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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		
	butcomes of dempedoic acid for LDL-C lowering th	erapy in patients at high
cardiovascular risk: a system	atic review and meta-analysis	
Short title: meta-analysis of ber	npedoic 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 bia
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### 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  $\geq$ 50% in patients at high cardiovascular risk, using maximally tolerated statin therapy and – if LDL-C levels remain  $\geq$ 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  $\leq$  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 6<sup>th</sup> 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 intentionto-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 fixedeffects model [13]. The summary *I*<sup>2</sup> statistic was used to quantify heterogeneity [14-16]. A Fixed-effects models were used throughout the study due to low I<sup>2</sup>, a confirmatory analysis using random-effects models [17] was additionally

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 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	Design	Den eletion	Groups	Sample size	FU	
(acronym)	Design	ropulation	Groups	(n)	(wks)	Енарония
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 <u>vs.</u> 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 <u>vs.</u> BA 180 mg/d <u>vs.</u> ezetimibe 10 mg/d* <u>vs.</u> 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 <u>vs.</u> placebo	779 (522 BA, 257 placebo)	52	Primary: 12-wk change (%) of LDL-C <u>Secondary</u> : 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 <u>Tertiary</u> : 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 $\geq 100 \text{ mg/dL}$ with a body mass index 25 - 35 kg/m <sup>2</sup> without lipid-lowering drugs	BA 80 mg/d for 2 wks followed by 120 mg/d for 2 <u>vs.</u> placebo	60 (30 BA; 30 placebo)	4	<u>Primary</u> : 4-wk change (%) of LDL-C <u>Secondary</u> : 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 <u>vs.</u> 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 <u>vs.</u> placebo	2230 (1488 BA, 742 placebo)	52	<u>Primary</u> : Number of participants with treatment related AEs <u>Secondary</u> : 12-wk, 24-wk, and 52-wk change (%) of LDL-C, non- HDL-C, TC, apoB, and hs-CRP

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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-densitylipoprotein 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.

ca. .nigh-density lp. .poprotein cholesterol; RCT=r.

### Table 2 – Patients characteristics

Publication, year	Arms	Age	Female	ASCVD	DM	AHT	BMI	CKD	TC	LDL-C	HDL-C	Non-HDL-	TG	apoB	hs-CRP
(acronym)		(y)	(%)	(%)	(%)	(%)	(kg/m <sup>2</sup> )	(%)	(mg/dL)	(mg/dL)	(mg/dL)	C (mg/dL)	(mg/dL)	(mg/dL)	(mg/L)
Ballantyne et al.[5],	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
2018	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
(CLEAR															
Tranquility)															
Ballantyne et al.[6],	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
2019	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],	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
2019	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
(CLEAR Wisdom)															
Gutierrez et al.[10],	BA	55.3	43.3	-	100	26.7	30.6		206.3	125.2	43.7	-	181.5	-	2.3
2014	Placebo	56.0	33.3	-	100	26.7	29.2		206.7	128.4	47.4	-	152.0	-	2.2
Laufs et al.[8],	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
2019	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
(CLEAR Serenity)															
Ray et al.[9],	BA	65.8	26.1	97.4	28.6	78.9	-	-	179.7	103.6	48.7	130.9	126	88.5	1.49
2019	Placebo	66.8	28.7	98.0	28.6	80.1	-	-	178.6	102.3	49.3	129.4	123	86.8	1.51
(CLEAR Harmony)															

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; hsCRP=high-sensitivity C-reactive protein; non-HDL-C=non-high

Page 11 of 28

BMJ Open

density lipoprotein cholesterol	l. Lipids are presented as means, hs-CRP as medians; † ASCVD and/or heterozygous familial Hypercholesterolemia. * not included in the me
analysis.	
	10
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### 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<sup>2</sup>=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<sup>2</sup>=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<sup>2</sup> = 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<sup>2</sup>=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<sup>2</sup>=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,

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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 -17.78 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 clarify the

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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

<u>Figure 1:</u> 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<sup>2</sup> measures heterogeneity; BA=bempedoic acid; M-H=Mantel-Haenszel.

<u>Figure 2:</u> 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<sup>2</sup> measures heterogeneity. BA=bempedoic acid; GFR=glomerular filtration rate; M-H=Mantel-Haenszel.

<u>Figure 3</u>: 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.

Review only

### Figure 1 – Efficacy outcomes of BA vs. placebo therapy

#### A) MACE

	BA	Placebo		Odds Ratio	Odds Ratio
Study or Subgroup	Events Tota	Events Total	Weight	M-H, Fixed, 95% C	I M-H, Fixed, 95% CI
Goldberg 2019	30 522	20 257	31.2%	0.72 [0.40, 1.30]	
Gutierrez 2014	0 30	1 30	1.8%	0.32 [0.01, 8.24]	
Laufs 2019	9 234	0 111	0.8%	9.39 [0.54, 162.88]	<b>,</b>
Ray 2019	68 1487	42 742	66.1%	0.80 [0.54, 1.19]	
Total (95% CI)	2273	1140	100.0%	0.84 [0.61, 1.15]	•
Total events	107	63			
Heterogeneity: Chi <sup>2</sup> = 3	8.38, df = 3 (P =	0.34); l <sup>2</sup> = 11%			
Test for overall effect:	Z = 1.11 (P = 0.	27)			Favours [BA] Favours [Placebo]

B) All-cause mortality

	BA		Place	bo		Odds Ratio		Odds	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C		M-H, Fixe	ed, 95% CI		
Ballantyne 2018	0	181	0	88		Not estimable					
Ballantyne 2019	0	218	0	55		Not estimable					
Goldberg 2019	6	522	2	257	50.0%	1.48 [0.30, 7.40]					
Laufs 2019	0	234	0	111		Not estimable					
Ray 2019	13	1487	2	742	50.0%	3.26 [0.73, 14.50]		-		_	
Total (95% CI)		2642		1253	100.0%	2.37 [0.80, 6.99]		-			
Total events	19		4								
Heterogeneity: Chi <sup>2</sup> = 0	0.50, df =	1 (P = 0	0.48); l² =	0%				01		+	100
Test for overall effect: 2	Z = 1.57 (	P = 0.1	2)				0.01	Favours [BA]	Favours [F	Placebo	]

#### C) Cardiovascular mortality

	BA		Place	bo		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Goldberg 2019	4	522	2	257	66.7%	0.98 [0.18, 5.41]	
Laufs 2019	0	234	0	111		Not estimable	
Ray 2019	6	1487	1	742	33.3%	3.00 [0.36, 24.98]	
Total (95% CI)		2243		1110	100.0%	1.66 [0.45, 6.04]	-
Total events	10		3				
Heterogeneity: Chi <sup>2</sup> =	0.66, df =	1 (P = (	0.42); l <sup>2</sup> =	0%		H	
Test for overall effect:	Z = 0.77 (	P = 0.4	4)			L. L.	Favours [BA] Favours [Placebo]

#### D) Nonfatal myocardial infarction

	BA		Placel	00		Odds Ratio		Odds Ratio		
Study or Subgroup	Events T	otal	Events	Total	Weight	M-H, Fixed, 95% C		M-H, Fixed, 95% C		
Goldberg 2019	6	522	9	257	38.2%	0.32 [0.11, 0.91]				
Gutierrez 2014	0	30	1	30	4.7%	0.32 [0.01, 8.24]			-	
Laufs 2019	1	234	0	111	2.2%	1.43 [0.06, 35.45]				
Ray 2019	19 1	1487	13	742	54.9%	0.73 [0.36, 1.48]				
Total (95% CI)	2	273		1140	100.0%	0.57 [0.32, 0.99]		•		
Total events	26		23							
Heterogeneity: Chi <sup>2</sup> =	2.05, df = 3 (	(P = 0)	.56); I <sup>2</sup> =	0%					10	400
Test for overall effect:	Z = 2.00 (P =	= 0.05	5)				0.01	Favours [BA] Favours [	Placebo]	100

