Journal of the American Heart Association

ORIGINAL RESEARCH

Bempedoic Acid for Prevention of Cardiovascular Events in People With Obesity: A CLEAR Outcomes Subset Analysis

Harold E. Bays, MD; LeAnne Bloedon, MS; Danielle Brennan, MS; Lei Lei, PhD; A. Michael Lincoff, MD; Stephen J. Nicholls, MBBS, PhD; Jorge Plutzky, MD; Heather A. Powell, PharmD; Steven E. Nissen, MD

BACKGROUND: Obesity and hypercholesterolemia independently increase cardiovascular disease risk. This analysis evaluated the efficacy and safety of bempedoic acid in people with obesity participating in the CLEAR (Cholesterol Lowering via Bempedoic Acid [ECT1002], an ACL-Inhibiting Regimen) Outcomes trial.

METHODS: CLEAR Outcomes randomized 13 970 patients to daily bempedoic acid 180 mg or placebo. Exploratory outcomes including major adverse cardiovascular events-4 (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization), low-density lipoprotein cholesterol, hs-CRP (high-sensitivity C-reactive protein), weight change, and safety were assessed over a median of 40.7 months in 6177 patients with baseline body mass index ≥30 kg/m^2.

RESULTS: In people with obesity, bempedoic acid resulted in placebo-corrected reductions in low-density lipoprotein cholesterol of −22.5% and hs-CRP of −23.2% at 6 months. Bempedoic acid treatment resulted in a major adverse cardiovascular events-4 reduction of 23% (hazard ratio [HR], 0.77 [95% CI, 0.67–0.89]) versus placebo. Nonfatal and fatal MI were reduced by 32% (HR, 0.68 [95% CI, 0.53–0.86]), coronary revascularization was reduced by 24% (HR, 0.76 [95% CI, 0.63–0.92]), and fatal and nonfatal stroke were reduced by 36% (HR, 0.64 [95% CI, 0.45–0.89]) compared with placebo. At month 36, mean±SD change in weight from baseline was −2.3 (6.3) kg for bempedoic acid and −1.4 (6.1) kg for placebo. Adverse events were reported in 87.4% of bempedoic acid patients and 86.7% of placebo patients. The mean±SD change in uric acid at 6 months was 0.81 (1.26) mg/dL for bempedoic acid versus −0.04 (1.05) mg/dL for placebo.

CONCLUSIONS: Among people with obesity, bempedoic acid reduced major adverse cardiovascular events, low-density lipoprotein cholesterol, and hs-CRP, with a safety profile consistent with previous reports.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique Identifier: NCT02993406.

Key Words: bempedoic acid ■ cardiovascular disease ■ cardiovascular risk ■ lipid lowering ■ obesity ■ statin intolerance

More than 40% of adults in the United States and almost 900 million adults worldwide are living with obesity.[1,2] According to both the American Heart Association and European Society of Cardiology, obesity directly contributes to cardiovascular risk factors (eg, dyslipidemia, type 2 diabetes, hypertension, and sleep disorders) and increases cardiovascular disease (CVD) and CVD mortality independently.[3,4] Among the adiposopathic consequences of obesity are adipose tissue immunopathies and endocrinopathies

Correspondence to: Harold E. Bays, MD, MFOMA, FTOS, FACC, FNLA, FASPC, Louisville Metabolic and Atherosclerosis Research Center, University of Louisville School of Medicine, 3288 Illinois Avenue, Louisville, KY 40213. Email: hbaysmd@outlook.com

This article was sent to Tiffany M. Powell-Wiley, MD, MPH, Associate Editor, for review by expert referees, editorial decision, and final disposition.

For Sources of Funding and Disclosures, see page 7 and 8.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Bempedoic acid administered to people with obesity participating in the CLEAR (Cholesterol Lowering via Bempedoic Acid [ECT1002], an ACL-Inhibiting Regimen) Outcomes study experienced a reduction in low-density lipoprotein cholesterol by 22.5% and hs-CRP (high-sensitivity C-reactive protein) by 23.2%.
- Among people with obesity, after a median follow-up of 40.7 months, bempedoic acid reduced the risk of major adverse cardiovascular events-4 versus placebo by 23% (absolute between-group difference of 3.2%), major adverse cardiovascular events-3 by 27%, risk of nonfatal and fatal myocardial infarction by 32%, coronary revascularization by 24%, and nonfatal and fatal stroke by 36%, with the hazard ratios for the individual components of the major adverse cardiovascular events-4 primary composite end point being directionally consistent with the overall study population.
- Bempedoic acid was associated with a similar safety profile in people living with obesity as the overall CLEAR Outcomes patient population.

What Are the Clinical Implications?

- Cardiovascular disease-event prevention among people with obesity at high cardiovascular disease risk involves reducing risk factors, such as reducing low-density lipoprotein cholesterol levels.
- In this analysis, bempedoic acid reduced low-density lipoprotein cholesterol levels and potentially reduced inflammation as reflected by a reduction in an inflammatory marker (hs-CRP), which may have contributed to the reduction in major adverse cardiac events.

Nonstandard Abbreviations and Acronyms

ACL	adenosine triphosphate–citrate lyase
MACE	major adverse cardiovascular event

that contribute to cardiovascular risk factors, such as type 2 diabetes, hypertension, and predisposition to thrombosis.[5–7] CVD risk is further increased when adiposopathic metabolic and immune abnormalities are coupled with the biomechanical and structural abnormalities that often accompany an increase in fat mass (eg, increased cardiac output, sleep apnea, impaired diastolic function, compression of kidneys, compression of venous return, and immobility leading to physical inactivity).[6–13] The increase in CVD risk, as well as increased risk of other diseases (eg, cancer) account for why obesity increases all-cause mortality.[14,15]

