

BMJ Open Clinical efficacy and safety outcomes of bempedoic acid for LDL-C lowering therapy in patients at high cardiovascular risk: a systematic review and meta-analysis

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ABSTRACT

Objectives Bempedoic acid (BA) is a novel oral low-density lipoprotein cholesterol lowering drug. This systematic review and meta-analysis aims to assess efficacy and safety for clinical outcomes in high cardiovascular (CV) risk patients.

Data sources MEDLINE, Cochrane Central Register of Controlled Trials, Google Scholar, Embase, ClinicalTrials.gov, Clinical Trial Results and the American College of Cardiology web site were searched.

Study selection Randomised controlled trials (RCTs) of BA versus placebo in high CV risk patients reporting clinical outcomes were included.

Main outcomes and measures Primary efficacy outcomes were major adverse cardiovascular events (MACE), all-cause mortality, CV mortality and non-fatal myocardial infarction (MI). Safety outcomes included new onset or worsening of diabetes mellitus (DM), muscular disorders, gout and worsening of renal function.

Results Six RCTs with a total of 3956 patients and follow-ups of four to 52 weeks were identified. Heterogeneity mainly derived from differing follow-up duration and baseline CV risk. No difference in MACE (OR 0.84; 95% CI 0.61 to 1.15), all-cause mortality (OR 2.37; CI 0.80 to 6.99) and CV mortality (OR 1.66; CI 0.45 to 6.04) for BA versus placebo was observed. BA showed beneficial trends for non-fatal MI (OR 0.57; CI 0.32 to 1.00) and was associated with a lower risk of new-onset or worsening of DM (OR 0.68; CI 0.49 to 0.94), but higher risk of gout (OR 3.29; CI 1.28 to 8.46) and a trend for muscular disorders (OR 2.60; CI 1.15 to 5.91) and worsening of renal function (OR 4.24; CI 0.98 to 18.39).

Conclusion BA in high CV risk patients showed no significant effects on major CV outcomes in short-term follow-up. Unfavourable effects on muscular disorders, renal function and gout sound a note of caution. Hence, further studies with longer term follow-up in carefully selected populations are needed to clarify the risk/benefit ratio of this novel therapy.

INTRODUCTION

Hypercholesterolemia is one of the major risk factors of cardiovascular (CV) disease, which is the leading cause of death worldwide.¹ The

Strengths and limitations of this study

- Randomised controlled trials (RCTs) investigating bempedoic acid in patients with high cardiovascular risk and in those with established atherosclerotic cardiovascular disease were included.
- Sole inclusion of RCTs may reduce selection bias.
- Major clinical outcomes including major adverse cardiovascular events, all-cause mortality, cardiovascular mortality and non-fatal myocardial infarction were analysed.
- Low event rates within limited follow-ups may cause imprecise effect estimates.
- Heterogeneity in length of follow-up and background lipid-lowering therapy may introduce bias.

current guideline on the management of blood cholesterol of the American College of Cardiology/American Heart Association recommends to reduce low-density lipoprotein cholesterol (LDL-C) levels by $\geq 50\%$ in patients at high CV risk, using maximally tolerated statin therapy and—if LDL-C levels remain ≥ 70 mg/dL—additional non-statin drugs, for example, ezetimibe (class I).² The European Society of Cardiology 2019 guideline even emphasises a lower LDL-C goal of absolute LDL-C levels < 55 mg/dL and a 50% relative LDL-C reduction from baseline in adults at very high CV risk (class I) under intensified lipid-lowering therapy.³ Additional proprotein convertase subtilisin/kexin type 9 (PCSK9)-inhibitors are recommended (class I, for both societies) in patients at very high risk, who are not achieving treatment goals on a maximum tolerated dose of a high-intensity statin and ezetimibe.^{2–4}

Bempedoic acid (BA) is a novel, oral, non-statin, once daily LDL-C lowering drug, which

acts as a direct competitive inhibitor of ATP citrate lyase, a key enzyme linking carbohydrate to lipid metabolism with the effect of upregulating hepatic LDL receptor expression and activity.⁵ Earlier in 2020, both the United States Food and Drug Administration and European Medicines Agency approved BA for treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or established atherosclerotic cardiovascular disease (ASCVD), who require additional reduction of LDL-C despite optimal diet and maximally tolerated statin therapy. Efficacy and safety of additional treatment with BA on maximally tolerated statin therapy have been investigated in randomised controlled trials (RCTs),^{6–11} however individual trial sample sizes were too small to judge CV efficacy outcomes.

