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Bempedoic Acid for Primary Prevention of Cardiovascular Events in Statin-Intolerant Patients

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IMPORTANCE The effects of bempedoic acid on cardiovascular outcomes in statin-intolerant patients without a prior cardiovascular event (primary prevention) have not been fully described.

OBJECTIVE To determine the effects of bempedoic acid on cardiovascular outcomes in primary prevention patients.

DESIGN, SETTING, AND PARTICIPANTS This masked, randomized clinical trial enrolled 13 970 statin-intolerant patients (enrollment December 2016 to August 2019 at 1250 centers in 32 countries), including 4206 primary prevention patients.

INTERVENTIONS Participants were randomized to oral bempedoic acid, 180 mg daily (n = 2100), or matching placebo (n = 2106).

MAIN OUTCOME MEASURES The primary efficacy measure was the time from randomization to the first occurrence of any component of a composite of cardiovascular death, nonfatal myocardial infarction (MI), nonfatal stroke, or coronary revascularization.

RESULTS Mean participant age was 68 years, 59% were female, and 66% had diabetes. From a mean baseline of 142.5 mg/dL, compared with placebo, bempedoic acid reduced low-density lipoprotein cholesterol levels by 30.2 mg/dL (21.3%) and high-sensitivity C-reactive protein levels by 0.56 mg/L (21.5%), from a median baseline of 2.4 mg/L. Follow-up for a median of 39.9 months was associated with a significant risk reduction for the primary end point (111 events [5.3%] vs 161 events [7.6%]; adjusted hazard ratio [HR], 0.70 [95% CI, 0.55-0.89]; $P = .002$) and key secondary end points, including the composite of cardiovascular death, MI, or stroke (83 events [4.0%] vs 134 events [6.4%]; HR, 0.64 [95% CI, 0.48-0.84]; $P < .001$); MI (29 events [1.4%] vs 47 events [2.2%]; HR, 0.61 [95% CI, 0.39-0.98]); cardiovascular death (37 events [1.8%] vs 65 events [3.1%]; HR, 0.61 [95% CI, 0.41-0.92]); and all-cause mortality (75 events [3.6%] vs 109 events [5.2%]; HR, 0.73 [95% CI, 0.54-0.98]). There was no significant effect on stroke or coronary revascularization. Adverse effects with bempedoic acid included a higher incidence of gout (2.6% vs 2.0%), cholelithiasis (2.5% vs 1.1%), and increases in serum creatinine, uric acid, and hepatic enzyme levels.

CONCLUSIONS In a subgroup of high-risk primary prevention patients, bempedoic acid treatment was associated with reduced major cardiovascular events.

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Visual Abstract
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Statins reduce atherogenic lipoproteins and are recommended by current guidelines for administration to patients at high risk for a first major adverse cardiovascular event (primary prevention).[1] However, the current recommendations are predominantly derived from clinical trials conducted several decades ago during the initial development of statins to reduce low-density lipoprotein cholesterol (LDL-C) levels.[2,3] Most contemporary cardiovascular outcome trials of lipid-lowering therapies have enrolled only participants with a prior cardiovascular event. Recent data are limited on the effects of statins or other adjunctive treatments in patients without a history of a cardiovascular event, leading some authors to question whether the benefits of cholesterol lowering exceed the harms in these patients.[4-7] Currently, lipid-lowering therapies are underutilized in high-risk primary prevention patients, particularly women and patients from racial and ethnic minority populations.[8-10] More than half of eligible patients do not currently receive lipid-lowering therapies.[9]

The CLEAR Outcomes (Cholesterol Lowering via Bempedoic Acid, an ACL-Inhibiting Regimen) trial reported cardiovascular outcomes in a mixed population of primary and secondary prevention patients unable or unwilling to take guideline-recommended doses of statins.[11] Among the 13 970 patients enrolled in the trial, 4206 (30%) had characteristics associated with a high risk of adverse cardiovascular outcomes but without a prior event. The current article reports a prespecified subgroup analysis of the effects of bempedoic acid on major adverse cardiovascular outcomes in this primary prevention population.

Key Points

Question In statin-intolerant primary prevention patients at high cardiovascular risk, does bempedoic acid reduce major adverse cardiovascular events?

Findings In this randomized trial of 13 970 patients, 4206 participants were enrolled with high cardiovascular risk but without a prior cardiovascular event. In this subgroup, bempedoic acid treatment, 180 mg daily, was associated with a significant reduction in major cardiovascular events (hazard ratio, 0.70).

Meaning These findings suggest that treatment with bempedoic acid in primary prevention patients has the potential to reduce major adverse cardiovascular events.

Methods

Trial Organization and Oversight

The rationale, design, and methods of the trial have been reported.[11,12] The trial was conducted at 1250 sites in 32 countries. The trial was designed by the Cleveland Clinic Coordinating Center for Clinical Research (C5Research) and an academic executive committee in collaboration with the sponsor, Esperion Therapeutics Inc. The protocol was approved by ethics committees at participating sites, and all patients provided written informed consent before enrollment (the study protocol and statistical analysis plan are available in Supplement 1). A contract research organization collected the data, which were transferred to C5Research at completion of the trial; C5Research statisticians conducted the analyses for this article. An independent data monitoring committee monitored the trial.

Trial Population

Primary prevention patients aged 18 to 85 years with an LDL-C level 100 mg/dL (2.59 mmol/L) or greater and with clinical features placing them at high risk for a first cardiovascular event were eligible. Criteria for high cardiovascular risk included risk scores described in eFigure 1 in Supplement 2,[13,14] a coronary artery calcium score greater than 400 Agatston units, or presence of either type 1 or 2 diabetes in women older than 65 years or men older than 60 years.

