Journal of the American Heart Association

BRIEF COMMUNICATION

Factors Associated With Enhanced Low-Density Lipoprotein Cholesterol Lowering With Bempedoic Acid

Christie M. Ballantyne, MD; Harold E. Bays, MD; Michael J. Louie, MD, MPH, MSc; Jeremy Smart, PharmD; Yang Zhang, PhD; Kausik K. Ray, MD, MPhil

BACKGROUND: Bempedoic acid (BA) inhibits ATP-citrate lyase in the cholesterol synthesis pathway and lowers low-density lipoprotein cholesterol (LDL-C). As with other lipid-lowering therapies, interindividual variation in response to BA was observed in clinical trials. We characterized LDL-C response to BA using guideline-defined statin intensity categories and identified clinical factors associated with enhanced LDL-C lowering with BA.

METHODS AND RESULTS: This post hoc analysis used pooled data from 4 phase 3 studies. Patients were randomized 2:1 to once-daily BA 180 mg (n=2321) or placebo (n=1167) for 12 to 52 weeks and grouped based on percent change in LDL-C from baseline to week 12 according to guideline-established statin intensity categories. Factors associated with ≥30% reduction in LDL-C were identified using logistic regression analyses. From baseline to week 12, BA lowered LDL-C levels comparable to a moderate- or high-intensity statin (≥30%) in 28.9% of patients; this degree of LDL-C lowering was observed in 50.9% of patients not receiving background statin therapy. In a multivariable analysis, the absence of statins, female sex, a history of diabetes, ezetimibe use, and higher high-sensitivity C-reactive protein level were associated with increased rates of achieving ≥30% LDL-C reduction with BA (P<0.01 for each).

CONCLUSIONS: A large percentage of patients receiving BA achieved LDL-C reductions comparable to a moderate- or high-intensity statin. Factors including statin absence, female sex, diabetes history, ezetimibe use, and a higher high-sensitivity C-reactive protein level may be useful to identify patients who may have a greater LDL-C reduction with BA.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifiers: NCT02666664, NCT02991118, NCT02988115, NCT03001076.

Key Words: atherosclerotic cardiovascular disease ■ statin intolerance

Interindividual variation in low-density lipoprotein cholesterol (LDL-C) reductions with lipid-lowering therapies (LLTs) has been reported.[1,2] Extrinsic factors, such as nonadherence to LLTs, changes in concurrent therapies, and inaccurate measurement of baseline LDL-C levels, and intrinsic factors, including age, sex, race or ethnicity, body weight, abdominal obesity, smoking status, variations in gastrointestinal absorption, baseline lipid or high-sensitivity C-reactive protein (hsCRP) levels, genetics, and drug–drug interactions all may contribute to the variation in response to LLTs.

Bempedoic acid is a prodrug metabolized in the liver by very-long-chain acyl-CoA synthetase 1 (ACSVL1) to form the pharmacologically active bempedoyl-CoA metabolite, which inhibits hepatic cholesterol synthesis and leads to upregulation of hepatic low-density lipoprotein receptors, increases low-density lipoprotein uptake and clearance, and lowers plasma LDL-C levels.

Correspondence to: Christie M. Ballantyne, MD, Department of Medicine, Baylor College of Medicine, One Baylor Plaza, BCM 285, Houston, TX 77030. Email: cmb@bcm.edu

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.121.024531

For Sources of Funding and Disclosures, see page 5.

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

Bempedoic acid (Nexletol®; Esperion Therapeutics, Ann Arbor, MI) and a fixed-dose combination of bempedoic acid plus ezetimibe (Nexlizet®; Esperion Therapeutics) are approved in the United States as adjuncts to diet and maximally tolerated statin therapy for patients with atherosclerotic cardiovascular disease and/or heterozygous familial hypercholesterolemia who require additional LDL-C lowering. In Europe, bempedoic acid (Nilemdo®; Daiichi Sankyo Europe, Munich, Germany) and bempedoic acid plus ezetimibe fixed-dose combination (Nustendi®; Daiichi Sankyo Europe) are approved with similar labels and additional indications including use alone or in combination with other LLTs in patients who are unable to take a statin.

In phase 3 studies, bempedoic acid lowered LDL-C levels compared with placebo by a mean of 18% among patients concurrently receiving a moderate- to high-intensity statin and 25% among patients who were receiving low-dose or no statin.[3] Guidelines on the management of blood cholesterol describe statin intensity based on the percentage of typical lowering of LDL-C with a reduction in LDL-C of at least 30% being comparable to a moderate- or high-intensity statin.[4] We sought to characterize LDL-C response to bempedoic acid using these statin intensity categories and identify factors associated with enhanced LDL-C lowering with bempedoic acid using pooled data from phase 3 studies.

