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# Bempedoic Acid and First and Recurrent Limb Outcomes in Statin-Intolerant Patients With Peripheral Artery Disease: Insights From the CLEAR Outcomes Trial

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**BACKGROUND:** Patients with peripheral artery disease (PAD) are at high risk of major adverse limb events (MALEs) and major adverse cardiovascular events (MACEs). Recently, bempedoic acid was shown to reduce MACEs in primary and secondary prevention patients. Whether bempedoic acid reduces the risk of MALE in patients with PAD is unknown.

**METHODS:** CLEAR Outcomes (Cholesterol Lowering via Bempedoic Acid [ETC1002], an ACL-Inhibiting Regimen) randomized 13 970 patients to bempedoic acid 180 mg or placebo from December 22, 2016, to August 14, 2019. The trial primary end point was MACE-4, defined as death resulting from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization. A clinical history of PAD was reported by investigators at baseline. Two blinded vascular medicine specialists independently adjudicated MALEs, including adverse events indicating worsening PAD symptoms leading to revascularization, chronic limb-threatening ischemia, and acute limb ischemia. Outcomes were assessed as time to first event and total (including recurrent) events with a negative binomial approach.

**RESULTS:** A total of 1624 of the enrolled patients (mean±SD age, 63.9±9.9 years; 915 [56.3%] female) had PAD at baseline. In patients with PAD in the placebo group, 69 (8.3%) had MALEs over a median of 40.6 months, with rate of recurrent events of 4.0%/y. Bempedoic acid reduced the risk of MALEs by 36% (hazard ratio, 0.64 [95% CI, 0.44–0.93]; $P$=0.018) Bempedoic acid reduced total MALEs by 45% (relative risk, 0.55 [95% CI, 0.35–0.85]; $P$=0.007). First MACE-4 or MALE was reduced overall by 13% (hazard ratio, 0.87 [95% CI, 0.80–0.95]) with consistent effects with PAD (hazard ratio, 0.82 [95% CI, 0.64–1.04]) and without PAD (hazard ratio, 0.87 [95% CI, 0.79–0.86]; $P_{interaction}$=NS) but not statistically significant within the PAD subgroup alone. Total MACE-4 or MALE was reduced (relative risk, 0.81 [95% CI, 0.73–0.90]) overall with consistent effects in PAD (relative risk, 0.71 [95% CI, 0.54–0.95]) and without PAD (relative risk, 0.82 [95% CI, 0.73–0.92]; $P_{interaction}$=NS).

**CONCLUSIONS:** Patients with PAD are at high risk of MALEs and MACEs. Bempedoic acid reduces both MACEs and MALEs in patients with atherosclerotic vascular disease, with notable absolute benefits in patients with PAD. These findings support (1) the importance of lowering low-density lipoprotein cholesterol in patients with PAD to reduce overall vascular risk and (2) the benefits of bempedoic acid in this population.

**GRAPHIC ABSTRACT:** A graphic abstract is available for this article.

**Key Words:** 8-hydroxy-2,2,14,14-tetramethylpentadecanedioic acid ■ cardiovascular diseases ■ peripheral arterial disease



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## Clinical Perspective

### What Is New?

- Patients with chronic peripheral artery disease have high rates of major adverse cardiovascular events and major adverse limb events, with the latter driven by revascularization procedures.
- Bempedoic acid is a novel low-density lipoprotein cholesterol–lowering drug that is oral and well tolerated and can be used alone or in combination with other low-density lipoprotein–lowering therapies; bempedoic acid reduces major adverse cardiovascular events and major adverse limb events.

### What Are the Clinical Implications?

- As guidelines recommend increasingly lower targets for low-density lipoprotein cholesterol in high-risk patients, including those with peripheral artery disease, more will require combination therapy to achieve those targets.
- Evidence for benefits for both major adverse cardiovascular events and major adverse limb events may support shared decision making in selecting optimal strategies for prevention in patients with peripheral artery disease.

## Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **CLEAR Outcomes** | Cholesterol Lowering via Bempedoic Acid [ETC1002], an ACL-Inhibiting Regimen |
| **hsCRP** | high-sensitivity C-reactive protein |
| **LDL** | low-density lipoprotein |
| **LDL-C** | low-density lipoprotein cholesterol |
| **MACE** | major adverse cardiovascular event |
| **MALE** | major adverse limb event |
| **PAD** | peripheral artery disease |
| **RR** | relative risk |
| **TEAE** | treatment-emergent adverse event |

Peripheral artery disease (PAD) is estimated to affect >200 million people worldwide.[1,2] Atherosclerosis is a systemic disease that affects multiple vascular territories; however, patients who manifest symptoms in the legs have been recognized to have a large burden of disease and high cardiovascular risk, particularly in the setting of polyvascular disease.[3,4] Despite the high risk of major adverse cardiovascular events (MACEs), the dominant morbidity in patients with PAD is experienced in the limbs, with high rates of progressive symptoms or threatened tissue loss leading to the need for revascularization or amputation.[5,6] Rates are particularly high when the total burden of events is considered, including recurrent events that are frequent in populations with PAD.[6,7] The underlying pathobiology of major adverse limb events (MALEs) is complex but includes plaque rupture with distal embolization, progressive atherosclerosis, microvascular disease, and thrombosis.[8]

Although statin therapy is foundational for low-density lipoprotein (LDL) lowering to reduce MACE risk, benefits for reducing MALEs have not been well demonstrated in pivotal randomized clinical trials.[1,2] More recently, the proprotein convertase subtilisin/kexin type 9 inhibitors evolocumab and alirocumab have been shown to reduce MACEs and MALEs in patients with PAD.[9,10] These analyses of demonstrated a relationship between rates of MALEs and achieved LDL cholesterol (LDL-C), suggesting that other mechanisms for lowering LDL-C may also reduce risk.[10,11]