To further evaluate this, we performed a systematic review and meta-analysis of RCTs to investigate BA efficacy with regard to CV outcomes and BA safety—based on all available evidence.

METHODS

This systematic review and the accompanied meta-analysis was performed according to established methods recommended by the Cochrane Collaboration guidelines and the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement.^{12,13} The review protocol was not registered.

Data sources and search strategy

The online database MEDLINE was systematically searched for published reports up until 1 November 2021. The following keywords were used during searches (in combinations, among others): *bempedoic acid*, *BA*, *ETC-1002*, *randomised controlled trial*, *hypercholesterolemia*. Additionally, the Cochrane Central Register of Controlled Trials, Google Scholar, Embase, ClinicalTrials.gov, Clinical Trial Results (www.clinicaltrialresults.org) and the American College of Cardiology web site (www.cardiosource.com) were non-systematically searched for ongoing trials and major congress proceedings. Article bibliographies were additionally screened and relevant articles were added to the systematic review process.

Study selection

All obtained references from primary searches were screened based on title and abstract and categorised further; if content was considered relevant, they were retrieved as full-text reports for detailed evaluation. All controlled trials randomising BA to placebo and reporting CV outcomes, which were available in English language and in full text, were eligible for inclusion. Non-randomised studies were excluded, as were trials without reports of clinical efficacy outcomes and trials investigating PCSK9-inhibitors or inclisiran additionally to BA. No restrictions on follow-up duration, populations or study size were applied.

Efficacy and safety outcomes

Clinical outcomes were defined according to individual study protocols and were analysed as reported. Primary efficacy outcomes of interest were major adverse cardiovascular events (MACE), all-cause mortality, CV mortality and non-fatal myocardial infarction (MI); additional efficacy outcomes of coronary and non-coronary revascularisation, non-fatal stroke, hospitalisation for heart failure and hospitalisation for unstable angina were also analysed. Safety outcomes included new onset or worsening of diabetes mellitus (DM), muscular disorders, gout/elevation in uric acid and worsening of renal function, among others. Drug efficacy on lipid levels was also assessed.

Data collection and quality assessment

Data from included trials were identified, abstracted into prespecified forms and analysed according to the intention-to-treat principle. Cross-checking between investigators was performed to assure internal validity; divergences between investigators were resolved by consensus. Bias risk was appraised¹³ and the grading of recommendation, assessment, development and evaluation (GRADE) working group certainty rating¹⁴ of primary outcomes was performed by two unblinded investigators, who cross-checked each other for errors.

Statistical analyses

RevMan V.5.3 (Cochrane Collaboration) was used for statistical computations. OR and 95% CI were used as summary statistics for dichotomous clinical outcome variables, Forest plots were used for graphical display. The Cochran-Mantel-Haenszel method was applied to compute summary statistics using a fixed-effects model.¹⁵ The summary I² statistic was used to quantify heterogeneity.^{16–18} Fixed-effects models were used throughout the study due to low I², and a confirmatory analysis using random-effects models¹⁹ was additionally performed.

To analyse BA effects on serum lipid levels, data were extracted using mean differences (MD) and SD. SD data in three trials^{6,7,9} were extracted from published figures using WebPlotDigitizer V.4.2 (<https://automeris.io/WebPlotDigitizer/>). A fixed-effects model was used to compute summary statistics, again according to the Cochran-Mantel-Haenszel method. Weighted MD with 95% CI were calculated for all lipid level outcome variables. Forest plots were generated for study-specific effect sizes along with 95% CIs and pooled effect measures. An alpha-error probability of $p < 0.05$ was considered statistically significant in all calculations. To ascertain validity of results and account for trial heterogeneity, especially inhomogeneous duration of follow-up, prespecified sensitivity analyses of primary clinical efficacy and safety outcomes stratified by duration of follow-up (short-term (<12 weeks) vs longer term (>12 weeks)) were conducted.

Patient and public involvement

No patient was involved in the study. Furthermore, patients or the public were not involved in the design, conduct, reporting and dissemination plans of our research.