METHODS

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

Study Design

This was a post hoc analysis using pooled data from 4 phase 3, randomized, double-blind, placebo-controlled studies of bempedoic acid. In all 4 studies, patients at high cardiovascular risk were randomized 2:1 to receive once-daily bempedoic acid 180 mg or placebo for 12 to 52 weeks. Details on these studies have been described previously. Briefly, patients in the CLEAR (Cholesterol Lowering via Bempedoic Acid, an ACL-Inhibiting Regimen) Harmony (NCT02666664) and CLEAR Wisdom (NCT02991118) studies were receiving maximally tolerated statins (which could include no statin); other LLTs were also allowed. Patients in the CLEAR Serenity (NCT02988115) and CLEAR Tranquility (NCT03001076) studies had a history of statin-associated side effects and were receiving stable low-dose statins or no statin at all. Patients in CLEAR Serenity and CLEAR Tranquility were permitted to receive other nonstatin LLTs; all patients in the CLEAR Tranquility study were receiving ezetimibe. All 4 studies were conducted in accordance with ethical principles established by the Declaration of Helsinki and Good Clinical Practices guidelines. All protocols were approved by independent ethics committees at each study site. All study participants provided written informed consent.

Patients

Patients were 18 years of age or older and despite stable LLT required additional lowering of LDL-C levels. Patients in the CLEAR Harmony and CLEAR Wisdom studies were required to have established atherosclerotic cardiovascular disease or heterozygous familial hypercholesterolemia. Patients in the CLEAR Serenity and CLEAR Tranquility studies received LLT as primary prevention because of multiple cardiovascular risk factors or as secondary prevention. Patients with LDL-C values at baseline and week 12 were included in this analysis. All patients provided informed written consent.

Assessment of Response

Patients were sorted based on their percent change in LDL-C from baseline to week 12 (primary end point for all 4 studies) using statin intensity categories established by the American College of Cardiology and American Heart Association: ≥50% LDL-C lowering (high-intensity statin), 30% to 49% LDL-C lowering (moderate-intensity statin), and <30% LDL-C lowering (low-intensity statin).[4] Data are reported as the percentage of patients who achieved at least a 30% reduction in LDL-C (comparable to a moderate- to high-intensity statin) or at least 50% reduction in LDL-C (comparable to a high-intensity statin).

Statistical Analysis

Data are presented as number and percentage for categorical variables and mean±SD or median (quartile [Q]1, Q3) for continuous variables. Simple logistic regression modeling of LDL-C response (30% or more reduction compared with baseline) using each baseline variable such as age, sex, race, body mass index (BMI), estimated glomerular filtration rate, cardiovascular risk, history of diabetes, history of hypertension, LDL-C levels, log of hsCRP levels, statin use, and ezetimibe use was performed. Odds ratio estimates and 95% Wald confidence and χ^2 P values were calculated. A multivariable logistic regression analysis adjusting for covariates was also performed. A stepwise process was used to select the variables. All covariates significant from univariable models were originally included, and the final model was achieved after covariates were removed if not significant within the model.

RESULTS

Patients

A total of 3488 patients were included in this analysis; 2321 patients were treated with bempedoic acid and 1167 received placebo (Table S1). Baseline demographics and characteristics were similar across treatment groups. Overall, the mean (SD) age was 65.5 years with 15.7% older than 75 years. Thirty-four percent of the patients were women. The mean (SD) BMI was 29.8 kg/m^2 (5.0 kg/m^2), with 85.1% of the patients being overweight or obese (BMI ≥25 kg/m^2). Twenty-eight percent of the patients had diabetes, and 78% had hypertension. Median (Q1, Q3) baseline hsCRP levels were 1.64 mg/L (0.820, 3.560 mg/L). Use of statin, ezetimibe, or other LLTs at baseline was similar across treatment groups. Eighty-one percent of the patients were receiving statin therapy at baseline, with 75.8% receiving moderate- to high-intensity statin and 5.0% receiving low- or very-low-intensity statin; 19.2% of the patients were not receiving statin therapy. Ezetimibe use at baseline was reported for 14.9% of patients.

Reduction in LDL-C Levels

At baseline, mean (SD) LDL-C levels were 114.2 mg/dL (36.7 mg/dL) for patients in the bempedoic acid group and 113.0 mg/dL (36.6 mg/dL) for patients in the placebo group. The mean (SD) percent change in LDL-C at week 12 was –17.98% (21.32%) for patients treated with bempedoic acid and +1.79% (22.65%) for patients receiving placebo. Interindividual variation in response was observed in both treatment groups (Figure S1). The median (Q1, Q3) percent change in LDL-C at week 12 was –19.66% (–32.03%, –5.51%) for patients treated with bempedoic acid compared with –0.67% (–9.63%, 10.19%) for patients receiving placebo. From baseline to week 12, bempedoic acid lowered LDL-C levels comparable to that of a moderate- or high-intensity statin (ie, at least 30%) in 28.9% of patients compared with 4.4% of patients receiving placebo. LDL-C levels were lowered comparable to a high-intensity statin (at least 50%) in 4.7% of patients treated with bempedoic acid and 1.1% of patients receiving placebo.

