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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

Short title: meta-analysis of bempedoic acid for LDL-C lowering therapy in CVD

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ABSTRACT

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

Study selection: Randomized controlled trials (RCTs) of BA vs. placebo in high cardiovascular risk patients reporting clinical efficacy and safety outcomes were included.

Main outcomes and measures: Primary efficacy outcomes were major adverse cardiovascular events (MACE), all-cause mortality, cardiovscular (CV) mortality and nonfatal 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 3,956 patients and follow-ups of four to 52 weeks were identified. There was no difference in MACE (odds ratio (OR) 0.84; 95% confidence interval (CI) 0.61, 1.15), all-cause mortality (OR 2.37; CI 0.80, 6.99) and CV mortality (OR 1.66; CI 0.45, 6.04) for BA vs. placebo. BA showed beneficial trends for nonfatal MI (OR 0.57; CI 0.32, 1.00) and was associated with a lower risk of new-onset or worsening of DM (OR 0.68; CI 0.49, 0.94), but higher risk of gout (OR 3.29; CI 1.28, 8.46), and a trend for muscular disorders (OR 2.60; CI 1.15, 5.91) and worsening of renal function (OR 4.24; CI 0.98, 18.39).

Conclusion: Bempedoic acid in high cardiovascular risk patients showed no significant effects on major cardiovascular outcomes in short-term follow-up. 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 are needed to clarify the risk/benefit ratio of this novel therapy.

Strengths and limitations of this study

- Randomized 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 nonfatal myocardial infarction were analyzed.
- Low event rates within limited follow-ups may cause imprecise effect estimates.

- Heterogeneity in length of follow-up may introduce bias.

INTRODUCTION

Hypercholesterolemia is one of the major risk factors of cardiovascular disease, which is the leading cause of death worldwide.[1] The 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 ≥50% in patients at high cardiovascular risk, using maximally tolerated statin therapy and – if LDL-C levels remain ≥70 mg/dL – additional non-statin drugs, e.g. ezetimibe (class I).[2] The European society of cardiology 2019 guideline even emphasizes 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 cardiovascular risk (class I) under intensified lipid-lowering therapy.[3] Additional proprotein convertase subtilisin/kexin type 9 (PSCK-9) inhibitors are recommended (class I, both guidelines) 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, 3]

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.[4] 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 randomized controlled trials (RCTs),[5-10] however individual trial sample sizes were too small to judge cardiovascular efficacy outcomes.

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

Methods

This systematic review and the accompagnied 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.[11, 12] The review protocol was not registered.

Data sources and search strategy

The online database MEDLINE was systematically searched for published reports up until June 6th 2020. The following keywords were used during searches (in combinations, among others): *bempedoic acid, BA, ETC-1002, randomized 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 categorized further; if content was considered relevant, they were retrieved as full text reports for detailed evaluation. All controlled trials randomizing BA to placebo and reporting cardiovascular outcomes, which were available in English language and in full text, were eligible for inclusion. Non-randomized studies were excluded, as were trials without reports of clinical efficacy outcomes. 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 analyzed as reported. Primary efficacy outcomes of interest were major adverse cardiovascular events (MACE), all-cause mortality, cardiovascular (CV) mortality, and nonfatal myocardial infarction (MI); additional efficacy outcomes of coronary and non-coronary revascularization, nonfatal stroke, hospitalization for heart failure, and hospitalization for unstable angina were also analyzed. 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 analyzed 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 appraised by two unblinded investigators, who cross-checked each other for errors.

Statistical analyses

RevMan 5.3 (Cochrane Collaboration) was used for statistical computations. Odds ratios (OR) and 95% confidence intervals (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 [13]. The summary I^2 statistic was used to quantify heterogeneity [14-16]. A Fixed-effects models were used throughout the study due to low I^2, a confirmatory analysis using random-effects models [17] was additionally

performed.

To analyze BA effects on serum lipid levels, data were extracted using mean differences (MD) and standard deviations (SD). SD data in three trials [5, 6, 8] were extracted from published figures using WebPlotDigitizer 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 mean differences 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 envolvement

Patients or the public were not involved in the design, conduct, reporting, dissemination plans of our research.

RESULTS

Study selection and patient population

The PRISMA flow chart of the systematic review process is depicted in Supplementary Figure 1: Of the 113 studies initially identified, 16 were excluded based on title/abstract and 84 studies for being editorials, reviews, other meta analyses or in vitro studies; seven trials did not meet explicit inclusion criteria due to non-randomized design or non-reporting of clinical outcomes; six studies comprising a total of 4,065 patients were finally included in the meta-analysis.[5-10]

Study and patients characteristics are reported in Table 1 and Table 2: Five studies were phase 3 RCTs published between 2018 and 2019, Gutierrez et al. was a phase 2b RCT published in 2014.[10] Three trials included patients treated with a maximally-tolerated statin background therapy,[6, 7, 9] three trials with statin intolerance or after after discontinuation of lipid-lowering therapy.[5, 8, 10] Patients were between 55 and 67 years old, most were overweight (average BMI of 29-31), suffered from a considerable cardiovascular 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. [7, 9, 10]

Table 1 – Study characteristics

Publication, year (acronym)	Design	Population	Groups	Sample size (n)	FU (wks)	Endpoints
Ballantyne et al.[5], 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 et al.[6], 2019	RCT (double-blind, phase 3)	ASCVD and/or HeFH with LDL-C >100mg/dL, or multiple CVD risk factors with LDL-C >130mg/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 et al.[7], 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 et al.[10], 2014	RCT (double-blind, phase 2b)	Type 2 diabetes and LDL-C ≥100 mg/dL with a body mass index 25 - 35 kg/m² 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 et al.[8], 2019 (CLEAR Serenity)	RCT (double-blind, phase 3)	Statin intolerance with ASCVD and/or HeFH with LDL-C >100mg/dL, or other patients with LDL-C >130mg/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 et al.[9], 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

Table 1: Study characteristics of all included trials, regarding study design, study population, characterization of groups, sample size, follow-up duration, and study endpoints. AE=adverse events; apoB=apolipoprotein B; ASCVD=atherosclerotic cardiovascular disease; BA=bempedoic acid; CVD= cardiovascular disease; d=day; FU=follow-up; HeFH=heterozygous familial hypercholesterolemia; HDL-C=high-density lipoprotein cholesterol; hs-CRP=high-sensitivity c-reactive-protein; LDL-C=low-density-lipoprotein cholesterol; non-HDL-C=non-high density lipoprotein cholesterol; RCT=randomized controlled trial; TC=total cholesterol; TG=triglycerides; wk=week. * not included in the meta analysis.

Table 2 – Patients characteristics

Publication, year (acronym)	Arms	Age (y)	Female (%)	ASCVD (%)	DM (%)	AHT (%)	BMI (kg/m²)	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 et al.[5], 2018 (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	25.0	19.3	58.0	30.5	80.7	208.6	123.0	57.1	151.6	153.0	115.8	2.26
Ballantyne et al.[6], 2019	BA+EZE	62.2	51.2	61.6 †	40.7	86.0	31.1	65.1	237.4	153.9	49.1	188.3	156.8	121.1	3.1
	BA	65.0	54.5	62.5 †	51.1	87.5	30.6	69.3	225.5	145.0	49.9	175.6	140.8	113.4	2.9
	EZE*	65.1	50.0	62.8 †	50.0	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	181.0	139.1	115.1	3.0
Goldberg et al.[7], 2019 (CLEAR Wisdom)	BA	64.1	37.2	27.1	29.7	83.9	30.0	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	143.0	118.6	1.88
Gutierrez et al.[10], 2014	BA	55.3	43.3	-	100	26.7	30.6	-	206.3	125.2	43.7	-	181.5	-	2.3
	Placebo	56.0	33.3	-	100	26.7	29.2	-	206.7	128.4	47.4	-	152.0	-	2.2
Laufs et al.[8], 2019 (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	141.0	2.92
	Placebo	65.1	55.0	25.3	23.4	67.6	30.6	85.6	241.1	155.6	50.4	190.7	164.0	141.9	2.78
Ray et al.[9], 2019 (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	98.0	28.6	80.1	-	-	178.6	102.3	49.3	129.4	123	86.8	1.51

Table 2: Patient characteristics of all included trials. BA=Bempedoic acid; EZE=ezetimibe; ASCVD=atherosclerotic cardiovascular disease; DM=diabetes mellitus; AHT=arterial hypertension; BMI=body mass index; CKD=chronic kidney disease (estimated glomerular filtration rate<90ml/min); TC=total cholesterol; LDL-C=low-density lipoprotein cholesterol; apoB=apolipoprotein B; HDL-C=high-density lipoprotein cholesterol; hsCRP=high-sensitivity C-reactive protein; non-HDL-C=non-high

density lipoprotein cholesterol. Lipids are presented as means, hs-CRP as medians; † ASCVD and/or heterozygous familial Hypercholesterolemia. * not included in the meta analysis.

Risk of bias in included studies

Risk of bias assessment of included studies is reported in Supplementary Table 1: All included RCTs were adequately controlled trials and exhibited a low risk of bias at study level, with some residual unclear risk.

Bempedoic acid efficacy for cardiovascular outcomes

Four RCTs with 3,413 patients reported data on MACE (Figure 1A),[7-10] with no significant difference with BA compared to 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; I^2=11%). Five RCTs with 3,895 patients were included in the analysis of all-cause mortality and three RCTs with 3,353 patients in the analysis of CV mortality (Figure 1B and 1C), but death was a very rare event and occurred only in two studies with longer follow-up.[5-9] 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; I^2=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; I^2 = 0%). Data from four RCTs with 3,413 subjects were analyzed on nonfatal MI (Figure 1D),[7-10] with a borderline-significant trend towards benefits of BA compared to 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; I^2=0%).

Meta-analysis of additional efficacy outcomes in 3 RCTs with 3353 patients are reported in Supplementary Figure 2:[7-9] There were no significant differences in coronary revascularization (OR 0.82; 95% CI 0.55 to 1.22; p=0.32; Supplementary Figure 2A). For non-coronary revascularization, there was a significant benefit observed in BA vs. placebo, albeit 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; I^2=0%; Supplementary Figure 2B).

There were no significant differences in nonfatal stroke (OR 1.26, 95% CI 0.42 to 3.76; p=0.68; Supplementary Figure 2C), hospitalization for heart failure (OR 2.33; 95% CI 0.67 to 8.11; p=0.19; Supplementary Figure 2D) or hospitalization for unstable angina (OR 0.94; 95% CI 0.51 to 1.74; p=0.84; Supplementary Figure 2E).

Bempedoic acid safety outcomes

Meta-analysis of 4 RCTs comprising 3,622 patients showed significantly lower rates of new-onset or worsening of DM for BA vs. placebo (3.8% (BA) vs. 5.5% (placebo);[5, 7-9] 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; Supplementary 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 nummerically 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; Supplementary Figure 3B).

Additional safety outcomes of upper respiratory tract infection (OR 0.82; 95% CI 0.63 to 1.06; p = 0.13; Supplementary Figure 3C), urinary tract infection (OR 0.84, 95% CI0.62 to 1.14; p = 0.25; Supplementary Figure 3D), neurocongnitive disorders (OR 1.00, 95% CI 0.58 to 1.74; p=0.99; Supplementary Figure 3E), and nasopharyngitis (OR 0.88; 95% CI 0.68 to 1.14; p=0.33; Supplementary Figure 3F) showed no significant differences between BA and placebo treatment.