Investigators were responsible for assessing the patient for statin intolerance. Patients had to report statin intolerance due to an adverse effect that started or increased during statin therapy and resolved or improved after statin therapy was discontinued. Entry criteria required inability to tolerate 2 or more statins at any dose or 1 statin and unwillingness to attempt a second statin or advised by a physician not to attempt taking a second statin. Both the patient and site investigator were required to provide written confirmation that the patient was statin intolerant and aware of the benefits of statins to reduce the risk of cardiovascular events, including death, and acknowledge that many patients unable to tolerate a statin can tolerate a different statin or dose. Patients could be enrolled if they tolerated a very low average daily statin dose, defined as rosuvastatin less than 5 mg, atorvastatin less than 10 mg, simvastatin less than 10 mg, lovastatin less than 20 mg, pravastatin less than 40 mg, fluvastatin less than 40 mg, or pitavastatin less than 2 mg. Other background lipid-lowering therapies were permitted, including ezetimibe, niacin, bile acid resins, fibrates, and/or proprotein convertase subtilisin/kexin type 9 inhibitors. The study design and primary publications provide the full inclusion and exclusion criteria.[11,12]

Study Procedures

Eligible patients entered a 4-week run-in period during which they were treated with single-masked placebo. If patients were intolerant to placebo treatment or if adherence was less than 80% by tablet count, they were not eligible for randomization. Patients who successfully completed the run-in period were randomly assigned in a 1:1 ratio to receive a 180-mg oral dose of bempedoic acid or matching placebo, administered daily. During the trial, LDL-C and high-sensitivity C-reactive protein (hsCRP) results were masked. Beginning 6 months after randomization, the central laboratory notified the investigator, who remained masked to treatment assignment, if the patient's LDL-C level was 25% or more higher than baseline. Repeat testing was performed after the patient was counseled about diet and encouraged to take all medications as prescribed. The patient returned for a repeat fasting blood lipid profile to confirm whether the LDL-C value exceeded the threshold criteria. If confirmed, the patient's treatment regimen for LDL-C lowering could be adjusted, per standard of care

and local practice. The flow of patients through the trial is shown in **Figure 1**.

Study End Points

The primary end point was the time to first occurrence of a composite of death from cardiovascular causes, nonfatal myocardial infarction (MI), nonfatal stroke, or coronary revascularization (4-component major adverse cardiovascular events [MACE]). Key secondary end points included (1) time to the first occurrence of a composite of cardiovascular death, nonfatal stroke, or nonfatal MI (3-component MACE); (2) fatal or nonfatal MI; (3) coronary revascularization; (4) fatal or nonfatal stroke; (5) cardiovascular death; and (6) all-cause mortality. Additional adjudicated time-to-event end points included hospitalization for unstable angina and a 5-component composite that included cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, and hospitalization for unstable angina. End points were adjudicated by C5Research clinical end points committee personnel masked to treatment assignments.

Statistical Analysis

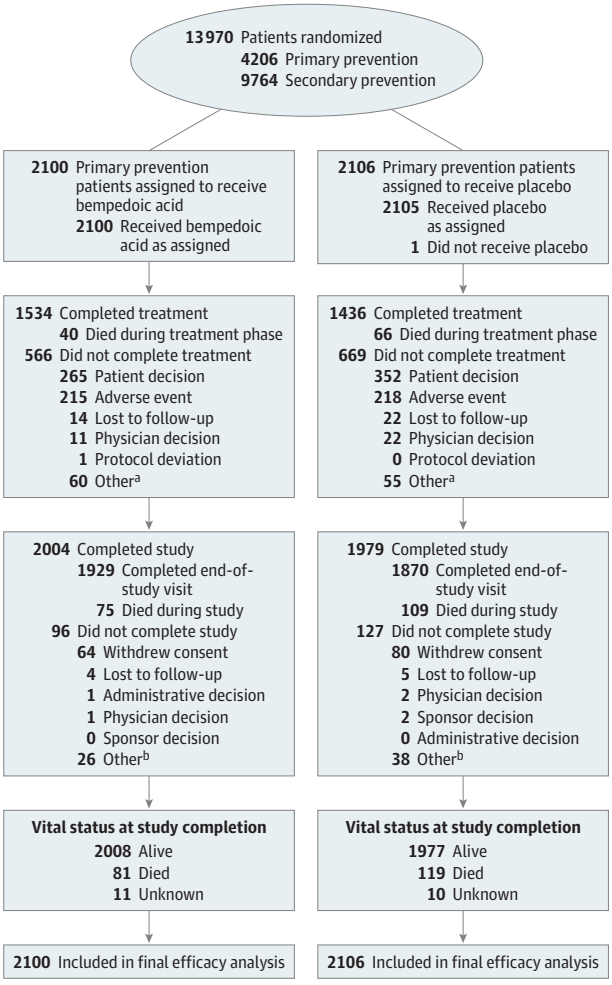
The efficacy end points were analyzed using a Cox proportional hazards model with treatment as a factor to generate the hazard ratio (HR) and 95% confidence interval. *P* values were obtained from a log-rank test (2-sided). Significance testing was performed using 2-sided tests ($\alpha = .05$). All efficacy outcomes were adjusted for baseline characteristics including geographic region, age, sex, race and ethnicity (assessed to determine if the response to treatment differed among individuals based on their racial or ethnic background), LDL-C level, body mass index, hsCRP level, estimated glomerular filtration rate, use of any lipid-modifying therapy at baseline, and glycemic status (diabetes, prediabetes, normoglycemia). A time-dependent covariate with treatment was created to assess for proportionality. The *P* value was not statistically significant; therefore, the assumption of proportional hazards was determined to be met. Change and percent change in lipids were calculated using least-square means adjusted for baseline. Hodges-Lehmann estimate of location shift was used to summarize changes in hsCRP and triglyceride levels. Baseline data for 2 patients with missing body mass index data were imputed for efficacy models using the average measurement of the overall cohort. The statistical analysis plan prespecified subgroup analyses for 4-component MACE and 3-component MACE. Therefore, *P* values are provided only for these end points. Efficacy analyses included all randomized patients based on the intent-to-treat principle. Outcomes were not adjusted for multiplicity. Adverse event summaries were based on the safety population that included all patients who underwent randomization and received at least 1 dose of study drug.