A mainstay of treatment among patients at high CVD risk is the effective management of CVD risk factors.[16] Clinically meaningful weight reduction, whether through use of antiobesity medications or bariatric surgery, may not only improve CVD risk factors (eg, blood glucose and blood pressure) and the biomechanical fat mass contributors to CVD but may also reduce the risk of CVD events.[17–19] Incident CVD event risk depends on cumulative prior exposure to low-density lipoprotein-cholesterol (LDL-C) and, independently, time course of area of accumulation.[20] Unfortunately, interventions that mildly to moderately reduce body fat typically result in only mild to modest decreases in LDL-C. Thus, according to a joint expert review from the Obesity Medicine Association and the National Lipid Association, "a dual priority is early intervention to prevent or treat both excess adiposity and elevated blood levels of atherogenic cholesterol (ie, increased LDL-C or non-HDL-C [high-density lipoprotein-cholesterol])."[21]

Bempedoic acid, an ACL (adenosine triphosphate–citrate lyase) inhibitor that decreases intrahepatic cholesterol production and upregulates LDL receptor expression, enhances clearance of circulating LDL particles and thus reduces LDL-C levels. In the cholesterol synthetic pathway, ACL activity precedes the production of acetyl coenzyme A, indicating that ACL inhibition may lower free fatty acid levels and potentially reduce insulin resistance without increasing adiposity.[22,23] Bempedoic acid 180 mg daily was studied in 13 970 patients unwilling or unable to take recommended statins who had, or were at high risk for, CVD in the CLEAR (Cholesterol Lowering via Bempedoic Acid [ECT1002], an ACL-Inhibiting Regimen) Outcomes trial.[24] Bempedoic acid reduced the incidence of the 4-component composite major adverse cardiovascular event (MACE) end point (defined as death from cardiovascular causes, nonfatal myocardial infarction [MI], nonfatal stroke, or coronary revascularization) versus placebo (11.7% versus 13.3%; hazard ratio [HR], 0.87 [95% CI, 0.79–0.96]; P=0.004), lowered LDL-C and hs-CRP (high-sensitivity C-reactive protein), and did not result in new-onset diabetes (in patients without diabetes at baseline) or worsened hemoglobin A1c (HbA1c; in patients with diabetes at baseline).[24,25]

This current report describes the efficacy and safety of bempedoic acid among people with obesity (baseline body mass index [BMI] ≥30 kg/m^2) enrolled in CLEAR Outcomes. Specifically, we aim to further characterize the effect of bempedoic acid on end points relative to people with obesity at high cardiovascular risk, including the individual MACE components,

changes in LDL-C and hs-CRP, weight, markers of glycemic risk, and safety.

METHODS

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedures.

The study design, full inclusion and exclusion criteria, and main results of CLEAR Outcomes have been published.[24,26] Briefly, CLEAR Outcomes was a randomized, double-blind, placebo-controlled clinical trial at 1250 sites in 32 countries evaluating bempedoic acid 180 mg or placebo daily in patients with statin intolerance who had elevated LDL-C and high cardiovascular risk. Patients were included if they were aged 18 to 85 years, with baseline LDL-C at least 100 mg/dL and a history of CVD (such as coronary artery disease, peripheral artery disease, or atherosclerotic cerebrovascular disease; ie, secondary prevention) or were without CVD but considered at high risk for a cardiovascular event based on a coronary artery calcium score >400 Agatston units, presence of either type 1 or 2 diabetes in women >65 years or men >60 years, Reynolds risk score >30%, or Systematic Coronary Risk Evaluation risk >7.5% over 10 years (ie, primary prevention). Investigators assessed and confirmed the diagnosis of statin intolerance, which for the purposes of this trial included adverse events that started or increased during statin therapy and resolved or improved after discontinuation. Entry criteria required inability to tolerate 2 or more statins at any dose, or 1 statin and being unable or unwilling to (or advised by a physician not to) attempt a second statin. Stable, concomitant treatment with a very low statin dose (below the lowest approved daily dose) without side effects was permitted, as was administration of other lipid-lowering therapy such as ezetimibe and PCSK9 (proprotein convertase subtilisin-kexin type 9) inhibitors.[24]

Patient sex, race, and ethnicity were self-reported. Local or central ethics committee approvals were obtained via the relevant authorities. Study participants provided written informed consent. Randomization occurred between December 2016 and August 2019 for 13 970 patients, with a median duration of follow-up of 40.6 months. The primary end point was time to first occurrence of the four-component composite of cardiovascular death, nonfatal MI, nonfatal stroke, or coronary revascularization (MACE-4). Key secondary end points included a 3-component composite of cardiovascular death, nonfatal MI, or stroke (MACE-3) and the individual components of the composite outcomes. Other secondary end points included change in LDL-C and other biomarkers at month 6 or 12. End points were adjudicated by a clinical events committee managed by the Cleveland Clinic Coordinating Center for Clinical Research blinded to trial-group assignment as has been previously described.[24]

Statistical Analysis

The prespecified subgroup analysis evaluated the efficacy and safety of bempedoic acid versus placebo among BMI category at baseline (<25, 25 to <30, and ≥30 kg/m^2) for the primary efficacy end point (MACE-4) and key secondary end point (MACE-3). The HR and 95% CI for the treatment effect of bempedoic acid versus placebo were estimated, with placebo as the reference group, within each BMI category via a Cox regression model. The proportional hazard assumption was evaluated and not violated. The HR was also adjusted post hoc within each BMI category for age, sex, geographic region, race, ethnicity, baseline lipid-modifying therapy, primary or secondary prevention, diabetes status, baseline hs-CRP, baseline LDL-C, and renal function by a calculated estimated glomerular filtration rate. Treatment effects of bempedoic acid versus placebo on LDL-C and HbA1c were estimated as least square means from an ANCOVA model of observed values adjusting for baseline. The median difference of hs-CRP between treatments was estimated as a location shift (Hodges-Lehmann) via a nonparametric method. Weight change from baseline was summarized for the safety population at 6-month intervals. An intention to treat population was analyzed for efficacy, and the safety analysis population, defined as all randomized study participants who received at least 1 dose of the study drug, was analyzed for safety. This current report focuses on the results in study participants with obesity, defined as BMI ≥30 kg/m^2. Analyses were conducted with SAS, version 9.4 (SAS Institute, Cary, NC).

