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Research

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

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Introduction:

- 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).

- 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.

- 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.

- Among the 13 970 patients enrolled in the trial, 4206 (30%) had characteristics associated with a high risk of advers 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.

Methods:

Trial Organization and Oversight:

The trial was conducted at 1250 sites in 32 countries.

The trial was designed by the Cleveland Clinic Coordinating Center for Clinical Research (C5Research) .

Trial Population :

- Primary prevention patients aged 18 to 85 years with an LDL-C level 100 mg/dL 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 score: ASCVD Risk over 10y > 7.5% or Reynolds Risk Score > 30% , 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.

- 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.

- 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.

Study End Points:

- **primary end point** :death from cardiovascular causes, nonfatal myocardial infarction (MI), nonfatal stroke, or coronary revascularization (4-component major adverse cardiovascular events [MACE]).

- **Key secondary end points** :(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.

Results:

Between December 2016 and August 2019, 22 084 patients were screened and 14 016 were randomized, with 13 970 included in the full analysis.

These baseline characteristics were similar in both treatment groups (Table 1) .

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

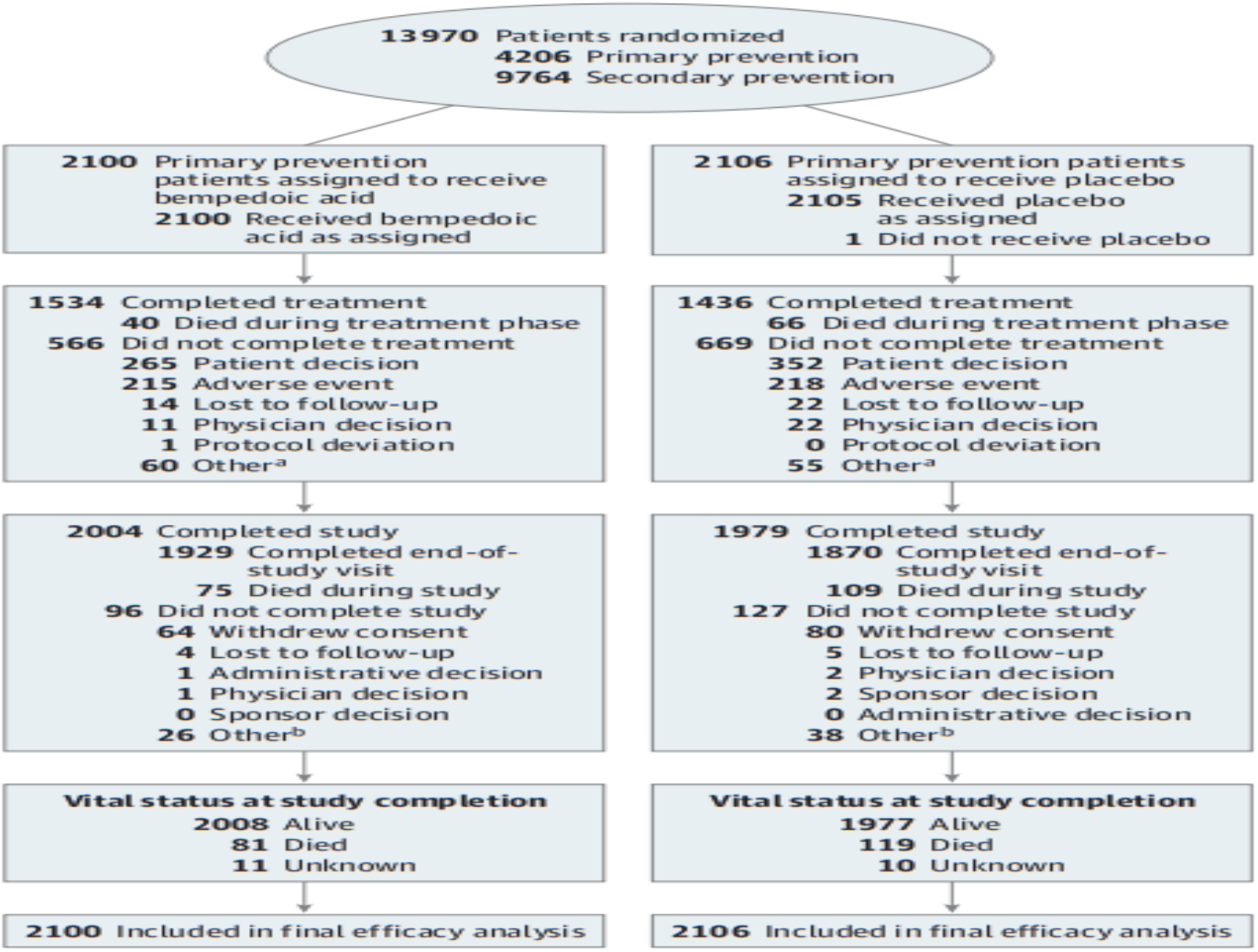


Table 1. Demographic and Baseline Characteristics of Patients

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)

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.

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

	Bempedoic acid			Placebo			Bempedoic acid vs placebo after 6 mo of treatment	
	Observed mean (SD) or median (IQR)			Observed mean (SD) or median (IQR)				
End point	Baseline	6 mo	Change, baseline to 6 mo (95% CI)[a]	Baseline	6 mo	Change, baseline to 6 mo (95% CI)[a]	Difference (95% CI)[a]	Difference, % (95% CI)[a]
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)

Clinical End Points:

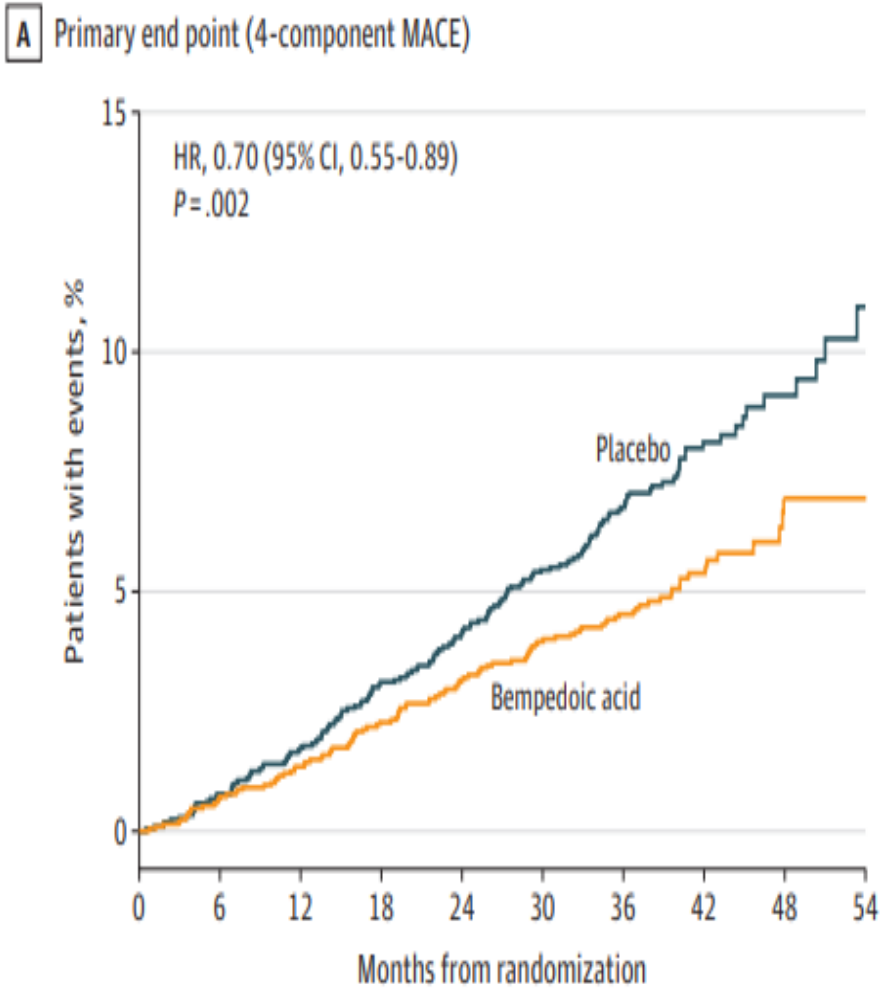
The primary 4-component composite end point occurred in111 patients (5.3%) in the bempedoic acid group and 161 patients (7.6%) in the placebo group (HR, 0.70 [95% CI, 0.55- 0.89]; *P* = .002) (Table 3 and Figure 2A) .