Bempedoic acid efficacy for serum lipid levels

Meta-analysis of effects of BA vs. placebo on serum lipid levels is summarized in Figure 3, forest plots showing individual and summary mean differences (MD) between groups are presented in Supplementary Figure 4. Overall, a MD in LDL-C levels of -19.93 % from baseline was observed with the use of BA compared to placebo (95% CI -21.55 to -18.31; p<0.01; Supplementary Figure 4A). Treatment with BA also significantly reduced total cholesterol (MD -12.43%; 95% CI -13.42 to -11.43, p<0.01; Supplementary Figure 4B), non-high density lipoprotein cholesterol (non-HDL-C) (MD -15.27%; 95% CI -16.59 to -13.95, p<0.01; Supplementary Figure 4C), and apolipoprotein B (apoB) (MD -13.20%; 95% CI -14.47 to -11.93, p<0.01; Supplementary Figure 4D) compared to placebo. A slight reduction in high-densitiy lipoprotein cholesterol levels was seen under BA compared to placebo (MD -7.5%, 95% CI -8.30 to -6.61, p<0.01; Supplementary Figure 4E); BA treatment did not influence triglyceride levels (MD 3.35%, 95% CI -1.78 to 8.49, p=0.20; Supplementary 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 randomized controlled trial evidence on efficacy and safety of BA vs. 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 myocardial infarction; 2) significant benefits regarding new-onset or worsening of diabetes mellitus, however detrimental effects on gout and possibly on renal function and muscular disorders; 3) significant decreases of

atherogenic serum lipid fractions e.g. LDL-C, TC, non-HDL and apoB.

Lowering serum LDL-C to guideline-recommended treatment goals is a cornerstone of cardiovascular 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.[18, 19] On the other hand, many patients do not attain treatment goals despite adequate high-intensity statin therapy.[20, 21] PCSK9-inhibitors – a novel alternative for highest-risk patients – hold disadvantages of high therapy costs and subcutaneous application.[22, 23] Thus, BA is a promising oral alternative for LDL-C lowering therapy in patients at high cardiovascular 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.

Although BA lead to a significant reduction of LDL-C from baseline, the 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 cardiovascular outcomes. 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 [22-24] or mortality [25, 26] in patients with high cardiovascular risk had a follow-up that was considerably longer (at least 2.2 to more than 6 years). Benefits of BA on major clinical outcomes could possibly be observed at longer follow-up. Additionally, included trials were not conducted exclusively in the setting of secondary prevention, which contributes to heterogeneity of our analysis. Whereas in secondary prevention of ASCVD a pharmacological reduction of LDL-C is known to improve clinical outcomes [27] – especially at higher baseline LDL-C levels [28] – evidence of beneficial effects of lowering LDL-C in patients without established ASCVD is less robust. [29] However, greatest benefits of lowering LDL-C on cardiovascular outcomes and mortality occur in patients with baseline LDL-C levels above 100 mg/dl, [28] which lets patient selection in all included trials seem appropriate. As meta-analysis showed a trend towards reduction of nonfatal MI with BA (OR 0.57; p=0.05) and significantly lower rates of new-onset or worsening of diabetes mellitus with BA (OR 0.68; p=0.02), which is an independent cardiovascular risk factor, there are indications that BA possibly holds the potential to improve clinical outcomes in selected patients at high cardiovascular risk.

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 cardiovascular risk, might counteract BA's LDL-C lowering potential for cardiovascular outcomes.

Further investigation of the risk/benefit ratio of BA in patients at high cardiovascular risk is needed to clarifiy the

potential role of BA in primary and secondary prevention. Results of the ongoing large scale CLEAR-Outcomes RCT (NCT02993406) including high cardiovascular 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 cardiovascular 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 analyzing secondary or exploratory endpoints in these trials: Low event rates within limited follow-ups cause imprecise effect estimates; heterogeneity between trials may be underestimated; variation in length of follow-up may introduce bias; multiple testing bears additional risk. Additional limitations include trial heterogeneity in study co-medication (no statin vs. maximal tolerated statin, additional ezetimibe) and selection of patients (patients with established ASCVD vs. patient at high cardiovascular risk). Therefore, results of this meta-analysis are exploratory and should be interpreted with caution.

CONCLUSION

Bempedoic acid in high cardiovascular risk patients showed no significant effects on major cardiovascular 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 are needed to clarify the risk/benefit ratio of this novel therapy.

Contributorship statement

YL, MB, and GW conceived and designed the study; YL, CP, and AK collected sources, selected studies and abstracted data; YL, AK, and TK performed doublechecks; YL and GW performed the statistical analysis; all authors analyzed and interpreted the data; YL and MB drafted the first manuscript version; NC, AI, MK, MB, CP, VS, and GW thoroughly revised it; all authors read, critically revised and accepted the submitted version of the manuscript.

Competing interests

The authors declare no conflicts of interest.

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Data sharing statement

All data relevant to the study are included in the article or uploaded as supplementary information.

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Figure legends

Figure 1: Individual and summary odds ratios with 95% confidence intervals for efficacy outcomes of MACE (A), all-cause mortality (B), cardiovascular mortality (C), and nonfatal myocardial infarction (D) for bempedoic acid vs. placebo therapy. Fixed effects model, Cochran-Mantel-Haenszel estimates; I^2 measures heterogeneity; BA=bempedoic acid; M-H=Mantel-Haenszel.

Figure 2: Individual and summary odds ratios with 95% confidence intervals 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; I^2 measures heterogeneity. BA=bempedoic acid; GFR=glomerular filtration rate; M-H=Mantel-Haenszel.

Figure 3: Summary mean differences with 95% confidence intervals for BA efficacy on serum lipid levels compared to 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=high-density-lipoprotein cholesterol; LDL-C=low-density-lipoprotein cholesterol.

Figure 1 – Efficacy outcomes of BA vs. placebo therapy

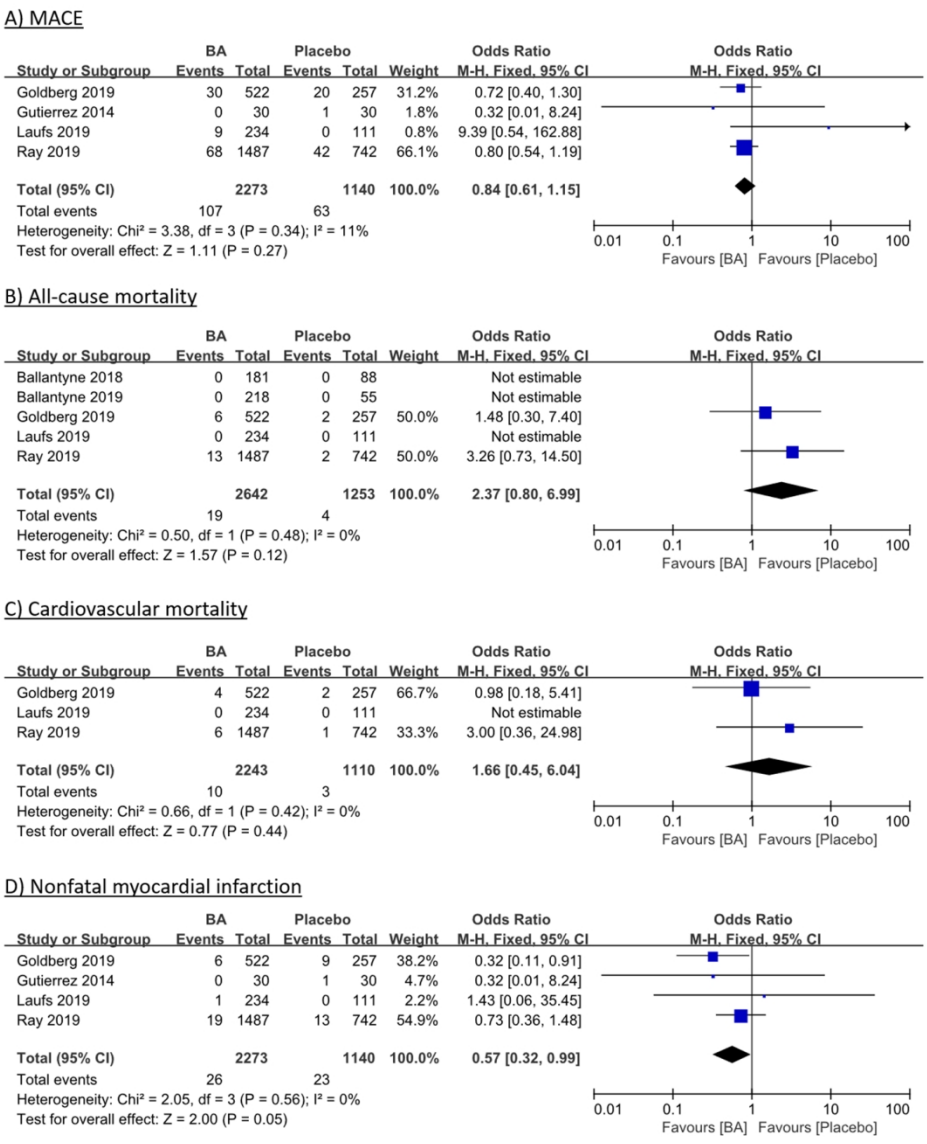

Figure 1: Individual and summary odds ratios with 95% confidence intervals for efficacy outcomes of MACE (A), all-cause mortality (B), cardiovascular mortality (C), and nonfatal myocardial infarction (D) for bempedoic acid vs. placebo therapy. Fixed effects model, Cochran-Mantel-Haenszel estimates; I² measures heterogeneity; BA=bempedoic acid; M-H=Mantel-Haenszel.

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Figure 2 – Safety outcomes of BA vs. placebo therapy

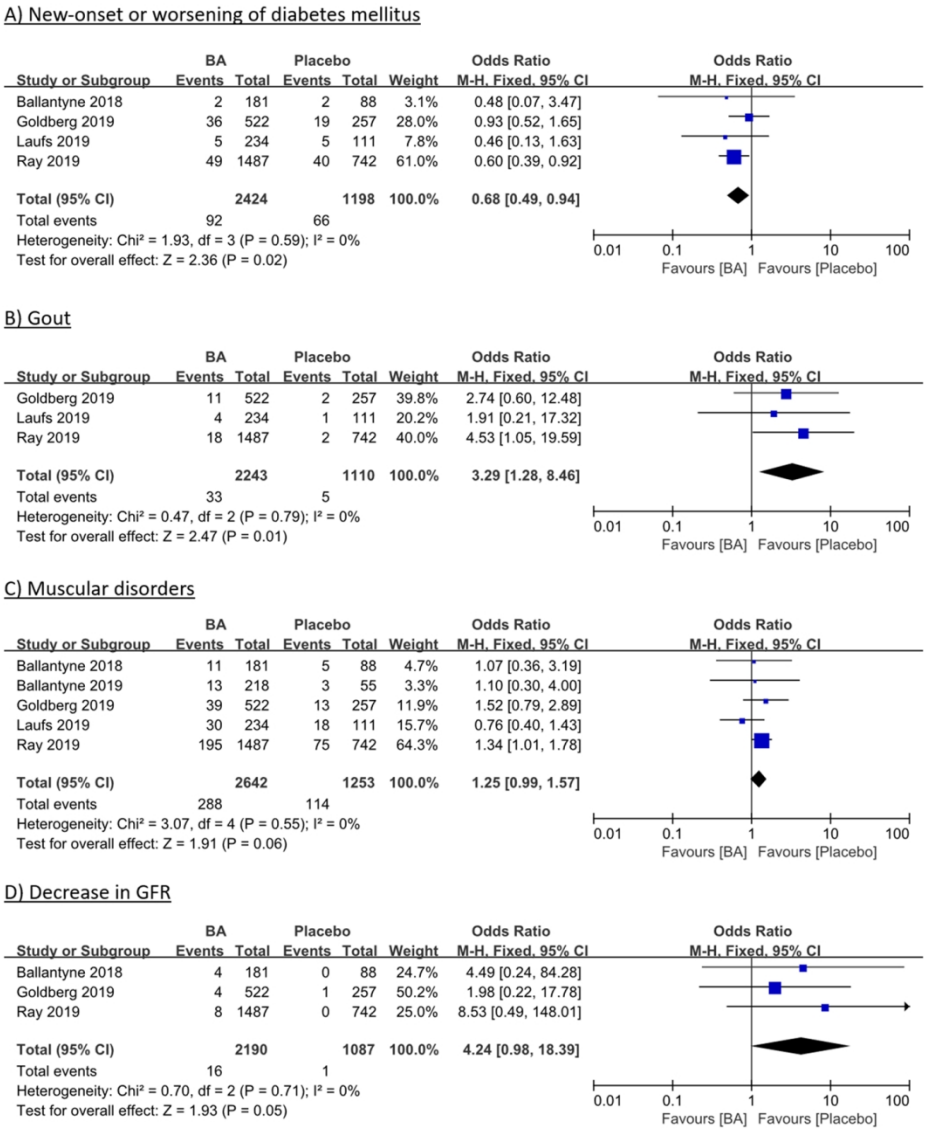

Figure 2: Individual and summary odds ratios with 95% confidence intervals for safety outcomes of new-onset or worsening of diabetes mellitus (A), gout (B), muscular disorders C), and decrease in GFR (D) for bempedoic vs. placebo therapy. Fixed effects model, Cochran-Mantel-Haenszel estimates; I² measures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