RESULTS

This analysis included 6179 (44.2%) patients with BMI ≥30 kg/m^2 from CLEAR Outcomes, of whom 3075 were randomized to bempedoic acid and 3104 to placebo. Patients with a BMI ≥30 kg/m^2 were followed for a median of 40.7 months, had a mean age of 65 years, 51% were women, and 92% were White. At enrollment, they had a mean body weight of 96 kg, mean BMI 34 kg/m^2, 68% had a prior history of atherosclerotic CVD, and 56% had diabetes. Mean LDL-C was 139 mg/dL, and 22% of patients were receiving a statin. Baseline characteristics for patients in the bempedoic acid and placebo groups are presented in Table 1.

In patients with BMI ≥30 kg/m^2, bempedoic acid treatment for 6 months resulted in a placebo-corrected change in LDL-C of −30.6 mg/dL (95% CI, -32.2 to −29.1). The percent changes in LDL-C, HDL, non-HDL,

Table 1. Select Demographics and Baseline Characteristics in Patients With BMI ≥30 kg/m²

	Bempedoic acid (n=3075)	Placebo (n=3104)
Age, y (mean±SD)	64.9±8.8	64.8±8.8
Female sex, n (%)	1553 (50.5)	1579 (50.9)
Race		
White, n (%)	2821 (91.7)	2847 (91.7)
American/Mexican Indian or Alaska Native	116 (3.8)	106 (3.4)
Black	92 (3.0)	95 (3.1)
Ethnicity		
Hispanic, n (%)	546 (17.8)	509 (16.4)
BMI, kg/m² (mean±SD)	34.4±4.1	34.5±4.2
Low-density lipoprotein cholesterol, mg/dL (mean±SD)	137.6±34.3	138.3±34.9
Non-HDL-C, mg/dL (mean±SD)	174.8±39.2	175.8±39.9
Total cholesterol, mg/dL (mean±SD)	222.1±40.1	223.0±40.6
HDL-C, mg/dL (mean±SD)	47.3±11.7	47.2±11.9
Triglycerides, mg/dL (median, IQR)	172.0 (130–231.5)	172.5 (132.0–231.0)
High-sensitivity C-reactive protein, mg/L (median, IQR)	3.00 (1.57–5.44)	2.98 (1.58–5.52)
Cardiovascular disease risk category, n (%)		
Primary prevention	976 (31.7)	1011 (32.6)
Secondary prevention	2099 (68.3)	2093 (67.4)
Coronary artery disease	1536 (50.0)	1527 (49.2)
Peripheral arterial disease	317 (10.3)	345 (11.1)
Cerebrovascular atherosclerotic disease	448 (14.6)	466 (15.0)
Diabetes, n (%)	1706 (55.5)	1753 (56.5)
Baseline statin use, n (%)	687 (22.3)	667 (21.5)
Baseline ezetimibe use, n (%)	329 (10.7)	358 (11.5)

BMI indicates body mass index; HDL-C, high density lipoprotein cholesterol; and IQR, interquartile range.

total cholesterol, triglycerides, and hs-CRP from baseline to 6 months are shown in Table 2. The reductions of both LDL-C and hs-CRP were sustained over the course of the trial. Participants with obesity who were treated with bempedoic acid showed a gradual weight reduction over the course of the study (Figure 1). The mean±SD change in weight from baseline was –1.1 (4.3) kg for bempedoic acid and –0.5 (4.1) kg for placebo at month 12 and –2.3 (6.3) kg for bempedoic acid and –1.4 (6.1) kg for placebo at month 36.

The primary MACE-4 end point in patients with BMI ≥30 kg/m² occurred in 11.6% bempedoic acid versus 14.8% placebo (HR, 0.77 [95% CI, 0.67–0.89]), representing a 23% risk reduction in MACE-4, as previously reported.[24] The Kaplan–Meier cumulative incidence of MACE-4 over time is depicted for bempedoic acid versus placebo in the people with obesity in Figure 2. For patients with BMI ≥30 kg/m², bempedoic acid reduced key secondary efficacy end points for MACE-3 (cardiovascular death, nonfatal MI, or nonfatal stroke) by 27% (HR, 0.73 [95% CI, 0.62–0.86]), nonfatal and fatal MI by 32% (HR, 0.68 [95% CI, 0.53–0.86]), coronary revascularization by 24% (HR, 0.76 [95% CI, 0.63–0.92]), and fatal and nonfatal stroke by 36% (HR, 0.64 [95% CI, 0.45–0.89]) (Table 2). HRs for the individual components of MACE-4 in people with obesity were all directionally consistent with the overall results. The post hoc covariates-adjusted HRs are all similar to the unadjusted and support the observed treatment effects.

The percentage of patients with BMI ≥30 kg/m² experiencing at least 1 investigator-reported adverse event was 87.4% and 86.7% in the bempedoic acid and placebo groups, respectively. Discontinuation rates due to treatment emergent adverse events for bempedoic acid were 10.6% versus 10.3% for placebo. Discontinuations due to myalgia occurred in 1.7% with bempedoic acid versus 1.5% with placebo. The observed mean±SD and percent change from baseline to 6 months in uric acid was 0.81 (1.26) mg/dL (15.6%) for bempedoic acid versus -0.04 (1.05) mg/dL (0.76%) for placebo, and for serum creatinine was 0.05 (0.17) mg/dL (6.2%) for bempedoic acid versus 0.02 (0.15) mg/dL (2.4%) for placebo. Investigator-reported adverse events included repeated and confirmed aspartate transaminase or alanine transaminase elevations >3 times the upper limit of normal (2.2% bempedoic acid versus 0.9% placebo), gout (3.9% bempedoic acid versus 2.6% placebo), and cholelithiasis (2.5% bempedoic acid versus 1.1% placebo). New-onset diabetes in those without a prior diagnosis of diabetes was reported as an adverse event in 20.5% receiving bempedoic acid and 22.0% receiving placebo. In all people with obesity, placebo-corrected change in HbA1c with bempedoic acid at 12 months compared with baseline was –0.03% (95% CI, –0.07 to 0.01).