RESULTS

Study selection and patient population

The PRISMA flow chart of the systematic review process is depicted in online supplemental figure 1. Of the 184 studies initially identified, 90 were excluded based on title/abstract and 79 studies for being editorials, reviews, other meta analyses or in vitro studies; nine trials did not

meet explicit inclusion criteria due to non-randomised design or non-reporting of clinical outcomes; six studies comprising a total of 3,956 patients were finally included in the meta-analysis.^{6–11}

Study and patients characteristics are reported in tables 1 and 2: five studies were phase 3 RCTs published between 2018 and 2019, Gutierrez *et al* was a phase 2b RCT published in 2014.¹¹ Three trials included patients treated with a maximally tolerated statin background therapy,^{7 8 10} three trials with statin intolerance or after after discontinuation of lipid-lowering therapy.^{6 9 11} Patients were between 55 and 67 years old, most were

Table 1 Study characteristics

Publication, year (acronym)	Design	Population	Groups	Sample size (n)	FU (wks)	Endpoints
Ballantyne <i>et al</i> , ⁶ 2018 (CLEAR Tranquility)	RCT (double-blind, phase 3)	Statin intolerance and LDL-C >100 mg/dL requiring further LDL-C lowering on no more than low-dose statin therapy	BA 180 mg/d+ezetimibe 10 mg/d vs placebo +ezetimibe 10 mg/d	269 (181 BA; 88 placebo)	12	Primary: 12 wk change (%) of LDL-C Secondary: 12 wk change (%) of non-HDL-C, TC, apoB, hs-CRP, TG and HDL-C
Ballantyne <i>et al</i> , ⁷ 2019	RCT (double-blind, phase 3)	ASCVD and/or HeFH with LDL-C >100 mg/dL, or multiple CVD risk factors with LDL-C >130 mg/dL on maximally tolerated statin therapy	BA 180 mg/d+ezetimibe 10 mg/d vs BA 180 mg/d vs ezetimibe 10 mg/d* vs placebo	382 (108 BA +ezetimibe; 110 BA; 55 placebo; 109 ezetimibe*)	12	Primary: 12 wk change (%) of LDL-C Secondary: 12 wk change (%) of non-HDL-C, TC, apoB, hs-CRP
Goldberg <i>et al</i> , ⁸ 2019 (CLEAR Wisdom)	RCT (double-blind, phase 3)	ASCVD and/or HeFH with LDL-C >70 mg/dL on maximal tolerated lipid-lowering therapy	BA 180 mg/d vs placebo	779 (522 BA, 257 placebo)	52	Primary: 12 wk change (%) of LDL-C Secondary: 24 wk change (%) of LDL-C; 12 wk change (%) of non-HDL-C, TC, apoB and hs-CRP; 12 wk and 24 wk absolute change of LDL-C Tertiary: 52 wk change (%) of LDL-C; 24 wk and 52 wk change (%) of non-HDL-C, TC, apoB, hs-CRP, HDL-C and TG
Gutierrez <i>et al</i> , ¹¹ 2014	RCT (double-blind, phase 2b)	Type 2 diabetes and LDL-C ≥100 mg/dL with a body mass index 25–35 kg/m ² without lipid-lowering drugs	BA 80 mg/d for 2 wks followed by 120 mg/d for 2 vs placebo	60 (30 BA; 30 placebo)	4	Primary: 4 wk change (%) of LDL-C Secondary: 4 wk change (%) of TC, non-HDL-C, HDL-C and TG
Laufs <i>et al</i> , ⁹ 2019 (CLEAR Serenity)	RCT (double-blind, phase 3)	Statin intolerance with ASCVD and/or HeFH with LDL-C >100 mg/dL or other patients with LDL-C >130 mg/dL requiring further LDL-C lowering on no more than low-dose statin therapy or other lipid-lowering drugs	BA 180 mg/d vs placebo	345 (234 BA, 111 placebo)	24	Primary: 12 wk change (%) of LDL-C Secondary: 24 wk change (%) of LDL-C; 12 wk and 24 wk change (%) of non-HDL-C, TC, apoB, hs-CRP, HDL-C and TG; 12 wk and 24 wk absolute change of LDL-C
Ray <i>et al</i> , ¹⁰ 2019 (CLEAR Harmony)	RCT (double-blind, phase 3)	ASCVD and/or HeFH with LDL-C >70 mg/dL on maximal tolerated lipid-lowering therapy	BA 180 mg/d vs placebo	2230 (1488 BA, 742 placebo)	52	Primary: number of participants with treatment-related AEs Secondary: 12 wk, 24 wk and 52 wk change (%) of LDL-C, non-HDL-C, TC, apoB and hs-CRP

Study characteristics of all included trials, regarding study design, study population, characterisation of groups, sample size, follow-up duration and study endpoints.

*Not included in the meta analysis.

AE, adverse events; apoB, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; BA, bempedoic acid; CVD, cardiovascular disease; d, day; FU, follow up; HDL-C, high-density lipoprotein cholesterol; HeFH, heterozygous familial hypercholesterolemia; hs-CRP, high-sensitivity c-reactive-protein; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high density lipoprotein cholesterol; RCT, randomised controlled trial; TC, total cholesterol; TG, triglycerides; wk, week.

