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Estimated cardiovascular benefits of bempedoic acid in patients with established cardiovascular disease

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ABSTRACT

Background and aims: Cardiovascular outcomes trials have demonstrated that lowering low-density lipoprotein cholesterol (LDL-C) reduces the risk for future cardiovascular events. We assessed the potential cardiovascular benefits of bempedoic acid through a simulation study in patients with atherosclerotic cardiovascular disease (ASCVD) and elevated LDL-C.

Methods: The validated SMART prediction model was used to estimate the baseline 10-year risk of three-point major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke) in patients with ASCVD who were enrolled in four Phase 3, randomized, placebo-controlled bempedoic acid studies. The predicted change in 10-year cardiovascular risk associated with bempedoic acid was estimated for each patient based on the Cholesterol Treatment Trialists' model. Data were analyzed in two cohorts: Cohort 1 included mostly patients treated with moderate-high intensity statins, and Cohort 2 included patients who were intolerant of more than low-intensity statin.

Results: A total of 2884 patients were included in Cohort 1 and 226 in Cohort 2. Weighted average baseline 10-year cardiovascular event risk was 26.1% and 31.6% for Cohorts 1 and 2, respectively. The least squares mean percent difference (95% confidence interval (CI) of the predicted absolute change in 10-year cardiovascular event risk with bempedoic acid was −3.3% (−3.7% to −2.9%) for patients in Cohort 1 and -6.0% (−7.7% to −4.3%) for patients in Cohort 2 compared with placebo (p < 0.0001 for both).

Conclusions: Among patients with ASCVD who could potentially benefit from additional LDL-C lowering, our simulation predicted a lower absolute cardiovascular event risk after initiating bempedoic acid as compared with placebo.

Introduction

Patients with established atherosclerotic cardiovascular disease (ASCVD) have a high risk of further cardiovascular events [1]. Results from randomized, controlled trials have demonstrated that lowering low-density lipoprotein cholesterol (LDL-C) via a variety of mechanisms reduces the risk of future cardiovascular events in this group [2–7]. In addition, based on current data there is no threshold below which additional LDL-C lowering does not confer additional cardiovascular benefit, with guidelines now recommending lower LDL-C targets for patients with ASCVD as compared with a decade ago [8,9]. Statins are the established first-line pharmacologic approach to lowering LDL-C. However, statins alone may be insufficient to achieve guideline recommendations for LDL-C lowering, and, in some cases, patients may be unable to tolerate effective doses of statins. Additional non-statin therapies are therefore needed [10].

Bempedoic acid is a first-in-class oral therapy that inhibits ATP citrate lyase (ACL), an enzyme in the cholesterol synthesis pathway upstream of 3-hydroxy-3-methyl-glutaryl CoA (HMG CoA) reductase [11], resulting in increased expression of LDL receptors. This in

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turn lowers circulating LDL-C, both in patients receiving moderate-to high-intensity statins, and in statin-intolerant patients receiving low- or very low-intensity statins, or no statin(s) [12—15]. Results from Mendelian randomization analyses have shown that inhibition of ACL reduces the incidence of cardiovascular events in proportion to the absolute change in LDL-C [16].

Results from previous studies have demonstrated that the reduction in absolute cardiovascular risk from LDL-C lowering is largely predictable, depending on the baseline risk and the magnitude of the absolute reduction in LDL-C from a given therapeutic approach [2,17—19]. To provide insights into the potential cardiovascular benefits to patients from using bempedoic acid to reduce LDL-C, we conducted a simulation study using pooled data from the Cholesterol Lowering via bEmpedoic acid, an ACL-Inhibiting Regimen (CLEAR) program [12—15,20]. We assessed the baseline 10-year risk of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke in study participants with ASCVD using the Second Manifestations of ARTerial disease (SMART) model [21], and then estimated the expected 10-year absolute risk reduction associated with the observed change in LDL-C with bempedoic acid, assuming the achieved changes in LDL-C were maintained over the 10 years [2].

Patients and methods

Patients

This analysis included data from patients with ASCVD (including coronary artery disease, cerebrovascular disease, peripheral artery disease, and abdominal aortic aneurysm) who were enrolled in four Phase 3, randomized (2:1), double-blind, placebo-controlled studies of bempedoic acid—CLEAR Harmony (NCT02666664) [12], CLEAR Wisdom (NCT02991118) [13], CLEAR Serenity (NCT02988115) [15], and CLEAR Tranquility (NCT03001076) [14]. The design and primary results from these studies have been published previously [12—15]. Two separate cohorts of patients with ASCVD were analyzed. Cohort 1 comprised patients enrolled in the CLEAR Harmony and CLEAR Wisdom studies who had baseline LDL-C levels ≥70 mg/dL and ≥100 mg/dL, respectively, despite taking maximally tolerated statins [12,13]. Cohort 2 included patients from the CLEAR Serenity and CLEAR Tranquility studies who had a history of statin intolerance and were receiving no more than low-dose statin (81.6% of whom were not receiving statins) [14,15]. Low-dose statin therapy was defined as an average daily dose of no more than rosuvastatin 5 mg, atorvastatin 10 mg, simvastatin 10 mg, lovastatin 20 mg, pravastatin 40 mg, fluvastatin 40 mg, or pitavastatin 2 mg. All patients included in Cohort 2 had baseline LDL-C levels ≥100 mg/dL. Although patients with heterozygous familial hypercholesterolemia (HeFH) were permitted in the four CLEAR Phase 3 trials, patients with HeFH without ASCVD were excluded from this analysis as HeFH is not accounted for in the SMART risk prediction tool. In the CLEAR Phase 3 trials, patients were randomized 2:1 to receive bempedoic acid 180 mg daily or placebo for 12—52 weeks, and the primary endpoint was the percent change in LDL-C from baseline to Week 12. LDL-C was calculated directly using the Friedewald formula, except in cases where triglyceride levels were >400 mg/dL or calculated LDL-C levels were ≤50 mg/dL; in these cases, a direct measure of LDL-C was conducted.