DISCUSSION

The statistical analysis plan of the CLEAR Outcomes trial included a prespecified analysis of MACE-4 and MACE-3 end points by BMI category.[24] The aim of this current analysis was to further characterize the effect of bempedoic acid on end points relative to people with obesity at high cardiovascular risk including the individual MACE components, changes in LDL-C and hs-CRP, weight, markers of glycemic risk, and safety.

In the people with obesity, compared with placebo at 6 months, bempedoic acid reduced LDL-C by 22.5% and hs-CRP by 23.2%. Most important, after a median duration of follow-up of 40.7 months bempedoic acid reduced the risk of MACE-4 versus placebo by 23% (absolute between-group difference of 3.2%), MACE-3 by 27%, the risk of nonfatal and fatal MI by

Table 2. Primary, Key Secondary, and Lipid and Biomarker End Points in Patients With Baseline BMI ≥30 kg/m²

	Bempedoic acid (n=3075)	Placebo (n=3104)	Hazard ratio (95% CI)
Primary efficacy end point			
MACE-4*, n (%)	357 (11.6)	459 (14.8)	0.77 (0.67 to 0.89)
Nonfatal MI, n (%)	101 (3.3%)	156 (5.0%)	0.64 (0.50 to 0.83)
Coronary revascularization, n (%)	193 (6.3)	253 (8.2)	0.76 (0.63 to 0.92)
Nonfatal stroke, n (%)	46 (1.5%)	80 (2.6%)	0.58 (0.40 to 0.83)
Death from cardiovascular causes, n (%)	119 (3.9)	127 (4.1)	0.95 (0.74 to 1.22)
Key secondary efficacy end points			
MACE-3†, n (%)	244 (7.9)	333 (10.7)	0.73 (0.62 to 0.86)
Fatal and nonfatal MI, n (%)	112 (3.6)	165 (5.3)	0.68 (0.53 to 0.86)
Fatal and nonfatal stroke, n (%)	54 (1.8)	85 (2.7)	0.64 (0.45 to 0.89)
Cardiovascular death, n (%)	119 (3.9)	127 (4.1)	0.95 (0.74 to 1.22)
All-cause mortality, n (%)	206 (6.7)	205 (6.6)	1.02 (0.84 to 1.24)
Change from baseline in secondary lipid and biomarker efficacy end points			
			Difference (%)
LS mean percent change in LDL-C at 6 mo (95% CI)	−23.3 (−24.1 to −22.4)	−0.8 (−1.6 to 0.1)	−22.5 (−23.7 to −21.2)
Median percent change in hs-CRP at 6 mo (95% CI)	−23.6 (−26.2 to −21.8)	2.3 (−1.3 to 4.9)	−23.2 (−26.1 to −20.3)
LS mean change in hemoglobin A1c at 12 mo (95% CI)	0.03 (0.00 to 0.06)	0.06 (0.04 to 0.09)	−0.03 (−0.07 to 0.01)
Change from baseline in tertiary lipid efficacy end points			
Non-HDL-C, mean % (±SD) change at 6 mo	−17.3±20.8	−0.8±20.6	−16.6 (−17.7 to −15.6)
Total cholesterol, mean % (±SD) change at 6 mo	−15.4±16.5	−0.7±15.8	−14.8 (−15.6 to −13.9)
HDL-C, mean % (±SD) change at 6 mo	−7.9±17.1	0.9±14.7	−8.8 (−9.6 to −8.0)
Triglycerides, median % (IQR) change at 6 mo	−0.08 (−21.1 to 25.8)	−1.43 (−19.6 to 18.5)	2.3 (0.6 to 4.0)

Difference (bempedoic acid vs placebo) is baseline-adjusted LS mean difference with 95% CI for LDL-C, non-HDL-C, HDL-C, and total cholesterol, and it is the location shift with 95% CI for hs-CRP and triglycerides.

BMI indicates body mass index; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; IQR, interquartile range LDL-C, low-density lipoprotein cholesterol; LS, least squares; MACE, major adverse cardiovascular events; and MI, myocardial infarction.

*MACE-4 was a composite of death from cardiovascular causes, nonfatal MI, nonfatal stroke, or coronary revascularization.

†MACE-3 was a composite of death from cardiovascular causes, nonfatal MI, or nonfatal stroke.

32%, coronary revascularization by 24%, and nonfatal and fatal stroke by 36%, with the HRs for the individual components of the MACE-4 primary composite end point being directionally consistent with the overall trial. The beneficial MACE outcomes of this analysis support that reducing both LDL-C and hs-CRP with bempedoic acid in people with obesity may have clinical relevance. Obesity is an inflammatory disease, helping to account for complications such as insulin resistance and type 2 diabetes, hypertension, and thrombosis.[5] An analysis of the CLEAR Outcomes data showed that inflammation as assessed by baseline hs-CRP was a stronger predictor of future cardiovascular events than baseline LDL-C.[27] Bempedoic acid reduces markers of inflammation such as hs-CRP in a manner similar to statins.[24,28] The baseline values of LDL-C (≥130 mg/dL) and hs-CRP (≥2 mg/L) in the people living with obesity in this analysis aligned with those in the CLEAR Outcomes population who were statin intolerant, who had the highest predicted risk of MACE events.[27] Inflammation has also been linked to insulin resistance.[29] Here, in people with obesity, as was seen in the analysis of the total study population, use of bempedoic acid was not associated with worsening HbA1c or greater reporting of new-onset diabetes versus placebo.[25]

Discontinuations due to any adverse event, including myalgia, were comparable between treatment groups in people with obesity. Consistent with the detailed safety analysis, and likely mediated by bempedoic acid's weak inhibition of OAT2 (type 2 organic anion transporter), patients treated with bempedoic acid experienced higher incidences of hyperuricemia and gout compared with those treated with placebo.[30,31]

Currently, statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) are the first treatment of choice to reduce LDL-C for the purpose of reducing CVD risk. However, many patients at high risk for CVD are unable to attain guideline-directed LDL-C levels with statin therapy alone or are unable or unwilling to take statins at guideline-recommended doses.[32,33] Prior reports suggest statin use may be associated with increases in body weight, insulin resistance, HbA1c, and diabetes risk.[34–38] In this analysis, patients treated with bempedoic acid with a BMI ≥30 kg/m² had no increased risk of new-onset diabetes and experienced