Bempedoic acid is a novel ATP citrate lyase inhibitor that lowers LDL-C.[12] It works upstream of statins in the cholesterol synthesis pathway and has been observed to have a low incidence of muscle-related adverse events.[12] In addition to lowering LDL-C, bempedoic acid has been observed to lower high-sensitivity C-reactive protein (hsCRP), which is associated with adverse outcomes in patients with PAD.[12,13] Recently the CLEAR Outcomes trial (Cholesterol Lowering via Bempedoic Acid [ETC1002], an ACL-Inhibiting Regimen) demonstrated that bempedoic acid reduces MACEs in patients with established atherosclerotic vascular disease or at high risk for cardiovascular disease.[14] Whether bempedoic acid reduces first and recurrent MALEs has not been described. The current analyses were designed to evaluate the effects of bempedoic acid on first and recurrent MALEs and the effects of the composite of MACE-4 and MALEs in patients with PAD at baseline.

## METHODS

### Study Design and Patient Population

Data supporting the findings of this study will not be made available to outside parties. The study results were previously published.[13,14] Briefly, CLEAR Outcomes (NCT02993406) was a randomized, double-blinded, placebo-controlled trial comparing 180 mg bempedoic acid with placebo in patients 18 to 85 years of age with history of or at high risk of cardiovascular diseases who were not able to take recommended statin treatment because of intolerance. The study allowed patients to take lipid-lowering therapies, in combination or alone, such as very low-dose statins (eg, <10 mg atorvastatin average daily dose), ezetimibe, niacin, bile acid resins, fibrate, or proprotein convertase subtilisin/kexin type 9 inhibitors. The study randomized a total of 13 970 statin-intolerant patients, including 1624 patients with PAD, to either bempedoic acid or placebo.[13,14] PAD was defined by clinical history (ie, symptoms of claudication or resting limb ischemia) and at least 1 of the

following: either ankle-brachial index <0.9 or angiogram showing ≥50% stenosis (ankle-brachial index was measured after a period of rest and with the patient in the supine position with a Doppler device) or peripheral arterial revascularization (surgical or percutaneous) occurring >90 days before screening or lower-extremity amputation due to peripheral vascular disease occurring >90 days before screening. A clinical history of PAD was reported by investigators at baseline. The institutional review boards or ethics committees of all participant research centers approved the study protocol. Written informed consent was obtained from all patients; patients were enrolled from December 22, 2016, to August 14, 2019. Study results in this article are reported in accordance with the EQUATOR Network guidance (see Supplemental Material).

## Study End Points

The trial primary end point was time to first MACE-4, including cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization, with the 3-point composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke (MACE-3) a key secondary end point.[13,14] The primary end point of the current analysis was time to first occurrence of MALEs, which included adverse events indicating worsening of PAD symptoms leading to revascularization, chronic limb-threatening ischemia, and acute limb ischemia. Potential MALE end points were ascertained through investigator reports of adverse events. Data, including verbatim terms, were reviewed by 2 independent, blinded vascular medicine specialists (M.P.B., M.E.C. were the reviewers). Systematic information on the urgency of lower-extremity revascularization was not available and therefore was not captured. The primary outcome of the current analysis was MALEs in patients with PAD. Additional outcomes included total MALEs, including recurrent events, as well as composites of total MACE-3 and MALEs and MACE-4 and MALEs. Outcomes were evaluated in patients with PAD and patients without PAD.

## Statistical Analysis

The study represents a post hoc analysis from the CLEAR Outcomes trial.[13,14] For the baseline analysis, the patients were analyzed in 2 groups according to PAD history. The baseline characteristics were presented by mean±SD, median and interquartile range according to variable distribution, or number and percent. The end-point analysis was obtained with a Cox proportional hazard model. For the first MACE and MALE, the results are described as hazard ratio (HR) with 95% CI. The assumption of proportional hazard was verified with a Schoenfeld residual–based test. The total events results are described as relative risk (RR) with 95% CI analyzed with a negative-binomial model. The analyses were adjusted for baseline characteristics, including geographic region, age, sex, race and ethnicity, LDL-C level, body mass index category, hsCRP level category, estimated glomerular filtration rate category, use of any lipid-modifying therapy at baseline, glycemic status (diabetes, prediabetes, normoglycemia), and cardiovascular disease risk category (for overall and patients without PAD). Event probabilities in each treatment group and absolute risk reductions with bempedoic acid compared with placebo were included as observed incidence rates and their difference. All the analyses were conducted with R version 4.5.1.

# RESULTS

## Baseline Characteristics

A total of 13 970 patients were enrolled in the study, with 1624 (12%) patients having known PAD at baseline. Baseline characteristics are shown in Table 1. Patients with PAD were younger than those without PAD (63.9 years versus 65.7 years, respectively; $P<0.0001$), and the majority of the subjects were White (n=1449, 89%), with more than half being female (n=915, 56%; Table 1). The baseline mean LDL-C level was 138.9 mg/dL; high-density lipoprotein cholesterol was 50.0 mg/dL; total cholesterol was 224.6 mg/dL; and median triglycerides level was 163.0 mg/dL in patients with PAD, with similar lipid measures in those without PAD (Table 1). The median hsCRP was 2.6 and 2.3 mg/dL in patients with and without PAD, respectively.