The CLEAR Phase 3 trials were approved by an institutional review board or independent ethics committee at each institution, and all trial participants provided written informed consent. The studies were conducted in compliance with ethical standards established by the Declaration of Helsinki.

Estimating risk of cardiovascular events

10-year cardiovascular risk at baseline

The validated SMART prediction model was used to estimate baseline individual 10-year risk of three-point major adverse cardiovascular events: cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke [21]. The SMART equation includes terms for age, sex, smoking status, systolic blood pressure, history of diabetes, history of coronary artery disease (defined as angina pectoris, myocardial infarction, or coronary revascularization), cerebrovascular disease, abdominal aortic aneurysm, peripheral artery disease, time since ASCVD diagnosis, high-density lipoprotein cholesterol (HDL-C), total cholesterol, estimated glomerular filtration rate (eGFR), and high-sensitivity C-reactive protein (hsCRP). Further information is provided in the Supplementary Material online. Missing baseline hsCRP was imputed using median values at baseline in all patients with ASCVD (six [0.2%] patients in Cohort 1 and 11 [4.9%] patients in Cohort 2 had missing hsCRP data). No other imputation was required.

Change in 10-year cardiovascular risk

To estimate the potential change in the 10-year cardiovascular risk with bempedoic acid treatment, the change from baseline in LDL-C levels after 12 weeks of treatment was first determined for each patient. Then, the Cholesterol Treatment Trialists' (CTT) coefficient for cardiovascular risk reduction was applied on the individual absolute change in LDL-C levels to estimate the relative risk reduction for each patient. In this model, a 1 mmol/L (39 mg/dL) decrease in LDL-C levels is estimated to result in a 22% decrease in the relative risk of major vascular events [2]. Finally, a new 10-year cardiovascular risk was calculated using the CTT-based relative risk change and applying it to the baseline risk estimated using the SMART model for each patient. There were six patients in cohort 1 who had a predicted risk score above 100 due to high baseline risk scores; these scores were set to 100.

Analysis of covariance (ANCOVA) was used to compare the difference in 10-year cardiovascular risk estimates between bempedoic acid and placebo at 12 weeks, with change from baseline as the dependent variable; study, treatment, and interactive voice response system stratification factor (Cohort 1 only) as fixed factors; and baseline 10-year cardiovascular disease risk score as a covariate. There were patients who were not identified as having HeFH by investigators but had LDL-C levels ≥250 mg/dL at baseline and thus could fulfil the Dutch Lipid Clinic Network definition of "probable or definite HeFH" [22]. As the SMART tool has not been assessed in patients with HeFH, a sensitivity analysis was performed in which patients with an LDL-C baseline value ≥ 6.5 mmol/L (251 mg/dL) were excluded to examine whether the overall findings changed materially.

In Cohort 1, patients were stratified by the patient's baseline cardiovascular risk according to the investigator and statin dose; therefore, the randomization strata were adjusted for the ANCOVA model. The ANCOVA model for Cohort 2 included study and treatment as fixed factors, and baseline 10-year cardiovascular disease risk score as a covariate.

Analyses were performed using SAS software, versions 9.2 and later (SAS Institute, Cary, North Carolina, USA). Three-dimensional histograms showing LDL-C and 10-year cardiovascular risk at baseline and Week 12 were generated using R statistical software, version 4.0.2 (2020-06-22) (R Foundation for Statistical Computing, Vienna, Austria). This was a simulation study. All data generated or analyzed during this study are included in this published article. No additional data will be shared.

Results

Patients

Baseline characteristics and demographics for Cohorts 1 and 2 are shown in Table 1. A total of 2884 patients were included in Cohort 1 (1924 bempedoic acid and 960 placebo), and 226 in Cohort 2 (156 bempedoic acid and 70 placebo). Baseline demographics and disease characteristics were well-balanced between bempedoic acid and placebo within each cohort. Consistent with the cohort entry criteria, most patients in Cohort 1 were receiving maximally tolerated moderate- or high-intensity statins, and most patients in Cohort 2 (statin-intolerant group) were not receiving statins at baseline. Patients in Cohort 1 tended to have lower mean LDL-C and

lower median hsCRP levels than did patients in Cohort 2. Fourteen patients (nine in Cohort 1 and five in Cohort 2) had baseline LDL-C levels ≥250 mg/dL.