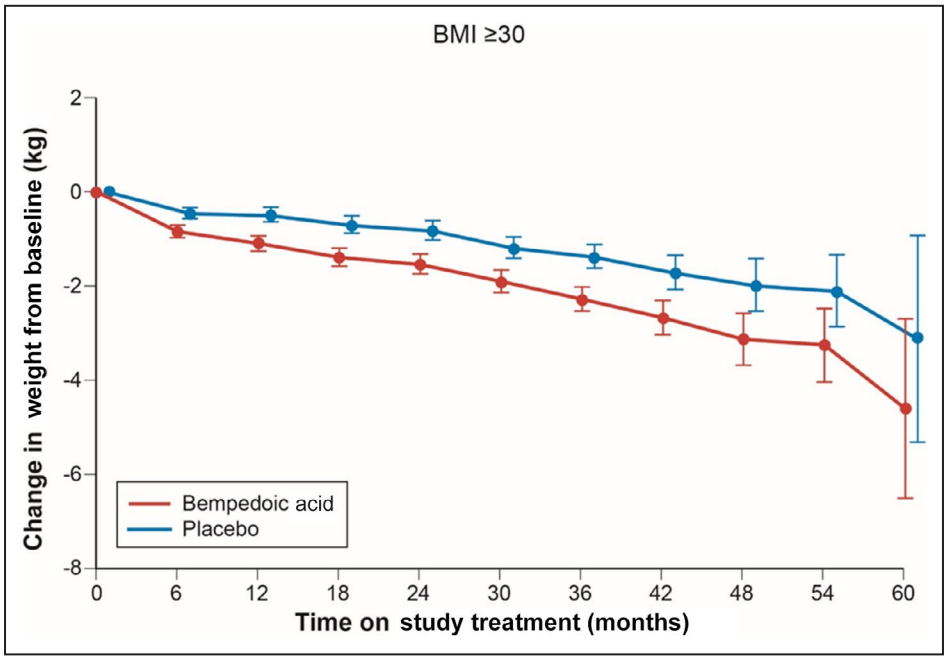

Figure 1. Change in body weight (kg) over time (months) in patients with baseline BMI ≥30 kg/m².
Error bars represent the 95% CI. BMI indicates body mass index.

mild, gradual weight loss over time with no difference in mean HbA1c at 12 months compared with placebo. These findings add clinical relevance to bempedoic acid for those patients at high metabolic risk who need additional LDL-C lowering.

Obesity and hypercholesterolemia are risk factors for CVD. Obesity is often associated with an atherogenic dyslipidemia pattern, characterized by elevated triglycerides, reduced HDL-C, and increased small dense LDL particles.[39] An increase in LDL-C is a risk factor for CVD, independent of the risks associated with obesity.[40] Given that increased adiposity and increased LDL-C represent modifiable CVD risk factors, then treatment objectives among people with obesity at high CVD risk and hypercholesterolemia include reduction of both body fat and LDL-C. This analysis of participants enrolled in CLEAR Outcomes with obesity provides evidence for CVD risk reduction with bempedoic acid in people with BMI ≥30 kg/m².

This analysis has several limitations. Although prespecified, it is a secondary analysis of a subpopulation in a larger randomized trial. Such analyses can result in false-positive findings due to the testing of multiple subgroups and may represent the play of chance. Additionally, this analysis was not powered to compare treatment effects between people living with obesity and those living without. Among the lower prespecified BMI subgroups, MACE-4 in these BMI categories occurred as follows: BMI <25 kg/m², bempedoic acid 10.9% versus placebo 10.7% (HR, 0.99 [95% CI, 0.76–1.29]); BMI 25 to <30 kg/m², bempedoic acid 12.2% versus placebo 12.5% (HR, 0.96 [95% CI, 0.83–1.12]).[24] Although the point estimates of HRs are closer to 1 in the lower BMI subgroups, the CIs are wide (due to smaller number of patients and lower event rates). The *P* value for interaction is greater than the nominal level of 0.05 without adjusting for multiplicity, thus we cannot conclude that the treatment effect is different based on this study. Although this analysis focused on people living with obesity, additional subgroup analyses might include the interrelationship of inflammation, cardiovascular outcomes, and other subgroups, such as those with and without diabetes, as well as those with baseline variances in blood pressure, triglyceride levels, renal function, and hepatic fat. Furthermore, 92% of participants evaluated in this analysis were White, potentially limiting the generalizability among other races. Finally, this study enrolled only participants intolerant to statins or able to tolerate only very low dose statins, limiting the generalizability regarding findings from this analysis for patients receiving guideline-recommended statin doses.

CONCLUSIONS

In people with obesity enrolled in the CLEAR Outcomes trial, bempedoic acid reduced cardiovascular risk, LDL-C, and hs-CRP, with a safety profile consistent with