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Figure 3 – Meta-analysis of BA efficacy on serum lipid levels

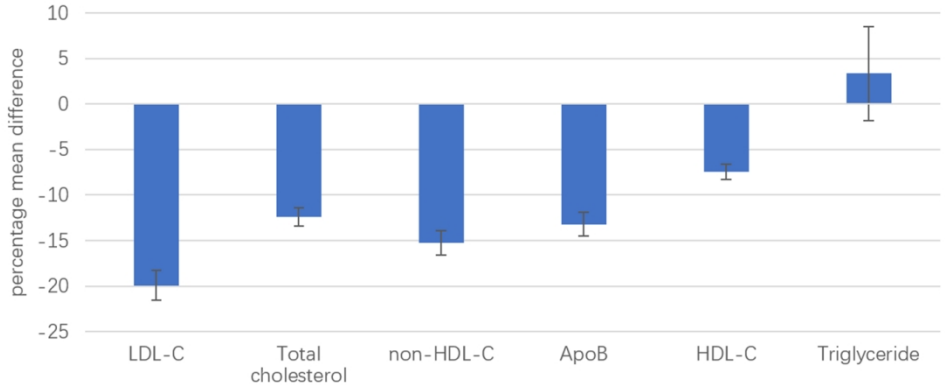


Figure 3: Summary mean differences with 95% confidence intervals for BA efficacy on serum lipid levels compared to placebo, for LDL-C, total cholesterol, non-HDL-C, apoB, HDL-C, and triglycerides. Fixed effects model, Cochran-Mantel-Haenszel estimates. apoB=apolipoprotein B; BA=bempedoic acid; HDL=high-density-lipoprotein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

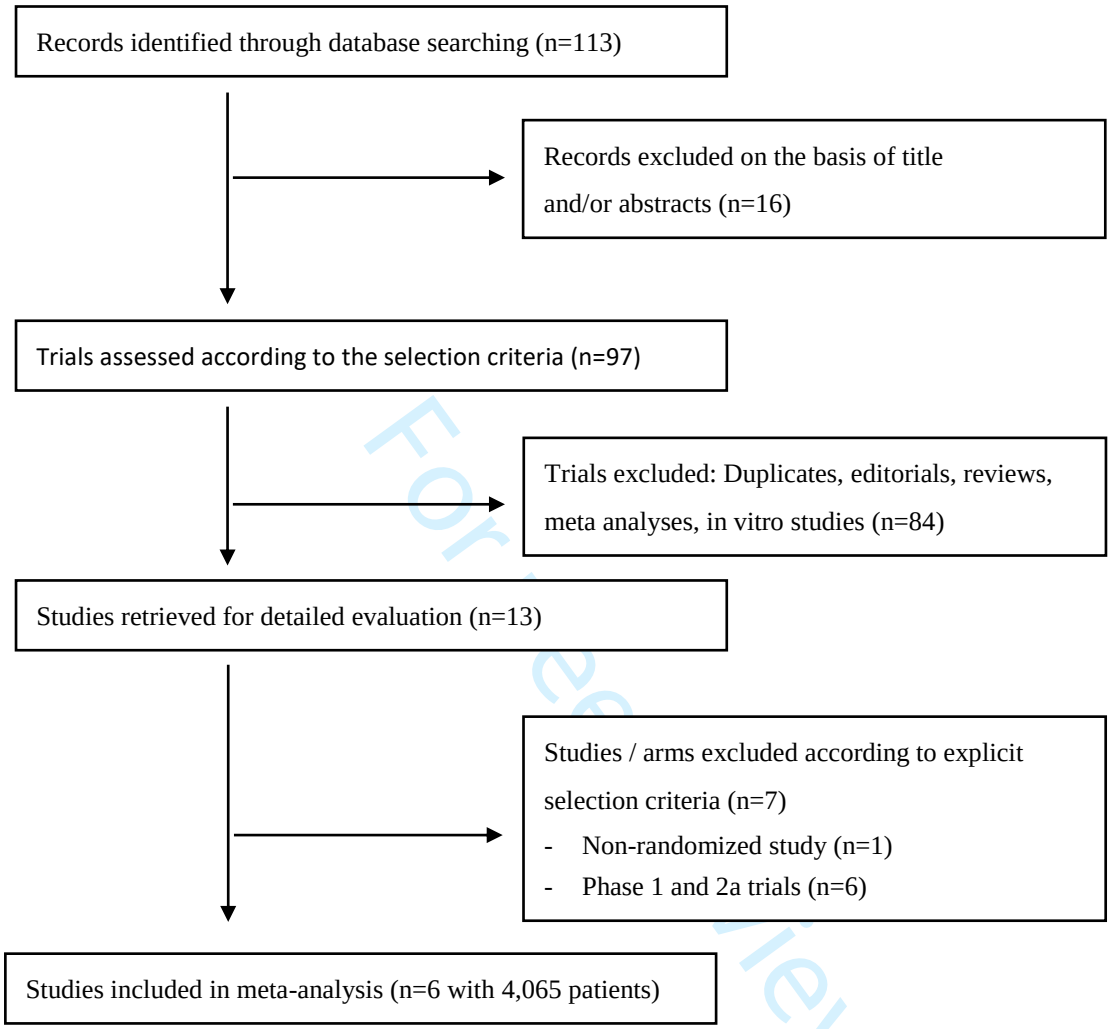
127x60mm (300 x 300 DPI)

Supplementary data

Supplementary Table 1 – Risk of bias in included trials

Supplementary Table 1: Risk of bias assessment of all included trials, according to the Cochrane collaboration guidelines (11).

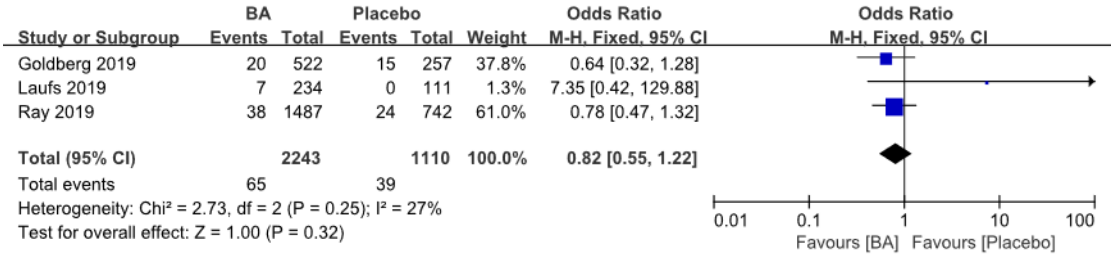
Supplementary Figure 1 – Summary PRISMA flow-chart of the systematic review process



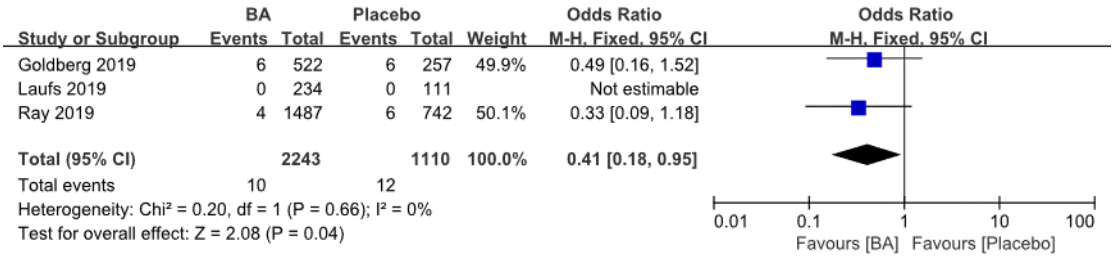
Supplementary Figure 1: PRISMA flow chart summarizing the systematic review process: A total of 113 records identified through database searching were evaluated and reduced to six studies included in quantitative synthesis. RCT=randomized, controlled trial.