LDL-cholesterol

The distribution of LDL-C levels at baseline in the two cohorts are shown in Fig. 1. In Cohort 1, most patients had baseline LDL-C levels of 70—110 mg/dL, and in Cohort 2, most patients had baseline LDL-C levels in the range of 100—150 mg/dL. After 12 weeks of treatment with bempedoic acid, there was a substantial shift from baseline in the distribution of LDL-C for both cohorts toward lower LDL-C levels (Fig. 1). The absolute mean reduction in LDL-C levels with bempedoic acid was 19.3 mg/dL (*vs* 0.5 mg/dL for placebo)

Table 1
Baseline demographics and disease characteristics.[a]

Parameter	Cohort 1		Cohort 2	
	Maximally tolerated statin		Statin intolerant	
	Bempedoic acid	Placebo	Bempedoic acid	Placebo
	(N = 1924)	(N = 960)	(N = 156)	(N = 70)
Age, years	65.7 ± 8.8	66.6 ± 8.4	68.0 ± 8.6	66.9 ± 8.3
Sex, n (%)				
Female	532 (28)	278 (29)	71 (46)	28 (40)
Male	1392 (72)	682 (71)	85 (54)	42 (60)
Race				
White	1835 (95)	924 (96)	149 (96)	62 (89)
Black/African American	61 (3)	25 (3)	7 (4)	7 (10)
Asian	16 (1)	7 (1)	0	0
Multiple/Other	12 (1)	4 (<1)	0	1 (1)
BMI, kg/m^2	29.8 ± 5.0[b]	29.7 ± 5.0[c]	29.6 ± 4.7	31.0 ± 5.3
Systolic BP, mmHg	133.5 ± 14.3	133.9 ± 14.1	128.3 ± 15.5	128.6 ± 12.0
Current smoker	352 (18)	157 (16)	23 (15)	11 (16)
History of diabetes	569 (30)	288 (30)	46 (30)	20 (29)
eGFR, mL/min/1.73m^2	77.1 ± 18.3	77.1 ± 17.5	75.9 ± 18.3	71.1 ± 16.6
ASCVD diagnoses				
Coronary heart disease	1733 (90)	857 (89)	112 (72)	60 (86)
Cerebrovascular disease	283 (15)	157 (16)	55 (35)	18 (26)
Peripheral artery disease	306 (16)	162 (17)	26 (17)	7 (10)
Abdominal aortic aneurysm	46 (2)	18 (2)	4 (3)	1 (1)
Time since first ASCVD diagnosis, years	10.1 ± 7.8	10.4 ± 7.5	10.6 ± 7.6	10.4 ± 7.1
Total cholesterol, mg/dL	183.8 ± 37.1	183.3 ± 37.0	227.1 ± 44.7	220.7 ± 47.3
LDL-C, mg/dL	106.2 ± 30.9	105.5 ± 29.9	141.2 ± 38.8	138.9 ± 42.1
HDL-C, mg/dL	49.2 ± 12.1	49.7 ± 11.9	52.1 ± 13.6	49.2 ± 14.1
Triglycerides, mg/dL	147.4 ± 74.0	144.5 ± 68.0	175.8 ± 89.3	171.4 ± 90.6
Apolipoprotein B, mg/dL	94.8 ± 26.3[d]	93.8 ± 26.6[e]	128.5 (29.4)[f]	129.7 (33.0)
hsCRP (mg/dL), median (Q1, Q3)	1.54 (0.78, 3.33)[g]	1.57 (0.83, 3.42)[h]	2.26 (1.08, 4.50)[f]	3.43 (1.41, 5.15)
LLT use				
Statin alone	1647 (86)	821 (86)	12 (8)	5 (7)
Statin plus other LLT	230 (12)	117 (12)	11 (7)	7 (10)
Other LLT alone	18 (1)	13 (1)	81 (52)	33 (47)
None	29 (2)	9 (1)	52 (33)	25 (36)
Ezetimibe use	113 (6)	60 (6)	69 (44)	31 (44)
Statin intensity				
High	975 (51)	485 (51)	—	—
Moderate	789 (41)	398 (41)	—	—
Low	113 (6)	55 (6)	23 (15)	12 (17)
None	47 (2)	22 (2)	133 (85)	58 (83)
Antiplatelet use	1697 (88)	834 (87)	115 (74)	53 (76)
Anticoagulant use	178 (9)	90 (9)	18 (12)	6 (9)

ASCVD: atherosclerotic cardiovascular disease; BMI: body mass index; BP: blood pressure; eGFR: estimated glomerular filtration rate; HDL-C: high-density lipoprotein cholesterol; hsCRP: high-sensitivity C-reactive protein; LDL-C: low-density lipoprotein cholesterol; LLT: lipid-lowering therapy.

[a] Values are n (%) or mean ± standard deviation, unless otherwise noted.
[b] n = 1922.
[c] n = 959.
[d] n = 1918.
[e] n = 954.
[f] n = 154.
[g] n = 1921.
[h] n = 957.