Table 2 Patients characteristics

Publication, year	Arms	Age (y)	Female		ASCVD		DM (%)	AHT (%)	BMI (kg/m ²)	CKD (%)	TC (mg/dL)	LDL-C (mg/dL)	HDL-C (mg/dL)	Non-HDL-C (mg/dL)	TG (mg/dL)	apoB (mg/dL)	hs-CRP (mg/L)
			(%)	(%)	(%)	(%)											
Ballantyne <i>et al</i> ⁶ , (CLEAR Tranquility)	BA	63.8	60.2	27.1	19.3	61.3	29.5	75.2	218.2	129.8	55.8	162.4	135.5	123.3	2.21		
	Placebo	63.7	63.6	25	19.3	58	30.5	80.7	208.6	123	57.1	151.6	153	115.8	2.26		
Ballantyne <i>et al</i> ⁷	BA+EZE	62.2	51.2	61.6 *	40.7	86	31.1	65.1	237.4	153.9	49.1	188.3	156.8	121.1	3.1		
	BA	65	54.5	62.5 *	51.1	87.5	30.6	69.3	225.5	145	49.9	175.6	140.8	113.4	2.9		
	EZE†	65.1	50	62.8 *	50	82.6	29.9	66.3	231.3	148.9	51.4	180.2	143.5	115.5	2.8		
	Placebo	65.4	41.5	63.4 *	41.5	63.4	30.7	53.6	231.3	152.8	50.3	181	139.1	115.1	3		
Goldberg <i>et al</i> ⁸ , (CLEAR Wisdom)	BA	64.1	37.2	27.1	29.7	83.9	30	79.6	202.1	119.4	51.4	150.7	139.3	116.2	1.61		
	Placebo	64.7	34.6	25.2	31.5	87.2	30.6	78.2	204.8	122.4	51.1	153.7	143	118.6	1.88		
Gutierrez <i>et al</i> ¹¹	BA	55.3	43.3	-	100	26.7	30.6	-	206.3	125.2	43.7	-	181.5	-	2.3		
	Placebo	56	33.3	-	100	26.7	29.2	-	206.7	128.4	47.4	-	152	-	2.2		
Laufs <i>et al</i> ⁹ , (CLEAR Serenity)	BA	65.2	56.8	27.1	26.9	67.5	30.1	75.2	245.7	158.5	52.2	193.5	156.5	141	2.92		
	Placebo	65.1	55	25.3	23.4	67.6	30.6	85.6	241.1	155.6	50.4	190.7	164	141.9	2.78		
Ray <i>et al</i> ¹⁰ , (CLEAR Harmony)	BA	65.8	26.1	97.4	28.6	78.9	-	-	179.7	103.6	48.7	130.9	126	88.5	1.49		
	Placebo	66.8	28.7	98	28.6	80.1	-	-	178.6	102.3	49.3	129.4	123	86.8	1.51		

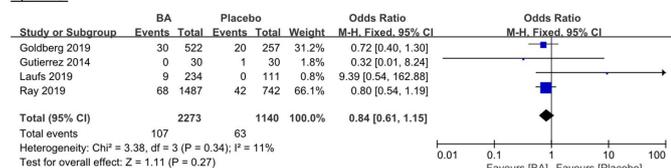
Patient characteristics of all included trials.

*ASCVD and/or heterozygous familial Hypercholesterolemia.

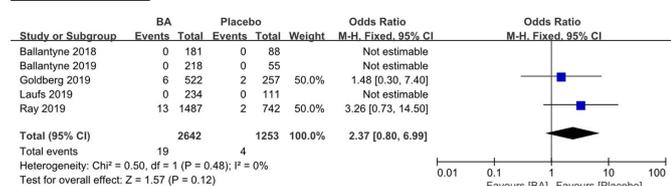
†Not included in the meta analysis.

AHT, arterial hypertension; apoB, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; BA, bempedoic acid; BMI, body mass index; CKD, chronic kidney disease (estimated glomerular filtration rate <90 mL/min); DM, diabetes mellitus; EZE, ezetimibe; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; y, years.