Supplementary Figure 2 – Additional efficacy outcomes of BA vs. placebo therapy

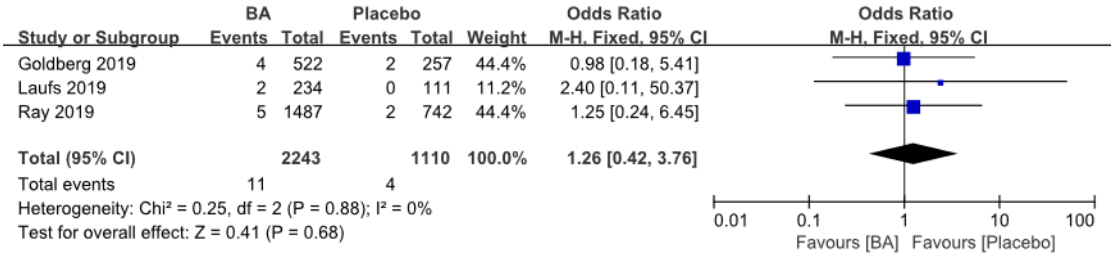
A) Coronary revascularization



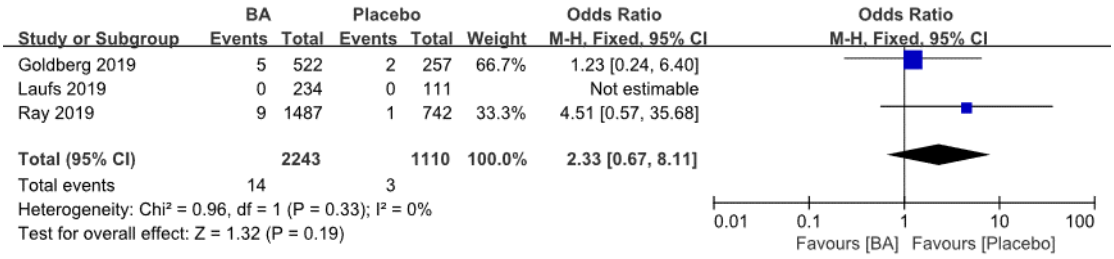
B) Non-coronary revascularization



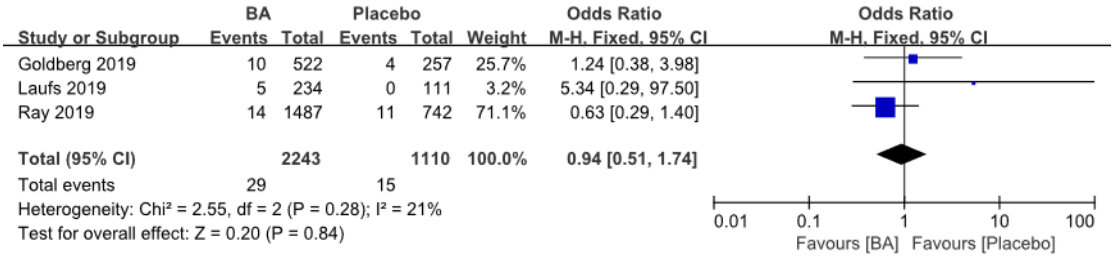
C) Nonfatal stroke



D) Hospitalization for heart failure



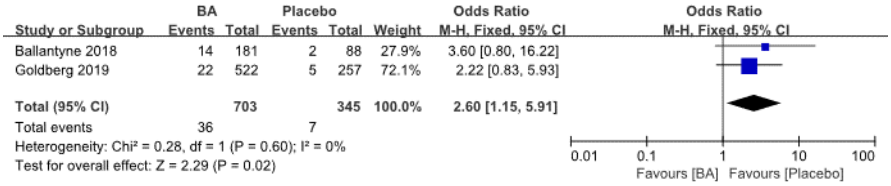
E) Hospitalization for unstable angina



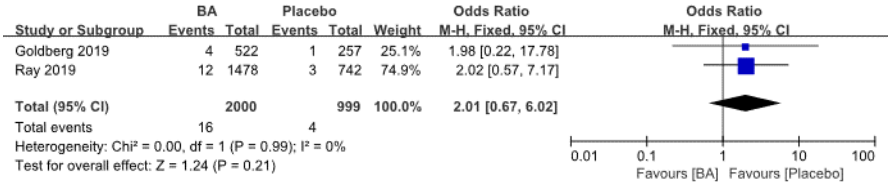
Supplementary Figure 2: Individual and summary odds ratios of additional efficacy outcomes of coronary (A) and non-coronary (B) revascularization, nonfatal stroke (C), hospitalization for heart failure (D), and unstable angina (E) for bempedoic acid vs. placebo therapy. Fixed effects model, Cochran-Mantel-Haenszel-estimates; Tau² and I² are measures of heterogeneity. BA=bempedoic acid; M-H=Mantel-Haenszel.

Supplementary Figure 3 – Additional safety outcomes of BA vs. placebo therapy

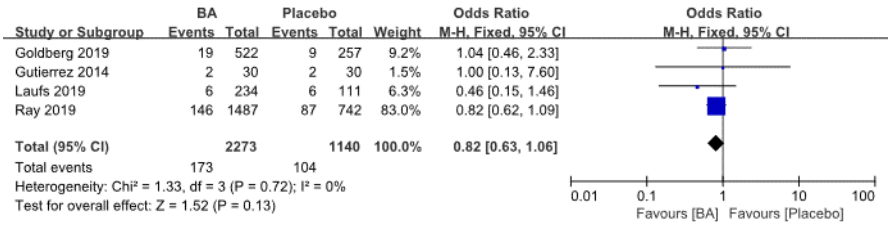
A) Elevation in uric acid



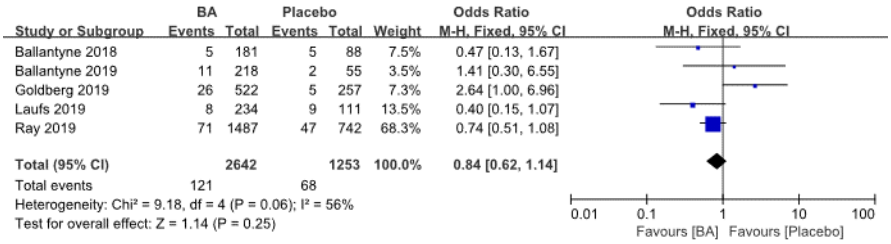
B) Increase in serum creatinine



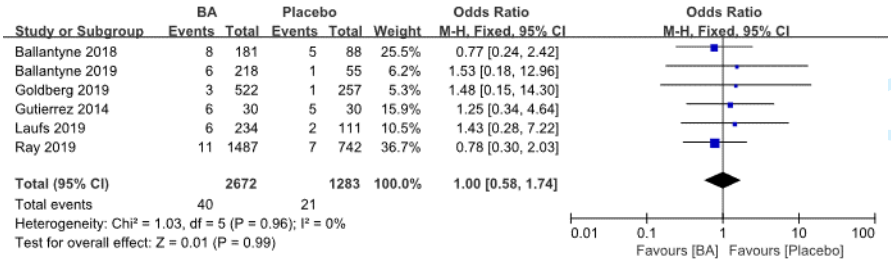
C) Upper respiratory tract infection



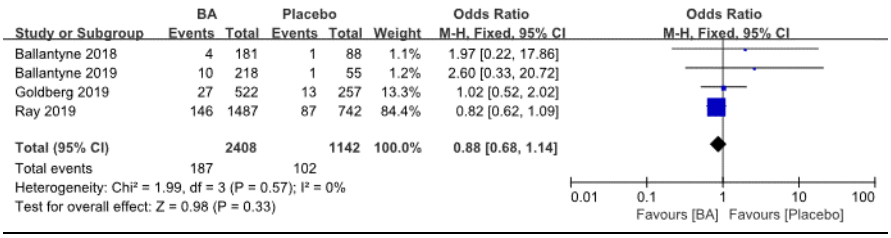
D) Urinary tract infection



E) Neurocognitive disorder



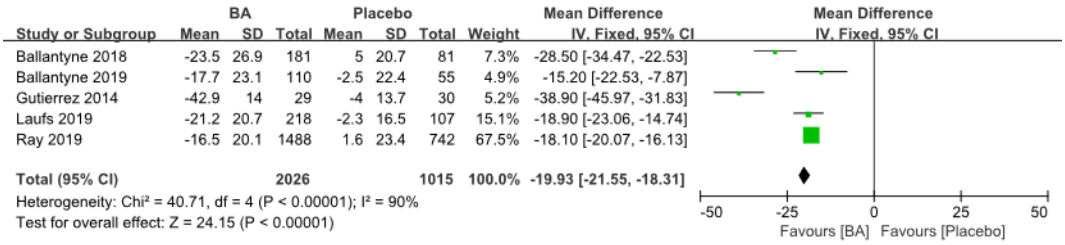
F) Nasopharyngitis



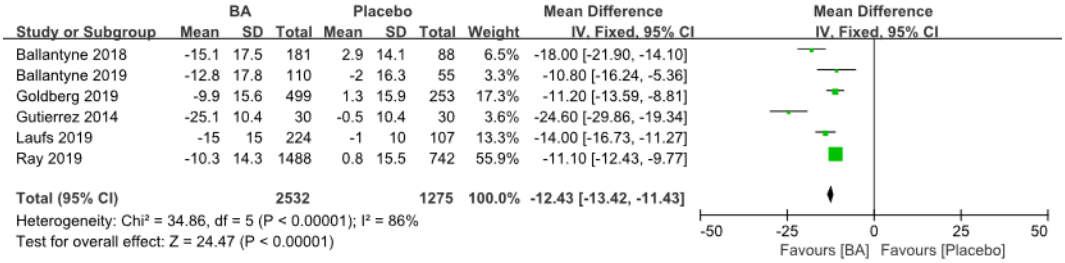
Supplementary Figure 3: Individual and summary odds ratios of additional safety outcomes of elevation in uric acid (A), increase in serum creatinine (B), upper respiratory tract infection (C), urinary tract infection (D), neurocognitive disorder (E), and nasopharyngitis (F) for BA vs. placebo therapy. Fixed effects model, Cochran-Mantel-Haenszel estimates; Tau² and I² are measures of heterogeneity. BA=bempedoic acid; M-H=Mantel-Haenszel.

Supplementary Figure 4 – Serum lipid levels of BA vs. placebo therapy

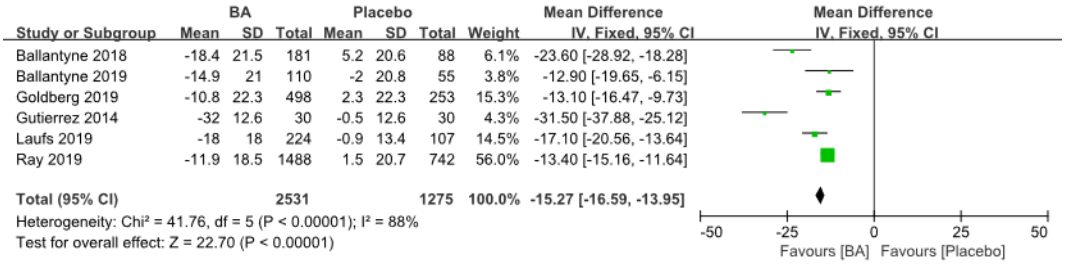
A) LDL-C



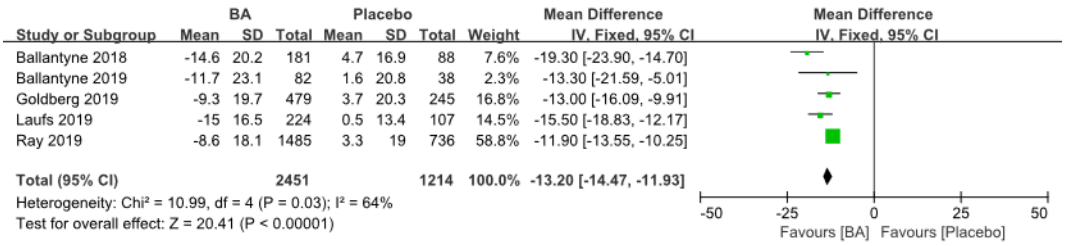
B) Total cholesterol



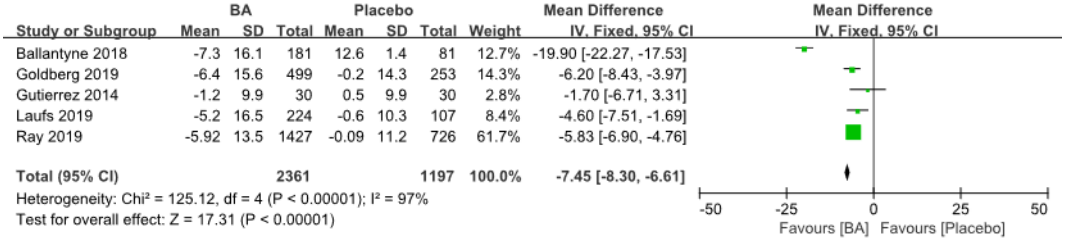
C) Non-HDL-C



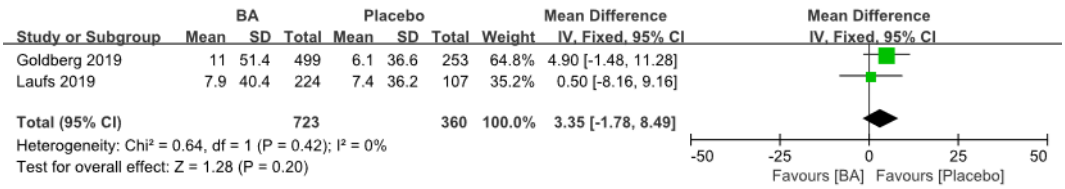
D) Apolipoprotein B



E) HDL-C



F) Trigylcerides



Supplementary Figure 4: Indivual and summary mean differences with 95% confidence intervals (corresponding to Figure 3) of serum lipid levels for bempedoic acid vs. placebo therapy: LDL-C (A), total cholesterol (B), Non-HDL-C (C), Apolipoprotein B (D), HDL-C (E), and triglycerides (F). Fixed effects model, Cochran-Mantel-Haenszel estimates; Tau² and I² are measures of heterogeneity. BA=bempedoic acid; HDL-C=high-density-lipoprotein cholesterol; LDL-C=low-density-lipoprotein cholesterol; M-H=Mantel-Haenszel; non-HDL-C=non-high density lipoprotein cholesterol.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3/4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	3/4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	4/5

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Supl.
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	5-9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	10
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Fig. 1/2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Fig. 1/2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Fig. 3
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11/12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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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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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

Short title: meta-analysis of bempedoic acid for LDL-C lowering therapy in CVD

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ABSTRACT

Objectives: Bempedoic acid (BA) is a novel oral low-density lipoprotein cholestrol 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: Randomized controlled trials (RCTs) of BA vs. 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 nonfatal 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 3,956 patients and follow-ups of four to 52 weeks were identified. Heterogeneity mainly derived from differing follow-up duration and baseline cardiovascular risk. No difference in MACE (odds ratio (OR) 0.84; 95% confidence interval (CI) 0.61, 1.15), all-cause mortality (OR 2.37; CI 0.80, 6.99), and CV mortality (OR 1.66; CI 0.45, 6.04) for BA vs. placebo was observed. BA showed beneficial trends for nonfatal MI (OR 0.57; CI 0.32, 1.00) and was associated with a lower risk of new-onset or worsening of DM (OR 0.68; CI 0.49, 0.94), but higher risk of gout (OR 3.29; CI 1.28, 8.46), and a trend for muscular disorders (OR 2.60; CI 1.15, 5.91) and worsening of renal function (OR 4.24; CI 0.98, 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.