The number needed to treat (NNT) to prevent 1 primary composite outcome was 43 patients.

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

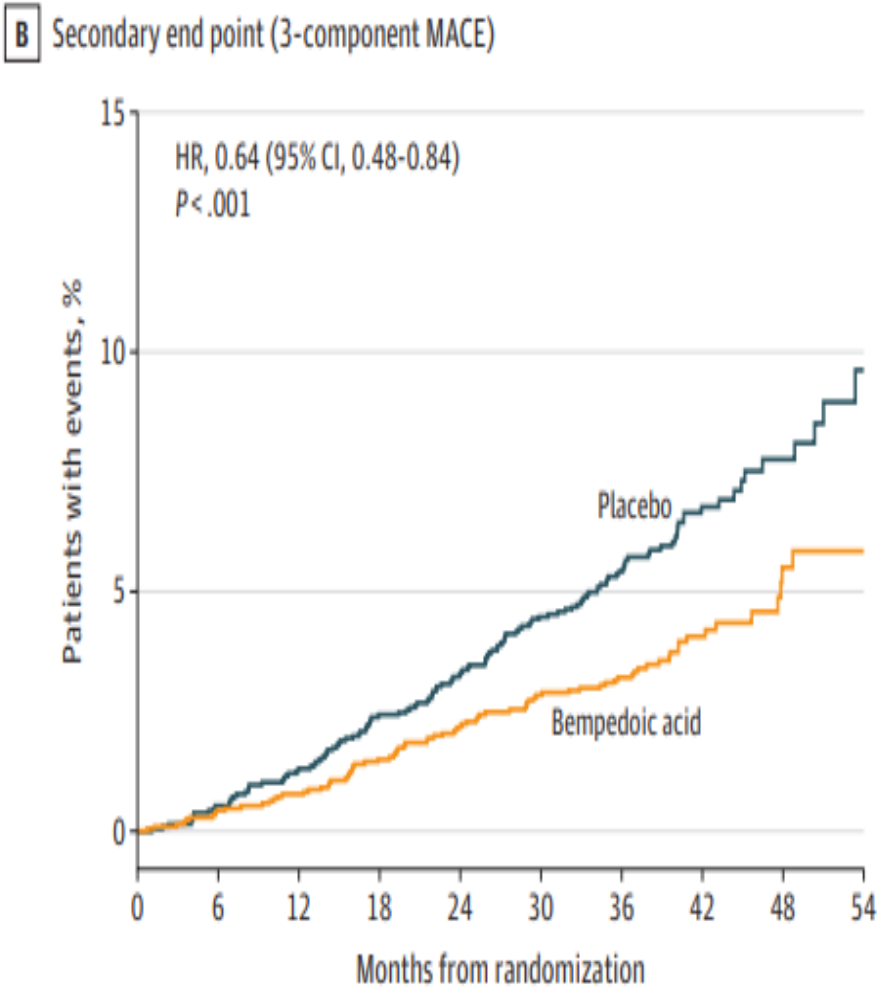
Outcome	No. of patients (%)		HR (95% CI)[a]	*P* value[b]
	Bempedoic acid (n = 2100)	Placebo (n = 2106)		
Person-years of follow-up[c]	6898	6807		
Primary efficacy end point (4-component MACE)[d]	111 (5.3)	161 (7.6)	0.70 (0.55-0.89)	.002
Secondary efficacy end points				
3-component MACE[e]	83 (4.0)	134 (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)	