Cohort 1: Maximally Tolerated Statins – Bempedoic Acid

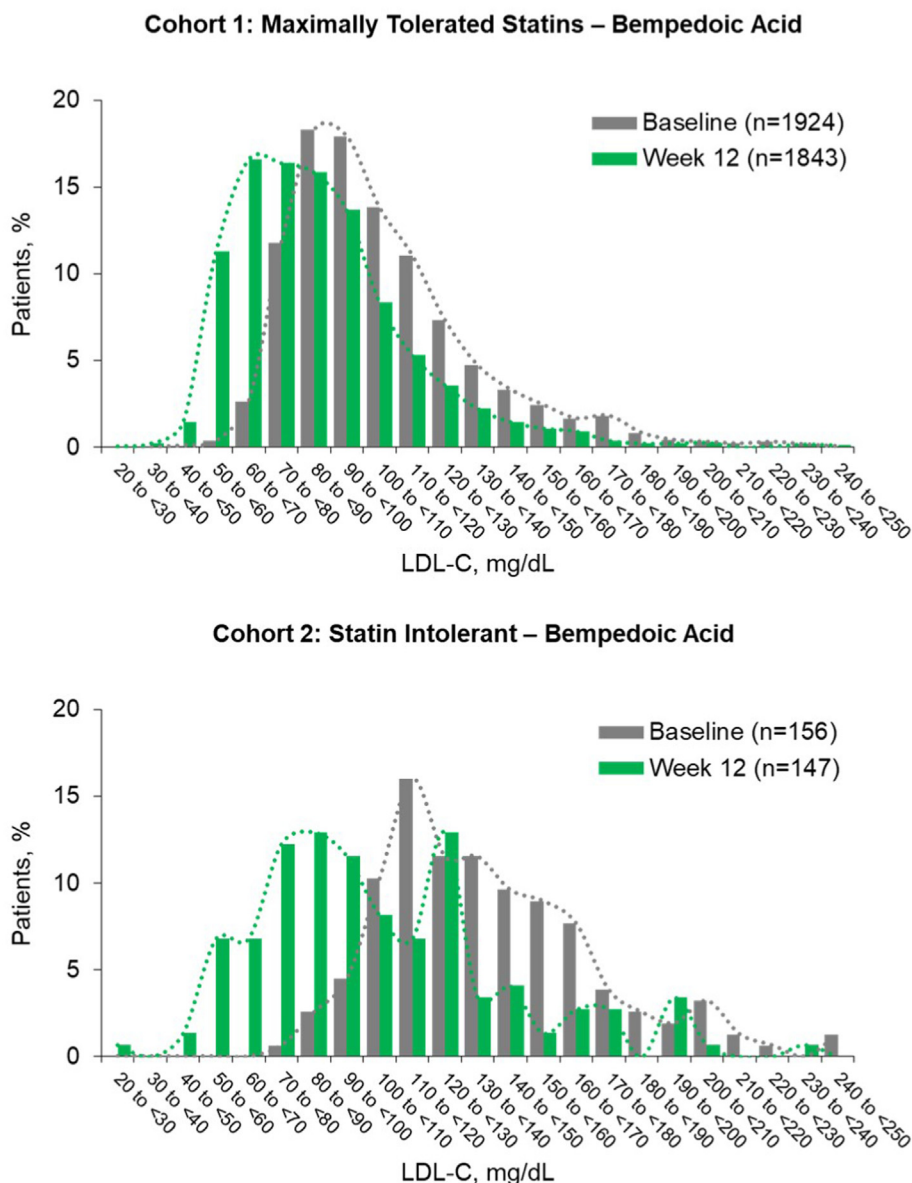## Cohort 2: Statin Intolerant – Bempedoic Acid

Fig. 1. Distribution of LDL-C levels at baseline and Week 12 in bempedoic acid−treated groups for Cohort 1 and Cohort 2. Patients with probable undiagnosed HeFH (baseline LDL-C levels ≥250 mg/dL) are not shown. LDL-C: low-density lipoprotein cholesterol. HeFH: heterozygous familial hypercholesterolemia.

among patients receiving maximally tolerated statins and 35.9 mg/dL (vs 2.2 mg/dL for placebo) among patients who were statin intolerant (Table 2). For those patients in Cohort 1 who were taking bempedoic acid, there was a corresponding placebo-corrected mean percent change in LDL-C levels at Week 12 of −18.5% (95% confidence interval (CI) −20.2, −16.7, p < 0.0001) and for Cohort 2 of −24.4% (95% CI -29.7, −19.1, p < 0.0001).

10-year cardiovascular risk

In Cohort 1, the mean (standard deviation [SD] baseline 10-year risks of a cardiovascular event predicted using the SMART model were 25.9% (15.8%) and 26.6% (15.5%) for the bempedoic acid and placebo groups, respectively. The corresponding risks in Cohort 2 were 31.9% (18.2%) and 30.9% (16.9%), (distributions for both cohorts are illustrated in Fig. 2). Almost half (42%) the patients in Cohort 1 had a predicted 10-year risk of cardiovascular events at baseline of ≥25%, whereas more than half (56%) the patients in Cohort 2 had a predicted 10-year risk at baseline of ≥25%.

