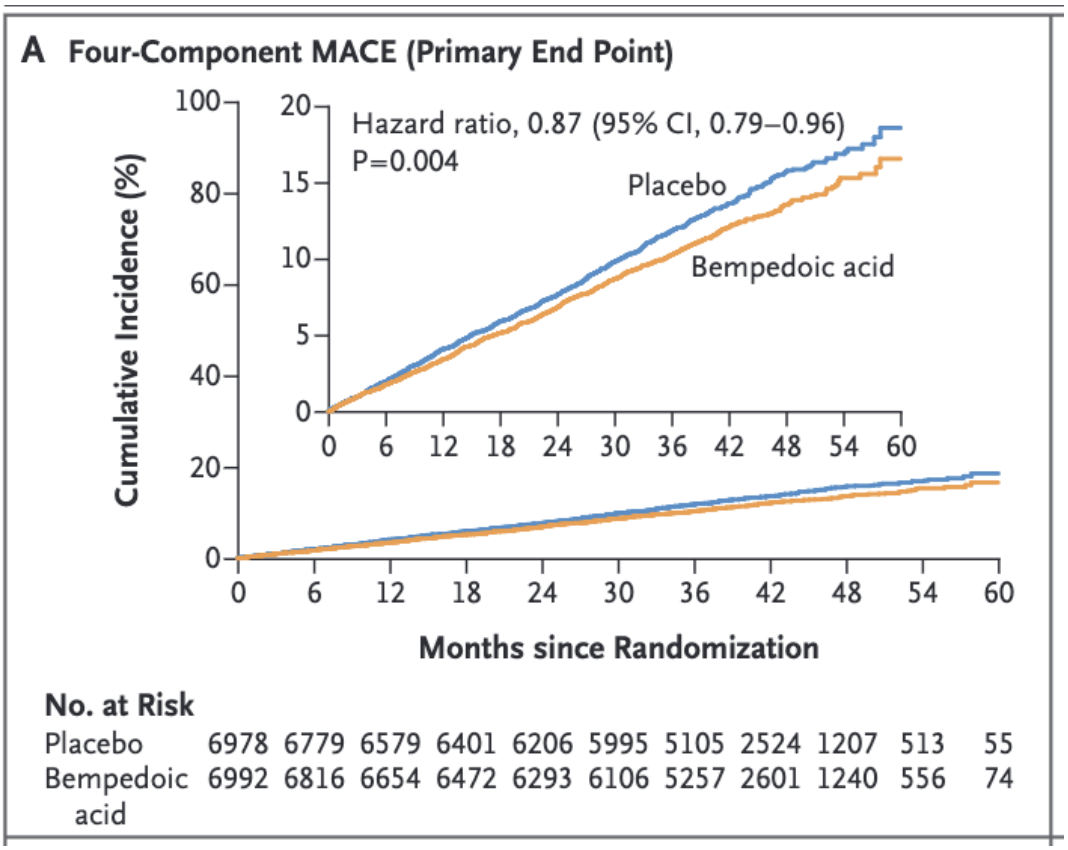
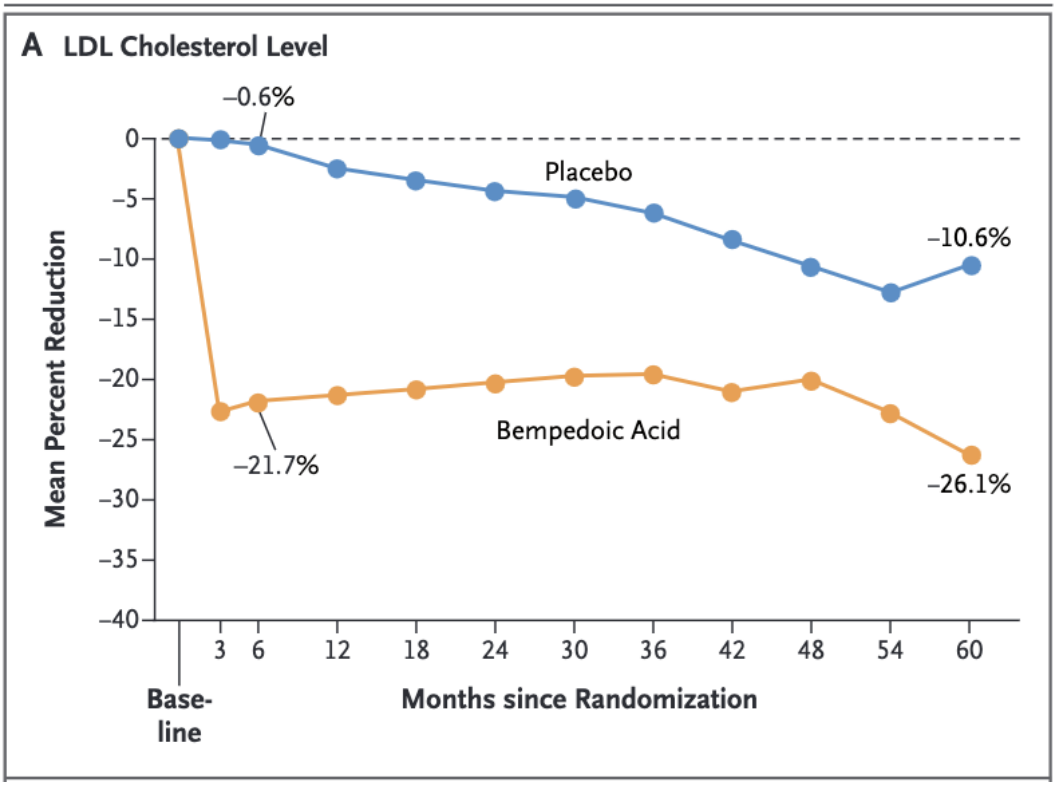
Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients

BACKGROUND AND OVERVIEW	
Citation	Nissen SE, Lincoff AM, Brennan D, et al. Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients. N Engl J Med. 2023;388(15):1353-1364. doi:10.1056/NEJMoa2215024
Background	Bempedoic acid is an adenosine triphosphate-citrate lyase (ACL) inhibitor that lowers low-density lipoprotein cholesterol (LDL-C) by inhibition of cholesterol synthesis in the liver. It is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or established atherosclerotic cardiovascular disease who require additional lowering of LDL-C. The effect of bempedoic acid on cardiovascular morbidity and mortality has not been determined.
Study Objective	Determine the effects of bempedoic acid on adverse cardiovascular events in a mixed population of patients for whom primary or secondary prevention is clinically indicated but who were unable or unwilling to take guideline-recommended doses of statins.
Funding	Esperion Therapeutics
METHODS	
Study design	● Randomized ● Double-blind ● Placebo controlled
Inclusion Criteria	● Age 18-85 years old ● Patients qualifying for primary or secondary prevention of CVD ● Unable or unwilling to receive statins owing to an adverse effect that had started or increased during statin therapy and resolved or improved after statin therapy was discontinued (statin intolerant)
Exclusion Criteria	● Pregnant or breastfeeding ● Lack of adherence (i.e., less than 80% of planned doses) ● Total fasting triglycerides >500 mg/dL (5.6 mmol/L) ● Recent (within 90 days prior to or during screening) acute CVD event ● Uncontrolled hypertension, defined as mean sitting systolic blood pressure ≥180 mmHg and/or diastolic blood pressure (DBP) ≥110 mmHg
Study Procedures	● 4-week run-in period during which patients received single-blind placebo ● If patients could not receive placebo because of unacceptable adverse effects or if adherence was less than 80% according to the tablet count, they were deemed to be ineligible for randomization ● Patients who successfully completed the run-in period were randomly assigned in a 1:1 ratio to receive bempedoic acid at a daily oral dose of 180 mg or matching placebo
Outcomes	Primary efficacy endpoint: ● Composite of major adverse CV events (death from CV causes, nonfatal MI, nonfatal stroke, coronary revascularization) assessed in a time-to-first-event analysis Secondary efficacy endpoints: ● Death from CV events, nonfatal stroke, or nonfatal MI ● Fatal or nonfatal MI ● Coronary revascularization ● Fatal or nonfatal stroke ● Death from cardiovascular causes ● Death from any cause
Statistical analyses	● 90% Power ● Alpha=0.05

	● Modified ITT ● Type I error was controlled using hierarchical testing. ● If the primary efficacy endpoint was significant then the secondary efficacy endpoints were tested hierarchically each at the 0.05 level
RESULTS	
Baseline characteristics	● Baseline characteristics were well matched between groups. ● Avg age: 65.5 ± 9.0 yrs ● Gender: 48.2 % female ● Race ~ 91.2 % white ● ~30% Primary Prevention ● Mean LDL: 139 mg/dL ● Diabetes: 45.6% ● Low dose statin 22.7% ● Ezetimibe: 11.5%
Sample Size	● 13,970 – Total enrolled ● 6,992 – Bempedoic Acid ● 6,978 – Placebo
Treatment Results	The incidence of a primary end-point event was significantly lower with bempedoic acid than with placebo (819 patients [11.7%] vs. 927 [13.3%]; hazard ratio, 0.87; 95% confidence interval [CI], 0.79 to 0.96; P=0.004) See graphs on page 3 NNT = 63 people
Adverse Events	● Incidence of hyperuricemia was higher in the bempedoic acid group than in the placebo group (10.9% vs. 5.6%) ●Gout (3.1% vs. 2.1%) ●Cholelithiasis (2.2% vs. 1.2%).
DISCUSSION & CONCLUSIONS	
Study strengths	● Trial design (randomized and double-blinded) ● Large sample size ● Patients followed for 40.6 months
Study limitations	● Patients with lack of adherence (<80% were excluded) ● Patient population primarily Caucasian making the study less applicable to patient populations in Central Arkansas ● Low baseline LDL (however, comparable to statin landmark trials) ● Exclusion of patients with uncontrolled hypertension or with A1C>10% ● Composite endpoint ● Patients who could not tolerate placebo due to adverse effects during the run-in period were excluded which could have allowed for side effect outcomes in the bempedoic acid group to be falsely statistically significant
Applicability and impact on pharmacists/healthcare providers	● Good option for patients unable to tolerate statin, or who need additional LDL-lowering therapy. ● Option for patients who want to avoid injections from PCSK9 Inhibitors.
Conclusions and recommendations	In patients that are unable or unwilling to take statins and require primary or secondary prevention of cardiovascular disease, bempedoic acid may be considered to prevent major cardiovascular adverse events. Future studies comparing bempedoic acid directly to statins, ezetimibe, and PCSK9 inhibitors would be beneficial.

Reviewed by Erica Smith, PharmD


A Four-Component MACE (Primary End Point)
Cumulative Incidence (%)
Hazard ratio, 0.87 (95% CI, 0.79–0.96)
P=0.004
Placebo
Bempedoic acid
Months since Randomization
No. at Risk
Placebo 6978 6779 6579 6401 6206 5995 5105 2524 1207 513 55
Bempedoic acid 6992 6816 6654 6472 6293 6106 5257 2601 1240 556 74


A LDL Cholesterol Level
Mean Percent Reduction
–0.6%
Placebo
–10.6%
–21.7%
Bempedoic Acid
–26.1%
Base-line
Months since Randomization