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



No. at risk

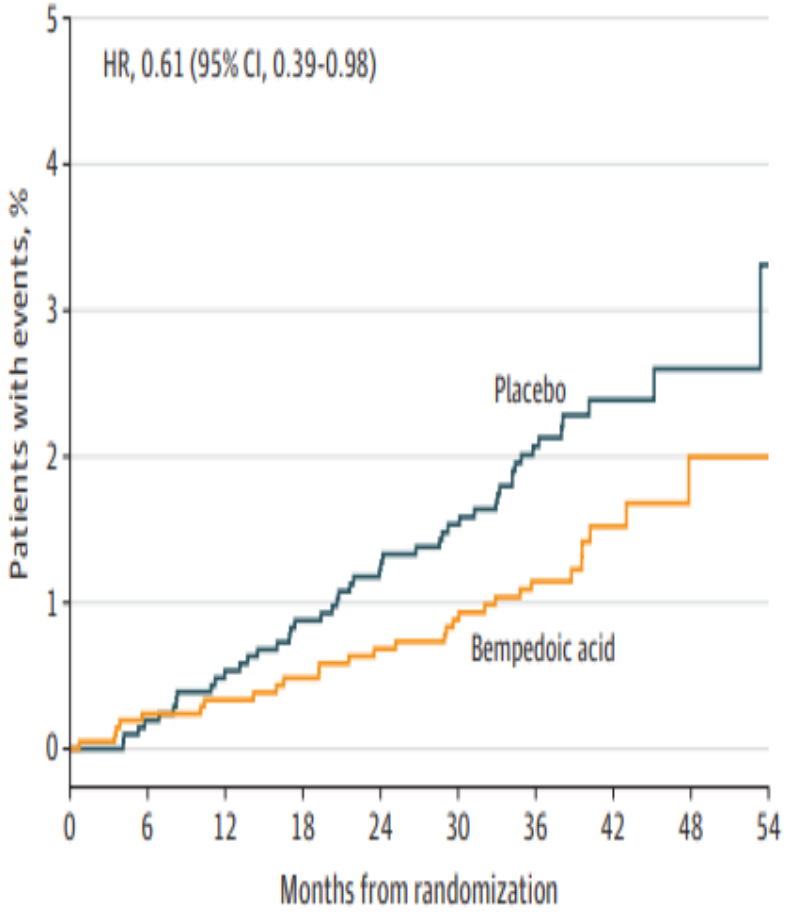
Placebo	2063	2024	1973	1921	1870	1617	753	304	117
Bempedoic acid	2069	2041	1996	1953	1923	1675	726	291	130