Results

Study Population

Between December 2016 and August 2019, 22 084 patients were screened and 14 016 were randomized, with 13 970 included in the full analysis after exclusion of 46 participants from a site determined to have created fraudulent patients. Within the full analysis set, 4206 patients (30%) met primary prevention criteria, 2100 randomized to the bempedoic acid treatment group and 2106 to the placebo group. For the pooled treatment groups, mean age was 67.9 (SD, 6.8) years, 59.0% of patients were female, 66.1% had diabetes, and 19.3% were taking a statin and 8.0% ezetimibe. Mean LDL-C level was 142.5 mg/dL, mean high-density lipoprotein cholesterol, 51.0 mg/dL; median triglycerides, 161.8 mg/dL (to convert cholesterol values to mmol, multiply by 0.0259); and median hsCRP, 2.4 mg/L. These baseline characteristics were similar in both treatment groups (**Table 1**). High-risk primary prevention patients were followed up for a median of 39.9 months. Complete assessment for the primary end point was available for 94.7% and vital status for 99.5% of these patients. Efficacy end points at sites in Ukraine were censored after the start of the conflict on February 24, 2022. The flow of patients through the trial is shown in Figure 1.

Figure 1. Flow of Patients Through the Trial (Primary Prevention)



[a] Premature termination of treatment (the war in Ukraine [45/115 patients]).

[b] Premature withdrawal from the trial (patient could not be contacted, but final vital status known; therefore, not counted as lost to follow-up [37/64]).

Table 1. Demographic and Baseline Characteristics of Patients

Characteristic	Bempedoic acid (n = 2100)	Placebo (n = 2106)
Age, mean (SD), y	67.9 (6.9)	68.0 (6.8)
Sex, No. (%)		
Female	1234 (58.8)	1247 (59.2)
Male	866 (41.2)	859 (40.8)
Race, No. (%)[a]		
American/Mexican Indian or Alaska Native	49 (2.3)	49 (2.3)
Black or African American	66 (3.1)	67 (3.2)
Native Hawaiian or Pacific Islander	8 (0.4)	6 (0.3)
White	1936 (92.2)	1913 (90.8)
Other	0	1
Ethnicity, No. (%)[a]		
Hispanic or Latino	399 (19.0)	378 (17.9)
Not Hispanic or Latino	1701 (81.0)	1728 (82.1)
Body mass index, mean (SD)[b]	30.2 (5.3)	30.4 (5.4)
>35, No. (%)	350 (16.7)	367 (17.4)
Systolic blood pressure, mean (SD), mm Hg	135.6 (13.8)	136.0 (13.6)
>140 mm Hg, No. (%)	729 (34.7)	750 (35.6)
Lipids, mean (SD), mg/dL		
LDL-C	142.2 (34.5)	142.7 (35.9)
HDL-C	51.1 (13.5)	50.9 (13.7)
Non-HDL-C	177.4 (38.7)	178.2 (41.2)
Total cholesterol	228.5 (40.2)	229.1 (42.3)
Triglycerides, median (IQR), mg/dL	162.0 (120.5-216.5)	161.5 (123.5-215.5)
hsCRP, median (IQR), mg/L	2.4 (1.2-4.5)	2.4 (1.2-4.6)
Baseline eGFR, mean (SD), mL/min/1.73 m^2	73.8 (17.3)	73.2 (17.8)
Cardiovascular risks, No. (%)		
Diabetes[c]	1369 (65.2)	1412 (67.0)
Inadequately controlled diabetes[d]	569 (27.1)	593 (28.2)
Hypertension	1853 (88.2)	1854 (88.0)
Chronic kidney disease	146 (7.0)	155 (7.4)
Criteria for increased risk, No. (%)		
Reynolds Risk Score >30% or SCORE Risk Score >7.5% over 10 y[e]	868 (41.3)	922 (43.8)
Coronary artery calcium score >400 AU	86 (4.1)	55 (2.6)
Patients with self-reported type 1 or 2 diabetes, aged >65 (women) or >60 y (men), No. (%)	1150 (54.8)	1187 (56.4)
Region, No. (%)		
Eastern Europe	1114 (53.0)	1117 (53.0)
North America	446 (21.2)	439 (20.8)
Latin America	280 (13.3)	257 (12.2)
Western Europe	168 (8.0)	180 (8.5)
Other[f]	92 (4.3)	113 (5.4)
Baseline statin use, No. (%)[g]	394 (18.8)	417 (19.8)
Baseline ezetimibe use, No. (%)	184 (8.8)	151 (7.2)

Abbreviations: eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; HDL-C, high-density lipoprotein cholesterol; SCORE, Systematic Coronary Risk Evaluation; AU, Agatston units.

SI conversion factors: To convert LDL-C, HDL-C, and total cholesterol values to mmol/L, multiply by 0.02586; triglyceride values to mmol/L, multiply by 0.01129.

[a] Race and ethnicity were self-reported. Participants could select more than 1 category, including "Other." Race and ethnicity were assessed to determine if the response to treatment differed among individuals based on their racial or ethnic background.

[b] Calculated as weight in kilograms divided by square of height in meters.

[c] At baseline, medical history of type 1 or 2 diabetes, prior glucose-lowering medication, hemoglobin A_{1c} level 6.5% (48 mmol/mol) or greater, or 2 or more measurements of fasting glucose 126 mg/dL (7.0 mmol/L) or greater.

[d] Patients with type 1 or 2 diabetes and a hemoglobin A_{1c} level 7.0% (53 mmol/mol) or greater at baseline.

[e] The REYNOLDS and SCORE risk calculators are described in eFigure 1 in Supplement 2.

[f] Includes Australia, India, New Zealand, South Africa, and Turkey.

[g] Patients could be enrolled if they were taking doses of a statin less than the lowest approved dose.

