcomes in high-risk patients with dysglycemia.

Efficacy:

- There was no significant difference in rates of cardiovascular death between groups
- Rates of total myocardial infarction and total stroke did not differ significantly between treatment groups

Safety:

- The discontinuation rates and overall rates were not significantly different between groups

Cost:

- The cost of using n-3 fatty acid must be balanced against the cost of using medications with proven cardiovascular benefit

Special Considerations/Populations:

- Patient population must be considered - the majority had established cardiovascular disease and were receiving standard therapy

Grade of Recommendation: **A**

PARADIGM-HF

McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371(11):993-1004.

Objective: To determine the effect of sacubitril-valsartan compared to enalapril on morbidity and mortality outcomes in patients with heart failure and reduced ejection fraction.

Primary Efficacy Measure: Composite of cardiovascular death or first heart failure hospitalization

Participants: Patients with heart failure and reduced ejection fraction (NYHA class II-IV)

- Age ~64 years; male ~79%
- LVEF ~30%
- NYHA class II ~70%; class III ~24%
- SBP ~122 mmHg; HR ~72 bpm
- Baseline beta-blocker ~93%; diuretic ~80%; mineralocorticoid antagonist ~55%

Inclusion Criteria:

- Age ≥ 18 years with LVEF ≤ 35% (originally 40%)
- NYHA functional class II-IV
- BNP ≥ 150 pg/mL (≥ 100 pg/mL if hospitalized for heart failure within previous 12 months)
- Receiving stable dosing of beta-blocker and ACEi/ARB for 4 weeks

Exclusion Criteria:

- Symptomatic hypotension
- SBP < 100 mmHg
- eGFR < 30 mL/min
- Serum potassium > 5.2 mmol/L
- History of angioedema

Drugs: Sacubitril/valsartan; enalapril

Design: Randomized, double-blind, active-controlled trial

Methods: Eligible patients underwent two single-blind run-in phases. First, all patients received enalapril 10 mg twice daily alone for 2 weeks and then all patients received ARNi therapy (sacubitril/valsartan) for 4-6 weeks (initially 49 mg/51 mg twice daily, then increased to 97 mg/103 mg twice daily) alone to ensure the side effect profile was acceptable. Those that successfully completed these run-in periods were then randomized to receive enalapril 10 mg twice daily or sacubitril-valsartan 97 mg/103 mg twice daily. Dosing could be reduced if appropriate.

Duration: Median follow-up period of 27 months

Statistical Analysis: It was determined that 2410 primary events would achieve 97% power (alpha = 0.05). Criteria for stopping the trial early was established by the safety and monitoring committee. The ITT population was used for the efficacy analyses.

Results: A total of 8399 patients underwent randomization. Baseline characteristics were similar between treatment groups. The trial was stopped early due to the results of the third interim analysis showing clear benefit of sacubitril/valsartan over enalapril. The average daily dosing of the study drugs was ~375 mg sacubitril/valsartan and ~19 mg enalapril. At 8 months, the decline in average KCCQ clinical summary score (used to subjectively assess heart failure symptoms and physical limitations) was significantly less in the sacubitril/valsartan group compared to enalapril (-2.99 vs -4.63; p=0.001). There was no significant difference in rates of angioedema.

Sacubitril/Valsartan (N=4187) Vs Enalapril (N=4212)

Composite of Cardiovascular Death or First Heart Failure Hospitalization:
914 (21.8%) vs 1117 (26.5%); HR 0.80 (95% CI 0.73-0.87)
p<0.001; ARR 4.69%; NNT ~22

Cardiovascular Death:
558 (13.3%) vs 693 (16.5%); HR 0.80 (95% CI 0.71-0.89)
p<0.001; ARR 3.13%; NNT ~32

First Heart Failure Hospitalization:
537 (12.8%) vs 658 (15.6%); HR 0.79 (95% CI 0.71-0.89)
p<0.001; ARR 2.80%; NNT ~36

All-Cause Mortality:
711 (17.0%) vs 835 (19.8%); HR 0.84 (95% CI 0.76-0.93)
p<0.001; ARR 2.84%; NNT ~36

Symptomatic Hypotension with SBP < 90 mmHg:
112 (2.67%) vs 59 (1.40%); p<0.001; ARI ~1.27%; NNH ~78

Limitations:

- Power set but not met - failed to achieve 2410 primary event outcomes (trial stopped early - clinical significance minimal)
- Patient population - cannot extrapolate trial results to those with preserved ejection fraction

Level of Evidence: Level II - with major limitations

Recommendation: For these reasons, I recommend the use of sacubitril/valsartan over enalapril to further reduce morbidity and mortality rates in heart failure patients with reduced ejection fraction. However, it would be reasonable to optimize standard heart failure therapy prior to initiation of sacubitril/valsartan to maximize the overall treatment benefit.

Efficacy:

- Rates of the primary composite outcome were significantly lower in the sacubitril/valsartan group compared to enalapril
- The individual components of cardiovascular death and first heart failure hospitalization were significantly lower in the sacubitril/valsartan group as well
- Average KCCQ score decline was significantly less in the sacubitril/valsartan group compared to enalapril (indicates less decline in quality of life)

Safety:

- There was no significant difference in the rates of angioedema
- Symptomatic hypotension (with SBP < 90 mmHg) did occur at significantly higher rates in the sacubitril/valsartan group compared to enalapril

Cost:

- The cost of using sacubitril/valsartan must be balanced against the cost-savings of preventing morbidity and mortality events in heart failure patients

Special Considerations/Populations:

- If switching from ACEi to ARNi (or vice versa) there must be a wash-out period of 36 hours to reduce the risk for angioedema
- It is important to note that all patients included in this trial were able to tolerate ACEi prior to starting ARNi therapy (due to trial design)

Grade of Recommendation: **A**

PARADISE-MI

Pfeffer MA, Claggett B, Lewis EF, et al. Angiotensin Receptor-Neprilysin Inhibition in Acute Myocardial Infarction. *N Engl J Med*. 2021;385(20):1845-1855.

Objective: To determine the effect of sacubitril-valsartan on the development of symptomatic heart failure and mortality in high-risk patients following an acute myocardial infarction.

Primary Efficacy Measure: Composite of cardiovascular death or incident heart failure (defined as heart failure hospitalization or outpatient episodes of symptomatic heart failure treated with IV or sustained oral diuretics)

Participants: Patients with acute myocardial infarction at risk for symptomatic heart failure

- Age ~64 years; male ~76%
- LVEF ~36%; pulmonary congestion ~54%
- BP ~121/74 mmHg; HR ~76 bpm
- Qualifying event STEMI ~76%; NSTEMI ~24%
- Baseline DAPT ~92%; beta-blocker ~85%; statin ~95%; ACEi/ARB ~78%

Inclusion Criteria:

- No previous history of heart failure
- Acute MI within previous 7 days
- Left ventricular systolic dysfunction (LVEF ≤ 40%), pulmonary congestion or both conditions PLUS one or more risk-augmenting factors (age ≥ 70, diabetes, previous myocardial infarction, eGFR < 60 mL/min, etc.)

Exclusion Criteria:

- Clinically unstable during 24 hours prior to randomization
- Persistent clinical heart failure at time of randomization
- eGFR < 30 mL/min
- Serum potassium > 5.2 mmol/L
- History of angioedema
- Inability to tolerate ACEi/ARB

Drugs: Sacubitril-valsartan; ramipril

Design: Randomized, double-blind, active-controlled trial

Methods: Eligible patients were randomized to receive sacubitril-valsartan or ramipril. Patients designated to receive sacubitril-valsartan that had received an ACEi within the previous 36 hours were given valsartan alone for the first two doses to minimize the risk for angioedema (blinding maintained). Targeted dosing was ramipril 5 mg twice daily and sacubitril-valsartan 97 mg/103 mg twice daily.

Duration: Median follow-up period of 22 months

Statistical Analysis: It was determined that 708 primary events would provide 80% power (alpha=0.05). The ITT population was used for the primary efficacy analysis. The COVID-19 pandemic prompted an additional interim analysis which led to the level of significance being adjusted to 0.0484 for the final primary efficacy analysis.

Results: A total of 5661 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. There was no significant difference in morbidity or mortality outcomes between treatment groups. Rates of laboratory abnormalities were similar between treatment groups. There was no severe airway compromise in any of the angioedema cases.

Sacubitril-Valsartan (N=2830) Vs Ramipril (N=2831)

Primary Composite Outcome:
338 (11.9%) vs 373 (13.2%); HR 0.90 (95% CI 0.78-1.04); p=0.17

Cardiovascular Death:
137 (4.84%) vs 136 (4.80%)

Heart Failure Hospitalization or Outpatient Treatment for Heart Failure:
201 (7.10%) vs 237 (8.37%); HR 0.84 (95% CI 0.70-1.02)

Angioedema:
14 (0.49%) vs 17 (0.60%); p=0.59

Hypotension:
802 (28.3%) vs 620 (21.9%); p<0.001

Limitations:

- Patient population - left ventricular systolic dysfunction and/or pulmonary congestion following acute myocardial infarction (with no history of heart failure)

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I do not recommend the use of sacubitril-valsartan over ramipril for reducing the risk of symptomatic heart failure development or mortality in high-risk patients with left-ventricular dysfunction/pulmonary congestion following an acute myocardial infarction.

Efficacy:

- There was no significant difference in the rates of the primary composite outcome or the individual components
- The ARNi treatment group demonstrated no significant difference in reducing the development of symptomatic heart failure or cardiovascular mortality compared to the ACEi treatment group, indicating a lack of added benefit compared to ramipril alone

Safety:

- While rates of angioedema were similar between groups, the rates of hypotension were significantly higher in the sacubitril-valsartan group

Cost:

- The cost of using sacubitril-valsartan over ramipril must be balanced against any potential cost-savings from reduced rates of heart failure hospitalization/outpatient treatment
- However, the cost of managing and treating hypotension events must also be considered

Special Considerations/Populations:

- Patients were at increased risk for developing symptomatic heart failure
- Trial results cannot be applied to patients with symptomatic heart failure following an acute myocardial infarction

Grade of Recommendation: **A**

PARAGON-HF

Solomon SD, McMurray JJV, Anand IS, et al. Angiotensin-Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction. *N Engl J Med*. 2019;381(17):1609-1620.

Objective: To compare the effect of sacubitril-valsartan to valsartan alone on morbidity and mortality outcomes in heart failure patients with preserved ejection fraction.

Primary Efficacy Measure: Composite of cardiovascular death and total heart failure hospitalizations

Participants: Patients with heart failure and preserved ejection fraction (NYHA class II-IV)

- Age ~73 years; male ~48%
- LVEF ~57%
- NYHA class II ~77%; class III ~19%; class IV ~0.5%
- SBP ~131 mmHg; HR ~70 bpm
- Baseline ACEi/ARB ~86%; beta-blocker ~80%; diuretic ~95%; MRA ~25%

Inclusion Criteria:

- Age ≥ 50 years
- LVEF ≥ 45% within previous 6 months
- NYHA functional class II-IV
- Evidence of structural heart disease

Exclusion Criteria:

- Prior LVEF < 40%
- Acute coronary syndrome/cardiac surgery/urgent PCI within previous 3 months
- Clinical event with potential to reduce LVEF within previous 6 months
- Current acute decompensated heart failure
- History of angioedema

Drugs: Sacubitril-valsartan; valsartan

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients underwent a run-in period involving trialing of valsartan and then sacubitril-valsartan. Patients who tolerated both medications were then randomized to receive valsartan (target dose 160 mg twice daily) or sacubitril-valsartan (target dose 97/103 mg twice daily). ACEi/ARBs were discontinued prior to the run-in period but all other background medications/heart failure therapies were continued.

Duration: Median follow-up period of 35 months (~3 years)

Statistical Analysis: It was determined that 1847 primary events would 95% power (alpha = 0.048). The ITT population was used for primary efficacy analyses.

Results: A total of 4822 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. Rates of the primary composite outcome were not significantly different between groups. Secondary analysis of NYHA class change from baseline to 8 months suggests treatment benefit favoring sacubitril-valsartan (more improvement and less worsening than valsartan alone). However, these results must be considered exploratory due to failure of prior hierarchical testing. Although rates of angioedema were significantly higher in the sacubitril/valsartan group there were no reports of airway compromise for any case.

Sacubitril-Valsartan (N=2407) Vs Valsartan (N=2389)

Composite of Cardiovascular Death and Total Heart Failure Hospitalizations:
894 vs 1009; RR 0.87 (95% CI 0.75-1.01); p=0.06

Cardiovascular Death:
204 (8.48%) vs 212 (8.87%); HR 0.95 (95% CI 0.79-1.16)

Total (first and recurrent) Heart Failure Hospitalizations:
690 vs 797; RR 0.85 (95% CI 0.72-1.00)

NYHA Class Change at 8 Months:
OR 1.45 (95% CI 1.13-1.86)

Improvement:
347/2316 (15.0%) vs 289/2302 (12.6%)

Unchanged:
1767/2316 (76.3%) vs 1792/2302 (77.8%)

Worsened:
202/2316 (8.72%) vs 221/2302 (9.60%)

Safety:

Hypotension with SBP < 100 mmHg:
380 (15.8%) vs 257 (10.8%); p<0.001; ARI 5.03%; NNH ~19

Angioedema:
14 (0.58%) vs 4 (0.17%); p=0.02; ARI 0.41%; NNH ~241

Limitations:

- Patient population - cannot extrapolate trial results to patients with heart failure reduced ejection fraction

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I do not recommend the use of sacubitril-valsartan over valsartan for further reduction of morbidity and mortality outcomes in heart failure patients with preserved ejection fraction. Instead, I recommend the optimization of current therapies (for heart failure and comorbid conditions) to help prevent disease progression and clinical worsening.

Efficacy:

- Rates of the primary composite outcome and individual components were not significantly different between treatment groups
- NYHA class change at 8 months indicates more improvement and less worsening with sacubitril-valsartan compared to valsartan alone, however these results must be considered exploratory
- The vast majority of patients (~76%) saw no change in NYHA class at 8 months

Safety:

- Rates of hypotension (SBP <100 mmHg) and angioedema were significantly higher in the sacubitril-valsartan group compared to valsartan alone, however there were no reported cases of airway compromise

Cost:

- The cost of using sacubitril-valsartan must be balanced against the cost of using valsartan

Special Considerations/Populations:

- Use of an ARB control may have blunted the observable treatment benefit more than use of an ACEi control (as seen in PARADIGM-HF) due to more complete inhibition of angiotensin II effects (clinical significance uncertain)

Grade of Recommendation: **A**

PARTNERS PrEP

Baeten JM, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *N Engl J Med*. 2012;367(5):399-410.

Objective: To determine the efficacy and safety of oral emtricitabine-tenofovir disoproxil fumarate (FTC-TDF) or TDF for prevention of HIV-1 infection in heterosexual men and women in serodiscordant relationships.

Primary Efficacy Measure: Incident HIV-1 infection in partners previously seronegative

Participants: Heterosexual couples in HIV-1 serodiscordant relationships

Inclusion Criteria:

- Heterosexual couples (one partner HIV-1 positive, one partner HIV-1 negative)

Exclusion Criteria:

- Impaired renal function
- Pregnancy or breastfeeding
- Hepatitis B infection

Drugs: Emtricitabine; tenofovir disoproxil fumarate

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients were randomized to receive TDF 300 mg, FTC-TDF 200 mg-300 mg or placebo once daily. All patients received risk-reduction counseling, condoms, and other HIV-1 prevention services.

Duration: Follow-up period of 36 months

Statistical Analysis: It was determined that 147 infections would provide 80% power (alpha=0.025). The modified ITT population (all patients except those that tested positive at enrollment) was used for the primary efficacy analysis.

Results: A total of 4758 patients underwent randomization (4747 included in final analysis). Baseline patient characteristics were similar between treatment groups. There was no significant difference in HIV-1 protective effects between TDF and FTC-TDF groups. Among the HIV-1 infection patients in the TDF and FTC-TDF groups, only 31% had detectable tenofovir levels (vs 82% of samples from seronegative patients). Rates of adverse events were similar across treatment groups. Gastrointestinal side effects were more commonly reported in the TDF and FTC-TDF groups compared to placebo. Clinically significant elevations in serum creatinine were not demonstrated.

TDF (N=1579) Vs Placebo (N=1578)

Incident HIV-1 Infection in Partners Previously Seronegative:
17 (1.08%) vs 52 (3.30%); HR 0.33 (95% CI 0.19-0.56)
p<0.001; ARR 2.22%; NNT ~46

FTC-TDF (N=1576) Vs Placebo (N=1578)

Incident HIV-1 Infection in Partners Previously Seronegative:
13 (0.82%) vs 52 (3.30%); HR 0.25 (95% CI 0.13-0.45)
p <0.001; ARR 2.47%; NNT ~41

Limitations:

- Power – failed to achieve 147 incident HIV-1 infections
    - Clinical significance likely low – statistical differences still demonstrated
- Patient population – heterosexual couples in a serodiscordant relationship

Level of Evidence: Level II – with major limitations

Recommendation: For these reasons, I recommend the use of TDF or TDF-FTC once daily for prevention of HIV-1 infection in heterosexual patients involved in a serodiscordant relationship. Additionally, a strong emphasis on adherence is necessary to optimize treatment benefit.

Efficacy:

- TDF and FTC-TDF both demonstrated significantly lower rates of incident HIV-1 infections
    - Benefit was consistent in male and female patients
- Rates of HIV-1 infection were similar between TDF and FTC-TDF groups
- Detectable levels of TDF were correlated with increased HIV-1 protection
    - Adherence is critical for achieving benefit of therapy

Safety:

- There was no evidence of clinically significant serum creatinine elevations, although this is a known concern with TDF usage
- Overall adverse event rates were similar across treatment groups
- Gastrointestinal side effects were more common in the active treatment groups

Cost:

- The cost of using TDF or FTC-TDF once daily must be balanced against the cost-savings of preventing lifelong HIV-1 infections

Special Considerations/Populations:

- Patient population was heterosexual

Grade of Recommendation: **B**

PATHWAY-2

Williams B, MacDonald TM, Morant S, et al. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomized, double-blind, crossover trial. *Lancet*. 2015;386(10008): 2059-2068.

Objective: To determine the optimal pharmacotherapy for treatment of drug-resistant hypertension.

Primary Efficacy Measure: Average home systolic blood pressure

- Recorded in morning and evening (in triplicate) for 4 consecutive days prior to study visits

Participants: Patients with drug-resistant hypertension

- Age ~62 years; male ~69%
- Home SBP ~148 mmHg; DBP ~84 mmHg
- Clinic SBP ~157 mmHg; DBP ~90 mmHg

Inclusion Criteria:

- Age 18-79 years
- Seated clinic SBP ≥ 140 mmHg and home SBP ≥ 130 mmHg
- ≥ 3 months of treatment with three antihypertensive medications (ACEi, CCB and diuretic) at maximally tolerated doses

Exclusion Criteria:

- Secondary hypertension
- Type 1 diabetes
- eGFR < 45 mL/min
- Repeated abnormal serum potassium levels

Drugs: Spironolactone; bisoprolol; doxazosin

Design: Randomized, double-blind, placebo-controlled, crossover trial

Methods: Eligible patients that successfully completed the run-in period were randomized to receive 4 cycles of antihypertensive therapy. The four cycles were: spironolactone 25-50 mg daily, doxazosin modified release 4-8 mg daily, bisoprolol 5-10 mg daily and placebo. Each cycle consisted of 6 weeks at the lower dose and 6 weeks at the higher dose (12 weeks per cycle). Blood pressure measurements were assessed using an automated blood pressure monitor.

Duration: 12 months

Statistical Analysis: It was determined that 294 randomized patients would provide 90% power (alpha=0.003). Hierarchical testing was performed for the primary efficacy outcome: (1) spironolactone vs placebo (2) spironolactone vs the average of doxazosin and bisoprolol groups (3) spironolactone vs doxazosin, and spironolactone vs bisoprolol. The ITT population (all patients with primary outcome data) was used for the efficacy analyses.

Results: A total of 335 patients underwent randomization (314 included in efficacy analyses). The use of spironolactone demonstrated the greatest reduction in home systolic blood pressure. When compared to the other drug cycles, spironolactone demonstrated significantly lower systolic blood pressure for all cases ($p<0.001$). The safety profiles of each drug treatment were similar.

Spironolactone

Average Home SBP (change from baseline):
134.9 mmHg (-12.8 mmHg)

Doxazosin

Average Home SBP (change from baseline):
139.0 mmHg (-8.7 mmHg)

Bisoprolol

Average Home SBP (change from baseline):
139.4 mmHg (-8.3 mmHg)

Placebo

Average Home SBP (change from baseline):
143.6 mmHg (-4.1 mmHg)

Limitations:

- This was a crossover trial (patients remained the same, in theory, during all drug cycles)
- Patient population – cannot apply trial results to patients without resistant hypertension
- Trial design – 12 weeks per treatment cycle may be too short to appropriately assess benefits and risks of each antihypertensive agent

Level of Evidence: Level I – with minor limitations

Recommendation: For these reasons, I recommend the use of spironolactone over doxazosin or bisoprolol for the treatment of drug-resistant hypertension.

Efficacy:

- Spironolactone demonstrated significantly greater reductions in systolic blood pressure compared to all other antihypertensive medications

Safety:

- The overall safety profiles were similar across antihypertensive treatments
    - However, the trial design/duration may have been too short for said adverse events to occur

Cost:

- The cost of using spironolactone over doxazosin or bisoprolol must be balanced against the cost-savings of lowering the risk for long-term cardiovascular and renal complications of uncontrolled hypertension

Special Considerations/Populations:

- Resistant hypertension: blood pressure above treatment goal despite the use of 3 or more antihypertensive agents
- Results of this trial suggest that sodium retention may be a significant contributor to the underlying cause of resistant hypertension
- The antihypertensive therapies included in this trial had different mechanisms of action
    - Doxazosin is a non-selective alpha-1 antagonist
    - Bisoprolol is a selective beta-1 antagonist
    - Spironolactone is an aldosterone antagonist

Grade of Recommendation: **A**

PEGASUS-TIMI 54

Bonaca MP, Bhatt DL, Cohen M, et al. Long-term use of ticagrelor in patients with prior myocardial infarction. *N Engl J Med*. 2015;372(19):1791-1800.

Objective: To determine the efficacy and safety of long-term ticagrelor plus aspirin (> 12 months) for secondary prevention of cardiovascular events in patients with prior myocardial infarction.

Primary Efficacy Measure: Composite of cardiovascular death, myocardial infarction or stroke

Primary Safety Measure: TIMI major bleeding

Participants: Patients with prior myocardial infarction at increased risk for cardiovascular events

- Age ~65 years; male ~76%
- Qualifying event STEMI ~54%; NSTEMI ~40%
- History of PCI ~83%
- Baseline statin ~93%; beta-blocker ~83%; ACEi/ARB ~80%; aspirin ~99%

Inclusion Criteria:

- Age ≥ 50 years
- Spontaneous myocardial infarction within prior 1-3 years
- One or more of the following risk factors: age ≥ 65, diabetes requiring medication, second myocardial infarction, multi-vessel coronary artery disease or eCrCl < 60 mL/min

Exclusion Criteria:

- Planned use of P2Y12 inhibitor, dipyridamole, cilostazol or anticoagulant
- Bleeding disorder
- History of ischemic stroke or intracranial bleeding
- CNS tumor
- Intracranial vascular abnormality
- Gastrointestinal bleeding within previous 6 months
- Major surgery within previous 30 days

Drug: Ticagrelor

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients were randomized to either ticagrelor 90 mg twice daily, ticagrelor 60 mg twice daily or matching placebo. All patients received aspirin 75 – 150 mg daily.

Duration: Median follow-up period of 33 months

Statistical Analysis: It was determined that 1360 primary events would provide 90% power for the analysis of the ticagrelor 90 mg group and 83% power for the analysis of the ticagrelor 60 mg group (alpha = 0.026 for final analysis). The ITT population was used for the primary efficacy analyses. The mITT population (patients that received at least one dose of study drug) was used for the safety analyses.

Results: A total of 21,162 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. The primary efficacy composite outcome occurred at significantly lower rates in both ticagrelor groups compared to placebo.

Bleeding events leading to transfusion occurred at significantly higher rates in the ticagrelor 90 mg and 60 mg groups compared to placebo (2.43% and 2.09%, vs 0.72%; $p<0.001$). Discontinuation due to a bleeding event was also significantly more frequent in the ticagrelor 90 mg and 60 mg groups compared to placebo (7.81% and 6.15%, vs 1.50%; $p<0.001$). There were no significant differences in the rates of fatal bleeding, hemorrhagic stroke or intracranial bleeding between treatment groups.

Ticagrelor 90 mg (N=7050) Vs Placebo (N=7067)

Composite of Cardiovascular Death, Myocardial Infarction or Stroke:
493 (6.99%) vs 578 (8.18%); HR 0.85 (95% CI 0.75-0.96)
p=0.008; ARR 1.19%; NNT ~85

Cardiovascular Death:
182 (2.58%) vs 210 (2.97%); HR 0.87 (95% CI 0.71-1.06); p=0.15

Myocardial Infarction:
275 (2.58%) vs 338 (4.78%); HR 0.81 (95% CI 0.69-0.95)
p=0.01; ARR 2.20%; NNT ~46

Stroke:
100 (1.42%) vs 122 (1.73%); HR 0.82 (95% CI 0.63-1.07); p=0.14

Safety:

Major Bleeding:
127/6988 (1.82%) vs 54/6996 (0.77%); HR 2.69 (95% CI 1.96-3.70)
p<0.001; ARI 1.05%; NNH ~95

Dyspnea:
1205/6988 (17.2%) vs 383/6996 (5.47%); HR 3.55 (95% CI 3.16-3.98)
p<0.001; ARI 11.8%; NNH ~8

Ticagrelor 60 mg (N=7045) Vs Placebo (N=7067)

Composite of Cardiovascular Death, Myocardial Infarction or Stroke:
487 (6.91%) vs 578 (8.18%); HR 0.84 (95% CI 0.74-0.95)
p=0.004; ARR 1.27%; NNT ~79

Cardiovascular Death:
174 (2.47%) vs 210 (2.97%); HR 0.83 (95% CI 0.68-1.01); p=0.07

Myocardial Infarction:
285 (4.05%) vs 338 (4.78%); HR 0.84 (95% CI 0.72-0.98); p=0.03

Stroke:
91 (1.29%) vs 122 (1.73%); HR 0.75 (95% CI 0.57-0.98); p=0.03

Safety:

Major Bleeding:
115/6958 (1.65%) vs 54/6996 (0.77%); HR 2.32 (95% CI 1.68-3.21)
p<0.001; ARI 0.88%; NNH ~113

Dyspnea:
987/6958 (14.2%) vs 383/6996 (5.47%); HR 2.81 (95% CI 2.50-3.17)
p<0.001; ARI 8.65%; NNH ~11

Limitations:

- Patient population must be considered - all had prior history of myocardial infarction
- Results in ticagrelor groups must be considered in addition to aspirin (75-150 mg)
- Treatment period must be considered (> 12 months)

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I recommend the use of ticagrelor plus aspirin (for extended duration) to reduce the risk for cardiovascular events in high-risk patients 1-3 years post-myocardial infarction. However, the increased bleeding risk must be carefully considered when deciding to initiate therapy and close monitoring is warranted. Additionally, tolerance issues due to increased rates of dyspnea raises significant concerns regarding adherence and overall clinical utility.

Efficacy:

- Both groups of ticagrelor demonstrated significantly lower rates of the primary composite outcome compared to the placebo group, driven primarily by lower rates of myocardial infarction and stroke
- There was no significant difference in the rate of cardiovascular death between groups

Safety:

- Major bleeding events occurred at significantly higher rates in both ticagrelor groups compared to placebo
- Bleeding events leading to transfusion and drug discontinuation were significantly higher in the both ticagrelor groups
- Dyspnea occurred at significantly higher rates in the ticagrelor groups compared to placebo

Cost:

- The cost of using ticagrelor must be balanced against the cost-savings of preventing cardiovascular events
    - However, the cost of treating bleeding events must also be considered

Special Considerations/Populations:

- The majority of patients had previously received dual antiplatelet therapy after their qualifying event (most had been discontinued due to enrollment being > 12 months post-qualifying event)
- This trial demonstrated benefit from long-term (> 12 months) dual antiplatelet therapy
    - Notable bleeding risk was also demonstrated

Grade of Recommendation: **A**

PIONEER 6

Husain M, Birkenfeld AL, Donsmark M, et al. Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med*. 2019;381(9):841-851.

Objective: To determine the effect of oral semaglutide on cardiovascular outcomes in patients with type 2 diabetes.

Primary Efficacy Measure: Composite of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke

Participants: Patients with type 2 diabetes at increased risk for cardiovascular event

- Age ~66 years; male ~69%
- HgA1c ~8.2%
- Established cardiovascular disease/chronic kidney disease ~85%

Inclusion Criteria:

- Type 2 diabetes
- Age ≥ 50 years with established cardiovascular or chronic kidney disease OR age ≥ 60 years with cardiovascular risk factors only

Exclusion Criteria:

- Treatment with GLP-1 agonist, DPP-4 inhibitor or pramlintide within previous 90 days
- NYHA class IV heart failure
- Planned revascularization surgery
- Myocardial infarction/stroke/unstable angina within previous 60 days
- Dialysis or eGFR < 30 mL/min
- Retinopathy/maculopathy resulting in active treatment

Drug: Oral semaglutide

Design: Randomized, double-blind, placebo-controlled, non-inferiority trial

Methods: Eligible patients were randomized to receive either oral semaglutide or matching placebo. Study medication was instructed to be taken with up to 120 mL of water each morning on an empty stomach at least 30 minutes prior to other food/drink/medications. Dosing was titrated (3 mg/day for 4 weeks, then 7 mg/day for 4 weeks) up to max of 14 mg/day unless side effects/tolerance issues warranted a dose reduction. Use of other glucose-lowering therapy was allowed.

Duration: Median follow-up period of 15.9 months

Statistical Analysis: The trial was designed to test for non-inferiority (NI margin = 1.8) and was to continue until a minimum of 122 primary events occurred to achieve 90% power (alpha = 0.05). If non-inferiority was proven for the primary outcome, then sequential testing for superiority would occur. The ITT population was used for the primary analyses.

Results: A total of 3183 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. The target dose of 14 mg/day was achieved in ~82% of the active treatment group. The average HgA1c change was greater in the oral semaglutide group compared to placebo (mean change from baseline -1.0% vs -0.3%). Adverse events leading to permanent discontinuation were notably higher in the oral semaglutide group (11.6% vs 6.5%), driven primarily by gastrointestinal disorders (6.8% vs 1.6%). Rates of pancreatitis and malignant neoplasms were similar between treatment groups.

Oral Semaglutide (N=1591) Vs Placebo (N=1592)

Cardiovascular Death, Non-Fatal Myocardial Infarction or Non-Fatal Stroke:
61 (3.83%) vs 76 (4.77%); HR 0.79 (95% CI 0.57-1.11); p=0.17

Cardiovascular Death:
15 (0.94%) vs 30 (1.88%); HR 0.49 (95% HR 0.27-0.92)

Non-Fatal Myocardial Infarction:
37 (2.33%) vs 31 (1.95%); HR 1.18 (95% CI 0.73-1.90)

Non-Fatal Stroke:
12 (0.75%) vs 16 (1.01%); HR 0.74 (95% CI 0.35-1.57)

Limitations:

- Cannot extrapolate results from the SUSTAIN 6 trial to the oral formulation of semaglutide (and vice versa)
- Patient population must be considered - vast majority had established cardiovascular or chronic kidney disease
- Cannot make claims about individual components of the primary composite outcome due to failure to demonstrate superiority for the composite as a whole (results must be considered exploratory)

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I recommend the use of oral semaglutide as a safe glucose-lowering medication for patients at increased risk for cardiovascular events. However, I do not recommend it for the purpose of reducing the risk of cardiovascular events.

Efficacy:

- Non-inferiority (but not superiority) was demonstrated for oral semaglutide compared to placebo regarding the primary composite outcome
- Mean HgA1c difference between treatment groups was -0.7% favoring the oral semaglutide group

Safety:

- Rates of permanent discontinuation due to adverse events were higher in the oral semaglutide group, driven primarily by gastrointestinal disorders
- Rates of pancreatitis and malignant neoplasms were not significantly different between treatment groups

Cost:

- The cost of using oral semaglutide must be balanced against the cost of using a GLP-1 agonist with demonstrated cardiovascular benefit

Special Considerations/Populations:

- Oral semaglutide represents a safe alternative to injectable GLP-1 receptor agonists, which may be preferable for patients unwilling/unable to use injectable medications

Grade of Recommendation: **A**

PIONEER AF-PCI

Gibson CM, Mehran R, Bode C, et al. Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI. *N Engl J Med*. 2016;375(25):2423-2434.

Objective: To compare the safety and efficacy of rivaroxaban plus P2Y12 inhibitor, rivaroxaban plus dual antiplatelet therapy and vitamin K antagonist plus dual antiplatelet therapy in atrial fibrillation patients post-PCI.

Primary Safety Measure: Clinically significant bleeding (composite of TIMI major bleeding, TIMI minor bleeding or bleeding requiring medical attention)

Secondary Efficacy Measure: Composite of cardiovascular death, myocardial infarction or stroke

Participants: Atrial fibrillation patients undergoing PCI with stent placement

- Age ~70 years; male ~74%
- CHADS2-VASc ≥ 2 ~90%
- Drug-eluting stent ~65%; bare-metal stent ~32%

Inclusion Criteria:

- Age ≥ 18 with non-valvular atrial fibrillation
- PCI with stent placement

Exclusion Criteria:

- History of stroke or TIA
- Gastrointestinal bleeding within previous 12 months
- CrCl < 30 mL/min
- Anemia of unknown cause with Hgb < 10 g/dL

Drugs: Rivaroxaban; P2Y12 inhibitor; vitamin K antagonist; aspirin

Design: Randomized, open-label, active-controlled trial

Methods: Eligible patients underwent randomization within 72 hours after stent sheath removal. Prior to randomization, the investigator determined the duration of dual antiplatelet therapy (1, 6 or 12 months) as well as the intended P2Y12 inhibitor (clopidogrel, prasugrel or ticagrelor). Group 1 received rivaroxaban 15 mg daily plus P2Y12 inhibitor (no aspirin) for 12 months. Group 2 received rivaroxaban 2.5 mg twice daily plus dual antiplatelet therapy (aspirin 75-100 mg) for 1, 6 or 12 months. Patients in Group 2 that completed 1 or 6 months then received rivaroxaban plus aspirin only for the remainder of the 12 month period. Group 3 received vitamin K antagonist therapy (target INR 2-3) plus dual antiplatelet therapy (aspirin 75-100 mg) for 1, 6 or 12 months. Patients in Group 2 that completed 1 or 6 months then received rivaroxaban 15 mg daily plus aspirin only for the remainder of the 12-month period. Patients in Group 3 that completed 1 or 6 months then received warfarin plus aspirin only for the remainder of the 12 month period.

Duration: 12 months

Statistical Analysis: It was determined that 2,100 randomized patients would provide roughly 80% power (alpha = 0.05). The mITT population (received at least one dose of study medication) was used for the safety and efficacy analyses.

Results: A total of 2124 patients underwent randomization of which 2099 received at least one dose of study medication. Baseline patient characteristics similar between treatment groups. Clopidogrel was the chosen P2Y12 inhibitor in ~93% of patients. Those treated with vitamin K antagonists were in target INR range ~65% of the time. While rates of the composite bleeding outcome were significantly higher in Group 3 compared to Groups 1 and 2, there was no significant difference in the rates of TIMI major or TIMI minor bleeding for any treatment group comparison. There was no significant difference in the rates of the individual components of the cardiovascular composite outcome for any treatment group comparison. Rates of stent thrombosis were not significantly different between treatment groups.

Rivaroxaban 15 mg Plus P2Y12 Inhibitor (N=696) Vs VKA Plus DAPT (N=697)

Composite of Clinically Significant Bleeding:
109 (15.7%) vs 167 (24.0%); HR 0.59 (95% CI 0.47-0.76)
p<0.001; ARI 8.30%; NNH ~12

Bleeding Requiring Medical Attention:
93 (13.4%) vs 139 (19.9%); HR 0.61 (95% CI 0.47-0.80)
p<0.001; ARI 6.58%; NNH ~15

Composite of Cardiovascular Death, Myocardial Infarction or Stroke:
41/694 (5.91%) vs 36/695 (5.18%); HR 1.08 (95% CI 0.69-1.68); p=0.75

Rivaroxaban 2.5 mg BID Plus DAPT (N=706) Vs VKA Plus DAPT (N=697)

Composite of Clinically Significant Bleeding:
117 (16.6%) vs 167 (24.0%); HR 0.63 (95% CI 0.50-0.80)
p<0.001; ARI 7.39%; NNH ~13

Bleeding Requiring Medical Attention:
102 (14.4%) vs 139 (19.9%); HR 0.67 (95% CI 0.52-0.86)
p=0.002; ARI 5.50%; NNH ~18

Composite of Cardiovascular Death, Myocardial Infarction or Stroke:
36/704 (5.11%) vs 36/695 (5.18%); HR 0.93 (95% CI 0.59-1.48); p=0.76

Groups 1 & 2 (N=1402) Vs Vitamin K Antagonist Plus DAPT (N=697)

Composite of Clinically Significant Bleeding:
226 (16.1%) vs 167 (24.0%); HR 0.61 (95% CI 0.50-0.75)
p<0.001; ARI 7.84%; NNH ~12

Bleeding Requiring Medical Attention:
195 (13.9%) vs 139 (19.9%); HR 0.64 (95% CI 0.51-0.80)
p<0.001; ARI 6.03%; NNH ~16

Limitations:

- Variable duration of triple therapy between groups 2 and 3 may serve as potential confounding factor (chosen at investigators discretion)
- Patient population must be considered - atrial fibrillation patients undergoing PCI plus stent placement

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I recommend the use of rivaroxaban 15 mg plus clopidogrel 75 mg daily for 12 months over triple therapy (using rivaroxaban or vitamin K antagonist) in atrial fibrillation patients undergoing PCI with stent placement. While the rivaroxaban 2.5 mg BID plus DAPT group had a similar safety profile compared to the rivaroxaban 15 mg plus P2Y12 inhibitor group, I prefer once daily dosing, when possible, for improved patient adherence.