No. at risk

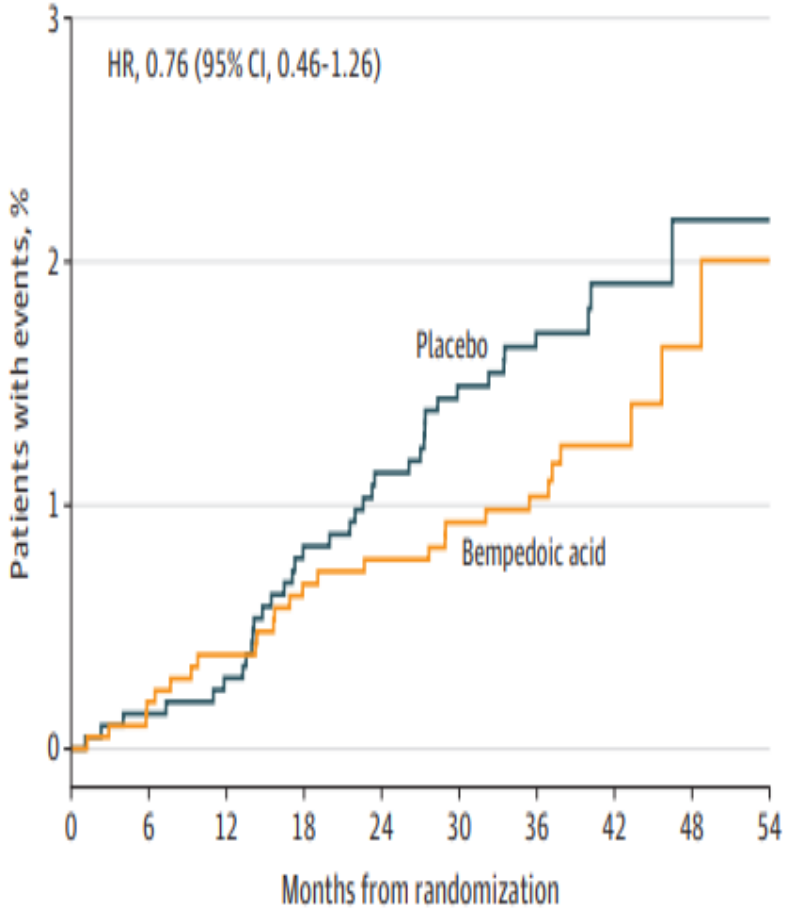
Placebo	2068	2033	1987	1939	1890	1640	760	307	118
Bempedoic acid	2075	2053	2012	1973	1946	1697	738	294	132

C Fatal or nonfatal myocardial infarction



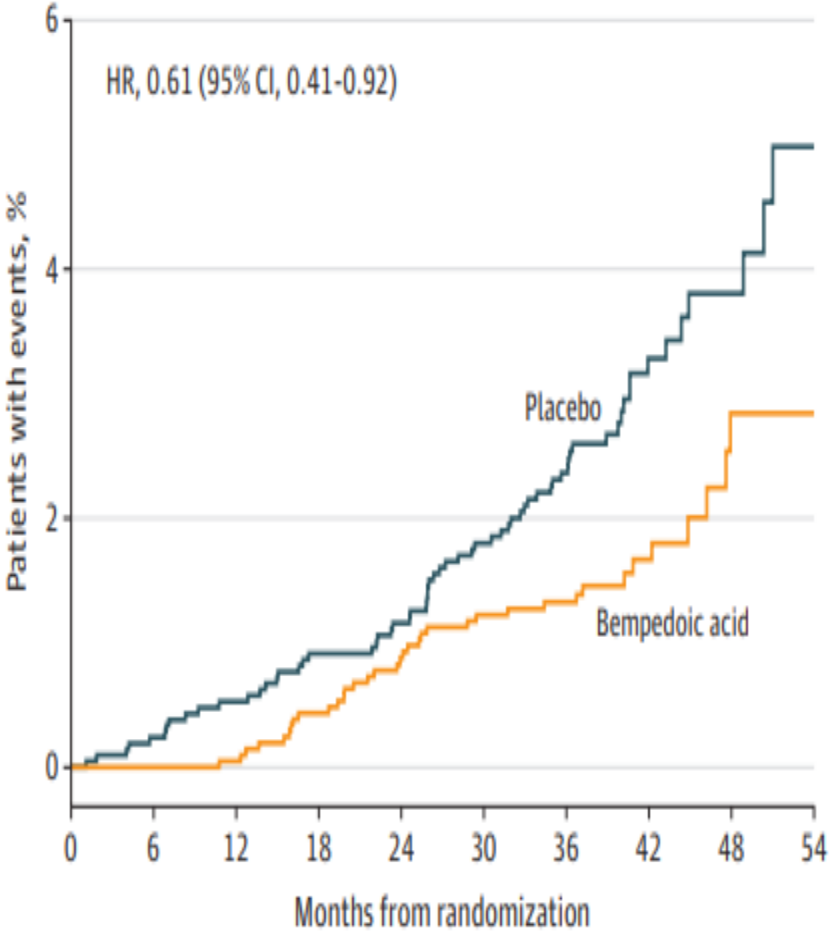
No. at risk									
Placebo	2069	2037	2000	1955	1913	1661	769	311	119
Bempedoic acid	2079	2059	2022	1984	1959	1709	747	295	133