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<sup>2</sup> 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

	BA		Place	bo		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I M-H, Fixed, 95% CI
Ballantyne 2018	2	181	2	88	3.1%	0.48 [0.07, 3.47]	
Goldberg 2019	36	522	19	257	28.0%	0.93 [0.52, 1.65]	
Laufs 2019	5	234	5	111	7.8%	0.46 [0.13, 1.63]	
Ray 2019	49	1487	40	742	61.0%	0.60 [0.39, 0.92]	-=-
Total (95% CI)		2424		1198	100.0%	0.68 [0.49, 0.94]	•
Total events	92		66				
Heterogeneity: Chi <sup>2</sup> = <sup>2</sup>	1.93, df =	3 (P = 0	0.59); l <sup>2</sup> =	0%			
Test for overall effect:	Z = 2.36 (	P = 0.0	2)				Favours [BA] Favours [Placebo]

#### <u>B) Gout</u>

	BA	Placebo		Odds Ratio	Odds Ratio
Study or Subgroup	Events Tota	I Events Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
Goldberg 2019	11 52	2 2 257	39.8%	2.74 [0.60, 12.48]	
Laufs 2019	4 23	4 1 111	20.2%	1.91 [0.21, 17.32]	
Ray 2019	18 148	7 2 742	40.0%	4.53 [1.05, 19.59]	
Total (95% CI)	2243	3 1110	100.0%	3.29 [1.28, 8.46]	-
Total events	33	5			
Heterogeneity: Chi <sup>2</sup> = (	).47, df = 2 (P =	= 0.79); I <sup>2</sup> = 0%			
Test for overall effect:	Z = 2.47 (P = 0	.01)			Favours [BA] Favours [Placebo]

#### C) Muscular disorders

	BA	Placebo		Odds Ratio	Odds Ratio
Study or Subgroup	Events Tota	I Events Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
Ballantyne 2018	11 18	1 5 88	4.7%	1.07 [0.36, 3.19]	
Ballantyne 2019	13 21	8 3 55	3.3%	1.10 [0.30, 4.00]	
Goldberg 2019	39 52	2 13 257	11.9%	1.52 [0.79, 2.89]	+
Laufs 2019	30 23	4 18 111	15.7%	0.76 [0.40, 1.43]	
Ray 2019	195 148	7 75 742	64.3%	1.34 [1.01, 1.78]	=
Total (95% CI)	264	2 1253	100.0%	1.25 [0.99, 1.57]	◆
Total events	288	114			
Heterogeneity: Chi <sup>2</sup> = 3	8.07, df = 4 (P =	= 0.55); l <sup>2</sup> = 0%			
Test for overall effect: 2	Z = 1.91 (P = 0	.06)			Favours [BA] Favours [Placebo]

#### D) Decrease in GFR

	BA	A Placebo			Odds Ratio	Ode		
Study or Subgroup	Events To	tal Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fi	xed, 95% Cl	
Ballantyne 2018	4 1	81 0	88	24.7%	4.49 [0.24, 84.28]			
Goldberg 2019	4 5	22 1	257	50.2%	1.98 [0.22, 17.78]			
Ray 2019	8 14	87 0	742	25.0%	8.53 [0.49, 148.01]	-		$\rightarrow$
Total (95% CI)	21	90	1087	100.0%	4.24 [0.98, 18.39]			
Total events	16	1						
Heterogeneity: Chi <sup>2</sup> = 0	.70, df = 2 (F	<sup>2</sup> = 0.71); l <sup>2</sup> =	0%				1 10	100
Test for overall effect: 2	Z = 1.93 (P =	0.05)				Favours [B/	A] Favours [Placebo	]

Figure 2: Individual and summary odds ratios with 95% confidence intervals for safety outcomes of newonset 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<sup>2</sup> measures heterogeneity. BA=bempedoic acid; GFR=glomerular filtration rate; M-H=Mantel-Haenszel.

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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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### <u>Supplementary data</u>

### Supplementary Table 1 – Risk of bias in included trials Blinding of participants/ personnel Blinding of outcome assessor Random sequence generation Incomplete outcome data Allocation concealment Selective Reporting Ballantyne et al. 2018 + + + + + (CLEAR Tranquility) ? + + + + + Ballantyne et al. 2019 Goldberg et al. 2019 (CLEAR Wisdom) + Gutierrez et al. 2014 ? ? ? + + Laufs et al. 2019 + + (CLEAR Serenity) Ray et al. 2019 + + + + + + (CLEAR Harmony) + ? low risk of bias unclear risk of bias high risk of bias