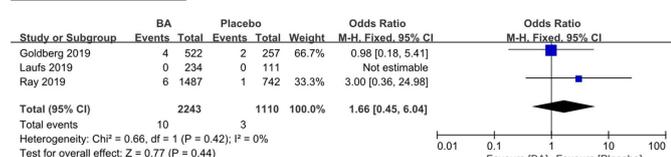
A) MACE



B) All-cause mortality



C) Cardiovascular mortality



D) Nonfatal myocardial infarction

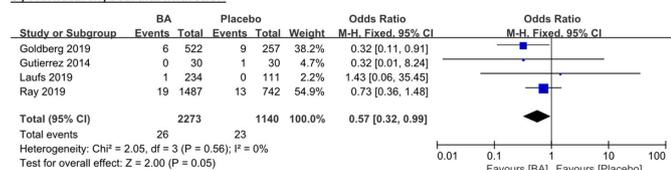


Figure 1 Individual and summary ORs with 95% CIs for efficacy outcomes of MACE (A), all-cause mortality (B), cardiovascular mortality (C) and non-fatal myocardial infarction (D) for bempedoic acid vs placebo therapy. Fixed-effects model, Cochran-Mantel-Haenszel estimates; I² measures heterogeneity; BA, bempedoic acid; MACE, major adverse cardiovascular events; M-H, Mantel-Haenszel.

overweight (average body mass index of 29–31), suffered from a considerable CV risk profile (high rates of ASCVD, DM, HeFH or chronic kidney disease (CKD)) and insufficient control of serum lipid levels (table 2). Duration of follow-up ranged from 4 to 52 weeks.^{8 10 11}

Quality and risk of bias of included studies

All included studies were adequately controlled, double-blind, without incomplete or selective reporting of data indicating a high quality. Some residual risk of bias regarding sequence generation,^{7 9 11} allocation concealment¹¹ and blinding of outcomes assessor remained unclear.¹¹ Risk of bias assessment of included studies according to Cochrane Collaboration guidelines¹³ is reported in online supplemental table 1. Certainty rating of consistency of estimated and true effects of primary outcomes according to GRADE working group¹⁴ revealed low certainty for MACE and all-cause mortality; certainty for CV mortality and non-fatal MI was rated moderate. GRADE rating is reported in online supplemental table 2.

Bempedoic acid efficacy for cardiovascular outcomes

Four RCTs with 3413 patients reported data on MACE (figure 1A),^{8–11} with no significant difference with BA compared with placebo in meta-analysis (4.7% (BA) vs

5.5% (placebo); OR 0.84, 95% CI 0.61 to 1.15; p=0.27; heterogeneity p=0.34; I²=11%). Five RCTs with 3895 patients were included in the analysis of all-cause mortality and three RCTs with 3353 patients in the analysis of CV mortality (figure 1B,C), but death was a very rare event and occurred only in two studies with longer follow-up.^{6–10}

There was no difference in all-cause mortality (0.7% (BA) vs 0.3% (placebo); OR 2.37; 95% CI 0.80 to 6.99; p=0.12; heterogeneity p=0.48; I²=0%) and in CV mortality (0.4% (BA) vs 0.3% (placebo); OR 1.66; 95% CI 0.45 to 6.04; p=0.44; heterogeneity p=0.42; I²=0%). Data from four RCTs with 3413 subjects were analysed on non-fatal MI (figure 1D),^{8–11} with a borderline-significant trend towards benefits of BA compared with placebo (1.1% (BA) vs 2.0% (placebo); OR 0.57; 95% CI 0.32 to 0.99; p=0.05; heterogeneity p=0.56; I²=0%).

Meta-analysis of additional efficacy outcomes in 3 RCTs with 3353 patients are reported in online supplemental figure 2^{8–10}. There were no significant differences in coronary revascularisation (OR 0.82; 95% CI 0.55 to 1.22; p=0.32; online supplemental figure 2A). For non-coronary revascularisation, there was a significant benefit observed in BA versus placebo, although at very low event rates (0.4% (BA) vs 1.1% (placebo); OR 0.41; 95% CI 0.18 to 0.95; p=0.04; heterogeneity p=0.66; I²=0%; online supplemental figure 2B).

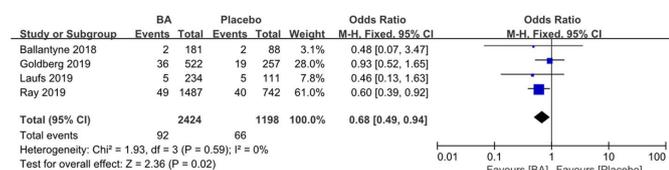
There were no significant differences in non-fatal stroke (OR 1.26, 95% CI 0.42 to 3.76; p=0.68; online supplemental figure 2C), hospitalisation for heart failure (OR 2.33; 95% CI 0.67 to 8.11; p=0.19; online supplemental figure 2D) or hospitalisation for unstable angina (OR 0.94; 95% CI 0.51 to 1.74; p=0.84; online supplemental figure 2E).