The degree of LDL-C lowering with bempedoic acid was affected by the presence or absence of background statin therapy. The median (Q1, Q3) percent change in LDL-C at week 12 with bempedoic acid was –17.93% (–29.75%, –4.53%) for patients receiving a statin and –30.40% (–40.22%, –16.54%) for patients not receiving a statin (Figure S2). In comparison, the median (Q1, Q3) percent change in LDL-C at week 12 with placebo was –0.85% (–9.77%, 10.53%) among patients receiving a statin and –0.17% (–8.63%, 9.09%) among patients not receiving a statin. With bempedoic acid treatment, a reduction in LDL-C of at least 30% was achieved by 50.9% of patients not receiving a statin (Figure 1). An additional reduction in LDL-C of at least 30% was achieved by 24.6% patients receiving background statin therapy. A higher proportion of patients treated with bempedoic acid achieved at least a 50% reduction in LDL-C in the absence of a statin than in the presence of a statin (9.5% versus 3.7%). Less than 5% of patients receiving placebo achieved at least a 30% reduction in LDL-C in either the presence or absence of a statin.

Factors Associated With at Least a 30% Reduction in LDL-C Levels

Based on a univariable logistic regression model, characteristics associated with achieving at least a 30% reduction in LDL-C included younger age, female sex, history of diabetes, higher baseline LDL-C, absence of a baseline statin, presence of baseline ezetimibe, higher baseline BMI, and higher baseline hsCRP levels (Table). When adjusting for covariates, female sex, a history of diabetes, absence of a baseline statin use, presence of baseline ezetimibe use, and higher hsCRP levels were associated with achieving at least a 30% reduction in LDL-C (Figure 2). For the final model, the C statistic (area under receiver operating characteristic curve) is 0.642 (95% CI, 0.617–0.668), and the Hosmer-Lemeshow test statistic is 3.128 (χ^2) (P=0.926).

DISCUSSION

Although most patients experience marked reductions in LDL-C with statin treatment, some will not be able to achieve treatment goals with statins alone. Among patients registered in the VOYAGER (indiVidual patient data meta-analysis Of statin therapY in At risk Groups: Effects of Rosuvastatin, atorvastatin, and simvastatin) database (a large database of patients [>32 000] who received atorvastatin, rosuvastatin, or simvastatin during 1 of 37 clinical trials), response to a statin varied from no response to up to an 80% reduction in LDL-C.[2] Similarly, results from a meta-analysis of 8 randomized controlled trials investigating simvastatin, lovastatin, pravastatin, atorvastatin, and rosuvastatin provided a wide range of LDL-C reductions from no response to up to a 90% reduction in LDL-C.[1] As with statins, we observed variability of response with bempedoic acid, with 28.9% of patients in the entire study population assigned to bempedoic acid achieving at least a 30% reduction in LDL-C; variability was also seen in the placebo group (4.4% achieved a 30% reduction in LDL-C).

Many patients cannot tolerate high-intensity statins because of muscle-related adverse reactions and are taking lower statin doses or alternative LLTs as options to lower LDL-C levels. In a real-world setting where

83% of patients were receiving low- or moderate-dose statins,[5] the proportion of patients who achieved at least a 30% reduction in LDL-C was 41.6%.[5] In our analysis, bempedoic acid allowed 50.9% of patients unable to take any statin to achieve at least a 30% reduction in LDL-C. Results from both univariable and multivariable analysis showed that the absence of statin use was associated with greater probability of achieving LDL-C lowering with bempedoic acid similar to that in which a moderate- or high-intensity statin was used. Bempedoic acid inhibits hepatic cholesterol synthesis upstream of statins. As monotherapy, bempedoic acid is not vying with statins to inhibit cholesterol synthesis, thus providing more opportunity to lower LDL-C with bempedoic acid alone than in combination with a background statin. Bempedoic acid and a proprotein convertase subtilisin/kexin type 9 inhibitor are options for patients who require additional lowering of LDL-C.[6]

Guidelines suggest the addition of ezetimibe to statin therapy to assist patients in reaching LDL-C treatment goals.[4] Variability of LDL-C lowering with ezetimibe either alone or in combination with statins is reported, with some indication that variability with a statin is lower with concomitant ezetimibe use.[7] Furthermore, greater reductions in LDL-C with ezetimibe when given in combination with a statin is reported among obese individuals.[8] Patients already receiving ezetimibe were more likely to achieve at least a 30% reduction in LDL-C when bempedoic acid was added to their regimen. Adherence to treatment tends to decrease with an increase in the number of medications. The fixed-dose combination of bempedoic acid plus ezetimibe may be particularly useful in optimizing patient LDL-C lowering, especially among patients taking other medications for comorbidities.

Results from multivariable analysis suggest that enhanced (≥30%) LDL-C lowering with bempedoic acid is more likely for women versus men, patients with diabetes versus patients without diabetes, and patients with higher versus patients with lower hsCRP levels. After middle age, women have a higher total atherogenic lipoprotein burden compared with men,[9] are more likely than men to experience statin intolerance, and less likely than men to be treated with any statin or guideline-recommended statin intensity.[10] Dyslipidemia is often uncontrolled in patients with diabetes,[11] and patients with diabetes are at higher risk of having a cardiovascular event.[12] Patients with higher hsCRP levels are also at a higher risk of having a cardiovascular event.[13] Therefore, bempedoic acid may be of particular benefit for patients who are often undertreated or unable to tolerate statins and who are at high-risk for cardiovascular disease, including women, patients with diabetes, and patients with elevated hsCRP levels.