Effects on LDL-C and hsCRP Levels

The effects of trial regimens on lipid parameters after 6 months of treatment and hsCRP level after 12 months of treatment are reported in **Table 2**. From a baseline mean LDL-C level of 142.2 mg/dL, least-square mean reduction in the bempedoic acid group compared with placebo after 6 months of treatment was 30.2 mg/dL (95% CI, -32.1 to -28.3), a least-square mean difference of 21.3%. With administration of additional lipid-modifying therapies to 12.4% of patients in the placebo group and 6.7% in the bempedoic acid group (eTable 1 in Supplement 2), the time-averaged difference in LDL-C level in the primary prevention subgroup over the course of the trial was 23.2 mg/dL (eFigure 2 in Supplement 2). From a median baseline value of 2.4 mg/L, after 12 months of treatment, using Hodges-Lehman estimate of location shift, bempedoic acid reduced hsCRP level by 0.34 mg/L (95% CI, −0.42 to −0.29) compared with a reduction of 0.01 mg/L (95% CI, −0.04 to 0.09) for placebo, a difference of 0.56 mg/L (21.5%).

Table 2. Effect of Trial Regimens on Lipid and Inflammatory Biomarkers

End point	Bempedoic acid			Placebo			Bempedoic acid vs placebo after 6 mo of treatment	
	Observed mean (SD) or median (IQR)		Change, baseline to 6 mo (95% CI)[a]	Observed mean (SD) or median (IQR)		Change, baseline to 6 mo (95% CI)[a]	Difference (95% CI)[a]	Difference, % (95% CI)[a]
	Baseline	6 mo		Baseline	6 mo			
Lipids, mg/dL								
Total cholesterol	228.5 (40.2)	191.1 (43.5)	−37.3 (−38.9 to −35.8)	229.1 (42.3)	225.2 (48.0)	−3.4 (−5.0 to −1.9)	−33.9 (−36.1 to −31.7)	−14.8 (−15.7 to −13.8)
HDL-C	51.1 (13.5)	47.6 (14.7)	−3.4 (−3.8 to −3.0)	50.9 (13.7)	50.9 (14.1)	−0.05 (−0.4 to 0.3)	−3.35 (−3.87 to −2.82)	−6.9 (−7.9 to −5.9)
LDL-C	142.2 (34.5)	108.2 (36.4)	−34.0 (−35.3 to −32.6)	142.7 (35.9)	138.6 (41.1)	−3.8 (−5.1 to −2.4)	−30.2 (−32.1 to −28.3)	−21.3 (−22.7 to −19.9)
Non-HDL-C	177.4 (38.7)	143.5 (41.8)	−34.0 (−35.5 to −32.5)	178.2 (41.2)	174.4 (46.6)	−3.4 (−4.8 to −1.9)	−30.6 (−32.7 to −28.5)	−17.3 (−18.5 to −16.1)
Triglycerides	162.0 (120.5 to 216.5)	156.0 (111.0 to 219.0)	−6.0 (−9.0 to −3.0)	161.5 (123.5 to 215.5)	160.0 (117.0 to 217.0)	−2.0 (−3.5 to 0.5)	−4.25 (−7.5 to −1.0)	−3.2 (−5.1 to −1.3)
	Baseline	12 mo	Change, baseline to 12 mo (95% CI)[b]	Baseline	12 mo	Change, baseline to 12 mo (95% CI)[b]	After 12 mo of treatment	After 12 mo of treatment
hsCRP, mg/L	2.39 (1.2 to 4.5)	1.75 (0.87 to 3.49)	−0.34 (−0.42 to −0.29)	2.44 (1.2 to 4.6)	2.52 (1.2 to 5.0)	0.01 (−0.04 to 0.09)	−0.56 (−0.68 to −0.44)	−21.5 (−25.4 to −17.6)

Abbreviations: hsCRP, high-sensitivity C-reactive protein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

SI conversion factors: To convert total cholesterol, HDL-C, and LDL-C values to mmol/L, multiply by 0.02586; triglyceride values to mmol/L, multiply by 0.01129.

[a] Least-square means are calculated for change and percent change from baseline for LDL, HDL, total cholesterol, and non-HDL-C.

[b] Hodges-Lehmann estimate of location shift is used to estimate change and percent change from baseline for hsCRP and triglycerides.

Clinical End Points

The primary 4-component composite end point occurred in 111 patients (5.3%) in the bempedoic acid group and 161 patients (7.6%) in the placebo group (HR, 0.70 [95% CI, 0.55-0.89]; *P* = .002) (**Table 3** and **Figure 2**A). The number needed to treat (NNT) to prevent 1 primary composite outcome was 43 patients. Bempedoic acid was associated with a significant reduction in the risk of the secondary 3-component composite end point of time to cardiovascular death, nonfatal MI, or stroke, which occurred in 83 patients (4.0%) in the bempedoic acid group and 134 patients (6.4%) in the placebo group (HR, 0.64 [95% CI, 0.48-0.84]; *P* < .001) (Table 3 and Figure 2B). For the other secondary end points, fatal or nonfatal MI occurred in 29 patients (1.4%) in the bempedoic acid group and 47 patients (2.2%) in the placebo group (adjusted HR, 0.61 [95% CI, 0.39-0.98]) (Table 3 and Figure 2C). Fatal or nonfatal stroke occurred in 27 patients (1.3%) in the bempedoic acid group and 37 patients (1.8%) in the placebo group (adjusted HR, 0.76 [95% CI, 0.46-1.26]) (Table 3 and Figure 2D). Cardiovascular death occurred in 37 patients (1.8%) in the bempedoic acid group and 65 patients (3.1%) in the placebo group (adjusted HR, 0.61 [95% CI, 0.41-0.92]) (Table 3 and Figure 2E). All-cause mortality occurred in 75 patients (3.6%) in the bempedoic acid group and 109 patients (5.2%) in the placebo group (adjusted HR, 0.73 [95% CI, 0.54-0.98]) (Table 3 and Figure 2F).