Bempedoic acid safety outcomes

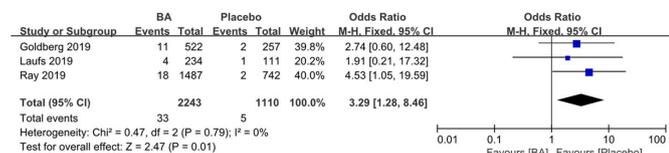
Meta-analysis of four RCTs^{6 8–10} comprising 3622 patients showed significantly lower rates of new-onset or worsening of DM for BA versus placebo (3.8% (BA) vs 5.5% (placebo); OR 0.68; 95% CI 0.49 to 0.94; p=0.02; figure 2A). In contrast, however, gout rates were significantly higher in BA treated patients (1.5% (BA) vs 0.5% (placebo); OR 3.29; 95% CI 1.28 to 8.46; p=0.01; figure 2B), which was mediated through elevation of serum uric acid (5.1% (BA) vs 2.0% (placebo); OR 2.60; 95% CI 1.15 to 5.91; p=0.02; online supplemental figure 3A). Muscular disorders were numerically more frequent under BA treatment (10.9% (BA) vs 9.1% (placebo); OR 1.25, 95% CI 0.99 to 1.57; p=0.06; figure 2C). Worsening of renal function was rare but numerically more frequent under BA treatment, evident in decreases of estimated glomerular filtration rate (0.7% (BA) vs 0.1% (placebo); OR 4.24; 95% CI 0.98 to 18.39; p=0.05; figure 2D) and increases in serum creatinine levels (0.8% (BA) vs 0.4% (placebo); OR 2.01; 95% CI 0.67 to 6.02; p=0.21; online supplemental figure 3B).

Additional safety outcomes of upper respiratory tract infection (OR 0.82; 95% CI 0.63 to 1.06; p=0.13; online supplemental figure 3C), urinary tract infection (OR

A) New-onset or worsening of diabetes mellitus



B) Gout



C) Muscular disorders



D) Decrease in GFR

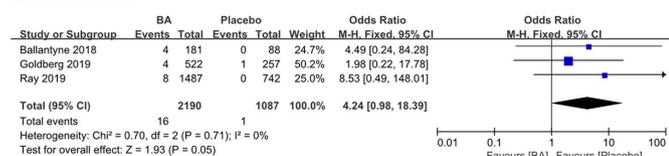


Figure 2 Individual and summary ORs with 95% CIs for safety outcomes of new-onset or worsening of diabetes mellitus (A), gout (B), muscular disorders (C) and decrease in GFR (D) for bempedoic vs placebo therapy. Fixed-effects model, Cochran-Mantel-Haenszel estimates; I² measures heterogeneity. BA, bempedoic acid; GFR, glomerular filtration rate; M-H, Mantel-Haenszel.

0.84, 95% CI 0.62 to 1.14; p=0.25; online supplemental figure 3D), neurocognitive disorders (OR 1.00, 95% CI 0.58 to 1.74; p=0.99; online supplemental figure 3E) and nasopharyngitis (OR 0.88; 95% CI 0.68 to 1.14; p=0.33; online supplemental figure 3F) showed no significant differences between BA and placebo treatment.

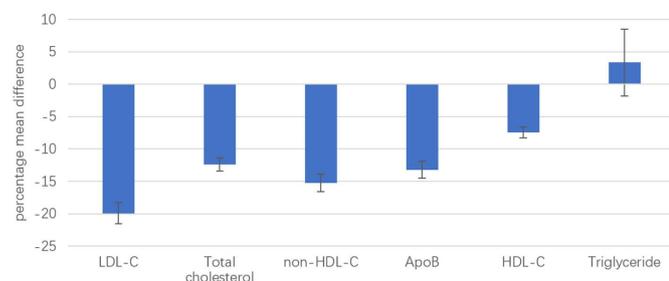


Figure 3 Summary mean differences with 95% CIs for BA efficacy on serum lipid levels compared with placebo, for LDL-C, total cholesterol, non-HDL-C, apoB, HDL-C and triglycerides. Fixed-effects model, Cochran-Mantel-Haenszel estimates. apoB, apolipoprotein B; BA, bempedoic acid; HDL-C, high-density-lipoprotein cholesterol; LDL-C, low-density-lipoprotein cholesterol.

