Bempedoic acid: a new player for statin-intolerant patients and beyond

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Purpose of review
Low-density lipoproteins (LDL) cause atherosclerotic cardiovascular disease, a condition associated with significant morbidity and mortality. Statins represent the cornerstone for preventing cardiovascular events in patients with elevated LDL-cholesterol (LDL-C) levels, however, they are associated with frequent musculoskeletal adverse effects, which lead to drug discontinuation or limit their use to low (and less effective) doses. Bempedoic acid (BA) is a newly approved, safe, cholesterol-lowering agent that inhibits ATP-citrate lyase, an enzyme upstream to 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase, the target of statins. Unlike statins, BA is not associated with musculoskeletal side effects, representing a promising drug for statin-intolerant patients. This review aims to summarize the current evidence on the efficacy, safety, and impact on clinical outcomes of BA, to review current indications for its use, and to highlight the ongoing clinical trials that will help deepen our knowledge of this promising compound.

Recent findings
BA improves clinical outcomes in statin-intolerant patients. Multiple ongoing studies are evaluating whether BA can be employed in other clinical settings.

Summary
BA safely and effectively reduces the levels of multiple atherogenic markers and can be employed to reach LDL-C targets independently from statin tolerance.

Keywords
bempedoic acid, cardiovascular outcomes, hypercholesterolemia, low-density lipoprotein cholesterol, statin-intolerance

INTRODUCTION

The key initiating event in atherogenesis is the retention of low-density lipoproteins (LDL) and other cholesterol-rich apolipoprotein (Apo) B-containing lipoproteins within the arterial wall [1,2]. Atherosclerotic cardiovascular disease (ASCVD) is associated with increased morbidity and mortality; however, maintaining low-density lipoprotein cholesterol (LDL-C) levels below guidelines-suggested thresholds in patients at risk or affected by ASCVD significantly improves their outcomes [3]. A linear relationship exists between the absolute reduction of LDL-C and the reduction in the incidence of major vascular events. For the reduction of 1.0 mmol/l (~39 mg/dl) of LDL-C, there is a reduction of approximately one-fifth in the rate of cardiovascular events (CVE) [4,5].

Statins (3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors) reduce endogenous cholesterol production and are the cornerstone for the prevention of cardiovascular events in patients with elevated LDL-C levels. However, they are associated with frequent musculoskeletal side effects, which lead to drug discontinuation or limit the use to low (and less effective) doses. Studies, including the Da Vinci study, revealed that only a small percentage of high-risk individuals achieve optimal LDL-C levels due to drug intolerance, poor adherence, or impractical stepwise strategies [6].

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KEY POINTS

- Reducing low-density lipoprotein cholesterol levels is associated with significant improvement in cardiovascular outcomes. Statins represent the cornerstone for the treatment of hypercholesterolemia, however, they are associated with significant skeletal-muscle-related adverse effects, which commonly lead to drug discontinuation.
- Bempedoic acid is a new, safe, and effective cholesterol-lowering agent that acts upstream to 3-hydroxy-3-methyl-glutaryl-CoA reductase, the target of statin. This compound is not associated with statin-related adverse events and has shown to improve clinical outcomes in statin-intolerant patients.
- Bempedoic acid positively affects multiple cardiometabolic parameters, and ongoing studies are testing whether its use can be extended to other populations at risk of cardiovascular events and for the treatment of other metabolic conditions.

Bempedoic acid (BA) is a new hypocholesterolemic drug that acts upstream of the enzyme 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase in the biosynthetic chain of hepatic cholesterol [7]. BA has shown to be effective in reducing atherogenic lipid levels, and to improve clinical outcomes in statin-intolerant patients, without evidence of skeletal-muscle-related side effects. Moreover, BA significantly reduces markers of inflammation and has a positive impact on cardiometabolic parameters.

This review aims to summarize the evidence on the efficacy and safety of BA, the current clinical indications, and the ongoing trials that will help us to implement its use.