Efficacy:

- Rates of the cardiovascular composite outcome and stent thrombosis were similar between treatment groups, although this trial was not powered to detect such differences

Safety:

- Bleeding rates were significantly higher in Group 3 (vitamin K antagonist plus DAPT) compared to Group 1 and Group 2
- Group 1 (rivaroxaban 15 mg plus P2Y12 inhibitor) and Group 2 (rivaroxaban 2.5 mg BID plus DAPT) had similar rates of clinically significant bleeding, although Group 1 was slightly lower

Cost:

- The cost of using rivaroxaban 15 mg plus clopidogrel must be balanced against the cost of using the other treatment regimens
    - The cost of INR monitoring for vitamin K antagonist therapy must be considered
- The cost-savings of avoiding a clinically significant bleeding event must also be considered

Special Considerations/Populations:

- Group 1 (rivaroxaban 15 mg plus P2Y12 inhibitor) received treatment for a set 12 months, which contrasts the other two groups which received triple therapy for varying periods
- Cannot apply trial results to patients with valvular atrial fibrillation
- Use of twice daily rivaroxaban demonstrated no clear benefit over once daily rivaroxaban

Grade of Recommendation: **A**

PLATO

Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361(11):1045-1057.

Objective: To determine the efficacy and safety of ticagrelor compared to clopidogrel for prevention of cardiovascular outcomes in patients with recent acute coronary syndrome.

Primary Efficacy Measure: Composite of cardiovascular death, myocardial infarction or stroke

Primary Safety Measure: Major bleeding event

Participants: Patients with recent acute coronary syndrome (with or without ST-segment elevation)

- Age ~62 years; male ~85%
- Qualifying event STEMI ~38%; NSTEMI ~42; unstable angina ~17%
- Stent placed post-qualifying event ~61%

Inclusion Criteria:

- Hospitalization for acute coronary syndrome (with or without ST-segment elevation) within the previous 24 hours

Exclusion Criteria:

- Fibrinolytic therapy within prior 24 hours
- Need for anticoagulation therapy
- Increased risk for bradycardia
- Use of strong 3A inhibitor/inducer

Drugs: Ticagrelor; clopidogrel

Design: Randomized, double-blind, active-controlled trial

Methods: Eligible patients were randomized to receive either ticagrelor 90 mg twice daily or clopidogrel 75 mg daily (plus matching placebo) for 12 months. Loading doses used were 180 mg ticagrelor or clopidogrel 300 mg. All patients received aspirin 75-100 mg daily.

Duration: 12 months

Statistical Analysis: It was determined that 1780 primary events would achieve 90% power (alpha=0.05). The ITT population was used for the primary efficacy analyses. The modified ITT population (all randomized patients that received at least one dose of study medication) was used for the safety analyses.

Results: A total of 18,624 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. Rates of the primary composite outcome were significantly lower in the ticagrelor group compared to clopidogrel. Additionally, the individual components of cardiovascular death and myocardial infarction occurred at significantly lower rates in the ticagrelor group. It is notable that rates of definite stent thrombosis occurred at significantly higher rates in the clopidogrel group. However, it is important to consider the significantly higher rates of dyspnea demonstrated in the ticagrelor group in terms of patient tolerance and overall clinical utility.

Ticagrelor (N=9333) Vs Clopidogrel (N=9291)

Composite of Cardiovascular Death, Myocardial Infarction or Stroke:
864 (9.26%) vs 1014 (10.9%); HR 0.84 (95% CI 0.77-0.92)
p<0.001; ARR 1.66%; NNT ~61

Cardiovascular Death:
353 (3.78%) vs 442 (4.76%); HR 0.79 (95% CI 0.69-0.91)
p=0.001; ARR 0.98%; NNT ~103

Myocardial Infarction:
504 (5.40%) vs 593 (6.38%); HR 0.84 (95% CI 0.75-0.95)
p=0.005; ARR 0.98%; NNT ~102

Stroke:
125 (1.34%) vs 106 (1.14%); HR 1.17 (95% CI 0.91-1.52); p=0.22

Definite Stent Thrombosis:
71/5640 (1.26%) vs 106/5649 (1.88%); HR 0.67 (95% CI 0.50-0.91)
p=0.009; ARR 0.62%; NNT ~162

Major Bleeding:
961/9235 (10.4%) vs 929/9186 (10.1%); HR 1.04 (95% CI 0.95-1.13); p=0.43

Dyspnea:
1270/9235 (13.8%) vs 721/9186 (7.85%); HR 1.84 (95% CI 1.68-2.02)
p<0.001; ARI 5.93%; NNH ~16

Limitations:
- Trial results must be considered in addition to low-dose aspirin
- Patient population must be considered - qualifying event primarily myocardial infarction

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I recommend the use of ticagrelor 90 mg twice daily (plus aspirin 81 mg daily) for 12 months over clopidogrel 75 mg daily to reduce the risk of cardiovascular morbidity and mortality in patients with recent acute coronary syndrome. However, the tolerance issues relating to dyspnea raises significant concerns regarding adherence and overall clinical utility.

Efficacy:
- Rates of the primary composite outcome were significantly lower in the ticagrelor group compared to clopidogrel
- The individual components of cardiovascular death and myocardial infarction were significantly lower in the ticagrelor treatment group
- Rates of definite stent thrombosis were significantly lower in the ticagrelor treatment group

Safety:
- The rates of major bleeding were not significantly different between treatment groups
- Dyspnea rates were significantly higher in the ticagrelor group compared to clopidogrel

Cost:
- The cost of using ticagrelor over clopidogrel must be balanced against the cost-savings achieved from preventing cardiovascular outcomes

Special Considerations/Populations:
- Ticagrelor is a reversible P2Y12 inhibitor - clopidogrel is an irreversible P2Y12 inhibitor
- The risk for ticagrelor-induced dyspnea must be considered due to its impact on adherence and tolerability

Grade of Recommendation: **A**

POET-COPD

Vogelmeier C, Hederer B, Glaab T, et al. Tiotropium versus salmeterol for the prevention of exacerbations of COPD. *N Engl J Med*. 2011;364(12):1093-1103.

Objective: To compare the effects of inhaled salmeterol and tiotropium on exacerbation rates (moderate and severe) in patients with COPD.

Primary Efficacy Measure: Time to first COPD exacerbation (moderate or severe)

- Defined as: increase in or new onset of one or more COPD *symptoms* (cough, sputum, wheezing dyspnea or chest tightness) with at least one symptom *lasting 3 days* (or longer) and leading to *prescription treatment* with systemic glucocorticoids, antibiotics or both (moderate exacerbation) or *hospitalization* (severe exacerbation)

Participants: Patients with moderate-to-severe COPD

- Age ~63 years; male ~75%
- Current smoker ~48%
- GOLD stage II ~48%; stage III ~42%; stage IV ~8%
- FEV_1 ~49% of predicted value post-bronchodilation; FEV_1/FVC ~52%
- Inhaled glucocorticoid ~53%; tiotropium ~30%; long-acting beta agonist ~52%

Inclusion Criteria:

- Age ≥ 40 years
- COPD diagnosis
- Smoking history of ≥ 10 pack-years
- $FEV_1 \leq 70\%$ of predicted value post-bronchodilation
- $FEV_1/FVC \leq 70\%$
- Documented history of one or more exacerbations (moderate or severe) within previous year

Exclusion Criteria:

- Asthma
- Myocardial infarction or heart failure hospitalization within prior year
- CrCl ≤ 50 mL/min
- Use of oral glucocorticoids > the equivalent of 10 mg prednisolone daily

Drugs: Salmeterol; tiotropium

Design: Randomized, double-blind, active-controlled trial

Methods: Following a two week run-in period, eligible patients were randomized to receive either inhaled tiotropium 18 mcg once daily or inhaled salmeterol 50 mcg twice daily (plus matching placebo doses). Patients receiving inhaled glucocorticoids were allowed to continue their treatment during the trial period. The use of other inhaled anticholinergics or long-acting beta agonists was not permitted.

Duration: 1 year

Statistical Analysis: It was determined that 6800 randomized patients would provide 80% power (alpha = 0.05). The modified ITT population (patients that received at least one dose of study drug) was used for efficacy and safety analyses.

Results: A total of 7384 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. Trial results showed that the time to first COPD exacerbation was 187 days in the tiotropium group and 145 days in the salmeterol group. Rates of adverse drug reactions were similar between treatment groups.

Tiotropium (N=3707) Vs Salmeterol (N=3669)

Time to First COPD Exacerbation:
187 days vs 145 days

Moderate or Severe COPD Exacerbation:
1277 (34.4%) vs 1414 (38.5%); HR 0.83 (95% CI 0.77-0.90)
p<0.001; ARR 4.09%; NNT ~25

Annual Exacerbation Rate (moderate or severe):
0.64 vs 0.72; RR 0.89 (95% CI 0.83-0.96); p=0.002

Moderate COPD Exacerbation:
1114 (30.1%) vs 1206 (32.9%); HR 0.86 (95% CI 0.79-0.93);
p<0.001; ARR 2.82%; NNT ~36

Severe COPD Exacerbation:
262 (7.07%) vs 336 (9.16%); HR 0.72 (95% CI 0.61-0.85)
p<0.001; ARR 2.09%; NNT ~48

Limitations:

- Patient population – cannot extrapolate results to patients with asthma or those without recent COPD exacerbation
- Patients were allowed to continue their inhaled glucocorticoids during trial period which is a potential confounding factor (however, this characteristic was evenly balanced between treatment groups)

Level of Evidence: Level I – with minor limitations

Recommendation: For these reasons, I recommend the use of inhaled tiotropium over inhaled salmeterol to reduce rates of moderate-to-severe exacerbations in patients with COPD.

Efficacy:

- The use of inhaled tiotropium demonstrated significantly greater benefit over inhaled salmeterol for prolonging the time to first COPD exacerbation (moderate or severe)
- Annual rates for both moderate and severe COPD exacerbation were significantly lower in the tiotropium group

Safety:

- Overall rates of adverse drug reactions were similar between treatment groups

Cost:

- The cost of using inhaled tiotropium over inhaled salmeterol must be balanced against the cost-savings achieved from reduced rates of COPD exacerbations

Special Considerations/Populations:

- Inhaled tiotropium and salmeterol are both long-acting bronchodilators

Grade of Recommendation: **A**

PRECISION

Nissen SE, Yeomans ND, Solomon DH, et al. Cardiovascular Safety of Celecoxib, Naproxen, or Ibuprofen for Arthritis. *N Engl J Med*. 2016;375(26):2519-2529.

Objective: To determine the effect of celecoxib on cardiovascular outcomes compared to ibuprofen and naproxen in patients with arthritis pain.

Primary Safety Measure: Composite of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke

Participants: Patients with arthritic pain at increased risk for cardiovascular event

- Age ~63 years; male ~35%
- Osteoarthritis ~90%
- Established cardiovascular disease ~23%; increased risk for cardiovascular event ~77%

Inclusion Criteria:

- Age ≥ 18 years
- Required daily treatment with NSAIDs for arthritis pain
- Established cardiovascular disease or increased risk for cardiovascular disease

Exclusion Criteria:

- Arthritis pain controlled adequately by acetaminophen

Drugs: Celecoxib; ibuprofen; naproxen

Design: Randomized, double-blind, active-controlled, non-inferiority trial

Methods: Eligible patients were randomized 1:1:1 to receive celecoxib 100 mg twice daily, ibuprofen 600 mg three times daily or naproxen 375 mg twice daily (plus matching placebo). Doses could be increased at the discretion of the investigators to celecoxib 200 mg twice daily, ibuprofen 800 mg three times daily or naproxen 500 mg twice daily. Esomeprazole 20-40 mg daily was used for gastric protection in all patients.

Duration: Mean follow-up period of ~34 months

Statistical Analysis: Naproxen was used as the primary comparator for the non-inferiority analysis. To demonstrate non-inferiority the following criteria were required: HR ≤ 1.12 with upper limit of CI < 1.33 in both ITT and on-treatment analysis populations. It was originally determined that 762 primary events would provide 90% for the non-inferiority analysis. However, due to lower than expected event rates it was recommended to amend the protocol to make the upper CI limit < 1.40 and require 580 primary events in the ITT population and 420 events in the on-treatment population to provide 80% power with a minimum of 18 months of follow-up. A p-value < 0.05 was considered statistically significant for the secondary safety measure and a p < 0.025 for the primary safety measure.

Results: A total of 24,222 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. The mean daily doses of the study medications were ~209 mg celecoxib, ~852 mg naproxen and ~2045 mg ibuprofen. Celecoxib demonstrated non-inferiority to naproxen in both the ITT and on-treatment analysis. Visual analog scale analysis showed statistically significant benefit of naproxen over both celecoxib and ibuprofen for pain control (p<0.001 and 0.01, respectively). However, the difference in the VAS was not considered clinically significant due to being < 13.7 mm. However, There was no significant difference in VAS measurements between celecoxib and ibuprofen (p=0.38).

Celecoxib (N=8072) Vs Naproxen (N=7969)

Cardiovascular Death, Non-Fatal Myocardial Infarction or Non-Fatal Stroke:
188 (2.33%) vs 201 (2.52%); HR 0.93 (95% 0.76-1.13); p=0.45
Rates of the individual components were not significantly different

Serious Gastrointestinal Events:
86 (1.07%) vs 119 (1.49%); HR 0.71 (95% CI 0.54-0.93)
p=0.01; ARI 0.43%; NNH ~223

Celecoxib (N=8072) Vs Ibuprofen (N=8040)

Cardiovascular Death, Non-Fatal Myocardial Infarction or Non-Fatal Stroke:
188 (2.33%) vs 218 (2.71%); HR 0.85 (95% CI 0.70-1.04); p=0.12
Rates of the individual components were not significantly different

Serious Gastrointestinal Events:
86 (1.07%) vs 130 (1.62%); HR 0.65 (95% CI 0.50-0.85)
p=0.002; ARI 0.57%; NNH ~176

Limitations:
- Use of esomeprazole in all patients likely reduced the overall rates of serious gastrointestinal events, however its use is reasonable to limit patient risk
- Patient population must be considered - vast majority of patients did not have established cardiovascular disease at baseline

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I recommend the use of celecoxib as an alternative to non-selective NSAIDs in arthritis patients at increased risk for cardiovascular events, especially in those with increased risk for gastrointestinal bleeds.

Efficacy:
- Celecoxib demonstrated non-inferiority to ibuprofen and naproxen regarding the cardiovascular composite outcome
- There was no significant difference in the rates of the primary composite outcome or the individual components between treatment groups

Safety:
- Rates of serious gastrointestinal events were significantly lower in the celecoxib group compared to naproxen and ibuprofen groups (despite use of esomeprazole in all patients)

Cost:
- The cost of using celecoxib must be balanced against the cost of using naproxen or ibuprofen
    - However, the cost-savings of avoiding serious gastrointestinal events must be considered

Special Considerations/Populations:
- Celecoxib is a COX-2 selective inhibitor and thus less likely to impact gastric mucosa compared to non-selective NSAIDs
- The use of daily esomeprazole must be considered when interpreting safety data

Grade of Recommendation: **A**

PROACTIVE

Dormandy JA, Charbonnel B, Eckland DJ, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomized controlled trial. *Lancet*. 2005;366(9493):1279-1289.

Objective: To determine the effect of pioglitazone on morbidity and mortality outcomes in patients with type 2 diabetes and evidence of cardiovascular disease.

Primary Efficacy Measure: Composite of death, non-fatal MI (including silent events), stroke, acute coronary syndrome, endovascular or surgical intervention on the coronary or leg arteries, or amputation above the ankle (time to first event)

Secondary Efficacy Measure: Composite of death, non-fatal MI (excluding silent events) and stroke

Participants: Patients with type 2 diabetes and evidence of cardiovascular disease

- Age ~62 years; male ~66%
- HgA1c ~7.8%
- Prior MI ~46%; prior PCI/CABG ~31%; objective CAD ~48%
    - Two or more macrovascular disease criteria ~48%

Inclusion Criteria:

- Age 35-75 years with type 2 diabetes
- HgA1c > 6.5%
- Evidence of cardiovascular disease (one or more of the following):
    - Myocardial infarction, stroke or PCI/CABG more than 6 months prior
    - Acute coronary syndrome more than 3 months prior
    - Objective evidence of coronary or peripheral artery disease

Exclusion Criteria:

- Type 1 diabetes
- Only receiving insulin for glucose-lowering therapy
- Heart failure (NYHA class II-IV)
- Elevated liver enzymes (2.5 times upper limit of normal)

Drug: Pioglitazone

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients were randomized to receive pioglitazone or matching placebo. Pioglitazone was dosed at 15 mg daily for the first month, 30 mg daily for the second month and 45 mg daily thereafter.

Duration: Average follow-up ~34 months

Statistical Analysis: It was determined that 5000 randomized patients and 760 primary outcomes would provide 91% power (alpha=0.05). An alpha value of 0.044 was used for the primary composite outcome to account for interim analyses. The ITT population was used for all analyses.

Results: A total of 5238 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. There was no significant difference in rates of the primary composite outcome between treatment groups. Additionally, no individual component of the composite outcome was significantly different between groups. The secondary composite outcome did demonstrate a statistically significant difference favoring the pioglitazone group. Again, it is important to note that no individual component of the composite outcome was significantly different between treatment groups.

However, rates of heart failure were significantly higher in the pioglitazone group. The NNH for heart failure occurrence was estimated to be less than the NNT for any potential benefit in terms of reduced rates of the secondary composite outcome. Reduction in HgA1c was greater with pioglitazone compared to placebo (-0.8% vs -0.3%; p<0.0001).

Pioglitazone (N=2605) Vs Placebo (N=2633)

Primary Composite Outcome:
514 (19.7%) vs 572 (21.7%); HR 0.90 (95% CI 0.80-1.02); p=0.095

All-Cause Mortality:
177 (6.79%) vs 186 (7.06%); HR 0.96 (95% CI 0.78-1.18)

Secondary Composite Outcome:
301 (11.6%) vs 358 (13.6%); HR 0.84 (95% CI 0.72-0.98)
p=0.027; ARR 2.04%; NNT ~49

Total Heart Failure Events (plus individual # of patients):
417 events vs 302 events
281 patients (10.8%) vs 198 patients (7.52%); p<0.0001
ARI ~3.27%; NNH ~30

Limitations:

- Patient population – type 2 diabetes with evidence of cardiovascular disease
- Investigator conclusion – claims cardiovascular benefit and limited safety concerns with pioglitazone (available trial data conflicts with this statement)

Level of Evidence: Level I – with minor limitations

Recommendation: For these reasons, I do not recommend the use of pioglitazone in patient with type 2 diabetes and evidence of cardiovascular disease. This is primarily due to a demonstrated net neutral effect on certain cardiovascular outcomes and increased rates of heart failure. Instead, I recommend the use of glucose-lowering agents with demonstrated cardiovascular safety and benefit (e.g. SGLT2 inhibitor or GLP-1 receptor agonist).

Efficacy:

- Rates of the primary composite outcome were not significantly different between groups
- The secondary composite outcome occurred at significantly lower rates in the pioglitazone group
    - However, no individual component of either composite outcome was significantly different between groups

Safety:

- Rates of heart failure occurred at significantly higher rates in the pioglitazone group

Cost:

- The cost of using pioglitazone must be considered in addition to the costs associated with increased rates of heart failure events

Special Considerations/Populations:

- Pioglitazone is a PPAR-gamma receptor agonist
- Any *potential* benefit of pioglitazone via reduced rates of the secondary composite outcomes is clearly outweighed by the demonstrated increased risk for heart failure events (NNT > NNH)
- All patients had evidence of cardiovascular disease

Grade of Recommendation: **A**

PROVE IT-TIMI 22

Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med*. 2004;350(15):1495-1504.

Objective: To determine the effect of high-intensity lipid-lowering therapy compared to standard lipid-lowering therapy on cardiovascular morbidity and mortality outcomes in patients with recent acute coronary syndrome.

Primary Efficacy Measure: Composite of all-cause mortality, myocardial infarction, hospitalization due to unstable angina, revascularization procedure and stroke

Participants: Patients with recent acute coronary syndrome

- Age ~58 years; male ~78%
- Qualifying event NSTEMI ~36%; STEMI ~34%; unstable angina ~29%
- Median LDL ~106 mg/dL

Inclusion Criteria:

- Age ≥ 18 years old
- Hospitalized for acute coronary syndrome or high-risk unstable angina within prior 10 days
- Stable condition at time of enrollment
- Total cholesterol ≤ 240 mg/dL (≤ 200 mg/dL if on long-term lipid-lowering therapy)

Exclusion Criteria:

- Life expectancy < 2 years
- Use of any statin dosed at 80 mg daily
- Use of fibrates or niacin that could not be discontinued
- PCI within previous 6 months or CABG within previous 2 months
- Substantial hepatic disease
- SCr > 2.0 mg/dL

Drugs: Atorvastatin; pravastatin

Design: Randomized, double-blind, active-controlled, non-inferiority trial

Methods: Eligible patients were to receive standard therapy for the acute coronary syndrome but were not to be treated with any lipid-lowering therapy other than the study medication. Eligible patients were randomized to either pravastatin 40 mg daily or atorvastatin 80 mg daily plus matching placebo. Pravastatin was to be increased to 80 mg daily in patients with LDL > 125 mg/dL on two consecutive visits.

Duration: Mean follow-up period of 24 months

Statistical Analysis: It was determined that enrolling 2000 patients per group (4000 total) and 925 primary events would provide 87% power. A NI margin of 1.17 was selected. The ITT population was used for all analyses. If non-inferiority of pravastatin to atorvastatin was not determined then subsequent testing for superiority would be performed.

Results: A total of 4162 patients underwent randomization. Baseline patient characteristics were similar between treatment groups except for history of peripheral artery disease (higher in pravastatin group). Non-inferiority of pravastatin to atorvastatin was not demonstrated. Atorvastatin was proven to be superior to pravastatin for prevention of cardiovascular morbidity and mortality. This benefit became evident 30 days into the trial.

Pravastatin (N=2063) Vs Atorvastatin (N=2099)

Cardiovascular Composite Outcome:
26.3% vs 22.4%; HR 0.84 (95% CI 0.74-0.95)
p=0.005; ARR 3.9%; NNT ~26

All-Cause Mortality:
3.2% vs 2.2%

Myocardial Infarction:
7.4% vs 6.6%

Hospitalization due to Unstable Angina:
5.1% vs 3.8%; p=0.02

Revascularization Procedure:
18.8% vs 16.3%; p=0.04

Stroke:
1.0% vs 1.0%

Event rates above are Kaplan-Meier estimates - actual number of events not reported

Median LDL:
95 mg/dL vs 62 mg/dL; p<0.001

Liver Enzymes > 3x Upper Limit of Normal:
1.1% vs 3.3%; p<0.001; ARI 2.2%; NNH ~45

Limitations:

- It is unclear if 925 events occurred due to all data being reported as Kaplan-Meier event rate estimates (significant difference still demonstrated - clinical relevance minimal)
- Patient population must be considered - qualifying event primarily myocardial infarction

Level of Evidence: Level II - with major limitations

Recommendation: For these reasons, I recommend the use of atorvastatin 80 mg over pravastatin 40 mg for prevention of future cardiovascular events in patients with recent acute coronary syndrome.

Efficacy:

- Non-inferiority of pravastatin to atorvastatin was not demonstrated
- Atorvastatin demonstrated superiority to pravastatin regarding the primary composite outcome
- Reductions in LDL were significantly greater in the atorvastatin group compared to pravastatin

Safety:

- Liver enzyme elevations occurred significantly more often in the atorvastatin group compared to placebo (known adverse effect of statins - can be monitored during therapy)

Cost:

- The cost of using atorvastatin over pravastatin must be balanced against the cost-savings of preventing cardiovascular events

Special Considerations/Populations:

- The statin doses used must be considered - cannot extrapolate results to other intensities
- The ending LDL values must be considered when interpreting trial results

Grade of Recommendation: **A**

Q-SYMBIO

Mortensen SA, Rosenfeldt F, Kumar A, et al. The effect of coenzyme Q10 on morbidity and mortality in chronic heart failure: results from Q-SYMBIO: a randomized double-blind trial. *JACC Heart Fail*. 2014;2(6):641-649.

Objective: To determine the effect of coenzyme Q10 on clinical outcomes in heart failure patients.

Short-Term Efficacy Measures: (1) NYHA functional class (2) 6 minute walking test (3) NT-pro BNP levels

Long-Term Efficacy Measure: Composite of cardiovascular death, heart failure hospitalization, mechanical implantation or urgent cardiac transplantation

Participants: Heart failure patients on standard medication therapy

- Age ~62 years; male ~72%
- LVEF ~31%; NYHA functional class III ~88%
- Baseline ACEi/ARB ~90%; beta-blocker ~74%; diuretic ~80%

Inclusion Criteria:

- Chronic heart failure with symptoms (no ejection fraction requirement)
- Receiving standard heart failure therapy
- NYHA functional class III-IV

Exclusion Criteria:

- Acute coronary syndrome within 6 weeks of enrollment
- Planned cardiac surgery
- Use of IV inotropes

Drug: Coenzyme Q10

Design: Randomized, double-blind, placebo-controlled trial

Methods: This study was designed with a 2-phase objective. The short-term assessment was a blinded evaluation of NYHA class and functional status (symptoms). The long-term assessment was to determine if coenzyme Q10 could reduce rates of cardiovascular morbidity and mortality. Eligible patients underwent a 2-week placebo run-in period and those who successfully completed it were randomized to receive coenzyme Q10 100 mg three times daily or matching placebo. All patients received standard heart failure therapy.

Duration: 106 weeks (~2 years)

Statistical Analysis: It was determined that 550 randomized patients would achieve 90% power. For the short-term endpoint a p-value ≤ 0.05 (in all three endpoints) would be considered statistically significant. For the long-term endpoint a p-value < 0.05 would be considered statistically significant.

Results: A total of 420 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. There was no significant difference in any of the short-term goals between treatment groups at 16 weeks. Overall adverse drug reaction rates were lower in the coenzyme Q10 treatment group.

Coenzyme Q10 (N=202) Vs Placebo (N=218)

Long-Term Composite Outcome:
30 (14.9%) vs 57 (26.1%); HR 0.50 (95% CI 0.32-0.80)
p=0.003; ARR 11.3%; NNT ~9

Cardiovascular Death:
18 (8.91%) vs 34 (15.6%); HR 0.51 (95% CI 0.28-0.92)
p=0.026; ARR 6.68%; NNT ~15

Heart Failure Hospitalization:
17 (8.42%) vs 31 (14.2%); HR 0.51 (95% CI 0.27-0.95)
p=0.033; ARR 5.80%; NNT ~18

NYHA Functional Class Improvement:
86 (42.6%) vs 68 (31.2%); p=0.028; ARR 11.4%; NNT ~9

Limitations:

- Power set but not met - failed to randomize 550 patients due to limited funding (clinical relevance likely low - statistically significant differences still demonstrated)
- Trial population size relatively small due to limited funding (coenzyme Q10 cannot be patented)
- Dosing of coenzyme Q10 must be considered - 100 mg three times daily

Level of Evidence: Level II - with major limitations

Recommendation: For these reasons, I recommend the use of coenzyme Q10 (in addition to standard therapy) to further reduce the rates of cardiovascular morbidity and mortality in heart failure patients.

Efficacy:

- There was no significant difference in any of the short-term efficacy measures between treatment groups
- Rates of the primary composite outcome were significantly lower in the coenzyme Q10 group compared to placebo
- The individual components of cardiovascular death and heart failure hospitalization were significantly lower in the coenzyme Q10 group compared to placebo
- Significantly more patients in the coenzyme Q10 group saw improvement in their NYHA functional class compared to placebo

Safety:

- Overall rates of adverse drug reactions were lower in the coenzyme Q10 group

Cost:

- The cost of using coenzyme Q10 must be balanced against the cost-savings of preventing cardiovascular morbidity and mortality outcomes

Special Considerations/Populations:

- Dosing of coenzyme Q10 must be considered - 100 mg three times daily (potential adherence barrier)
- Trial results must be considered in addition to standard heart failure therapy

Grade of Recommendation: **B**

RACE II

Van Gelder IC, Groenveld HF, Crijns HJ, et al. Lenient versus strict rate control in patients with atrial fibrillation. *N Engl J Med*. 2010;362(15):1363-1373.

Objective: To determine the effect of lenient rate control compared to strict rate control on clinical outcomes in patients with atrial fibrillation.

Primary Efficacy Measure: Composite of cardiovascular death, heart failure hospitalization, stroke, systemic embolism, major bleeding, arrhythmic events, sustained ventricular tachycardia, cardiac arrest, life-threatening adverse drug reactions due to rate control medications or pacemaker implantation

Participants: Patients with atrial fibrillation

- Age ~68 years; male ~66%
- $CHADS_2$ score 0-1 ~61%; score = 2 ~26%; score 3-6 ~13%
- BP ~136/93 mmHg; HR ~96 bpm
- Managed on beta-blocker alone ~45%

Inclusion Criteria:

- Permanent atrial fibrillation for up to 12 months
- Age ≤ 80 years
- Average resting HR > 80 bpm
- Current use of oral anticoagulant therapy (or aspirin)

Exclusion Criteria:

- Paroxysmal atrial fibrillation
- Contraindications for strict or lenient rate control
- Unstable heart failure
- History of any stroke
- Cardiac surgery within previous 3 months

Treatment: Lenient rate control (resting HR < 110 bpm); strict rate control (resting HR < 80 bpm)

Design: Randomized, open-label, active-controlled, non-inferiority trial

Methods: Eligible patients were randomized to receive strict rate control (target resting HR < 80 bpm) or lenient rate control (target resting HR < 110 bpm). Beta-blockers, non-DHP calcium channel blockers and digoxin were to be used alone or in combination to achieve the target heart rate.

Duration: Follow-up period of 2 to 3 years

Statistical Analysis: It was determined that 250 randomized patients per treatment group would provide 80% power (alpha = 0.05). To demonstrate non-inferiority the upper limit of the 90% confidence interval for the absolute difference between treatment groups needed to be < 10%. However, due to changes in the treatment period the estimated cumulative incidences at 3 years were used to assess for non-inferiority. The ITT population was used for the primary analyses.

Results: A total of 614 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. In the lenient rate control group ~98% of patients achieved target heart rate compared to ~67% in the strict rate control group. In the lenient control group, the majority of patients (~42%) were managed on a beta-blocker alone whereas the majority of the strict control group (~37%) required a beta-blocker plus digoxin. Additionally, the average beta-blocker dose was significantly lower in the lenient rate control group ($p<0.001$). Average heart rates at the end of the follow-up period were 85 bpm in the lenient rate control group and 76 bpm in the strict rate control group ($p<0.001$). There was no significant difference in rates of the individual components of the composite outcome.

Lenient Rate Control (N=311) Vs Strict Rate Control (N=303)

Primary Composite Outcome:
38 (12.2%) vs 43 (14.2%); HR 0.84 (90% CI 0.58-1.21)

Lenient rate control demonstrated non-inferiority compared to strict rate control
Absolute rate difference -2.0% (90% CI -7.6% to 3.5%)

Limitations:

- Open-label trial design
- Trial population size relatively small

Level of Evidence: Level I - with major limitations

Recommendation: For these reasons, I recommend the use of lenient rate control over strict rate control in patients with atrial fibrillation.

Efficacy:

- Lenient rate control demonstrated non-inferiority to strict rate control regarding the rates of the primary composite outcome
- Average HR 85 bpm in lenient rate control group (~98% achieved target HR < 110 bpm)
- Average HR 76 bpm in strict rate control group (~67% achieved target HR < 80 bpm)
- The strict rate control group required significantly more medications at higher doses compared to the lenient rate control group

Safety:

- Overall rates of adverse drug reactions due to rate control medications were lower in the lenient rate control group

Cost:

- The cost-savings of using fewer medications at lower dosages for lenient rate control must be considered

Special Considerations/Populations:

- It is possible that the difference in average heart rates between treatment groups was not great enough to demonstrate the true treatment effect of each rate control strategy
    - While lenient rate control demonstrated non-inferiority to strict rate control it is important to note that the average heart rate for the lenient rate control group was 85 bpm (which is closer to goal for strict control than lenient control) - this must be considered when interpreting trial results

Grade of Recommendation: **A**

RALES

Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med*. 1999;341(10):709-717.

Objective: To determine the effect of spironolactone on morbidity and mortality outcomes in patients with severe heart failure.

Primary Efficacy Measure: All-cause mortality

Secondary Efficacy Measures: (1) Cardiovascular death (2) Cardiovascular hospitalization (3) Change in NYHA class

Participants: Patients with severe heart failure receiving standard therapy

- Age ~65 years; male ~73%
- LVEF ~25%
- NYHA class III ~70%; class IV ~28%
- Baseline ACEi ~94%; loop diuretic 100%; digoxin ~73%

Inclusion Criteria:

- NYHA class III-IV at time of enrollment (class IV within previous 6 months)
- Receiving ACEi and loop diuretic
- LVEF ≤ 35%

Exclusion Criteria:

- Operable heart disease or congenital heart disease
- Unstable angina
- Heart transplant patient
- Serum potassium > 5 mmol/L or SCr > 2.5 mg/dL

Drug: Spironolactone

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients were randomized to receive spironolactone 25 mg daily or matching placebo. After 8 weeks the dose of spironolactone could be increased to 50 mg daily.

Duration: Mean follow-up period of 24 months

Statistical Analysis: Power was set at 90% (alpha = 0.05) with no specific criteria mentioned. The safety monitoring committee had pre-specified criteria for stopping the trial early. The ITT population was used for the primary efficacy analyses.

Results: The trial was stopped early at the recommendation of the safety monitoring committee due to the demonstrated effect of spironolactone on all-cause mortality. A total of 1663 patients had undergone randomization. Baseline patient characteristics were similar between treatment groups. NYHA functional class had improved in 41% of spironolactone patients (33% in placebo), remained same in 31% (18% in placebo) and worsened in 38% (48% in placebo). The difference between groups in NYHA functional status change was significant ($p<0.001$). The mean dose of spironolactone was 26 mg daily. Serum creatinine and potassium levels were statistically significantly higher in the spironolactone group compared to placebo ($p<0.001$) but these differences were not considered clinically significant.

Spironolactone (N=822) Vs Placebo (N=841)

All-Cause Mortality:
284 (34.5%) vs 386 (45.9%); RR 0.70 (95% CI 0.60-0.82)
p<0.001; ARR 11.3%; NNT ~9

Cardiovascular Death:
226 (27.5%) vs 314 (37.3%); RR 0.69 (95% CI 0.58-0.82)
p<0.001; ARR 9.84%; NNT ~11

Worsening Heart Failure Death:
127 (15.5%) vs 189 (22.5%); RR 0.64 (95% CI 0.51-0.80)
p<0.001; ARR 7.02%; NNT ~15

First Heart Failure Hospitalization:
215 (26.2%) vs 300 (35.7%); RR 0.65 (95% CI 0.54-0.77)
p<0.001; ARR 9.52%; NNT ~11

Total Heart Failure Hospitalizations:
413 vs 663

Male Gynecomastia:
55 (6.69%) vs 8 (0.95%); p<0.001; ARI 5.74%; NNH ~17

Limitations:

- Power set but uncertain if met - clinical significance is likely low due to trial being stopped early because of clear demonstrated benefit as well as the significant differences between treatment groups
- Patient population must be considered - all had severe heart failure

Level of Evidence: Level II - with major limitations

Recommendation: For these reasons, I recommend the use of spironolactone (in addition to standard therapy) to further reduce the risk of cardiovascular morbidity and mortality outcomes in patients with severe heart failure.

Efficacy:

- The rate of all-cause mortality was significantly lower in the spironolactone group compared to placebo
    - Rates of cardiovascular death and death due to worsening heart failure were also significantly lower in the spironolactone treatment group
- Heart failure hospitalizations (first and total) were lower in the spironolactone group
- Significantly more patients in the spironolactone group saw improvement in their NYHA functional class compared to placebo

Safety:

- Rates of overall adverse drug reactions were similar between treatment groups
- Rates of male gynecomastia were significantly higher in the spironolactone group
- While serum creatinine and potassium elevations were significantly greater in the spironolactone group the investigators considered it not to be clinically significant

Cost:

- The cost of using spironolactone must be balanced against the cost-savings of preventing cardiovascular morbidity and mortality outcomes
- However, the cost of monitoring serum creatinine and potassium must also be considered

Special Considerations/Populations:

- Trial results must be considered in addition to standard heart failure therapy

Grade of Recommendation: **B**

RE-ALIGN

Eikelboom JW, Connolly SJ, Brueckmann M, et al. Dabigatran versus warfarin in patients with mechanical heart valves. *N Engl J Med*. 2013;369(13):1206-1214.

Objective: To determine the optimal dosing regimen for dabigatran in preventing thromboembolic events in patients with mechanical heart valves.

Primary Efficacy Measure: Trough plasma level of dabigatran

Participants: Patients with prosthetic valves

- Age ~56 years; male ~65%
- CrCl ~107 mL/min
- Aortic valve replacement ~68%

Inclusion Criteria:

- Age 18-75 years
- Undergoing mechanical valve implant in aortic or mitral position (or both) OR received mechanical valve implant in mitral position more than 3 months ago

Exclusion Criteria:

- Previous prosthetic heart valve replacement
- Acute coronary syndrome within previous month
- Uncontrolled hypertension
- History of hemorrhagic stroke
- CrCl < 40 mL/min
- Abnormal liver function

Drugs: Dabigatran; warfarin

Design: Randomized, open-label, active-controlled, phase II trial

Methods: Eligible patients were randomized to receive anticoagulation with dabigatran or warfarin in a 2:1 ratio. The starting dose of dabigatran was based on renal function using pharmacokinetic data from the RE-LY trial. Doses were adjusted to achieve plasma trough levels ≥ 50 ng/mL. If the target trough could not be achieved with highest dosing of dabigatran the patient would be switched to a non-study vitamin K antagonist. Additionally, if renal function declined to < 30 mL/min or dropped ≥ 50% from baseline CrCl then dabigatran would be discontinued and non-study anticoagulation initiated. The target INR in the warfarin group was 2.0 - 3.0 in patients with mechanical aortic valves with no additional risk factors (lower risk for thromboembolic events) and 2.5 - 3.5 in patients with mechanical aortic valves with additional risk factors or those with mechanical mitral valves.

Duration: 12 weeks

Statistical Analysis: It was determined that 405 randomized patients would achieve a dosing regimen that would result in <10% of patients having trough levels < 50 ng/mL. The ITT population was used for all analyses. A p-value < 0.05 indicates statistical significance. If this phase II trial was successful a phase III trial powered for efficacy and safety would be approved.