The prevalence of risk factors was similar in patients with and without PAD, whereas established coronary artery disease was less common in those with PAD (n=434, 26.7%) compared with those without PAD (6676, 54.1%). In terms of vascular history, 397 of patients (24.4%) with PAD had a prior limb event ,including revascularization or amputation. Overall use of background lipid lowering was similar regardless of PAD history, with 21.0% (n=341) with PAD and 22.9% (n=2833) without PAD on very low-dose statins; 11.6% (n=189) and 11.5% (n=1423), respectively, on ezetimibe; and 0.7% (n=12) and 0.6% (n=73), respectively, on proprotein convertase subtilisin/kexin type 9 inhibitors.



## Impact of Bempedoic Acid in the LDL-C Levels of Patients With PAD

In patients with PAD, the least-squares mean percent change in LDL-C levels after 6 months of treatment was −23.6% with bempedoic acid and −1.0% with placebo. The time-averaged difference in the reduction in LDL-C level between the bempedoic acid group and the placebo group over the duration of the trial was 22.2 mg/dL (0.57 mmol/L) and consistent with the results of the overall trial. At 6 months, the difference in the median hsCRP level was −25.9% (95% CI, −31.7 to −20.0) in favor of bempedoic acid.

## Risk of MACEs and MALEs in Patients Taking Placebo With PAD Compared With Those Without PAD

A total of 282 patients had MALEs over the duration of the trial, with 239 (85%) as adverse events indicating worsening PAD leading to revascularization, 38 (13%) with chronic limb-threatening ischemia, and 25 (9%) with acute limb ischemia (Table S1). At a median of 40.6

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**Table 1. Baseline Characteristics of Study Patients by PAD Status at Baseline**

| Variable | Patients with PAD (n=1624) | Patients with no PAD (n=12 346) | *P* value |
|---|---|---|---|
| Age, mean, y | 63.9 (9.9) | 65.7 (8.8) | <0.0001 |
| Female sex, n (%) | 915 (56.3) | 5825 (47.2) | <0.0001 |
| Race, n (%) | | | |
| White | 1449 (89.2) | 11 283 (91.4) | <0.0001 |
| Hispanic or Latino, n (%) | 462 (28.4) | 1871 (15.2) | <0.0001 |
| BMI, mean±SD, kg/m$^2$ | 29.6±5.4 | 30.0±5.2 | 0.0037 |
| LDL-C | | | |
| Mean±SD, mg/dL | 138.9±33.5 | 139.0±35.2 | 0.91 |
| Distribution, n (%) | | | 0.84 |
| <130 mg/dL | 714±44.0 | 5449±44.1 | |
| ≥130 to <160 mg/dL | 512±31.5 | 3951±32.0 | |
| ≥160 mg/dL | 398±24.5 | 2946±23.9 | |
| HDL cholesterol, mg/dL | 50.0±13.2 | 49.5±13.3 | 0.13 |
| Non–HDL cholesterol, mg/dL | 174.6±38.3 | 173.8±40.0 | 0.43 |
| Total cholesterol, mg/dL | 224.6±39.1 | 223.2±41.1 | 0.20 |
| Triglycerides, median (IQR), mg/dL | 163.0 (119.5–223.5) | 177.7 (117.5–214.5) | 0.03 |
| High-sensitivity CRP, median (IQR), mg/dL | 2.6 (1.4–5.3) | 2.3 (1.1–4.4) | <0.0001 |
| eGFR, n (%) | | | 0.0023 |
| ≥90 mL·min$^{-1}$·1.73$^{-2}$ | 341 (21.0) | 2108 (17.1) | |
| ≥60 to <90 mL·min$^{-1}$·1.73$^{-2}$ | 956 (58.9) | 7648 (61.9) | |
| ≥30 to <60 mL·min$^{-1}$·1.73$^{-2}$ | 321 (19.8) | 2560 (20.7) | |
| Comorbidities, n (%) | | | |
| Current smoker | 373 (23.0) | 2670 (21.6) | 0.0003 |
| History of hypertension | 1308 (80.5) | 10 568 (85.6) | <0.0001 |
| Diabetes | 709 (43.7) | 5664 (45.9) | 0.23 |
| Coronary artery disease | 434 (26.7) | 6676 (54.1) | <0.0001 |
| Previous myocardial infarction | 236 (14.5) | 4237 (34.3) | <0.0001 |
| Cerebrovascular atherosclerotic disease | 149 (9.2) | 1918 (15.5) | <0.0001 |
| Ischemic stroke | 91 (5.6) | 1570 (12.7) | <0.0001 |
| PAD characteristics | | | |
| Lower-extremity amputation | 30 (1.8) | 0 (0) | <0.0001 |
| Lower-extremity revascularization | 367 (22.6) | 0 (0) | <0.0001 |
| Lipid-lowering medications, n (%) | | | |
| Statin | 341 (21.0) | 2833 (22.9) | 0.35 |
| Ezetimibe | 189 (11.6) | 1423 (11.5) | 0.89 |
| PCSK9i | 12 (0.7) | 73 (0.6) | 0.55 |

Data are expressed as mean±SD, median (interquartile range), or number (percent).

BMI indicates body mass index; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HDL, high density lipoprotein; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; PAD, peripheral artery disease; and PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor.



months of follow-up in patients randomized to placebo, the rate of ≥1 MALEs was 2.2%, with rates of 8.3% and 1.4% in those with and without PAD, respectively. When we consider total events, rates per 100 patient-years were ≈8-fold higher in patients with than in those without PAD (4.0 versus 0.5 per 100 patient-years). Rates for total MACE-3 (n/100 patient-years; 6.5 for PAD, 6.2 for no PAD) and MACE-4 (n/100 patient-years; 4.0 for PAD, 3.3 for no PAD) were similar regardless of PAD history; however, because of their higher risk of MALEs, patients with PAD had higher rates of the broad vascular end point of MACE-4 or MALEs (10.5 for PAD, 6.7 for PAD) and MACE-3 or MALEs (8.0 for PAD, 3.8 for no PAD).