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



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

### A) Coronary revascularization

	BA		Placeb	00		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I	M-H, Fixed, 95% CI
Goldberg 2019	20	522	15	257	37.8%	0.64 [0.32, 1.28]		
Laufs 2019	7	234	0	111	1.3%	7.35 [0.42, 129.88]		
Ray 2019	38	1487	24	742	61.0%	0.78 [0.47, 1.32]		
Total (95% CI)		2243		1110	100.0%	0.82 [0.55, 1.22]		-
Total events	65		39					
Heterogeneity: Chi <sup>2</sup> = 2	2.73, df = 2	2 (P = (	).25); l <sup>2</sup> =	27%			0.01	0.1 1 10 100
l est for overall effect:	Z = 1.00 (I	P = 0.3	2)					Favours [BA] Favours [Placebo]
B) Non-coronary	revascu	lariza	tion					
	BA		Placeb	00		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	1	M-H, Fixed, 95% Cl
Goldberg 2019	6	522	6	257	49.9%	0.49 [0.16, 1.52]		
Laufs 2019	0	234	0	111		Not estimable		_
Ray 2019	4	1487	6	742	50.1%	0.33 [0.09, 1.18]		
Total (95% CI)		2243		1110	100.0%	0.41 [0.18, 0.95]		
Total events	10		12				L	
Heterogeneity: Chi <sup>2</sup> = (	0.20, df =	1 (P = (	).66); l <sup>2</sup> =	0%			0.01	0.1 1 10 10
Test for overall effect:	Z = 2.08 (I	P = 0.0	4)					Favours [BA] Favours [Placebo]
C) Norfatal start								
<u>U) Nonfatal stroke</u>	<u>e</u>							
	BA		Placeb	00		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C		M-H, Fixed, 95% Cl
		500	2	257	44 4%	0.98 [0.18, 5,41]		
Goldberg 2019	4	SZZ	_	201	11.170			
Goldberg 2019 Laufs 2019	4	522 234	0	111	11.2%	2.40 [0.11, 50.37]		
Goldberg 2019 Laufs 2019 Ray 2019	4 2 5	234 1487	0	111 742	11.2% 44.4%	2.40 [0.11, 50.37] 1.25 [0.24, 6.45]		
Goldberg 2019 Laufs 2019 Ray 2019	4 2 5	234 1487	0	111 742	11.2% 44.4%	2.40 [0.11, 50.37] 1.25 [0.24, 6.45]		
Goldberg 2019 Laufs 2019 Ray 2019 Total (95% Cl)	4 2 5	234 1487 2243	0	111 742 1110	11.2% 44.4%	2.40 [0.11, 50.37] 1.25 [0.24, 6.45] <b>1.26 [0.42, 3.76]</b>		
Goldberg 2019 Laufs 2019 Ray 2019 Total (95% CI) Total events	4 2 5 11	234 1487 2243	0 2 4	111 742 1110	11.2% 44.4% 100.0%	2.40 [0.11, 50.37] 1.25 [0.24, 6.45] 1.26 [0.42, 3.76]		
Goldberg 2019 Laufs 2019 Ray 2019 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = (	4 2 5 11 0.25, df = 2	234 1487 2243 2 (P = (	0 2 4 0.88); I <sup>2</sup> =	111 742 1110 0%	11.2% 44.4%	2.40 [0.11, 50.37] 1.25 [0.24, 6.45] 1.26 [0.42, 3.76]	0.01	
Goldberg 2019 Laufs 2019 Ray 2019 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 0 Test for overall effect:	4 2 5 0.25, df = 2 Z = 0.41 (f	234 1487 <b>2243</b> 2 (P = 0 P = 0.6	0 2 4 0.88); I <sup>2</sup> = 8)	111 742 1110 0%	11.2% 44.4% 100.0%	2.40 [0.11, 50.37] 1.25 [0.24, 6.45] 1.26 [0.42, 3.76]	L 0.01	0.1 1 10 10 Favours [BA] Favours [Placebo]
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Goldberg 2019 Laufs 2019 Ray 2019 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = ( Test for overall effect: D) Hospitalization	4 2 5 0.25, df = 2 Z = 0.41 (f	2243 2243 2243 2 (P = 0 P = 0.6	0 2 (0.88);   <sup>2</sup> = 8)	111 742 1110 0%	11.2% 44.4% 100.0%	2.40 [0.11, 50.37] 1.25 [0.24, 6.45] <b>1.26 [0.42, 3.76]</b>	0.01	0.1 1 10 100 Favours [BA] Favours [Placebo]
Goldberg 2019 Laufs 2019 Ray 2019 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = ( Test for overall effect: D) Hospitalization	4 2 5 0.25, df = $2$ Z = 0.41 (f	224 1487 2243 2 (P = 0 P = 0.6 art fai	0 2 0.88); I <sup>2</sup> = 8) <u>(lure</u>	111 742 1110 0%	11.2% 44.4%	2.40 [0.11, 50.37] 1.25 [0.24, 6.45] <b>1.26 [0.42, 3.76]</b>	0.01	0.1 1 10 100 Favours [BA] Favours [Placebo]
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Goldberg 2019 Laufs 2019 Ray 2019 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = ( Test for overall effect: D) Hospitalization	4 2 5 11 0.25, df = <i>i</i> Z = 0.41 (i <u>n for hea</u> <u>BA</u> <u>Events</u>	224 234 1487 2243 2 (P = ( P = 0.6 art fai	$\frac{1}{2}$ $\frac{4}{2}$ $\frac{3}{2}$ $\frac{1}{2}$ $\frac{1}$	111 742 1110 0%	11.2% 44.4% 100.0%	2.40 [0.11, 50.37] 1.25 [0.24, 6.45] 1.26 [0.42, 3.76] 0dds Ratio <u>M-H, Fixed, 95% C</u>	0.01	Odds Ratio M-H, Fixed, 95% Cl
Goldberg 2019 Laufs 2019 Ray 2019 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = ( Test for overall effect: D) Hospitalization Goldberg 2019	$4 \\ 2 \\ 5 \\ 11 \\ 0.25, df = 2 \\ Z = 0.41 (i \\ h for hea \\ BA \\ Events \\ 5 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0$	522 234 1487 <b>2243</b> 2 (P = 0 P = 0.6 art fai	2 4 0.88); I <sup>2</sup> = 8) <u>Ilure</u> Placeb <u>Events</u> 2 0	111 742 1110 0% 0%	11.2% 44.4% 100.0% <u>Weight</u> 66.7%	2.40 [0.11, 50.37] 1.25 [0.24, 6.45] 1.26 [0.42, 3.76] 0dds Ratio <u>M-H, Fixed, 95% C</u> 1.23 [0.24, 6.40] Not estimable	0.01	0.1 1 10 10 Favours [BA] Favours [Placebo] Odds Ratio M-H, Fixed, 95% Cl