Although based on pooled data from 4 randomized placebo-controlled studies, this was a post hoc analysis. Other limitations include the smaller (19%) proportion of patients not receiving a statin compared with patients receiving background statin therapy. No change or an increase in LDL-C was observed in 18% of patients receiving bempedoic acid. No response or hyporesponse has been reported with statins and other

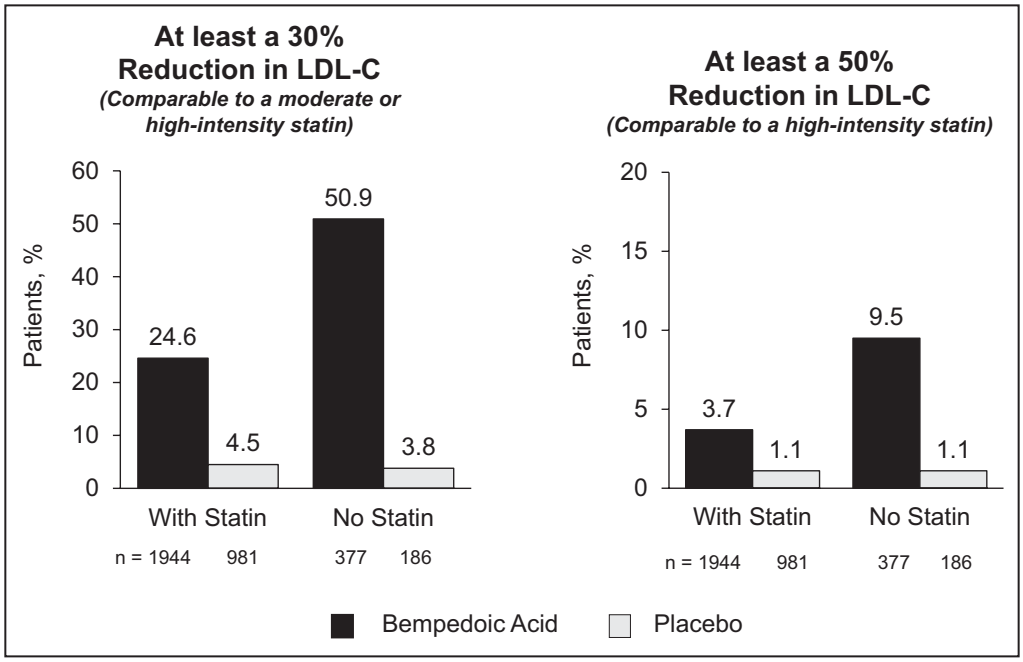


Figure 1. Proportion of patients achieving at least a 30% or at least a 50% reduction in LDL-C with bempedoic acid or placebo.
LDL-C indicates low-density lipoprotein cholesterol.

Table. Effect of Baseline Variables on Achieving at Least a 30% Reduction in LDL-C Among Patients Treated With Bempedoic Acid (Univariable Analysis)

Characteristic	OR (95% CI)*	*P* value
Age, y	0.989 (0.980–0.999)	0.0280
Sex (women vs men)	1.643 (1.365–1.978)	<0.0001
Race (non-White† vs White)	0.949 (0.642–1.403)	0.7941
Baseline LDL-C, mg/dL	1.014 (1.012–1.017)	<0.0001
eGFR category, mL/min per 1.73 m^2		
≥90 vs <30 mL/min per 1.73 m^2	0.844 (0.076–9.373)	0.8684
60–89 vs <30 mL/min per 1.73 m^2	0.770 (0.070–8.516)	0.6450
30–≤59 vs <30 mL/min per 1.73 m^2	0.961 (0.086–10.715)	0.8063
Baseline statin (no vs yes)	3.175 (2.532–3.984)	<0.0001
Baseline ezetimibe use (yes vs no)	2.076 (1.643–2.623)	<0.0001
HeFH with/without ASCVD vs ASCVD only	1.032 (0.641–1.662)	0.8956
History of diabetes (yes vs no)	1.348 (1.108–1.639)	0.0028
History of hypertension (yes vs no)	1.027 (0.828–1.274)	0.8101
Baseline BMI, kg/m^2	1.025 (1.007–1.043)	0.0053
Baseline hsCRP levels‡, mg/L	1.245 (1.147–1.353)	<0.0001

ASCVD indicates atherosclerotic cardiovascular disease; BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; HeFH, heterozygous familial hypercholesterolemia; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; and OR, odds ratio.

*OR is defined as the odds of being a responder (achieving at least a 30% reduction in LDL-C levels) compared with being a nonresponder, based on logistic regression model without adjusting for other covariates.

†Non-White: Black or African American, Asian, Native Hawaiian or other Pacific Islander, American Indian or Alaska Native, Other, Multiple.

‡Log transformed before entry into the logistic transformation model, so the OR relates to a relative scale rather than to milligrams per liter.