The first occurrence of the 5-component composite of death from cardiovascular causes, MI, stroke, coronary revascularization, or hospitalization for unstable angina occurred in 112 patients (5.3%) in the bempedoic acid group and 164 patients (7.8%) in the placebo group (HR, 0.69 [95% CI, 0.54-0.88]) (Table 3; eFigure 3 in Supplement 2). Coronary revascularization occurred in 50 patients (2.4%) in the bempedoic acid group and 68 patients (3.2%) in the placebo group (HR, 0.71 [95% CI 0.49-1.03]) (Table 3; eFigure 4 in Supplement 2). Hospitalization for unstable angina occurred in 10 patients (0.5%) in the bempedoic acid group and 17 patients (0.8%) in the placebo group (HR, 0.58 [95% CI, 0.26-1.27]) (Table 3; eFigure 5 in Supplement 2). Unadjusted analyses of the primary and secondary end points showed results similar to those from the adjusted analyses (eTable 2 in Supplement 2).

Adverse Effects

Adverse events are reported in **Table 4**. There were no between-group differences in serious adverse events or adverse events leading to drug discontinuation. However, investigator-reported prespecified adverse events included more frequent elevations in hepatic enzyme levels (4.5% vs 2.6%) and more frequent kidney adverse events (10.3% vs 8.1%) in the bempedoic acid group compared with the placebo group. Myalgias were reported in 4.2% of bempedoic acid-treated patients compared with 5.9% of placebo-treated patients. A higher incidence of hyperuricemia (12.1% vs 6.3%), gout (2.6% vs 2.0%), and cholelithiasis (2.5% vs 1.1%) occurred in the bempedoic acid group. Rates of new-onset diabetes and the change in hemoglobin A_{1c} levels in patients with diabetes at baseline were similar in both randomized groups.

Table 3. Time to Event Efficacy End Points for the Bempedoic Acid Treatment Group Compared With Placebo Group

Outcome	No. of patients (%)		HR (95% CI)[a]	*P* value[b]
	Bempedoic acid (n = 2100)	Placebo (n = 2106)		
Person-years of follow-up[c]	6898	6807		
Primary efficacy end point (4-component MACE)[d]	111 (5.3)	161 (7.6)	0.70 (0.55-0.89)	.002
Secondary efficacy end points				
3-component MACE[e]	83 (4.0)	134 (6.4)	0.64 (0.48-0.84)	<.001
5-component MACE[f]	112 (5.3)	164 (7.8)	0.69 (0.54-0.88)	
End point components				
All-cause mortality	75 (3.6)	109 (5.2)	0.73 (0.54-0.98)	
Cardiovascular death	37 (1.8)	65 (3.1)	0.61 (0.41-0.92)	
Fatal and nonfatal MI	29 (1.4)	47 (2.2)	0.61 (0.39-0.98)	
Fatal and nonfatal stroke	27(1.3)	37 (1.8)	0.76 (0.46-1.26)	
Coronary revascularization	50 (2.4)	68 (3.2)	0.71 (0.49-1.03)	
Hospitalization for unstable angina	10 (0.5)	17 (0.8)	0.58 (0.26-1.27)	

Abbreviations: HR, hazard ratio; MACE, major adverse cardiovascular events; MI, myocardial infarction.

[a] Hazard ratios adjusted for baseline characteristics including geographic region, age, sex, race, ethnicity, baseline low-density lipoprotein cholesterol level, body mass index, high-sensitivity C-reactive protein level, estimated glomerular filtration rate, use of any lipid-modifying therapy at baseline, and diabetes status (diabetes, prediabetes, normoglycemia).

[b] From the log-rank test.

[c] Person-years of follow-up for the primary end point (4-component MACE).

[d] The primary efficacy end point (4-component MACE) is the time to first occurrence of an adjudicated event for a composite that includes death from cardiovascular causes, nonfatal MI, nonfatal stroke, or coronary revascularization.

[e] Time to first occurrence of the composite end point of death from cardiovascular causes, nonfatal MI, or nonfatal stroke (3-component MACE).

[f] Time to first occurrence of death from cardiovascular causes, nonfatal MI, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina (5-component MACE).