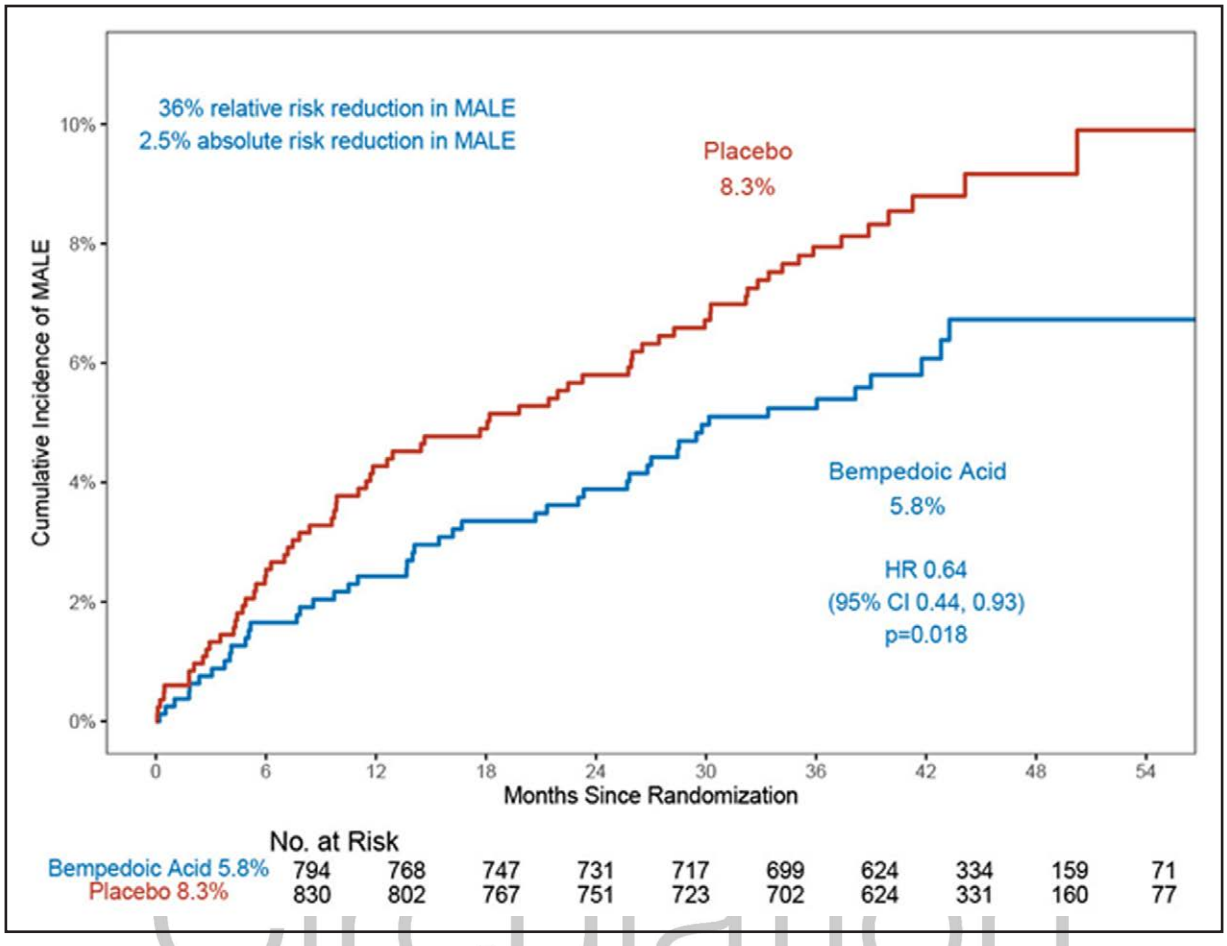


**Figure 1. MALEs in patients with PAD comparing bempedoic acid with placebo.**
Major adverse limb event (MALE) was defined as a composite of all worsening peripheral artery disease symptoms that lead to spontaneous reporting of an adverse event and to revascularization, chronic limb-threatening ischemia, and acute limb ischemia. Hazard ratio and relative risk reduction are adjusted for covariates, whereas the absolute risk reduction is unadjusted and reflects the difference between event frequencies.



## Bempedoic Acid and MALEs in Patients With PAD

In patients with PAD, bempedoic acid reduced the risk of MALEs by 36% (5.8% versus 8.3%; HR, 0.64 [95% CI, 0.44–0.93]; *P*=0.018; Table 2 and Figure 2), translating into an absolute risk reduction of 2.5% at a median of 40 months. When we consider total MALEs, there was a consistent pattern of benefit for bempedoic acid for both first and subsequent events (Figure 2). Total, including recurrent, MALEs were reduced with bempedoic acid (n/100 patient-years; 2.9 with bempedoic acid versus 4.0 with placebo; RR, 0.55 [95% CI, 0.35–0.85]; *P*=0.007; Table 2 and Figure 3). There was no heterogeneity for the effect of bempedoic acid on the basis of PAD (Figure 3, Table S2, and Figure S1).