LLTs, which has often contributed to a lack of adherence to the study drug.[14,15] Pharmacokinetics data are not available to determine adherence to either bempedoic acid or statin in either treatment arm. Most of the patients in this analysis were White and non-Hispanic, which might limit generalizability of the results. Finally, although one might predict greater potential reductions in atherosclerotic cardiovascular disease among those with the most robust LDL-C lowering, bempedoic acid has other effects that may influence atherosclerotic risk including hsCRP lowering. Therefore, the clinical implications of these findings await the results of the ongoing CLEAR Outcomes trial (n=14 014), which is examining the effects of bempedoic acid on LDL-C levels and cardiovascular outcomes in patients with statin intolerance, has enrolled 6755 (48.2%) women and 5998 (42.8%) patients with diabetes. For all the patients enrolled in the CLEAR Outcomes trial, the mean (SD) baseline BMI is 29.9 kg/m^2 (5.2 kg/m^2), and the median (Q1, Q3) hsCRP level is 2.3 mg/L (1.2, 4.5 mg/L).

Based on our analysis, about 25% of patients receiving background statin therapy and are initiating bempedoic acid should be expected to achieve at least an additional 30% reduction in LDL-C levels.

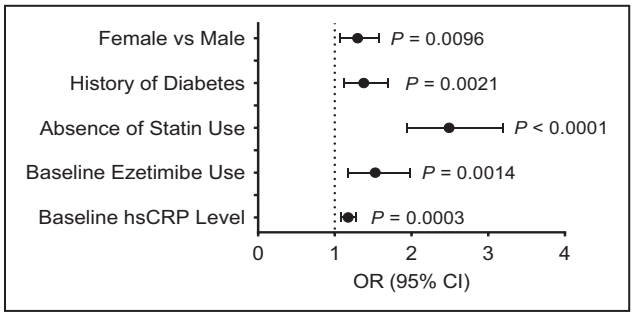


Figure 2. Multivariable analysis of baseline variables on achieving at least a 30% reduction in low-density lipoprotein cholesterol among patients treated with bempedoic acid.
CI indicates confidence interval; hsCRP, high-sensitivity C-reactive protein; and OR, odds ratio.

Approximately 50% of patients unable to take any statin should be expected to achieve LDL-C lowering comparable to that of a moderate- or high-intensity statin. Our findings may also help clinicians identify the clinical features of patients, including those having a history of statin intolerance, female sex, having diabetes, and having higher baseline hsCRP levels, that suggest these patients are more likely to achieve enhanced LDL-C lowering with bempedoic acid.

ARTICLE INFORMATION

Received November 1, 2021; accepted May 24, 2022.

Affiliations

Department of Medicine, Baylor College of Medicine, Houston, TX (C.M.B.); Louisville Metabolic and Atherosclerosis Research Center, Louisville, KY (H.E.B.); Esperion Therapeutics, Inc., Ann Arbor, MI (M.J.L., J.S., Y.Z.); and Department of Primary Care and Public Health, Imperial College London, London, United Kingdom (K.K.R.).

Acknowledgments

Author contributions: Esperion participated in the study design; research; data collection; analysis and interpretation of data; and writing, reviewing, and approving the article for publication. All authors had access to the data and participated in the development, review, and approval of the article. Medical writing support, funded by Esperion, was provided by Dr L. D. Shrode of JB Ashtin, who developed the first draft based on an author-approved outline and assisted in implementing author revisions. JB Ashtin adheres to Good Publication Practice guidelines and International Committee of Medical Journal Editors recommendations. Esperion had the opportunity to review the article draft for factual accuracy; the authors maintained full control of the article and determined the final content.

Sources of Funding

This analysis and the clinical trials included in this analysis were funded by Esperion Therapeutics, Inc.

Disclosures

Dr Ballantyne discloses the following relationships: research grant(s)/support paid to his institution from Abbott Diagnostic, Akcea, Amarin, Amgen, Arrowhead, Esperion, Ionis, Merck, Novartis, Novo Nordisk, Regeneron, Roche Diagnostic, National Institutes of Health, American Heart Association, and American Diabetes Association (ADA); consultant for 89Bio, Abbott Diagnostic, Alnylam Pharmaceuticals, Althera, Amarin, Amgen, Arrowhead, AstraZeneca, Denka Seiken, Eli Lilly, Esperion, Genentech, Gilead, Illumina, Matinas BioPharma Inc., Merck, New Amsterdam, Novartis, Novo Nordisk, Pfizer, Regeneron, Roche Diagnostic, and Sanofi-Synthelabo. Dr Bays

discloses the following relationships: research grants for his research site from 89Bio, Acasti, Akcea, Allergan, Alon Medtech/Epitomee, Amarin, Amgen, AstraZeneca, Axsome, Boehringer Ingelheim, Civi, Eli Lilly, Esperion, Evidera, Gan and Lee, Home Access, Janssen, Johnson and Johnson, Lexicon, Matinas, Merck, Metavant, Novartis, NovoNordisk, Pfizer, Regeneron, Sanofi, Selecta, TIMI, and Urovant; consultant and/or advisor for 89Bio, Amarin, Esperion, Matinas, and Gelesis; and speaker for Esperion. Dr Louie discloses the following relationships: full-time employment with Esperion Therapeutics, Inc., with the potential to own Esperion stock and/or stock options. Dr Smart discloses the following relationships: former full-time employment with Esperion Therapeutics, Inc., with the potential to own Esperion stock and/or stock options. Dr Zhang discloses the following relationships: full-time employment with Esperion Therapeutics, Inc., with the potential to own Esperion stock and/or stock options. Prof Ray discloses the following relationships: research grant(s)/support from Amgen, Daiichi Sankyo, MSD, Pfizer, Regeneron, and Sanofi (all paid to the institution, not to the individual); consultant for and/or honoraria from Abbott, AbbVie, Akcea, Algorithm, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Cerenis, Cipla, Daiichi Sankyo, Dr Reddy's Laboratories, Eli Lilly, Esperion, Kowa, Lupin, Medco, MSD, New Amsterdam Pharma, Novartis, Novo Nordisk, Pfizer, Regeneron, Resverlogix, Sanofi, Silence Therapeutics, Takeda, and Zuellig Pharma. Prof Ray acknowledges support from the National Institute for Health Research Imperial Biomedical Research Center.

