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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

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Trials Indexed Alphabetically

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 additional 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 quick biostatistics 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.

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 due to the trial being 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**

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**

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**

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**

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. doi:10.1056/NEJMoa1901963

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**

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**

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 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**

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**

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**

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**

“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.

High-Powered Medicine includes concise, clinically relevant data with evidence-based recommendations from over 175 landmark trials spanning more than 30 years which can then be paired with one’s own clinical expertise to optimize pharmacotherapy.