## MACE or MALE Outcomes With Bempedoic Acid

The composite of the trial primary outcome and MALEs (MACE-4+MALEs) was reduced overall (HR, 0.87 [95% CI, 0.80–0.95]; *P*=0.002; Table S3), as was the composite of the key secondary outcome and MALEs (MACE-3+MALEs: HR, 0.85 [95% CI, 0.77–0.94]; *P*=0.002; Table S3), with consistent effects in patients with and without PAD but without reaching statistical significance in the PAD subgroup alone ($P_{interaction}$= NS; Figure 3 and Table S3). When we consider total, including recurrent, events, the composites of MACE-4+MALEs and MACE-3+MALEs were reduced by bempedoic acid by 19% (RR, 0.81 [95% CI, 0.73–0.89]; *P*<0.001) and 18% (RR, 0.82 [95% CI, 0.73–0.92]; *P*<0.001), respectively, with consistent effects, reaching statistical significance in those with and without PAD ( $P_{interaction}$=NS; Table S2).

## Total MACE or MALE Outcomes With Bempedoic Acid in Patients With PAD

When we consider total, including recurrent, events of MACEs or MALEs in patients with PAD, bempedoic acid reduced the composite of MACE-4+MALEs by 29% (n/100 patient-years; 8.6 with bempedoic

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**Table 2. Efficacy End Points in Patients With PAD**

| End point | Bempedoic acid (n=794) | Placebo (n=830) | Risk (95% CI) | *P* value |
|---|---|---|---|---|
| Time to first event, n, n/N% | | | | |
| MALEs | 46, 5.8 | 69, 8.3 | HR, 0.64 (0.44–0.93) | 0.018 |
| MACE-4+MALEs | 129, 16.2 | 150, 18.1 | HR, 0.82 (0.64–1.04) | 0.095 |
| MACE-3+MALEs | 109, 13.7 | 133, 16.0 | HR 0.78 (0.61–1.01) | 0.062 |
| Total (including recurrent) events, N, n/100 patient-y | | | | |
| MALEs, n, % | 78, 2.9 | 114, 4.0 | RR, 0.55 (0.35–0.85) | 0.007 |
| MACE-4+MALEs | 234, 8.6 | 298, 10.5 | RR, 0.71 (0.54–0.95) | 0.017 |
| MACE-3+MALEs | 166, 6.1 | 228, 8.0 | RR, 0.65 (0.48–0.88) | 0.004 |

MACE indicates major adverse cardiovascular event; MACE-3, 3-point composite of cardiovascular death, myocardial infarction, or stroke; MACE-4, 4-point composite of cardiovascular death, myocardial infarction, stroke, or coronary revascularization; MALE, major adverse limb event; and PAD, peripheral artery disease.

acid versus 10.5 with placebo; RR, 0.71 [95% CI, 0.54–0.95]; *P*=0.017) and the composite of MACE-3+MALEs by 35% (n/100 patient-years; 6.1 with bempedoic acid versus 8.0 with placebo; RR, 0.65 [95% CI, 0.48–0.88]; *P*=0.004; Table S2). In absolute terms, events for both composites were reduced by 1.9 per 100 patient-years (Figure 4). Effects were consistent regardless of PAD history (Tables S2 and S4). The nominal *P* values for treatment and PAD subgroup interaction are all >0.05.

## Bempedoic Acid and hsCRP

The benefit of bempedoic acid in terms of MALE and MACE outcomes was assessed stratified by hsCRP. Overall, rates of MALEs were higher in patients with hsCRP ≥2 mg/dL versus <2 mg/dL at baseline (2.5% versus 1.8%). The benefit of bempedoic acid on MACE-4 or MALEs was similar in those with high hsCRP at baseline (HR, 0.86 [95% CI, 0.77–0.96]) compared with those without high hsCRP at baseline (HR, 0.88 [95% CI, 0.77–1.02]; Figure S2).