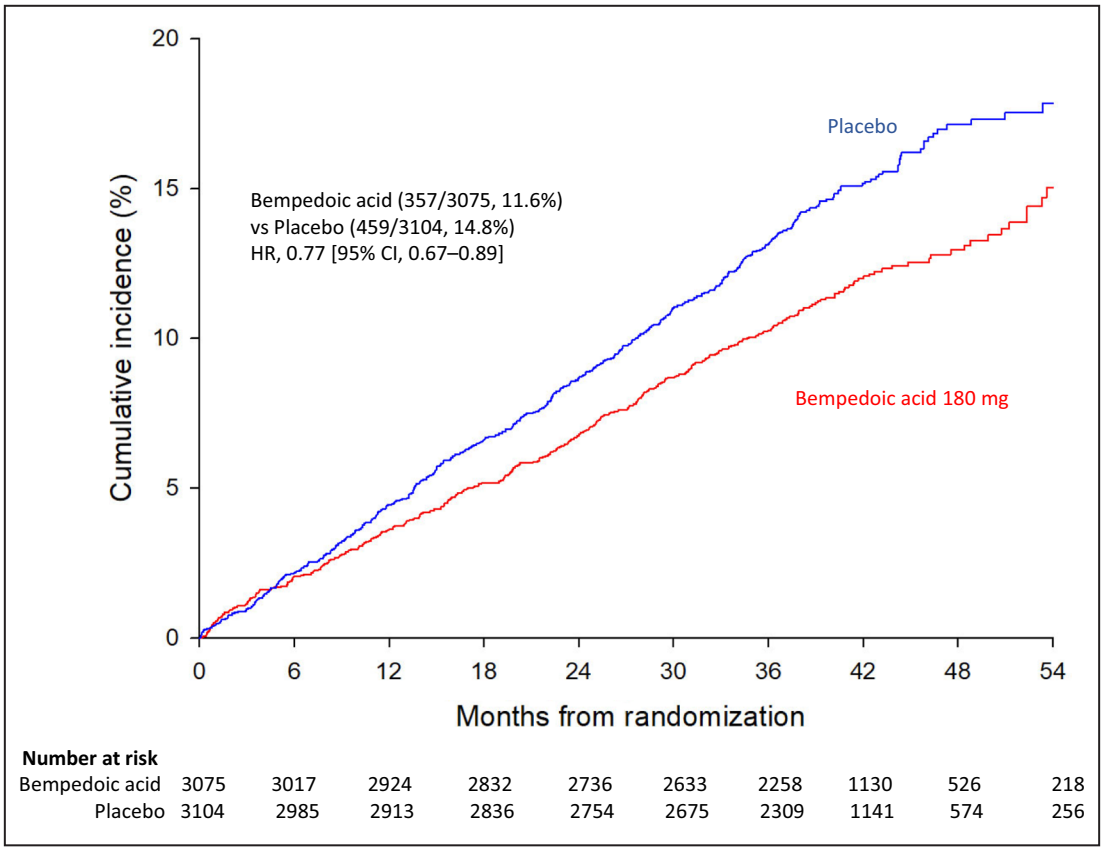

Figure 2. Kaplan–Meier curve of MACE-4 (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization) in patients with baseline BMI ≥30 kg/m².
BMI indicates body mass index; HR, hazard ratio; and MACE, major adverse cardiovascular event.

previous reports. Thus, in addition to reduction in excess adiposity, bempedoic acid may be a clinically relevant option to improve CVD outcomes in people who are statin intolerant and living with obesity who have elevated LDL-C and are at high cardiovascular risk.

ARTICLE INFORMATION

Received July 24, 2024; accepted January 6, 2025.

Affiliations

Louisville Metabolic and Atherosclerosis Research Center, Louisville, KY (H.E.B.); Esperion Therapeutics, Inc., Ann Arbor, MI (L.B., L.L., H.A.P.); Cleveland Clinic, Cleveland, OH (D.B., A.M.L., S.E.N.); Victorian Heart Institute, Monash University, Melbourne, Australia (S.J.N.); and Brigham and Women's Hospital, Harvard University, Boston, MA (J.P.).

Acknowledgments

The authors offer appreciation to all study investigators, clinical site staff, and study participants. Editorial support for preparation of this article was provided by Peter Herout, PharmD, of Esperion Therapeutics, Inc. Harold E. Bays was involved in the concept/design of the article, data interpretation, and writing of the first draft of the article. Danielle Brennan and Lei Lei conducted the statistical analysis and verification of the data. All authors critically reviewed and edited the article and approved the final version of the article for submission. Artificial intelligence was not used in the writing of this article.

Sources of Funding

This work was financially supported by Esperion Therapeutics, Inc. Esperion was involved in the design of the CLEAR Outcomes study in collaboration with an expert steering committee, in the conduct of the study, and in data collection and management. Esperion was involved in the analysis and interpretation of the data; preparation, review, and approval of the article; and decision to submit the article for publication but had no veto authority with respect to publication or control of the decision regarding choice of journal for submission.

Disclosures

Dr Bays' research site institution has received research grants from Esperion, as well as Abbvie, AstraZeneca, Merck, New Amsterdam, Novartis, and Pfizer. L. Bloedon and H.A. Powell are employees of Esperion Therapeutics, Inc., and may own shares of Esperion stock as compensation. L. Lei was employed as a contractor with Esperion Therapeutics, Inc., at the time of writing of the manusript. Dr Lincoff has received Esperion research funding for this trial; received grants from Eli Lilly, AbbVie, CSL, AstraZeneca, and Novartis; and received personal fees from Novo Nordisk, Glaxo, Akebia, Endologix, Fibrogen, Provention, and Becton Dickinson. Dr Plutzky reported Esperion Therapeutics (clinical trial, consultant), Boehringer Ingelheim (grant support, clinical trial), Novo Nordisk (consultant, SELECT Steering Comm), New Amsterdam, Novartis (grant support, consultant), Altimmune (consultant), Avilar (consultant), Bain Capital (consultant), Kailera (consultant), and Corcept (consultant). Dr Nissen received grant support from Esperion for the CLEAR Outcomes Trial. Cleveland Clinic Center for Clinical Research has received funding to perform clinical trials from Abbvie, AstraZeneca, Arrowhead, Amgen, Bristol Myers Squibb, Eli Lilly, Medtronic, MyoKardia, New Amsterdam Pharmaceuticals, Novartis, and Silence Therapeutics. Dr Nissen is involved in these clinical trials but receives no personal remuneration for his participation. S.J. Nicholls has received research support from AstraZeneca, Amgen, Anthera, CSL Behring, Cerenis, Eli Lilly, Esperion, Resverlogix, Novartis, InfraReDx, and Sanofi-Regeneron and is a consultant for Amgen, Akcea, AstraZeneca, Boehringer Ingelheim, CSL Behring, Eli Lilly, Esperion, Kowa, Merck, Takeda, Pfizer, Sanofi-Regeneron, Vaxxinity, CSL Sequiris, and Novo Nordisk. D. Brennan has no disclosures to report.