Strengths and limitations of this study

- Randomized 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 nonfatal myocardial infarction were analyzed.
- 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.

INTRODUCTION

Hypercholesterolemia is one of the major risk factors of cardiovascular disease, which is the leading cause of death worldwide.[1] The 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 ≥50% in patients at high cardiovascular risk, using maximally tolerated statin therapy and – if LDL-C levels remain ≥70 mg/dL – additional non-statin drugs, e.g. ezetimibe (class I).[2] The European society of cardiology 2019 guideline even emphasizes 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 cardiovascular risk (class I) under intensified lipid-lowering therapy.[3] Additional proprotein convertase subtilisin/kexin type 9 (PSCK-9)-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 randomized controlled trials (RCTs),[6-11] however individual trial sample sizes were too small to judge cardiovascular efficacy outcomes.

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

Methods

This systematic review and the accompagnied 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 November 1st 2021. The following keywords were used during searches (in combinations, among others): *bempedoic acid, BA, ETC-1002, randomized 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 categorized further; if content was considered relevant, they were retrieved as full text reports for detailed evaluation. All controlled trials randomizing BA to placebo and reporting cardiovascular outcomes, which were available in English language and in full text, were eligible for inclusion. Non-randomized 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 analyzed as reported. Primary efficacy outcomes of interest were major adverse cardiovascular events (MACE), all-cause mortality, cardiovascular (CV) mortality, and nonfatal myocardial infarction (MI); additional efficacy outcomes of coronary and non-coronary revascularization, nonfatal stroke, hospitalization for heart failure, and hospitalization for unstable angina were also analyzed. 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 analyzed 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 appraised [13] and the grading of recommendation, assessment, development and evaluation (GRADE) working group certainty rating [14] of primary outcomes was performed by two unblinded investigators, who cross-checked each other for errors.

Statistical analyses

RevMan 5.3 (Cochrane Collaboration) was used for statistical computations. Odds ratios (OR) and 95% confidence intervals (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 I^2 statistic was used to quantify heterogeneity.[16-18] A Fixed-effects models were used throughout the study due to low I², a confirmatory analysis using random-effects models [19] was additionally performed.

To analyze BA effects on serum lipid levels, data were extracted using mean differences (MD) and standard deviations (SD). SD data in three trials [6, 7, 9] were extracted from published figures using WebPlotDigitizer 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 mean differences 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 envolvement

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

Ethics statement

An ethics approval is not required for this review and meta-analysis not directly involving humans or animals. Manuscripts of all included individual trials provide an ethics approval statement.

RESULTS

Study selection and patient population

The PRISMA flow chart of the systematic review process is depicted in Supplementary 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-randomized 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 Table 1 and Table 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 overweight (average BMI of 29-31), suffered from a considerable cardiovascular 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]

Table 1 – Study characteristics

Publication, year (acronym)	Design	Population	Groups	Sample size (n)	FU (wks)	Endpoints
Ballantyne et al.[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 et al.[7], 2019	RCT (double-blind, phase 3)	ASCVD and/or HeFH with LDL-C >100mg/dL, or multiple CVD risk factors with LDL-C >130mg/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 et al.[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 et al.[11], 2014	RCT (double-blind, phase 2b)	Type 2 diabetes and LDL-C ≥100 mg/dL with a body mass index 25 - 35 kg/m² 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 et al.[9], 2019 (CLEAR Serenity)	RCT (double-blind, phase 3)	Statin intolerance with ASCVD and/or HeFH with LDL-C >100mg/dL, or other patients with LDL-C >130mg/dL requiring	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,

		further LDL-C lowering on no more than low-dose statin therapy or other lipid-lowering drugs				HDL-C, and TG; 12-wk and 24-wk absolute change of LDL-C
Ray et al.[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

Table 1: Study characteristics of all included trials, regarding study design, study population, characterization of groups, sample size, follow-up duration, and study endpoints. AE=adverse events; apoB=apolipoprotein B; ASCVD=atherosclerotic cardiovascular disease; BA=bempedoic acid; CVD= cardiovascular disease; d=day; FU=follow-up; HeFH=heterozygous familial hypercholesterolemia; HDL-C=high-density lipoprotein cholesterol; hs-CRP=high-sensitivity c-reactive-protein; LDL-C=low-density-lipoprotein cholesterol; non-HDL-C=non-high density lipoprotein cholesterol; RCT=randomized controlled trial; TC=total cholesterol; TG=triglycerides; wk=week. * not included in the meta analysis.

Table 2 – Patients characteristics

Publication, year (acronym)	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 et al.[6], 2018 (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	25.0	19.3	58.0	30.5	80.7	208.6	123.0	57.1	151.6	153.0	115.8	2.26
Ballantyne et al.[7], 2019	BA+EZE	62.2	51.2	61.6 †	40.7	86.0	31.1	65.1	237.4	153.9	49.1	188.3	156.8	121.1	3.1
	BA	65.0	54.5	62.5 †	51.1	87.5	30.6	69.3	225.5	145.0	49.9	175.6	140.8	113.4	2.9
	EZE*	65.1	50.0	62.8 †	50.0	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	181.0	139.1	115.1	3.0
Goldberg et al.[8], 2019 (CLEAR Wisdom)	BA	64.1	37.2	27.1	29.7	83.9	30.0	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	143.0	118.6	1.88
Gutierrez et al.[11], 2014	BA	55.3	43.3	-	100	26.7	30.6	-	206.3	125.2	43.7	-	181.5	-	2.3
	Placebo	56.0	33.3	-	100	26.7	29.2	-	206.7	128.4	47.4	-	152.0	-	2.2
Laufs et al.[9], 2019 (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	141.0	2.92
	Placebo	65.1	55.0	25.3	23.4	67.6	30.6	85.6	241.1	155.6	50.4	190.7	164.0	141.9	2.78
Ray et al.[10], 2019 (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	98.0	28.6	80.1	-	-	178.6	102.3	49.3	129.4	123	86.8	1.51

Table 2: Patient characteristics of all included trials. BA=Bempedoic acid; EZE=ezetimibe; ASCVD=atherosclerotic cardiovascular disease; DM=diabetes mellitus; AHT=arterial hypertension; BMI=body mass index; CKD=chronic kidney disease (estimated glomerular filtration rate<90ml/min); TC=total cholesterol; LDL-C=low-

density lipoprotein cholesterol; apoB=apolipoprotein B; HDL-C=high-density lipoprotein cholesterol; hsCRP=high-sensitivity C-reactive protein; non-HDL-C=non-high density lipoprotein cholesterol. Lipids are presented as means, hs-CRP as medians; † ASCVD and/or heterozygous familial Hypercholesterolemia. * not included in the meta analysis.

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 concealment,[11] and blinding of outcomes assessor remained unclear.[11] Risk of bias assessment of included studies according to Cochrane Collaboration guidelines [13] is reported in Supplementary Table 1. Certainty rating of consistency of estimated and true effects of primary outcomes according to GRADE working group [14] revealed low certainty for MACE and all-cause mortality; certainty for CV mortality and nonfatal MI was rated moderate. GRADE rating is reported in Supplementary Table 2.

Bempedoic acid efficacy for cardiovascular outcomes

Four RCTs with 3,413 patients reported data on MACE (Figure 1A),[8-11] with no significant difference with BA compared to 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; I^2=11%). Five RCTs with 3,895 patients were included in the analysis of all-cause mortality and three RCTs with 3,353 patients in the analysis of CV mortality (Figure 1B and 1C), 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; I^2=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; I^2 = 0%). Data from four RCTs with 3,413 subjects were analyzed on nonfatal MI (Figure 1D),[8-11] with a borderline-significant trend towards benefits of BA compared to 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; I^2=0%).

Meta-analysis of additional efficacy outcomes in 3 RCTs with 3353 patients are reported in Supplementary Figure 2:[8-10] There were no significant differences in coronary revascularization (OR 0.82; 95% CI 0.55 to 1.22; p=0.32; Supplementary Figure 2A). For non-coronary revascularization, there was a significant benefit observed in BA vs. placebo, albeit 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; I^2=0%; Supplementary Figure 2B).

There were no significant differences in nonfatal stroke (OR 1.26, 95% CI 0.42 to 3.76; p=0.68; Supplementary Figure 2C), hospitalization for heart failure (OR 2.33; 95% CI 0.67 to 8.11; p=0.19; Supplementary Figure 2D) or hospitalization for unstable angina (OR 0.94; 95% CI 0.51 to 1.74; p=0.84; Supplementary Figure 2E).

Bempedoic acid safety outcomes

Meta-analysis of four RCTs comprising 3,622 patients showed significantly lower rates of new-onset or worsening of DM for BA vs. placebo (3.8% (BA) vs. 5.5% (placebo);[6, 8-10] 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; Supplementary 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 nummerically 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; Supplementary Figure 3B).

Additional safety outcomes of upper respiratory tract infection (OR 0.82; 95% CI 0.63 to 1.06; p = 0.13; Supplementary Figure 3C), urinary tract infection (OR 0.84, 95% CI 0.62 to 1.14; p=0.25; Supplementary Figure 3D), neurocongnitive disorders (OR 1.00, 95% CI 0.58 to 1.74; p=0.99; Supplementary Figure 3E), and nasopharyngitis (OR 0.88; 95% CI 0.68 to 1.14; p=0.33; Supplementary Figure 3F) showed no significant differences between BA and placebo treatment.

Bempedoic acid efficacy for serum lipid levels

Meta-analysis of effects of BA vs. placebo on serum lipid levels is summarized in Figure 3, forest plots showing individual and summary mean differences (MD) between groups are presented in Supplementary Figure 4. Overall, a MD in LDL-C levels of -19.93 % from baseline was observed with the use of BA compared to placebo (95% CI -21.55 to -18.31; p<0.01; Supplementary Figure 4A). Treatment with BA also significantly reduced total cholesterol (MD -12.43%; 95% CI -13.42 to -11.43, p<0.01; Supplementary Figure 4B), non-high density lipoprotein cholesterol (non-HDL-C) (MD -15.27%; 95% CI -16.59 to -13.95, p<0.01; Supplementary Figure 4C), and apolipoprotein B (apoB) (MD -13.20%; 95% CI -14.47 to -11.93, p<0.01; Supplementary Figure 4D) compared to placebo. A slight reduction in high-densitiy lipoprotein cholesterol levels was seen under BA compared to placebo (MD -7.5%, 95% CI -8.30 to -6.61, p<0.01; Supplementary Figure 4E); BA treatment did not influence triglyceride levels (MD 3.35%, 95% CI -1.78 to 8.49, p=0.20; Supplementary 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 randomized controlled trial evidence on efficacy and safety of BA vs. 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 myocardial infarction; 2) significant benefits regarding new-onset or worsening of diabetes mellitus, albeit detrimental effects on gout and possibly on renal function and muscular disorders; 3) significant decreases of atherogenic serum lipid fractions e.g. LDL-C, TC, non-HDL and apoB.