The observed absolute decrease in LDL-C after 12 weeks of treatment with bempedoic acid resulted in a shift in the predicted 10-year cardiovascular risk toward lower levels (Fig. 2). The mean (SD) predicted relative risk reduction from baseline with bempedoic acid using CTT-based estimates were 10.6% (14.1%) for Cohort 1 and 18.9% (17.3%) for Cohort 2, compared with essentially no change in the group taking placebo (Table 2). These predicted relative risk reductions corresponded to an absolute change (95% CI) in 10-year cardiovascular risk of −3.3% (−3.7 to −2.9) for Cohort 1 and -6.0% (−7.7 to −4.3) for Cohort 2 (p < 0.0001 for both) in favour of bempedoic acid vs placebo. Fig. 3 shows the relationship between LDL-C and the 10-year cardiovascular risk for individual patients both at baseline and after 12 weeks of bempedoic acid treatment in the 2 cohorts; the bars represent the proportion of patients in each LDL-C group by 10-year cardiovascular risk group. There was a substantial shift toward lower predicted 10-year cardiovascular risk accompanying lower LDL-C levels with bempedoic acid treatment in both cohorts. The shift toward lower predicted 10-year cardiovascular risk was most apparent among patients who

Table 2
LDL-C levels and 10-year CV risk estimates at baseline and Week 12.[a]

Parameter	Cohort 1 Maximally tolerated statins		Cohort 2 Statin intolerant	
	Bempedoic acid (n = 1924)	Placebo (n = 960)	Bempedoic acid (n = 156)	Placebo (n = 70)
LDL-C				
Baseline, mg/dL	106.2 ± 30.9	105.5 ± 29.9	141.2 ± 38.8	138.9 ± 42.1
Week 12, mg/dL	86.8 ± 28.3 (n = 1843)	105.9 ± 33.6 (n = 939)	105.2 ± 39.9 (n = 147)	136.9 ± 43.4 (n = 68)
Change from baseline, mg/dL	−19.3 ± 25.0	0.5 ± 25.2	−35.9 ± 32.5	−2.2 ± 26.4
Percent change from baseline				
LS mean ± SE	−16.6 ± 0.5	1.9 ± 0.7	−24.8 ± 1.8	−0.4 ± 2.0
Difference of LS means *vs* placebo (95% CI)	−18.5 (−20.2, −16.7)		−24.4 (−29.7, −19.1)	
P-value	<0.0001		<0.0001	
10-year CV event risk				
Baseline (SMART), %	25.9 ± 15.8	26.6 ± 15.5	31.9 ± 18.2	30.9 ± 16.9
Week 12				
CTT-based relative risk change, %	10.6 ± 14.1 (n = 1843)	−1.6 ± 17.5 (n = 939)	18.9 ± 17.3 (n = 147)	0.06 ± 15.7 (n = 68)
Change in absolute risk, %	−2.8 ± 4.5	0.5 ± 5.6	−5.8 ± 6.4	0.4 ± 5.2
Predicted 10-year risk of CV events, %				
LS mean ± SE	23.2 ± 0.1	26.5 ± 0.2	25.6 ± 0.5	31.6 ± 0.7
Difference of LS mean vs placebo (95% CI)[b]	−3.3 (−3.7 to −2.9)		−6.0 (−7.7 to −4.3)	
P-value	<0.0001		<0.0001	

LS means, 95% CIs, and p-values are based on an ANCOVA with change from baseline as the dependent variable; study, treatment, and IVRS stratification factor as fixed factors; and baseline as a covariate.
ANCOVA: analysis of covariance; CI: confidence interval; CTT: Cholesterol Treatment Trialists' coefficient; CV: cardiovascular; IVRS: interactive voice response system; LDL-C: low-density lipoprotein cholesterol; LS: least squares; SD: standard deviation; SE: standard error; SMART: Secondary Manifestations of ARTerial disease.
  [a] Values are mean ± SD, unless otherwise indicated.

were statin intolerant (Cohort 2). Results from a sensitivity analysis showed similar results when patients with baseline LDL-C levels ≥250 mg/dL were excluded (Supplementary Material Table S1).

Discussion

Current approaches to secondary prevention of cardiovascular events are multifactorial and include diet- and lifestyle-based approaches alongside a range of other well-established interventions. Although patients with ASCVD are collectively considered to be high risk, absolute risk varies considerably among individuals in this group. The SMART risk score, derived from an epidemiological cohort study [21], has been validated in multiple trial populations and a routine care population, and recalibrated in patient registries [23–25]. This model offers a quantitative approach to estimating both residual risk in patient populations with ASCVD and the absolute benefits of optimized first-line therapies [21,23]. In addition, the model can help to estimate the absolute treatment benefits of potential add-on adjunctive therapies, especially when results of clinical outcomes trials are not yet available [25]. Use of the SMART score may also aid patient-physician shared decision making, by quantifying individual treatment benefits. There are now several LDL-C lowering therapies that can be considered for use in combination with statins or without statins for patients who are unable to tolerate statin therapy that should be incorporated into these models [26]. As the absolute benefits from lipid-lowering therapies are largely predictable, based on absolute baseline risk and LDL-C levels [2], public health strategies could model which patients to target with specific therapies, taking into account differential costs, availability of therapies, and patient preferences [27,28].