MECHANISM OF ACTION

BA (8-hydroxy-2,2,14,14 tetramethyl- pentadecanedioic acid, ETC-1002) is a prodrug, which is activated by the enzyme very-long-chain acyl-CoA synthetase 1 (ACSVL1) into bempedoyl-CoA. Bempedoyl-CoA inhibits the activity of ATP-citrate lyase (ACL), hampering the formation of cytosolic acetyl-CoA, the substrate for the de novo synthesis of cholesterol. The reduction of endogenous cholesterol synthesis in the hepatocytes, upregulates LDL receptors (LDL-R), ultimately increasing Apo-B-containing lipoproteins uptake from the bloodstream (Fig. 1).

BA acts on the same pathway of statins since ACL is located upstream of the enzyme targeted by statins [hepatic 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase]. Although statins may interfere with HMG-CoA reductase in nonhepatic cells, BA activity is mostly limited to hepatocytes, as ACSVL1 is absent in most other tissues, including skeletal muscle cells [7,8▪].

The clinical implication of this observation is that, although BA inhibits the same metabolic pathway as statins (endogenous synthesis of cholesterol), it can overcome the limits of muscular adverse events typical of statins, as it is not active at a muscular level.

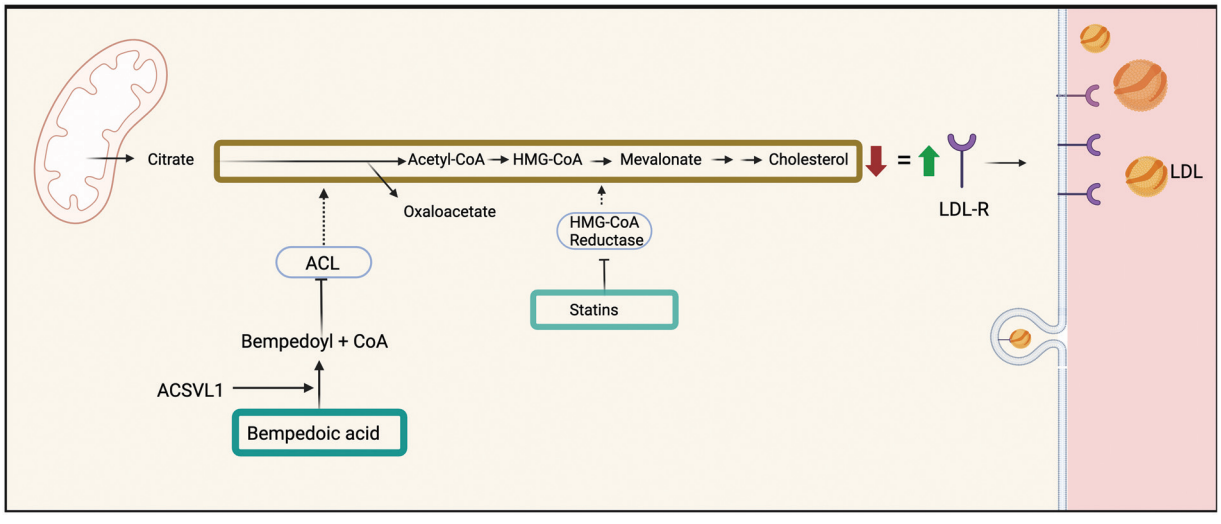

FIGURE 1. Bempedoic acid mechanism of action. BA is activated in hepatic cells by the enzyme very-long-chain acyl-CoA synthetase 1 (ACSVL1) into bempedoyl-CoA. Bempedoyl-CoA inhibits the activity of ATP-citrate lyase (ACL), which catalyzes the formation of acetyl-CoA and oxalacetate from the citrate, which comes from the mitochondria as a result of Kreb's cycle. Inhibiting the production of acetyl-coA reduces endogenous cholesterol synthesis, which upregulates the synthesis and display of low-density lipoprotein cholesterol receptor (LDL-R), increasing the uptake of LDL from the bloodstream.