REFERENCES

1. Bryan S, Afful J, Carroll M, Te-Ching C, Orlando D, Fink S, Fryar C. *NHSR 158. National Health and Nutrition Examination Survey 2017–March 2020 Pre-pandemic Data Files*. Hyattsville, MD: National Center for Health Statistics; 2021. doi: 10.15620/cdc:106273
2. World Health Organization. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight.
3. Powell-Wiley TM, Poirier P, Burke LE, Després J-P, Gordon-Larsen P, Lavie CJ, Lear SA, Ndumele CE, Neeland IJ, Sanders P, et al. Obesity and cardiovascular disease: a scientific statement from the American Heart Association. *Circulation*. 2021;143:e984–e1010. doi: 10.1161/CIR.0000000000000973
4. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, Benetos A, Biffi A, Boavida J-M, Capodanno D, et al. 2021 ESC guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J*. 2021;42:3227–3337. doi: 10.1093/eurheartj/ehab484
5. Bays HE, Bindlish S, Clayton TL. Obesity, diabetes mellitus, and cardiometabolic risk: an Obesity Medicine Association (OMA) clinical practice statement (CPS) 2023. *Obesity Pillars*. 2023;5:100056. doi: 10.1016/j.obpill.2023.100056
6. Clayton TL, Fitch A, Bays HE. Obesity and hypertension: Obesity Medicine Association (OMA) clinical practice statement (CPS) 2023. *Obesity Pillars*. 2023;8:100083. doi: 10.1016/j.obpill.2023.100083
7. Bindlish S, Ng J, Ghusn W, Fitch A, Bays HE. Obesity, thrombosis, venous disease, lymphatic disease, and lipedema: an Obesity Medicine Association (OMA) clinical practice statement (CPS) 2023. *Obesity Pillars*. 2023;8:100092. doi: 10.1016/j.obpill.2023.100092
8. Ashraf MJ, Baweja P. Obesity: the "huge" problem in cardiovascular diseases. *Mo Med*. 2013;110:499–504.
9. Pennings N, Golden L, Yashi K, Tondt J, Bays HE. Sleep-disordered breathing, sleep apnea, and other obesity-related sleep disorders: an Obesity Medicine Association (OMA) clinical practice statement (CPS) 2022. *Obesity Pillars*. 2022;4:100043. doi: 10.1016/j.obpill.2022.100043
10. Bays HE. Evaluation and practical management of increased visceral fat. *J Am Coll Cardiol*. 2022;79:1266–1269. doi: 10.1016/j.jacc.2022.01.039
11. de Wit-Verheggen VHW, Altintas S, Spee RJM, Mihl C, van Kuijk SMJ, Wildberger JE, Schrauwen-Hinderling VB, Kietselaer BLJH, van de Weijer T. Pericardial fat and its influence on cardiac diastolic function. *Cardiovasc Diabetol*. 2020;19:129. doi: 10.1186/s12933-020-01097-2
12. Wilby ML. Physical mobility impairment and risk for cardiovascular disease. *Health Equity*. 2019;3:527–531. doi: 10.1089/heq.2019.0065
13. Forhan M, Gill SV. Obesity, functional mobility and quality of life. *Best Pract Res Clin Endocrinol Metab*. 2013;27:129–137. doi: 10.1016/j.beem.2013.01.003
14. Fitch AK, Bays HE. Obesity definition, diagnosis, bias, standard operating procedures (SOPs), and telehealth: an Obesity Medicine Association (OMA) clinical practice statement (CPS) 2022. *Obesity Pillars*. 2022;1:100004. doi: 10.1016/j.obpill.2021.100004
15. Di Angelantonio E, Bhupathiraju SN, Wormser D, Gao P, Kaptoge S, de Gonzalez AB, Cairns BJ, Huxley R, Jackson CL, Joshy G, et al. Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. *Lancet*. 2016;388:776–786. doi: 10.1016/S0140-6736(16)30175-1
16. Bays HE, Agarwala A, German C, Satish P, Iluyomade A, Dudum R, Thakkar A, Al Rifai M, Mehta A, Thobani A, et al. Ten things to know about ten cardiovascular disease risk factors—2022. *Am J Prev Cardiol*. 2022;10:100342.
17. Iwamoto SJ, Abushamat LA, Zaman A, Millard AJ, Cornier M-A. Obesity management in cardiometabolic disease: state of the art. *Curr Atheroscler Rep*. 2021;23:59. doi: 10.1007/s11883-021-00953-0
18. Srinivasan M, Thangaraj SR, Arzoun H, Thomas SS, Mohammed L. The impact of bariatric surgery on cardiovascular risk factors and outcomes: a systematic review. *Cureus*. 2022;14:e23340. doi: 10.7759/cureus.23340
19. Lincoff AM, Brown-Frandsen K, Colhoun HM, Deanfield J, Emerson SS, Esbjerg S, Hardt-Lindberg S, Hovingh GK, Kahn SE, Kushner RF, et al. Semaglutide and cardiovascular outcomes in obesity without diabetes. *N Engl J Med*. 2023;389:2221–2232. doi: 10.1056/NEJMoa2307563
20. Domanski MJ, Tian X, Wu CO, Reis JP, Dey AK, Gu Y, Zhao L, Bae S, Liu K, Hasan AA, et al. Time course of LDL cholesterol exposure and cardiovascular disease event risk. *J Am Coll Cardiol*. 2020;76:1507–1516. doi: 10.1016/j.jacc.2020.07.059
21. Bays HE, Kirkpatrick C, Maki KC, Toth PP, Morgan RT, Tondt J, Christensen SM, Dixon D, Jacobson TA. Obesity, dyslipidemia, and cardiovascular disease: a joint expert review from the Obesity Medicine Association and the National Lipid Association 2024. *Obesity Pillars*. 2024;10:100108. doi: 10.1016/j.obpill.2024.100108