Goldberg 2019 Laufs 2019 Ray 2019 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = ( Test for overall effect: D) Hospitalization Goldberg 2019 Laufs 2019 Ray 2019	$4 \\ 2 \\ 5 \\ 11 \\ 0.25, df = 2 \\ Z = 0.41 (f \\ 1 \\ for hea \\ Events \\ 5 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0$	522 234 1487 <b>2243</b> 2 (P = 0 P = 0.6 art fai 522 234 1487	4 0.88); I <sup>2</sup> = 8) <u>Ilure</u> Placek <u>Events</u> 2 0	111 742 1110 0% 0% <u>Total</u> 257 111 742	11.2% 44.4% 100.0% <u>Weight</u> 66.7%	2.40 [0.11, 50.37] 1.25 [0.24, 6.45] 1.26 [0.42, 3.76] 0dds Ratio <u>M-H. Fixed, 95% C</u> 1.23 [0.24, 6.40] Not estimable 4 51 [0 57, 25 68]	0.01	0.1 1 10 100 Favours [BA] Favours [Placebo] Odds Ratio M-H, Fixed, 95% Cl
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Goldberg 2019 Laufs 2019 Ray 2019 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = ( Test for overall effect: D) Hospitalization Goldberg 2019 Laufs 2019 Ray 2019 Total (95% CI) Total events	4 2 5 11 0.25, df = 2 Z = 0.41 (f <u>a for hea</u> <u><b>BA</b></u> <u><b>Events</b></u> 5 0 9	$522 \\ 234 \\ 1487 \\ 2243 \\ 2 (P = 0.6 \\ art fai \\ 522 \\ 234 \\ 1487 \\ 2243 \\ \end{cases}$	- 2 4 0.88); I <sup>2</sup> = 8) <u>Ilure</u> Placet <u>Events</u> 2 0 1	207 1111 742 1110 0% 0% <u>Total</u> 257 111 742 1110	11.2% 44.4% 100.0% <u>Weight</u> 66.7% 33.3% 100.0%	2.40 [0.11, 50.37] 1.25 [0.24, 6.45] 1.26 [0.42, 3.76] 0dds Ratio M-H, Fixed, 95% C 1.23 [0.24, 6.40] Not estimable 4.51 [0.57, 35.68] 2.33 [0.67, 8.11]	0.01	0.1 1 10 10 Favours [BA] Favours [Placebo] Odds Ratio M-H, Fixed, 95% Cl
Goldberg 2019 Laufs 2019 Ray 2019 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = ( Test for overall effect: D) Hospitalization Goldberg 2019 Laufs 2019 Ray 2019 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = (	4 2 5 11 0.25, df = ; Z = 0.41 (I <u>n for hea</u> <u>BA</u> <u>Events</u> 5 0 9 14 0.96, df = ;	522 234 1487 2243 2 (P = 0) art fai 522 234 1487 2243 1 (P = 0)	2 4 0.88); I <sup>2</sup> = 8) <u>Ilure</u> Placeb Events 2 0 1 3 0.33): I <sup>2</sup> =	111 742 1110 0% <u>Total</u> 257 111 742 1110	11.2%           44.4%           100.0%           Weight           66.7%           33.3%           100.0%	2.40 [0.11, 50.37] 1.25 [0.24, 6.45] 1.26 [0.42, 3.76] 0dds Ratio <u>M-H, Fixed, 95% C</u> 1.23 [0.24, 6.40] Not estimable 4.51 [0.57, 35.68] 2.33 [0.67, 8.11]	⊢	0.1 1 10 100 Favours [BA] Favours [Placebo] Odds Ratio M-H, Fixed, 95% Cl
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Goldberg 2019 Laufs 2019 Ray 2019 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = ( Test for overall effect: D) Hospitalization Goldberg 2019 Laufs 2019 Ray 2019 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = ( Test for overall effect: <u>E) Hospitalization</u>	$\begin{array}{c} 4 \\ 2 \\ 5 \\ 11 \\ 0.25, df = 2 \\ Z = 0.41 (l) \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1$	$522 \\ 234 \\ 1487 \\ 2243 \\ 2 (P = () \\ P = 0.6 \\ art fai \\ 522 \\ 234 \\ 1487 \\ 2243 \\ 1 (P = () \\ 1 \\ P = 0.1 \\ art fai \\ 1 \\ P = 0.1 \\ art fai \\ 1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0$	- - 2 - - - - - - - -	207 1111 742 1110 0% 0% 1110 0% 1110 0% 1110 0%	11.2% 44.4% 100.0% <u>Weight</u> 66.7% 33.3% 100.0% <u>Weight</u>	2.40 [0.11, 50.37] 1.25 [0.24, 6.45] 1.26 [0.42, 3.76] 0dds Ratio <u>M-H, Fixed, 95% C</u> 1.23 [0.24, 6.40] Not estimable 4.51 [0.57, 35.68] 2.33 [0.67, 8.11] 0dds Ratio <u>M-H, Fixed, 95% C</u>	0.01	Odds Ratio M-H, Fixed, 95% Cl 0.1 1 0 10 Odds Ratio 0.1 1 0 10 Favours [BA] Favours [Placebo] 0.1 1 0 10 Favours [BA] Favours [Placebo]
Goldberg 2019 Laufs 2019 Ray 2019 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = ( Test for overall effect: D) Hospitalization Goldberg 2019 Laufs 2019 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = ( Test for overall effect: <u>E) Hospitalization</u> Goldberg 2019	$\begin{array}{c} 4 \\ 2 \\ 5 \\ 11 \\ 0.25, df = 2 \\ Z = 0.41 (l) \\ a for hea \\ BA \\ Events \\ 5 \\ 0 \\ 9 \\ 14 \\ 0.96, df = 2 \\ I = 1.32 (l) \\ a for uns \\ BA \\ Events \\ 10 \\ 10 \\ 10 \\ 10 \\ 10 \\ 10 \\ 10 \\ 10$	$522 \\ 234 \\ 1487 \\ 2243 \\ 2 (P = () \\ P = 0.6 \\ art fai \\ 522 \\ 234 \\ 1487 \\ 2243 \\ 1 (P = () \\ 1 \\ 1 \\ 0 \\ 0$	$\begin{array}{c} & & \\$	200 1111 742 1110 0% 742 257 111 742 1110 0%	11.2% 44.4% 100.0% <u>Weight</u> 66.7% 33.3% 100.0% <u>Weight</u> 25.7%	2.40 [0.11, 50.37] 1.25 [0.24, 6.45] 1.26 [0.42, 3.76] 0dds Ratio <u>M-H, Fixed, 95% C</u> 1.23 [0.24, 6.40] Not estimable 4.51 [0.57, 35.68] 2.33 [0.67, 8.11] 0dds Ratio <u>M-H, Fixed, 95% C</u> 1.24 [0.38, 3.98]	0.01	Odds Ratio M-H, Fixed, 95% Cl 0.1 1 0 100 0.1 1 0 100 0.1 1 0 100 Favours [BA] Favours [Placebo] 0.1 1 0 100 Favours [BA] Favours [Placebo]