Results: A total of 252 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. Patients in the dabigatran group (all doses) were in therapeutic range ~86% of the time. Only the dosing regimen of 150 mg twice daily resulted in patients being above target range > 90% of the time (~98%). Patients in the warfarin group were in therapeutic range ~50% of the time. This trial was stopped early on the recommendation of the safety monitoring board due to demonstration of excess thromboembolic events and bleeding in the dabigatran group. All patients were then switched to a non-study vitamin K antagonist.

Dabigatran (N=168) Vs Warfarin (N=84)

Death:
1 vs 2

Stroke:
9 vs 0

TIA:
3 vs 2

Myocardial Infarction:
3 vs 0

Valve Thrombosis:
5 vs 3

Total Bleeding:
45 (26.8%) vs 10 (11.9%); HR 2.45 (95% CI 1.23-4.86)
p=0.01; ARI 14.9%; NNH ~6

Major Bleeding:
7 (4.17%) vs 2 (2.38%); HR 1.76 (95% CI 0.37-8.46); p=0.48

Limitations:

- Power set but not met - trial stopped early due to safety concerns
  - Clinical significance minimal
- Phase II trial - not powered for clinical outcomes
- Open-label trial design

Level of Evidence: Level II - with major limitations

Recommendation: For these reasons, I do not recommend the use of dabigatran for prevention of thromboembolic events in patients with mechanical valve implants.

Efficacy:

- Target levels of dabigatran were achieved > 90% of the time using the dosing strategy of 150 mg twice daily
- Increased rates of thromboembolic events in the dabigatran group led to early trial termination

Safety:

- Significantly higher bleeding rates in the dabigatran group led to early trial termination

Cost:

- The cost of using dabigatran must be considered in addition to the cost of treating excess thromboembolic events and bleeding episodes

Special Considerations/Populations:

- Patient population must be considered - all patients had mechanical valve implants
- Results cannot be extrapolated to patients with bioprosthetic valves

Grade of Recommendation: **B**

RECORD

Home PD, Pocock SJ, Beck-Nielsen H, et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicenter, randomized, open-label trial. *Lancet*. 2009;373(9681):2125-2135.

Objective: To determine the effect of rosiglitazone on cardiovascular outcomes in patients with type 2 diabetes.

Primary Efficacy Measure: Composite of cardiovascular hospitalization or death (time to first event)

Participants: Patients with type 2 diabetes

- Age ~58 years; male ~51%
- HgA1c ~7.9%

Inclusion Criteria:

- Age 40-75 years with type 2 diabetes
- Receiving metformin or sulfonylurea at max tolerated dosing
- HgA1c 7.0-9.0%
- BMI > 25

Exclusion Criteria:

- Hospitalization for major cardiovascular event within previous 3 months
- Heart failure

Drugs: Rosiglitazone; glyburide; gliclazide; glimepiride; metformin

Design: Randomized, open-label, active-controlled, non-inferiority trial

Methods: Eligible patients were randomized to receive rosiglitazone (plus metformin or sulfonylurea) or metformin plus sulfonylurea. Choice of sulfonylurea (glimepiride, gliclazide or glyburide) depended on local investigator practice. Dosing of trial medications were adjusted to target a HgA1c goal of 7.0% or less. Rosiglitazone was to be titrated to a max of 8 mg daily. A max daily dose of 2550 mg was allowed for metformin. The max daily doses of glyburide, gliclazide and glimepiride were set at 15 mg, 240 mg and 4 mg, respectively. Additional glucose-lowering therapies were not allowed.

Duration: Mean follow-up period of 5.5 years

Statistical Analysis: It was determined that 4000 randomized patients followed for a median period of 6 years would provide 99% power for assessing the non-inferiority of rosiglitazone to the active-control group. A non-inferiority margin of 1.20 was used. The ITT population was used for the non-inferiority analysis.

Results: A total of 4458 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. Rosiglitazone demonstrated non-inferiority to the active-control group for the primary composite outcome. There was no significant difference in the rates of the individual components of the composite outcome, except for heart failure events (fatal and non-fatal), which was significantly higher in the rosiglitazone treatment group. Rates of bone fractures were significantly higher in the rosiglitazone group. Hyperglycemia occurred at significantly lower rates in the rosiglitazone group compared to placebo (1.2% vs 2.5%; p=0.0027).

Rosiglitazone (N=2220) Vs Active Control (N=2227)

Cardiovascular Hospitalization or Death:
321 (14.5%) vs 323 (14.5%); HR 0.99 (95% CI 0.85-1.16); p=0.93

Heart Failure:
61 (2.75%) vs 29 (1.30%); HR 2.10 (95% CI 1.35-3.27)
p=0.001; ARI 1.45%; NNH ~69

Patients with Reported Bone Fracture(s):
185 (8.33%) vs 118 (5.30%); p<0.0001; ARI 3.0.3%; NNH ~33

Limitations:

- Power set but not met – however, criteria for determining non-inferiority was still achieved
- Open-label trial design – clinical significance low (objective efficacy outcomes)

Level of Evidence: Level II – with major limitations

Recommendation: For these reasons, I do not recommend the use of rosiglitazone (in addition to metformin or sulfonylurea) for the treatment of type 2 diabetes. While overall rates of cardiovascular morbidity and mortality were similar between treatment groups there were notable concerns demonstrated regarding increased occurrence of heart failure and bone fracture. Instead, I recommend the use of glucose-lowering agents with demonstrated cardiovascular safety and benefit (e.g. SGLT2 inhibitor or GLP-1 receptor agonist).

Efficacy:

- Rates of overall cardiovascular morbidity and mortality (via the composite outcome) were not significantly difference between treatment groups
- However, a significantly higher rate of heart failure was demonstrated in the rosiglitazone group

Safety:

- Rates of hyperglycemia were significantly lower in the rosiglitazone group, however, rates of bone fracture were significantly higher

Cost:

- The cost of using rosiglitazone must be considered in addition to the cost of treating and managing increased rates of heart failure and bone fracture events

Special Considerations/Populations:

- Rosiglitazone is a PPAR-gamma receptor agonist
- AVANDIA (rosiglitazone) was previously recalled due to safety concerns surrounding increased rates of cardiovascular events and severe restrictions were placed on its use
    - These restrictions were eventually removed in 2015

Grade of Recommendation: **B**

RE-DUAL PCI

Cannon CP, Bhatt DL, Oldgren J, et al. Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation. *N Engl J Med*. 2017;377(16):1513-1524.

Objective: To determine the efficacy and safety of dabigatran plus P2Y12 inhibitor compared to triple therapy with vitamin K antagonist in patients with atrial fibrillation post-PCI.

Primary Safety Measure: Composite of major bleeding or clinically relevant non-major bleeding

Secondary Efficacy Measure: Composite of death, myocardial infarction, stroke, systemic embolism and unplanned revascularization

Participants: Patients with non-valvular atrial fibrillation receiving PCI

- Age ~71 years; age ~76%
- Average $CHADS_2VASc$ score > 3
- Drug-eluting stent ~83%; bare-metal stent ~15%

Inclusion Criteria:

- Age ≥ 18 years
- Non-valvular atrial fibrillation
- Received PCI with bare-metal stent or drug-eluting stent within previous 120 hours due to stable coronary artery disease or acute coronary syndrome

Exclusion Criteria:

- Mechanical heart valve
- CrCl < 30 mL/min

Drugs: Dabigatran; warfarin

Design: Randomized, open-label, active-controlled, non-inferiority trial

Methods: After successful PCI, eligible patients were randomized to receive one of three treatments: (1) dabigatran 110 mg twice daily plus clopidogrel/ticagrelor (2) dabigatran 150 mg twice daily plus clopidogrel/ticagrelor (3) warfarin (target INR 2.0-3.0) plus aspirin (≤ 100 mg/day) plus clopidogrel/ticagrelor. In the triple therapy group, aspirin was stopped after 1 month in patients with a bare-metal stent and after 3 months in patients with a drug-eluting stent. Clopidogrel was to be dosed at 75 mg daily and ticagrelor at 90 mg twice daily. All patients were to receive a P2Y12 inhibitor for at least 12 months after randomization (choice of P2Y12 agent left to investigator).

Duration: Mean follow-up period of 14 months

Statistical Analysis: This trial was designed to test non-inferiority of the two dual therapy treatments compared to triple therapy with a vitamin K antagonist regarding the primary safety outcome. The non-inferiority margin was set at 1.38 for both safety and efficacy analyses. The ITT population was used for the primary analyses. It was determined that 167 patient events per group would provide 83.6% power for non-inferiority testing (alpha = 0.025). The pre-specified hierarchical testing is as follows: non-inferiority for the dabigatran 110 mg group regarding bleeding rates, non-inferiority for the dabigatran 150 mg group regarding bleeding rates, non-inferiority for the combined dabigatran groups for the efficacy composite outcome, superiority for dabigatran 110 mg group regarding bleeding rates, non-inferiority for combined dabigatran groups for death or thrombotic event, superiority for dabigatran 150 mg group regarding bleeding rates.

Results: A total of 2725 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. The vast majority of patients (~88%) received clopidogrel as the P2Y12 inhibitor. Patients randomized to triple therapy with vitamin K antagonist were in the target INR range 64% of the time. The rates of stent thrombosis did not differ significantly between treatment groups (p>0.05). Non-inferiority was demonstrated for both the 110 mg and 150 mg dual therapy groups compared to triple therapy. Hierarchical testing failed at testing non-inferiority for the composite for combined thromboembolic event or death (p=0.11). Non-inferiority can be claimed regarding the primary safety endpoint, but superiority cannot be claimed for both dabigatran groups (only the 110 mg group).

Dabigatran 110 mg (N=981) Vs VKA Triple Therapy (N=981)

Bleeding Composite:
151 (15.4%) vs 264 (26.9%); HR 0.52 (95% CI 0.42-0.63)
p<0.001; ARR 11.5%; NNT ~9

Major Bleeding:
49 (4.99%) vs 90 (9.17%); HR 0.52 (95% CI 0.37-0.74)
p<0.001; ARR 4.18%; NNT ~24

Cardiovascular Composite Outcome:
149 (15.2%) vs 131 (13.4%); HR 1.13 (95% CI 0.90-1.43); p=0.30

Dabigatran 150 mg (N=763) Vs VKA Triple Therapy (N=764)*

Bleeding Composite:
154 (20.2%) vs 196 (25.7%); HR 0.72 (95% CI 0.58-0.88)
p=0.002; ARR 5.74%; NNT ~19

Major Bleeding:
43 (5.64%) vs 64 (8.38%); HR 0.64 (95% CI 0.43-0.94)
p=0.02; ARR 2.74%; NNT ~37

Cardiovascular Composite Outcome:
90 (11.8%) vs 98 (12.8%); HR 0.89 (95% CI 0.67-1.19); p=0.44

** Triple therapy only included patients eligible for dabigatran 150 mg dual therapy*

Limitations:

- Power set but not met - not every treatment group experienced 167 bleeding events (clinical significance low)
- Superiority of dual therapy with dabigatran (overall) to triple therapy with vitamin K antagonists cannot be claimed due to failure of hierarchical testing
- Preferred duration of therapy cannot be interpreted from this trial

Level of Evidence: Level II - with major limitations

Recommendation: For these reasons, I recommend the use of dabigatran (110 mg or 150 mg twice daily) plus clopidogrel 75 mg daily over triple therapy with vitamin K antagonist in patients non-valvular atrial fibrillation receiving PCI with stenting.

Efficacy:

- There was no significant difference between either dabigatran groups compared to the triple therapy group regarding the cardiovascular composite outcome
- There was no significant difference in rates of stent thrombosis between treatment groups

Safety:

- Use of dabigatran 110 mg or 150 mg twice daily plus P2Y12 inhibitor demonstrated non-inferiority to triple therapy with vitamin K antagonist regarding the primary safety outcome
- The dabigatran 110 mg group demonstrated superiority to triple therapy with vitamin K antagonist regarding the primary safety outcome
- The dabigatran 150 mg group had significantly lower bleeding rates compared to the triple therapy vitamin K antagonist group, however superiority cannot be claimed due to prior failure of hierarchical testing

Cost:

- The cost of using dabigatran must be balanced against the cost-savings of preventing bleeding events
    - The cost-savings due to lack of need for INR testing with dabigatran must also be considered

Special Considerations/Populations:

- While superiority cannot be claimed for both dabigatran groups due to failure in the hierarchical testing the confidence intervals and ARRs demonstrate a clear difference in bleeding rates compared to triple therapy with vitamin K antagonist
    - Overall, dabigatran plus P2Y12 inhibitor demonstrated improved safety and similar efficacy compared to triple therapy in this patient population
- Clopidogrel was the primary P2Y12 inhibitor used

Grade of Recommendation: **B**

REDUCE

Leuppi JD, Schuetz P, Bingisser R, et al. Short-term vs conventional glucocorticoid therapy in acute exacerbations of chronic obstructive pulmonary disease: the REDUCE randomized clinical trial. *JAMA*. 2013;309(21):2223-2231.

Objective: To determine the effect of 5-day and 14-day courses of glucocorticoids on clinical outcomes in patients with acute COPD exacerbations.

Primary Efficacy Measure: Time to next COPD exacerbation during the following 6 months

Participants: Adults hospitalized for acute COPD exacerbation

- Age ~70 years; male ~40%
- Current smoker ~45%
- GOLD grade III ~33%; grade IV ~54%

Inclusion Criteria:

- Age 40 years or more
- Hospitalization for acute COPD exacerbation
    - Two or more of the following: change in dyspnea, cough or sputum quantity/purulence
- Twenty pack-years or more of tobacco smoking

Exclusion Criteria:

- History of asthma
- FEV_1/FVC ratio > 0.70 (post-bronchodilator)
- Diagnosis of pneumonia
- Estimated lifespan of less than 6 months due to comorbid condition
- Pregnancy or lactation

Drug: Prednisone

Design: Randomized, double-blind, placebo-controlled, non-inferiority trial

Methods: Eligible patients received one dose of methylprednisolone 40 mg intravenously on day 1, followed by oral prednisone 40 mg once daily on days 2-5. Thereafter, patients were randomized to receive either prednisone 40 mg or matching placebo once daily for days 6-14. Broad-spectrum antibiotics, SABAs and ICS-LAMAs were given to all patients.

Duration: 180 days

Statistical Analysis: It was determined that 150 randomized patients in each treatment group would provide 85% power (alpha=0.05). A non-inferiority margin of 1.515 was used. The ITT and per-protocol populations were used in the efficacy analyses.

Results: A total of 311 patients underwent randomization and were included in the efficacy analysis. Baseline patient characteristics were similar between treatment groups, with the exception of sex. Significantly more female patients were randomized into the 14-day treatment group compared to the 5-day treatment group (46.5% vs 32.7%, respectively; p=0.02).

The 5-day treatment group demonstrated non-inferiority to the 14-day treatment group in both analysis populations (ITT and PP). In patients that experienced a COPD exacerbation during the follow-up period the median time to event was ~44 days in the 5-day treatment group and ~29 days in the 14-day treatment group.

14-Day Treatment (N=155) Vs 5-Day Treatment (N=156)

COPD Exacerbation:
57 (36.8%) vs 56 (35.9%); HR 0.95 (90% CI 0.70-1.29)
~ ITT population ~

57 (38.3%) vs 54 (36.7%); HR 0.93 (90% CI 0.68-1.26)
~ Per-protocol population ~

Limitations:

- Patient population – cannot apply trial results to patients with asthma
- The use of broad-spectrum antibiotics, SABAs and ICS-LAMAs in all patients must be considered when interpreting trial results

Level of Evidence: Level I – with minor limitations

Recommendation: For these reasons, I recommend the use of 5-days of glucocorticoid therapy over 14-days in patients with acute COPD exacerbation.

Efficacy:

- The use of 5-days of glucocorticoid therapy was determined to be non-inferior to 14-days of glucocorticoid therapy in terms of COPD exacerbation in the following 6 month period
- The time to next COPD exacerbation was longer in the 5-day treatment group compared to the 14-day group

Safety:

- There were no notable differences in safety outcomes reported

Cost:

- The cost-savings of using a shorter-course of glucocorticoid therapy must be considered

Special Considerations/Populations:

- The majority of patients were GOLD grade III or higher (indicates greater severity of disease)
- The use of supportive therapy (e.g., SABAs, antibiotics) must be considered in addition to glucocorticoid usage
- The shorter course of therapy offers the added benefit of decreased exposure to glucocorticoids

Grade of Recommendation: **A**

REDUCE-IT

Bhatt DL, Steg PG, Miller M, et al. Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia. *N Engl J Med*. 2019;380(1):11-22.

Objective: To determine the effect of icosapent ethyl ester (in addition to statin therapy) on cardiovascular event outcomes in high-risk patients with hypertriglyceridemia.

Primary Efficacy Measure: Composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, coronary revascularization or unstable angina

Participants: Patients with hypertriglyceridemia at increased risk for cardiovascular events

- Age ~64 years; male ~71%
- Median triglycerides ~216 mg/dL; LDL ~75 mg/dL
- Established cardiovascular disease ~71%; type 2 diabetes ~58%
- Moderate intensity statin ~62%; high-intensity ~31%

Inclusion Criteria:

- Age ≥ 45 with established cardiovascular disease OR age ≥ 50 with diabetes and one or more cardiovascular risk factor
- Fasting triglycerides 150-499 mg/dL (protocol later changed the lower limit to 200 mg/dL)
- LDL 41-100 mg/dL
- Stable statin dose for 4 weeks

Exclusion Criteria:

- Severe heart failure or severe liver disease
- HgA1c > 10%
- Planned cardiac surgery
- History of pancreatitis

Drug: Icosapent ethyl ester (purified EPA)

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients were randomized to receive icosapent ethyl 2 grams twice daily or matching placebo.

Duration: Median follow-up period of 4.9 years

Statistical Analysis: It was determined that 7990 randomized patients and 1612 primary events would achieve 90% power (alpha = 0.0437). The primary efficacy analysis was based on the first occurrence of the composite outcome. The ITT population was used for all analyses.

Results: A total of 8179 patients underwent randomization. Baseline patient characteristics were similar between treatment groups, except for median LDL level which was significantly lower in the icosapent ethyl group ($p=0.03$). At last visit, the triglycerides levels were significantly lower in the icosapent group compared to placebo (-45 mg/dL vs -13.0 mg/dL; $p<0.001$). Overall adverse drug reaction rates and discontinuation rates were similar between treatment groups. Rates of hospitalization due to atrial fibrillation were significantly higher in the treatment group (3.1% vs 2.1%; $p=0.004$). There was no significant difference in bleeding rates between treatment groups.

Icosapent Ethyl Ester (N=4089) Vs Placebo (N=4090)

Primary Composite Outcome:
705 (17.2%) vs 901 (22.0%); HR 0.75 (95% CI 0.68-0.83)
p<0.001; ARR 4.79%; NNT ~21

Cardiovascular Death:
174 (4.26%) vs 213 (5.21%); HR 0.80 (95% CI 0.66-0.98)
p=0.03; ARR 0.95%; NNT ~105

Total Myocardial Infarction:
250 (6.11%) vs 355 (8.68%); HR 0.69 (95% CI 0.58-0.81)
p<0.001; ARR 2.57%; NNT ~39

Total Stroke:
98 (2.40%) vs 134 (3.28%); HR 0.72 (95% CI 0.55-0.93)
p=0.01; ARR 0.88%; NNT ~114

Revascularization:
216 (5.28%) vs 321 (7.85%); HR 0.65 (95% CI 0.55-0.78)
p<0.001; ARR 2.57; NNT ~39

Hospitalization for Unstable Angina:
108 (2.64%) vs 157 (3.84%); HR 0.68 (95% CI 0.53-0.87)
p=0.002; ARR 1.20%; NNT ~84

Limitations:

- Power set but not met - primary event threshold not met (significant differences still seen - clinical relevance minimal)
- Icosapent ethyl ester was added to stable statin therapy - must be considered when interpreting trial results

Level of Evidence: Level II - with major limitations

Recommendation: For these reasons, I recommend the use of icosapent ethyl ester (in addition to statin therapy) to further reduce the risk of cardiovascular morbidity and mortality in high-risk patients with hypertriglyceridemia.

Efficacy:

- Rates of the cardiovascular composite outcome were significantly lower in the icosapent ethyl ester group compared to placebo
- All individual components of the composite outcome occurred at significantly lower rates in the icosapent ethyl ester compared to the placebo group
- Reduction in triglyceride levels was significantly greater with icosapent ethyl ester

Safety:

- Overall adverse drug reactions and discontinuation rates were similar between groups
- Rates of hospitalization due to atrial fibrillation were significantly higher in the icosapent ethyl ester group

Cost:

- The cost of using icosapent ethyl ester must be balanced against the cost-savings from preventing cardiovascular events

Special Considerations/Populations:

- It is important to note that all patients were receiving stable statin therapy in addition to study medication
- The majority of patients had established cardiovascular disease at baseline

Grade of Recommendation: **B**

RE-LY

Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361(12):1139-1151.

Objective: To determine the efficacy and safety of dabigatran compared to warfarin for prevention of thromboembolic events in high-risk patients with atrial fibrillation.

Primary Efficacy Measure: Composite of stroke or systemic embolism

Primary Safety Measure: Major bleeding

Participants: Patients with atrial fibrillation at increased risk for stroke or embolism

- Age ~72 years; male ~63%
- $CHADS_2$ ~2.1
- BP ~131/77 mmHg
- Baseline ACEi/ARB ~66%; beta-blocker ~63%; vitamin K antagonist ~49%

Inclusion Criteria:

- Documented atrial fibrillation plus one or more of the following:
  - Previous stroke/TIA
  - LVEF < 40%
  - NYHA class II-IV
  - Age ≥ 75
  - Age ≥ 65 plus diabetes /hypertension/coronary artery disease

Exclusion Criteria:

- Severe heart-valve disorder
- Recent stroke
- Increased hemorrhage risk
- CrCl < 30 mL/min
- Active liver disease

Drugs: Dabigatran; warfarin

Design: Randomized, placebo-controlled, non-inferiority trial

Methods: Eligible patients were randomized to receive either blinded dabigatran (110 mg or 150 mg twice daily) or open-label warfarin (target INR 2.0-3.0).

Duration: Median follow-up period of 2.0 years

Statistical Analysis: It was initially determined that 15,000 randomized patients would achieve 84% power for non-inferiority. However, the sample size was increased to 18,000 patients in order to maintain power in the case of low event rate. To achieve non-inferiority for dabigatran versus warfarin the upper bound of the 97.5% CI must be < 1.46 for each dosing group. If both dabigatran groups demonstrated non-inferiority, then testing for superiority would occur. The ITT population was used for all analyses.

Results: A total of 18,113 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. Patients in the warfarin group were within the target INR range 64% of the time. Both dabigatran groups demonstrated non-inferiority to warfarin regarding the primary efficacy measure. The dabigatran 150 mg group demonstrated significantly lower rates of the primary efficacy composite outcome warfarin group.

Dabigatran 110 mg (N=6015) Vs Warfarin (N=6022)

Composite of Stroke or Systemic Embolism:
182 (3.03%) vs 199 (3.30%); HR 0.91 (95% CI 0.74-1.11); p=0.34

Total Stroke:
171 (2.84%) vs 185 (3.07%); HR 0.92 (95% CI 0.74-1.13); p=0.41

Pulmonary Embolism:
14 (0.23%) vs 11 (0.18%); HR 1.26 (95% CI 0.57-2.78); p=0.56

Major Bleeding:
322 (5.35%) vs 397 (6.59%); HR 0.80 (95% CI 0.69-0.93)
p=0.003; ARR 1.24%; NNT ~81

Gastrointestinal Bleeding:
133 (2.21%) vs 120 (1.99%); HR 1.10 (95% CI 0.86-1.41); p=0.43

Intracranial Bleeding:
27 (0.45%) vs 87 (1.44%); HR 0.31 (95% CI 0.20-0.47)
p<0.001; ARR 1.00%; NNT ~100

Dabigatran 150 mg (N=6076) Vs Warfarin (N=6022)

Composite of Stroke or Systemic Embolism:
134 (2.21%) vs 199 (3.30%); HR 0.66 (95% CI 0.53-0.82)
p<0.001; ARR 1.10%; NNT ~91

Total Stroke:
122 (2.01%) vs 185 (3.07%); HR 0.64 (95% CI 0.51-0.81)
p<0.001; ARR 1.06%; NNT ~94

Pulmonary Embolism:
18 (0.30%) vs 11 (0.18%); HR 1.61 (95% CI 0.76-3.42); p=0.21

Major Bleeding:
375 (6.17%) vs 397 (6.59%); HR 0.93 (95% CI 0.81-1.07); p=0.31

Gastrointestinal Bleeding:
182 (3.00%) vs 120 (1.99%); HR 1.50 (95% 1.19-1.89)
p<0.001; ARI 1.00%; NNH ~99

Intracranial Bleeding:
36 (0.59%) vs 87 (1.44%); HR 0.40 (95% CI 0.27-0.60)
p<0.001; ARR 0.85%; NNT ~117

Limitations:

- Open-label trial design
- Patient population must be considered (high-risk atrial fibrillation patients)

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I recommend the use of dabigatran 150 mg twice daily over warfarin therapy for prevention of thromboembolic events in high-risk atrial fibrillation patients.

Efficacy:

- Both groups of dabigatran (110 mg and 150 mg) demonstrated non-inferiority to warfarin regarding the composite of thromboembolic events
- Dabigatran 150 mg twice daily demonstrated superiority to warfarin regarding the reduction of the thromboembolic composite outcome

Safety:

- Both groups of dabigatran (110 mg and 150 mg) demonstrated non-inferiority to warfarin regarding the rates of major bleeding
    - Dabigatran 110 mg twice daily demonstrated superiority to warfarin regarding rates of major bleeding
- Sites of major bleeding events were primarily gastrointestinal
- Rates of intracranial bleeding were significantly lower in both dabigatran groups
- Rates of gastrointestinal bleeding were significantly higher in the dabigatran 150 mg group

Cost:

- The cost of using dabigatran must be balanced against the cost-savings achieved from reduced rates of thromboembolic events

Special Considerations/Populations:

- The results of this trial cannot be extrapolated to other DOACs

Grade of Recommendation: **A**

RENAAL

Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med*. 2001;345(12):861-869.

Objective: To determine the effect of losartan on renal disease progression in patients with type 2 diabetes and nephropathy.

Primary Efficacy Measure: Composite of serum creatinine doubling, ESRD or death

Participants: Patients with type 2 diabetes and nephropathy

- Age ~60 years; male ~63%
- HgA1c ~8.5%; SCr ~1.9 mg/dL; UACR ~1250 mg/g
- BP ~152/82 mmHg; HR ~70 bpm
- Baseline antihypertensive usage ~93% (ACEi/ARB ~51%; CCB ~71%)

Inclusion Criteria:

- Age 31 to 71 years
- Type 2 diabetes and nephropathy (UACR ≥ 300 and SCr 1.3 to 3 mg/dL)
- HgA1c < 12%

Exclusion Criteria:

- Renal artery stenosis
- Type 1 diabetes
- Non-diabetic renal disease
- Myocardial infarction or CABG within previous month
- History of heart failure
- Cerebrovascular accident or PCI within previous 6 months
- TIA within previous year

Drug: Losartan

Design: Randomized, double-blind, placebo-controlled trial

Methods: The use of any ACEi or ARB was discontinued and replaced by open-label medications to manage hypertension. Eligible patients were randomized to receive either losartan 50 mg daily or placebo (in addition to standard antihypertensive therapy). After 4 weeks the dose of losartan was increased to 100 mg daily if the target blood pressure of <140/90 mmHg was not achieved. After 8 more weeks if the target blood pressure was not achieved then additional antihypertensive medications would be added.

Duration: Mean follow-up period of 3.4 years

Statistical Analysis: It was determined that 1320 randomized patients would achieve 95% power. A p-value of ≤ 0.048 was required for the primary efficacy analyses to be considered statistically significant (p-value < 0.05 for all other outcomes). The ITT population was used for the efficacy analyses.

Results: A total of 1513 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. The trial was stopped early due to new evidence that ACEis may be effective in reducing cardiac event rates in patients with renal disease. The dose of losartan 100 mg was used in 71% of patients. The average blood pressure at the end of the trial was 140/74 mmHg in the losartan group compared to 142/74 mmHg in the placebo group. Discontinuation rates were higher in the placebo group compared to the losartan group.

Losartan (N=751) Vs Placebo (N=762)

Primary Composite Outcome:
327 (43.5%) vs 359 (47.1%); RRR 16% (95% CI 2% to 28%)
p=0.02; ARR 3.57%; NNT ~28

Serum Creatinine Doubling:
162 (21.6%) vs 198 (26.0%); RRR 25% (95% CI 8% to 39%)
p=0.006; ARR 4.41%; NNT ~23

End-Stage Renal Disease:
147 (19.6%) vs 194 (25.6%); RRR 28% (95% CI 11% to 42%)
p=0.002; ARR 6.02%; NNT ~17

Death:
158 (21.0%) vs 155 (20.3%); RRR -2% (95% CI -27% to 19%); p=0.88

Limitations:

- Patient population must be considered – type 2 diabetes and nephropathy (patients with non-diabetic nephropathy were excluded from this trial)
- Trial stopped early - however, the clinical relevance is likely minimal due to the significant differences demonstrated

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I recommend the use of losartan to reduce renal disease progression in patients with type 2 diabetes and nephropathy.

Efficacy:

- Rates of the primary composite outcome were significantly lower in the losartan group compared to placebo
- The individual components of serum creatinine doubling and ESRD were also significantly lower in the losartan group
- The average blood pressure at the end of the trial was similar between treatment groups (treatment benefit demonstrated beyond blood pressure lowering effect)

Safety:

- Rates of discontinuation were higher in the placebo group

Cost:

- The cost of using losartan must be balanced against the cost-savings from preventing renal disease progression

Special Considerations/Populations:

- Results from this trial cannot be extrapolated to ACEis

Grade of Recommendation: **A**

REPRIEVE

Grinspoon SK, Fitch KV, Zanni MV, et al. Pitavastatin to Prevent Cardiovascular Disease in HIV Infection. *N Engl J Med*. 2023;389(8):687-699.

Objective: To determine the efficacy and safety of pitavastatin for primary prevention of atherosclerotic cardiovascular disease in low-to-moderate risk patients with HIV.

Primary Efficacy Measure: Composite of cardiovascular death, myocardial infarction, hospitalization for unstable angina, stroke, transient ischemic attack, peripheral arterial ischemia, revascularization (coronary, carotid or peripheral artery) or death due to an undetermined cause

Participants: Patients with HIV at a low-to-moderate risk for atherosclerotic cardiovascular disease

- Age ~50 years; male 69%
- Cisgender ~95%; transgender ~2%
- Median 10-year ASCVD risk score ~5% (<7.5% for ~75%); LDL ~108 mg/dL
- Undetectable HIV-1 RNA count ~88%; CD4+ count >500 cells/mm3 ~68%

Inclusion Criteria:

- Age 40-75 years
- Diagnosis of HIV infection
- Stable antiretroviral therapy for previous 180 days
- CD4+ cell count > 100 cells/mm3
- Low-to-moderate risk for ASCVD (10-year ASCVD risk score ≤ 15%)

Exclusion Criteria:

- Established atherosclerotic cardiovascular disease
- Use of statin medication within the previous 90 days

Drug: Pitavastatin calcium

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients were randomized to receive pitavastatin 4 mg or matching placebo once daily. All patients received educational material regarding lifestyle modifications (e.g., physical activity, diet, medication adherence).

Duration: Median follow-up period of 5.1 years

Statistical Analysis: It was determined that 7700 randomized patients would provide 85% power (alpha=0.05). The ITT population was used for the efficacy analysis.

Results: A total of 7769 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. The trial was terminated early at the recommendation of the data and safety monitoring board due to evidence of clear treatment benefit during an interim analysis. At 12 months, LDL had decreased to 74 mg/dL in the pitavastatin group and 105 mg/dL in the placebo group.

The rate of incident diabetes mellitus was significantly higher in the pitavastatin group compared to placebo (ARI 1.22%; NNH ~81). Additionally, rates of myalgia or myopathy were significantly higher with pitavastatin (ARI 0.97%; NNH ~102). There was no significant difference in the rates of liver dysfunction or rhabdomyolysis between treatment groups.

Pitavastatin (N=3888) Vs Placebo (N=3881)

Primary Composite Outcome:
89 (2.29%) vs 136 (3.50%); HR 0.65 (95% CI 0.48-0.90); p=0.002; ARR 1.22%; NNT ~83

Cardiovascular Death:
12 (0.31%) vs 16 (0.41%); HR 0.75 (95% CI 0.36-1.59)

Cardiac Ischemia or Myocardial Infarction:
26 (0.67%) vs 47 (1.21%); HR 0.56 (95% CI 0.34-0.90); ARR 0.54%; NNT ~185

Stroke or Transient Ischemic Attack:
29 (0.75%) vs 44 (1.13%); HR 0.66 (95% CI 0.41-1.05)

Cardiac Catheterization or Revascularization:
18 (0.46%) vs 31 (0.80%); HR 0.59 (95% CI 0.33-1.05)

Limitations:
- Trial results can only be applied to patients with HIV without established ASCVD
- Patient population were all categorized as low-to-moderate risk for developing ASCVD
- Cannot make direct comparisons to other statins (placebo-controlled trial)

Level of Evidence: Level I – with minor limitations

Recommendation: For these reasons, I recommend the use of pitavastatin for primary prevention of atherosclerotic cardiovascular disease in low-to-moderate risk patients with HIV.

Efficacy:
- Rates of the primary composite outcome occurred at significantly lower rates in the pitavastatin group
- Treatment benefit was driven largely by significantly lower rates of cardiac ischemia or myocardial infarction
- Predictably, LDL levels were notably lower in the pitavastatin group at 12 months

Safety:
- Rates of incident diabetes and myalgia/myopathy occurred at significantly higher rates in the pitavastatin group

Cost:
- The cost of using pitavastatin must be balanced against the cost-savings achieved from preventing cardiovascular morbidity and mortality outcomes

Special Considerations/Populations:
- Patients with HIV are at an increased risk for atherosclerotic cardiovascular disease
- Trial investigators state that the frequency of diabetes mellitus that occurred in both pitavastatin and placebo groups falls within the expected range for patients age 45-64 years living in the United States
- Many statins interact with antiretroviral medication (protease inhibitors and pharmacokinetic boosters, in particular) due to inhibition of CYP450 enzymes
    - Pitavastatin has minimal CYP450 metabolism and a comparatively lower potential for drug interactions

Grade of Recommendation: **A**

REWIND

Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomized placebo-controlled trial. *Lancet*. 2019;394(10193):121-130.

Objective: To determine the effect of dulaglutide on cardiovascular outcomes in patients with type 2 diabetes.

Primary Efficacy Measure: Composite of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke

Participants: Patients with type 2 diabetes at increased risk for cardiovascular events

- Age ~66 years; male ~53%
- HgA1c ~7.3%
- Established cardiovascular disease ~31%

Inclusion Criteria:

- Patients with type 2 diabetes and HgA1c ≤ 9.5%
- Receiving a max of 2 oral glucose-lowering agents with/without basal insulin
- BMI ≥ 23
- Age ≥ 50 with established vascular disease; or age ≥ 55 with myocardial ischemia, artery stenosis ≥ 50%, left ventricular hypertrophy, eGFR < 60 mL/min or albuminuria; age ≥ 60 with 2 of following: tobacco use, dyslipidemia, hypertension or abdominal obesity

Exclusion Criteria:

- eGFR < 15 mL/min
- Severe hypoglycemia within previous 12 months
- Life expectancy < 1 year
- Coronary/cerebrovascular event within previous 2 months
- Plans for revascularization

Drug: Dulaglutide

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients underwent a 3-week single-blind placebo run-in period. Patients continued their glucose-lowering therapy except for DPP-4 inhibitors or GLP-1 receptor agonists (which were discontinued at the start of the run-in period). Those who successfully completed the run-in period were randomized to receive either dulaglutide 1.5 mg weekly subcutaneous injections or matching placebo. All comorbid conditions were treated according to local guidelines.

Duration: Median follow-up period of 5.4 years

Statistical Analysis: It was determined that 9600 randomized patients and 1200 primary outcomes would achieve 90% power (alpha = 0.05). The ITT population was used for all efficacy and safety analyses.

Results: A total of 9901 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. Overall, patients treated with dulaglutide had a significantly lower HgA1c (-0.61%; $p<0.0001$) compared to placebo. There was no significant difference between treatment groups in the rates of discontinuation, pancreatitis, pancreatic cancer, thyroid cancer, serious GI events or any cancer. Gastrointestinal adverse drug reactions were significantly higher in the dulaglutide group than placebo (47.4% vs 34.1%; $p<0.0001$).

Dulaglutide (N=4949) Vs Placebo (N=4952)

Composite of Cardiovascular Death, Myocardial Infarction or Stroke:
594 (12.0%) vs 663 (13.4%); HR 0.88 (95% CI 0.79-0.99)
p=0.026; ARR 1.37%; NNT ~73

Cardiovascular Death:
317 (6.41%) vs 346 (6.99%); HR 0.91 (95% CI 0.78-1.06); p=0.21

Non-Fatal Myocardial Infarction:
205 (4.14%) vs 212 (4.28%); HR 0.96 (95% CI 0.79-1.16); p=0.65

Non-Fatal Stroke:
135 (2.73%) vs 175 (3.53%); HR 0.76 (95% CI 0.61-0.95)
p=0.017; ARR 0.81%; NNT ~125

Limitations:

- Patient population must be considered - vast majority did not have established cardiovascular disease at baseline

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I recommend the use of weekly dulaglutide injections as a safe glucose-lowering therapy in high-risk patients with type 2 diabetes.

Efficacy:

- Rates of the primary composite outcome were significantly lower in the dulaglutide group compared to placebo
    - Only the rates of the individual component of non-fatal stroke were significantly lower than placebo
- The average HgA1c was significantly lower in the dulaglutide group compared to placebo

Safety:

- There was no significant difference in the rates of cancer or pancreatitis
- Rates of gastrointestinal adverse events were significantly higher in the dulaglutide group compared to placebo

Cost:

- The cost of using dulaglutide must be balanced against the cost-savings from preventing a cardiovascular event

Special Considerations/Populations:

- Results cannot be extrapolated to other GLP-1 receptor agonists
- The majority of patients did not have established cardiovascular disease at baseline

Grade of Recommendation: **A**

ROCKET AF

Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365(10):883-891.

Objective: To determine the efficacy and safety of rivaroxaban compared to warfarin for prevention of thromboembolic events in patients with atrial fibrillation.