Despite the use of high- or moderate-intensity statins in 91.8% of patients, the baseline weighted mean 10-year cardiovascular event risk among patients in Cohort 1 was high at 26.1% due to comorbidities and suboptimal LDL-C control enhancing residual risk. However, by Week 12, bempedoic acid had reduced LDL-C levels by 19.3 mg/dL compared with an increase in levels of 0.5 mg/dL for patients receiving placebo. If this reduction in LDL-C was maintained with continued treatment over 10 years, the predicted impact with bempedoic acid on the 10-year cardiovascular risk

would translate to a 10.6% risk reduction relative to baseline, and an absolute difference of 3.3% compared with the placebo group. Among patients in Cohort 2, unsurprisingly because of their history of being intolerant to statins, mean baseline LDL-C levels were higher (140.5 mg/dL), and there was a higher weighted mean 10-year predicted risk of cardiovascular disease of 31.6%. Bempedoic acid produced an absolute reduction in LDL-C levels of 35.9 mg/dL in Cohort 2 compared with a reduction of 2.2 mg/dL for patients receiving placebo. If maintained over 10 years with treatment, the reduction in LDL-C with bempedoic acid therapy would be expected to result in a 18.9% relative reduction in cardiovascular risk. Thus, the predicted 10-year cardiovascular risk with bempedoic acid would be estimated to be 6.0% lower with bempedoic acid than with placebo.

As ACL, the target for bempedoic acid, is part of the same cholesterol synthesis pathway that is targeted by statins, the LDL-C lowering capacity of bempedoic acid depends in part on the intensity of concurrent statin use. Patients who are statin-intolerant represent a patient population with a high unmet need. These patients have higher LDL-C levels and a corresponding higher risk of cardiovascular events, especially if there is a patient history of ASCVD. Currently, bempedoic acid is being studied in a large, long-term cardiovascular outcomes trial (CLEAR Outcomes; clinicaltrials. gov identifier NCT02993406) that has enrolled 14,015 patients who are intolerant to statins [29]. The population enrolled in the CLEAR Outcomes study is broadly similar to the population of statin-intolerant patients in Cohort 2 analyzed here. However, patients enrolled in the CLEAR Outcomes study have a lower use of ezetimibe (12%) than do those in Cohort 2 in the current analysis (44% in the bempedoic acid treatment group). The CLEAR Outcomes study has more than 95% power to detect a 17% relative risk reduction in cardiovascular events. Given the similar patient populations, and assuming that the baseline LDL-C and annualized cardiovascular risk in the CLEAR Outcomes study are similar to the baseline LDL-C levels and risk seen in the statin-intolerant patients in Cohort 2 in the present study, then with a similar absolute reduction in LDL-C, we would predict that the relative risk reduction in the CLEAR Outcomes study could be about 20%, similar to the risk reduction that was calculated in this study. Inflammation is also a component
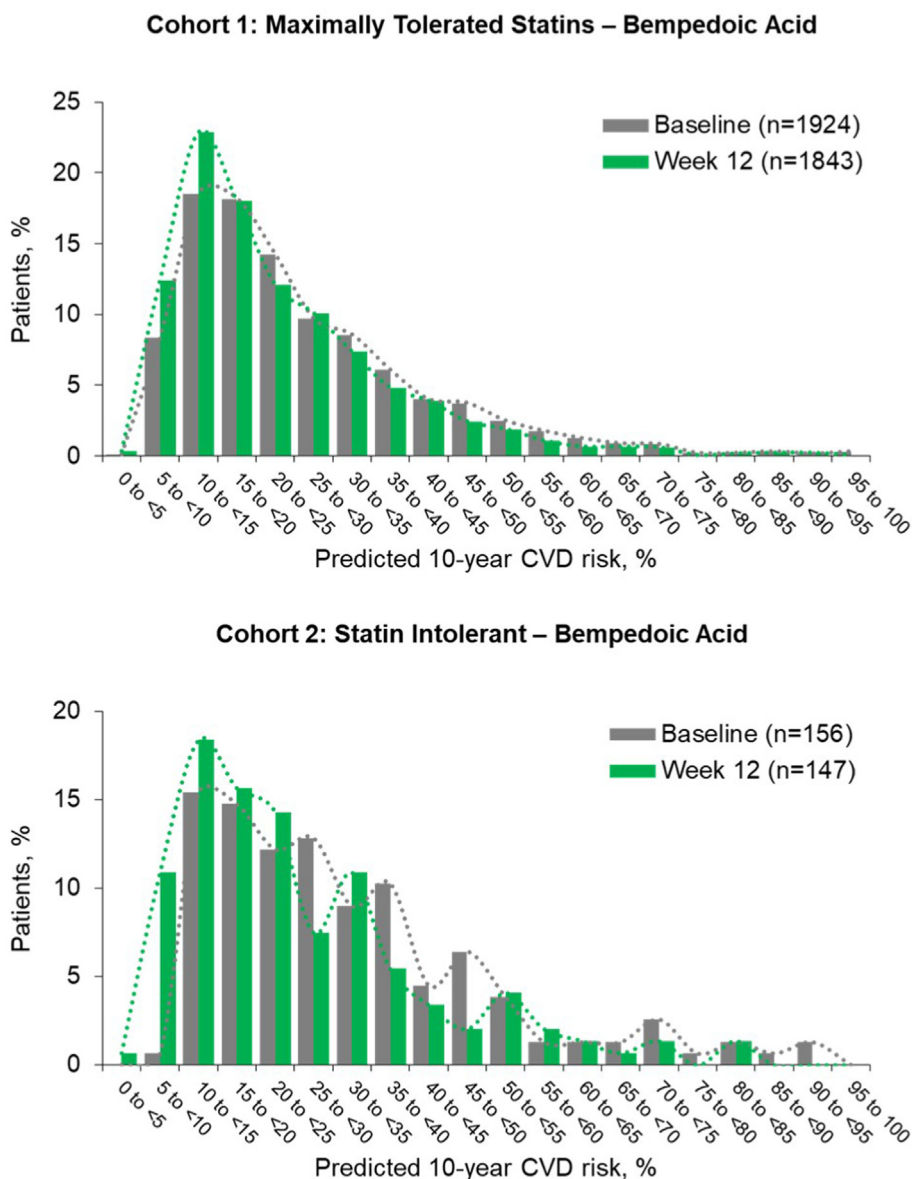
Fig. 2. Distribution of predicted 10-year cardiovascular risk at baseline and Week 12 for Cohort 1 and Cohort 2 using the Secondary Manifestations of ARTerial disease (SMART) Prediction Model; assumes that a reduction in LDL-C is sustained throughout 10 years of treatment with bempedoic acid. CVD: cardiovascular disease; LDL-C: low-density lipoprotein cholesterol.