Lowering serum LDL-C to guideline-recommended treatment goals is a cornerstone of cardiovascular 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 cardiovascular 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 to placebo led to highly significant reductions in major atherogenic lipid fractions of LDL-C, Non-HDL 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, 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 cardiovascular outcomes. In addition, combined outcome of MACE associated with higher event rates and than singular outcomes increasing likelihood of detecting benefical 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 cardiovascular 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 cardiovascular 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 outcomes [34] – especially at higher baseline LDL-C levels [35] – 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 cardiovascular 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 heterogenious baseline risk and limited transferability of results to other populations. As meta-analysis showed a trend towards reduction of nonfatal MI with BA (OR 0.57; p=0.05) and significantly lower rates of new-onset or worsening of diabetes mellitus with BA (OR 0.68; p=0.02), which is an independent cardiovascular risk factor, there are indications that BA possibly holds the potential to improve clinical outcomes in selected patients at high cardiovascular risk. A recently published meta-analysis of BAs efficacy for prevention of cardiovascular 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 cardiovascular risk, might counteract BA's LDL-C lowering potential for cardiovascular outcomes.

Further investigation of the risk/benefit ratio of BA in patients at high cardiovascular risk is needed to clarifiy the potential role of BA in primary and secondary prevention. Results of the ongoing large scale CLEAR-Outcomes RCT including approximately 14.000 patients (NCT02993406) including high cardiovascular 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 cardiovascular 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 analyzing 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 co-medication (no statin vs. maximal tolerated statin, additional ezetimibe) and selection of patients regarding baseline cardiovascular risk and potential benefical effects of lipid-lowering (patients with established ASCVD vs. patient at high cardiovascular risk). Generally, pooled sample size is still limited compared to 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 cardiovascular risk as given by current ESC 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 musclular 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 analyzing relevant clinical outcomes.

CONCLUSION

Meta-analysis of bempedoic acid vs. placebo in patients at high cardiovascular risk showed no significant effects on major cardiovascular 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.

Contributorship statement

YL, MB, and GW conceived and designed the study; YL, CP, and AK collected sources, selected studies and abstracted data; YL, AK, and TK performed doublechecks; YL and GW performed the statistical analysis; all authors

analyzed and interpreted the data; YL and MB drafted the first manuscript version; NC, AI, MK, MB, CP, VS, and GW thoroughly revised it; all authors read, critically revised and accepted the submitted version of the manuscript.

Competing interests

MB reported personal fees for speaking at an expert meeting in lipidology sponsored by Daiichi-Sankyo after primary submission of the current work. The other authors declare no conflicts of interest.

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Data sharing statement

All data relevant to the study are included in the article or uploaded as supplementary information.

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Figure legends

Figure 1: Individual and summary odds ratios with 95% confidence intervals for efficacy outcomes of MACE (A), all-cause mortality (B), cardiovascular mortality (C), and nonfatal myocardial infarction (D) for bempedoic acid vs. placebo therapy. Fixed effects model, Cochran-Mantel-Haenszel estimates; I^2 measures heterogeneity; BA=bempedoic acid; M-H=Mantel-Haenszel.

Figure 2: Individual and summary odds ratios with 95% confidence intervals 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; I^2 measures heterogeneity. BA=bempedoic acid; GFR=glomerular filtration rate; M-H=Mantel-Haenszel.

Figure 3: Summary mean differences with 95% confidence intervals for BA efficacy on serum lipid levels compared to 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=high-density-lipoprotein cholesterol; LDL-C=low-density-lipoprotein cholesterol.

Figure 1 – Efficacy outcomes of BA vs. placebo therapy

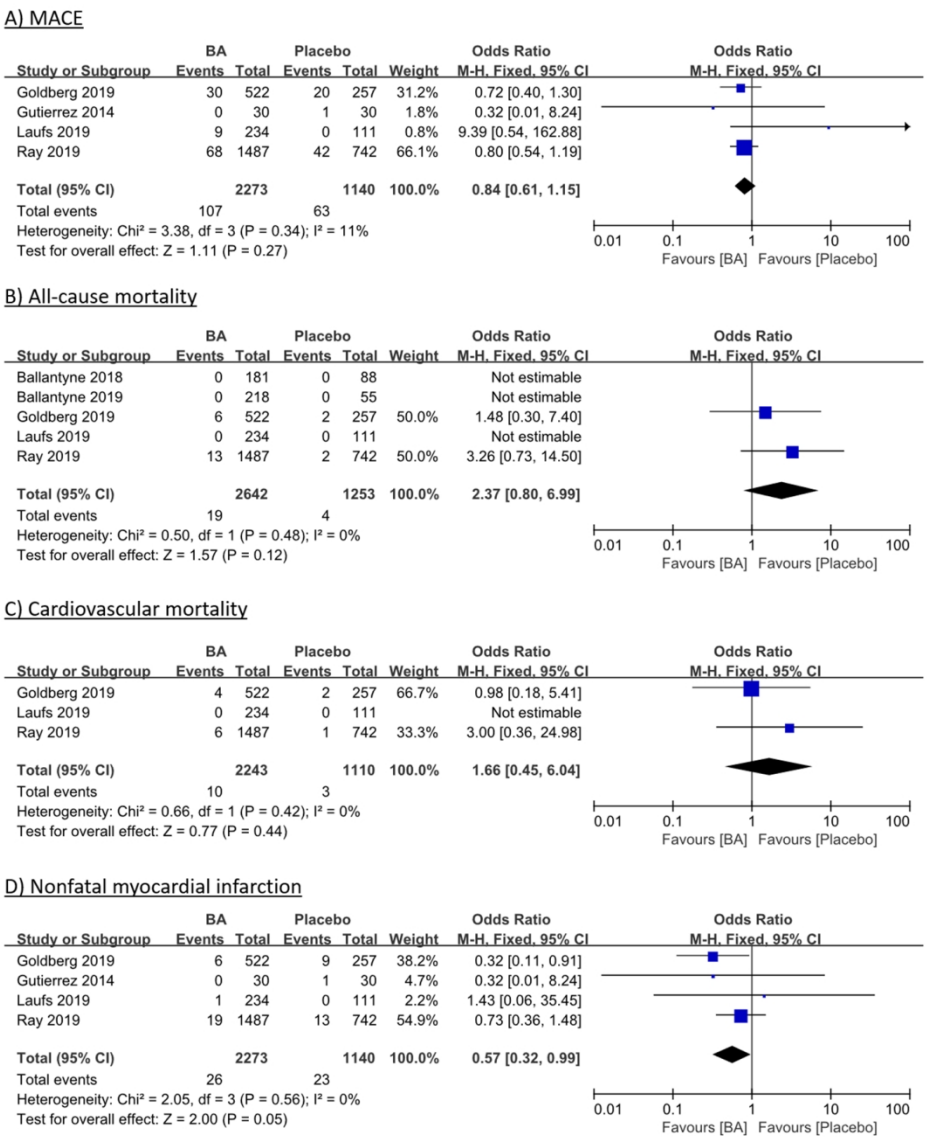

Figure 1: Individual and summary odds ratios with 95% confidence intervals for efficacy outcomes of MACE (A), all-cause mortality (B), cardiovascular mortality (C), and nonfatal myocardial infarction (D) for bempedoic acid vs. placebo therapy. Fixed effects model, Cochran-Mantel-Haenszel estimates; I² measures heterogeneity; BA=bempedoic acid; M-H=Mantel-Haenszel.

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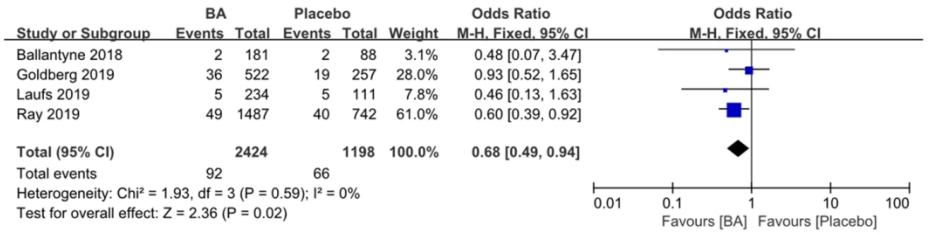
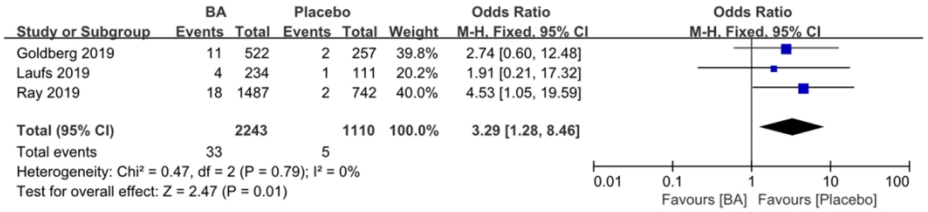
Figure 2 – Safety outcomes of BA vs. placebo therapy

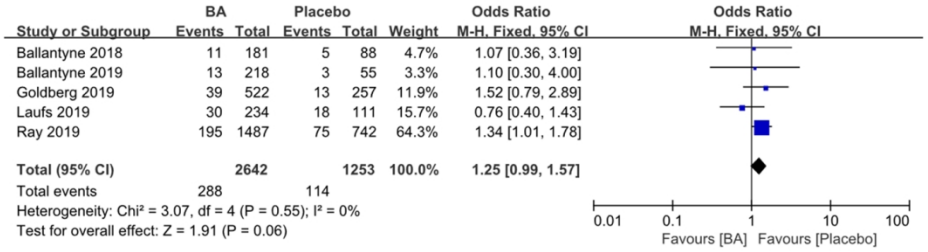
A) New-onset or worsening of diabetes mellitus



B) Gout



C) Muscular disorders



D) Decrease in GFR

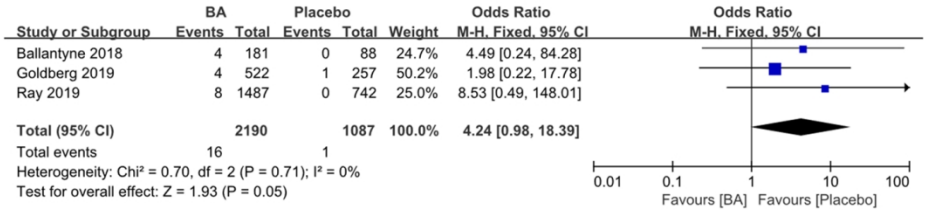


Figure 2: Individual and summary odds ratios with 95% confidence intervals for safety outcomes of new-onset or worsening of diabetes mellitus (A), gout (B), muscular disorders C), and decrease in GFR (D) for bempedoic vs. placebo therapy. Fixed effects model, Cochran-Mantel-Haenszel estimates; I² measures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

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Figure 3 – Meta-analysis of BA efficacy on serum lipid levels