EFFICACY IN REDUCING ATHEROGENIC LIPID MARKERS AND HIGH-SENSITIVE C-REACTIVE PROTEIN

BA reduces multiple atherogenic lipid biomarkers, including LDL-C, non-HDL-C, total cholesterol, and apoB levels. Moreover, it has been shown to significantly reduce high-sensitive C-reactive protein (hs-CRP) levels, a biomarker associated with inflammation and cardiovascular disease.

The efficacy and safety of BA has been confirmed in the 'Cholesterol Lowering via Bempedoic acid, an ACL-Inhibiting Regimen' (CLEAR) phase III, randomized, double-blind, placebo-controlled trials, which included patients affected by hypercholesterolemia who did not reach their LDL-C target. So far, five CLEAR studies have been conducted, including CLEAR Tranquility, CLEAR Serenity, CLEAR Wisdom, CLEAR Harmony, and CLEAR Outcomes studies.

The CLEAR Tranquility and the CLEAR Serenity trials aimed to assess the effect of BA in patients with a history of statin intolerance who required additional LDL lowering despite being on lipid-lowering agents. For this purpose, in the CLEAR Tranquility study, a total of 269 patients were enrolled, underwent a 4-week-run-in phase with ezetimibe 10 mg/day, and were subsequently randomized in a 2 : 1 fashion to BA 180 mg/day ($n = 181$) or placebo ($n = 88$) for 12 weeks (while continuing ezetimibe) [9]. On the other hand, in the CLEAR Serenity study, 345 patients were enrolled, were asked to continue their LLT and were randomized in a 2 : 1 fashion to BA or placebo for 12 weeks [9]. In both trials, the primary endpoint was the % change in LDL-C levels from baseline to week 12 between treatment groups, and secondary endpoints included the assessment of the effect of BA on other atherogenic markers and drug safety (results reported in Table 1). Notably, effects on HDL-C were negligible in both groups, and there was no difference in triglyceride levels.

The CLEAR Wisdom study aimed to assess the efficacy of BA on top of maximal tolerated LLT (including statins) in patients at high cardiovascular risk. A total of 779 participants were randomized in a 2 : 1 fashion to BA 180 mg/day or placebo for 52 weeks. The primary efficacy endpoint was the percentage change from baseline to week 12 in LDL-C levels, which was significantly higher in the BA group as compared to placebo (–15.1% vs. 2.4%, respectively; $P < 0.001$), an effect which was consistent in patients receiving low-moderate or high-intensity statin and was confirmed at 52 weeks. At 12 and 24 weeks, a significant reduction in non-HDL-C, total cholesterol, apoB, and hsCRP in the BA group was reported ($P < 0.05$, Table 1) [10].

Unlike previous studies, the CLEAR Harmony (NCT02666664) trial was designed to assess the safety of BA. Indeed, the primary endpoint of the trial was overall safety, which included the incidence of adverse events and changes in safety laboratory variables. The study included 2230 patients who were randomized in a 2 : 1 fashion to BA 180 mg/day or placebo for 52 weeks. The principal efficacy endpoint, however, was the % change in LDL-C from baseline to week 12. BA significantly reduced LDL-C at 12 weeks as compared to placebo ($P < 0.001$) (Table 1), an effect which was consistent at week 24 (difference, −16.1 percentage points; 95% CI, −18.2 to −14.0; $P < 0.001$) and at week 52, although with a slight attenuation. The effectiveness remained consistent regardless of the type and intensity of background LLT and the population subgroups, except with a greater magnitude of effect in women (P interaction = 0.03) [11]. An open extension of the CLEAR Harmony study confirmed the long-term efficacy (study follow-up arrived at 130 weeks) of BA in reducing LDL-C [12].

Table 1 also reports the results of two phase II trials, NCT03051100 [13] and NCT03193047 [14], which describe the effect of BA in combination with statin and ezetimibe or when added on top of Evolocumb, a proprotein convertase subtilisin/kexin type 9 inhibitor.