Primary Efficacy Measure: Composite of total stroke and systemic embolism

Primary Safety Measure: Clinically relevant bleeding

Participants: Patients with non-valvular atrial fibrillation at increased risk for thromboembolic event

- Age ~73 years; male ~60%
- Persistent atrial fibrillation ~80%
- $CHADS_2$ score ~3.5

Inclusion Criteria:

- Age ≥ 18 years with non-valvular atrial fibrillation
- Moderate-high stroke risk:
  - History of stroke/TIA/systemic embolism, or
  - $CHADS_2$ score ≥ 2

Exclusion Criteria:

- Mitral valve stenosis
- Planned cardioversion
- Active endocarditis
- Prosthetic heart valve
- Increased bleeding risk

Drugs: Rivaroxaban; warfarin

Design: Randomized, double-blind, active-controlled, non-inferiority trial

Methods: Eligible patients were randomized to receive either rivaroxaban 20 mg (15 mg if CrCl 30-49 mL/min) or warfarin (target INR 2.0-3.0) plus matching placebo. The use of aspirin ≤ 100 mg/day was allowed.

Duration: Median follow-up period of 707 days (~2 years)

Statistical Analysis: It was determined that 14,000 randomized patients and 363 primary events would provide 95% power for non-inferiority. A non-inferiority margin of 1.46 was used (alpha = 0.025). If non-inferiority was achieved, then sequential testing for superiority would then be performed using the as-treated population (received one or more doses of study medication and were followed for events regardless of adherence). The per-protocol population (and ITT population) were used for the primary non-inferiority analysis.

Results: A total of 14,264 patients underwent randomization. Baseline patient characteristics were similar between treatment groups except for previous myocardial infarction (higher in the warfarin treatment group). Patients in the warfarin group were within target INR range ~55% of the time. Non-inferiority was demonstrated in both the per-protocol and ITT population analyses. There were conflicting results between the per-protocol and ITT analyses when testing for superiority. The per-protocol analysis demonstrated superiority of rivaroxaban over warfarin, but the ITT analysis failed to demonstrate a significant difference between treatment groups (p=0.12). However, subgroup analysis of the ITT population demonstrated that while on treatment patients in the rivaroxaban group demonstrated significantly lower rates of the primary outcome. The rates of the individual components of the composite outcome were not reported.

Rivaroxaban (N=6958) Vs Warfarin (N=7004)
Per-Protocol Population

Primary Composite Outcome - Non Inferiority:
188 (2.70%) vs 241 (3.44%); HR 0.79 (95% CI 0.66-0.96); p<0.001

Rivaroxaban (N=7061) Vs Warfarin (N=7082)
As-Treated Population

Primary Composite Outcome - Superiority:
189 (2.68%) vs 243 (3.43%); HR 0.79 (0.65-0.95)
p=0.02; ARR 0.75%; NNT ~133

Rivaroxaban (N=7081) Vs Warfarin (N=7090)
ITT Population

Primary Composite Outcome - Superiority:
269 (3.80%) vs 306 (4.32%); HR 0.88 (95% CI 0.75-1.03); p=0.12

Safety:

Rivaroxaban (N=7111) Vs Warfarin (N=7125)

Clinically Relevant Bleeding:
1475 (20.7%) vs 1449 (20.3%); HR 1.03 (95% CI 0.96-1.11); p=0.44

Fatal Bleeding:
27 (0.38%) vs 55 (0.77%); HR 0.50 (95% CI 0.31-0.79)
p=0.003; ARI 0.39%; NNH ~254

Intracranial Hemorrhage:
55 (0.77%) vs 84 (1.18%); HR 0.67 (95% CI 0.47-0.93)
p=0.02; ARI 0.41%; NNH ~246

Major Bleeding:
395 (5.55%) vs 386 (5.42%); HR 1.04 (95% CI 0.90-1.20); p=0.58

Gastrointestinal Bleeding:
224 (3.15%) vs 154 (2.16%); p<0.001; ARI 0.99%; NNH ~101

Limitations:

- Multiple analyses with differing results depending on which patient population is used - interpret cautiously
- Cannot extrapolate results to other DOACs

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I recommend the use of rivaroxaban over warfarin for prevention of thromboembolic events in high-risk patients with non-valvular atrial fibrillation.

Efficacy:

- Rivaroxaban demonstrated non-inferiority to warfarin regarding the primary composite outcome
- Conflicting results regarding superiority of rivaroxaban over warfarin depending on the patient population used for analyses (per-protocol and as-treated analysis demonstrated superiority; ITT analysis failed to demonstrate superiority)
- Subgroup analysis of ITT population showed that while on-treatment, rates of the primary outcome were significantly lower in the rivaroxaban treatment group

Safety:

- Rates of clinically relevant bleeding and major bleeding were not significantly different between treatment groups
- Rates of fatal bleeding and intracranial hemorrhage were significantly lower in the rivaroxaban group compared to warfarin
- Rates of gastrointestinal bleeding were significantly higher in the rivaroxaban group

Cost:

- The cost of using rivaroxaban must be balanced against the cost of using warfarin and monitoring INR
- The cost-savings of preventing thromboembolic events must also be considered

Special Considerations/Populations:

- Cannot apply results to patients with valvular atrial fibrillation

Grade of Recommendation: **A**

SAVE

Pfeffer MA, Braunwald E, Moyé LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. *N Engl J Med*. 1992;327(10):669-677.

Objective: To determine the effect of captopril on morbidity and mortality outcomes in patients post-myocardial infarction with baseline left ventricular dysfunction (but not overt heart failure requiring vasodilator therapy).

Primary Efficacy Measures: (1) All-cause mortality (2) Cardiovascular death (3) Heart failure hospitalization

Participants: Patients post-myocardial infarction with asymptomatic left-ventricular dysfunction

- Age ~60 years; male ~82%
- LVEF ~31%
- BP ~112/70 mmHg; HR ~78 bpm

Inclusion Criteria:

- Age 21 to 80 years
- Survived first 3 days post-myocardial infarction
- LVEF ≤ 40%

Exclusion Criteria:

- SCr > 2.5 mg/dL
- Contraindication to ACEi use

Drug: Captopril

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients were randomized to receive placebo or captopril. The initial dosing was 12.5 mg with a target dose of 25 mg three times daily during hospital stay (outpatient target 50 mg three times daily).

Duration: Mean follow-up period of 42 months (~3.5 years)

Statistical Analysis: It was determined that 2200 randomized patients would achieve 90% power (alpha = 0.05). The ITT population was used for all analyses.

Results: A total of 2231 patients underwent randomization. Baseline characteristics were similar between treatment groups. Average blood pressure was significantly lower in the captopril group at 1-year compared to placebo (125/77 mmHg vs 119/74 mmHg; $p<0.001$). There was increased diuretic use in patients assigned to the placebo group ($p=0.002$). Rates of dizziness, cough and diarrhea were significantly higher in the captopril group compared to placebo.

Captopril (N=1115) Vs Placebo (N=1116)

All-Cause Mortality:
228 (20.4%) vs 275 (24.6%); RRR 19% (95% CI 3% to 32%)
p=0.019; ARR 4.19%; NNT ~24

Cardiovascular Death:
188 (16.9%) vs 234 (21.0%); RRR 21% (95% CI 5% to 35%)
p=0.014; ARR 4.11%; NNT ~25

Recurrent Myocardial Infarction:
133 (11.9%) vs 170 (15.2%); RRR 25% (95% CI 5% to 40%)
p=0.015; ARR 3.30%; NNT ~31

Heart Failure Hospitalization:
154 (13.8%) vs 192 (17.2%); RRR 22% (95% CI 4% to 37%)
p=0.019; ARR 3.39%; NNT ~30

Limitations:

- External validity - results cannot be applied to patients with preserved ejection fraction

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I recommend the use of captopril to reduce the risk for morbidity and mortality outcomes in patients post-myocardial infarction with left-ventricular dysfunction.

Efficacy:

- Rates of all-cause mortality, cardiovascular death, recurrent myocardial infarction and heart failure hospitalization were significantly lower in the captopril group compared to placebo

Safety:

- Adverse drug reactions of dizziness, cough and diarrhea occurred significantly more often in the captopril group

Cost:

- The cost of using captopril must be balanced against the cost-savings of preventing cardiovascular morbidity and mortality outcomes

Special Considerations/Populations:

- Patient population was acute post-myocardial infarction patients with asymptomatic left-ventricular dysfunction (no overt heart failure at baseline)

Grade of Recommendation: **A**

SAVOR-TIMI 53

Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2013;369(14):1317-1326.

Objective: To determine the effect of saxagliptin on cardiovascular outcomes in high-risk patients with type 2 diabetes.

Primary Efficacy Measure: Composite of cardiovascular death, non-fatal myocardial or non-fatal ischemic stroke

Participants: Patients with type 2 diabetes at increased risk for cardiovascular event

- Age ~65 years; male ~67%
- HgA1c ~8.0%
- Baseline cardiovascular disease ~79%

Inclusion Criteria:

- Patients with type 2 diabetes
- HgA1c 6.5%-12%
- Age ≥ 40 years plus established cardiovascular disease (coronary/cerebrovascular/peripheral artery disease); age ≥ 55 (men) or 60 (women) plus one or more risk factors (dyslipidemia, hypertension or active smoker)

Exclusion Criteria:

- Incretin-based therapy within previous 6 months
- ESRD plus long-term dialysis
- Renal transplant
- SCr > 6 mg/dL

Drug: Saxagliptin

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients were randomized to receive either saxagliptin 5 mg daily (2.5 mg if eGFR ≤ 50 mL/min) or matching placebo. Additional glucose-lowering therapy (other than incretin-based medications) was allowed at the discretion of the investigating physician.

Duration: Median follow-up period of 2.1 years

Statistical Analysis: The trial was designed to be a superiority trial with pre-specified testing for non-inferiority followed by testing for superiority. It was determined that 1040 primary events would provide 98% power for non-inferiority (NI margin set at 1.3) and 85% power for superiority (alpha=0.05). The ITT population was used for primary efficacy analyses.

Results: A total of 16,492 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. At the end of the treatment period average HgA1c was significantly lower in the saxagliptin group (7.6% vs 7.9%; $p<0.001$). There was no significant difference in the rates of pancreatitis or pancreatic cancer.

Saxagliptin (N=8280) Vs Placebo (N=8212)

Primary Composite Outcome:
613 (7.40%) vs 609 (7.42%); HR 1.00 (95% CI 0.89-1.12); p=0.99

Cardiovascular Death:
269 (3.25%) vs 260 (3.17%); HR 1.03 (95% CI 0.87-1.22); p=0.72

Non-Fatal Myocardial Infarction:
265 (3.20%) vs 278 (3.39%); HR 0.95 (95% CI 0.80-1.12); p=0.52

Non-Fatal Ischemic Stroke:
157 (1.90%) vs 141 (1.72%); HR 1.11 (95% CI 0.88-1.39); p=0.38

Heart Failure Hospitalization:
289 (3.49%) vs 228 (2.78%); HR 1.27 (95% CI 1.07-1.51)
p=0.007; ARI 0.71%; NNH ~141

Hypoglycemia:
1264 (15.3%) vs 1104 (13.4%); p<0.001; ARI 1.82%; NNH ~54

Limitations:

- Patient population must be considered - majority of patients had established cardiovascular disease at baseline

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I do not recommend the use of saxagliptin for glucose-lowering therapy in patients with type 2 diabetes at increased risk for cardiac events. Instead, I recommend the use of a glucose-lowering therapy with demonstrated cardiovascular benefit (such as GLP-1 RA or SGLT2i) or an agent with net cardiovascular safety (no increased risk of heart failure hospitalization).

Efficacy:

- The saxagliptin group demonstrated non-inferiority, but not superiority, to the placebo group regarding the primary composite outcome
- The rates of the individual components of the primary composite were similar between treatment groups
- Rates of heart failure hospitalization were significantly higher in the saxagliptin group compared to placebo

Safety:

- Rates of hypoglycemia were significantly higher in the saxagliptin group compared to placebo
- There was no significant difference in the rates of pancreatitis or pancreatic cancer between treatment groups

Cost:

- The cost of using saxagliptin must be balanced against the cost of using a glucose-lowering therapy with demonstrated cardiovascular benefit

Special Considerations/Populations:

- Results in this trial cannot be extrapolated to other DPP-4 inhibitors
- This trial demonstrates safety concerns regarding heart failure hospitalization and lack of demonstrated cardiovascular benefit over placebo

Grade of Recommendation: **A**

SCALE

Pi-Sunyer X, Astrup A, Fujioka K, et al. A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management. *N Engl J Med*. 2015;373(1):11-22.

Objective: To determine the efficacy and safety of high-dose liraglutide (3.0 mg daily) for weight loss in overweight/obese patients without baseline diabetes.

Primary Efficacy Measures: (1) Weight change from baseline (2) Proportion of patients that lost 5% or more of their baseline body weight (3) Proportion of patients that lost 10% or more of their baseline body weight

Participants: Overweight or obese adults without baseline diabetes

- Age ~45 years; male ~22%
- Weight ~106 kg (~233 lbs); BMI ~38
- HgA1c ~5.6%

Inclusion Criteria:

- Age ≥ 18 years
- BMI ≥ 30 (or ≥ 27 if the patient had dyslipidemia or hypertension)

Exclusion Criteria:

- Type 1 or type 2 diabetes
- Use of medications likely to cause significant weight gain or weight loss
- Previous bariatric surgery
- History of pancreatitis, major depressive disorder or other severe psychiatric disorder
- Personal or familial history of multiple endocrine neoplasia type 2 or familial medullary thyroid carcinoma

Drug: Liraglutide

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients were randomized (2:1 ratio) to receive subcutaneous liraglutide injections or matching placebo. Dosing for the liraglutide group was started at 0.6 mg daily with weekly increases of 0.6 mg/day increments to max of 3.0 mg daily. Both treatment groups were provided lifestyle modification counseling. Patients that successfully completed 56 weeks of treatment with liraglutide were randomized to continued treatment or placebo for an additional 12 weeks to assess safety and efficacy after discontinuation. Patients that successfully completed the 56 weeks of placebo treatment continued to receive placebo for the additional 12 week period.

Duration: 56 weeks

Statistical Analysis: It was determined that 2400 randomized patients to the liraglutide group and 1200 randomized patients to the placebo group would provide the trial 99% power (alpha = 0.05). The modified ITT population (randomized patients that received at least one dose of study medication and had at least one assessment after baseline) was used for the efficacy analyses. The safety analyses consisted of all randomized patients that received at least one dose of study medication.

Results: A total of 3731 patients underwent randomization. Baseline characteristics were similar between treatment groups. All coprimary outcomes demonstrated significant benefit of liraglutide over placebo. Reduction in HgA1c was significantly greater with the liraglutide group compared to the placebo group (-0.29% vs -0.07%; p<0.001). However, a clinically significant change in HgA1c is generally considered 0.5% or more. The most common adverse effects reported with liraglutide were gastrointestinal in nature (e.g. nausea, vomiting, diarrhea). Gallbladder-related adverse events occurred more often in the liraglutide group than placebo (2.5% vs 1.0%). There was a total of 4 adjudicated acute pancreatitis events in the liraglutide group and zero reported in the placebo group.

Liraglutide (N=2437) Vs Placebo (N=1225)

Change in Body Weight:
-8.0% vs -2.6%; -5.4% (95% CI -5.8 % to -5.0%); p<0.001

-8.4 kg (18.5 lbs) vs -2.8 kg (6.2 lbs); p<0.001

Proportion of Patients that Lost 5% or More of Baseline Body Weight:
63.2% vs 27.1%; OR 4.8 (95% CI 4.1-5.6); p<0.001

Proportion of Patients that Lost 10% or More of Baseline Body Weight:
33.1% vs 10.6%; OR 4.3 (95% CI 3.5-5.3); p<0.001

Limitations:

- Patient population must be considered – patients with type 1 and type 2 diabetes at baseline were excluded
- Dosing of liraglutide must be considered – titrated to max of 3.0 mg daily
- Trial results must be considered in addition to lifestyle modification counseling

Level of Evidence: Level I – with minor limitations

Recommendation: For these reasons, I recommend the use of liraglutide 3.0 mg as a therapeutic option to achieve significant weight loss in overweight and obese patients without baseline diabetes.

Efficacy:

- Body weight reduction was significantly greater in the liraglutide group compared to placebo
- The proportion of patients achieving a 5% or greater weight reduction or a 10% or greater weight reduction was significantly higher in the liraglutide group

Safety:

- Rates of gastrointestinal adverse events were more common in the liraglutide group
    - This is a predictable side effect of this class of medications
- Gallstone-related events occurred more frequently in the liraglutide treatment group, although the overall occurrence was low

Cost:

- The cost of using liraglutide 3.0 mg daily must be balanced against the cost-savings from preventing long-term complications of obesity (e.g., cardiovascular events and diabetes)

Special Considerations/Populations:

- Trial results must be considered in addition to lifestyle modification counseling
- The dosing of liraglutide used in this trial (3.0 mg daily) was higher than the dosing typically used for type 2 diabetes (1.8 mg daily)

Grade of Recommendation: **A**

SCD-HeFT

Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med*. 2005;352(3):225-237.

Objective: To compare the effects of implantable cardioverter-defibrillator (ICD) and amiodarone on sudden death in patients with congestive heart failure.

Primary Efficacy Measure: All-cause mortality

Participants: Patients with congestive heart failure

- Age ~60 years; male ~77%
- LVEF ~25%
- BP ~118/70 mmHg; HR ~73 bpm

Inclusion Criteria:

- Age ≥ 18 years
- Chronic, stable congestive heart failure
- LVEF ≤ 35%
- NYHA class II or III

Exclusion Criteria:

- Clinically unstable heart failure
- LVEF > 35%

Drug: Amiodarone

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients were randomized to receive ICD therapy, amiodarone or placebo. If appropriate, patients were required to receive beta-blocker and ACEi therapy. Amiodarone treatment consisted of 800 mg daily for 1 week followed by 400 mg daily for 3 weeks for the loading dose. Thereafter, patients weighing more than 200 lbs received 400 mg daily, patients weighing 150-200 lbs received 300 mg daily and patients weighing less than 150 lbs received 200 mg daily. The ICD therapy was designed to only correct rapid and sustained ventricular tachycardia or fibrillation. The detection rate was set for 187 bpm or more.

Duration: Median follow-up period of 45.5 months

Statistical Analysis: The trial was designed to achieve 90% power, assuming a 10% annual mortality rate in the placebo group (alpha = 0.025). The ITT population was used for the efficacy analyses.

Results: A total of 2521 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. The median dose of amiodarone was 300 mg daily. All-cause mortality was significantly lower in the ICD therapy group compared to placebo. Mortality rates were similar between amiodarone and placebo groups. However, subgroup analysis demonstrated a significantly higher mortality risk in patients with NYHA class III heart failure ($p=0.01$). The only notable adverse effects in the amiodarone group were increased rates of tremor (4%) and hypothyroidism (6%) compared to placebo ($p=0.02$ and $p<0.001$, respectively). Complications of ICD therapy that were considered clinically significant (e.g., hospitalization, surgical correction, unanticipated surgery) occurred in 5% of patients during implantation and in 9% of patients during the trial. During the trial period ~31% of the ICD group received a shock from their device (annual rate of ICD shocks ~7.5%).

Amiodarone (N=845) Vs Placebo (N=847)

All-Cause Mortality:
240 (28.4%) vs 244 (28.8%); HR 1.06 (97.5% CI 0.86-1.30); p=0.53

ICD Therapy (N=829) Vs Placebo (N=847)

All-Cause Mortality:
182 (22.0%) vs 244 (28.8%); HR 0.77 (97.5% CI 0.62-0.96)
p=0.007; ARR 6.85%; NNT ~15

Limitations:

- Power set but not met – annual mortality rate in the placebo group was less than 10%
    - Clinical significance likely low due to significant differences demonstrated between placebo and ICD therapy group
- ICD type and programming must be considered (single-lead, shock-only)

Level of Evidence: Level II – with major limitations

Recommendation: For these reasons, I recommend the use of ICD therapy to improve survival rates in patients with congestive heart failure. Additionally, I do not recommend the use of amiodarone to improve survival in this patient population due to lack of demonstrated benefit (and potentially demonstrated harm) and safety concerns with chronic therapy.

Efficacy:

- The use of ICD therapy demonstrated significantly lower mortality rates compared to placebo therapy
- Mortality rates were similar between amiodarone and placebo groups
    - However, subgroup analysis demonstrated significantly higher mortality rates in patients with NYHA class III heart failure compared to placebo

Safety:

- Rates of tremor and hypothyroidism were significantly higher in the amiodarone group
- Clinically significantly ICD complications occurred in 5% of patients during implantation and in 9% of patients during the trial

Cost:

- The cost of using ICD therapy must be balanced against the cost-savings associated with lower mortality outcomes

Special Considerations/Populations:

- The ICD was single-lead and programmed for shock only

Grade of Recommendation: **B**

SCORED

Bhatt DL, Szarek M, Pitt B, et al. Sotagliflozin in Patients with Diabetes and Chronic Kidney Disease. *N Engl J Med*. 2021;384(2):129-139.

Objective: To determine the safety and efficacy of sotagliflozin for prevention of cardiovascular outcomes in patients with type 2 diabetes and chronic kidney disease (with or without albuminuria) at increased risk for cardiac events.

Primary Efficacy Measure: Total cardiovascular deaths and heart failure hospitalization/urgent visits

- Changed from co-primary endpoints of 1st occurrence of MACE and 1st occurrence of cardiovascular death or heart failure hospitalization

Secondary Efficacy Measures: (1) Total heart failure hospitalizations/urgent visits (2) cardiovascular death

Participants: Patients with type 2 diabetes and CKD at increased-risk for cardiovascular events

- Age ~69 years; male ~55%
- HgA1c ~8.3%; eGFR ~44 mL/min; UACR ~74 mg/g
- Baseline ACEi ~38%; ARB ~49%; beta-blocker ~62%
- History of heart failure ~31%

Inclusion Criteria:

- Age ≥ 18 years
- Type 2 diabetes with HgA1c ≥ 7%
- eGFR 25-60 mL/min
- Increased risk for cardiovascular events

Exclusion Criteria:

- History of diabetic ketoacidosis
- Planned use of SGLT2 inhibitor during study

Drug: Sotagliflozin

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients were randomized to receive sotagliflozin 200 mg once daily or matching placebo (in addition to standard therapy). The sotagliflozin dose could be increased to 400 mg daily if tolerated.

Duration: Median follow-up period of 16 months

Statistical Analysis: It was initially determined that 10,500 randomized patients and 1189 events would be required to determine non-inferiority regarding first occurrence of MACE and 844 events to determine superiority regarding first occurrence of cardiovascular death or heart failure hospitalization. Despite a change in primary endpoint, investigators state the trial remained adequately powered. The ITT population was used for the efficacy analyses.

Results: A total of 10,584 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. While rates of the cardiovascular composite outcome were significantly lower in the sotagliflozin group compared to placebo, there was no significant difference in the rates of the renal composite outcome. Rates of severe hypoglycemia and urinary tract infections were similar between groups, however diabetic ketoacidosis, genital mycotic infection and diarrhea occurred significantly more often with sotagliflozin.

Sotagliflozin (N=5292) Vs Placebo (N=5292)

Total Number of Cardiovascular Deaths and Heart Failure Hospitalization/Urgent Visits:
400 vs 530; HR 0.74 (95% CI 0.63-0.88); p<0.001

Total Heart Failure Hospitalizations and Urgent Visits:
245 vs 360; HR 0.67 (95% CI 0.55-0.82); p<0.001

Cardiovascular Death:
155 (2.93%) vs 170 (3.21%); HR 0.90 (95% CI 0.73-1.12); p=0.35

Safety:
Diabetic Ketoacidosis:
30/5291 (0.57%) vs 14/5286 (0.26%); p=0.02; ARI 0.30%; NNH ~331

Genital Mycotic Infection:
125/5291 (2.36%) vs 45/5286 (0.85%); p<0.001; ARI 1.51%; NNH ~66

Diarrhea:
448/5291 (8.47%) vs 315/5286 (5.96%); p<0.001; ARI 2.51%; NNH ~39

Limitations:

- Loss of funding - led to inability to continue trial for the intended follow-up period
- Patient population - type 2 diabetes with CKD at increased risk for cardiovascular events

Level of Evidence: Level I - with major limitations

Recommendation: For these reasons, I recommend the use of sotagliflozin as a safe glucose-lowering therapy in patients with type 2 diabetes and chronic kidney disease at increased risk for cardiovascular events. While there is a general lack of renal benefit demonstrated there is clear evidence of cardiovascular safety and benefit, specifically regarding heart failure hospitalization/urgent visits.

Efficacy:

- The revised primary composite outcome occurred at significantly lower rates in the sotagliflozin treatment group
    - However, the rates of cardiovascular death were not significantly different between groups
    - This indicates that the primary benefit demonstrated by sotagliflozin was reduced total heart failure hospitalizations and urgent visits in a patient population where the majority did not have a history of heart failure
- There was no significant different in the rates of the renal composite outcome

Safety:

- Rates of diabetic ketoacidosis, genital mycotic infections and diarrhea were significantly higher in the sotagliflozin treatment group compared to placebo
- Patient intolerance of sotagliflozin-induced diarrhea must be considered

Cost:

- The cost of using sotagliflozin must be balanced against the cost-savings of preventing heart failure hospitalization and urgent visits
- The cost of treating and mycotic infections must also be considered

Special Considerations/Populations:

- There was no UACR requirement for this trial
- Sotagliflozin inhibits SGLT1/2 - SGLT1 inhibition delays intestinal glucose absorption
- Most patients did not have a history of heart failure

Grade of Recommendation: **A**

SEARCH

Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) Collaborative Group, Armitage J, Bowman L, et al. Intensive lowering of LDL cholesterol with 80 mg versus 20 mg simvastatin daily in 12,064 survivors of myocardial infarction: a double-blind randomized trial. *Lancet*. 2010;376(9753):1658-1669.

Objective: To determine the efficacy and safety of intensive simvastatin therapy compared to standard simvastatin therapy in patients at high-risk for cardiovascular events.

Primary Efficacy Measure: Major vascular events (composite of coronary death, myocardial infarction, stroke or arterial revascularization)

Participants: Patients with established ASCVD (prior myocardial infarction)

- Age ~64 years; male ~83%
- Baseline statin ~3/4^{ths}
- Total cholesterol ~163 mg/dL; LDL ~96 mg/dL; HDL ~40 mg/dL

Inclusion Criteria:

- Age 18-80 years
- Prior myocardial infarction
- Current statin usage or clear indication for statin
- Total cholesterol > 135 mg/dL (on statin therapy) or > 174 mg/dL (not on statin therapy)

Exclusion Criteria:

- Chronic liver disease or abnormal liver function
- Severe renal disease or evidence of renal impairment
- Concurrent treatment with fibrates or high-dose niacin

Drug: Simvastatin

Design: Randomized, double-blind, placebo-controlled trial

Methods: All eligible patients underwent a run-in period where they received simvastatin 20 mg daily to assess tolerance and adherence. During this period, they were instructed to discontinue any non-study statin medication. Patients that successfully completed the trial run-in period were randomized to receive simvastatin 20 mg daily or simvastatin 80 mg daily (plus matching placebo). Due to a lower than expected difference in cholesterol levels between the treatment groups the primary efficacy outcome was changed from major coronary events (composite of coronary death, myocardial infarction or coronary revascularization) to major vascular events (composite of coronary death, myocardial infarction, stroke or arterial revascularization).

Duration: Average follow-up period of 6.7 years

Statistical Analysis: It was determined that 2800 primary events would provide 90% power (alpha=0.05). The ITT population was used for the efficacy analysis.

Results: A total of 12,064 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. The overall average difference in lipid values between the 80 mg group and the 20 mg group was -15.5 mg/dL for total cholesterol, -13.5 mg/dL for LDL and +0.77 mg/dL for HDL. While the simvastatin 80 mg group demonstrated greater LDL reduction there was no significant difference in rates of the primary efficacy outcome of major vascular events (or major coronary events). Rates of myopathy were significantly higher in the simvastatin 80 mg group.

Simvastatin 80 mg (N=6031) Vs Simvastatin 20 mg (N=6033)

Composite of Major Vascular Events:
1477 (24.5%) vs 1553 (25.7%); HR 0.94 (95% CI 0.88-1.01); p=0.10

Composite of Major Coronary Events:
1189 (19.7%) vs 1225 (20.3%); HR 0.96 (95% CI 0.89-1.04); p=0.37

Definite Myopathy:
53 (0.88%) vs 2 (0.03%); RRR 26.6% (95% CI 6.5% to 109.3%)
p<0.0001; ARI 0.85%; NNH ~118

Rhabdomyolysis:
7 (0.12%) vs 0 (0.0%)

Limitations:

- Primary endpoint changed during trial – clinical significance low (results consistent)
- Patient population must be considered – all had established cardiovascular disease

Level of Evidence: Level I – with minor limitations

Recommendation: For these reasons, I do not recommend the use of simvastatin 80 mg over simvastatin 20 mg for prevention of cardiovascular events in high-risk patients. Instead, I recommend the use of high-intensity statins, such as atorvastatin and rosuvastatin, for patients with established cardiovascular disease.

Efficacy:

- There was no significant difference in major vascular or major coronary event rates between groups
- Predictably, simvastatin 80 mg demonstrated greater reduction in total and LDL cholesterol compared to simvastatin 20 mg
    - However, the reduction was apparently insufficient to yield improved outcomes

Safety:

- Rates of myopathy were significantly higher in the simvastatin 80 mg group
- There were seven cases of rhabdomyolysis in the 80 mg group and zero in the 20 mg group

Cost:

- The cost of using simvastatin 80 mg must be considered in addition to the increased costs of monitoring for and managing myopathy and rhabdomyolysis

Special Considerations/Populations:

- Simvastatin is a not a high-intensity statin at any dose
- There are notable drug interactions to consider when using simvastatin
    - Heavily metabolized via CYP3A4
    - Yields concerns for increased risk for myopathy (due to elevated drug levels)
- Simvastatin is considered to be the highest-risk statin for causing myopathy (most lipophilic)
- Other high-intensity statins are available that are less prone to drug-interactions and myopathy, such as rosuvastatin and atorvastatin
- This trial demonstrates a lack of increased efficacy with simvastatin 80 mg and concerns relating to tolerance and safety (e.g. myopathy, rhabdomyolysis).

Grade of Recommendation: **A**

SELECT

Lincoff AM, Brown-Frandsen K, Colhoun HM, et al. Semaglutide and cardiovascular outcomes in obesity without diabetes. *N Engl J Med*. Published online November 11, 2023: NEJMoa2307563.

Objective: To determine the effect of semaglutide on cardiovascular outcomes in overweight/obese patients with established cardiovascular disease and without diabetes.

Primary Efficacy Measure: Composite of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke (time to first event)

Secondary Efficacy Measures: (1) cardiovascular death (2) composite of cardiovascular death and hospitalization or urgent medical visit for heart failure (3) all-cause mortality

Participants: Overweight/obese patients with established cardiovascular disease but without diabetes

- Age ~62 years; male ~73%
- BMI ~33; body weight ~97 kg (~213 lbs)
- Qualifying event: myocardial infarction only ~68%; stroke only ~18%
- BP ~131/79 mmHg; HR ~ 69 bpm; HgA1c ~5.78%
- Total cholesterol ~153 mg/dL; HDL ~44 mg/dL; LDL ~78 mg/dL
- Baseline antiplatelet ~86%; statin ~88%; beta-blocker ~70%; ACEi ~45%; ARB ~29%

Inclusion Criteria:

- Age ≥ 45 years and BMI ≥ 27
- Established cardiovascular disease (myocardial infarction, stroke or symptomatic PAD)

Exclusion Criteria:

- Diagnosis of diabetes or HgA1c ≥ 6.5%
- Use of glucose-lowering medication or GLP-1 RA within previous 90 days
- NYHA class IV heart failure
- End-stage renal disease or dialysis
- Cardiovascular or neurological event within previous 60 days
- Planned revascularization procedure

Drug: Semaglutide

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients were randomized to receive subcutaneous semaglutide or matching placebo once weekly. Dosing was started at 0.24 mg weekly and titrated every 4 weeks (0.5 mg, 1.0 mg, 1.7 mg) to a target of 2.4 mg weekly.

Duration: Mean follow-up period of ~40 months

Statistical Analysis: It was determined that 17,500 randomized patients and 1225 primary endpoints would provide 90% power (alpha=0.025). The ITT population was used for the efficacy analyses. If the primary endpoint was significantly lower with semaglutide the secondary efficacy endpoints would be tested in hierarchical order as listed above.

Results: A total of 17,604 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. At week 104, the average body weight reduction was -9.39% in the semaglutide group and -0.88% in the placebo group. HgA1c changed by -0.31% in the semaglutide group and by +0.01% in the placebo group.

While rates of the primary composite outcome were significantly lower in the semaglutide group, hierarchical testing of the secondary efficacy outcomes failed at cardiovascular death. Additional analysis of the secondary outcomes must be considered exploratory and be interpreted cautiously. Adverse events leading to permanent discontinuation were significantly higher in the semaglutide group than placebo, primarily due to gastrointestinal disorders (10% vs 2%; p<0.001) and gall-bladder related disorders (2.8% vs 2.3%; p=0.04). Malignant neoplasms occurred at similar rates between groups.

Semaglutide (N=8033) Vs Placebo (N=8801)

Primary Composite Outcome:
569 (7.08%) vs 701 (7.97%); HR 0.80 (95% CI 0.72-0.90)
p<0.001; ARR 0.88%; NNT ~114

Cardiovascular Death:
223 (2.78%) vs 262 (2.98%); HR 0.85 (95% CI 0.71-1.01); p=0.07

Non-Fatal Myocardial Infarction:
234 (2.91%) vs 322 (3.66%); HR 0.72 (95% CI 0.61-0.85)
ARR 0.75%; NNT ~135

Non-Fatal Stroke:
154 (1.92%) vs 165 (1.87%); HR 0.93 (95% CI 0.74-1.15)

Limitations:

- Patient population – cannot apply trial results to patients with diabetes or without cardiovascular disease

Level of Evidence: Level I – with minor limitations

Recommendation: For these reasons, I recommend the use of weekly semaglutide injections as a safe and effective weight loss therapy with clear cardiovascular benefit in overweight or obese patients with established cardiovascular disease but without diabetes.

Efficacy:

- Rates of the primary composite outcome were significantly lower in the semaglutide group
- Of the individual components of the composite outcome, only non-fatal myocardial infarction occurred at significantly lower rates compared to placebo

Safety:

- Rates of permanent discontinuation due to adverse effects were significantly higher with semaglutide, primarily due to gastrointestinal and gall-bladder related
- Rates of malignant neoplasm did not occur at significantly different rates between groups

Cost:

- The cost of using weekly subcutaneous semaglutide must be balanced against the cost-savings achieved from prevention cardiovascular morbidity and mortality outcomes

Special Considerations/Populations:

- This trial demonstrates cardiovascular benefit of GLP-1 RA therapy in patients without diabetes

Grade of Recommendation: **A**

SENIORS

Flather MD, Shibata MC, Coats AJ, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). *Eur Heart J*. 2005;26(3):215-225.

Objective: To determine the effect of nebivolol on morbidity and mortality outcomes in elderly patients with heart failure.

Primary Efficacy Measure: Composite of all-cause mortality or cardiovascular hospitalization

Participants: Elderly patients with heart failure (primarily reduced ejection fraction)

- Age ~76 years; male ~63%
- LVEF ~36%; HR ~79 bpm; BP ~139/81 mmHg
- NYHA class II ~56%; class III ~39%
- Baseline ACEi ~82%; diuretic ~86%; aldosterone antagonist ~27%

Inclusion Criteria:

- Age ≥ 70 years
- Chronic heart failure
    - LVEF ≤ 35% within previous 6 months, or
    - Heart failure hospitalization within previous 12 months

Exclusion Criteria:

- New heart failure therapy within previous 6 weeks
- Change in cardiovascular drug therapy within previous 2 weeks
- Heart failure due to uncorrected valvular disease
- Current use of beta-blocker
- Significant renal or hepatic dysfunction
- Cerebrovascular accident within previous 3 months

Drug: Nebivolol

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients were randomized to receive nebivolol or matching placebo. Dosing was started at 1.25 mg daily and was increased every 1-2 weeks (as tolerated) to a maximum dose of 10 mg daily.

Duration: Mean follow-up period of 21 months

Statistical Analysis: It was determined that 1700 randomized patients would achieve 90% power (alpha = 0.05). The ITT population was used for the primary efficacy analyses.

Results: A total of 2128 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. The average dose of nebivolol was 7.7 mg daily with ~68% of patients achieving the max daily dosage of 10 mg.

Nebivolol (N=1067) Vs Placebo (N=1061)

Composite of All-Cause Mortality or Cardiovascular Hospitalization:
332 (31.1%) vs 375 (35.3%); HR 0.86 (95% CI 0.74-0.99)
p=0.039; ARR 4.23%; NNT ~24

All-Cause Mortality:
169 (15.8%) vs 192 (18.1%); HR 0.88 (95% CI 0.71-1.08); p=0.21

Cardiovascular Hospitalization:
256 (24.0%) vs 276 (26.0%); HR 0.90 (95% CI 0.76-1.06); p=0.20

Safety:

Bradycardia:
118 (11.1%) vs 28 (2.64%)

Limitations:

- Patient population must be considered - all patients were of advanced age (> 70 years)
- Results cannot be extrapolated to other beta-blockers

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I do not recommend the use of nebivolol for reduction of morbidity and mortality outcomes in elderly patients with heart failure.

Efficacy:

- Rates of primary composite outcome were significantly lower in the nebivolol group compared to placebo
    - However, the individual rates of all-cause mortality and cardiovascular hospitalization were not significantly different between treatment groups

Safety:

- Rates of bradycardia were notably higher in the nebivolol group compared to placebo

Cost:

- The use of nebivolol must be balanced against the cost of using a beta-blocker with demonstrated morbidity and mortality benefit (metoprolol succinate, carvedilol, etc.)

Special Considerations/Populations:

- While there was no upper limit for ejection fraction in patients hospitalized for heart failure in the prior year, the vast majority of patients (~64%) had a baseline LVEF ≤ 35%
- The age of the patient population in this trial and dosage of nebivolol must be considered

Grade of Recommendation: **A**

SHEP

Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group. *JAMA*. 1991;265(24):3255-3264.