Bempedoic acid efficacy for serum lipid levels

Meta-analysis of effects of BA versus placebo on serum lipid levels is summarised in figure 3, forest plots showing individual and summary MD between groups are presented in online supplemental figure 4. Overall, a MD in LDL-C levels of -19.93% from baseline was observed with the use of BA compared with placebo (95% CI -21.55 to -18.31 ; $p < 0.01$; online supplemental figure 4A). Treatment with BA also significantly reduced total cholesterol (MD -12.43% ; 95% CI -13.42 to -11.43 , $p < 0.01$; online supplemental figure 4B), non-high density lipoprotein cholesterol (non-HDL-C) (MD -15.27% ; 95% CI -16.59 to -13.95 , $p < 0.01$; online supplemental figure 4C) and apolipoprotein B (apoB) (MD -13.20% ; 95% CI -14.47 to -11.93 , $p < 0.01$; online supplemental figure 4D) compared with placebo. A slight reduction in high-density lipoprotein cholesterol levels was seen under BA compared with placebo (MD -7.5% , 95% CI -8.30 to -6.61 , $p < 0.01$; online supplemental figure 4E); BA treatment did not influence triglyceride levels (MD 3.35% , 95% CI -1.78 to 8.49 , $p = 0.20$; online supplemental figure 4F).

Sensitivity analyses

Prespecified sensitivity analyses of primary clinical efficacy and safety outcomes stratified by duration of follow-up (short-term (<12 weeks) vs longer term (>12 weeks)) were conducted to account for heterogeneity of follow-up of included trials. No changes of the overall effects were observed for any of the primary outcomes.

DISCUSSION

This is a systematic review and meta-analysis of all currently available RCT evidence on efficacy and safety of BA versus placebo therapy with respect to clinical outcomes. The main findings are that—compared with placebo—BA therapy had (1) no significant effects on efficacy outcomes of MACE, mortality or MI; (2) significant benefits regarding new-onset or worsening of DM, although detrimental effects on gout and possibly on renal function and muscular disorders; (3) significant decreases of atherogenic serum lipid fractions for example, LDL-C, total cholesterol, non-HDL-C and apoB.

Lowering serum LDL-C to guideline-recommended treatment goals is a cornerstone of CV disease prevention.^{2 3} Administration of statins is the first-line therapy to reduce serum LDL-C, however a proportion of patients develops statin-associated muscle symptoms and other side effects with impact on treatment adherence.^{20 21} On the other hand, many patients do not attain treatment goals despite adequate high-intensity statin therapy.^{22 23} PCSK9-inhibitors—a novel alternative for highest-risk patients—hold disadvantages of high therapy costs and subcutaneous application.^{24 25} Thus, BA is a promising oral alternative for LDL-C lowering therapy in patients at high CV risk with either statin intolerance or inadequate treatment goal attainment. It has been

approved by the United States Food and Drug Administration and European Medicines Agency earlier in 2020.

Several pooled analyses of trials investigating effects of BA have been performed at the same time by other groups.^{26–30} The majority of those focused on BAs capacities in lipid-lowering with comparable results to the current analysis: Allocation to BA as compared with placebo led to highly significant reductions in major atherogenic lipid fractions of LDL-C, non-HDL-C and apoB.^{26–29} In contrast, primary interest of the current meta-analysis was to assess evidence on BAs efficacy in improving relevant clinical outcomes, which is the fundamental objective of pharmacological lipid-lowering. The current work is, along with another recent publication,³⁰ the first to provide information on this.

Although BA showed a significant reduction of LDL-C, non-HDL-C and apoB from baseline, current pooled analysis could not find relevant impact on major clinical outcomes. Primarily, duration of follow-up ranging from 4 to 52 weeks across included trials was presumably too short to observe an effect of reduced LDL-C and other atherogenic lipid fractions on major CV outcomes. In addition, combined outcome of MACE associated with higher event rates and than singular outcomes increasing likelihood of detecting beneficial treatment effects was extractable from four of six RCTs only, which assumeably may have limited sample size too much to observe short-term effects.