22. Ference BA, Ray KK, Catapano AL, Ference TB, Burgess S, Neff DR, Oliver-Williams C, Wood AM, Butterworth AS, Di Angelantonio E, et al. Mendelian randomization study of *ACLY* and cardiovascular disease. *N Engl J Med*. 2019;380:1033–1042. doi: 10.1056/NEJMoa1806747
23. Kain V, Kapadia B, Misra P, Saxena U. Simvastatin may induce insulin resistance through a novel fatty acid mediated cholesterol independent mechanism. *Sci Rep*. 2015;5:13823. doi: 10.1038/srep13823
24. Nissen SE, Lincoff AM, Brennan D, Ray KK, Mason D, Kastelein JJP, Thompson PD, Libby P, Cho L, Plutzky J, et al. Bempedoic acid and cardiovascular outcomes in statin-intolerant patients. *N Engl J Med*. 2023;388:1353–1364. doi: 10.1056/NEJMoa2215024
25. Ray KK, Nicholls SJ, Li N, Louie MJ, Brennan D, Lincoff AM, Nissen SE. Efficacy and safety of bempedoic acid among patients with and without diabetes: prespecified analysis of the CLEAR outcomes randomised trial. *Lancet Diabetes Endocrinol*. 2024;12:19–28.
26. Nicholls S, Lincoff AM, Bays HE, Cho L, Grobbee DE, Kastelein JJ, Libby P, Moriarty PM, Plutzky J, Ray KK, et al. Rationale and design of the CLEAR-outcomes trial: evaluating the effect of bempedoic acid on cardiovascular events in patients with statin intolerance. *Am Heart J*. 2021;235:104–112.
27. Ridker PM, Lei L, Louie MJ, Haddad T, Nicholls SJ, Lincoff AM, Libby P, Nissen SE; CLEAR Outcomes Investigators. Inflammation and cholesterol as predictors of cardiovascular events among 13 970 contemporary high-risk patients with statin intolerance. *Circulation*. 2024;149:28–35.
28. Ridker PM, Lei L, Ray KK, Ballantyne CM, Bradwin G, Rifai N. Effects of bempedoic acid on CRP, IL-6, fibrinogen and lipoprotein(a) in patients with residual inflammatory risk: a secondary analysis of the CLEAR harmony trial. *J Clin Lipidol*. 2023;17:297–302. doi: 10.1016/j.jacl.2023.02.002
29. Ndumele CE, Pradhan AD, Ridker PM. Interrelationships between inflammation, C-reactive protein, and insulin resistance. *J Cardiometab Syndr*. 2006;1:190–196. doi: 10.1111/j.1559-4564.2006.05538.x
30. Biolo G, Vinci P, Mangogna A, Landolfo M, Schincariol P, Fiotti N, Mearelli F, Di Girolamo FG. Mechanism of action and therapeutic use of bempedoic acid in atherosclerosis and metabolic syndrome. *Front Cardiovasc Med*. 2022;9:1–10. doi: 10.3389/fcvm.2022.1028355
31. Bays HE, Bloedon LT, Lin G, Powell HA, Louie MJ, Nicholls SJ, Lincoff AM, Nissen SE. Safety of bempedoic acid in patients at high cardiovascular risk and with statin intolerance. *J Clin Lipidol*. 2024;18:e59–e69.
32. Nelson AJ, Haynes K, Shambhu S, Eapen Z, Cziraky MJ, Nanna MG, Calvert SB, Gallagher K, Pagidipati NJ, Granger CB. High-intensity statin use among patients with atherosclerosis in the U.S. *J Am Coll Cardiol*. 2022;79:1802–1813. doi: 10.1016/j.jacc.2022.02.048
33. Cannon CP, de Lemos JA, Rosenson RS, Ballantyne CM, Liu Y, Gao Q, Palagashvilli T, Alam S, Mues KE, Bhatt DL, et al. Use of lipid-lowering therapies over 2 years in GOULD, a registry of patients with atherosclerotic cardiovascular disease in the US. *JAMA Cardiol*. 2021;6:1060–1068. doi: 10.1001/jamacardio.2021.1810
34. Sattar N, Preiss D, Murray HM, Welsh P, Buckley BM, de Craen AJM, Seshasai SRK, McMurray JJ, Freeman DJ, Jukema JW, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *Lancet*. 2010;375:735–742.
35. Preiss D, Rao S, Seshasai K, Welsh P, Murphy SA, Ho JE, Waters DD, DeMicco DA, Barter P, Cannon CP, et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy. *JAMA*. 2011;305:2556–2564.
36. Swerdlow DI, Preiss D, Kuchenbaecker KB, Holmes MV, Engmann JEL, Shah T, Sofat R, Stender S, Johnson PCD, Scott RA, et al. HMG-coenzyme a reductase inhibition, type 2 diabetes, and bodyweight: evidence from genetic analysis and randomised trials. *Lancet*. 2015;385:351–361. doi: 10.1016/S0140-6736(14)61183-1
37. Singh P, Zhang Y, Sharma P, Covassin N, Soucek F, Friedman PA, Somers VK. Statins decrease leptin expression in human white adipocytes. *Physiol Rep*. 2018;6:e13566. doi: 10.14814/phy2.13566
38. Reith C, Preiss D, Blackwell L, Emberson J, Spata E, Davies K, Halls H, Harper C, Holland L, Wilson K, et al. Effects of statin therapy on diagnoses of new-onset diabetes and worsening glycaemia in large-scale

randomised blinded statin trials: an individual participant data meta-analysis. *Lancet Diabetes Endocrinol*. 2024;12:306–319. doi: 10.1016/S2213-8587(24)00040-8

39. Bays HE, Toth PP, Kris-Etherton PM, Abate N, Aronne LJ, Brown WV, Gonzalez-Campoy JM, Jones SR, Kumar R, La Forge R, et al. Obesity, adiposity, and dyslipidemia: a consensus statement from the National Lipid Association. *J Clin Lipidol*. 2013;7:304–383. doi: 10.1016/j.jacl.2013.04.001
40. Jayaraman S, Pérez A, Miñambres I, Sánchez-Quesada JL, Gursky O. LDL binding to cell receptors and extracellular matrix is proatherogenic in obesity but improves after bariatric surgery. *J Lipid Res*. 2023;64:100451. doi: 10.1016/j.jlr.2023.100451