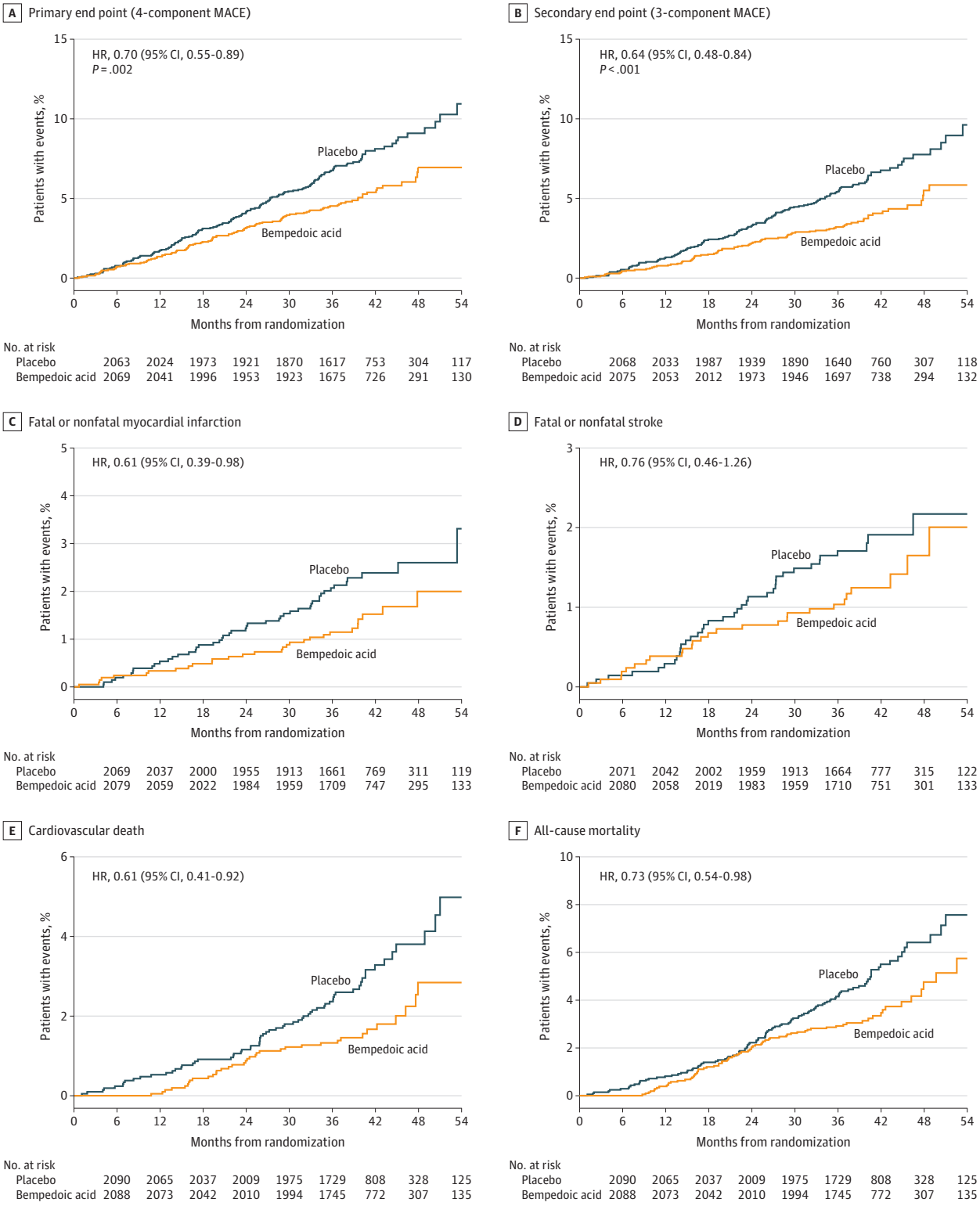
Discussion

In patients with elevated cardiovascular risk but without a prior clinical event, this prespecified subgroup analysis showed that administration of bempedoic acid in patients unable or unwilling to take guideline recommended doses of a statin was associated with a significant reduction in the primary end point, 4-component MACE (2.3% absolute risk reduction). The NNT to prevent 1 primary event was 43 patients. This primary prevention cohort was a prespecified subgroup that represented 30% of the total enrolled within a larger trial that included a mixed population of primary and secondary prevention patients.[11] Treatment was also associated with significant benefits for several key secondary end points, including the prespecified 3-component MACE (2.4% absolute risk reduction); an NNT of 42 patients to prevent 1 event; and significant reductions in MI, cardiovascular death, and all-cause mortality. Stroke and coronary revascularization were not significantly reduced. Although prespecified, this study reports on outcomes in a subgroup within a larger clinical trial; therefore, the results should be interpreted as hypothesis-generating rather than definitive evidence of benefits. Adverse events included a higher incidence of gout, elevated hepatic enzyme levels, and increased serum creatinine levels.

After 6 months of treatment, bempedoic acid, compared with placebo, reduced levels of LDL-C by 30.2 mg/dL (21.3%) and hsCRP by 0.56 mg/L (21.5%). Although the time-averaged difference in LDL-C over the duration of the trial was moderate (23.2 mg/dL [16.3%]), there were substantial reductions in major adverse cardiovascular outcomes and cardiovascular and all-cause mortality. These findings emphasize the potential value of lipid-modulating therapy in patients who have had no prior cardiovascular event but who have a high risk for a first event, a population that is currently undertreated.[8-10,15-18] Because diabetes was an enrollment criterion for increased cardiovascular risk, approximately two-thirds of the participants had previously diagnosed diabetes. The current findings support the guideline recommendation that primary prevention patients with diabetes should be treated with statins to lower cholesterol levels.

Only 1 major clinical trial during the last decade has reported on the effects of lipid-lowering treatment in patients without a prior cardiovascular event. The Heart Outcomes Prevention Evaluation 3 (HOPE-3), published in 2016, showed that low-dose statin therapy reduced the composite cardiovascular outcome by 24% but had no significant effect on mortality.[19] The 2 classic trials of primary prevention patients published in the 1990s showed a reduction in morbidity but not mortality.[2,3] The Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) study published 15 years ago showed a 44% reduction in the primary composite outcome and a 20% reduction in all-cause mortality with statin therapy in primary prevention patients with an hsCRP level greater than 2.0 mg/L.[20] Although the current study was not designed to assess factors mediating the results, both LDL-C and hsCRP levels were significantly reduced. Reduction in LDL-C has been strongly associated with improved cardiovascular outcomes, and 3 recent trials have demonstrated favorable effects with anti-inflammatory therapies.[21-24]

Figure 2. Time to First Incidence of Primary End Point, Key Secondary End Point, and End Point Components



Four-component major adverse cardiovascular events (MACE) indicates a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization; 3-component MACE, a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. *P* values were calculated using the log-rank test. The median follow-up time was 39.9 months. HR indicates hazard ratio.

Table 4. Investigator-Reported Adverse Events and Safety Laboratory Findings (Safety Population)[a]