BEMPEDOIC ACID AND CLINICAL OUTCOMES IN STATIN-INTOLERANT PATIENTS

BA has proven to improve cardiovascular outcomes in statin-intolerant (i.e., being unable or unwilling to receive statins owing to an adverse effect) patients who needed LLT for primary (high risk) or secondary prevention of cardiovascular events (CVE), and who were not at target with their LDL-C (fasting LDL-C ≥100 mg/dl). This evidence comes from a double-blind, randomized, placebo-controlled trial: the CLEAR Outcomes trial. A total of 13 970 patients were randomized in a 1 : 1 ratio to receive BA 180 mg/day ($n = 6992$) or placebo ($n = 6978$), and the primary endpoint was a composite of major adverse cardiovascular events (MACE), including death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization (assessed in a time-to-first-event analysis). The pandemic created challenges in achieving complete follow-up, although full outcome data were available in 95.3% of patients, and vital status was determined in 99.4%. After a median follow up of 40.6 months, BA significantly reduced the risk of MACE by 13% [hazard ratio (HR), 0.87; 95% CI,0.79 to 0.96; $P = 0.004$], the risk of 3-component MACE (death from cardiovascular causes, nonfatal stroke, or nonfatal myocardial

Table 1. Effect of BA on atherogenic lipids and hs-CRP in phase II and phase III clinical trials, reporting the background use of commonly employed LDL-C lowering agents

Study	Population	Intervention	Background LLT allowed[a]	LDL-C reduction	Non-HDL-C reduction	TC reduction	ApoB reduction	hs-CRP reduction
CLEAR Tranquility[c]	-Statin-intolerance -LDL-C ≥100 mg/dl (not at target)	BA 180 mg/day on top of stable Eze 10 mg	Low-dose statins	−28.5% [95% CI: −34.4%, −22.5%]	−23.6% ± 2.8%	−18.0% ± 2.0%	−19.3% ± 2.3%	−31%
CLEAR Serenity [c]	-Statin-intolerance -LDL-C ≥130 mg/dl (1ry prevention) or LDL-C ≥ 100 mg/dl (2ry prevention-HeFH)	BA180 mg/day	-Low-dose statins -Eze -PCSK9 inh.	−21.4% [95% CI: −25.1%, −17.7%]	−17.9% [95% CI −21.1%, −14.8%]	−14.8% [95% CI, −17.3%, −12.2%]	−15.0% [95% CI, −18.1%, −11.9%]	−24.3%
CLEAR Wisdom [c]	-High CV risk -maximal tolerated LLT -LDL-C >70 mg/dl[b]	BA 180 mg/day	-Statin -Eze -PCSK9 inh.	-17.4% [95% CI, −21.0% to −13.9%]	-13.0% [95% CI, −16.3% to −9.8%]	-11.2% [95% CI, −13.6% to −8.8%]	-13.0% [95% CI, −16.1% to −9.9%]	-8.7%
CLEAR Harmony [c]	-ASCVD and/or HeFH -maximal tolerated statin -LDL-C >70 mg/dl	BA 180 mg/day	-Statin -Eze -PCSK9 inh. (only after week 24, if needed)	−18.1 [95% CI: −20%, −16.1%]	−13.3% [95% CI: −15.1%, −11.6%]	−11.1% [95% CI: −12.5%, −9.8%]	−11.9% [95% CI: −13.6%, −10.2%]	−21.5%
NCT03051100 [e] (Phase II)	Wash out from any LLT	BA 180 mg + Eze 10 mg + Atorvastatin 20 mg	-No other than intervention	−60.5% [95% CI, − 68.0 to − 53.0%]	−58.7% [95% CI, − 64.9 to − 52.6%]	−46.0% [95% CI, − 51.6 to − 40.4%]	−54.1% [95% CI, − 59.7 to − 48.6%]	−41.9%
NCT03193047 [d] (Phase II)	Wash out from any LLT	BA180 mg/day on top of stable Evolocumab 420 mg/month	-No other than intervention	−30.3% [95% CI, − 41.3 to − 19.2%]	−24.2 [95% CI, − 34 to − 14.5%]	−17.5 [95% CI, − 25.2 to − 9.8%]	−24.5 [95% CI, − 33.2 to− 15.7%]	−28.5%