of residual cardiovascular risk, and reductions in inflammation, independent of changes in LDL-C, have been shown to reduce cardiovascular risk [30–33]. Since bempedoic acid has also been associated with a 20%–30% reduction in hsCRP, a marker of inflammation, in phase 3 trials [34], its anti-inflammatory effects could result in additional cardiovascular risk reduction beyond that associated with LDL-C reduction.

The limitations of the present study merit consideration. We conducted a simulation study based on an established model to predict 10-year residual risk among patients with ASCVD rather than observed events in the study population. As a result, the true event rates could be higher or lower than those predicted. We also simulated the treatment benefits that would be expected if the absolute differences in LDL-C observed over 12 weeks (the time point at which the primary efficacy endpoint was evaluated in these lipid-lowering studies) were maintained with continued treatment over a 10-year time horizon. This scenario assumes that

there is no discontinuation of active therapy and that the treatment effects are constant over that period. Sustained LDL-C lowering with bempedoic acid and concomitant maximally tolerated statins has been reported through 2.5 years [35]. Unfortunately, long-term persistence rates with lipid-lowering therapies are quite poor [36]. However, assuming a constant treatment effect over a longer time horizon, this may in fact be a conservative estimate as comparison of epidemiological and genetic studies performed over 12–50 years suggest that there may be greater treatment effects with longer exposure, whereas trial-based estimates have been evaluated over 5–7 years at most [2,18]. In addition to its effects on LDL-C, bempedoic acid has also demonstrated significant reductions in hsCRP levels [12–15]. A change in hsCRP, which has also been shown to be an independent predictor of reduced ASCVD risk, was not accounted for in the CTT model [37,38]. Although our analyses do not prove cardiovascular benefits with bempedoic acid treatment, results from a Mendelian randomization analysis suggests that a
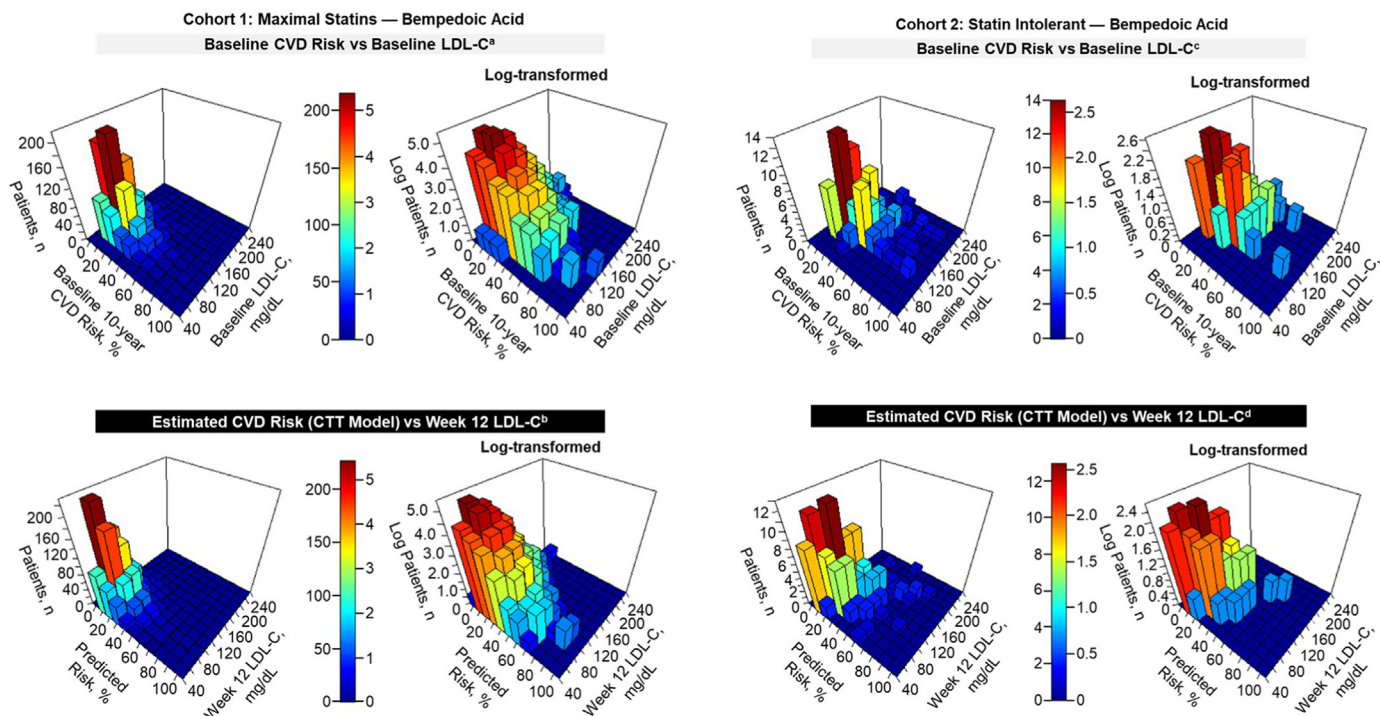
Fig. 3. Distribution of LDL-C levels and predicted 10-year cardiovascular disease risk at baseline and 12 weeks for Cohort 1 and Cohort 2. Risk at Week 12 was estimated based on the decrease in risk due to LDL-C reduction using the Cholesterol Treatment Trialists' (CTT) model. The panels on the left show the total number of patients, and the panels on the right show the log-transformed frequency to help visualize the changes more clearly. [a]Five patients with baseline LDL-C levels >260 mg/dL are not included in the figure. [b]One patient with Week 12 LDL-C level >260 mg/dL and five patients with Week 12 LDL-C levels <40 mg/dL are not included in the figure. [c]Two patients with baseline LDL-C levels >260 mg/dL are not included in the figure. [d]One patient with a Week 12 level <40 mg/dL is not included in the figure. CVD: cardiovascular disease; LDL-C: low-density lipoprotein cholesterol.