	No. (%)	
	Bempedoic acid (n = 2104)	Placebo (n = 2101)
Serious treatment-emergent adverse event	418 (19.9)	438 (20.8)
Adverse event leading to drug discontinuation	209 (9.9)	209 (9.9)
Any treatment-emergent adverse event	1785 (84.8)	1744 (83.0)
Worsening hyperglycemia[b]	297/1372 (21.6)	294/1408 (20.9)
Muscular disorders	269 (12.8)	291 (13.9)
Hyperuricemia	254 (12.1)	133 (6.3)
Kidney impairment	216 (10.3)	170 (8.1)
New-onset diabetes		
Patients with prediabetes at baseline[c]	45/538 (8.4)	46/548 (8.4)
Patients without diabetes at baseline	47/732 (6.4)	48/693 (6.9)
Myalgias	88 (4.2)	124 (5.9)
Hypoglycemia	104 (4.9)	81 (3.9)
Elevated hepatic enzymes	94 (4.5)	55 (2.6)
Malignancies	84 (4.0)	86 (4.1)
Atrial fibrillation	53 (2.5)	52 (2.5)
Gout	55 (2.6)	41 (2.0)
Cholelithiasis	53 (2.5)	24 (1.1)
Tendinopathies	37 (1.8)	34 (1.6)
Discontinuation of treatment due to myalgia	29 (1.4)	35 (1.7)
Adjudicated tendon rupture	29 (1.4)	18 (0.9)
Neurocognitive disorders	9 (0.4)	19 (0.9)
Laboratory results after 6 mo, mg/dL		
Change from baseline in uric acid level, mean (SD)	0.80 (1.1)	−0.01 (1.0)
Uric acid >8.5 mg/dL, No. (%)	215/1996 (10.8)	82/1993 (4.1)
Change from baseline in creatinine levels, mean (SD)	0.05 (0.19)	0.02 (0.14)
Creatinine >1.5 mg/dL, No. (%)	65/1996 (3.3)	52/1993 (2.6)
Laboratory results after 12 mo		
Change from baseline in HbA_{1c}, (%)[d]	0.03 (0.79)	0.06 (0.77)
in patients without diabetes at baseline	0.02 (0.26)	0.06 (0.31)
in patients with diabetes at baseline	0.03 (0.96)	0.06 (0.91)
Enzyme abnormalities at any visit, No. (%)		
Creatine kinase levels >10× ULN		
Single occurrence	5 (0.2)	2 (0.1)
Repeated and confirmed	0	0
Alanine aminotransferase level >3× ULN[e]	44 (2.1)	40 (1.9)
Aspartate aminotransferase level >3× ULN[e]	72 (3.5)	27 (1.3)

Abbreviations: HbA_{1c}, hemoglobin A_{1c}; ULN, upper limit of normal.

[a] All reported adverse events other than the laboratory findings represent the investigator's judgment. Specific guidance was not provided.

[b] In patients with diabetes at baseline.

[c] Patients with prediabetes at baseline were defined as: No past medical history of diabetes and with hemoglobin A_{1c} level of 5.7% or greater and less than 6.5% or 1 or more measurement of fasting glucose 100 mg/dL (5.6 mmol/L) or greater, but not more than 1 value of fasting glucose 126 mg/dL (7.0 mmol/L) or greater. Patients with normoglycemia at baseline did not meet criteria for prediabetes.

[d] Not a prespecified safety measure.

[e] Repeated and confirmed.

Primary prevention patients are currently undertreated with lipid-modulating therapies.[4-7] In a registry of nearly 50 000 US patients with LDL-C levels greater than 190 mg/dL but without cardiovascular disease, only 58.5% were taking a statin.[15] Another study of US patients eligible for treatment based on current guidelines reported that 53% of patients treated in cardiology practices were not taking a statin.[16] In a Danish study of more than 90 000 patients, 81% of primary prevention patients with a 10-year risk greater than 10% for a cardiovascular event were not treated to LDL-C goals according to the European guidelines.[17] In a registry that studied reasons why eligible patients were not taking a statin, 59% reported never being offered treatment, 10% declined a statin, and 31% discontinued therapy.[18] Statin use in primary prevention patients was particularly low in minority groups in a recent national survey.[10] Current guidelines do not specifically address the use of nonstatin treatments in high-risk primary prevention patients.

The Cholesterol Treatment Trialists Collaboration (CTTC) meta-analysis reported on outcomes for statin treatment in patients without vascular disease.[24] The CTTC analysis showed a 22% reduction in major coronary events for each 38.7-mg/dL (1-mmol/L) decrease in LDL-C level and a 15% reduction in vascular death. In the current study, a time-averaged reduction of 23.2 mg/dL (0.60 mmol/L) was associated with larger reductions in cardiovascular morbidity and mortality than predicted by the CTTC analysis. The CTTC analysis reported that the benefits of lowering LDL-C level were consistent across a wide spectrum of baseline risk

varying from less than 5% to 30% or greater. However, a more recent modeling study challenged these findings, suggesting that benefits would exceed harms only for patients at higher risk levels, particularly women.[6] In the current study, women comprised nearly 60% of the population.

Limitations

This study has several limitations. First, this 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. However, the consistency of event reduction for the primary end point, secondary end points, and components of end points strengthens the likelihood that these results are reliable. Second, because the sample size represented a fraction of the total enrolled population, the number of events was smaller, resulting in wider confidence intervals. Third, the inclusion of patients who reported inability to tolerate statins resulted in a high mean baseline LDL-C level. The effects of cholesterol lowering on cardiovascular events in populations with lower pretreatment LDL-C levels was not studied. Fourth, the trial selected patients using specific criteria for a high level of risk of a first cardiac event. Whether outcomes would be similar in patients identified using other criteria for an increased risk remains uncertain.

Conclusion

In primary prevention patients unable to tolerate recommended doses of statins, bempedoic acid was associated with a significant reduction in the primary composite end point, time to death from cardiovascular causes, nonfatal MI, nonfatal stroke, or coronary revascularization. Treatment was also associated with significant reductions in MI, cardiovascular death, and all-cause mortality.

ARTICLE INFORMATION

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Concept and design: Nissen, Nicholls, Ridker, Mason, Kastelein, Cho, Libby, Foody, Louie, Lincoff.
Acquisition, analysis, or interpretation of data: Nissen, Menon, Nicholls, Brennan, Laffin, Ridker, Ray, Cho, Libby, Li, Foody, Louie, Lincoff.
Drafting of the manuscript: Nissen, Brennan, Cho, Libby, Li, Louie.
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Supervision: Nissen, Nicholls, Ray, Foody.