ApoB, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; BA, bempedoic acid; CV, cardiovascular risk; Eze, ezetimibe; HDL, high-density lipoprotein; HeFH, heterozygous familiar hypercholesterolemia; hs-CRP, high-sensitive C-reactive protein; LDL-C, low-density lipoprotein cholesterol; LLT, lipid lowering therapy; PCSK 9 inh., proprotein convertase subtilisin/kexin type 9 inhibitors; TC, total cholesterol.

[a]Only the use of statins, ezetimibe and PCSK9 inhibitors was reported.

[b]LDL-C levels:1 week before randomization.

All % reductions refer to the intervention-placebo between-group difference at different timepoints.

[c]Reductions measured at 12 weeks from randomization.

[d]Reductions measured at 2 months from randomization.

[e]Reductions measured at 6 weeks from randomization.

infarction) by 15%, myocardial infarction by 23% and coronary revascularization by 19% [15▪▪]. (Fig. 2).

At 6 months, the observed difference in the LDL-C % reduction between BA and placebo groups was 21.1%, however, this effect was attenuated over time after the introduction of other LLTs (difference between-groups in LDL-C % reduction at the end of the study: 15.9%).

A prespecified sub-analysis of the CLEAR Outcome trial, which included only patients enrolled for primary prevention ($n = 4206$, without a prior cardiovascular event), has shown that BA significantly reduced MACE (~30%) and 3-component MACE (~36%) in this subpopulation, compared to placebo. Moreover, a significant reduction in MI (~39%), cardiovascular death (~39%) and all-cause mortality (~27%) was also described, however, these endpoints were not prespecified [16]. Overall, the results of this sub-analysis must be interpreted with caution as, despite more than 38 sub-analyses were originally planned, there was no adjustment for multiple testing, increasing the chance of a false-positive finding (inflation of type I error). Moreover, the trial was underpowered to detect a significant difference in the outcomes between the treatment and the placebo groups of this subpopulation, increasing the risk of imprecise estimates (including false-negative findings or overestimation of the magnitude of the effect) [17▪▪]. Ultimately, these results should be considered hypothesis-generating and could pave the way for future clinical trials.

Overall, the CLEAR Outcome trial included only statin-intolerant patients, and it needs to be clarified if the clinical benefit reported can be generalized to statin-tolerant patients or whether the effect of BA is enhanced in patient on primary or secondary prevention.

SAFETY

Results from clinical trials support the safety of BA. In a pooled analysis of the CLEAR studies, the exposure-adjusted treatment-emergent adverse events (TEAE) were 87.1/100 patient year (PY) vs. 82.9/100 (PY) in the BA and in the placebo group, respectively, with no single TEAE influencing the difference in rates. In the BA group, the TEAE leading more frequently to discontinuation were muscle spasms, headache, diarrhea, and pain in the extremities. No differences in serious AEs were observed [18]. Safety outcomes of interest were elevated liver enzymes, muscular symptoms, uric acid elevation and gout, and new onset/worsening of diabetes.

Elevation of liver enzymes [alanine aminotransferase (ALT) and aspartate aminotransferase (AST) $>3 \times$ upper limit of normal (ULN)] has been reported with BA; however, without concomitant elevation in bilirubin levels ($\geq 2 \times$ ULN) or cholestasis. Moreover, the elevation of liver enzymes was asymptomatic and returned to baseline with continued treatment or after discontinuation [19].

Muscular symptoms occurred in 15.4/100 PY in the BA group vs. 11.9/100 PY in the placebo group, however, skeletal muscle AE (myalgia and muscle weakness) were reported with similar incidence in both groups. No cases of myopathy or rhabdomyolysis have been reported, although three cases of myositis occurred in the BA group. All of these 3 patients were on background statin, including simvastatin 40 mg. Notably, BA increases plasma concentrations of statins, and doses of simvastatin >40 mg should not be used concomitantly with BA [18].