Supplemental Material

Table S1
Figures S1–S2

REFERENCES

1. Boekholdt SM, Hovingh GK, Mora S, Arsenault BJ, Amarenco P, Pedersen TR, LaRosa JC, Waters DD, DeMicco DA, Simes RJ, et al. Very low levels of atherogenic lipoproteins and the risk for cardiovascular events: a meta-analysis of statin trials. *J Am Coll Cardiol*. 2014;64:485–494. doi: 10.1016/j.jacc.2014.02.615
2. Karlson BW, Wiklund O, Palmer MK, Nicholls SJ, Lundman P, Barter PJ. Variability of low-density lipoprotein cholesterol response with different doses of atorvastatin, rosuvastatin, and simvastatin: results from VOYAGER. *Eur Heart J Cardiovasc Pharmacother*. 2016;2:212–217. doi: 10.1093/ehjcvp/pvw006
3. Banach M, Duell PB, Gotto AM Jr, Laufs U, Leiter LA, Mancini GBJ, Ray KK, Flaim J, Ye Z, Catapano AL. Association of bempedoic acid administration with atherogenic lipid levels in phase 3 randomized clinical trials of patients with hypercholesterolemia. *JAMA Cardiol*. 2020;5:1124–1135. doi: 10.1001/jamacardio.2020.2314
4. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;139:e1082–e1143. doi: 10.1161/CIR.0000000000000625
5. Vupputuri S, Joski PJ, Kilpatrick R, Woolley JM, Robinson BE, Farkouh ME, Yun H, Safford MM, Muntner P. LDL cholesterol response and statin adherence among high-risk patients initiating treatment. *Am J Manag Care*. 2016;22:e106–e115.
6. Handelsman Y, Jellinger PS, Guerin CK, Bloomgarden ZT, Brinton EA, Budoff MJ, Davidson MH, Einhorn D, Fazio S, Fonseca VA, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the management of dyslipidemia and prevention of cardiovascular disease algorithm—2020 executive summary. *Endocr Pract*. 2020;26:1196–1224. doi: 10.4158/CS-2020-0490
7. Descamps O, Tomassini JE, Lin J, Polis AB, Shah A, Brudi P, Hanson ME, Tershakovec AM. Variability of the LDL-C lowering response to ezetimibe and ezetimibe + statin therapy in hypercholesterolemic patients. *Atherosclerosis*. 2015;240:482–489. doi: 10.1016/j.atherosclerosis.2015.03.004
8. Robinson JG, Ballantyne CM, Hsueh WA, Rosen JB, Lin J, Shah AK, Tomassini JE, Lowe RS, Tershakovec AM. Age, abdominal obesity, and baseline high-sensitivity C-reactive protein are associated with low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, and apolipoprotein B responses to ezetimibe/simvastatin and atorvastatin in patients with metabolic syndrome. *J Clin Lipidol*. 2013;7:292–303. doi: 10.1016/j.jacl.2013.03.007
9. Swiger KJ, Martin SS, Blaha MJ, Toth PP, Nasir K, Michos ED, Gerstenblith G, Blumenthal RS, Jones SR. Narrowing sex differences in lipoprotein cholesterol subclasses following mid-life: the very large database of lipids (VLDL-10B). *J Am Heart Assoc*. 2014;3:e000851. doi: 10.1161/JAHA.114.000851
10. Nanna MG, Wang TY, Xiang Q, Goldberg AC, Robinson JG, Roger VL, Virani SS, Wilson PWF, Louie MJ, Koren A, et al. Sex differences in the use of statins in community practice. *Circ Cardiovasc Qual Outcomes*. 2019;12:e005562. doi: 10.1161/CIRCOUTCOMES.118.005562
11. Jacobs MJ, Kleisli T, Pio JR, Malik S, L'Italien GJ, Chen RS, Wong ND. Prevalence and control of dyslipidemia among persons with diabetes in the United States. *Diabetes Res Clin Pract*. 2005;70:263–269. doi: 10.1016/j.diabres.2005.03.032
12. Glovaci D, Fan W, Wong ND. Epidemiology of diabetes mellitus and cardiovascular disease. *Curr Cardiol Rep*. 2019;21:21. doi: 10.1007/s11886-019-1107-y
13. Buckley DI, Fu R, Freeman M, Rogers K, Helfand M. C-reactive protein as a risk factor for coronary heart disease: a systematic review and meta-analyses for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2009;151:483–495. doi: 10.7326/0003-4819-151-7-200910060-00009
14. Bays HE, Rosenson RS, Baccara-Dinet MT, Louie MJ, Thompson D, Hovingh GK. Assessment of the 1% of patients with consistent <15% reduction in low-density lipoprotein cholesterol: pooled analysis of 10 phase 3 ODYSSEY alirocumab trials. *Cardiovasc Drugs Ther*. 2018;32:175–180. doi: 10.1007/s10557-018-6784-z
15. Trompet S, Postmus I, Slagboom PE, Heijmans BT, Smit RA, Maier AB, Buckley BM, Sattar N, Stott DJ, Ford I, et al. Non-response to (statin) therapy: the importance of distinguishing non-responders from non-adherers in pharmacogenetic studies. *Eur J Clin Pharmacol*. 2016;72:431–437. doi: 10.1007/s00228-015-1994-9