Goldberg 2019 Laufs 2019 Ray 2019 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = ( Test for overall effect: D) Hospitalization Goldberg 2019 Laufs 2019 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = ( Test for overall effect: <u>E) Hospitalization</u> Goldberg 2019 Laufs 2019	$\begin{array}{c} 4 \\ 2 \\ 5 \\ 11 \\ 0.25, df = 2 \\ Z = 0.41 (l) \\ a for hez \\ BA \\ Events \\ 5 \\ 0 \\ 9 \\ 14 \\ 0.96, df = 1 \\ Z = 1.32 (l) \\ a for uns \\ BA \\ Events \\ 10 \\ 5 \\ 10 \\ 10 \\ 10 \\ 10 \\ 10 \\ 10 \\ 10 \\ 10$	522 234 1487 2243 2 (P = () art fai 522 234 1487 2243 1487 2243 1 (P = () 1 + 2 + 2 + 2 + 2 + 2 + 2 + 2 + 2 + 2 +	$\begin{array}{c} 0 \\ 2 \\ 4 \\ 0.88);  2^2 = \\ 8 \\ \end{array}$ Placek: Events 2 0 1 0.33);  2^2 = \\ 9 \\ 0 \\ 0 \\ 1 \\ 0.33);  2^2 = \\ 9 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0	111 742 1110 0% 700 700 700 700 700 700 700 700 700	11.2% 11.2% 44.4% 100.0% Weight 66.7% 33.3% 100.0% Weight 25.7% 3.2%	2.40 [0.11, 50.37] 1.25 [0.24, 6.45] 1.26 [0.42, 3.76] 0dds Ratio M-H. Fixed, 95% C 1.23 [0.24, 6.40] Not estimable 4.51 [0.57, 35.68] 2.33 [0.67, 8.11] 0dds Ratio M-H. Fixed, 95% C 1.24 [0.38, 3.98] 5.34 [0.29, 97.50]	0.01	Odds Ratio M-H, Fixed, 95% Cl 0.1 1 0 100 0.1 1 0 100 0.1 1 0 100 Favours [BA] Favours [Placebo] 0dds Ratio M-H, Fixed, 95% Cl 0dds Ratio
Goldberg 2019 Laufs 2019 Ray 2019 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = ( Test for overall effect: . D) Hospitalization Goldberg 2019 Laufs 2019 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = ( Test for overall effect: . E) Hospitalization Goldberg 2019 Laufs 2019 Ray 2019	$\begin{array}{c} 4 \\ 2 \\ 5 \\ \end{array}$ 11 0.25, df = $2 \\ Z = 0.41$ (I 1 0.75, df = $2 \\ \end{array}$ BA Events 5 0 9 14 0.96, df = $2 \\ Z = 1.32$ (I 1 1 for uns BA Events 10 5 14 1 5 14	$522 \\ 234 \\ 1487 \\ 2243 \\ 2 (P = (  P = 0.6 \\ 1487 \\ 522 \\ 234 \\ 1487 \\ 2243 \\ 1487 \\ 2243 \\ 1 (P = (  P = 0.1 \\ 522 \\ 234 \\ 1487 \\ 522 \\ 234 \\ 1487 \\ 1$	$\begin{array}{c} & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ \hline \\ & \\ &$	1111 742 1110 0% <u>Total</u> 257 111 742 1110 0% <u>Total</u> 257 111 257 111 742	11.2% 11.2% 44.4% 100.0% Weight 66.7% 33.3% 100.0% Weight 25.7% 3.2% 71.1%	2.40 [0.11, 50.37] 1.25 [0.24, 6.45] 1.26 [0.42, 3.76] 1.26 [0.42, 3.76] 0.42, 3.76] 1.23 [0.24, 6.40] Not estimable 4.51 [0.57, 35.68] 2.33 [0.67, 8.11] 0dds Ratio M-H. Fixed, 95% C 1.24 [0.38, 3.98] 5.34 [0.29, 97.50] 0.63 [0.29, 1.40]	0.01	Odds Ratio M-H. Fixed, 95% Cl Odds Ratio M-H. Fixed, 95% Cl Odds Ratio M-H. Fixed, 95% Cl
Goldberg 2019 Laufs 2019 Ray 2019 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = ( Test for overall effect: D) Hospitalization Goldberg 2019 Laufs 2019 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = ( Test for overall effect: E) Hospitalization Study or Subgroup Goldberg 2019 Laufs 2019	$\begin{array}{c} 4 \\ 2 \\ 5 \\ 11 \\ 0.25, df = 2 \\ Z = 0.41 (I) \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1$	$522 \\ 234 \\ 1487 \\ 2243 \\ 2 (P = (P = 0.6 \\ art fai \\ 522 \\ 234 \\ 1487 \\ 2243 \\ 1487 \\ 2243 \\ 1487 \\ 2243 \\ 1487 \\ 522 \\ 234 \\ 1487$	$\begin{array}{c} - \\ - \\ 0 \\ 2 \end{array}$ $\begin{array}{c} 4 \\ 0.88); \  ^2 = \\ 8 \end{array}$ $\begin{array}{c} \\ \hline \\ $	207 1111 742 1110 0% 700 700 700 1111 742 1110 0% 700 700 700 700 700 700 700 700 700	Weight 44.4% 100.0% Weight 66.7% 33.3% 100.0% Weight 25.7% 3.2% 71.1%	2.40 [0.11, 50.37] 1.25 [0.24, 6.45] 1.26 [0.42, 3.76] 1.26 [0.42, 3.76] 0.42, 3.76] 1.23 [0.24, 6.40] Not estimable 4.51 [0.57, 35.68] 2.33 [0.67, 8.11] 0.44 [0.38, 3.98] 5.34 [0.29, 97.50] 0.63 [0.29, 1.40] 0.04 [0.14 [0	0.01	Odds Ratio M-H. Fixed, 95% CI Odds Ratio M-H. Fixed, 95% CI Odds Ratio M-H. Fixed, 95% CI
Goldberg 2019 Laufs 2019 Ray 2019 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = ( Test for overall effect: D) Hospitalization Goldberg 2019 Laufs 2019 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = ( Test for overall effect: <u>E) Hospitalization</u> Goldberg 2019 Laufs 2019 Total effect:	$\begin{array}{c} 4 \\ 2 \\ 5 \\ 11 \\ 0.25, df = ; \\ Z = 0.41 (I) \\ a for heacher \\ BA \\ Events \\ 5 \\ 0 \\ 9 \\ 14 \\ 0.96, df = : \\ Z = 1.32 (I) \\ a for uns \\ BA \\ Events \\ 10 \\ 5 \\ 14 \\ 2 \\ 14 \\ 2 \\ 14 \\ 2 \\ 14 \\ 2 \\ 2 \\ 14 \\ 2 \\ 2 \\ 14 \\ 2 \\ 2 \\ 14 \\ 2 \\ 2 \\ 2 \\ 2 \\ 2 \\ 2 \\ 2 \\ 2 \\ 2 \\ 2$	$522 \\ 234 \\ 1487 \\ 2243 \\ 2 (P = 0.6 \\ 0 \\ 1487 \\ 1487 \\ 2243 \\ 1 (P = 0.1 \\ 0 \\ 0$	$\frac{1}{2}$ $\frac{4}{2}$ $\frac{4}{2}$ $\frac{1}{2}$ $\frac{1}$	200 1111 742 1110 0% 00 1111 742 1110 0% 1111 0% 1111 0%	Weight 44.4% 100.0% Weight 66.7% 33.3% 100.0% Weight 25.7% 3.2% 71.1% 100.0%	Odds Ratio M-H, Fixed, 95% C 1.26 [0.42, 3.76] 1.26 [0.42, 3.76] 1.26 [0.42, 3.76] 1.23 [0.24, 6.40] Not estimable 4.51 [0.57, 35.68] 2.33 [0.67, 8.11] Odds Ratio M-H, Fixed, 95% C 1.24 [0.38, 3.98] 5.34 [0.29, 97.50] 0.63 [0.29, 1.40] 0.94 [0.51, 1.74]	0.01	Odds Ratio M-H, Fixed, 95% CI 0.1 1 0 100 M-H, Fixed, 95% CI 0.1 1 0 100 Favours [BA] Favours [Placebo] Odds Ratio M-H, Fixed, 95% CI