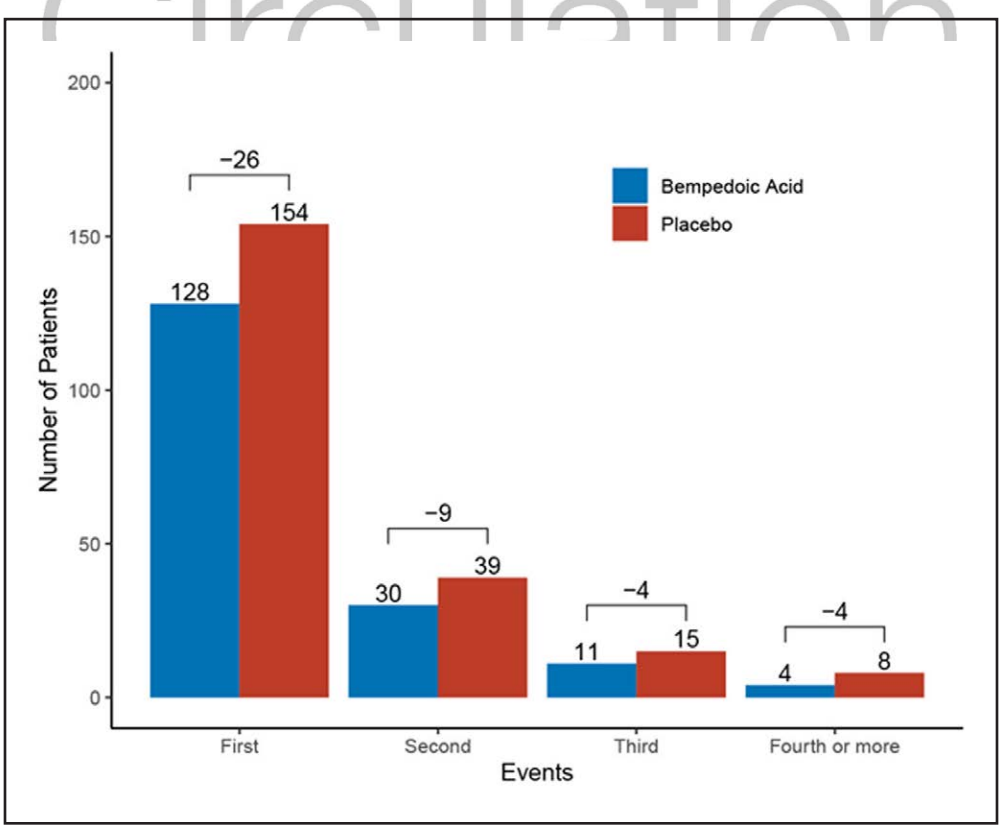


**Figure 2. Difference in MALEs for first and subsequent events.**
Major adverse limb event (MALE) was defined as a composite of all worsening peripheral artery disease symptoms that lead to spontaneous reporting of an adverse event and to revascularization, chronic limb-threatening ischemia, and acute limb ischemia.

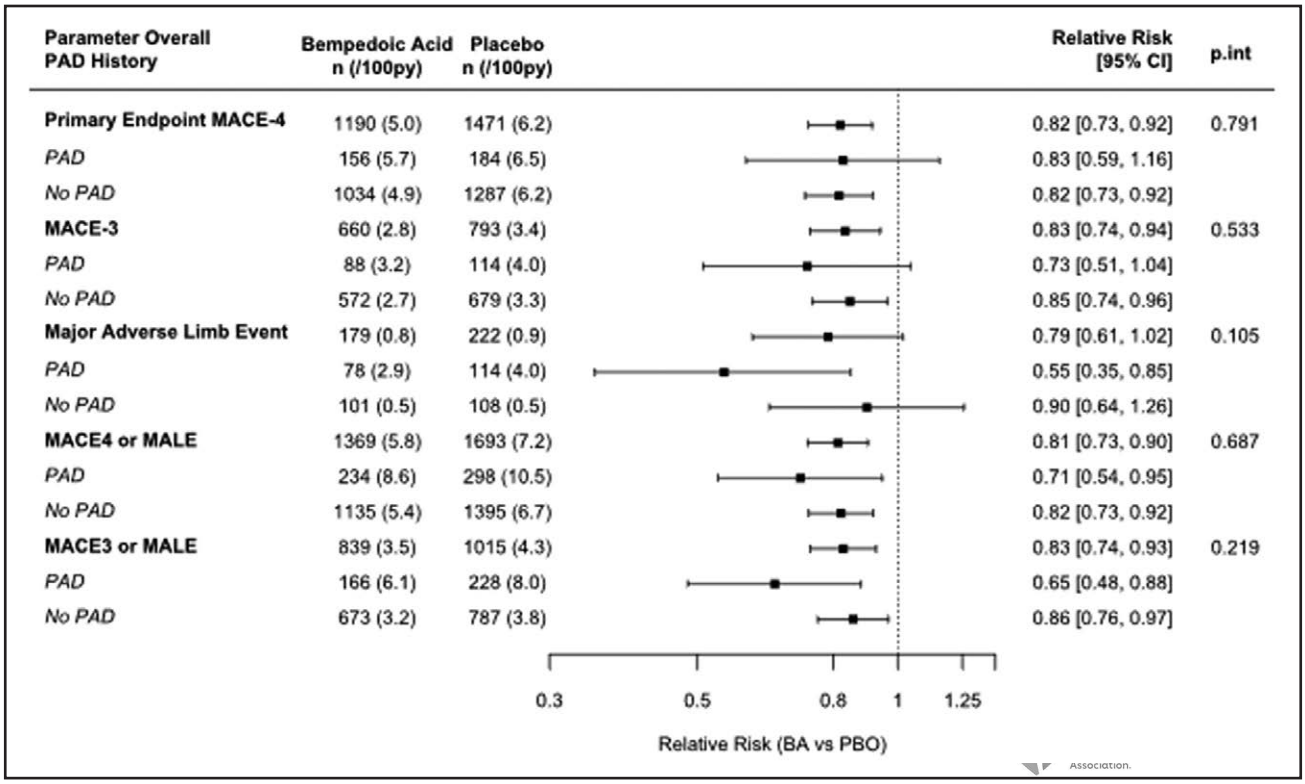


**Figure 3. Total MALEs in patients with and without PAD comparing bempedoic acid versus placebo.**
Major adverse limb event (MALE) was defined as a composite of all worsening peripheral artery disease (PAD) symptoms that lead to spontaneous reporting of an adverse event and to revascularization, chronic-limb threatening ischemia, and acute limb ischemia. BA indicates bempedoic acid; MACE, major adverse cardiovascular event; NS, not significant; and PBO, placebo.