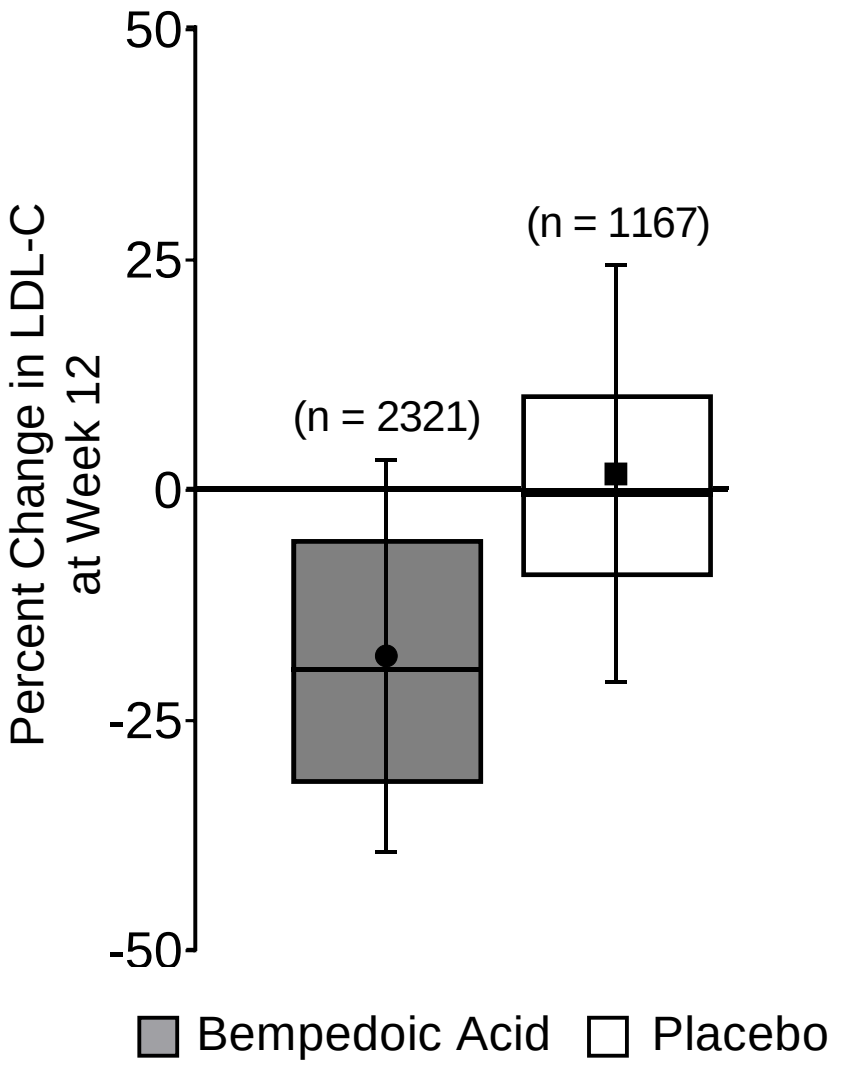
SUPPLEMENTAL MATERIAL

Table S1. Baseline Demographics and Disease Characteristics.