Objective: To determine the effect of antihypertensive treatment on rates of stroke in patients > 60 years old with isolated systolic hypertension.

Primary Efficacy Measure: Total stroke (fatal and non-fatal)

Participants: Patients > 60 years old with isolated systolic hypertension

- Age ~72 years; male ~42%
- BP ~170/77 mmHg; HR ~71 bpm

Inclusion Criteria:

- Age > 60 years
- SBP > 160 mmHg and < 219 mmHg
- DBP < 90 mmHg

Exclusion Criteria:

- History of major cardiovascular disease
- Cancer
- Alcoholic liver disease
- Renal dysfunction

Drugs: Chlorthalidone; atenolol

Design: Randomized, double-blind, placebo-controlled trial

Methods: Isolated systolic hypertension was defined as SBP > 160 mmHg and DBP < 90 mmHg. Patients were randomized into either active treatment or matching placebo groups. The goal SBP for individuals with baseline SBP > 180 mmHg was < 160 mmHg. Those with baseline SBP 160-179 mmHg had a goal SBP reduction of 20 mmHg or more. The active treatment group received chlorthalidone 12.5 mg daily for step 1 therapy. If the SBP goal wasn't achieved at the follow-up visit the dose was doubled to 25 mg daily. Atenolol 25 mg (or matching placebo) would be added for those still failing to achieve the goal BP with step 1 therapy. Atenolol was allowed to be doubled in patients above their SBP goal at follow-up visits.

Duration: Average follow-up period of 4.5 years

Statistical Analysis: It was determined that 4800 randomized patients would achieve 90% power (alpha = 0.05). The ITT population was used for primary efficacy analyses.

Results: A total of 4736 patients underwent randomization. Baseline patient characteristics were similar between treatment groups with the exception of "no limitation of activities of daily living" which was significantly higher in the active treatment group. At year 5, the average blood pressure was ~144/68 mmHg in the active treatment group and ~155/71 mmHg in the placebo group. Approximately half of the active treatment group was receiving chlorthalidone only. Overall, abnormal serum biochemical values were more common in the active treatment group.

Active Treatment (N=2365) Vs Placebo (N=2371)

Total Stroke:
103 (4.36%) vs 159 (6.71%); RR 0.64 (95% CI 0.50-0.82)
p=0.0003; ARR 2.34%; NNT ~43

Fatal Stroke:
10 (0.42%) vs 14 (0.59%); RR 0.71 (95% CI 0.31-1.59)

Non-Fatal Stroke:
96 (4.06%) vs 149 (6.28%); RR 0.63 (95% CI 0.49-0.82)
ARR 2.23%; NNT ~45

Fatal Myocardial Infarction:
15 (0.63%) vs 26 (1.10%); RR 0.57 (95% CI 0.30-1.08)

Non-Fatal Myocardial Infarction:
50 (2.11%) vs 74 (3.12%); RR 0.67 (95% CI 0.47-0.96)
ARR 1.01%; NNT ~100

Limitations:

- Patient population must be considered - all had isolated systolic hypertension
- Patient age must be considered - all over 60 years old

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I recommend the use of antihypertensive therapy (specifically chlorthalidone) to reduce stroke event rates in elderly patients with isolated systolic hypertension.

Efficacy:

- Rates of total stroke (and non-fatal stroke) were significantly lower in the active treatment group compared to placebo
- Non-fatal myocardial infarction occurred at significantly lower rates in the active treatment group

Safety:

- Abnormal laboratory values were more common in the active treatment group compared to placebo

Cost:

- The cost of using chlorthalidone with/without atenolol must be balanced against the cost-savings of preventing a cardiovascular event, primarily non-fatal stroke

Special Considerations/Populations:

- Results cannot be applied to younger demographic or those without isolated systolic hypertension

Grade of Recommendation: **A**

SHIFT

Swedberg K, Komajda M, Böhm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomized placebo-controlled study. *Lancet*. 2010;376(9744):875-885.

Objective: To determine the effect of ivabradine on morbidity and mortality outcomes in heart failure patients with reduced ejection fraction.

Primary Efficacy Measure: Composite of cardiovascular death or heart failure hospitalization

Participants: Patients with heart failure and reduced ejection fraction with raised resting heart rate despite use of max tolerated beta-blocker dose

- Age ~60 years; male ~76%
- LVEF ~29%; BP ~122/76 mmHg; HR ~80 bpm
- NYHA class II ~49%; class III ~50%
- Beta-blocker ~89%; ACEi ~78%; diuretic ~83%; aldosterone antagonist ~60%

Inclusion Criteria:

- Age ≥ 18 years
- Sinus rhythm and resting HR ≥ 70 bpm
- Stable symptomatic chronic heart failure for 4 weeks
- LVEF ≤ 35%
- Heart failure hospitalization within previous 12 months
- Stable on optimal standard therapy for 4 weeks

Exclusion Criteria:

- Myocardial infarction within previous 2 months
- Atrial fibrillation or flutter
- Symptomatic hypotension
- Ventricular/atrioventricular pacing for 40% or more per day

Drug: Ivabradine

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients were required to be on optimized standard heart failure therapy for at least 4 weeks prior to randomization. Use of non-DHP CCBs (diltiazem, verapamil, etc.), class I antiarrhythmic drugs and strong 3A4 inhibitors were not allowed during the trial. All patients underwent a two week run-in period of ivabradine 5 mg twice daily. Following the run-in period patients were randomized to receive ivabradine or matching placebo. The ivabradine dose was increased to 7.5 mg twice daily (unless resting HR ≤ 60 bpm).

Duration: Median follow-up period of ~23 months

Statistical Analysis: It was determined that 6500 randomized patients and 1600 primary events would achieve 90% power (alpha = 0.05). The ITT population was used for all primary analyses.

Results: A total of 6558 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. Only ~26% of patients were receiving target beta-blocker dosing at baseline, primarily due to hypotension and fatigue. The average ivabradine dosing after year one was ~6.5 mg twice daily. Overall, the average HR for each treatment group was ~75 bpm in the placebo group and ~67 bpm in the ivabradine group (average difference of ~8.1 bpm). The effect of ivabradine was consistent across subgroup analyses except for heart rate, where the treatment effect was only significant in those with a baseline HR of 77 bpm or higher. Discontinuation rates due to bradycardia (symptomatic and asymptomatic) was significantly higher in the ivabradine group.

Ivabradine (N=3241) Vs Placebo (N=3264)

Composite of Cardiovascular Death or Heart Failure Hospitalization:
793 (24.5%) vs 937 (28.7%); HR 0.82 (95% CI 0.75-0.90)
p<0.0001; ARR 4.24%; NNT ~24

Cardiovascular Death:
449 (13.9%) vs 491 (15.0%); HR 0.91 (95% CI 0.80-1.03); p=0.128

Heart Failure Hospitalization:
514 (15.9%) vs 672 (20.6%); HR 0.74 (95% CI 0.66-0.83)
p<0.0001; ARR 4.73%; NNT ~22

Heart Failure Death:
113 (3.49%) vs 151 (4.63%); HR 0.74 (95% CI 0.58-0.94)
p=0.014; ARR 1.14%; NNT ~88

NYHA Functional Class Improvement:
887 (27.4%) vs 776 (23.8%); p=0.001; ARR 3.59%; NNT ~28

Safety:

Symptomatic Bradycardia:
150 (4.63%) vs 32 (0.98%); p<0.0001; ARI 3.66%; NNH ~27

Atrial Fibrillation:
306 (9.44%) vs 251 (7.69%); p=0.012; ARI 1.77%; NNH ~57

Phosphenes (transient visual abnormality):
89 (2.75%) vs 17 (0.52%); p<0.0001; ARI 2.23%; NNH ~44

Limitations:

- Results must be considered in addition to standard heart failure therapy
- All patients had raised resting HR and sinus rhythm (no atrial fibrillation patients included)

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I recommend the use of ivabradine (in addition to standard heart failure therapy) to further reduce morbidity rates and improve functional status in heart failure patients with reduced ejection fraction and elevated resting heart rate.

Efficacy:

- The rates of the primary composite outcome were significantly lower in the ivabradine group compared to placebo (however, only the individual component of heart failure hospitalization was significantly reduced - no significant difference in mortality rates)
- Rates of heart failure death were significantly lower in the ivabradine group
- Significantly more patients saw NYHA class improvement with ivabradine

Safety:

- Rates of atrial fibrillation and discontinuation due to bradycardia were significantly higher in the ivabradine group

Cost:

- The cost of using ivabradine must be balanced against the cost-savings of preventing heart failure hospitalizations

Special Considerations/Populations:

- Patients were receiving max tolerated beta-blocker dose and had elevated resting heart rate
- Cannot extrapolate treatment results to patients with preserved ejection fraction

Grade of Recommendation: **A**

SOCRATES

Johnston SC, Amarenco P, Albers GW, et al. Ticagrelor versus Aspirin in Acute Stroke or Transient Ischemic Attack. *N Engl J Med*. 2016;375(1):35-43.

Objective: To determine the efficacy of ticagrelor compared to aspirin for prevention of TIA/stroke in patients after acute cerebral ischemia.

Primary Efficacy Measure: Composite of stroke, myocardial infarction or death

Secondary Efficacy Measure: Ischemic stroke

Primary Safety Measure: Major bleeding

Participants: Patients with acute stroke/TIA

- Age ~66 years; male ~58%
- Qualifying event ischemic stroke ~73%; TIA ~27%

Inclusion Criteria:

- Acute ischemic stroke (with NIHSS score ≤ 5) or high-risk TIA (with $ABCD^2$ score ≥ 4)
  - NIHSS scores range from 0-42 (higher score, more severe stroke)
  - $ABCD^2$ scores range from 0-7 (higher score, higher risk for stroke)
- Randomized within 24 hours of symptom onset
- Age ≥ 40 years
- Intracranial bleeding ruled out via MRI/CT scan

Exclusion Criteria:

- Antiplatelet/anticoagulant therapy planned
- Revascularization surgery planned
- Under suspicion that TIA/stroke was of cardioembolic origin
- Gastrointestinal bleed within prior 6 months
- Major surgery within 30 days
- Severe liver disease or receiving dialysis

Drugs: Ticagrelor; aspirin

Design: Randomized, double-blind, active-controlled trial

Methods: Eligible patients were randomized within 24 hours of symptom onset to receive either ticagrelor or aspirin, plus matching placebo. Loading doses were used in both groups (180 mg ticagrelor and 300 mg aspirin) followed by either ticagrelor 90 mg twice daily or aspirin 100 mg daily.

Duration: 90 days

Statistical Analysis: It was determined that 844 primary events were required to achieve 88.7% power for the primary efficacy outcome (alpha = 0.0498). The secondary efficacy outcome (ischemic stroke) would only be tested if there was a significant difference in the primary efficacy outcome. The ITT population was used for the efficacy analyses.

Results: A total of 13,307 patients underwent randomization. Baseline patient characteristics were similar between treatment groups except for history of hypertension (higher in aspirin group) and history of diabetes (higher in ticagrelor group). Dyspnea was more common in the ticagrelor group compared to aspirin (6.2% vs 1.4%, respectively).

Ticagrelor (N=6589) Vs Aspirin (N=6610)

Primary Composite Outcome:
442 (6.71%) vs 497 (7.52%); HR 0.89 (95% CI 0.78-1.01); p=0.07

Ischemic Stroke:
385 (5.84%) vs 441 (6.67%); HR 0.87 (95% CI 0.76-1.00); p=0.046
Cannot be considered statistically significant due to failure of hierarchical testing

Myocardial Infarction:
25 (0.38%) vs 21 (0.32%); HR 1.20 (95% CI 0.67-2.14); p=0.55

Death:
68 (1.03%) vs 58 (0.88%); HR 1.18 (95% CI 0.83-1.67); p=0.36

Major Bleeding:
31 (0.47%) vs 38 (0.57%); HR 0.83 (95% CI 0.52-1.34); p=0.45

Limitations:

- Trial duration must be considered - 90 day period may not have been sufficient to observe true treatment difference
- Patient population must be considered - all had acute TIA/stroke with no evidence of intracranial bleeding

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I do not recommend ticagrelor over aspirin for secondary prevention in patients with acute cerebrovascular event due to lack of improved efficacy or safety.

Efficacy:

- There was no significant difference in rates of the primary composite outcome between treatment groups
- The rates of individual components of the composite outcome were not significantly different between treatment groups

Safety:

- There was no significant difference in the rates of major bleeding between treatment groups

Cost:

- The cost of using ticagrelor must be balanced against the cost of using aspirin

Special Considerations/Populations:

- Dosing of aspirin used in this trial must be considered - 100 mg daily

Grade of Recommendation: **A**

SOLOIST-WHF

Bhatt DL, Szarek M, Steg PG, et al. Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure. *N Engl J Med*. 2021;384(2):117-128.

Objective: To determine the safety and efficacy of sotagliflozin in patients with type 2 diabetes and heart failure recently hospitalized for acute decompensation.

Primary Efficacy Measure: Total cardiovascular deaths and heart failure hospitalization/urgent visits

- Changed from first occurrence of cardiovascular death or heart failure hospitalization due to funding loss

Secondary Efficacy Measures: (1) Total heart failure hospitalizations/urgent visits (2) cardiovascular death

Participants: Patients with type 2 diabetes and heart failure hospitalized for acute decompensation

- Age ~69 years; male ~67%
- HgA1c ~7.1%; LVEF ~35%
- ACEi ~40%; ARB ~42%; beta-blocker ~92%; MRA ~64%; loop diuretic ~95%

Inclusion Criteria:

- Age 18-85 years with type 2 diabetes
- Hospitalization for heart failure and treatment with IV loop diuretics
- Heart failure diagnosis ≥ 3 months previously
- Chronic treatment with loop diuretic for ≥ 30 days prior to qualifying event
- BNP ≥ 150 pg/mL at time of randomization

Exclusion Criteria:

- Clinically unstable at time of randomization
- End-stage heart failure
- Recent acute coronary syndrome, stroke, PCI/CABG
- eGFR < 30 mL/min

Drug: Sotagliflozin

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients were randomized to receive sotagliflozin 200 mg once daily or matching placebo. The first dose was given before or within 3 days of hospital discharge. The sotagliflozin dose could be increased to 400 mg daily, if tolerated.

Duration: Median follow-up period of 9 months

Statistical Analysis: It was initially determined that 4000 randomized patients and 1341 primary events would provide 90% power (alpha = 0.05). The ITT population was used for all efficacy analyses. Hierarchical sequential testing was specified for the secondary endpoints of total heart failure hospitalizations/urgent visits and cardiovascular death.

Results: A total of 1222 patients underwent randomization before enrollment was terminated due to loss of funding. Baseline patient characteristics were similar between treatment groups. The initial primary composite outcome demonstrated similar results as the revised composite outcome which indicates that the demonstrated benefit of sotagliflozin in this trial lies primarily with reduction of heart failure hospitalization, not cardiovascular death (HR 0.71; 95% CI 0.56-0.89). Rates of diabetic ketoacidosis were similar between groups, however diarrhea, urinary tract infections and severe hypoglycemia were more common with sotagliflozin.

Sotagliflozin (N=608) Vs Placebo (N=614)

Total Number of Cardiovascular Deaths and Heart Failure Hospitalization/Urgent Visits:
245 vs 355; HR 0.67 (95% CI 0.52-0.85); p<0.001

Total Heart Failure Hospitalizations and Urgent Visits:
194 vs 297; HR 0.64 (95% CI 0.49-0.83); p<0.001

Cardiovascular Death:
51 (8.39%) vs 58 (9.45%); HR 0.84 (95% CI 0.58-1.22); p=0.36

Diabetic Ketoacidosis:
2/605 (0.33%) vs 4/611 (0.65%)

Severe Hypoglycemia:
9/605 (1.49%) vs 2/611 (0.33%)

Urinary Tract Infection:
52/605 (8.60%) vs 44/611 (7.20%)

Diarrhea:
42/605 (6.94%) vs 25/611 (4.09%)

Limitations:

- Loss of funding led to substantially reduced patient enrollment and failure to meet power requirements (clinical significance uncertain; significant differences still detected)
- Patient population - patients with type 2 diabetes and heart failure with hospitalization due to decompensation (sotagliflozin started before or within 3 days of discharge)

Level of Evidence: Level II - with major limitations

Recommendation: For these reasons, I recommend the use of sotagliflozin (in addition to standard therapy) to further reduce morbidity outcomes in patients with type 2 diabetes and heart failure with recent hospitalization due to decompensation.

Efficacy:

- The revised primary composite outcome occurred significantly less often in the sotagliflozin group compared to placebo, however this benefit was driven primary by reductions in hospitalizations
    - Rates of heart failure hospitalizations/urgent visits were significantly lower in the sotagliflozin group
- There was no significant difference in the rates of cardiovascular deaths between groups
- The initial primary composite outcome (first occurrence of cardiovascular death or heart failure hospitalization) demonstrated similar benefit as the revised outcome, indicating that the demonstrated benefit of sotagliflozin was primarily due to reduced heart failure hospitalization

Safety:

- While rates of diabetic ketoacidosis were similar between groups, severe hypoglycemia and urinary tract infections occurred more often in the sotagliflozin group

Cost:

- The cost of using sotagliflozin must be balanced against the cost-savings of reduced heart failure hospitalizations
- However, the cost of treating severe hypoglycemic events and UTIs must also be considered

Special Considerations/Populations:

- Sotagliflozin is a dual SGLT1/2 inhibitor - SGLT1 inhibition delays intestinal glucose absorption
- Primary endpoint is a composite of the first and all subsequent events (not just first event)
- While the trial did allow for heart failure patients with preserved and reduced ejection fraction, the majority of patients did not have preserved ejection fraction (~79%)
- Trial duration of ~9 months may be insufficient to demonstrate true treatment effect of sotagliflozin (additional trials of longer duration are warranted)

Grade of Recommendation: **B**

SOLVD

SOLVD Investigators, Yusuf S, Pitt B, Davis CE, Hood WB, Cohn JN. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med*. 1991;325(5):293-302.

Objective: To determine the effect of enalapril on mortality outcomes in patients with heart failure and reduced ejection fraction.

Primary Efficacy Measure: All-cause mortality

Participants: Patients with heart failure and reduced ejection fraction

- Age ~61 years; male ~80%
- LVEF ~25%
- NYHA class II ~57%; class III ~30%; class IV ~2%
- BP ~125/77 mmHg; HR ~80 bpm
- Digoxin ~67%; diuretics ~85%; beta-blockers ~7%

Inclusion Criteria:

- Congestive heart failure (symptomatic)
- LVEF ≤ 35%
- Receiving conventional therapy for heart failure (other than ACEi)

Exclusion Criteria:

- Age > 80 years
- Valvular disease requiring surgery
- Unstable angina pectoris
- Myocardial infarction in previous 30 days
- Severe pulmonary disease
- SCr > 2.0 mg/dL

Drug: Enalapril

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients underwent a run-in period where all received enalapril 2.5 mg twice daily for 2-7 days to assess tolerance and adherence. Following that, all patients received matching placebo for 14-17 days to identify those with worsening clinical conditions. Patients that successfully completed the entire run-in period were randomized to receive enalapril or matching placebo. The dosing of enalapril was started at 2.5 mg twice daily or 5 mg twice daily and was to be titrated up to a maximum of 10 mg twice daily (or max tolerated dosage).

Duration: Average follow-up period of 41.4 months

Statistical Analysis: It was determined that 2500 randomized patients would achieve 90% power (one-sided alpha=0.025).

Results: A total of 2569 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. At the final visit, the average dose of enalapril was 16.6 mg daily with the majority of patients (49.3%) taking 10 mg twice daily. The adverse drug reactions of dizziness/fainting and cough occurred at significantly higher rates in the enalapril group compared to placebo. Rates of angioedema were not significantly different between treatment groups. Elevations in serum creatinine and potassium levels were more common in the enalapril group.

Enalapril (N=1285) Vs Placebo (N=1284)

All-Cause Mortality:
452 (35.2%) vs 510 (39.7%); RRR 16% (95% CI 5% to 26%)
p<0.0036; ARR 4.54%; NNT ~22

Cardiovascular Death:
399 (31.1%) vs 461 (35.9%); RRR 18% (95% CI 6% to 28%)
p<0.002; ARR 4.85%; NNT ~21

Worsening Heart Failure Death:
209 (16.3%) vs 251 (19.5%); RRR 22% (95% CI 6% to 35%)
p<0.0045; ARR 3.28%; NNT ~31

First Heart Failure Hospitalization:
332 (25.8%) vs 470 (36.6%); p<0.001; ARR 10.8%; NNT ~10

Total Hospitalizations:
683 vs 971

Limitations:

- Cannot extrapolate results to patients with heart failure and preserved ejection fraction

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I recommend the use of enalapril to further reduce morbidity and mortality outcomes in patients with heart failure and reduced ejection fraction.

Efficacy:

- Rates of all-cause mortality, cardiovascular death and death from worsening heart failure were all significantly lower in the enalapril group compared to placebo
- Hospitalizations were notably lower in the enalapril group

Safety:

- Serum creatinine and potassium elevations were more frequent in the enalapril group
- Rates of dizziness/fainting and cough were significantly higher in the enalapril group

Cost:

- The cost of using enalapril must be balanced against the cost-savings of preventing morbidity and mortality outcomes in patients with heart failure

Special Considerations/Populations:

- Patient population must be considered - all patients had reduced ejection fraction

Grade of Recommendation: **A**

SONIC

Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med*. 2010;362(15):1383-1395.

Objective: To determine the efficacy and safety of infliximab and azathioprine as monotherapy and in combination for inducing and maintaining remission in patients with active Crohn's disease.

Primary Efficacy Measure: Corticosteroid-free clinical remission at 26 weeks

- Clinical remission defined as CDAI score < 150
- Corticosteroid-free clinical remission defined as < 6 mg/day budesonide and no systemic corticosteroids for ≥ 3 weeks

Participants: Crohn's disease patients with moderate-to-severe symptoms

- Age ~34 years; male ~52%
- CDAI score ~287
- Area of GI tract involved: ileum or colon ~98%
  - Ileum only ~35%; colon only ~24%; ileum and colon ~41%
- Baseline corticosteroid use ~27%

Inclusion Criteria:

- Age ≥ 21 years
- Presence of Crohn's disease ≥ 6 weeks
- Crohn's Disease Activity Index (CDAI) score 220-450
  - Severe disease: > 450; remission: < 150
- Corticosteroid-dependent, under consideration for second course of corticosteroids within 12 months, or unresponsive to ≥ 4 weeks of mesalamine (≥ 2.4 grams/day) or budesonide (≥ 6 mg/day)

Exclusion Criteria:

- Prior treatment with azathioprine, 6-mercaptopurine, methotrexate or an anti-TNF biologic
- Short bowel syndrome, stricture, abscess or recent GI surgery (within previous 6 months)
- History of tuberculosis
- Opportunistic infection within previous 6 months
- Active hepatitis B or C infection
- HIV infection
- Multiple sclerosis

Drugs: Infliximab; azathioprine

Design: Randomized, double-blind, active-controlled trial

Methods: Eligible patients were randomized to receive intravenous infliximab 5 mg/kg plus oral placebo, oral azathioprine 2.5 mg/kg daily plus placebo infusions, or combination therapy of infliximab and azathioprine. The infliximab infusions were given at weeks 0, 2, 6 and then every 8 weeks thereafter. Use of oral mesalamine, budesonide and systemic corticosteroids was allowed. Ileocolonoscopy was performed at baseline and repeated at 26 weeks.

Duration: 26 weeks

Statistical Analysis: It was determined that 500 randomized patients would provide 95% power (alpha=0.05). The primary efficacy analysis was performed sequentially: azathioprine vs combination therapy, then azathioprine vs infliximab (only if first analysis achieved statistical significance). The ITT population was used for the efficacy analysis. The modified ITT population (all randomized patients that received at least one dose of study drug) was used for the safety analysis.

Results: A total of 508 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. Combination therapy with oral azathioprine and intravenous infliximab demonstrated superiority to oral azathioprine alone for the primary efficacy outcome. Likewise, intravenous infliximab demonstrated superiority to oral azathioprine. It is worth noting that this trial did not specify testing for infliximab versus combo therapy (however, results are included below). Significantly more patients demonstrated mucosal healing in the combination and infliximab groups compared to oral azathioprine alone. Adverse event rates were generally similar across treatment groups with the exception of infusion reactions, which was significantly higher in the infliximab monotherapy group.

Azathioprine (N=170) Vs Combo Therapy (N=169)

Corticosteroid-free Clinical Remission at 26 weeks:
51 (30.0%) vs 96 (56.8%); OR 3.1 (95% CI 2.0-4.9)
p<0.001; ARR 26.8%; NNT ~4

Azathioprine (N=170) Vs Infliximab (N=169)

Corticosteroid-free Clinical Remission at 26 weeks:
51 (30.0%) vs 75 (44.4%); OR 1.9 (95% CI 1.2-2.9)
p=0.006; ARR 14.4%; NNT ~7

Infliximab (N=169) Vs Combo Therapy (N=169)

Corticosteroid-free Clinical Remission at 26 weeks:
75 (44.4%) vs 96 (56.8%); OR 1.7 (95% CI 1.1-2.6)
p=0.02; ARR 12.4%; NNT ~8

Limitations:

- Patient population – Crohn's disease patients with moderate-to-severe symptoms
- Sample size relatively small (clinical significance uncertain)

Level of Evidence: Level I – with minor limitations

Recommendation: For these reasons, I recommend the use of infliximab infusions plus oral azathioprine over infliximab and azathioprine monotherapy treatment strategies to achieve and maintain steroid-free clinical remission in patients with moderate-to-severe Crohn's disease.

Efficacy:

- Combination therapy achieved significantly greater rates of steroid-free clinical remission compared to oral azathioprine alone
- Infliximab infusion monotherapy demonstrated significantly greater rates of steroid-free clinical remission compared to oral azathioprine alone
- Mucosal healing was significantly greater in the combination and infliximab groups compared to oral azathioprine

Safety:

- Adverse reactions were generally similar across treatment groups, however, infusion reactions were significantly higher in the infliximab monotherapy group

Cost:

- The cost of using combination therapy over infliximab or azathioprine monotherapy must be balanced against the cost-savings of avoiding disease complications

Special Considerations/Populations:

- Crohn's disease involves chronic inflammation of the gastrointestinal tract
- The patient population included in this trial had moderate-to-severe symptoms

Grade of Recommendation: **A**

SPARCL

Amarenco P, Bogousslavsky J, Callahan A 3rd, et al. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med*. 2006;355(6):549-559.

Objective: To determine the effect of high-intensity statin therapy on secondary stroke prevention in patients with no known coronary heart disease.

Primary Efficacy Measure: First fatal or nonfatal stroke

Secondary Efficacy Measures: (1) Stroke or TIA (2) major coronary event (cardiovascular death, non-fatal myocardial infarction, resuscitation after cardiac arrest) (3) major cardiovascular event (stroke plus any major coronary event) (4) acute coronary event (5) any coronary event (6) revascularization (7) any cardiovascular event

Participants: Patients with recent stroke or TIA (without known coronary heart disease)

- Age ~63 years; male ~60%
- BP ~139/82 mmHg
- Ischemic stroke ~66%; hemorrhagic stroke ~2%; TIA ~31%
- Time from initial event ~86 days
- LDL ~133 mg/dL; HDL ~50 mg/dL; total cholesterol ~211 mg/dL
- Baseline antiplatelet ~87%; ACEi ~28%; beta-blocker ~18%

Inclusion Criteria:

- Age ≥ 18 years
- Ischemic stroke, hemorrhagic stroke or TIA within previous 1-6 months
    - Those with hemorrhagic stroke were only included if they were thought to be at risk for coronary heart disease or ischemic stroke
- Ambulatory (modified Rankin score ≤ 3)
- LDL ≥ 100 mg/dL and < 190 mg/dL

Exclusion Criteria:

- Atrial fibrillation
- Cardiac source of embolism
- Subarachnoid hemorrhage
- Pregnancy or breastfeeding
- Active liver disease or hepatic dysfunction

Drug: Atorvastatin

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients were required to stop any lipid-lowering therapy 30 days prior to the initial screening. Patients were then randomized to receive atorvastatin 80 mg or placebo. All patients were recommended to follow the NCEP Step 1 diet during the trial.

Duration: Median follow-up period of 4.9 years

Statistical Analysis: It was determined that 4200 randomized patients and 540 primary events would provide 90% power (alpha=0.048). The ITT population was used for the efficacy analyses.

Results: A total of 4731 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. Average LDL levels during the trial were 72.9 mg/dL in the atorvastatin group and 128.5 mg/dL in the placebo group. Average HDL levels during the trial were 52.1 mg/dL in the atorvastatin group and 51.0 mg/dL in the placebo group. Average total cholesterol levels during the trial were 147.2 mg/dL in the atorvastatin group and 208.4 mg/dL in the placebo group. There was one event of resuscitation after cardiac arrest in each group.

Post hoc analysis demonstrated a significant difference in treatment effect according to the type of stroke that occurred. Cases of rhabdomyolysis were infrequent, but occurred at similar rates between groups. Persistent elevation in liver function enzymes (> 3 times ULN) was more common in the atorvastatin group compared to placebo (2.2% vs 0.5%, p<0.001). No cases of liver failure were reported.

Atorvastatin (N=2365) Vs Placebo (N=2366)

First Fatal or Non-Fatal Stroke:
265 (11.2%) vs 311 (13.1%); HR 0.84 (95% CI 0.71-0.99)
p=0.03; ARR 1.94%; NNT ~52

Ischemic Stroke:
218 (9.22%) vs 274 (11.6%); HR 0.78 (95% CI 0.66-0.94)

Hemorrhagic Stroke:
55 (2.33%) vs 33 (1.39%); HR 1.66 (95% CI 1.08-2.55)

Non-Fatal Stroke:
247 (10.4%) vs 280 (11.8%); HR 0.87 (95% CI 0.73-1.03); p=0.11

Fatal Stroke:
24 (1.01%) vs 41; HR 0.57 (95% CI 0.35-0.95)
p=0.03; ARR 0.72%; NNT ~140

Transient Ischemic Attack:
153 (6.47%) vs 208 (8.79%); HR 0.74 (95% CI 0.60-0.91)
p=0.004; ARR 2.32%; NNT ~44

Cardiovascular Death:
40 (1.69%) vs 39 (1.65%); HR 1.00 (95% CI 0.64-1.56); p=1.00

Non-Fatal Myocardial Infarction:
43 (1.82%) vs 82 (3.47%); HR 0.51 (95% CI 0.35-0.74)
p<0.001; ARR 1.65%; NNT ~61

Acute Coronary Event:
101 (4.27%) vs 151 (6.38%); HR 0.65 (95% CI 0.50-0.84)
p=0.001; ARR 2.11%; NNT ~48

Revascularization:
94 (3.97%) vs 163 (6.89%); HR 0.55 (95% CI 0.43-0.72)
p<0.001; ARR 2.91%; NNT ~35

Limitations:

- Patient population – cannot extrapolate results to those with known coronary heart disease
- Dose of atorvastatin used in this trial must be considered when interpreting results

Level of Evidence: Level I – with minor limitations

Recommendation: For these reasons, I recommend the use of atorvastatin 80 mg for secondary prevention of ischemic stroke or transient ischemic attack in patients with no known history of coronary artery disease.

Efficacy:

- The atorvastatin group demonstrated significantly lower rates of fatal or non-fatal stroke
    - Individual rates of fatal stroke were significantly lower in the atorvastatin group
    - *Post hoc analysis* demonstrated an imbalance in the treatment benefit of atorvastatin according to the type of stroke (lower rates with ischemic stroke, higher rates with hemorrhagic stroke)
- Rates of transient ischemic attack, non-fatal myocardial infarction, acute coronary event and revascularization occurred at significantly lower rates in the atorvastatin group
- Rates of cardiovascular death were similar between groups

Safety:

- Cases of rhabdomyolysis were infrequent, but occurred at similar rates between groups
- Persistent elevation in liver function enzymes (> 3 times ULN) was more common in the atorvastatin group compared to placebo
    - No cases of liver failure were reported

Cost:

- The cost of using atorvastatin 80 mg daily must be balanced against the cost-savings achieved from lower rates of morbidity and mortality outcomes
- The cost of routing lipid panels must also be considered

Special Considerations/Populations:

- Patients included in this trial did not have known history of coronary artery disease
- The primary outcome of this trial must be considered in terms of secondary stroke prevention
- Risk of stroke is related to LDL level, therefore routine monitoring for adequate LDL reduction is necessary while using atorvastatin

Grade of Recommendation: **A**

SPRINT

SPRINT Research Group, Wright JT Jr, Williamson JD, et al. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. *N Engl J Med*. 2015;373(22):2103-2116.

Objective: To determine the effect of intensive blood pressure control compared to standard blood pressure control on cardiovascular outcomes in patients without diabetes.

Primary Efficacy Measure: Composite of cardiovascular death, myocardial infarction, acute coronary syndrome, stroke or heart failure

Participants: Patients with hypertension without diabetes or previous stroke

- Age ~68 years; male ~64%
- BP ~140/78 mmHg
- Established cardiovascular disease at baseline ~20%
- Framingham 10-year cardiovascular risk score ~25%

Inclusion Criteria:

- Age > 50 years
- SBP 130-180 mmHg
- Increased risk of cardiovascular events (one or more of the following):
    - Clinical/subclinical cardiovascular disease other than stroke
    - Chronic kidney disease (eGFR 20 mL/min to less than 60 mL/min)
    - Framingham 10-year cardiovascular risk score > 15%
    - Age > 75 years

Exclusion Criteria:

- Prior stroke
- Diabetes

Drug: n/a

Design: Randomized, open-label, active-controlled trial

Methods: Eligible patients were randomized to either standard blood pressure therapy (target SBP < 140 mmHg) or intensive pressure therapy (target SBP < 120 mmHg). After randomization, hypertension treatments were adjusted accordingly. Investigators were allowed to prescribe any antihypertensive medication(s) but were encouraged to use those with the strongest evidence in reducing cardiovascular events. Thiazide diuretics were encouraged as first line agents (with preference for chlorthalidone). Medications were adjusted to achieve target blood pressure goals (SBP < 120 mmHg for intensive therapy; SBP 135-139 mmHg for standard therapy). Medication dosages were reduced in the standard therapy group if SBP went < 130 mmHg.

Duration: Median follow-up period of 3.26 years

Statistical Analysis: It was determined that 9250 randomized patients would achieve 88.7% power (alpha=0.05). The ITT population was used for all analyses.

Results: A total of 9361 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. The trial was stopped early at the recommendation of the safety committee due to the demonstrated benefit of intensive therapy over standard therapy. The average SBP was 121.5 mmHg in the intensive therapy group and 134.6 mmHg in the standard therapy group. The average number of antihypertensive medications was ~2.8 in the intensive therapy group and ~1.8 in the standard therapy group.

Intensive Therapy (N=4678) Vs Standard Therapy (N=4683)

Primary Composite Outcome:
243 (5.19%) vs 319 (6.81%); HR 0.75 (95% CI 0.64-0.89)
p<0.001; ARR 1.62%; NNT ~62

Cardiovascular Death:
37 (0.79%) vs 65 (1.39%); HR 0.57 (95% CI 0.38-0.85)
p=0.005; ARR 0.60%; NNT ~168

Myocardial Infarction:
97 (2.07%) vs 116 (2.48%); HR 0.83 (95% CI 0.64-1.09); p=0.19

Acute Coronary Syndrome:
40 (0.86%) vs 40 (0.85%); HR 1.00 (95% CI 0.64-1.55); p=0.99

Stroke:
62 (1.33%) vs 70 (1.49%); HR 0.89 (95% CI 0.63-1.25); p=0.50

Heart Failure:
62 (1.33%) vs 100 (2.14%); HR 0.62 (95% CI 0.45-0.84)
p=0.002; ARR 0.81%; NNT ~124

All-Cause Mortality:
155 (3.31%) vs 210 (4.48%); HR 0.73 (95% CI 0.60-0.90)
p=0.003; ARR 1.17%; NNT ~86

Safety:

Hypotension:
110 (2.35%) vs 66 (1.41%); p=0.001; ARI 0.94%; NNH ~106

Syncope:
107 (2.29%) vs 80 (1.71%); p=0.05

Electrolyte Abnormalities:
144 (3.08%) vs 107 (2.28%); p=0.02; ARI 0.79%; NNH ~126

Acute Kidney Injury/Acute Renal Failure:
193 (4.13%) vs 117 (2.50%); p<0.001; ARI 1.63%; NNH ~61

≥ 30% Reduction in GFR to <60 mL (in patients without baseline CKD):
127/3332 (3.81%) vs 37/3345 (1.11%); HR 3.49 (95% CI 2.44-5.10)
p<0.001; ARI 2.71%; NNH ~37

Limitations:

- Open-label trial design
- Patient population must be considered - patients with diabetes were not included

Level of Evidence: Level I - with major limitations

Recommendation: For these reasons, I recommend the use of intensive blood pressure control (SBP < 120 mmHg) over standard blood pressure control (SBP < 140 mmHg) to reduce cardiovascular morbidity and mortality in patients without diabetes or prior stroke. However, the risk for adverse outcomes due to intensive antihypertensive therapy must be considered for each patient.

Efficacy:

- Rates of the primary composite outcome were significantly lower in the intensive blood pressure group compared to standard therapy
- The individual rates of cardiovascular death and heart failure were significantly lower in the intensive therapy group
- All-cause mortality was significantly lower in the intensive therapy group compared to standard therapy

Safety:

- Adverse drug reactions of hypotension, syncope and electrolyte abnormalities occurred significantly more often in the intensive therapy group
- Acute kidney injury/acute renal failure occurred at significantly higher rates in the intensive therapy group
- Patients without baseline chronic kidney disease were significantly more likely to experience significant decreases in GFR in the intensive therapy group compared to standard therapy

Cost:

- The cost of targeting a lower SBP must be balanced against the cost-savings of preventing cardiovascular morbidity and mortality
    - However, the cost of monitoring and managing changes in electrolytes and renal function must also be considered

Special Considerations/Populations:

- Cannot extrapolate results to patients with prior stroke or diabetes
- Thiazide diuretics (specifically chlorthalidone) were encouraged as first-line agents for managing hypertension

Grade of Recommendation: **A**

STEP 1

Wilding JPH, Batterham RL, Calanna S, et al. Once-Weekly Semaglutide in Adults with Overweight or Obesity. *N Engl J Med*. 2021;384(11):989-1002.

Objective: To determine the efficacy and safety of semaglutide 2.4 mg weekly injection for weight loss in overweight or obese patients without diabetes.