## Bempedoic Acid Adverse Events in Patient With PAD

The safety of bempedoic acid in patients with PAD was assessed for treatment-emergent adverse events (TEAEs), serious TEAEs, TEAEs leading to treatment discontinuation, common (incidence >5% and more frequent than placebo) TEAEs, and other events of clinical interest, including myalgia, hyperuricemia, gout, and tendon rupture (Table 3). The incidence of TEAEs, serious TEAEs, and TEAEs leading to study treatment discontinuation in patients with PAD was comparable between those on bempedoic acid and those on placebo (85.8% and 85.2%, 32.6% and 30.3%, and 11.0% and 8.4%, respectively). The most common TEAEs observed in patients on bempedoic acid compared with those on placebo were hypertension (13.4% and 12.5%, respectively), hyperuricemia (10.7% and 5.4%), arthralgia (7.8% and 7.0%), and nasopharyngitis (6.1% and 4.9%). Other adverse events of clinical interest observed with bempedoic acid and placebo are myalgia (5.2% and 5.3%, respectively), gout (2.9% and 1.3%), and adjudicated tendon rupture (0.6% and 0.8%). With regard to hyperuricemia and gout, renal function is an important consideration. Although there was a significant difference in those with and without PAD (Table 1), similar proportions of patients with and without PAD had impaired renal function (estimated glomerular filtration rate <60 $mL{\cdot}min^{-1}{\cdot}1.73^{-2}$; 19.8% with PAD, 20.7% without PAD) as well as the proportion with an estimated glomerular filtration rate of ≥90 $mL{\cdot}min^{-1}{\cdot}1.73^{-2}$ (21% with PAD, 17.1% without PAD).

## DISCUSSION

The present analysis provides several novel observations from the CLEAR Outcomes trial. First, despite the PAD population being composed of a primarily low-risk PAD population, with approximately three-quarters never having a prior lower-extremity event, the incidence of MALEs was high, with ≈2.5% of patients experiencing at least 1 MALE event and ≈4 events per 100 patient-years when recurrent events were included. Second, bempedoic acid reduced first and recurrent MALEs in patients with PAD by 36% and 45% respectively. Finally, when combined with total broader cardiovascular composites, the overall effect of bempedoic acid was large in absolute terms at ≈1.9 per 100 patient-years. The last finding underscores the importance and impact of efforts to reduce LDL-C in high-risk vascular populations, including patients with lower-extremity PAD.

Patients with PAD have been recognized as having a high risk of MACEs and have frequently been included in

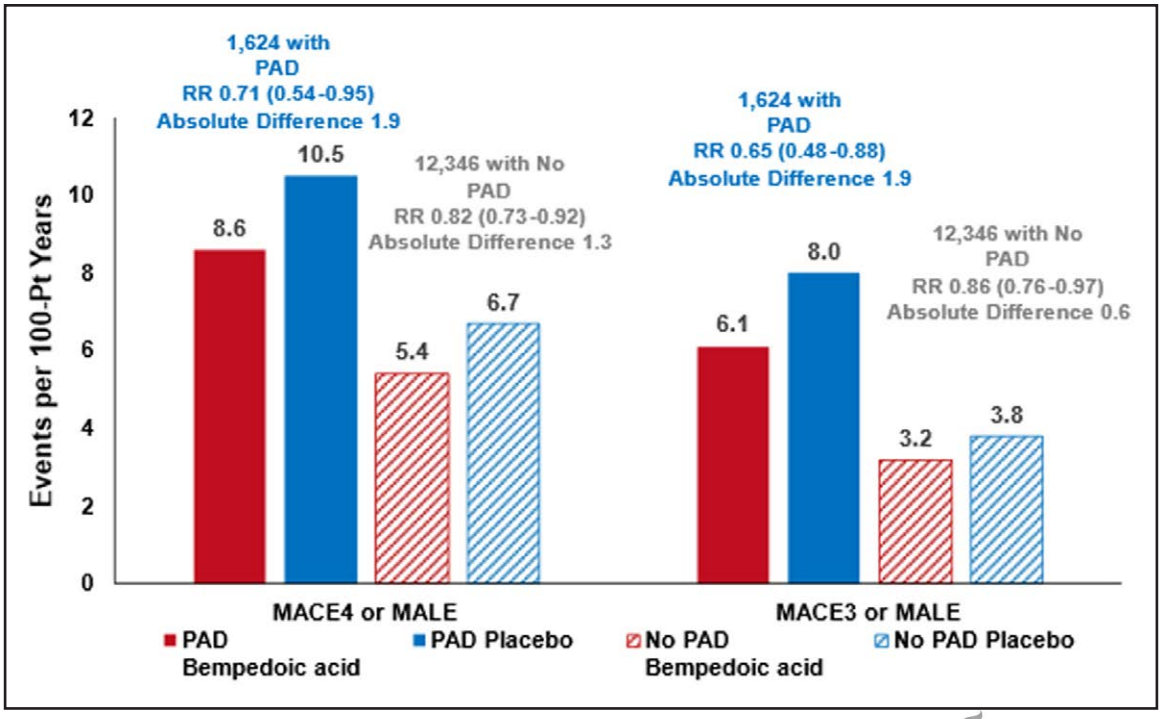


**Figure 4. Rates of total (first and recurrent) MACEs and MALEs with bempedoic acid vs placebo in patients with and without PAD at baseline.**

Major adverse limb event (MALE) was defined as a composite of all worsening peripheral artery disease (PAD) symptoms that lead to spontaneous reporting of an adverse event and to revascularization, chronic limb-threatening ischemia, and acute limb ischemia. Rates are expressed in number/100 patient-years. MACE indicates major adverse cardiovascular events; and RR, relative risk.



trials of potential cardiometabolic therapies.[1,2] Traditionally, therapies focused on reducing limb outcomes have focused on higher-risk populations, including patients with chronic limb-threatening ischemia or in the postrevascularization setting.[15,16] Analyses from long-term trials have shown that patients with a prior revascularization are at roughly 4-fold higher risk of MALEs long term.[17–20] Nonetheless, the present analysis is a reminder that in patients with symptomatic PAD, even in the chronic setting, rates of MALEs are significant particularly when recurrent events are considered. These data support the inclusion of MALE outcomes in trials studying stable PAD populations, including those without prior revascularization, and highlight the clinical importance of considering MALE risk across the spectrum of symptomatic PAD.[21,22]