A significant increase in serum-uric acid (SUA), as well as blood urea nitrogen (BUN) and creatinine levels, was reported in clinical studies. These alterations appear to be the consequence of the inhibitory effect of BA on the renal transporter OAT-2. Notably, these alterations occurred at 4 weeks, remained stable, and returned to baseline after treatment discontinuation. Clinically speaking, the alteration in creatinine levels does not appear to indicate worsening renal function. On the other hand, elevation in SUA is associated with a higher incidence of hyperuricemia and gout, especially in patients with a medical history of gout or predisposed to gout [19].

Results from clinical and population-genetic studies suggest that statins may increase the incidence of new-onset type II diabetes or worsen glycemic control. However, data suggest that this does not hold for BA. BA does not worsen glycemic variables or increase the incidence of new-onset diabetes at 1 year, and its effect on atherogenic lipids is consistent across different glycemic strata [20]. Some authors suggest that BA could improve glycemic control.

Evidence from the CLEAR Outcome study reported an increased incidence of cholelithiasis in the BA group compared to the placebo group (2.2% vs. 1.2%) [15▪▪]. It is hypothesized that BA interacts with multiple transporters involved in the disposition of cholesterol and bile acids, including organic anion transport proteins 1B1 and 1B3 (OATP1B1/3). By inhibiting OATP1B1, BA hampers bile salt uptake in the enterohepatic circulation, resulting in an imbalance between cholesterol and bile salts concentration in the gallbladder and triggering stone formation [21▪].