Primary Efficacy Measure: (1) Percentage change in body weight from baseline to week 68 (2) Body weight reduction of 5% or more from baseline to week 68

Participants: Overweight or obese patients without diabetes

- Age ~46 years; male ~25%
- Weight ~105 kg (231 lbs); BMI ~38

Inclusion Criteria:

- Age ≥ 18
- BMI ≥ 30 (≥ 27 if one or more weight related coexisting conditions)
- At least one self-reported failed dietary effort to lose weight

Exclusion Criteria:

- Diabetes
- HgA1c ≥ 6.5%
- History of chronic pancreatitis (or acute pancreatitis within previous 180 days)
- Previous surgical obesity treatment
- Use of anti-obesity medication within previous 90 days

Drug: Semaglutide 2.4 mg weekly injection

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients were randomized 2:1 to receive semaglutide or matching placebo. Semaglutide was titrated from 0.25 mg weekly to a maintenance dose of 2.4 mg weekly (dose increased every 4 weeks). All patients received lifestyle interventions and counseling every 4 weeks focusing on reduced calorie intake and increased physical activity (recorded by patient).

Duration: 68 weeks

Statistical Analysis: It was determined that 1950 randomized patients would provide 99% power for the co-primary endpoints (alpha=0.05). The ITT population was used for the primary efficacy analyses. The mITT population was used for the safety analyses.

Results: A total of 1961 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. Patients in the semaglutide group reported significantly greater improvements in physical function and quality of life compared to placebo. Gastrointestinal side effects (nausea/vomiting/diarrhea/constipation) were more commonly reported in the semaglutide group compared to placebo (74.2% vs 47.9%). Gastrointestinal side effects were also the most commonly reported cause of permanent discontinuation in the semaglutide group. Gallstones occurred more often in the semaglutide group (1.8% vs 0.6%).

Semaglutide (N=1306) Vs Placebo (N=655)

Percent Change from Baseline to Week 68:
-14.85% vs -2.41% (95% CI -13.37% to -11.51%); p<0.001

Participants with Body Weight Reduction ≥ 5% at Week 68:
86.4% vs 31.5%; OR 11.2 (95% CI 8.9-14.2); p<0.001

Participants with Body Weight Reduction ≥ 10% at Week 68:
69.1% vs 12.0%; OR 14.7 (95% CI 11.1-19.4); p<0.001

Participants with Body Weight Reduction ≥ 15% at Week 68:
50.5% vs 4.9%; OR 19.3 (95% CI 12.9-28.8); p<0.001

Participants with Body Weight Reduction ≥ 20% at Week 68:
32.0% vs 1.7%; OR 26.9 (95% CI 14.2-51.0)

Limitations:

- Patient population must be considered
  - Patients with diabetes not included
  - Primarily female trial population
- Treatment effect must be considered in addition to routine lifestyle counseling and modification
- The average calorie intake/physical activity for each group was not reported - potential confounding factor

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I recommend the use of injectable semaglutide (in addition to lifestyle counseling and modification) to achieve significant weight loss in overweight/obese patients without diabetes.

Efficacy:

- The semaglutide group demonstrated significantly greater weight loss compared to placebo
- Significantly more patients in the semaglutide group achieved ≥ 5% body weight reduction

Safety:

- Gastrointestinal adverse drug reactions were more common in the semaglutide group than placebo and were also the most common cause of permanent discontinuation
- Gallstones occurred more often in the semaglutide group than placebo

Cost:

- The cost of using injectable semaglutide must be balanced against the cost-savings of achieving significant body-weight reduction (in terms of preventing/reducing the risk for comorbid conditions)
- Insurance may pose a barrier to patient access (via prior authorizations/restricted formulary) as this is a high-cost medication that the majority of patients will not be able to afford without

Special Considerations/Populations:

- Body-weight loss of ≥ 5% is typically considered clinically significant

Grade of Recommendation: **A**

STRONG-HF

Mebazaa A, Davison B, Chioncel O, et al. Safety, tolerability and efficacy of up-titration of guideline-directed medical therapies for acute heart failure (STRONG-HF): a multinational, open-label, randomized, trial. *Lancet*. 2022;400(10367):1938-1952.

Objective: To determine the effect of rapid up-titration of pharmacotherapy following hospitalization for acute heart failure on clinical outcomes.

Primary Efficacy Measure: Composite of heart failure readmission or all-cause mortality at 180 days

Secondary Efficacy Measures: Change in quality of life from baseline at 90 days (via visual analog scale)

Participants: Patients hospitalized for acute heart failure

- Age ~63 years; male ~61%
- SBP ~123 mmHg; NT-proBNP (prior to randomization) ~3454 pg/mL
- LVEF ≤ 40% ~68%; > 40% ~32% (mean LVEF ~36%)
- NYHA class II ~31%; class III ~42%; class IV ~22%
- ACEi ~39%; ARB ~17%; ARNi ~8%; beta-blocker ~36%; MRA ~95%; loop diuretic ~96%

Inclusion Criteria:

- Age 18-85 years
- Hospitalized for acute heart failure within the previous 72 hours
- Hemodynamically stable
- Elevated NT-proBNP at screening (>2500 pg/mL) with 10% decrease prior to randomization, yet still >1500 pg/mL
- Lack of optimal dosing for heart failure pharmacotherapy within the two days prior to discharge

Exclusion Criteria:

- Clear intolerance to high-dose of beta-blocker, ACEi or ARB therapy

Drug: n/a

Design: Randomized, open-label, active-comparator trial

Methods: Eligible patients were randomized to standard care or treatment intensification. In the standard care group, patients received usual care following discharge according to local guidelines and were followed-up after 90 days. In the treatment intensification group, patients were started on ACEi/ARB or ARNi, beta-blocker and mineralocorticoid receptor antagonist (MRA) within two days prior to expected discharge, at ≥ 50% the optimal dosing. Patients in the treatment intensification group were seen 1, 2, 3 and 6 weeks following randomization. Up-titration to optimal dosing occurred within the first two weeks following randomization.

Dose increases would not occur for ACEi/ARB/ARNi or MRA if the patient's SBP was <95 mmHg, serum potassium >5.0 mEq/L or eGFR >30 mL/min. The dose of beta-blocker would not be increased if the patient's heart rate was <55 bpm or SBP <95 mmHg. If the patient's follow-up NT-proBNP was increased by 10% or more from baseline, increasing the dose of beta-blocker was not encouraged. Rather, a dose increase of diuretic therapy was encouraged.

The optimal dosing for select drugs in this trial includes: spironolactone 50 mg/day, carvedilol 50 mg BID, metoprolol succinate 200 mg/day, lisinopril 35 mg/day, ramipril 10 mg/day (or 5 mg BID), losartan 150 mg/day, olmesartan 40 mg/day, irbesartan 300 mg/day and sacubitril-valsartan 97-103 mg BID.

Duration: 180 days

Statistical Analysis: It was determined that 1800 randomized patients would provide 89% power (alpha=0.05). The ITT population was used for all efficacy and safety analyses.

Results: A total of 1078 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. During a prespecified interim analysis, the data and safety monitoring board recommended early termination of the trial due to clearly demonstrated benefit of treatment intensification over standard care.

Rates of the primary composite outcome at 90 days were similar between treatment groups. Likewise, the individual rates of all-cause mortality and heart failure readmission at 90 days were not significantly different between groups. Patients in the treatment intensification group experienced a significantly greater improvement in quality of life at 90 days compared to standard care (10.72 vs 7.22; p<0.0001). At 90 days, blood pressure, heart rate, respiratory rate and body weight were all significantly lower in the treatment intensification group compared to standard care (p<0.01). The most common adverse effects were cardiac failure (15% in treatment intensification vs 14% standard care), hypotension (5% vs <1%), hyperkalemia (3% vs 0%) and renal impairment (3% vs <1%).

Treatment Intensification (N=542) Vs Standard Care (N=536)

** A total of 1008 patients were followed until 180 days **

Composite of Heart Failure Readmission or All-Cause Mortality at 180 Days:
74/506 (14.6%) vs 109/502 (21.7%); RR 0.66 (95% CI 0.50-0.86)
p=0.0021; ARR 7.09%; NNT ~15

All-Cause Mortality at 180 Days:
39/506 (7.71%) vs 48/502 (9.56%); RR 0.84 (95% CI 0.56-1.26); p=0.42

Heart Failure Readmission at 180 Days:
47/506 (9.29%) vs 74/502 (14.7%); RR 0.56 (95% CI 0.38-0.81)
p=0.0011; ARR 5.45%; NNT ~19

Limitations:

- Power set but not met due to trial being stopped early – clinical significance low
- Open-label trial design
- The optimal dosing used in this trial must be considered when interpreting the results

Level of Evidence: Level II – with major limitations

Recommendation: For these reasons, I recommend treatment intensification using rapid up-titration of pharmacotherapy over standard care in patients following hospitalization for acute heart failure to further reduce the risk for short-term morbidity and mortality outcomes.

Efficacy:

- Rates of the primary composite outcome were significantly lower in the treatment intensification group at 180 days compared to standard care
- While rates of the individual component of heart failure readmission at 180 days were significantly lower in the treatment intensification group, rates of all-cause mortality were similar between groups
- Improvement in quality of life at 90 days was significantly greater in the treatment intensification group

Safety:

- Rates of cardiac failure, hypotension, hyperkalemia and renal impairment were predictably higher in the treatment intensification group

Cost:

- The cost of pursuing optimal dosing must be balanced against the cost-savings achieved from reduced morbidity and mortality outcomes, specifically, reduced heart failure readmission rates

Special Considerations/Populations:

- SGLT2i therapy was not approved for use in heart failure in many countries at the time of this study
- The majority of included patients had heart failure with reduced ejection fraction (LVEF $\leq 40\%$)

Grade of Recommendation: **A**

SURMOUNT-1

Jastreboff AM, Aronne LJ, Ahmad NN, et al. Tirzepatide Once Weekly for the Treatment of Obesity. *N Engl J Med*. 2022;10.1056/NEJMoa2206038.

Objective: To determine the safety and efficacy of tirzepatide for weight loss in overweight or obese adults without diabetes.

Primary Efficacy Measure: (1) Percent change in body weight from baseline at 72 weeks (2) Weight reduction of 5% or more at 72 weeks

Participants: Overweight/obese patients without diabetes

- Age ~45 years; male ~32%
- Body weight ~105 kg (~231 lbs); BMI ~38
- Duration of obesity ~14 years

Inclusion Criteria:

- ≥ 18 years old
- BMI ≥ 30 (or ≥ 27 if one or more weight related complication present)
- One or more unsuccessful dietary attempts for weight loss

Exclusion Criteria:

- Diabetes
- > 5 kg change in body weight within previous 90 days
- Prior or planned weight loss surgery
- Treated with weight loss medication within previous 90 days

Drug: Tirzepatide (subcutaneous injection)

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients underwent randomization (1:1:1:1) to receive weekly tirzepatide injections (5 mg, 10 mg or 15 mg) or placebo. All patients received lifestyle interventions (balanced meals, 500 calorie deficits daily, 150 minutes of weekly physical activity) as adjunct therapy. Dosing of tirzepatide was initiated at 2.5 mg weekly and increased every 4 weeks until week 20 (or until designated max dosing achieved).

Duration: 72 weeks

Statistical Analysis: It was determined that 2400 randomized patients would provide 90% power (alpha=0.025) for determining superiority of tirzepatide (10 mg and 15 mg dosing) to placebo. The ITT population was used for the efficacy and safety analysis.

Results: A total of 2539 patients underwent randomization. Baseline characteristics were similar between treatment groups. At week 72, patients in the tirzepatide treatment groups (5 mg, 10 mg and 15 mg) demonstrated significantly greater weight loss compared to placebo ($p< 0.001$). The most common adverse drug reactions in the tirzepatide treatment group were gastrointestinal in nature (nausea, diarrhea, constipation, etc.). While the overall rates of gallbladder related issues were low, there were numerically more events of cholecystitis with tirzepatide than placebo. However, it is difficult to attribute this to the medication itself as gallbladder-related events can be observed following significant weight loss due to bariatric surgery.

Results at 72 weeks	5 mg (N=630)	10 mg (N=636)	15 mg (N=630)	Placebo (N=643)
Percent Change in Body Weight:	-15%	-19.5%	-20.9%	-3.1%
Weight reduction > 5%: (% of patients)	85.1%	88.9%	90.9%	34.5%
Weight reduction > 10%	68.5%	78.1%	83.5%	18.8%
Weight reduction > 15%	48.0%	66.6%	70.6%	8.8%
Weight reduction > 20%	30.0%	50.1%	56.7%	3.1%

Adverse Effects	5 mg (N=630)	10 mg (N=636)	15 mg (N=630)	Placebo (N=643)
Nausea	24.6%	33.3%	31.0%	9.5%
Diarrhea	18.7%	21.1%	23.0%	7.3%
Constipation	16.8%	17.1%	11.7%	5.8%
Cholelithiasis	1.1%	1.4%	0.6%	0.9%
Cholecystitis	0.6%	0.5%	0%	0%

Limitations:

- Cannot extrapolate trial results to patients with diabetes

Level of Evidence: Level I – with minor limitations

Recommendation: For these reasons, I recommend the use of weekly tirzepatide injections (at highest tolerated dosing) to achieve significant weight reduction in overweight and obese adult patients without diabetes.

Efficacy:

- Tirzepatide demonstrated significantly greater weight loss compared to placebo

Safety:

- The most common adverse effects in the tirzepatide groups were gastrointestinal, which is a predictable reaction given the class of medication
- Gallbladder-related events were infrequent but numerically higher in the tirzepatide group

Cost:

- The cost of using weekly tirzepatide injections must be balanced against the cost-savings achieved from reducing the risk for comorbid complications (diabetes, cardiovascular events, etc.)

Special Considerations/Populations:

- Weight reduction of 5% or greater is considered clinically significant in terms of having a meaningful positive impact on patient health
- Tirzepatide is a dual GIP/GLP-1 receptor agonist
- Start titration low and increase slowly to identify max tolerated dosing for greatest treatment effect

Grade of Recommendation: **A**

SURMOUNT-2

Garvey WT, Frias JP, Jastreboff AM, et al. Tirzepatide once weekly for the treatment of obesity in people with type 2 diabetes (SURMOUNT-2): a double-blind, randomized, multicenter, placebo-controlled, phase 3 trial. Lancet. Published online June 26, 2023: S0140-6736(23)01200-X.

Objective: To determine the safety and efficacy of tirzepatide for weight loss in overweight or obese adults with type 2 diabetes.

Primary Efficacy Measures: (1) Percent change in body weight from baseline to week 72 (2) Weight loss of ≥ 5% from baseline at week 72

Participants: Overweight or obese adults with type 2 diabetes

- Age ~54 years; male ~49%
- Weight ~101 kg; BMI ~36
- HgA1c ~8%; duration of diabetes ~8.5 years

Inclusion Criteria:

- Adults with type 2 diabetes
- BMI ≥ 27
- HgA1c 7.0-10%

Exclusion Criteria:

- Body weight change ≥ 5 kg within the previous 3 months
- Previous/planned anti-obesity surgical procedure
- Current use of anti-obesity medications
- Current use of DPP-4 inhibitor, GLP-1 receptor agonist or any injectable medication for the management of type 2 diabetes

Drug: Tirzepatide

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients were randomized to receive either tirzepatide once weekly subcutaneous injections or matching placebo. Initial dosing was 2.5 mg weekly. Thereafter, dosing was increased by 2.5 mg increments every 4 weeks until the target dosing (10 mg or 15 mg) was achieved. All patients received lifestyle management counseling focusing on reduced caloric intake (500 calorie deficit per day) and increased physical activity (at least 150 minutes per week). Glucose-lowering therapies were kept stable, if possible.

Duration: 72 weeks

Statistical Analysis: It was determined that 900 randomized patients would provide 90% power (alpha=0.025). The ITT population was used for efficacy and safety analyses.

Results: A total of 938 patients underwent randomization. Baseline characteristics were similar between treatment groups. At week 72 patients in the tirzepatide treatment groups (10 mg and 15 mg) demonstrated significantly greater weight loss compared to placebo ($p<0.0001$). Additionally, the tirzepatide groups had a significantly greater proportion of patients achieve clinically significant weight loss (≥ 5%) compared to placebo ($p<0.0001$). HgA1c reduction was predictably greater in the tirzepatide groups ($p<0.0001$). The most common adverse effects in the tirzepatide groups were gastrointestinal in nature (e.g., nausea, diarrhea, constipation).

Results at 72 weeks	10 mg (N=312)	15 mg (N=311)	Placebo (N=315)
Percent Change in Body Weight:	-12.8%	-14.7%	-3.2%
Weight reduction ≥ 5% (% of patients)	79.2%	82.6%	32.4%
Weight reduction ≥ 10%	60.6%	65.0%	9.52%
Weight reduction ≥ 15%	39.7%	47.9%	2.54%
Weight reduction ≥ 20%	21.5%	30.9%	0.95%
Change in HgA1c	-2.07%	-2.08%	-0.51%

Limitations:

- Patient population – cannot apply trial results to patients without type 2 diabetes

Level of Evidence: Level I – with minor limitations

Recommendation: For these reasons, I recommend the use of weekly tirzepatide injections (at the highest tolerated dosing) to achieve clinically significant weight reduction in overweight and obese adult patients with type 2 diabetes.

Efficacy:

- Tirzepatide demonstrated significantly greater weight loss compared to placebo

Safety:

- The most common adverse effects in the tirzepatide groups were gastrointestinal in nature, which is a predictable reaction for this class of medication

Cost:

- The cost of using weekly tirzepatide injections must be balanced against the cost-savings achieved from reducing the risk for comorbid complications (e.g., diabetes and cardiovascular events)

Special Considerations/Populations:

- Weight reduction of ≥ 5% is typically considered clinically significant
- Tirzepatide is a dual GIP/GLP-1 receptor agonist
- Starting the titration low and increasing slow will help identify the max-tolerated dosing

Grade of Recommendation: **A**

SURPASS-2

Frías JP, Davies MJ, Rosenstock J, et al. Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes. *N Engl J Med*. 2021;385(6):503-515.

Objective: To determine the safety and efficacy of tirzepatide compared to semaglutide for treatment of type 2 diabetes.

Primary Efficacy Measure: Change in HgA1c from baseline to week 40

Secondary Efficacy Measures: (1) Change in body weight (2) HgA1c < 7.0% (3) HgA1c < 5.7%

Participants: Patients with type 2 diabetes inadequately controlled on metformin

- Age ~57 years; male ~47%
- HgA1c ~8.3%; duration of diabetes ~8.6 years
- BMI ~34; weight ~94 kg (207 lbs)

Inclusion Criteria:

- Age ≥ 18 years
- Type 2 diabetes inadequately controlled with metformin 1500 mg daily
- HgA1c 7.0-10.5%
- BMI ≥ 25 and stable weight during the previous 3 months

Exclusion Criteria:

- Type 1 diabetes
- eGFR < 45 mL/min
- History of pancreatitis

Drugs: Tirzepatide; semaglutide

Design: Randomized, open-label, active-controlled, non-inferiority trial

Methods: Eligible patients were randomized 1:1:1:1 to receive weekly tirzepatide injections at doses of 5 mg, 10 mg or 15 mg, or weekly semaglutide 1 mg injections for a treatment period of 40 weeks. Dosing for tirzepatide was initiated at 2.5 mg weekly and increased every 4 weeks until the target dose was achieved. Dosing for semaglutide was initiated at 0.25 mg weekly and increased every 4 weeks until the target dose of 1 mg was achieved. For both treatment arms, after the target dose was achieved it was continued for the trial duration. The use of additional glucose-lowering agents was allowed.

Duration: 40 weeks

Statistical Analysis: It was determined that 1872 randomized patients would provide 90% power to determine non-inferiority of tirzepatide (10-15 mg) to semaglutide regarding HgA1c reduction (alpha=0.025). A non-inferiority margin of 0.3% was specified. The modified ITT population (all randomized patients that received one dose of study medication) was used for safety and efficacy analyses. If non-inferiority was demonstrated, hierarchical testing for superiority would occur.

Results: A total of 1878 patients underwent randomization and received one dose of study medication. Baseline patient characteristics were similar between treatment groups. Gastrointestinal adverse effects (nausea, vomiting, diarrhea) were the primary reason for early discontinuation of either study medication. Overall, GI adverse effects occurred at higher rates in the tirzepatide 10 mg and 15 mg groups compared to semaglutide 1 mg (46.1% vs 44.9% vs 41.2%, respectively). Tirzepatide 5 mg demonstrated a slightly lower rate of 40.0% for GI adverse effects. Pancreatitis was rare and occurred at similar rates across treatment groups.

Tirzepatide 15 mg (N=470) Vs Semaglutide 1 mg (N=469)

Change in HgA1c from Baseline:
-2.30% vs -1.86%

HgA1c Treatment Difference:
-0.45% (95% CI -0.57% to -0.32%); p<0.001

Change in Body Weight (plus treatment difference):
-11.2 kg vs -5.7 kg
-5.5 kg (-6.4 kg to -4.6 kg); p<0.001

Achieved HgA1c < 7.0%:
86% vs 79%; p<0.05

Achieved HgA1c < 5.7%:
46% vs 19%; p<0.001

Tirzepatide 10 mg (N=469) Vs Semaglutide 1 mg (N=469)

Change in HgA1c from Baseline:
-2.24% vs -1.86%

HgA1c Treatment Difference:
-0.39% (95% CI -0.51% to -0.26%); p<0.001

Change in Body Weight (plus treatment difference):
-9.3 kg vs -5.7 kg
-3.6 kg (95% CI -4.5 kg to -2.7 kg); p<0.001

Achieved HgA1c < 7.0%:
86% vs 79%; p<0.05

Achieved HgA1c < 5.7%:
40% vs 19%; p<0.001

Tirzepatide 5 mg (N=470) Vs Semaglutide 1 mg (N=469)

Change in HgA1c from Baseline:
-2.01% vs -1.86%

HgA1c Treatment Difference:
-0.15% (95% CI -0.28% to -0.03%); p=0.02

Change in Body Weight (plus treatment difference):
-7.6 kg vs -5.7 kg
-1.9 kg (95% CI -2.8 kg to -1.0 kg); p<0.001

Achieved HgA1c < 7.0%:
82% vs 79%

Achieved HgA1c < 5.7%:
27% vs 19%

Limitations:

- Semaglutide dosing – currently approved at 2 mg per week for type 2 diabetes (not available at time of trial)
    - Cannot extrapolate trial results to this higher dosing

Level of Evidence: Level I – with minor limitations

Recommendation: For these reasons, I recommend the use of tirzepatide (10-15 mg) weekly injections over semaglutide 1 mg weekly injections for the treatment of type 2 diabetes in this patient population. However, it should be noted that semaglutide is currently available at a higher dose (2 mg weekly) and a head-to-head trial has not been conducted to determine non-inferiority or superiority of tirzepatide.

Efficacy:

- All doses of tirzepatide demonstrated non-inferiority and subsequent superiority to semaglutide 1 mg for HgA1c reduction and body-weight reduction
- Significantly more patients in the tirzepatide 10 mg and 15 mg groups achieved HgA1c <7.0% and HgA1c <5.7% compared to semaglutide 1 mg

Safety:

- The primary reason for early discontinuation for all groups was due to gastrointestinal adverse effects
- Rates of pancreatitis were similar across treatment groups

Cost:

- The cost of using tirzepatide (10-15 mg weekly injections) over semaglutide 1 mg weekly injections must be balanced against the cost-savings of preventing long-term complications of type 2 diabetes (due to increased rates of patients achieving target glycemic goals)

Special Considerations/Populations:

- Tirzepatide is a dual GIP/GLP-1 receptor agonist; semaglutide is a GLP-1 receptor agonist
- HgA1c reduction of -0.5% is considered clinically significant
- Weight loss of 5% or more (over 6-12 months) is considered clinically significant

Grade of Recommendation: **A**

SUSTAIN-6

Marso SP, Bain SC, Consoli A, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med*. 2016;375(19):1834-1844.

Objective: To determine the effects of semaglutide on cardiovascular outcomes in patients with type 2 diabetes.

Primary Efficacy Measure: Composite of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke

Participants: Patients with type 2 diabetes at increased risk for cardiovascular events

- Age ~65 years; male ~61%
- HgA1c ~8.7%
- Baseline cardiovascular disease ~59%

Inclusion Criteria:

- Patient with type 2 diabetes and HgA1c ≥ 7%
- Age ≥ 50 years with cardiovascular disease/CKD stage III OR age ≥ 60 years with one or more cardiovascular risk factors

Exclusion Criteria:

- Use of DPP-4 inhibitor within previous 30 days
- Use of GLP-1 receptor agonist within previous 90 days
- Use of mealtime insulin within previous 90 days
- Acute coronary/cerebrovascular event within previous 90 days
- History of pancreatitis
- Planned revascularization or long-term dialysis

Drug: Semaglutide

Design: Randomized, double-blind, placebo-controlled, non-inferiority trial

Methods: Eligible patients were randomized 1:1:1:1 to receive semaglutide 0.5 mg or 1 mg once weekly subcutaneous injections or matching placebo injections. The dose titration was started at 0.25 mg weekly for 4 weeks, then increased to 0.5 mg weekly for 4 weeks, then increased to 1 mg weekly or continued at 0.5 mg weekly for the maintenance dose. The use of other glucose-lowering agents (except GLP-1 receptor agonists or DPP-4 inhibitors) were permitted to achieve standards of care.

Duration: Median follow-up period of 2.1 years

Statistical Analysis: It was determined that 3260 randomized patients and 122 primary events would achieve 90% power for non-inferiority (NI margin = 1.80; alpha = 0.05). This trial was not powered for superiority testing. The ITT population was used for the primary efficacy analyses.

Results: A total of 3297 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. At week 104, the mean HgA1c was 7.6% and 7.3% in the semaglutide 0.5 mg and 1 mg groups and 8.3% in the placebo groups ($p<0.001$). Semaglutide demonstrated non-inferiority to placebo regarding the rates of the primary composite outcome. The treatment effect of semaglutide was consistent in both 0.5 mg and 1 mg groups. Discontinuation because of adverse effects was higher in the semaglutide treatment groups, primarily due to nausea.

Semaglutide (N=1648) Vs Placebo (N=1649)

Primary Composite Outcome:
108 (6.55%) vs 146 (8.85%); HR 0.74 (95% CI 0.58-0.95)
p=0.02; ARR 2.30%; NNT ~44
Trial not powered for superiority - interpret results with caution

Cardiovascular Death:
44 (2.67%) vs 46 (2.79%); HR 0.98 (95% CI 0.65-1.48); p=0.92

Non-Fatal Myocardial Infarction:
47 (2.85%) vs 64 (3.88%); HR 0.74 (95% CI 0.51-1.08); p=0.12

Non-Fatal Stroke:
27 (1.64%) vs 44 (2.67%); HR 0.61 (95% CI 0.38-0.99)
p=0.04; ARR 1.03%; NNT ~98
Trial not powered for superiority - interpret results cautiously

Limitations:

- Trial not powered for superiority (only non-inferiority can be claimed)
- Significant difference in mean HgA1c between treatment groups may have influenced the trial results (potential confounding factor)

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I recommend the use of weekly semaglutide injections as a safe and effective glucose-lowering therapy in patients with type 2 diabetes and an increased risk for cardiovascular events. While event rates were lower in the semaglutide group superiority cannot be claimed based on trial design.

Efficacy:

- Semaglutide demonstrated non-inferiority (but not superiority) to placebo regarding the rates of the primary composite outcome
- Rates of the primary composite outcome, including the individual component of non-fatal stroke, were significantly lower with semaglutide compared to placebo (superiority cannot be claimed)
- There was a significant difference in mean HgA1c between the active and placebo treatment groups favoring semaglutide

Safety:

- Rates of discontinuation due to adverse effects were higher with semaglutide, primarily because of gastrointestinal effects (particularly nausea)

Cost:

- The cost of using weekly semaglutide injections must be balanced against the cost-savings of preventing a cardiovascular outcome
- However, the cost of using an alternative GLP-1 receptor agonist with proven superiority to placebo (instead of non-inferiority alone) should also be considered

Special Considerations/Populations:

- Although the use of additional glucose-lowering agents was allowed there was still a significantly greater decrease in mean HgA1c with semaglutide compared to placebo

Grade of Recommendation: **A**

SWORD

Waldo AL, Camm AJ, deRuyter H, et al. Effect of d-sotalol on mortality in patients with left ventricular dysfunction after recent and remote myocardial infarction. The SWORD Investigators. Survival With Oral d-Sotalol. *Lancet*. 1996;348(9019):7-12.

Objective: To determine the effect of d-sotalol on morbidity and mortality outcomes in patients with prior myocardial infarction and left ventricular dysfunction.

Primary Efficacy Measure: All-cause mortality

Secondary Efficacy Measure: Cardiovascular mortality

Participants: Heart failure patients with prior myocardial infarction

- Age ~60 years; male ~86%
- LVEF ~31%; HR ~73 bpm
- NYHA class II ~72%; class III ~22%
- Baseline diuretic ~49%; beta-blocker ~33%; ACEi ~71%

Inclusion Criteria:

- Age ≥ 18 years
- LVEF ≤ 40%
- Recent MI (within previous 6-42 days) or remote MI (> 42 days) with overt heart failure

Exclusion Criteria:

- Unstable angina pectoris
- NYHA class IV heart failure
- History of life-threatening arrhythmia
- Serum potassium < 4.0 mmol/L
- CrCl < 50 mL/min
- QTc > 460 ms

Drug: d-sotalol

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients were randomized to receive d-sotalol or matching placebo. The starting dose of d-sotalol was 100 mg twice daily for 1 week. If tolerated the dose was increased to 200 mg twice daily for the duration of the study. If the QTc ever exceeded 560 ms the dose was reduced. If the QTc persisted above 560 ms after the dose reduction the medication was discontinued.

Duration: Mean follow-up period of 148 days (due to early termination of the trial)

Statistical Analysis: It was determined that 6374 randomized patients would provide 90% power (alpha = 0.05). However, due to early trial termination (for safety concerns) this criterion was not met.

Results: A total of 3121 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. The trial was terminated early due to excess mortality rates demonstrated in the d-sotalol treatment group. The vast majority of fatal events in both treatment groups was cardiovascular in origin, specifically related to arrhythmia. Subgroup analysis demonstrated consistent findings.

d-Sotalol (N=1549) Vs Placebo (N=1572)

All-Cause Mortality:
78 (5.04%) vs 48 (3.05%); RR 1.65 (95 CI 1.15-2.36)
p=0.006; ARI 1.98%; NNH ~50

Cardiovascular Mortality:
73 (4.71%) vs 45 (2.86%); RR 1.65 (95% CI 1.14-2.39)
p=0.008; ARI 2.86%; NNH ~54

Cardiovascular Death due to Presumed Arrhythmic Causes:
56 (3.62%) vs 32 (2.04%); RR 1.77 (95% CI 1.15-2.74)
p=0.008; ARI 1.58%; NNH ~63

Limitations:

- Power set but not met – due to early trial termination for safety concerns
    - Clinical significance likely low
- Results cannot be extrapolated to sotalol due to the differing pharmacological properties
    - d-sotalol does not possess beta-blocking characteristics (sotalol does)

Level of Evidence: Level II – with major limitations

Recommendation: For these reasons, I do not recommend the use of d-sotalol to reduce morbidity and mortality outcomes in patients with prior myocardial infarction and left-ventricular dysfunction.

Efficacy:

- The d-sotalol treatment group demonstrated a significantly higher mortality rate compared to placebo
    - The majority of demonstrated mortality events were cardiovascular in origin, specifically due to arrhythmia

Safety:

- The trial was terminated early due to an excess in mortality demonstrated in the d-sotalol group

Cost:

- The cost of using d-sotalol must be considered in addition to the costs associated with increased cardiovascular events and patient mortality

Special Considerations/Populations:

- d-sotalol is an isomer of the racemic mixture of sotalol
- While sotalol possesses beta-blocking and potassium-blocking properties, d-sotalol only possesses the potassium-blocking properties
- This trial was designed to test d-sotalol for secondary prevention, not suppression of arrhythmia

Grade of Recommendation: **B**

TECOS

Green JB, Bethel MA, Armstrong PW, et al. Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med*. 2015;373(3):232-242.

Objective: To determine the effect of sitagliptin on cardiovascular outcomes in high-risk patients with type 2 diabetes.

Primary Efficacy Measure: Composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke or hospitalization for unstable angina

Participants: Patients with type 2 diabetes and established cardiovascular disease

- Age ~66 years; male ~71%
- HgA1c ~7.2%
- Baseline coronary artery disease ~74%; cerebrovascular disease ~25%

Inclusion Criteria:

- Patients ≥ 50 years old with type 2 diabetes
- HgA1c 6.5% to 8.0%
- Managed on ≤ 2 oral agents (metformin, pioglitazone or sulfonylurea) or insulin with/without metformin
- Established cardiovascular disease (coronary, cerebrovascular or PAD)

Exclusion Criteria:

- Use of DPP-4 inhibitor/GLP-1 receptor agonist/TZD (other than pioglitazone) during the preceding 3 months
- History of ≥ 2 episodes of severe hypoglycemia within previous 12 months
- eGFR < 30 mL/min

Drug: Sitagliptin

Design: Randomized, double-blind, placebo-controlled, non-inferiority trial

Methods: Eligible patients were randomized to receive either sitagliptin 100 mg daily (50 mg daily if eGFR 30-50 mL/min) or matching placebo. The use of additional glucose-lowering agents was encouraged to achieve treatment goals for patients.

Duration: Median follow-up period of 3.0 years

Statistical Analysis: It was determined that 611 primary events were required to achieve 90% power for non-inferiority (NI margin = 1.30) and 1300 events would provide ~81% power for sequential superiority testing (if appropriate). The per protocol population and ITT population were used for the primary efficacy analyses.

Results: A total of 14,735 patients underwent randomization (14,671 included in the ITT population). Baseline patient characteristics were similar between treatment groups. The overall mean difference in HgA1c was -0.29% favoring the sitagliptin group. Sitagliptin demonstrated non-inferiority (but not superiority) to placebo regarding the primary composite outcome. There was no significant difference in rates of heart failure hospitalization. Results were consistent for both per-protocol and ITT population analyses. Rates of adverse drug reactions (including pancreatitis and pancreatic cancer) were similar between treatment groups.

Sitagliptin (N=7257) Vs Placebo (N=7266)

Primary Composite Outcome:
695 (9.58%) vs 695 (9.57%); HR 0.98 (95% CI 0.88-1.09); p<0.001
** p-value above is for non-inferiority **

Cardiovascular Death:
311 (4.29%) vs 291 (4.00%)

Non-Fatal Myocardial Infarction:
275 (3.79%) vs 286 (3.94%)

Non-Fatal Stroke:
145 (2.00%) vs 157 (2.16%)

Hospitalization for Unstable Angina:
108 (1.49%) vs 117 (1.61%)

Heart Failure Hospitalization:
228 (3.14%) vs 229 (3.15%); HR 1.00 (95% CI 0.83-1.20); p=0.98

Limitations:

- Patient population must be considered - glucose levels relatively controlled (average HgA1c ~7.2%) and no severe renal impairment

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I recommend the use of sitagliptin as a safe glucose-lowering agent in patients with type 2 diabetes and established cardiovascular disease without severe renal impairment.

Efficacy:

- Sitagliptin demonstrated non-inferiority (but not superiority) to placebo regarding the cardiovascular composite outcome
- There was no significant difference in rates of heart failure hospitalization between treatment groups
- The average HgA1c difference was -0.29% favoring the sitagliptin group

Safety:

- The rates of adverse drug reactions were similar between treatment groups

Cost:

- The cost of using sitagliptin must be balanced against the cost of using other DPP-4 inhibitors (or glucose-lowering agents with proven cardiovascular benefit)

Special Considerations/Populations:

- While sitagliptin demonstrates cardiovascular safety in patients with type 2 diabetes and established cardiovascular disease it is reasonable to utilize glucose-lowering agents with demonstrated cardiovascular benefit (in addition to safety) if possible

Grade of Recommendation: **A**

TNT

LaRosa JC, Grundy SM, Waters DD, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med*. 2005;352(14):1425-1435.

Objective: To determine the effect of high-intensity statin therapy (target LDL 75 mg/dL) on cardiovascular outcomes in patients with stable coronary heart disease compared to moderate statin therapy (target LDL 100 mg/dL).

Primary Efficacy Measure: Composite of coronary heart disease death, non-fatal myocardial infarction, total stroke or cardiac resuscitation

Participants: Patients with stable coronary heart disease

- Age ~61 years; male ~81%
- LDL ~152 mg/dL (~98 mg/dL after run-in period)
- Prior myocardial infarction ~58%; angina ~82%

Inclusion Criteria:

- Age 35-75 years
- Clinically evident coronary heart disease (prior myocardial infarction, angina with evidence of atherosclerosis or history of coronary revascularization)

Exclusion Criteria:

- Hypersensitivity to statins
- Active liver disease or dysfunction
- Pregnancy or breastfeeding

Drug: Atorvastatin

Design: Randomized, double-blind, active-controlled trial

Methods: Eligible patients were randomized to receive either atorvastatin 10 mg daily (target LDL goal 100 mg/dL) or atorvastatin 80 mg daily (target LDL goal 75 mg/dL). All lipid-lowering therapies were discontinued at screening and patients underwent a washout period of 1-8 weeks. Patients with LDL levels 130-250 mg/dL and triglycerides ≤ 600 mg/dL underwent a 6-week run-in period with atorvastatin 10 mg daily to ensure that all patients had cholesterol levels consistent with the guidelines at the time. After the run-in period, patients with LDL < 130 mg/dL were randomized to 10 mg or 80 mg atorvastatin.

Duration: Median follow-up period of 4.9 years

Statistical Analysis: It was determined that a total of 950 primary events (750 coronary events plus 200 stroke events) were required to achieve 85% power (alpha = 0.05). The ITT population was used for all analyses.

Results: A total of 10,001 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. Average LDL levels were 77 mg/dL in the atorvastatin 80 mg group and 101 mg/dL in the atorvastatin 10 mg group. There was no noted increase in adverse drug reactions in patients with very low LDL levels (<70 mg/dL) compared to those with higher LDL levels. Discontinuation rates were significantly higher in the high-intensity group compared to moderate-intensity (7.2% vs 5.3%; p<0.001). However, rates of treatment related myalgias were not significantly different between treatment groups. A total of 5 cases of rhabdomyolysis were reported (two in high-intensity group and 3 in moderate-intensity group).