D Fatal or nonfatal stroke



No. at risk									
Placebo	2071	2042	2002	1959	1913	1664	777	315	122
Bempedoic acid	2080	2058	2019	1983	1959	1710	751	301	133

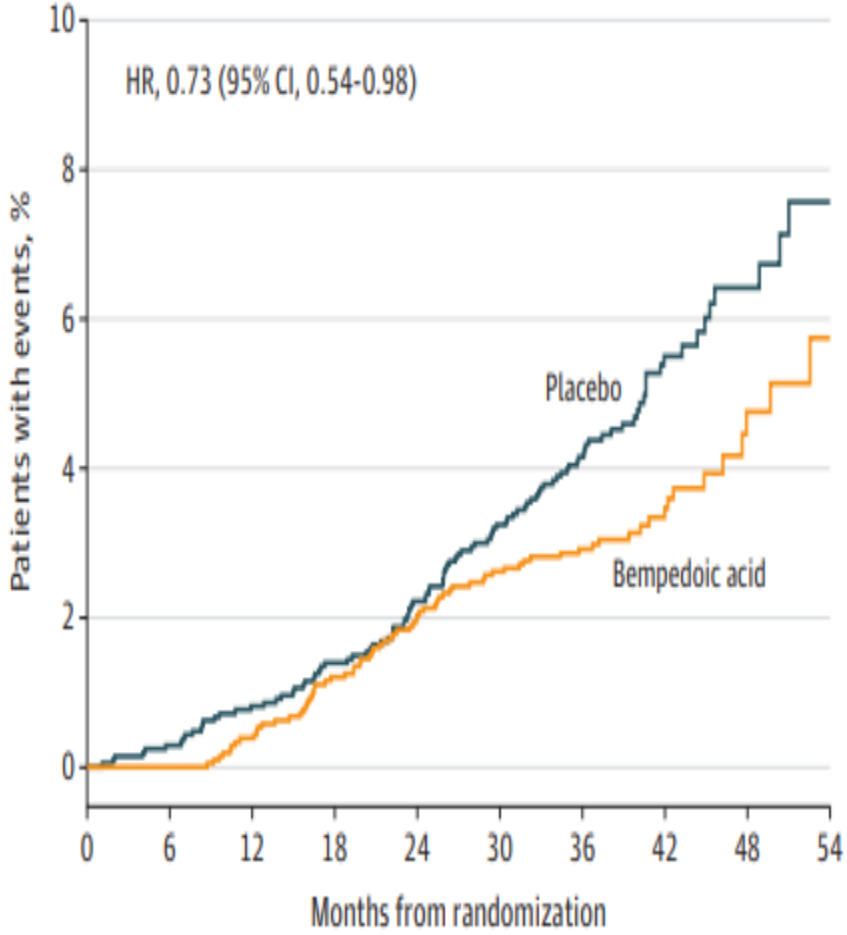
E Cardiovascular death



No. at risk

Placebo	2090	2065	2037	2009	1975	1729	808	328	125
Bempedoic acid	2088	2073	2042	2010	1994	1745	772	307	135

F All-cause mortality



No. at risk

Placebo	2090	2065	2037	2009	1975	1729	808	328	125
Bempedoic acid	2088	2073	2042	2010	1994	1745	772	307	135

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.

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)

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.

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.

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%).

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.

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.

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.

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.

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.

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.

The Cholesterol Treatment Trialists Collaboration (CTTC) meta-analysis reported on outcomes for statin treatment in patients without vascular disease.The CTTC analysis showed a 22% reduction in major coronary events for each 38.7-mg/dL decrease in LDL-C level and a 15% reduction in vascular death.

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 endpoint, secondary endpoints, and components of endpoints strengthens the likelihood that these results are reliable.

Second, the inclusion of patients who reported inability to tolerate statins resulted in 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.

third, 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 .