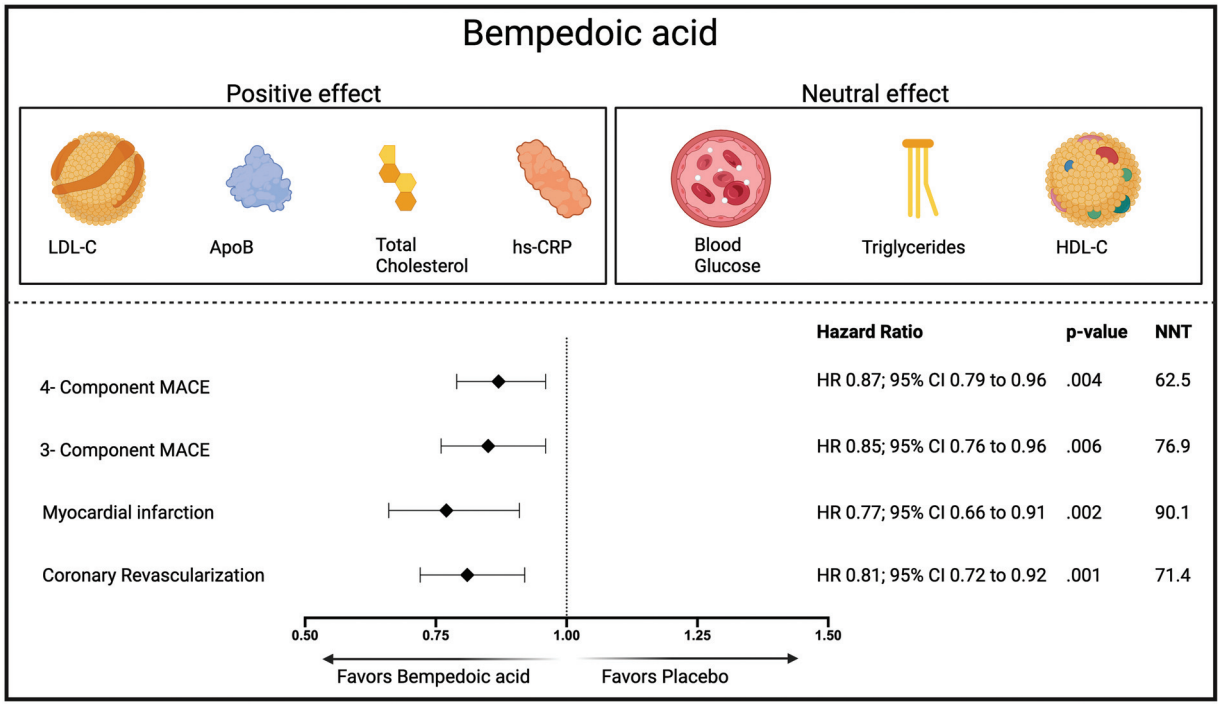

FIGURE 2. Summary of the effects of bempedoic acid. Top part of the figure: effect of bempedoic acid on atherosclerosis-associated biomarkers. Bottom part: summary of the impact of bempedoic acid on cardiovascular outcomes, reporting results from the Clear Outcomes study. Number needed to treat (NNT) was calculated as the inverse of absolute risk reduction (control group event rate – experimental group event rate). Values were taken from the original study [15]. Four-component MACE: death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization. 3-component MACE: death from cardiovascular causes, nonfatal stroke, or nonfatal myocardial infarction. ApoB, apolipoprotein B; HDL, high density lipoprotein; LDL-C, low-density lipoprotein cholesterol; NNT, number needed to treat; hs-CRP, high-sensitive C-reactive protein.

CLINICAL INDICATIONS OF BEMPEDOIC ACID

BA (180 mg) and its fixed combination with ezetimibe (180 mg/10 mg) can be used in addition to existing therapies to achieve further LDL-C reduction in patients who do not reach their target. It can be administered with or without food at a time most convenient for the patient, and it is not metabolized by (and does not inhibit or induce) cytochrome P450 enzymes.

Based on published data, the ideal candidate for the BA is a patient intolerant to statins or in whom the desired LDL-C level is missed by 20% [19].

ONGOING TRIALS AND FUTURE PERSPECTIVES

Multiple ongoing studies are investigating whether the efficacy and safety of BA for the treatment of hypercholesterolemia are confirmed in particular populations including lactating and breastfeeding women (NCT05103254 [22], NCT06021951 [23]), children affected by familial hypercholesterolemia (CLEAR- Path 1 [24]), patients who have recently suffered from cardiovascular events (CLEAR-ACS study [25]) and Asian patients (NCT05687071 [26], NCT05683340 [27]).

Other studies are testing whether BA could be used to improve metabolic conditions like non-alcoholic fatty liver disease (NAFLD) or for reducing arterial wall inflammation in patients with HIV. Animal studies suggest that BA ameliorates hepatic lipid accumulation and other hallmarks of nonalcoholic fatty liver disease, however, whether this effect is confirmed in humans is unknown and is currently investigated in the B-Lift study [28]. On the other hand, patients affected by HIV are more likely to develop cardiovascular diseases, and antiretroviral medications may worsen cardiometabolic parameters. In these patients, atherosclerosis is characterized by heightened arterial inflammation, and BA may represent a valid tool to improve this condition by reducing cholesterol levels and inflammation. Currently, this hypothesis is being tested in the CLEAR-HIV study [29] (Table 2).