Atorvastatin 80 mg (N=4995) Vs Atorvastatin 10 mg (N=5006)

Primary Composite Outcome:
434 (8.69%) vs 548 (10.9%); HR 0.78 (95% CI 0.69-0.89)
p<0.001; ARR 2.26%; NNT ~45

Coronary Heart Disease Death:
101 (2.02%) vs 127 (2.54%); HR 0.80 (95% CI 0.61-1.03); p=0.09

Non-Fatal Myocardial Infarction:
243 (4.86%) vs 308 (6.15%); HR 0.78 (95% CI 0.66-0.93)
p=0.004; ARR 1.29%; NNT ~78

Total Stroke:
117 (2.34%) vs 155 (3.10%); HR 0.75 (95% CI 0.59-0.96)
p=0.02; ARR 0.75%; NNT ~133

Cardiac Resuscitation:
25 (0.50%) vs 26 (0.52%); HR 0.96 (95% CI 0.56-1.67); p=0.89

Safety:

ALT/AST Elevations 3x Upper Limit of Normal:
60 (1.20%) vs 9 (0.18%); p<0.001; ARI 1.02%; NNH ~97

Limitations:

- Patient population must be considered - all had established coronary heart disease and elevated LDL levels

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I recommend the use of high-intensity statin therapy (atorvastatin 80 mg) to target an LDL level of 75 mg/dL over moderate-intensity statin therapy (atorvastatin 10 mg) to further reduce rates of cardiovascular morbidity and mortality in patients with coronary heart disease and elevated LDL levels.

Efficacy:

- Rates of the primary composite outcome were significantly lower in the high-intensity treatment group compared to the moderate-intensity treatment group
    - The rates of the individual components of non-fatal myocardial infarction and total stroke were significantly lower in the high-intensity treatment group
- Average LDL levels were significantly lower in the high-intensity treatment group

Safety:

- Discontinuation rates as well as elevated liver enzymes occurred significantly more often in the high-intensity treatment group
- Rates of treatment related myalgia and rhabdomyolysis were similar between groups

Cost:

- The cost of using atorvastatin 80 mg (versus 10 mg) must be balanced against the cost-savings achieved from preventing cardiovascular morbidity and mortality outcomes, specifically non-fatal myocardial infarction and stroke

Special Considerations/Populations:

- The trial results must be considered in the context of using atorvastatin 80 mg to target an average LDL level of 75 mg/dL

Grade of Recommendation: **A**

TOPCAT

Pitt B, Pfeffer MA, Assmann SF, et al. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med*. 2014;370(15):1383-1392.

Objective: To determine the effect of spironolactone on cardiovascular outcomes in patients with heart failure and preserved ejection fraction.

Primary Efficacy Measure: Composite of cardiovascular death, aborted cardiac arrest or heart failure hospitalization

Participants: Patients with heart failure and preserved ejection fraction

- Age ~69 years; male ~48%
- LVEF ~56%
- BP ~130/80 mmHg; HR ~68
- NYHA class II ~63%; class III ~33%

Inclusion Criteria:

- Age ≥ 50 years
- One or more signs/symptoms of heart failure
- LVEF ≥ 45%
- SBP < 140 mmHg
- Serum potassium levels < 5 mmol/L
- Heart failure hospitalization within prior 12 months (or elevated BNP within prior 60 days)

Exclusion Criteria:

- Life expectancy < 3 years
- eGFR < 30 mL/min
- SCr ≥ 2.5 mg/dL

Drug: Spironolactone

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients were randomized to either spironolactone or matching placebo. Spironolactone was dosed at 15 mg/day initially and would be increased to a max of 45 mg/day during the first 4 months of the trial period. Patients were to continue other medications for heart failure or coexisting conditions.

Duration: Mean follow-up period of 3.3 years

Statistical Analysis: It was determined that 551 primary outcomes would be required to achieve 80% power (alpha = 0.05). The ITT population was used for the primary efficacy analyses.

Results: A total of 3445 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. At month 8, the average dose of spironolactone was 25 mg daily. Discontinuation due to either hyperkalemia, abnormal renal function or breast tenderness/enlargement was significantly higher in the spironolactone group compared to placebo.

Spironolactone (N=1722) Vs Placebo (N=1723)

Primary Composite Outcome:
320 (18.6%) vs 351 (20.4%); HR 0.89 (95% CI 0.77-1.04); p=0.14

Cardiovascular Death:
160 (9.29%) vs 176 (10.2%); HR 0.90 (95% CI 0.73-1.12); p=0.35

Aborted Cardiac Arrest:
3 (0.17%) vs 5 (0.29%); HR 0.60 (95% CI 0.14-2.50); p=0.48

Heart Failure Hospitalization:
206 (12.0%) vs 245 (14.2%); HR 0.83 (95% CI 0.69-0.99)
p=0.04; ARR 2.26%; NNT ~45

Safety:

Hyperkalemia:
322 (18.7%) vs 157 (9.11%); p<0.001; ARI 9.59%; NNH ~10

SCr Increase:
175 (10.2%) vs 120 (6.96%); p<0.001; ARI 3.20%; NNH ~31
Doubling to value outside the upper limit of normal

Gynecomastia:
43 (2.50%) vs 5 (0.29%); p<0.001; ARR 2.21%; NNH ~45

Limitations:

- Patient population must be considered - cannot extrapolate results to patients with reduced ejection fraction

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I do not recommend the use of spironolactone (in addition to standard therapy) to further reduce the risk of morbidity and mortality outcomes in heart failure patients with preserved ejection fraction.

Efficacy:

- There was no significant difference in the rates of the primary composite outcome between treatment groups
    - Heart failure hospitalization occurred at significantly lower rates in the spironolactone group

Safety:

- Rates of hyperkalemia, SCr increase and gynecomastia were all significantly higher in the spironolactone group

Cost:

- The cost of using spironolactone must be balanced against the cost-savings of preventing heart failure hospitalization
    - However, the cost of monitoring and managing changes in serum creatinine and potassium must also be considered

Special Considerations/Populations:

- Study population was entirely heart failure patients with preserved ejection fraction
- This trial demonstrated morbidity (but not mortality) benefit
    - However, said benefit is likely outweighed by safety concerns in many cases

Grade of Recommendation: **A**

TORCH

Calverley PM, Anderson JA, Celli B, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med*. 2007;356(8):775-789.

Objective: To determine the effect of combined LABA-ICS (salmeterol-fluticasone) therapy on mortality outcomes in COPD patients (compared to LABA and ICS monotherapy).

Primary Efficacy Measure: All-cause mortality

Secondary Efficacy Measure: Frequency of exacerbations

- Exacerbation defined as a symptomatic deterioration requiring antibiotic therapy, systemic corticosteroids or hospitalization

Participants: Patients with COPD (current or former smoker)

- Age ~65 years; male ~75%
- Current smoker ~43%
- FEV_1 ~44% of predicted value; FEV_1/FVC ratio ~0.49

Inclusion Criteria:

- Age 40-80 years with COPD
- Current smoker (or former, with 10-pack-year history)
- $FEV_1 < 60\%$ of predicted value
- FEV_1 increase of < 10% of predicted value following 400 mcg albuterol
- $FEV_1/FVC \text{ ratio} \leq 0.70$

Exclusion Criteria:

- Asthma
- Other respiratory disorder(s)
- Long-term oxygen therapy
- Long-term oral corticosteroid therapy

Drugs: Salmeterol-fluticasone (LABA-ICS); salmeterol (LABA); fluticasone (ICS)

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients were randomized to receive salmeterol-fluticasone 50 mcg-500 mcg, salmeterol 50 mcg, fluticasone 500 mcg or matching placebo (all given twice daily). Medication was administered via dry powder inhaler.

Duration: 3 years

Statistical Analysis: It was determined that 1510 randomized patients per treatment group would provide 90% power (alpha = 0.05). The ITT population was used for the efficacy analyses.

Results: A total of 6184 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. Adherence rates (~88-89%) were similar between all treatment groups. COPD exacerbation was the most common adverse event reported. There was no significant difference in the rates of bone fractures or bone mineral density. Mortality was primarily due to an even balance of cardiovascular and pulmonary causes. Mortality rates were only significantly different when comparing fluticasone monotherapy to salmeterol-fluticasone combination therapy. However, rates of annual COPD exacerbation were significantly lower in the salmeterol-fluticasone group compared to all other treatment groups. Respiratory function and health status was most improved in the combination therapy group.

Placebo (N=1524) Vs Salmeterol-Fluticasone (N=1533)

All-Cause Mortality:
231 (15.2%) vs 193 (12.6%); HR 0.825 (95% CI 0.681-1.002); p=0.052
This comparison was adjusted to account for the interim analysis

231 (15.2%) vs 193 (12.6%); HR 0.82 (95% CI 0.677-0.993)
p=0.04; ARR 2.57%; NNT ~39
This comparison was not adjusted for the interim analysis

Annual Exacerbation Rate (moderate or severe):
1.13 vs 0.85; RR 0.75 (95% CI 0.69-0.81); p<0.001

Pneumonia Incidence Rate:
12.3% vs 19.6%; p<0.001

Salmeterol (N=1521) Vs Salmeterol-Fluticasone (N=1533)

All-Cause Mortality:
205 (13.5%) vs 193 (12.6%); HR 0.932 (95% CI 0.765-1.134); p=0.48

Annual Exacerbation Rate (moderate or severe):
0.97 vs 0.85; RR 0.88 (95% 0.81-0.95); p=0.002

Pneumonia Incidence Rate:
13.3% vs 19.6%

Fluticasone (N=1534) Vs Salmeterol-Fluticasone (N=1533)

All-Cause Mortality:
246 (16.0%) vs 193 (12.6%); HR 0.774 (95% CI 0.641-0.934); p=0.007

Annual Exacerbation Rate (moderate or severe):
0.93 vs 0.85; RR 0.91 (95% CI 0.84-0.99); p=0.02

Pneumonia Incidence Rate:
18.3% vs 19.6%

Limitations:

- Asthma patients were excluded from this trial – cannot extrapolate results to these patients

Level of Evidence: Level I – with minor limitations

Recommendation: For these reasons, I recommend the use of LABA-ICS combination therapy over LABA or ICS monotherapy to further reduce rates of COPD exacerbation in this patient population.

Efficacy:

- After accounting for the interim analysis, there was no significant difference in mortality rates between the combination LABA-ICS group and placebo group (or salmeterol group)
    - Mortality rates were significantly lower in the LABA-ICS group when compared to the ICS monotherapy group
- Annual COPD exacerbation rates were significantly lower in the LABA-ICS group when compared to any of the other treatment groups
- Respiratory function and health status was most improved from baseline in the LABA-ICS group

Safety:

- Pneumonia occurred at significantly higher rates in the ICS group and LABA-ICS group when compared to placebo
    - However, there was only 1 more pneumonia-related death in the LABA-ICS group compared to placebo (6 more in the ICS group compared to placebo)

Cost:

- The cost of using LABA-ICS therapy over LABA or ICS monotherapy must be balanced against the cost-savings achieved from reducing the annual rate of COPD exacerbation

Special Considerations/Populations:

- Prevention of COPD exacerbations is a key treatment goal in this patient population

Grade of Recommendation: **A**

TRITON-TIMI 38

Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007;357(20):2001-2015.

Objective: To determine the effect of prasugrel compared to clopidogrel on cardiovascular outcomes in patients with acute coronary syndrome and PCI.

Primary Efficacy Measure: Composite of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke

Primary Safety Measure: TIMI major bleeding

Participants: Patients with acute coronary syndrome and scheduled PCI

- Age ~61 years; male ~74%
- Unstable angina/NSTEMI ~74%; STEMI ~26%
- Baseline stenting: bare metal stent only ~47%; one or more drug-eluting stents ~47%

Inclusion Criteria:

- Acute coronary syndrome (unstable angina, NSTEMI and STEMI)
    - Unstable angina or NSTEMI: ischemic symptoms lasting > 10 minutes and occurring within 72 hours of randomization, TIMI risk score ≥ 3 and ST-segment deviation ≥ 1 mm (or elevated levels of cardiac biomarkers indicating necrosis)
    - STEMI: could enroll within 12 hours after symptom onset if PCI was planned (or within 14 days after receiving medical treatment for STEMI)

Exclusion Criteria:

- Increased bleeding risk
- Anemia or thrombocytopenia

Drugs: Prasugrel; clopidogrel

Design: Randomized, double-blind, active-controlled trial

Methods: Eligible patients received a loading dose of either prasugrel 60 mg or clopidogrel 300 mg anytime up to 1 hour after leaving the catheter lab. After PCI completion, patients were continued on maintenance therapy of either prasugrel 10 mg daily or clopidogrel 75 mg daily. All patients were required to take aspirin 75-162 mg once daily.

Duration: Median follow-up period of 14.5 months

Statistical Analysis: It was determined that 875 primary events were required to achieve 90% power (alpha = 0.05). The ITT population was used for the efficacy analyses and the mITT population (patients that received at least one dose of drug) was used for the safety analyses.

Results: A total of 13,608 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. Subgroup analyses demonstrated that patients ≥ 75 years old and those < 60 kg had no increased benefit with prasugrel compared to clopidogrel. Additionally, patients with prior stroke or TIA demonstrated no added benefit plus increased bleed risk with prasugrel. Patients age < 75 years weighing > 60 kg with no prior stroke or TIA had significantly lower rates of the primary composite outcome on subgroup analysis. Results from the subgroup analysis must be interpreted cautiously as this trial was not powered to detect such differences.

Prasugrel (N=6813) Vs Clopidogrel (N=6795)

Primary Composite Outcome:
643 (9.44%) vs 781 (11.5%); HR 0.81 (95% CI 0.73-0.90)
p<0.001; ARR 2.06%; NNT ~49

Cardiovascular Death:
133 (1.95%) vs 150 (2.21%); HR 0.89 (95% CI 0.70-1.12); p=0.31

Non-Fatal Myocardial Infarction:
475 (6.97%) vs 620 (9.12%); HR 0.76 (95% CI 0.67-0.85)
p<0.001; ARR 2.15%; NNT ~47

Non-Fatal Stroke:
61 (0.90%) vs 60 (0.88%); HR 1.02 (95% CI 0.71-1.45); p=0.93

Stent Thrombosis:
68 (1.00%) vs 142 (2.09%); HR 0.48 (95% CI 0.36-0.64)
p<0.001; ARR 1.09%; NNT ~92

TIMI Major Bleeding:
146 (2.14%) vs 111 (1.63%); HR 1.32 (95% CI 1.03-1.68)
p=0.03; ARI 0.51%; NNH ~194

Limitations:
- Subgroup analysis must be interpreted cautiously as this trial was not powered to detect such differences
- Patient population must be considered (PCI following acute coronary syndrome)

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I recommend the use of prasugrel over clopidogrel for use in dual antiplatelet therapy in most patients (age < 75 years, weight > 60 kg, no prior stroke or TIA) following an acute coronary syndrome and percutaneous coronary intervention. However, the increased risk for major bleeding with prasugrel use must be considered.

Efficacy:
- The rates of the primary composite outcome were significantly lower in the prasugrel group compared to clopidogrel
- The individual rate of non-fatal myocardial infarction was significantly lower with prasugrel
- Stent thrombosis occurred at significantly lower rates in the prasugrel group compared to clopidogrel

Safety:
- TIMI major bleeding occurred at significantly higher rates in the prasugrel group

Cost:
- The cost of using prasugrel must be balanced against the cost-savings of preventing a cardiovascular outcome, particularly non-fatal myocardial infarction
    - However, the cost of treating a major bleeding episode must also be considered

Special Considerations/Populations:
- Results of the subgroup analysis may lead to hesitancy in using prasugrel due to concerns of waning benefit in elderly patients over time, however dual antiplatelet therapy is not necessarily a life-long treatment and the continued need for said therapy should be evaluated periodically
- The majority of patients had unstable angina or NSTEMI for the qualifying event

Grade of Recommendation: **A**

UPLIFT

Tashkin DP, Celli B, Senn S, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med*. 2008;359(15):1543-1554.

Objective: To determine the long-term effects of tiotropium on clinical outcomes in COPD patients.

Primary Efficacy Measures: (1) Annual rate of decline in average FEV_1 before use of study drug and short-acting bronchodilator (2) annual rate of decline in average FEV_1 after use of study drug and short-acting bronchodilator

Secondary Efficacy Measures: (1) Quality of life (2) COPD exacerbations

- COPD exacerbation was defined as an increase in or new onset of more than one of the following symptoms lasting 3 or more days and requiring treatment with antibiotic or systemic corticosteroid: cough, sputum, sputum purulence, wheezing or dyspnea

Participants: COPD patients

- Age ~65 years; male ~74%
- FEV_1 ~48% of predicted value (post-bronchodilation)
- GOLD stage II ~45%; stage III ~44%
- Baseline long-acting beta agonist ~60%; inhaled corticosteroid ~62%

Inclusion Criteria:

- Age ≥ 40 years
- COPD diagnosis
- Smoking history of at least 10-pack years
- $FEV_1 \leq 70\%$ of predicted value (post-bronchodilation)
- $FEV_1/FVC \leq 70\%$ (post-bronchodilation)

Exclusion Criteria:

- Asthma
- COPD exacerbation or respiratory infection within previous 4 weeks
- Supplemental oxygen use > 12 hours per day
- History of pulmonary resection

Drug: Tiotropium

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients received either inhaled tiotropium 18 mcg or matching placebo once daily. The use of other respiratory medications (except inhaled anticholinergics) was allowed. After the trial completion, all patients received ipratropium 40 mcg four times daily and returned for a final assessment 30 days after.

Duration: Median treatment period of 1436 days (~3.9 years)

Statistical Analysis: It was determined that 5821 randomized patients would achieve 90% power (alpha = 0.05). All randomized patients that received study drugs and had three data points or more were included in the efficacy analyses. All randomized patients that received study drugs were included in the safety analyses.

Results: A total of 5993 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. There was no significant difference in the rates of FEV_1 decline (before or after bronchodilation) between treatment groups. However, annual rates of COPD exacerbations were significantly lower in the tiotropium group. Quality of life scores demonstrated a statistically higher quality of life within the tiotropium group; however, this statistical benefit is not considered clinically meaningful.

Tiotropium (N=2986) Vs Placebo (N=3006)

Average Annual Rate of FEV_1 Decline:

Before Bronchodilation:
30 mL/year vs 30 mL/year; p=0.95

After Bronchodilation:
40 mL/year vs 42 mL/year; p=0.21

Annual Rate of COPD Exacerbation (per patient-year):
0.73 vs 0.85; RR 0.86 (95% CI 0.81-0.91); p<0.001

Limitations:

- The use of other respiratory medications was allowed – potential confounding factor
- Trial results must be considered in addition to use of baseline respiratory medications

Level of Evidence: Level I – with minor limitations

Recommendation: For these reasons, I recommend the use of inhaled tiotropium to further reduce the rate of exacerbations in COPD patients. It is important to note that the morbidity benefit demonstrated in this trial was seen when used in addition to other inhaled respiratory medications (e.g. LABAs, ICS) and that is why optimization of a patient's current COPD current is reasonable prior to the addition of other agents.

Efficacy:

- The annual rate of FEV_1 decline (pre- and post-bronchodilation) was not significantly different between treatment groups
- Rate of COPD exacerbation was significantly lower in the tiotropium treatment group

Safety:

- Overall adverse event rates were similar between treatment groups
- The most common adverse event was COPD exacerbations

Cost:

- The cost of using inhaled tiotropium (in addition to baseline respiratory medications) must be balanced against the cost-savings achieved from lower rates of COPD exacerbations

Special Considerations/Populations:

- Tiotropium is a long-acting anticholinergic medication
- Trial design allowed for the use of other respiratory medications

Grade of Recommendation: **A**

VADT

Duckworth W, Abraira C, Moritz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med*. 2009;360(2):129-139.

Objective: To determine the effect of intensive glucose control versus standard glucose control on cardiovascular outcomes in patients with type 2 diabetes.

Primary Efficacy Measure: Composite of cardiovascular death, myocardial infarction, stroke, new or worsening congestive heart failure, surgical intervention for cardiac, cerebrovascular, or peripheral vascular disease, inoperable coronary artery disease and amputation for ischemic gangrene (time to first event)

Secondary Efficacy Measures: Microvascular complications (retinopathy, nephropathy, neuropathy)

Participants: Patients with type 2 diabetes non-responsive to current glucose-lowering therapy

- Age ~60 years; male ~97%
- HgA1c ~9.4%; duration of diabetes ~12 years
- BP ~131/76 mmHg; total cholesterol ~184 mg/dL; HDL ~36 mg/dL; LDL ~108 mg/dL
- Prior cardiovascular event ~40%; prior microvascular complication ~62%

Inclusion Criteria:

- Veterans age ≥ 41 years with type 2 diabetes
- Non-responsive to at least one oral agent and/or daily insulin injections
    - Defined as HgA1c > 4 standard deviations above the average of 7.5% (or ≥8.3%)

Exclusion Criteria:

- HgA1c < 7.5%
- Cardiovascular event within previous 6 months
- Advanced congestive heart failure
- Severe angina
- Life expectancy of less than 7 years
- BMI > 40
- SCr > 1.6 mg/dL
- ALT > 3 times the upper limit of normal

Drugs: n/a

Design: Randomized, open-label, active-comparator trial

Methods: Eligible patients were randomized to intensive glucose control or standard care. Patients with a BMI ≥27 were started on metformin plus rosiglitazone. Patients with a BMI <27 were started on glimepiride plus rosiglitazone. Patients in the intensive glucose control group were started at full doses, while those in the standard care group were started at half-dose. Insulin would be added rather than adjusting the dose of oral medication in patients not achieving HgA1c <6% in the intensive care group and <9% in the standard care group. Further therapy adjustments would follow the trial protocol, which did allow for the use of any approved medication. The target HgA1c for the intensive therapy group was ≤ 6% (while avoiding hypoglycemia) and 8-9% for the standard care group. Cardiovascular risk factors of hypertension and hyperlipidemia were treated uniformly in both groups. Unless contraindicated, all patients received aspirin and statin therapy.

Duration: Median follow-up period of 5.6 years

Statistical Analysis: It was determined that 1700 randomized patients would provide 86% power (alpha=0.05). The ITT population was used for all analyses. To account for an interim analysis, 0.0357 was determined to be the level of significance for the primary composite outcome.

Results: A total of 1791 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. After 6 months of follow-up, HgA1c had stabilized at 6.9% in the intensive therapy group and 8.4% in the standard therapy group. There was no significant difference in the rates of the primary composite outcome or the rates of the individual components between groups. Of the microvascular complications, only progression of albuminuria was significantly less frequent in the intensive therapy group. Rates of retinopathy, neuropathy and decline in renal function were not significantly different between groups.

Intensive Therapy (N=892) Vs Standard Care (N=899)

Primary Composite Outcome:
235 (26.3%) vs 264 (29.4%); HR 0.88 (95% CI 0.74-1.05); p=0.14

Increase in Albuminuria:
63/693 (9.09%) vs 97/703 (13.9%); p=0.01; ARR 4.71%; NNT ~22

Serious Hypoglycemia:
* *Fatal, life-threatening, disabling, incapacitating or requiring medical intervention* *
76 (8.52%) vs 28 (3.11%); p<0.001; ARI 5.41%; NNH ~18

Limitations:
- Open-label trial design
- Several of the initial glucose-lowering medications used in this trial are high-risk for hypoglycemia

Level of Evidence: Level I – with minor limitations

Recommendation: For these reasons, I do not recommend the use of intensive glucose-control over standard care to further reduce rates of macrovascular and microvascular outcomes in patients with type 2 diabetes.

Efficacy:
- Rates of the primary composite outcome (representing macrovascular events) were not significantly different between treatment groups
- Of the microvascular outcomes, only increase in albuminuria was significantly lower in the intensive therapy group compared to standard care

Safety:
- Predictably, rates of serious hypoglycemia were significantly higher in the intensive therapy group

Cost:
- The cost of intensive therapy must be balanced against the potential cost-savings of reducing the progression of albuminuria
    - The cost of monitoring for and managing hypoglycemia must also be considered

Special Considerations/Populations:
- The NNH for severe hypoglycemia is less than the NNT for increase in albuminuria, which indicates that the benefit of intensive therapy is not outweighed by the risk for significant harm

Grade of Recommendation: **A**

Val-HeFT

Cohn JN, Tognoni G; Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med*. 2001;345(23):1667-1675.

Objective: To determine the effect of valsartan on morbidity and mortality outcomes in patients with heart failure and reduced ejection fraction.

Primary Efficacy Measures: (1) All-cause mortality (2) Composite of all-cause mortality, cardiac arrest with resuscitation, heart failure hospitalization or use of IV inotropic/vasodilator drugs for ≥ 4 hours without hospitalization

Participants: Patients with heart failure and reduced ejection fraction

- Age ~63 years; male ~80%
- LVEF ~27%
- NYHA class II ~62%; class III ~36%
- Baseline ACEi ~93%; digoxin ~67%; diuretic ~85%; beta-blocker ~35%

Inclusion Criteria:

- Age ≥ 18 years
- History and clinical findings for heart failure for 3 months or more
- NYHA functional class II-IV (clinically stable)
- Stable heart failure therapy for 2 weeks (e.g., ACEi, diuretics, digoxin, beta-blockers)
- LVEF < 40%

Exclusion Criteria:

- Pregnant/nursing females
- Right-sided heart failure caused by pulmonary disease
- Acute myocardial infarction, cardiac surgery or angioplasty within previous 3 months
- Clinically significant renal, hepatic or hematological disorders

Drug: Valsartan

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients underwent a 2-4 week placebo run-in period to assess compliance and clinical stability. Those that successfully completed the run-in period were then randomized to either valsartan or matching placebo. Valsartan was initially dosed at 40 mg twice daily and the dose was to be doubled every two weeks until the target dose of 160 mg twice daily was achieved.

Duration: Mean follow-up period of 23 months

Statistical Analysis: It was determined that 906 deaths would provide 90% power (overall alpha=0.05). The level of significance for each coprimary endpoint was set at 0.02532.

Results: A total of 5010 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. The target dose of 160 mg twice daily was achieved in 84% of patients (average dose 254 mg/day). Significantly more patients in the valsartan group saw NYHA class improvement compared to placebo (23.1% vs 20.7%; $p<0.001$). Adverse events leading to discontinuation were significantly more common in the valsartan group, particularly dizziness and renal impairment. Additionally, increases in SCr (0.18 mg/dL vs 0.10 mg/dL; $p<0.001$) and potassium (0.12 mg/dL vs 0.07 mg/dL; $p<0.001$) were significantly higher in the valsartan group. However, rates of dyspnea, fatigue, edema and rales were significantly lower in the valsartan group ($p<0.01$).

Valsartan (N=2511) Vs Placebo (N=2499)

All-Cause Mortality:
495 (19.7%) vs 484 (19.4%); RR 1.02 (98% CI 0.88-1.18); p=0.80

Composite Outcome:
723 (28.8%) vs 801 (32.1%); RR 0.87 (97.5% CI 0.77-0.97)
p=0.009; ARR 3.26%; NNT ~31

Heart Failure Hospitalization:
346 (13.8%) vs 455 (18.2%); p<0.001; ARR 4.43%; NNT ~23

Cardiac Arrest With Resuscitation:
16 (0.64%) vs 26 (1.04%)

IV Inotropic/Vasodilator Therapy:
5 (0.20%) vs 5 (0.20%)

Limitations:

- Results should be interpreted as valsartan in addition to standard heart failure therapy, which included ACEis in the vast majority of patients at baseline (~93%)

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I do not recommend the use of valsartan in addition to standard therapy (specifically ACEi) in patients with heart failure with reduced ejection fraction. While the use of ACEi plus ARB may be reasonable in certain patients on optimal therapy to further reduce rates of morbidity the treatment risk must be carefully considered and weighed against any potential benefit.

Efficacy:

- There was no significant difference in the rates of all-cause mortality between groups
- Rates of the composite outcome of morbidity and mortality were significantly lower in the valsartan group, driven primarily by reductions in heart failure hospitalization (only individual component significantly lower than placebo)
- Significantly more patients in the valsartan group experienced improvement in their NYHA functional class

Safety:

- Treatment discontinuation due to adverse reactions was significantly more common in the valsartan group, particularly for adverse drug reactions of dizziness (1.6% vs 0.4%; p<0.001) and renal impairment (1.1% vs 0.2%; p<0.001)
- Increases in SCr and potassium levels were significantly higher in the valsartan group compared to placebo
- However, rates of dyspnea, fatigue, edema and rales were significantly lower in patients treated with valsartan

Cost:

- The cost of using valsartan must be balanced against the cost-savings of preventing heart failure hospitalization
- However, the cost of monitoring and managing increased adverse drug reactions must also be considered

Special Considerations/Populations:

- Only a small portion of patients included in this trial were on both ACEi and beta-blocker at baseline, despite guideline recommendations
- This trial demonstrated safety concerns and limited morbidity benefit with combination ACEi/ARB therapy (~93% of patients using ACEi at baseline)

Grade of Recommendation: **A**

VALIANT

Pfeffer MA, McMurray JJ, Velazquez EJ, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both.
N Engl J Med. 2003;349(20):1893-1906.

Objective: To determine the effect of valsartan (alone or in addition to ACEi) compared to ACEi alone on mortality outcomes in patients with heart failure or left-ventricular dysfunction.

Primary Efficacy Measure: All-cause mortality

Participants: Patients with acute myocardial infarction plus evidence of heart failure, left-ventricular dysfunction or both

- Age ~65 years; male ~69%
- LVEF ~35%; BP ~123/72 mmHg; HR ~76 bpm
- Baseline ACEi ~39%; beta-blocker ~70%; loop or thiazide diuretic ~50%

Inclusion Criteria:

- Age ≥ 18 years
- Acute myocardial infarction within previous 10 days plus signs of heart failure or evidence of left-ventricular dysfunction (LVEF ≤ 35% on echocardiography or contrast angiography, and/or LVEF ≤ 40% on radionuclide ventriculography)
- SBP > 100 mmHg
- SCr < 2.5 mg/dL

Exclusion Criteria:

- Significant valvular disease
- Previous intolerance/contraindication to ACEi/ARB therapy

Drugs: Valsartan; captopril

Design: Randomized, double-blind, active-controlled, non-inferiority trial

Methods: Eligible patients were randomized to receive valsartan 20 mg daily, captopril 6.25 mg daily or valsartan 20 mg plus captopril 6.25 mg once daily. Dosing was to be increased at the investigator discretion with the goal of achieving target dosing (valsartan 160 mg twice daily, captopril 50 mg three times daily, valsartan 80 mg twice daily plus captopril 50 mg three times daily) within the first 3 months.

Duration: Median follow-up period of 24.7 months

Statistical Analysis: The trial was designed to compare valsartan alone and captopril alone as well as valsartan plus captopril versus captopril alone (alpha = 0.0253 for both comparisons). It was determined that 14,500 randomized patients and 2700 deaths would provide 86-95% power. The ITT population was used for the primary analyses. If valsartan failed to prove superior to captopril, then non-inferiority (NI margin = 1.13) would be assessed.

Results: A total of 14,703 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. After year one, the average dose in the valsartan group was 247 mg/day, 117 mg/day in the captopril group and valsartan 116 mg/day plus captopril 107 mg/day in the combo therapy group. Valsartan demonstrated non-inferiority (but not superiority) to captopril regarding the outcome of all-cause mortality. Overall rates of discontinuation due to adverse effects (including hypotension and renal causes) were significantly higher in the combination therapy group compared to captopril alone. A post-hoc analysis demonstrated benefit of combination therapy over captopril alone regarding hospitalization for heart failure or myocardial infarction. However, it is important to note that this trial was not powered to detect this outcome and that it is a post-hoc analysis.

Valsartan (N=4909) Vs Captopril (N=4909)

All-Cause Mortality:
979 (19.9%) vs 958 (19.5%); HR 1.00 (97.5% CI 0.90-1.11); p=0.98

Hypotension Resulting in Permanent Discontinuation:
70/4885 (1.43%) vs 41/4879 (0.84%); p<0.05; ARI 0.59%; NNH ~168

Valsartan Plus Captopril (N=4885) Vs Captopril (N=4909)

All-Cause Mortality:
941 (19.3%) vs 958 (19.5%); HR 0.98 (97.5% CI 0.89-1.09); p=0.73

Hypotension Resulting in Permanent Discontinuation:
90/4862 (1.85%) vs 41/4879 (0.84%)
p<0.05; ARI 1.01%; NNH ~98

Renal Causes for Permanent Discontinuation:
61/4862 (1.25%) vs 40/4879 (0.82%); p<0.05; ARI 0.43%; NNH ~230

Limitations:
- Power set but not met - failed to achieve 2700 deaths (non-inferiority still demonstrated; clinical significance minimal)
- Patient population - acute myocardial infarction plus heart failure or LV dysfunction

Level of Evidence: Level II - with major limitations

Recommendation: For these reasons, I do not recommend the use of valsartan plus captopril over captopril alone for reducing mortality rates in patients with acute myocardial infarction plus heart failure or left ventricular dysfunction (or both). However, I do recommend the use of valsartan as an effective alternative to captopril in this high-risk patient population.

Efficacy:
- Valsartan demonstrated non-inferiority (but not superiority) to captopril regarding the outcome of all-cause mortality
- Rates of all-cause mortality were not significantly different between the valsartan plus captopril group and the captopril alone group
- While post-hoc analysis demonstrated benefit of valsartan plus captopril over captopril alone regarding hospitalization for heart failure or myocardial infarction this trial was not powered to detect said difference

Safety:
- Rates of permanent discontinuation due to adverse effects (notably hypotension and renal causes) were significantly higher in the combination group compared to captopril alone
- Rates of hypotension leading to permanent discontinuation were significantly higher in the valsartan group compared to the captopril group

Cost:
- The cost of using valsartan plus captopril must be balanced against the cost of using captopril alone as well as the cost of monitoring and managing adverse effects caused by combination ACEi/ARB therapy
- Also, the cost of using valsartan must be balanced against the cost of using captopril

Special Considerations/Populations:
- High-risk population (acute myocardial infarction plus heart failure or LV dysfunction)
- Dosing frequency of captopril must be considered – TID dosing may not be preferable in certain patients with adherence issues

Grade of Recommendation: **B**

VA NEPHRON-D

Fried LF, Emanuele N, Zhang JH, et al. Combined angiotensin inhibition for the treatment of diabetic nephropathy. *N Engl J Med*. 2013;369(20):1892-1903.

Objective: To determine the efficacy and safety of ACEi plus ARB therapy for reducing the progression of proteinuric diabetic nephropathy.

Primary Efficacy Measure: Composite of eGFR decrease (≥ 30 mL/min if baseline ≥ 60 mL/min; ≥ 50% if baseline < 60 mL/min), end-stage renal disease (dialysis or eGFR < 15 mL/min) or death

Secondary Efficacy Measure: Composite of eGFR decrease or end-stage renal disease

Participants: Patients with diabetic kidney disease

- Age ~65 years; male ~99%
- HgA1c ~7.8%; eGFR ~54 mL/min; UACR ~852 mg/g
- BP ~137/73 mmHg
- Baseline ACEi ~68%; baseline ARB ~18%

Inclusion Criteria:

- Veterans Affairs patients with type 2 diabetes
- eGFR 30-89.9 mL/min
- UACR ≥ 300 mg/g

Exclusion Criteria:

- Non-diabetic kidney disease
- Serum potassium > 5.5 mmol/L
- Current treatment with sodium polystyrene sulfonate (treats hyperkalemia)

Drugs: Lisinopril; losartan

Design: Randomized, double-blind, active-controlled trial

Methods: Eligible patients underwent a run-in period involving titration of losartan from 50 mg daily to 100 mg daily. Patients that successfully achieved losartan 100 mg daily for 30 days (serum potassium < 5.5 mmol/L and SCr increase < 30% from baseline) were randomized to receive the additional therapy of lisinopril 10 mg or placebo once daily. The dose of lisinopril was increased (as tolerated) every 2 weeks to a max of 40 mg daily.

Duration: Median follow-up period of 2.2 years

Statistical Analysis: It was determined that 1644 randomized patients and 759 primary events would provide 85% power (alpha = 0.05). The ITT population was used for the efficacy analyses.

Results: A total of 1448 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. The trial ended early at the recommendation of the safety monitoring committee due to concerns regarding increased rates of acute kidney injury and hyperkalemia in the ACEi plus ARB treatment group. There was no significant difference in rates of the primary or secondary composite outcomes. Additionally, there was no significant difference in the individual components of either composite outcome. Rates of cardiovascular events were similar between treatment groups.

ARB (N=724) Vs ACEi plus ARB (N=724)

Primary Composite Outcome:
152 (21.0%) vs 132 (18.2%); HR 0.88 (95% CI 0.70-1.12); p=0.30

eGFR Decrease (≥ 30 mL/min or ≥ 50%):
78 (10.8%) vs 59 (8.15%); p=0.17

End-Stage Renal Disease:
43 (5.94%) vs 27 (3.73%); HR 0.66 (95% CI 0.41-1.07); p=0.07

Death:
60 (8.29%) vs 63 (8.70%); HR 1.04 (95% CI 0.73-1.49); p=0.75

Myocardial Infarction, Heart Failure or Stroke:
136 (18.8%) vs 134 (18.5%); HR 0.97 (95% CI 0.76-1.23); p=0.79

Safety

Acute Kidney Injury:
80 (11.0%) vs 130 (18.0%); HR 1.70 (95% CI 1.3-2.2)
p<0.001; ARI 6.91%; NNH ~14

Hyperkalemia:
32 (4.42%) vs 72 (9.94%); HR 2.8 (95% CI 1.8-4.3)
p<0.001; ARI ~5.52%; NNH ~18

Limitations:

- Power set but not met – however, the trial was stopped early and significant differences in safety (hyperkalemia and acute kidney injury) were still demonstrated
- Patient population – consisted entirely of VA patients (limits external validity)

Level of Evidence: Level II – with major limitations

Recommendation: For these reasons, I do not recommend the use of combination ACEi/ARB therapy over ARB monotherapy for slowing the progression of diabetic kidney disease. The combination of ACEi and ARB therapy shows increased risk of harm with no evidence of benefit and therefore should be avoided.