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independent statistician (Danielle Brennan, MS). The academic authors made the decision to publish the manuscript and take responsibility for the completeness and accuracy of the data. The first author drafted the manuscript with input from all authors. The sponsor was permitted to review the manuscript and make suggestions, but the final decisions on content were performed by the academic authors. While the executive committee and coordinating center had confidentiality agreements with the sponsor, there were no contractual limits on the rights of the academic authors to publish.

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REFERENCES

1. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2019;74(10):e177-e232. doi:10.1016/j.jacc.2019.03.010

2. Shepherd J, Cobbe SM, Ford I, et al; West of Scotland Coronary Prevention Study Group. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med*. 1995;333(20):1301-1307. doi:10.1056/NEJM199511163332001

3. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. *JAMA*. 1998;279(20):1615-1622. doi:10.1001/jama.279.20.1615

4. Redberg RF, Katz MH. Statins for primary prevention: the debate is intense, but the data are weak. *JAMA Intern Med*. 2017;177(1):21-23. doi:10.1001/jamainternmed.2016.7585

5. Byrne P, Cullinan J, Smith SM. Statins for primary prevention of cardiovascular disease. *BMJ*. 2019;367:l5674. doi:10.1136/bmj.l5674

6. Yebyo HG, Aschmann HE, Puhan MA. Finding the balance between benefits and harms when using statins for primary prevention of cardiovascular disease: a modeling study. *Ann Intern Med*. 2019;170(1):1-10. doi:10.7326/M18-1279

7. Byrne P, Demasi M, Jones M, Smith SM, O'Brien KK, DuBroff R. Evaluating the association between low-density lipoprotein cholesterol reduction and relative and absolute effects of statin treatment: a systematic review and meta-analysis. *JAMA Intern Med*. 2022;182(5):474-481. doi:10.1001/jamainternmed.2022.0134

8. Navar AM, Wang TY, Li S, et al. Lipid management in contemporary community practice: results from the Provider Assessment of Lipid Management (PALM) registry. *Am Heart J*. 2017;193:84-92. doi:10.1016/j.ahj.2017.08.005

9. Gamboa CM, Safford MM, Levitan EB, et al. Statin underuse and low prevalence of LDL-C control among US adults at high risk of coronary heart disease. *Am J Med Sci*. 2014;348(2):108-114. doi:10.1097/MAJ.0000000000000292

10. Jacobs JA, Addo DK, Zheutlin AR, et al. Prevalence of statin use for primary prevention of atherosclerotic cardiovascular disease by race, ethnicity, and 10-year disease risk in the US: National Health and Nutrition Examination Surveys, 2013 to March 2020. *JAMA Cardiol*. 2023;8(5):443-452. doi:10.1001/jamacardio.2023.0228

11. Nissen SE, Lincoff AM, Brennan D, et al; CLEAR Outcomes Investigators. Bempedoic acid and cardiovascular outcomes in statin-intolerant patients. *N Engl J Med*. 2023;388(15):1353-1364. doi:10.1056/NEJMoa2215024

12. Nicholls S, Lincoff AM, Bays HE, 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. doi:10.1016/j.ahj.2020.10.060

13. Ridker PM, Buring JE, Rifai N, Cook NR. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score. *JAMA*. 2007;297(6):611-619. doi:10.1001/jama.297.6.611

14. Conroy RM, Pyörälä K, Fitzgerald AP, et al; SCORE Project Group. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J*. 2003;24(11):987-1003. doi:10.1016/S0195-668X(03)00114-3

15. Virani SS, Kennedy KF, Akeroyd JM, et al. Variation in lipid-lowering therapy use in patients with low-density lipoprotein cholesterol ≥190 mg/dL: insights from the National Cardiovascular Data Registry–Practice Innovation and Clinical Excellence Registry. *Circ Cardiovasc Qual Outcomes*. 2018;11(5):e004652. doi:10.1161/CIRCOUTCOMES.118.004652

16. Pokharel Y, Tang F, Jones PG, et al. Adoption of the 2013 American College of Cardiology/American Heart Association cholesterol management guideline in cardiology practices nationwide. *JAMA Cardiol*. 2017;2(4):361-369. doi:10.1001/jamacardio.2016.5922

17. Langsted A, Freiberg JJ, Nordestgaard BG. Extent of undertreatment and overtreatment with cholesterol-lowering therapy according to European guidelines in 92,348 Danes without ischemic cardiovascular disease and diabetes in 2004-2014. *Atherosclerosis*. 2017;257:9-15. doi:10.1016/j.atherosclerosis.2016.11.025

18. Bradley CK, Wang TY, Li S, et al. Patient-reported reasons for declining or discontinuing statin therapy: insights from the PALM registry. *J Am Heart Assoc*. 2019;8(7):e011765. doi:10.1161/JAHA.118.011765

19. Yusuf S, Bosch J, Dagenais G, et al; HOPE-3 Investigators. Cholesterol lowering in intermediate-risk persons without cardiovascular disease. *N Engl J Med*. 2016;374(21):2021-2031. doi:10.1056/NEJMoa1600176

20. Ridker PM, Danielson E, Fonseca FA, et al; JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med*. 2008;359(21):2195-2207. doi:10.1056/NEJMoa0807646

21. Mihaylova B, Emberson J, Blackwell L, et al; Cholesterol Treatment Trialists' (CTT) Collaborators. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet*. 2012;380(9841):581-590. doi:10.1016/S0140-6736(12)60367-5

22. Ridker PM, Everett BM, Thuren T, et al; CANTOS Trial Group. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med*. 2017;377(12):1119-1131. doi:10.1056/NEJMoa1707914

23. Tardif JC, Kouz S, Waters DD, et al. Efficacy and safety of low-dose colchicine after myocardial infarction. *N Engl J Med*. 2019;381(26):2497-2505. doi:10.1056/NEJMoa1912388

24. Nidorf SM, Fiolet ATL, Mosterd A, et al; LoDoCo2 Trial Investigators. Colchicine in patients with chronic coronary disease. *N Engl J Med*. 2020;383(19):1838-1847. doi:10.1056/NEJMoa2021372