Table 2. Ongoing studies on bempedoic acid

Study	Population	Intervention	Comparator	Main outcome(s)	Design
BA Pregnancy Surveillance Program (NCT05103254)	Pregnant women who have been exposed to BA or BA + Eze	N/A	N/A	Major congenital malformations from birth up to 12 months	Observational cohort study
Milk-Only Lactation Study to Evaluate the Concentration of BA and BA/Ezetimibe Fixed Combination Drug Product in the Breast Milk of Healthy Lactating Women. (NCT06021951)	Participants are not pregnant but lactating women (18–45 y.o.) for at least 4 weeks	BA or BA + Eze for 6 consecutive doses	N/A	Daily infant dose – relative infant dose (%)	Phase 4, randomized, parallel assignment
B-LIFT (NCT06035874)	Patients with T2DM on standard antidiabetic agents with HbA1c >9% and documented hepatic steatosis	BA 180 mg/day	Placebo	Difference of the change in liver fat content from 0 to 24 weeks	RCT
CLEAR Path 1 (NCT05694260)	Children aged 6–17 y.o. with diagnosis of HeFH, on treatment with approved stable LLT, with fasting LDL-C ≥ 130 mg/dl	3 cohorts: 1st:16–30 kg, BA 60 mg/day for 8 wks, followed by 90 mg for 8 wks. 2nd: 30–60 kg, BA 120 mg/day for 8wks, followed by 150 mg/day for 8 wks. 3rd: >60 kg, BA 180 mg/day for 8wks.	N/A	PK	Interventional, nonrandomized; parallel assignment
CLEAR HIV (NCT05488431)	Patients ≥40 y.o. with documented HIV infection on continuous treatment with antiretroviral and suppressed HIV infection, LDL-C ≥70 mg/dl, with documented CVD or 1 CV risk factor. Target to background ratio of >1.6 of the most diseases segment of the carotid/aorta at baseline (which means evidence of arterial inflammation) assessed by FDG-PET/CT.	BA 180 mg/day for 52 weeks	Placebo for 52 weeks	Change in Target-to-background ratio from baseline to follow-up study at 52 weeks at FDG PET/CT	Phase 2 study; Randomized; Parallel assignment.
CLEAR ACS (NCT05263778)	Patients with a recent ACS (NSTEMI, STEMI treated with PCI and/or CABG) (up to 14 days postdischarge)	BA + EZE for 12 weeks + open label extension of 12 weeks where all the patients received the treatment.	Placebo for 12 weeks	Percentage (%) change from baseline to week 12 in LDL-C level	Prospective, virtual, electronic health record -based, randomized, double-blind, placebo-controlled, parallel-group, pragmatic clinical trial
A Long-term Trial of ETC-1002 in Patients With Hyper-LDL Cholesterolemia (NCT05687071)	(Japanese center) with inadequate response to statin or safety concerns/intolerance	BA 180 mg/day for 52 weeks	N/A	TEAE, % change in LDL-C from baseline to week 52	Phase 3, nonrandomized, single group assignment
A Confirmatory Trial of ETC-1002 in Patients With Hyper-LDL Cholesterolemia (NCT05683340)	(Japanese center) with inadequate response to statin or safety concerns/intolerance	BA 180 mg/day for 12 weeks	Placebo	% change in LDL-C from baseline to week 12	Placebo-controlled, Randomized, Multicenter, Double-blind, Parallel-group Trial
MILOS (NCT04579367) and MILOS-Spain (NCT05798390)	Adult patients with primary hypercholesterolemia or mixed dyslipidemia	BA or BA + Eze		Patients characteristics and mean changes from baseline to 12 months in: SCORE system score, SMART score, Framingham risk score. Mean change from baseline in LDL-C and other atherosclerosis biomarkers, and more	Observational study

ACS, acute coronary syndrome; BA, bempedoic acid; CV: cardiovascular risk; Eze: ezetimibe 10 mg/day; FDG PET/CT, fluorodeoxyglucose-positron emission tomography computed tomography; HeFH, heterozygous familiar hypercholesterolemia; HIV, human immunodeficiency virus; LDL-C, low-density lipoprotein cholesterol; LLT, lipid lowering therapy; PCI, percutaneous coronary intervention; PK, pharmacokinetics; RCT, randomized controlled trial; TEAE: treatment emergent adverse events; T2DM, type 2 diabetes mellitus.

CONCLUSION

BA is a safe and effective cholesterol-lowering agent and significantly improves the outcomes of statin-intolerant patients who need additional LDL-C reduction (Fig. 2). The impact of BA on clinical outcomes of statin-tolerant patients has not been tested yet, however, BA can still be employed in those patients who are not able to achieve their LDL-C target. BA has shown to reduce hs-CRP and not negatively impact glycemic parameters. Finally, ongoing trials will provide more information on this compound and its impact on NAFLD and arterial wall inflammation.

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Conflicts of interest

C.I. has received speaker honoraria from Novartis, Amgen and Sanofi.

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