Goldberg 2019 Laufs 2019 Ray 2019 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = ( Test for overall effect: D) Hospitalization Goldberg 2019 Laufs 2019 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = ( Test for overall effect: E) Hospitalization Goldberg 2019 Laufs 2019 Total events Heterogeneity: Chi <sup>2</sup> = ( Test for overall effect: E) Hospitalization Goldberg 2019 Laufs 2019 Ray 2019 Total (95% CI) Total (95% CI) Total events	4 2 5 11 0.25, df = ; Z = 0.41 (f 1 for head BA Events 5 0 9 14 0.96, df = ; Z = 1.32 (f 1 for uns BA Events 14 0.96, df = ; 2 = 1.32 (f 1 for uns 14 0.96, df = ; 14 0.96, df = ; 14 0.96, df = ; 14 0.96, df = ; 14 0.96, df = ; 10 10 10 10 10 10 10 10 10 10	522 234 1487 2243 2 (P = (P = 0.6) 322 234 1487 2243 1 (P = 0.1) 3222 234 1 (P = 0.1) 522 234 1 (P = 0.1) 2243 234 1 (P = 0.1) 1 (P = 0.1) 1 (P = 0.1) 224 234 1 (P = 0.1) 234 1 (P = 0.1) 234 234 234 234 234 234 234 243 243 244 243 244 243 244 243 244 243 244 2 2 2 2 2 2 2 2	$\frac{1}{1}$	200 1111 742 1110 0% 00 100 1110 0% 1110 0% 1110 0% 100 100	11.2%           11.2%           44.4%           100.0%           Weight           66.7%           33.3%           100.0%           Weight           25.7%           3.2%           71.1%           100.0%	Odds Ratio M-H, Fixed, 95% C 1.26 [0.42, 3.76] 1.26 [0.42, 3.76] 1.26 [0.42, 3.76] 0.123 [0.24, 6.40] Not estimable 4.51 [0.57, 35.68] 2.33 [0.67, 8.11] Odds Ratio M-H, Fixed, 95% C 1.24 [0.38, 3.98] 5.34 [0.29, 97.50] 0.63 [0.29, 1.40] 0.94 [0.51, 1.74]	0.01	Odds Ratio 0.1 1 10 100 Favours [BA] Favours [Placebo] Odds Ratio M-H, Fixed, 95% Cl 0.1 1 10 100 Favours [BA] Favours [Placebo] Odds Ratio M-H, Fixed, 95% Cl 0
Goldberg 2019 Laufs 2019 Ray 2019 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = ( Test for overall effect: D) Hospitalization Goldberg 2019 Laufs 2019 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = ( Test for overall effect: E) Hospitalization Goldberg 2019 Laufs 2019 Total events Heterogeneity: Chi <sup>2</sup> = ( Caldberg 2019 Laufs 2019 Total (95% CI) Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 3 Total (95% CI)	$\begin{array}{c} 4 \\ 2 \\ 5 \\ 11 \\ 0.25, df = 2 \\ Z = 0.41 (i \\ a for hea \\ BA \\ Events \\ 5 \\ 0 \\ 9 \\ 14 \\ 0.96, df = 2 \\ 1 \\ 12 \\ 14 \\ 10 \\ 5 \\ 14 \\ 29 \\ 2.55, df = 2 \\ 2 \\ 2 \\ 2.55, df = 2 \\ 2 \\ 2 \\ 2 \\ 2 \\ 2 \\ 2 \\ 2 \\ 2 \\ 2 \\$	522 234 1487 2243 $2 (P = (P = 0.6 + 10^{-1})^{-1}$ 522 234 1487 2243 $1 (P = 0.1 + 10^{-1})^{-1}$ 522 234 $1 (P = 0.2 + 10^{-1})^{-1}$ $1 (P = 0.2 + 10^{-1})^{-1}$ $2 (P = 0.2 + 10^{-1})$	$\begin{array}{c} - \\ - \\ 0 \\ 2 \\ 2 \\ - \\ - \\ - \\ - \\ - \\ - \\ - \\ -$	200 1111 742 1110 0% 00 100 1110 0% 1110 0% 1110 0% 100 100	11.2%           11.2%           44.4%           100.0%           Weight           66.7%           33.3%           100.0%           Weight           25.7%           3.2%           71.1%           100.0%	Odds Ratio M-H, Fixed, 95% C 1.26 [0.42, 3.76] 1.26 [0.42, 3.76] 1.26 [0.42, 3.76] 1.23 [0.24, 6.40] Not estimable 4.51 [0.57, 35.68] 2.33 [0.67, 8.11] Odds Ratio M-H, Fixed, 95% C 1.24 [0.38, 3.98] 5.34 [0.29, 97.50] 0.63 [0.29, 1.40] 0.94 [0.51, 1.74]	0.01	Odds Ratio 0.1 1 10 100 Favours [BA] Favours [Placebo] Odds Ratio M-H, Fixed, 95% Cl 0.1 1 10 100 Favours [BA] Favours [Placebo] Odds Ratio M-H, Fixed, 95% Cl 0.1 1 10 100
Goldberg 2019 Laufs 2019 Ray 2019 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = ( Test for overall effect: D) Hospitalization Goldberg 2019 Laufs 2019 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = ( Test for overall effect: E) Hospitalization Goldberg 2019 Laufs 2019 Total events Heterogeneity: Chi <sup>2</sup> = ( Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 3 Coldberg 2019 Laufs 2019 Ray 2019 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 3 Test for overall effect:	$\begin{array}{c} 4 \\ 2 \\ 5 \\ 11 \\ 0.25, df = 2 \\ Z = 0.41 (i \\ a \\ for hea \\ ba \\ constant \\ BA \\ constant \\ BA \\ constant \\ consta$	$522 \\ 234 \\ 1487 \\ 2243 \\ 2 (P = (P = 0.6 \\ P = 0.6 \\ 1487 \\ 2243 \\ 1487 \\ 2243 \\ 1 (P = 0.1 \\ 1487 \\ 2243 \\ 1487 \\ 2243 \\ 2243 \\ 2 (P = 0.8 \\ P = 0.8 \\ 2 (P = 0.8 \\ P = 0.8 \\ 2 (P = 0.8 \\ P = 0.8 \\ 2 (P = 0.8 \\ P = 0.8 \\ 2 (P = 0.8 \\ 2 $	$\begin{array}{c} & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ \hline \\ & \\ &$	207 1111 742 1110 0% 0% 0% 1111 742 1110 0% 1110 0% 100 100 100 100	11.2%         11.2%         44.4%         100.0%         Weight         66.7%         33.3%         100.0%         Weight         25.7%         3.2%         71.1%         100.0%	Odds Ratio M-H, Fixed, 95% C 1.26 [0.42, 3.76] 1.26 [0.42, 3.76] 1.26 [0.42, 3.76] 1.23 [0.24, 6.40] Not estimable 4.51 [0.57, 35.68] 2.33 [0.67, 8.11] Odds Ratio M-H, Fixed, 95% C 1.24 [0.38, 3.98] 5.34 [0.29, 97.50] 0.63 [0.29, 1.40] 0.94 [0.51, 1.74]	0.01	Odds Ratio 0.1 1 10 100 Favours [BA] Favours [Placebo] Odds Ratio M-H, Fixed, 95% Cl 0.1 1 10 100 Favours [BA] Favours [Placebo] Odds Ratio M-H, Fixed, 95% Cl 0.1 1 0 100 Favours [BA] Favours [Placebo]