Characteristic	Bempedoic Acid (n=2321)	Placebo (n=1167)
Mean age, y ± SD	65.3 ± 9.2	66.0 ± 8.9
Male, % (n)	66.2 (1537)	65.6 (766)
Race, % (n)		
White	94.5 (2194)	94.5 (1103)
Black or African American	3.7 (87)	3.8 (44)
Asian	1.1 (25)	0.9 (11)
Native Hawaiian or Other Pacific Islander	0.2 (5)	0.2 (2)
American Indian or Alaska Native	0.1 (3)	0.2 (2)
Multiple	0.1 (3)	0.3 (3)
Other	0.2 (4)	0.2 (2)
Ethnicity		
Hispanic or Latino, % (n)	5.0 (115)	4.5 (53)
Not Hispanic or Latino, % (n)	95.0 (2206)	95.5 (1114)
ASCVD, % (n)	85.8 (1992)	86.9 (1014)
History of diabetes, % (n)	28.0 (649)	27.9 (326)
History of hypertension, % (n)	77.5 (1798)	79.1 (923)
BMI, kg/m^2, mean ± SD	29.8 ± 5.1	29.8 ± 5.0
Total cholesterol, mg/dL, mean ± SD	193.6 ± 43.8	192.2 ± 43.8
Non-HDL-C, mg/dL, mean ± SD	143.4 ± 42.1	141.8 ± 41.9
LDL-C, mg/dL, mean ± SD	114.2 ±36.7	113.0 ± 36.6
Triglycerides, mg/dL, median (Q1, Q3)	150.8 ± 74.6	148.7 ±72.0
Apo B, mg/dL, mean ± (SD)	102.0 ± 31.0	100.7 ± 31.4
hsCRP, mg/L, median (Q1, Q3)	1.62 (0.81, 3.54)	1.68 (0.86, 3.62)
Background statin intensity, % (n)		
High	42.6 (989)	42.7 (498)
Moderate	32.9 (763)	33.8 (394)
Low	5.1 (119)	4.9 (57)
None	19.4 (450)	18.7 (218)
Background ezetimibe, % (n)	15.1 (351)	14.6 (170)

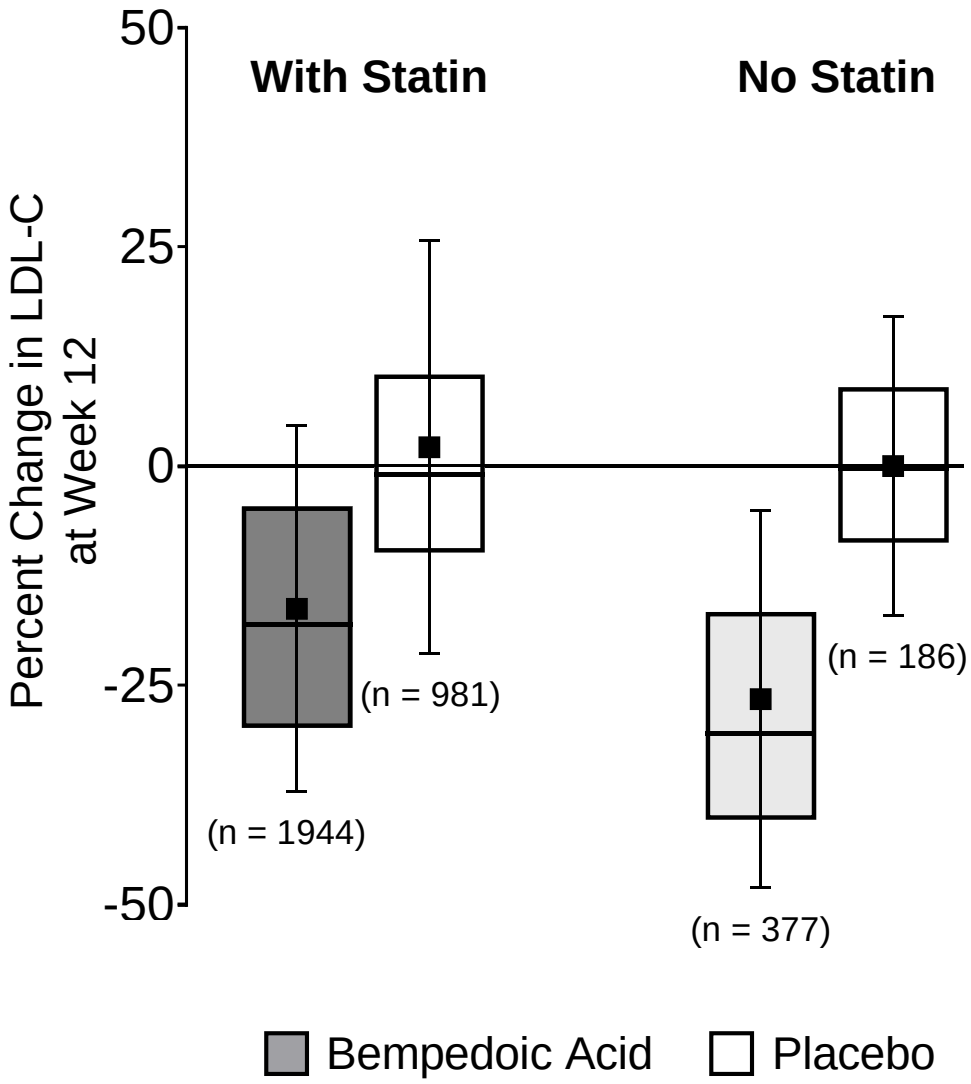
Apo B indicates apoprotein B; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non–high-density lipoprotein cholesterol.

Figure S1. Box and whisker plot of percent change in LDL-C at week 12.



The symbols and small error bars represent the mean (SD). The median is represented by the horizontal line within the box, with the lower portion of the box indicating quartile 1 and the upper portion of the box indicating quartile 3.

Figure S2. Box and whisker plot of percent change in LDL-C at week 12 by background statin use.



The symbols and small error bars represent the mean (SD). The median is represented by the horizontal line within the box, with the lower portion of the box indicating quartile 1 and the upper portion of the box indicating quartile 3.