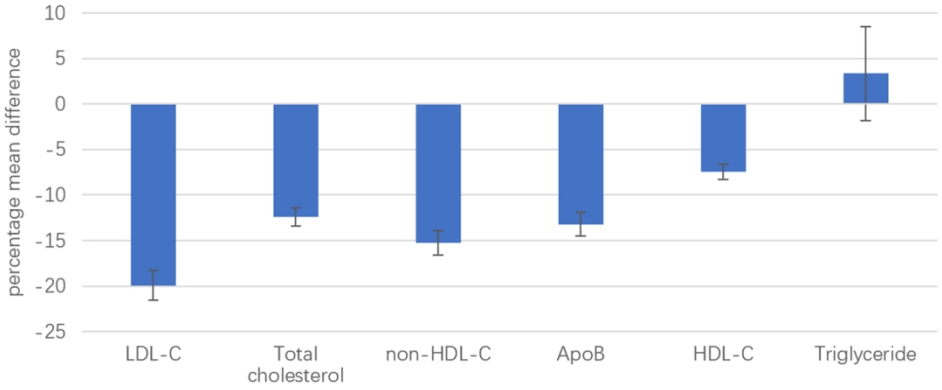

Figure 3: Summary mean differences with 95% confidence intervals for BA efficacy on serum lipid levels compared to placebo, for LDL-C, total cholesterol, non-HDL-C, apoB, HDL-C, and triglycerides. Fixed effects model, Cochran-Mantel-Haenszel estimates. apoB=apolipoprotein B; BA=bempedoic acid; HDL=high-density-lipoprotein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

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Supplementary data

Supplementary Table 1 – Risk of bias in included trials

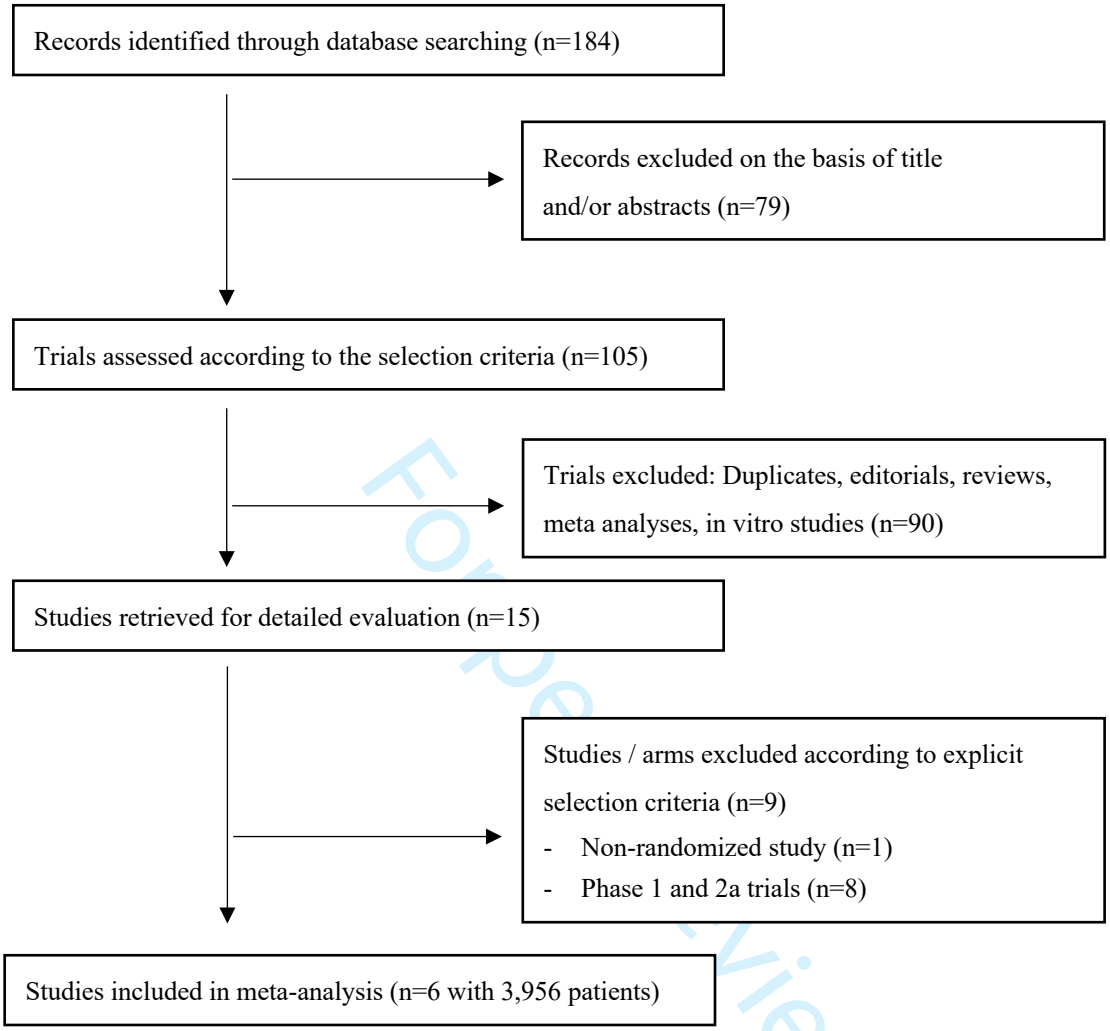
Supplementary Table 1: Risk of bias assessment of all included trials, according to the Cochrane collaboration guidelines.

Supplementary Table 2 – GRADE assessment of primary outcomes

Outcome (No. of studies)	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Summary of findings		
							No. of subjects BA/placebo	Pooled OR (95% CI)	Certainty rating
MACE (4)	RCT	Not serious	Serious[a]	Not serious	Serious[c]	Undetected	2273/1140	0.84 (0.61-1.15)	⊕⊕○○ Low
All-cause mortality (5)	RCT	Not serious	Not serious	Serious[b]	Serious[d]	Undetected	2642/1253	2.37 (0.80-6.99)	⊕⊕○○ Low
Cardiovascular mortality (3)	RCT	Not serious	Not serious	Not serious	Serious[e]	Undetected	2243/1110	1.66 (0.45-6.04)	⊕⊕⊕○ Moderate
Nonfatal myocardial infarction (4)	RCT	Not serious	Not serious	Not serious	Serious[f]	Undetected	2273/1140	0.57 (0.32-0.99)	⊕⊕⊕○ Moderate

Supplementary Table 2: The grading of recommendation, assessment, development and evaluation (GRADE) working group assessment of primary outcomes. Ratings: Very low=the true effect is likely to be substantially different from the estimated effect; Low=the true effect may be substantially different from the estimated effect; Moderate=the true effect is likely to be close to the estimated effect; High=very confident that the true effect is close to the estimated effect. [a] Inconsistency of direction of effect; [b] Outcome time frame insufficient; [c] Small number of included studies/pooled estimate not consistent with benefit and harm; [d] Rare event/pooled estimate not consistent with benefit and harm; [e] Rare event/small number of included studies/pooled estimate not consistent with benefit and harm; [f] Small number of included studies. BA=bempedoic acid, CI=confidence interval; MACE=major adverse cardiovascular events; RCT=randomized controlled tiral.

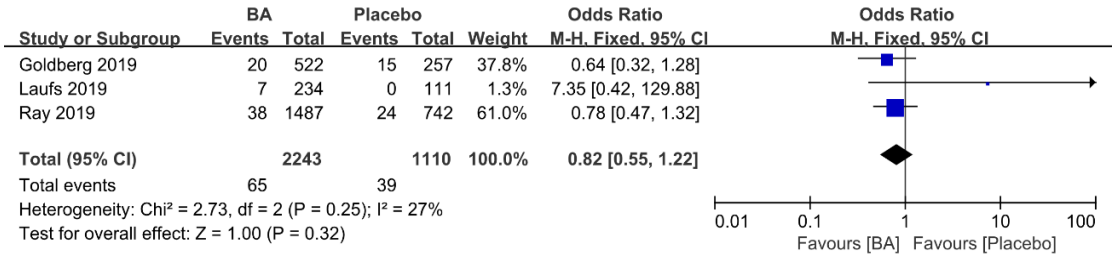
Supplementary Figure 1 – Summary PRISMA flow-chart of the systematic review process



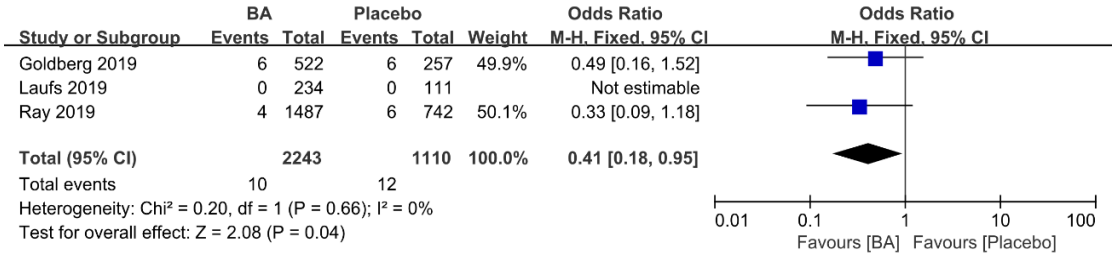
Supplementary Figure 1: PRISMA flow chart summarizing the systematic review process: A total of 184 records identified through database searching were evaluated and reduced to six studies included in quantitative synthesis. RCT=randomized controlled trial.