Although no formal effect modification for MALEs was seen on the basis of known PAD at baseline, the effect in those with PAD appeared more robust, suggesting that MALEs in the group without PAD may have been more biologically heterogeneous, including those modifiable by LDL lowering (eg, plaque mediated) versus purely thrombotic (eg, artery to artery embolism or cardiac embolism). Greater granularity in data collection, imaging collection, and adjudication in future trials may better elucidate this potential heterogeneity. Bempedoic acid reduced MALEs in patients with PAD. Effects appeared early, at 6 months of treatment, and continued over time, resulting in a meaningful reduction during follow-up. Similar to the effects for MALEs observed with proprotein convertase subtilisin/kexin type 9 inhibitors, the benefits of bempedoic acid were apparent early and were of greater magnitude in relative terms than those for MACEs.[9,10] Taken together, these trials highlight the importance and impact of LDL-C lowering for patients with PAD and the utility of combination therapies to reduce MALEs. Recent implementation studies have highlighted that the use of early, upfront combination therapy in patients with PAD can get more patients to goal earlier.[23] Such strategies not only may translate into early benefits from treating unmitigated LDL-C risk to life and limb but also have been shown to be associated with long-term benefits and legacy effects.[24] The magnitude of risk and of potential benefits is amplified when we consider the totality of vascular risks, including MACEs and MALEs.[6]

Bempedoic acid reduces LDL-C and hsCRP, with the present analysis highlighting the importance of LDL-C as a target for reducing MALE risk.[10,11] Recent trials showing MALE benefits for glucagon-like peptide-1 receptor agonist agents such as semaglutide have raised the question of mechanism and highlighted the potential limb benefits of anti-inflammatory therapies.[21,22] In this context, it is possible that the hsCRP lowering of bempedoic acid also contributed to the observed benefits beyond LDL-C lowering. Future trials of anti-inflammatory therapies will elucidate whether

**Table 3. Safety End Points in Patients With PAD**

| Event | Bempedoic acid (n=793), n (%) | Placebo (n=829), n (%) |
|---|---|---|
| Any TEAE | 680 (85.8) | 706 (85.2) |
| Any serious TEAE | 217 (32.6) | 210 (30.3) |
| Any TEAE related to study treatment | 137 (17.3) | 106 (12.8) |
| Any TEAE leading to study treatment discontinuation | 87 (11.0) | 70 (8.4) |
| Any TEAE by maximum severity | | |
| Mild | 198 (25.0) | 195 (23.5) |
| Moderate | 310 (39.1) | 331 (39.9) |
| Severe | 172 (21.7) | 180 (21.7) |
| Common (incidence ≥5% and more frequent in bempedoic acid than placebo) TEAEs | | |
| Hypertension | 106 (13.4) | 104 (12.5) |
| Hyperuricemia | 85 (10.7) | 45 (5.4) |
| Arthralgia | 62 (7.8) | 58 (7.0) |
| Nasopharyngitis | 48 (6.1) | 41 (4.9) |
| Other adverse events | | |
| Myalgia | 41 (5.2) | 44 (5.3) |
| Gout | 23 (2.9) | 11 (1.3) |
| Adjudicated tendon rupture | 5 (0.6) | 7 (0.8) |

PAD indicates peripheral artery disease; and TEAE, treatment-emergent adverse event.

targeting both LDL-C and inflammatory axes of risk provides complementary benefits.

The incidence of adverse events and overall safety profile for bempedoic acid appeared consistent with the overall CLEAR Outcomes population regardless of PAD status at baseline, with comparable rates of TEAEs, severe TEAEs, and TEAEs leading to discontinuation. Adverse events of clinical interest, including myalgia and tendon rupture, were balanced between treatment arms in patients with PAD. Bempedoic acid may increase serum levels of uric acid through inhibition of organic anion transporter 2, which mediates renal transport of serum uric acid.[25] Consistent with the overall CLEAR Outcomes population, the incidence of gout (2.9% and 1.3%, respectively) and hyperuricemia (10.7% and 5.4%) was higher in patients on bempedoic acid compared with those on placebo, and clinical monitoring, with treatment as appropriate, for signs and symptoms of hyperuricemia is warranted.

## Limitations

There are several limitations to the current post hoc analysis. Patients enrolled in CLEAR Outcomes were not screened for PAD; therefore, patients with undiagnosed PAD were not included in the prespecified subgroup. The observation of MALEs in the group with no PAD at baseline, coupled with the absence of universal screening for PAD, supports the observation that PAD is underdiagnosed. Nonetheless, misclassification of patients with PAD to no PAD at baseline would not be expected to modify observations in terms of the effects of bempedoic acid. Another limitation is that although MALEs were defined with an established process and by blinded reviewers, they were ascertained post hoc and from safety data without supplemental source documentation; thus, some details such as urgency were not available for systematic collection. In addition, the PAD subgroup of CLEAR Outcomes represented only 12% of the population and thus was underpowered to demonstrate significant differences between treatment arms for the primary end point. Nonetheless, formal subgroup analyses did not show heterogeneity of effect on this basis, nor would this be expected based on the mechanism of LDL lowering.

## Conclusions

Bempedoic acid significantly reduces MACEs and MALEs in patients with PAD and appears to have greater benefit in terms of total events. These results reinforce the importance of having the LDL-C–lowering therapy as a priority for patients with PAD because of its safety and effectiveness in reducing the risk of ischemic events, particularly for MALEs. These findings suggest the use of bempedoic acid to optimize outcomes in patients with PAD.



## ARTICLE INFORMATION

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## Supplemental Material

Tables S1–S4
Figures S1 and S2

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