(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 58 effects model, Cochran-Mantel-Haenszel-estimates; Tau<sup>2</sup> and I<sup>2</sup> are measures of heterogeneity. BA=bempedoic acid; M-H=Mantel-Haenszel. 59 60

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



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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; Tau<sup>2</sup> and I<sup>2</sup> are measures of heterogeneity. BA=bempedoic acid; M-H=Mantel-Haenszel.

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

	A) LDL-C												
_			BA		Pla	cebo			Mean Difference		Mean Di	fference	
	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% C		IV, Fixed	I, 95% CI	
	Ballantyne 2018	-23.5	26.9	181	5 3	20.7	81	7.3%	-28.50 [-34.47, -22.53]	-	-		
	Ballantyne 2019	-17.7	23.1	110	-2.5	22.4	55	4.9%	-15.20 [-22.53, -7.87]				
	Gutierrez 2014	-42.9	20.7	29	-4	13.7	30	5.2%	-38.90 [-45.97, -31.83]		_		
	Lauis 2019 Pay 2019	-21.2	20.7	210	-2.3	10.5	742	15.1%	-18.10 [-23.06, -14.74]				
	Ray 2015	-10.5	20.1	1400	1.0	23.4	/42	07.5%	-10.10[-20.07, -10.13]		_		
	Total (95% CI)			2026			1015	100.0%	-19.93 [-21.55, -18.31]		•		
	Heterogeneity: Chi <sup>2</sup> = 4	10.71, df	f = 4 (F	<pre>&lt; 0.00</pre>	001); l² :	= 90%	5			-50	-25 (	25	50
	Test for overall effect:	Z = 24.1	5 (P <	0.0000	1)					-00	Favours [BA]	Favours [Placebo]	50
_	B) Total cholest	erol											
	Church and Carbonness		BA	Tetel	Pla	cebo	Tetel	14/	Mean Difference		Mean Di	fference	
-	Ballantuno 2018	_15_1	17.5	191	20	14.1	10tal	6.5%	-19 00 [-21 00 -14 10]			1, 95% CI	
	Ballantyne 2019	-12.8	17.8	110	_2.0	16.3	55	3.3%	-10.80 [-21.30, -14.10]				
	Goldberg 2019	-9.9	15.6	499	1.3	15.9	253	17.3%	-11.20 [-13.59, -8.81]		-		
	Gutierrez 2014	-25.1	10.4	30	-0.5	10.4	30	3.6%	-24.60 [-29.86, -19.34]				
	Laufs 2019	-15	15	224	-1	10	107	13.3%	-14.00 [-16.73, -11.27]		-		
	Ray 2019	-10.3	14.3	1488	0.8	15.5	742	55.9%	-11.10 [-12.43, -9.77]		•		
	T ( ) (0.5% O)						4075	400.00/					
	Total (95% CI)			2532	0041-12	0.00	1275	100.0%	-12.43 [-13.42, -11.43]	L			
	Test for overall effect:	34.86, 01 7 = 24.4	7 / P ~	0.00	001); I* : 1)	= 86%	0			-50	-25 0	25	50
	rescior overall effect; a	<u> </u>	r (P <	0.0000	.,						Favours [BA]	Favours [Placebo]	
(	C) Non-HDL-C												
-		•											
			BA		Pla	cebo			Mean Difference		Mean Di	fference	
-	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% C		IV, Fixed	i, 95% Cl	
	Ballantyne 2018	-18.4	21.5	181	5.2	20.6	88	6.1%	-23.60 [-28.92, -18.28]				
	Ballantyne 2019	-14.9	21	110	-2 :	20.8	55	3.8%	-12.90 [-19.65, -6.15]		_		
	Goldberg 2019 Gutierrez 2014	-10.8	12.3	498	2.3	126	253	15.3%	-13.10 [-16.47, -9.73]	_			
	Laufs 2019	-32	12.0	224	-0.5	13.4	107	14.5%	-17 10 [-20 56 -13 64]		-		
	Ray 2019	-11.9	18.5	1488	1.5	20.7	742	56.0%	-13.40 [-15.16, -11.64]		•		
	1009 2010	1110	1010	1100	1.0 1			00.070	torre [ torret the i]				
	Total (95% CI)			2531			1275	100.0%	-15.27 [-16.59, -13.95]		•		
	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4	1.76, df	f = 5 (F	2531 P < 0.00	001); l² :	= 88%	1275	100.0%	-15.27 [-16.59, -13.95]	-50	-25	25	50
	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: 2	11.76, df Z = 22.7	f = 5 (F 0 (P <	2531 > < 0.00 0.0000	001); l² : 1)	= 88%	1275	100.0%	-15.27 [-16.59, -13.95]	-50	◆ -25 C Favours [BA]	) 25 Favours [Placebo]	50
	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: 7	11.76, df Z = 22.7	f = 5 (F 0 (P <	2531 > < 0.00 0.0000	001); l² = 1)	= 88%	1275	100.0%	-15.27 [-16.59, -13.95]	-50	◆ -25 C Favours [BA]	) 25 Favours [Placebo]	50
1	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: 2	41.76, df Z = 22.7	f = 5 (F 0 (P <	2531 P < 0.00 0.0000	001); l² : 1)	= 88%	1275	100.0%	-15.27 [-16.59, -13.95]	-50	-25 C Favours [BA]	) 25 Favours [Placebo]	50
]	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: 2 D) Apolipoprote	41.76, df Z = 22.7 ein B	f = 5 (F 0 (P <	2531 > < 0.00 0.0000	001); l² : 1)	= 88%	1275	100.0%	-15.27 [-16.59, -13.95]	-50	-25 C Favours [BA]	) 25 Favours [Placebo]	50
]	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: 2 D) Apolipoprote	41.76, df Z = 22.7 ein B	f = 5 (F 0 (P < BA	2531 > < 0.00 0.0000	001); I² : 1) Pla	= 88%	1275	100.0%	-15.27 [-16.59, -13.95] Mean Difference	-50	-25 C Favours [BA] Mean Dir	1 25 Favours [Placebo]	50
]	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: 2 D) Apolipoprote Study or Subgroup	11.76, df Z = 22.7 ein B	f = 5 (F 0 (P < BA SD	2531 < 0.00 0.0000 Total	001); I <sup>2</sup> : 1) Pla <u>Mean</u>	= 88% cebo <u>SD</u>	1275	100.0%	-15.27 [-16.59, -13.95] Mean Difference IV, Fixed, 95% C	-50	-25 C Favours [BA] Mean Dif	) 25 Favours [Placebo] fference 3, 95% Cl	50
] -	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: 2 D) Apolipoprote Study or Subgroup Ballantyne 2018 Ballantyne 2018	11.76, df Z = 22.7 ein B Mean -14.6	f = 5 (F 0 (P < BA SD 20.2	2531 P < 0.00 0.0000 Total 181	001); I <sup>2</sup> : 1) Pla <u>Mean</u> 4.7	= 88% cebo <u>SD</u> 16.9	1275 Total 88	100.0% Weight 7.6%	-15.27 [-16.59, -13.95] Mean Difference IV. Fixed, 95% CI -19.30 [-23.90, -14.70] 42.20(21.45, -5.50]	-50	-25 C Favours [BA] Mean Dif	) 25 Favours [Placebo] fference a, 95% Cl	50
<u>]</u> 	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: 2 D) Apolipoprote Study or Subgroup Ballantyne 2018 Ballantyne 2019 Goldbøre 2019	41.76, df Z = 22.7 ein B Mean -14.6 -11.7	f = 5 (F 0 (P < BA 20.2 23.1 19 7	2531 < 0.00 0.0000 Total 181 82 479	001); I <sup>2 =</sup> 1) Pla <u>Mean</u> 4.7 1.6	= 88% cebo <u>SD</u> 16.9 20.8	1275 Total 88 38 245	100.0% Weight 7.6% 2.3% 16.8%	-15.27 [-16.59, -13.95] Mean Difference IV. Fixed, 95% CI -19.30 [-23.90, -14.70] -13.30 [-21.59, -5.01] -13.30 [-6 09, 991]	-50	-25 Favours [BA] Mean Dit	1 25 Favours [Placebo] fference 3, 95% Cl	50
]	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: 3 D) Apolipoprote Study or Subgroup Ballantyne 2018 Ballantyne 2019 Goldberg 2019 Laufs 2019	Mean -14.6 -11.7 -9.3 -15	f = 5 (F 0 (P < BA 20.2 23.1 19.7 16 5	2531 2 < 0.00 0.0000 Total 181 82 479 224	001); l <sup>2</sup> = 1) Pla <u>Mean</u> 4.7 1.6 3.7	= 88% cebo SD 16.9 20.8 20.3 13.4	<b>Total</b> 88 38 245 107	100.0% Weight 7.6% 2.3% 16.8% 14.5%	-15.27 [-16.59, -13.95] Mean Difference IV. Fixed, 95% C -19.30 [-23.90, -14.70] -13.30 [-21.59, -5.01] -13.00 [-16.09, -9.91] -15.50 [-18.83, -12.17]	-50	-25 Favours [BA] Mean Dif	) 25 Favours [Placebo] fference 1, 95% Cl	