Large-scale RCTs investigating LDL-C lowering agents such as statins, ezetimibe or PCSK9-inhibitors that could demonstrate a beneficial effect of LDL-C lowering on MACE^{24 25 31} or mortality^{32 33} in patients with high CV risk had a follow-up that was considerably longer (at least 2.2 to more than 6 years) with larger sample sizes. Benefits of BA on major clinical outcomes could possibly be observed at longer follow-up or if more or larger trials would be retrievable. Additionally, included trials were not conducted exclusively in the setting of secondary prevention, which contributes to heterogeneity of populations regarding baseline CV risk among included studies and requires careful interpretation of results. Whereas in secondary prevention of ASCVD, a pharmacological reduction of LDL-C is known to improve clinical outcomes³⁴—especially at higher baseline LDL-C levels³⁵—evidence of beneficial effects of lowering LDL-C in patients without established ASCVD is less robust.³⁶ However, greatest benefits of lowering LDL-C on CV outcomes and mortality occur in patients with baseline LDL-C levels above 100 mg/dL,³⁵ which lets patient selection in all included trials seem appropriate despite heterogeneous baseline risk and limited transferability of results to other populations. As meta-analysis showed a trend towards reduction of non-fatal MI with BA (OR 0.57; $p=0.05$) and significantly lower rates of new-onset or worsening of DM with BA (OR 0.68; $p=0.02$), which is an independent CV risk factor, there are indications that BA possibly holds the potential to improve clinical outcomes in selected patients at high CV risk. A recently published

meta-analysis of BAs efficacy for prevention of CV events and diabetes found results differing to the present study. Although only two trials were included in pooled analysis, the authors concluded a significant reduction in MACE. However, studies of Laufs *et al* and Gutierrez *et al* were not included for the outcome of MACE despite event rates could be extracted.³⁰

The safety profile of BA found in the current analysis certainly sounds a note of caution that should not be ignored. It has to be questioned, whether adverse effects on muscular disorders (OR 2.60; $p=0.03$), gout (OR 3.29; $p=0.01$) and renal function (increase in creatinine OR 3.53; $p=0.05$), which are also associated with increased CV risk, might counteract BA's LDL-C lowering potential for CV outcomes.

Further investigation of the risk/benefit ratio of BA in patients at high CV risk is needed to clarify the potential role of BA in primary and secondary prevention. Results of the ongoing large-scale CLEAR-Outcomes RCT including approximately 14000 patients (NCT02993406) including high CV risk patients with statin intolerance and baseline LDL-C above 100 mg/dL plans to evaluate an estimated treatment duration of 3.75 years and will help to understand the effects of BA on CV outcomes. Study completion of CLEAR-Outcomes is expected for December 2022.

Limitations

Meta-analysis is currently the only feasible way to explore clinical efficacy and safety of BA, however comes with a number of inherent limitations that arise from analysing secondary or exploratory endpoints in these trials. Low event rates within limited follow-ups cause imprecise effect estimates leading to low-moderate certainty of consistency of estimated and true effects. Variation in length of follow-up may introduce bias; multiple testing bears additional risk. Additional limitations include trial heterogeneity in study comedication (no statin vs maximal tolerated statin, additional ezetimibe) and selection of patients regarding baseline CV risk and potential beneficial effects of lipid-lowering (patients with established ASCVD vs patient at high CV risk). Generally, pooled sample size is still limited compared with other outcome trials in lipid-lowering therapy. Therefore, results of this meta-analysis are exploratory and should be interpreted with caution and evidence is limited to give a recommendation for treatment with BA.

Future directions

If results of large-scale CLEAR-Outcomes RCT (NCT02993406) will be positive for primary endpoint of MACE BA might be an integral part of pharmacological lowering of LDL-C for different reasons. Ambitious treatment goal of LDL-C <55 mg/dL for very high CV risk as given by current European Society of Cardiology guidelines is not achievable in a proportion of patients by ezetimibe added to high-intensity statin only. In many of them, LDL-C is still above treatment goal but <100 mg/dL. In

this range, addition of a PCSK9-inhibitor is not assuredly effective in improving outcomes but causes high treatment costs.^{35 37} Here, BA could be an effective alternative with lower treatment costs when smaller reductions of LDL-C are needed to achieve treatment goal. Moreover, patients with statin-intolerance caused by muscle symptoms not requiring intense LDL-C lowering due to baseline risk or baseline LDL-C might profit from a statin-free regimen including BA and ezetimibe since rates of muscular disorders appear low not markedly exceeding placebo in current meta-analysis. BAs potential in these specific settings has to be evaluated by future adequately designed RCTs analysing relevant clinical outcomes.

CONCLUSION

Meta-analysis of bempedoic acid versus placebo in patients at high CV risk showed no significant effects on major CV outcomes in short-term follow-up, despite significant reductions of LDL-C and other atherogenic lipid fractions. Unfavourable effects on muscular disorders, renal function and the incidence of gout sound a note of caution. Hence, further studies with longer term follow-up conducted in carefully selected populations are needed to clarify the risk/benefit ratio of this novel therapy.

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