decrease in the risk of a cardiovascular event with every decrease of 10 mg/dL in LDL-C should be similar whether inhibiting ATP citrate lyase (ACL, the target of bempedoic acid), HMG CoA reductase (the target of statins), Niemann-Pick C1-Like 1 (NPC1L1, the target of ezetimibe), or proprotein convertase subtilisin-kexin type 9 (PCSK9, the target of monoclonal antibodies) [16]. Thus, we believe, our simulation provides plausible estimates of cardiovascular benefit.

Our simulation suggests that additional LDL-C lowering with bempedoic acid could produce significant cardiovascular risk reduction among patients with ASCVD. The absolute benefits are likely to be greater among patients with higher predicted risk and higher baseline LDL-C levels as currently being studied in the ongoing CLEAR Outcomes trial.

Author contributions

KKR contributed to the conception and design of the analysis. All authors contributed to the acquisition, analysis, or interpretation of data. All authors critically reviewed and revised the manuscript during development and approved the final document for submission. All authors agree to be accountable for all aspects of the work ensuring integrity and accuracy.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests.

LHG has no potential conflicts of interest to declare. AJM has no potential conflicts of interest to declare. CMB has received research grant(s)/support paid to his institution from Abbott Diagnostic, Akcea, Amarin, Amgen, Esperion, Ionis, Novartis, Regeneron, Roche Diagnostic, Sanofi-Synthelabo, National Institutes of Health, American Heart Association, and American Diabetes Association. He has also served as a consultant for Abbott Diagnostics, Amarin, Amgen, Astra Zeneca, Boehringer Ingelheim, Eli Lilly, Esperion, Intercept, Ionis, Matinas BioPharma, Merck, Novartis, Novo Nordisk, Regeneron, Roche Diagnostic, and Sanofi-Synthelabo. KKR has received research grant(s)/support from Amgen, Daiichi Sankyo, MSD, Pfizer, Regeneron, and Sanofi (all paid to his institution). He has served as a consultant for or received honoraria from Abbott, AbbVie, Akcea, Algorithm, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Cerenis, Cipla, Daiichi Sankyo, Dr. Reddy's Laboratories, Eli Lilly, Esperion, Kowa, Lupin, Medco, MSD, New Amsterdam Pharma, Novartis, Novo Nordisk, Pfizer, Regeneron, Resverlogix, Sanofi, Silence Therapeutics, Takeda, and Zuellig Pharma. MJL is a full-time employee of Esperion Therapeutics, Inc., and may hold stock and/or stock options. AF is a former full-time employee of Esperion Therapeutics, Inc., and may hold stock and/or stock options.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.athplu.2022.05.003.

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