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Effect of Bempedoic Acid vs Placebo Added to Maximally Tolerated Statins on Low-Density Lipoprotein Cholesterol in Patients at High Risk for Cardiovascular Disease

The CLEAR Wisdom Randomized Clinical Trial

Anne C. Goldberg, MD; Lawrence A. Leiter, MD; Erik S. G. Stroes, MD, PhD; Seth J. Baum, MD; Jeffrey C. Hanselman, MS; LeAnne T. Bloedon, MS, RD; Narendra D. Lalwani, PhD, MBA; Pragna M. Patel, PharmD; Xin Zhao, MD, MA; P. Barton Duell, MD

RobotReviewer report

Risk of bias table

trial	design	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment
Goldberg AC, 2019	RCT	+	+	+	+

Trial summaries

n	Participants	Interventions	Outcomes	punchline	finding
779	patients at high cardiovascular risk receiving maximally tolerated lipid-lowering therapy, Patients at High Risk for Cardiovascular Disease, 779 randomized patients (mean age, 64.3 years; 283 women [36.3%]), 740 (95.0%) completed the trial, patients at high risk for cardiovascular disease receiving maximally tolerated statins, 91 clinical sites in North America and Europe from November 2016 to September 2018, with a final date of follow-up of September 22, 2018, 779 patients with atherosclerotic cardiovascular disease, heterozygous familial hypercholester-olemia, or both met randomization criteria, which included LDL-C level 70 mg/dL (1.8 mmol/L) or greater while receiving maximally tolerated lipid-lowering therapy, patients who do not achieve sufficient reduction in low-density lipoprotein cholesterol (LDL-C) level with available lipid-	Bempedoic Acid vs Placebo, bempedoic acid vs placebo, bempedoic acid, placebo	LDL-C levels, nasopharyngitis, high-sensitivity C-reactive protein, LDL-C level, hyperuricemia, density lipoprotein cholesterol, apolipoprotein B, urinary tract infection, total cholesterol, changes in levels of lipids, lipoproteins, and biomarkers, Low-Density Lipoprotein Cholesterol, mean LDL-C level	Significant reductions with bempedoic acid vs placebo were observed at week 12 for non-high-density lipoprotein cholesterol (-10.8% vs 2.3%; difference,-13.0% [95% CI,-16.3% to-9.8%]; P < .001), total cholesterol (-9.9% vs 1.3%; difference,-11.2% [95% CI,-13.6% to-8.8%]; P < .001), apolipoprotein B (-9.3% vs 3.7%; difference,-13.0% [95% CI,-16.1% to-9.9%]; P < .001), and high-sensitivity C-reactive protein (median,-18.7% vs-9.4%;	,Üì sig decrease

lowering therapies

Characteristics of studies

Goldberg AC, 2019

Population	1. Subgroup analyses for the primary end point and for safety assessments were performed in the following groups: cardiovascular disease risk category (ASCVD vs heterozygous familial hypercholesterolemia), baseline statin intensity (low/moderate [including no statin] vs high), baseline LDL-C category (<130 mg/dL, ,â•130 and <160 mg/dL, ,â•160 mg/dL), history of diabetes, age (<65 years, ,â•65 to <75 years, ,â•75 years), race, sex, body mass index category (<25, ,â•25 and <30, ,â•30), and region. 2. Patients were excluded from the study if they had a total fasting triglycer- ide level of 500 mg/dL (5.6 mmol/L) or higher, body mass index 50 or greater (calculated as weight in kilograms divided by height in meters squared), severe renal impairment (esti- mated glomerular filtration rate 3. Among 779 randomized patients (mean age, 64.3 years; 283 women [36.3%]), 740 (95.0%) completed the trial.
Interventio n	1. INTERVENTIONS Patients were randomized 2:1 to treatment with bempedoic acid (180 mg) (n = 522) or placebo (n = 257) once daily for 52 weeks. 2. After completing a 1-week screening period and 4-week placebo run-in phase, patients were randomized 2:1 to treatment with bempedoic acid (180 mg) or placebo once daily for 52 weeks. 3. Maximally tolerated lipid-lowering therapy was determined by the investigator and included a maximally tolerated statin dose alone or in combination with other approved lipid-lowering therapies, excluding simvastatin at an average daily dose of 40 mg or greater, mipomersen, lomitapide, lipoprotein apheresis, or gemfibrozil.
Outcomes	1. Secondary efficacy end points were the percent change from baseline to week 24 in LDL-C and to week 12 in levels of non-HDL-C, total cholesterol, apoB, and hsCRP as well as absolute change from baseline to weeks 12 and 24 in LDL-C. Tertiary efficacy end points included week 24 and 52 data for efficacy mea- sures and percent changes from baseline in levels of triglyc- erides and HDL-C. Statistical Analysis 2. Assessments Blood samples for assessment of fasting lipids, includ- ing levels of LDL-C, high-density lipoprotein cholesterol (HDL-C), non-HDL-C, total cholesterol, and triglycerides were collected at baseline and at weeks 4, 12, 24, and 52 (to convert LDL-C, HDL-C, and total cholesterol values to mmol/L, multiply by 0.0259; to convert triglyceride values to mmol/L, multiply by 0.0113). 3. The primary end point was percent change from baseline in LDL-C level at week 12.

Bias	Judgement	Support for judgement
Random sequence generation	low	1. Randomization was performed centrally using an interactive web response system, with stratification by presence of heterozygous familial hypercholesterolemia and baseline statin intensity (low-, moderate-, or high-intensity 15). 2. After completing a 1-week screening period and 4-week placebo run-in phase, patients were randomized 2:1 to treatment with bempedoic acid (180 mg) or placebo once daily for 52 weeks. 3. The sponsor, clinical site personnel, and patients were blinded to study treatment and lipid mea- sures for 52 weeks.
Allocation concealment	low	1. Randomization was performed centrally using an interactive web response system, with stratification by presence of heterozygous familial hypercholesterolemia and baseline statin intensity (low-,

		moderate-, or high-intensity 15). 2. After completing a 1-week screening period and 4-week placebo run-in phase, patients were randomized 2:1 to treatment with bempedoic acid (180 mg) or placebo once daily for 52 weeks. 3. We also thank IQVIA for their oversight of patient randomization, clinical laboratory services, statistical analyses, clinical monitoring, data management, and clinical programming and thank the independent expert committee for clinical event adjudication.
Blinding of participants and personnel	low	1. The sponsor, clinical site personnel, and patients were blinded to study treatment and lipid mea- sures for 52 weeks. 2. Four events (0.8%) in the bempedoic acid group (including the death from unknown cause) and 2 events (0.8%) in the placebo group were positively adjudicated as car- diovascular deaths (eTable 5 in Supplement 3). 3. Gout and increased blood uric acid level were experienced, respectively, by 2.1% and 2.7% of patients in the bempedoic acid group and 0.8% and 0.4% of patients in the placebo group.
Blinding of outcome assessment	low	1. The sponsor, clinical site personnel, and patients were blinded to study treatment and lipid mea- sures for 52 weeks. 2. Data collection, management, and analysis were performed on behalf of the sponsor by IQVIA. 3. All fatal adverse events were assessed by the investigator as un-related to study drug.

References

1. Goldberg AC et al. Effect of Bempedoic Acid vs Placebo Added to Maximally Tolerated Statins on Low-Density Lipoprotein Cholesterol in Patients at High Risk for Cardiovascular Disease Pharmacotherapy 2019. 18(3); 183-8 PMID: 1608850