Supplementary Figure 2 – Additional efficacy outcomes of BA vs. placebo therapy

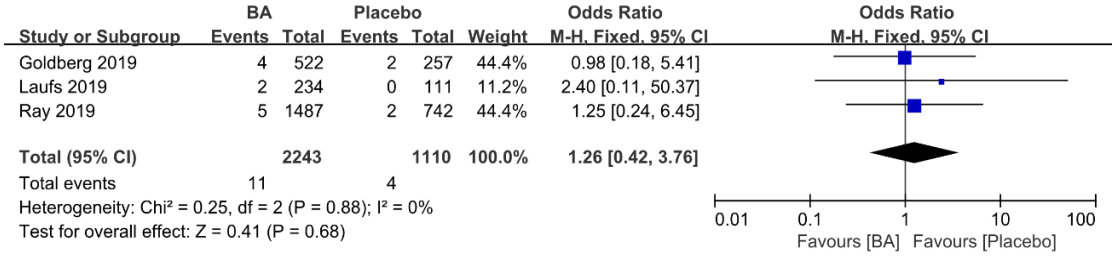
A) Coronary revascularization



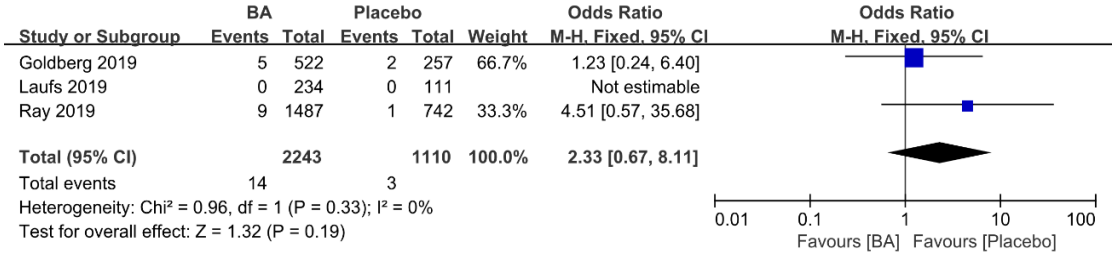
B) Non-coronary revascularization



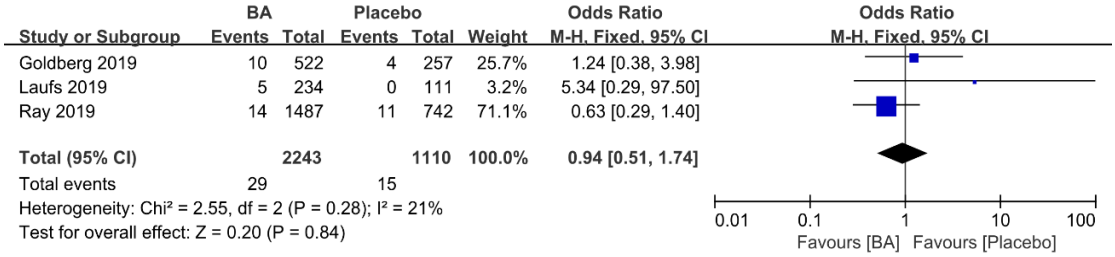
C) Nonfatal stroke



D) Hospitalization for heart failure



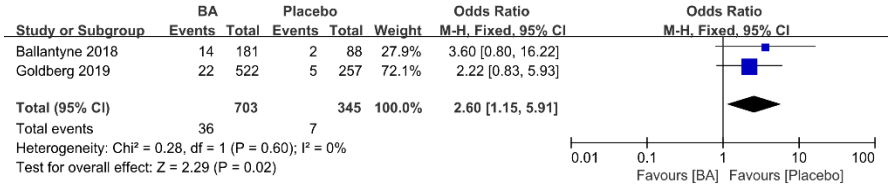
E) Hospitalization for unstable angina



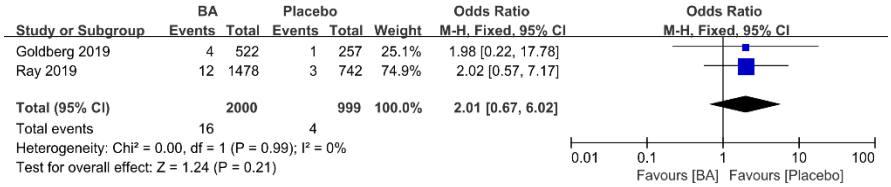
Supplementary Figure 2: Individual and summary odds ratios of additional efficacy outcomes of coronary (A) and non-coronary (B) revascularization, nonfatal stroke (C), hospitalization for heart failure (D) or unstable angina (E) for bempedoic acid vs. placebo therapy. Fixed effects model, Cochran-Mantel-Haenszel-estimates; Tau² and I² are measures of heterogeneity. BA=bempedoic acid; M-H=Mantel-Haenszel.

Supplementary Figure 3 – Additional safety outcomes of BA vs. placebo therapy

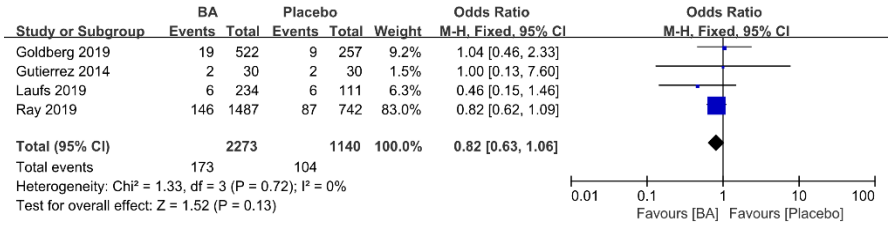
A) Elevation in uric acid



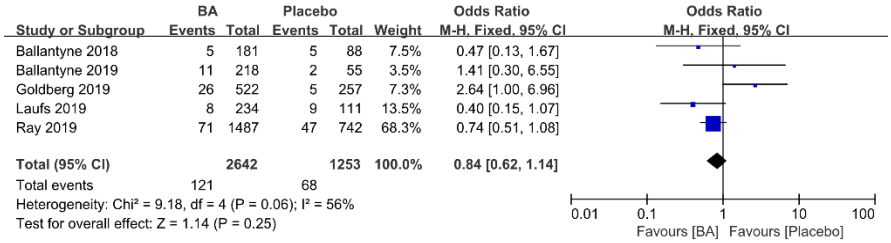
B) Increase in serum creatinine



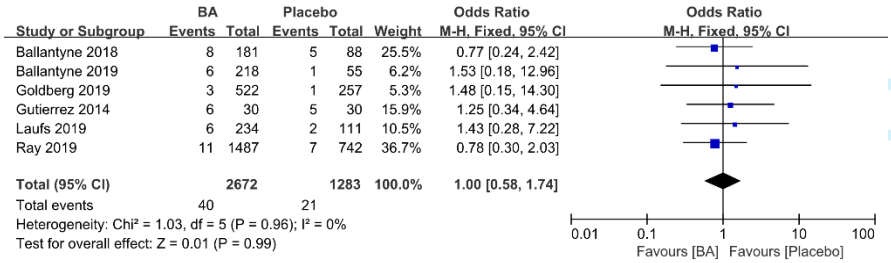
C) Upper respiratory tract infection



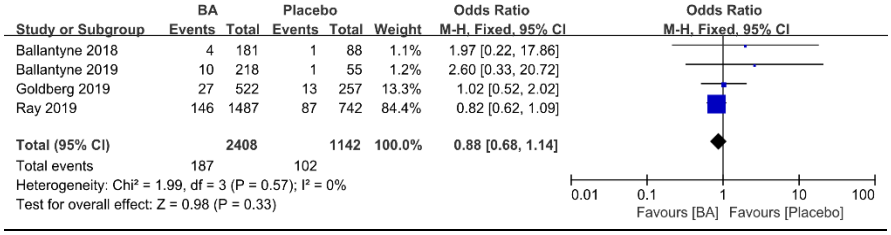
D) Urinary tract infection



E) Neurocognitive disorder



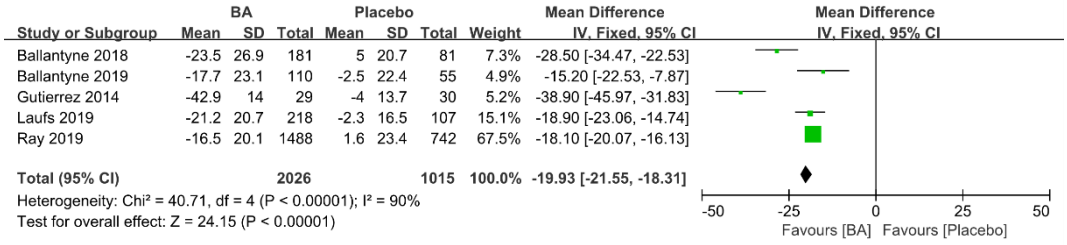
F) Nasopharyngitis



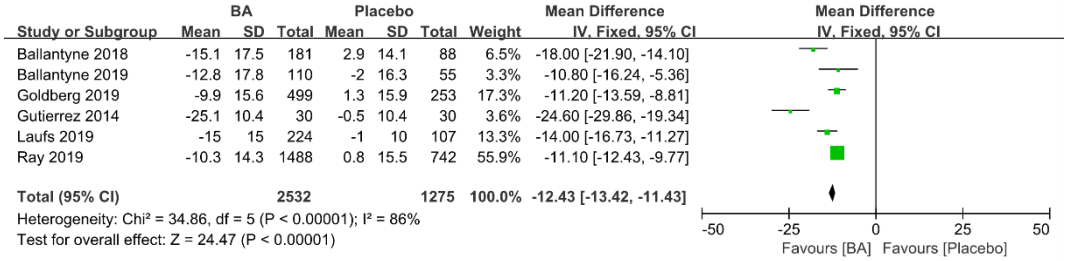
Supplementary Figure 3: Individual and summary odds ratios of additional safety outcomes of elevation in uric acid (A), upper respiratory tract infection (B), urinary tract infection (C), neurocognitive disorder (D), nasopharyngitis (E) and increase in serum creatinine (F) for BA vs. placebo therapy. Fixed effects model, Cochran-Mantel-Haenszel estimates; Tau² and I² are measures of heterogeneity. BA=bempedoic acid; M-H=Mantel-Haenszel.

Supplementary Figure 4 – Serum lipid levels of BA vs. placebo therapy

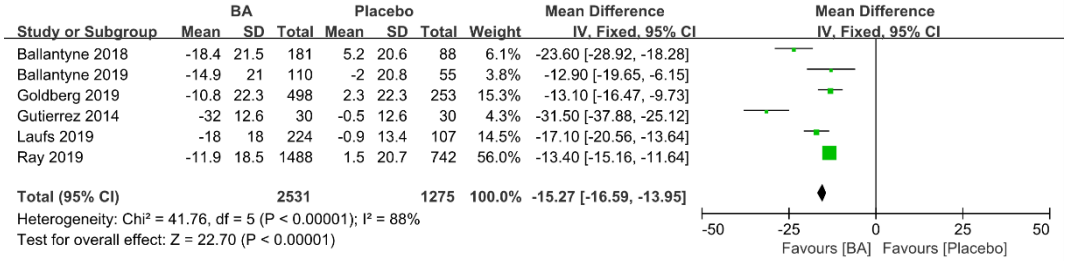
A) LDL-C



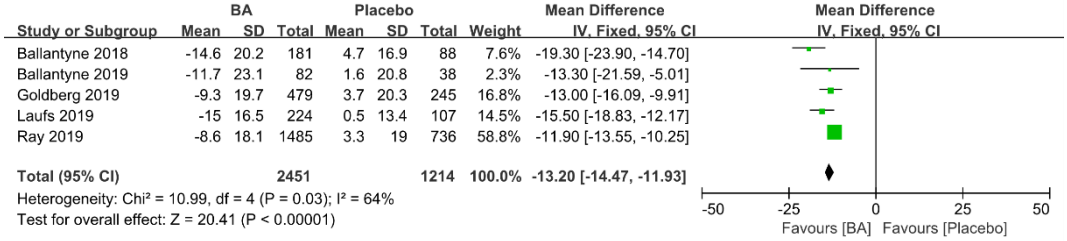
B) Total cholesterol



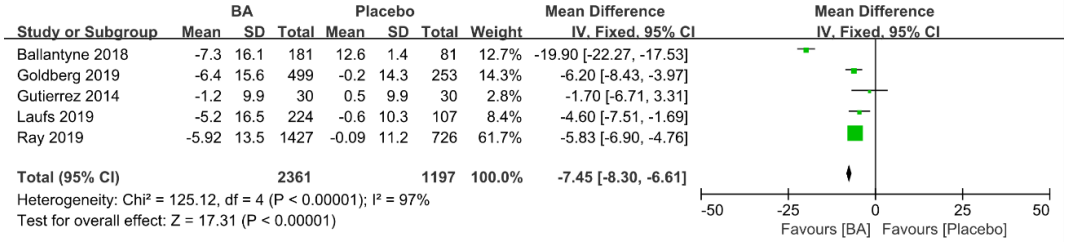
C) Non-HDL-C



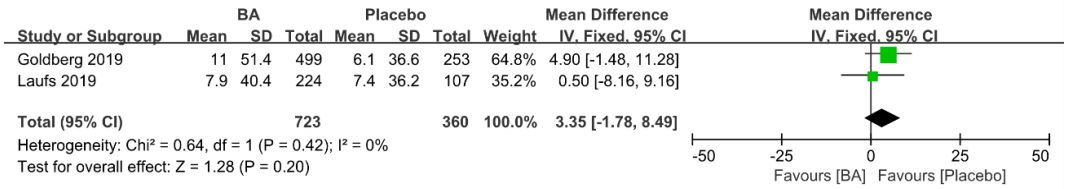
D) Apolipoprotein B



E) HDL-C



F) Trigylcerides



Supplementary Figure 4: Indivual and summary mean differences with 95% confidence intervals (corresponding to Figure 3) of serum lipid levels for bempedoic acid vs. placebo therapy: LDL-C (A), total cholesterol (B), Non-HDL-C (C), Apolipoprotein B (D), HDL-C (E) and triglycerides (F). Fixed effects model, Cochran-Mantel-Haenszel estimates; Tau² and I² are measures of heterogeneity. BA=bempedoic acid; HDL-C=high-density-lipoprotein cholesterol; LDL-C=low-density-lipoprotein cholesterol; M-H=Mantel-Haenszel; non-HDL-C=non-high density lipoprotein cholesterol.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3/4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	3/4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	4/5

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Supl.
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	5-9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	10
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Fig. 1/2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Fig. 1/2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Fig. 3
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11/12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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