Efficacy:

- There was no significant difference in the rates of the primary or secondary renal composite outcomes
    - Rates of the individual components of the composites were not significantly different
- There was no significant difference in the rates of the cardiovascular composite outcome

Safety:

- The trial was stopped early due to safety concerns
- Rates of hyperkalemia and acute renal injury were significantly higher in the ACEi plus ARB group

Cost:

- The cost of monitoring and managing hyperkalemia and acute renal injury must be considered in addition to the added cost of using ACEi in addition to ARB therapy

Special Considerations/Populations:

- Conditional power calculations estimate that even if the trial was continued there would not be a significant difference in the primary composite outcome between treatment groups

Grade of Recommendation: **B**

VAST-D

Mohamed S, Johnson GR, Chen P, et al. Effect of Antidepressant Switching vs Augmentation on Remission Among Patients With Major Depressive Disorder Unresponsive to Antidepressant Treatment: The VAST-D Randomized Clinical Trial. *JAMA*. 2017;318(2):132-145.

Objective: To compare the efficacy and safety of different treatment strategies (i.e. switching or augmenting) in patients with depression unresponsive to current therapy.

Primary Efficacy Measure: Remission (QIDS-C16 score ≤ 5 at two consecutive follow-up visits during acute treatment phase)

- QIDS-C16 score ranges from 0-27 (higher score, more severe symptoms of depression)

Secondary Efficacy Measures: (1) QIDS-C16 score reduction ≥ 50% from baseline to week 12 (2) CGI Improvement Scale Rating of 1 (very much improved) or 2 (much improved) at any scheduled visit through week 12

Participants: Patients with major depressive disorder unresponsive to current therapy

- Age ~54 years; male ~85%
- Number of previous antidepressant courses ~2 (median)
- QIDS-C16 ~17

Inclusion Criteria:

- Veterans' Health Administration (VHA) patients
- Age ≥ 18 years
- Diagnosis of major depressive disorder (MDD)
- Unresponsive to at least one course of antidepressant therapy
    - 6-8 weeks of SSRI, SNRI or mirtazapine

Exclusion Criteria:

- Suicidal ideation requiring inpatient treatment
- Currently treated with bupropion or any antipsychotic
- Dementia
- History of bipolar disorder, schizophrenia, psychosis
- Seizure disorder

Drugs: Aripiprazole, bupropion SR

Design: Randomized, active-controlled trial

Methods: Eligible patients were randomized to one of three treatment groups. Patients would be switched from their current therapy to bupropion SR (switch group) or have current therapy augmented with bupropion SR (augment-bupropion group) or aripiprazole (augment-aripiprazole group). After randomization, both patient and investigator were informed of the assigned treatment group. Bupropion SR dosing was titrated (as tolerated) from 150 mg daily to 300 mg-400 mg daily. Aripiprazole dosing was titrated (as tolerated) from 2 mg daily to 5 mg-15 mg daily. This acute treatment phase lasted 12 weeks.

Duration: 12 weeks

Statistical Analysis: It was determined that 1518 randomized patients would achieve 90% power for the primary efficacy measure comparing the augmented-aripiprazole group to the switch group (alpha=0.05) and the augmented-bupropion group to the switch group (alpha=0.025). A level of significance of 0.025 was used for the secondary efficacy measures.

Results: A total of 1522 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. Both switch and augment-bupropion groups achieved the max dose of bupropion SR 200 mg BID at 12 weeks. The augment-aripiprazole group achieved aripiprazole 10 mg daily at 12 weeks. There was no significant difference in serious adverse event rates between treatment groups. Anxiety occurred at significantly lower rates in the augment-aripiprazole group. However, rates of weight gain (≥ 7%), somnolence and extrapyramidal symptoms were significantly higher in the augment-aripiprazole group compared to the switch group and augment-bupropion group.

Switch Group (N=511) Vs Augment-Bupropion Group (N=506)

Remission:
114 (22.3%) vs 136 (26.9%); RR 1.20 (95% CI 0.97-1.50); p=0.09

≥ 50% Reduction in QIDS-C16 Score from Baseline:
319 (62.4%) vs 332 (65.6%); RR 1.05 (95% CI 0.96-1.15); p=0.29

CGI Improvement:
356 (69.7%) vs 376 (74.3%); RR 1.07 (95% CI 0.99-1.15); p=0.10

Switch Group (N=511) Vs Augment-Aripiprazole Group (N=505)

Remission:
114 (22.3%) vs 146 (28.9%); RR 1.30 (95% CI 1.05-1.60); p=0.02

≥ 50% Reduction in QIDS-C16 Score from Baseline:
319 (62.4%) vs 375 (74.3%); RR 1.19 (95% CI 1.09-1.29); p<0.001

CGI Improvement:
356 (69.7%) vs 400 (79.2%); RR 1.14 (95% CI 1.06-1.22); p<0.001

Augment-Bupropion (N=506) Vs Augment-Aripiprazole Group (N=505)

Remission:
136 (26.9%) vs 146 (28.9%); RR 1.08 (95% CI 0.88-1.31); p=0.47

≥ 50% Reduction in QIDS-C16 Score from Baseline:
332 (65.6%) vs 375 (74.3%); RR 1.13 (95% CI 1.04-1.23); p=0.003

CGI Improvement:
376 (74.3%) vs 400 (79.2%); RR 1.07 (95% CI 1.00-1.14); p=0.07

Limitations:

- All patients were from the VA Health System – external validity limited
- Open-label trial design (lack of blinding)
- Short trial duration – cannot extrapolate results or make assumptions regarding long term effects of treatment
- Trial results must be considered in relation to previous/current pharmacotherapy (primarily SSRI or SNRI)

Level of Evidence: Level I – with major limitations

Recommendation: For these reasons, I do not recommend switching therapy to bupropion in patients with major depressive disorder unresponsive to current treatment. Instead, I recommend using aripiprazole (over bupropion) to augment pharmacotherapy. However, it is important to individualize treatment (particularly in psychiatric patients) and consider drug side-effect profiles when making therapy changes.

Efficacy:

- Both augment-bupropion and augment-aripiprazole groups demonstrated significantly greater rates of remission compared to the switch group
    - There was no significant difference in the remission rates between the augment groups
- The augment-aripiprazole group demonstrated significantly greater improvement in QIDS-C16 score compared to augment-bupropion

Safety:

- Rates of serious adverse effects were similar between treatment groups
- Rates of weight gain (≥ 7%), somnolence and extrapyramidal symptoms were significantly higher in the augment-aripiprazole group
    - However, rates of anxiety were lowest in this treatment group

Cost:

- The cost of using aripiprazole to augment current therapy must be balanced against the cost of using other treatment options as well as the value provided to the patient in terms of improved quality of life

Special Considerations/Populations:

- While the duration was not extensive and the patient population limits external validity the results do help provide useful information on how to guide pharmacotherapy choices in patients that are not sufficiently responsive
- Open-label trial design raises the potential for patient and investigator bias

Grade of Recommendation: **B**

VERTIS CV

Cannon CP, Pratley R, Dagogo-Jack S, et al. Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes. *N Engl J Med*. 2020;383(15):1425-1435.

Objective: To determine the effect of ertugliflozin on cardiovascular outcomes in patients with type 2 diabetes.

Primary Efficacy Measure: Composite of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke

Secondary Efficacy Measures: (1) Composite of cardiovascular death and heart failure hospitalization (2) Cardiovascular death (3) Composite of renal death, renal replacement therapy or doubling of serum creatinine

Participants: Patients with type 2 diabetes and established cardiovascular disease

- Age ~64 years; male ~70%
- HgA1c ~8.2%
- Coronary artery disease ~76%; cerebrovascular disease ~23%

Inclusion Criteria:

- Age ≥ 40 years with type 2 diabetes
- HgA1c 7.0% to 10.5%
- Established atherosclerotic cardiovascular disease

Exclusion Criteria:

- Type 1 diabetes
- History of diabetic ketoacidosis
- eGFR < 30 mL/min

Drug: Ertugliflozin

Design: Randomized, double-blind, placebo-controlled, non-inferiority trial

Methods: Eligible patients were randomized to receive ertugliflozin 5 mg or 15 mg or matching placebo once daily. The use of additional glucose-lowering medications was allowed to treat according to standards of care.

Duration: Mean follow-up period of 3.5 years

Statistical Analysis: It was determined that 8000 randomized patients and 939 primary events would achieve 96% power for non-inferiority. A non-inferiority margin of 1.3 was used. The data from both ertugliflozin groups would be pooled and analyzed for the primary composite outcome. If non-inferiority was demonstrated then sequential testing of secondary outcomes for superiority would occur. The modified ITT population (all randomized patients that received one or more doses of study medication) was used for the non-inferiority analysis. The ITT population was used for superiority analyses.

Results: A total of 8246 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. The average change in HgA1c from baseline to week 18 was -0.70% in the 5 mg group, -0.72% in the 15 mg group and -0.22% in the placebo group. Non-inferiority of ertugliflozin to placebo was demonstrated for the primary efficacy outcome. Rates of the key secondary outcomes were not significantly different between treatment groups. While rates of heart failure hospitalization were notably lower in the ertugliflozin group compared to placebo this result must be considered exploratory due to failure of prior hierarchical testing.

Ertugliflozin (N=5499) Vs Placebo (N=2747)

Primary Composite Outcome:
653/5493 (11.9%) vs 327/2745 (11.9%); HR 0.97 (95.6% CI 0.85-1.11)
The mITT population was used for the non-inferiority analysis

Cardiovascular Death:
341 (6.20%) vs 184 (6.70%); HR 0.92 (95.8% CI 0.77-1.11)

Non-Fatal Myocardial Infarction:
310 (5.64%) vs 148 (5.39%); HR 1.04 (95% CI 0.86-1.27)

Non-Fatal Stroke:
157 (2.86%) vs 78 (2.84%); HR 1.00 (95% CI 0.76-1.32)

Heart Failure Hospitalization:
139 (2.53%) vs 99 (3.60%); HR 0.70 (95% CI 0.54-0.90)

Safety:

Urinary Tract Infection - 5 mg Vs Placebo:
336/2746 (12.2%) vs 279/2745 (10.2%); p=0.02; ARI 2.07%; NNH ~48

Urinary Tract Infection - 15 mg Vs Placebo:
330/2747 (12.0%) vs 279/2745 (10.2%); p=0.03; ARI 1.84%; NNH ~54

Female Genital Mycotic Infection - 5 mg Vs Placebo:
48/798 (6.02%) vs 20/844 (2.37%); p<0.001; ARI 3.65%; NNH ~27

Female Genital Mycotic Infection - 15 mg Vs Placebo:
65/832 (7.81%) vs 20/844 (2.37%); p<0.001; ARI 5.44%; NNH ~18

Male Genital Mycotic Infection - 5 mg Vs Placebo:
86/1948 (4.41%) vs 22/1901 (1.16%); p<0.001; ARI 3.26%; NNH ~30

Male Genital Mycotic Infection - 15 mg Vs Placebo:
98/1915 (5.12%) vs 22/1901 (1.16%); p<0.001; ARI 3.96%; NNH ~25

Limitations:

- Patient population - all had established cardiovascular disease and type 2 diabetes

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I recommend the use of ertugliflozin as a safe glucose-lowering therapy in patients with type 2 diabetes and established cardiovascular disease. However, I do not recommend the use of ertugliflozin to reduce rates of cardiovascular morbidity and mortality in high-risk patients with type 2 diabetes. It would be reasonable to utilize a SGLT2 inhibitor with demonstrated cardiovascular benefit in this patient population.

Efficacy:

- Ertugliflozin demonstrated non-inferiority to placebo regarding the rates of the primary composite outcome of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke
    - Individual rates of the composite outcome were not significantly different between treatment groups
- While rates of heart failure hospitalization were notably lower in the ertugliflozin treated patients this result cannot be considered significant due to prior failure of hierarchical testing

Safety:

- Overall rates of adverse drug reactions were similar between treatment groups
    - Rates of urinary tract infections and genital mycotic infections were significantly higher in the ertugliflozin treated patients

Cost:

- The cost of using ertugliflozin must be balanced against the cost of using a SGLT2 inhibitor with demonstrated cardiovascular benefit

Special Considerations/Populations:

- Cannot apply trial results to other SGLT2 inhibitors (and vice versa)

Grade of Recommendation: **A**

V-HeFT I

Cohn JN, Archibald DG, Ziesche S, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans Administration Cooperative Study. *N Engl J Med*. 1986;314(24):1547-1552.

Objective: To determine the effect of vasodilator therapy on mortality outcomes in patients with chronic congestive heart failure.

Primary Efficacy Measure: All-cause mortality

Participants: Male patients with congestive heart failure receiving digoxin and a diuretic

- Age ~58 years
- LVEF ~30%

Inclusion Criteria:

- Male patients age 18-75 with chronic congestive heart failure
- Evidence of cardiac dilation or LVEF < 45%
- Reduced exercise tolerance
- Receiving digoxin and diuretic therapy

Exclusion Criteria:

- Exercise tolerance limited by chest pain
- Myocardial infarction within previous 3 months
- Obstructive valvular disease or obstructive myocardial disease
- Chronic pulmonary disease
- Requirement of antihypertensive medication (beta-blockers, CCBs, etc.) other than diuretics

Drugs: Hydralazine; isosorbide dinitrate; prazosin

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible clinically stable patients were randomized to either prazosin 2.5 mg QID and placebo QID, hydralazine 37.5 mg QID and isosorbide dinitrate 20 mg QID or two sets of matching placeboes QID. After 2 weeks the dosing for each group was increased to 2 tablets QID in the absence of side effects. Digoxin and diuretic dosing were adjusted to achieve optimal serum levels and fluid balance.

Duration: Mean follow-up period of 2.3 years

Statistical Analysis: It was determined that 720 randomized patients would achieve 84% power (alpha=0.05). The ITT population was used for the primary analysis.

Results: A total of 642 patients underwent randomization. Baseline patient characteristics were similar between treatment groups, except for a higher cardiothoracic ratio and lower exercise tolerance in the prazosin group. Average dosing was as follows: prazosin 18.6 mg/day, hydralazine 270 mg/day, isosorbide dinitrate 136 mg/day. Results support the hypothesis that hydralazine/isosorbide reduces mortality for an initial 3 years, followed by a diminishing treatment effect. The most common adverse drug reactions in the hydralazine/isosorbide treatment group were headache and dizziness.

Prazosin (N=183) Vs Placebo (N=273)

All-Cause Mortality:
91 (49.7%) vs 120 (44.0%); p>0.05

Hydralazine Plus Isosorbide Dinitrate (N=186) Vs Placebo (N=273)

All-Cause Mortality:
72 (38.7%) vs 120 (44.0%); p=0.046; ARR 5.25%; NNT ~20

Limitations:

- Power set but not met - failed to randomize 720 patients
- Mortality benefit of hydralazine/isosorbide appears to wane after 3 years (possibly due to small number of remaining patients)
- Female patients were not included in this trial

Level of Evidence: Level II - with major limitations

Recommendation: For these reasons, I do not recommend the use of prazosin to reduce mortality rates in patients with congestive heart failure. Instead, I recommend the use of hydralazine plus isosorbide dinitrate. However, it is important to note that recommended heart failure therapy has changed significantly since the publishing of this trial which limits the applicability of the results. Therefore, it would be reasonable to optimize currently recommended heart failure therapy prior to considering the addition of hydralazine plus isosorbide dinitrate.

Efficacy:

- Mortality rates were not significantly different between prazosin and placebo groups
- The hydralazine/isosorbide group demonstrated significantly lower rates of all-cause mortality compared to placebo, however, this treatment effect only last 3 years before diminishing

Safety:

- The hydralazine/isosorbide dinitrate group demonstrated the highest overall rates of adverse drug reactions, most notably dizziness and headache

Cost:

- The cost of using hydralazine/isosorbide must be balanced against the cost-savings of reducing mortality rates over a 3 year period

Special Considerations/Populations:

- Treatment benefit of hydralazine/isosorbide can only be extended to 3 years based on the results in this trial
- It is important to consider the baseline medications used in these heart failure patients (digoxin and diuretic)

Grade of Recommendation: **B**

V-HeFT II

Cohn JN, Johnson G, Ziesche S, et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med*. 1991;325(5):303-310.

Objective: To determine the effect of hydralazine plus isosorbide dinitrate compared to enalapril on mortality outcomes in patients with heart failure and reduced ejection fraction.

Primary Efficacy Measure: All-cause mortality

Participants: Male heart failure patients with reduced ejection fraction receiving digoxin and diuretic

- Age ~61 years
- LVEF ~29%
- NYHA class II ~51%; class III ~43%

Inclusion Criteria:

- Males age 18-75 with chronic heart failure
- Cardiac dysfunction (cardiothoracic ratio ≥ 0.55, LVEF < 45%, etc.)
- Reduced exercise tolerance

Exclusion Criteria:

- Myocardial infarction or cardiac symptoms within previous 3 months
- Exercise limited by angina
- Obstructive valvular/lung disease

Drugs: Hydralazine; isosorbide dinitrate; enalapril

Design: Randomized, double-blind, active-controlled trial

Methods: All eligible patients were established on optimal dosing of digoxin and diuretic prior to randomization. Patients were randomized to either enalapril 5 mg twice daily or hydralazine 37.5 mg QID plus isosorbide dinitrate 20 mg QID (plus matching placebo). After two weeks the dosing would be doubled, if tolerated. The use of other vasodilators or antihypertensives was discouraged.

Duration: Mean follow-up period of 2.5 years

Statistical Analysis: Criteria for meeting power was not mentioned in this trial. The level of significance was set at 0.042 and the ITT population was used for the primary analyses.

Results: A total of 804 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. The average dosing was 15 mg/day in the enalapril group and 199 mg/day hydralazine plus 100 mg/day isosorbide dinitrate in the combination group. Overall, all-cause mortality was not significantly different between treatment groups (p=0.08). However, cumulative all-cause mortality at 2 years was significantly lower in the enalapril treatment group (262 vs 239; 25% vs 18%; p=0.016). While both enalapril and hydralazine/isosorbide treatment groups demonstrated increases in LVEF, the increase was significantly greater in the hydralazine/isosorbide treatment group after week 13 (+3.30% vs +2.10%; p=0.026).

Enalapril (N=403) Vs Hydralazine Plus Isosorbide Dinitrate (N=401)

All-Cause Mortality:
132 (32.8%) vs 153 (38.2%); p=0.08

Sudden Cardiac Death (no warning):
41 (10.2%) vs 63 (15.7%); p=0.015; ARR 5.54%; NNT ~19

Sudden Cardiac Death (with warning):
16 (3.97%) vs 29 (7.23%); p=0.032; ARR 3.26%; NNT ~31

Death Due to Pump Failure:
50 (12.4%) vs 40 (9.98%); p=0.44

Limitations:

- Power not mentioned
- Baseline medication usage (or lack thereof) should be considered when interpreting results

Level of Evidence: Level II - with major limitations

Recommendation: For these reasons, I recommend the use of enalapril over hydralazine/isosorbide dinitrate to further reduce mortality rates in male patients with heart failure and reduced ejection fraction. While there may be benefit in using both agents (enalapril plus hydralazine/isosorbide) this was not studied in the trial.

Efficacy:

- Overall rates of all-cause mortality were not significantly difference between treatment groups but were notably lower in the enalapril group
- However, after two years the mortality rate was significantly lower in the enalapril group
- Rates of sudden cardiac death (with or without warning) were significantly lower in the enalapril group, however rates of death due to pump failure were similar between groups
- Increase in LVEF was significantly greater in the hydralazine/isosorbide group compared to enalapril

Safety:

- Rates of cough and symptomatic hypotension were significantly higher with enalapril
- Rates of headache were significantly higher in the hydralazine/isosorbide group

Cost:

- The cost of using enalapril must be balanced against the cost of using hydralazine plus isosorbide dinitrate

Special Considerations/Populations:

- All patients were established on optimal dosing of digoxin plus diuretic prior to randomization to trial medications

Grade of Recommendation: **B**

VICTORIA

Armstrong PW, Pieske B, Anstrom KJ, et al. Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med*. 2020;382(20):1883-1893.

Objective: To determine the efficacy and safety of vericiguat in patients with heart failure and reduced ejection fraction and recent decompensation.

Primary Efficacy Measure: Composite of cardiovascular death or first heart failure hospitalization

Participants: Patients with HFrEF with recent decompensation/evidence of worsening heart failure

- Age ~67 years; male ~76%
- LVEF ~29%; NYHA class II ~59%; NYHA class III ~40%
- Hospitalized for heart failure within previous 3 months ~67%
- Triple therapy (beta-blocker, mineralocorticoid antagonist & ACEi/ARB/ARNi) ~60%

Inclusion Criteria:

- Age ≥ 18 years
- Chronic heart failure with LVEF ≤ 45%
- NYHA functional class II-IV
- Elevated natriuretic peptide levels within previous 30 days (ex. BNP ≥ 300 pg/mL)
- Evidence of worsening heart failure:
    - Hospitalized within previous 3 months,
    - Hospitalized within previous 3-6 months, or
    - Received IV diuretics without hospitalization within previous 3 months

Exclusion Criteria:

- SBP < 100 mmHg
- Use of long-acting nitrates/PDE-5 inhibitors/guanylate cyclase stimulators
- Use of IV inotropes or implanted left-ventricular assist devices

Drug: Vericiguat

Design: Randomized, double-blind, placebo-controlled trial

Methods: Eligible patients were randomized to receive either vericiguat 2.5 mg daily (target dose 10 mg daily) or matching placebo. Guideline-based medication therapy (including ARNis) in addition to study drugs was encouraged in this trial.

Duration: Median follow-up period of 10.8 months

Statistical Analysis: It was determined that 4872 randomized patients and 782 primary events would achieve 80% power (alpha=0.025). The ITT population was used for primary efficacy analyses.

Results: A total of 5050 patients underwent randomization. Baseline patient characteristics were similar between treatment groups. The majority of patients (~67%) had experienced heart failure hospitalization within the previous 3 months of randomization. At 12 months, ~90% of all patients were receiving the target dose of 10 mg daily. Overall rates of adverse drug reactions, including hypotension and syncope, were similar between treatment groups.

Vericiguat (N=2526) Vs Placebo (N=2524)

Composite of Cardiovascular Death or First Heart Failure Hospitalization:
897 (35.5%) vs 972 (38.5%); HR 0.90 (95% CI 0.82-0.98)
p=0.02; ARR 3.00%; NNT ~34

Cardiovascular Death:
206 (8.16%) vs 225 (8.91%)
Not preceded by heart failure hospitalization

First Heart Failure Hospitalization:
691 (27.4%) vs 747 (29.6%); HR 0.90 (95% CI 0.81-1.00)
Confidence interval contains 1.00

Total Heart Failure Hospitalizations:
1123 vs 1336; HR 0.91 (95% CI 0.84-0.99); p=0.02
Patients could be hospitalized more than once

Cardiovascular Death (total):
414 (16.4%) vs 441 (17.5%); HR 0.93 (95% CI 0.81-1.06)
Including deaths preceded by heart failure hospitalization

All-Cause Mortality:
512 (20.3%) vs 534 (21.2%); HR 0.95% (95% CI 0.84-1.07); p=0.38
Not preceded by heart failure hospitalization

Limitations:

- Patient population - HFrEF plus evidence of recent decompensation (high-risk group)
- Cannot extrapolate results to patients with heart failure and preserved ejection fraction

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I recommend the use of vericiguat to further reduce morbidity outcomes, specifically recurrent heart failure hospitalizations, in patients with heart failure and reduced ejection fraction with evidence of recent decompensation. However, due to the limited demonstrated benefit I recommend vericiguat be reserved as a last-line agent for patients with recurrent hospitalizations already receiving optimized guideline directed medication therapy.

Efficacy:

- Rates of the primary composite outcome were significantly lower in the vericiguat group compared to placebo, however the individual components of cardiovascular death and first heart failure hospitalization were not significantly different
- Only total heart failure hospitalizations were significantly lower in the vericiguat group
- Rates of cardiovascular death and all-cause mortality were not significantly different between groups

Safety:

- Rates of hypotension and syncope were not significantly different between treatment groups

Cost:

- The cost of using vericiguat must be balanced against the cost-savings of preventing recurrent heart failure hospitalizations

Special Considerations/Populations:

- The trial results must be considered in addition to guideline directed medication therapy
- Vericiguat did not demonstrate a significant mortality benefit over placebo
- Even in this high-risk group (~67% hospitalized within previous 3 months) vericiguat only demonstrated significant benefit regarding total heart failure hospitalizations

Grade of Recommendation: **A**

VITAL (Omega-3 Fatty Acid)

Manson JE, Cook NR, Lee IM, et al. Marine n-3 Fatty Acids and Prevention of Cardiovascular Disease and Cancer. *N Engl J Med*. 2019;380(1):23-32.

Objective: To determine the effect of omega-3 fatty acid supplementation on cancer and cardiovascular outcomes.

Primary Efficacy Measures: (1) Invasive cancer of any type (2) Major cardiovascular events (composite of myocardial infarction, stroke and cardiovascular death)

Participants: Middle-age to elderly patients with no personal history of cancer or cardiovascular disease

- Age ~67 years; male ~49%
- Hypertension treated with medication ~50%
- Baseline use of cholesterol-lowering medication ~38%

Inclusion Criteria:

- Males age 50 years and older
- Females age 55 years and older
- No history of cancer (except non-melanoma skin cancer)
- No history of cardiovascular disease

Exclusion Criteria:

- Allergy to fish
- Unwillingness to discontinue other fish oil supplementation during trial period

Drug: Omega-3 fatty acid (EPA 460 mg plus DHA 380 mg)

Design: Randomized, double-blind, placebo-controlled trial (two-by-two factorial design)

Methods: The purpose of the Vital Research Group is to assess the effects of vitamin D and omega-3 fatty acid supplementation on cancer and cardiovascular outcomes. To achieve this the trial was set up with a two-by-two factorial design to allow for testing of both supplements simultaneously. Eligible patients underwent randomization to receive cholecalciferol 2000 IU once daily or matching placebo. From there, all patients would be randomized to receive either omega-3 fatty acid 1000 mg once daily (containing EPA 460 mg plus DHA 380 mg) or matching placebo. This creates a total of four treatment groups: (1) active cholecalciferol and active omega-3 (2) active cholecalciferol and placebo omega-3 (3) placebo cholecalciferol and active omega-3 (4) placebo cholecalciferol and placebo omega-3. The results relating to the effect of omega-3 fatty acid supplementation on cancer and cardiovascular outcomes are reviewed here. See the VITAL (Vitamin D) trial review for information on the effect of vitamin D3 supplementation on said outcomes.

Duration: Median follow-up period of 5.3 years

Statistical Analysis: It was determined that 10,000 randomized male patients and 10,000 randomized female patients would provide at least 85% power (alpha = 0.05). This assumes that only one active agent (cholecalciferol or omega-3 fatty acid) would be effective regarding the primary objectives. The ITT population was used for analyses.

Results: A total of 25,871 patients underwent randomization (criteria for power met). Baseline patient characteristics were similar between groups. The average adherence rates were ~93% in the omega-3 fatty acid group and ~82% in the placebo group. There was no significant difference in rates of invasive cancer or cardiovascular outcomes between treatment groups. Rates of myocardial infarction (a component of the cardiovascular composite outcome) were significantly lower in the omega-3 fatty acid group. However, due to the trial design said results must be considered exploratory. Rates of adverse effects relevant to omega-3 fatty acid supplementation (e.g., GI symptoms, increased bleeding) were similar between treatment groups.

Omega-3 Fatty Acid (N=12,933) Vs Placebo (N=12,938)

Invasive Cancer:
820 (6.34%) vs 797 (6.16%); HR 1.03 (95% CI 0.93-1.13)

Cardiovascular Composite Outcome:
386 (2.98%) vs 419; (3.24%) HR 0.92 (95% CI 0.80-1.06)

Myocardial Infarction:
145 (1.12%) vs 200 (1.54%); HR 0.72 (95% CI 0.59-0.90)

Limitations:

- Trial duration may have been insufficient to determine true treatment benefit of supplementation regarding the prevention of cancer (two-year follow-up trial currently in-progress)
- Patient population – no personal history of cancer or cardiovascular disease

Level of Evidence: Level I – with minor limitations

Recommendation: For these reasons, I do not recommend the use of omega-3 fatty acid supplementation for prevention of cancer or cardiovascular disease. Omega-3 fatty acid supplementation may be appropriately used for several other indications but should be carefully justified according to patient-specific factors and/or lab values.

Efficacy:

- There was no significant difference in the rate of invasive cancer or cardiovascular outcomes between treatment groups
- While there was evidence suggestive cardiovascular benefit (in terms of lower rates of myocardial infarction) these results must be considered exploratory

Safety:

- There were similar rates of adverse events relating to omega-3 fatty acid supplementation

Cost:

- The cost of daily omega-3 fatty acid supplementation must be balanced against any potential treatment benefit

Special Considerations/Populations:

- Patient population – no personal history of cancer or cardiovascular disease
- The selected dose of omega-3 fatty acid used in this trial matches the American Heart Association's recommendation for cardio protection

Grade of Recommendation: **A**

VITAL (Vitamin D)

Manson JE, Cook NR, Lee IM, et al. Vitamin D Supplements and Prevention of Cancer and Cardiovascular Disease. *N Engl J Med*. 2019;380(1):33-44.

Objective: To determine the effect of vitamin D3 supplementation on cancer and cardiovascular outcomes.

Primary Efficacy Measures: (1) Invasive cancer of any type (2) Major cardiovascular events (composite of myocardial infarction, stroke and cardiovascular death)

Participants: Middle-age to elderly patients with no personal history of cancer or cardiovascular disease

- Age ~67 years; male ~49%
- Baseline 25-hydroxyvitamin D level ~31 ng/mL
- Hypertension treated with medication ~50%
- Baseline use of cholesterol-lowering medication ~38%

Inclusion Criteria:

- Males age 50 years and older
- Females age 55 years and older
- No history of cancer (except nonmelanoma skin cancer)
- No history of cardiovascular disease

Exclusion Criteria:

- Renal failure or dialysis
- History of hypercalcemia
- Consuming greater than 800 IU of vitamin D supplements daily

Drug: Cholecalciferol (vitamin D3)

Design: Randomized, double-blind, placebo-controlled trial (two-by-two factorial design)

Methods: The purpose of the Vital Research Group is to assess the effects of vitamin D and omega-3 fatty acid supplementation on cancer and cardiovascular outcomes. To achieve this the trial was set up with a two-by-two factorial design to allow for testing of both supplements simultaneously. Eligible patients underwent randomization to receive cholecalciferol 2000 IU once daily or matching placebo. From there, all patients would be randomized to receive either omega-3 fatty acid 1000 mg once daily or matching placebo. This creates a total of four treatment groups: (1) active cholecalciferol and active omega-3 (2) active cholecalciferol and placebo omega-3 (3) placebo cholecalciferol and active omega-3 (4) placebo cholecalciferol and placebo omega-3. The results relating to the effect of cholecalciferol supplementation on cancer and cardiovascular outcomes are reviewed here. See the VITAL (Omega-3) trial review for information on the effect of omega-3 fatty acid supplementation on said outcomes.

Duration: Median follow-up period of 5.3 years

Statistical Analysis: It was determined that 10,000 randomized male patients and 10,000 randomized female patients would provide at least 85% power (alpha = 0.05). This assumes that only one active agent (cholecalciferol or omega-3 fatty acid) would be effective regarding the primary objectives. The ITT population was used for analyses.

Results: A total of 25,871 patients underwent randomization (criteria for power met). Baseline patient characteristics were similar between groups. The average adherence rates were ~82% in the cholecalciferol group and ~80% in the placebo group. There was no significant difference in rates of invasive cancer or cardiovascular outcomes between treatment groups. Sub-group analysis revealed evidence suggesting treatment benefit regarding lower rates of invasive cancer in patients with a BMI < 25 (or median BMI < 27.1). However, the trial was not designed to detect said differences and said results must be considered exploratory. Rates of adverse events relating to vitamin D supplementation were similar between treatment groups.

Cholecalciferol (N=12,927) Vs Placebo (N=12,944)

Invasive Cancer:
793 (6.13%) vs 824 (6.37%); HR 0.96 (95% CI 0.88-1.06)

Sub-group Analysis of Patients with BMI < 25:
206 vs 278; HR 0.76 (95% CI 0.63-0.90)

Sub-group Analysis of Patients with Median BMI <27.1:
361 vs 421; HR 0.86 (95% CI 0.75-0.99)

Cardiovascular Composite Outcome:
396 (3.06%) vs 409 (3.16%); HR 0.97 (95% CI 0.85-1.12)

Limitations:
- Trial duration may have been insufficient to determine true treatment benefit of supplementation regarding the prevention of cancer (two-year follow-up trial currently in-progress)
- Patient population – no personal history of cancer or cardiovascular disease

Level of Evidence: Level I – with minor limitations

Recommendation: For these reasons, I do not recommend the use of cholecalciferol supplementation for prevention of cancer or cardiovascular disease. Cholecalciferol supplementation may be appropriately used for several other indications (e.g., treatment of vitamin D deficiency, prevention of osteoporosis) but should be carefully justified according to patient-specific factors and/or lab values.

Efficacy:
- There was no significant difference in the rate of invasive cancer or cardiovascular outcomes between treatment groups
- While there was evidence of cancer benefit in patients with lower baseline BMI these results must be considered exploratory

Safety:
- There were similar rates of adverse events relating to vitamin D supplementation

Cost:
- The cost of daily cholecalciferol supplementation (2000 IU) must be balanced against any potential treatment benefit

Special Considerations/Populations:
- Patient population – no personal history of cancer or cardiovascular disease

Grade of Recommendation: **A**

WAVE

Warfarin Antiplatelet Vascular Evaluation Trial Investigators, Anand S, Yusuf S, et al. Oral anticoagulant and antiplatelet therapy and peripheral arterial disease. *N Engl J Med*. 2007;357(3):217-227.

Objective: To determine the effect of anticoagulation in addition to antiplatelet therapy compared to antiplatelet therapy alone on cardiovascular outcomes in patients with peripheral artery disease.

Primary Efficacy Measures: (1) Composite of myocardial infarction, stroke or cardiovascular death (2) Composite of myocardial infarction, stroke, severe ischemia of peripheral or coronary arteries leading to urgent intervention or cardiovascular death

Participants: Patients with peripheral artery disease

- Age ~64 years; male ~74%
- ABI ~0.83; peripheral artery disease of lower extremities ~82%
- Baseline aspirin ~92%

Inclusion Criteria:

- Age 35 to 85 years
- Peripheral artery disease

Exclusion Criteria:

- Indication for oral anticoagulant therapy
- Actively bleeding
- High bleed risk
- Stroke within previous 6 months
- Required dialysis

Drugs: Warfarin (anticoagulation); clopidogrel/ticlopidine/aspirin (antiplatelet)

Design: Randomized, open-label, active-controlled trial

Methods: Eligible patients underwent a 2 to 4 week run-in period consisting of both anticoagulant and antiplatelet therapy. Antiplatelet agents included aspirin (81-325 mg/day), ticlopidine or clopidogrel. Warfarin was the primary anticoagulant used (target INR 2.0-3.0). Achievement of a stable target INR during the run-in period allowed for randomization to antiplatelet monotherapy or antiplatelet plus anticoagulant therapy. Dual antiplatelet therapy was not allowed unless the patient had an acute coronary syndrome or coronary stent during the follow-up period.

Duration: Mean follow-up period of 35 months

Statistical Analysis: It was initially determined that 2400 randomized patients would achieve 80% power (alpha=0.029 for each co-primary endpoint). However, due to slower than expected recruitment the steering committee stopped enrollment at 2,161 patients and extended the follow-up period to 3.5 years for the 1396 patients already enrolled in the study to maintain power. The ITT population was used for the primary efficacy analyses.

Results: A total of 2161 patients underwent randomization. Baseline patient characteristics were similar between treatment groups with the exception of coronary artery disease, which was higher in patients randomized to the antiplatelet group (p=0.02). The average INR in patients receiving anticoagulation was 2.2 with therapeutic levels 62% of the time. Neither co-primary endpoint was significantly different between treatment groups, nor were the individual components of the composite outcomes (with the exception of hemorrhagic stroke). There was no significant difference in the rates of fatal bleeding between treatment groups.

Anticoagulation Plus Antiplatelet (N=1080) Vs Antiplatelet Only (N=1081)

Primary Outcome #1:
132 (12.2%) vs 144 (13.3%); RR 0.92 (95% CI 0.73-1.16); p=0.48

Primary Outcome #2:
172 (15.9%) vs 188 (17.4%); RR 0.91 (95% CI 0.74-1.12); p=0.37

Hemorrhagic Stroke:
14 (1.30%) vs 0 (0%); RR 15.2 (95% CI 2.0-115.6)
p=0.001; ARR 1.30%; NNH ~77

Safety:

Life-Threatening Bleed:
43 (3.98%) vs 13 (1.20%); RR 3.41 (95% CI 1.84-6.35)
p<0.001; ARI 2.78%; NNH ~36

Intracranial Bleed:
14 (1.30%) vs 0 (0%); RR 15.2 (95% 2.0-115.6)
p=0.001; ARI 1.30%; NNH ~77

Moderate Bleed:
31 (2.87%) vs 11 (1.02%); RR 2.82 (95% CI 1.43-5.58)
p=0.002; ARI 1.85%; NNH ~54

Minor Bleed:
417 (38.6%) vs 115 (10.6%); RR 3.63 (95% CI 3.01-4.38)
p<0.001; ARI 28.0%; NNH ~3

Limitations:
- Open-label trial design
- Proportion of which antiplatelet agents were used is unknown
- Criteria for meeting power was adjusted after trial start

Level of Evidence: Level I - with minor limitations

Recommendation: For these reasons, I do not recommend the use of anticoagulation therapy in addition to antiplatelet therapy over antiplatelet therapy alone for prevention of cardiovascular events in patients with peripheral artery disease.

Efficacy:
- Rates of co-primary endpoints were not significantly difference between treatment groups
- Hemorrhagic stroke occurred at a significantly higher rates in the combination therapy group compared to antiplatelet therapy alone

Safety:
- Rates of life-threatening bleeds, intracranial bleeds, moderate and minor bleeding events were all significantly higher in the combination therapy group
- However, rates of fatal bleeding events were not significantly different between groups

Cost:
- The cost of using anticoagulation therapy in addition to antiplatelet therapy must be considered in addition to the cost of treating bleeding episodes
- The cost of monitoring INR must also be considered

Special Considerations/Populations:
- The patient population had primarily peripheral artery disease of the lower extremities

Grade of Recommendation: **A**

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“Good doctors use both individual clinical expertise and the best available external evidence, and neither alone is enough.”

- David Sackett, MD

While one’s clinical expertise increases with experience and practice, the ability to grow and maintain a working knowledge of available research and trials is severely limited by the finite hours per day, few of which can be freely dedicated to said task.

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