<u>]</u> 	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: 3 D) Apolipoprote Study or Subgroup Ballantyne 2018 Ballantyne 2019 Goldberg 2019 Laufs 2019 Ray 2019	H1.76, df Z = 22.7 ein B -14.6 -11.7 -9.3 -15 -8.6	F = 5 (F 0 (P < BA 20.2 23.1 19.7 16.5 18.1	2531 2 < 0.00 0.0000 Total 181 82 479 224 1485	001); l <sup>2</sup> : 1) <u>Plac</u> <u>Mean</u> 4.7 1.6 3.7 3.3	= 88% cebo SD 16.9 20.8 20.3 13.4 19	1275 Total 88 38 245 107 736	<b>Weight</b> 7.6% 2.3% 16.8% 14.5% 58.8%	-15.27 [-16.59, -13.95] Mean Difference IV. Fixed, 95% Cf -19.30 [-23.90, -14.70] -13.30 [-21.59, -5.01] -13.00 [-16.09, -9.91] -15.50 [-18.83, -12.17] -11.90 [-13.55, -10.25]	-50	-25 C Favours [BA] Mean Dir IV, Fixed	) 25 Favours [Placebo] fference d, 95% Cl	
<u>]</u> -	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: 3 D) Apolipoprote Study or Subgroup Ballantyne 2018 Ballantyne 2019 Goldberg 2019 Laufs 2019 Ray 2019	Mean -14.6 -11.7 -9.3 -15 -8.6	F = 5 (F 0 (P < BA 20.2 23.1 19.7 16.5 18.1	2531 < 0.00 0.0000 Total 181 82 479 224 1485	001);   <sup>2</sup> : 1) Pla <u>Mean</u> 4.7 1.6 3.7 3.3	= 88% cebo SD 16.9 20.8 20.3 13.4 19	<b>Total</b> 88 38 245 107 736	Weight 7.6% 2.3% 14.5% 58.8%	-15.27 [-16.59, -13.95] Mean Difference IV. Fixed, 95% CI -19.30 [-23.90, -14.70] -13.30 [-21.59, -5.01] -13.00 [-16.09, -9.91] -15.50 [-18.83, -12.17] -11.90 [-13.55, -10.25]	-50	-25 Favours [BA] Mean Dir IV, Fixed	) 25 Favours [Placebo] fference 4, 95% Cl	50
<u>]</u> -	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: 2 D) Apolipoprote Study or Subgroup Ballantyne 2018 Ballantyne 2019 Goldberg 2019 Laufs 2019 Ray 2019 Total (95% CI)	Mean -14.6 -11.7 -9.3 -8.6	<b>BA</b> 20.2 23.1 19.7 16.5 18.1	2531 < 0.00 0.0000 Total 181 82 479 224 1485 2451	Plae 1) Plae 4.7 1.6 3.7 3.7 3.3	= 88% cebo <u>SD</u> 16.9 20.8 20.3 13.4 19	<b>Total</b> 88 38 245 107 736 <b>1214</b>	100.0% Weight 7.6% 2.3% 16.8% 14.5% 58.8% 100.0%	-15.27 [-16.59, -13.95] Mean Difference IV. Fixed, 95% C -19.30 [-23.90, -14.70] -13.30 [-21.59, -5.01] -13.00 [-16.09, -9.91] -15.50 [-18.83, -12.17] -11.90 [-13.55, -10.25] -13.20 [-14.47, -11.93]	-50	-25 C Favours [BA] Mean Dir IV, Fixed	) 25 Favours [Placebo] fference d, 95% Cl	50
<u>]</u> -	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: 2 D) Apolipoprote Study or Subgroup Ballantyne 2018 Ballantyne 2019 Goldberg 2019 Laufs 2019 Ray 2019 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 1	Mean -14.6 -11.7 -9.3 -15 -8.6	F = 5 (F 0 (P < BA 20.2 23.1 19.7 16.5 18.1	2531 < 0.00 0.0000 Total 181 82 479 224 1485 2451 > = 0.03	001); l <sup>2</sup> = 1) Plae <u>Mean</u> 4.7 1.6 3.7 3.3 3.3 ); l <sup>2</sup> = 64	cebo SD 16.9 20.8 13.4 19	<b>Total</b> 88 38 245 107 736 <b>1214</b>	Weight 7.6% 2.3% 16.8% 14.5% 58.8% 100.0%	-15.27 [-16.59, -13.95] Mean Difference IV. Fixed, 95% C -19.30 [-23.90, -14.70] -13.30 [-21.59, -5.01] -13.00 [-16.09, -9.91] -15.50 [-18.83, -12.17] -11.90 [-13.55, -10.25] -13.20 [-14.47, -11.93]	-50	-25 C Favours [BA]	) 25 Favours [Placebo] fference d, 95% Cl	50
]	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: 2 D) Apolipoprote Study or Subgroup Ballantyne 2018 Ballantyne 2019 Goldberg 2019 Laufs 2019 Ray 2019 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect: 2	Mean -14.6 -11.7 -9.3 -15 -8.6 10.99, df Z = 20.4	BA 50 (P < 20.2 23.1 19.7 16.5 18.1 f = 4 (F 1 (P <	2531 < 0.00 0.0000 Total 181 82 479 224 1485 2451 > = 0.03 0.0000	001); l <sup>2</sup> = 1) <u>Plac</u> <u>Mean</u> 4.7 <sup>-1</sup> 1.6 : 3.7 : 0.5 <sup>-1</sup> 3.3 ); l <sup>2</sup> = 64 1)	cebo SD 16.9 20.8 20.3 13.4 19	1275 Total 88 38 245 107 736 1214	Weight 7.6% 2.3% 16.8% 14.5% 58.8%	-15.27 [-16.59, -13.95] Mean Difference IV. Fixed, 95% CI -19.30 [-23.90, -14.70] -13.30 [-21.59, -5.01] -13.30 [-16.99, -9.91] -15.50 [-18.83, -12.17] -11.90 [-13.55, -10.25] -13.20 [-14.47, -11.93]	-50	-25 ( Favours [BA] Mean Dir IV, Fixed	) 25 Favours [Placebo] fference d, 95% Cl	50
]	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: 2 D) Apolipoprote Study or Subgroup Ballantyne 2018 Ballantyne 2019 Goldberg 2019 Laufs 2019 Ray 2019 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect: 2	Mean -14.6 -14.6 -11.7 -9.3 -15 -8.6 10.99, df Z = 20.4	f = 5 (F 0 (P < BA 20.2 23.1 19.7 16.5 18.1 f = 4 (F f = 4 (P <	2531 < 0.00 0.0000 Total 181 82 479 224 1485 2451 > = 0.03 0.0000	001); l <sup>2</sup> = 1) <u>Plac</u> <u>Mean</u> 4.7 1.6 2 3.7 2 0.5 3.3 ); l <sup>2</sup> = 64 1)	cebo SD 16.9 20.8 20.3 13.4 19	1275 Total 88 38 245 107 736 1214	<b>Weight</b> 7.6% 2.3% 16.8% 14.5% 58.8% 100.0%	-15.27 [-16.59, -13.95] Mean Difference IV. Fixed, 95% Cf -19.30 [-23.90, -14.70] -13.30 [-21.59, -5.01] -13.00 [-16.99, -9.91] -15.50 [-18.83, -12.17] -11.90 [-13.55, -10.25] -13.20 [-14.47, -11.93]	-50	-25 C Favours [BA] Mean Dir IV. Fixed 	) 25 Favours [Placebo] fference d, 95% Cl	50
]	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: 2 D) Apolipoprote Study or Subgroup Ballantyne 2018 Ballantyne 2019 Goldberg 2019 Laufs 2019 Ray 2019 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect: 2 E) HDL-C	41.76, df Z = 22.7 ein B -14.6 -11.7 -9.3 -15 -8.6 10.99, df Z = 20.4	F = 5 (F 0 (P < BA 20.2 23.1 19.7 16.5 18.1 f = 4 (F f = 4 (P <	2531 < 0.00 0.0000 Total 181 82 479 224 1485 2451 < 0.03 0.0000	001); l <sup>2</sup> = 1) 4.7 1.6 3.7 3.7 3.3 3.3 ); l <sup>2</sup> = 64 1)	<b>cebo</b> <u>SD</u> 16.9 20.3 13.4 19	Total 88 38 245 107 736 1214	100.0% Weight 7.6% 2.3% 16.8% 14.5% 58.8% 100.0%	-15.27 [-16.59, -13.95] Mean Difference IV. Fixed, 95% CI -19.30 [-23.90, -14.70] -13.30 [-21.59, -5.01] -13.30 [-16.09, -9.91] -15.50 [-18.83, -12.17] -11.90 [-13.55, -10.25] -13.20 [-14.47, -11.93]	-50	-25 C Favours [BA] Mean Dif IV. Fixed -25 C Favours [BA]	25 Favours [Placebo] fference 1, 95% Cl	
] - ]	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: 2 D) Apolipoprote Study or Subgroup Ballantyne 2018 Ballantyne 2019 Goldberg 2019 Laufs 2019 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect: 2 E) HDL-C	41.76, df z = 22.7 ein B -14.6 -11.7 -9.3 -15 -8.6 10.99, df z = 20.4	F = 5 (F 0 (P < BA 20.2 23.1 19.7 16.5 18.1 f = 4 (F f = 4 (P < BA	2531 < 0.00 0.0000 Total 181 82 479 224 1485 2451 > = 0.03 0.0000	001); l <sup>2</sup> = 1) Plac <u>Mean</u> 4.7 - 1.6 : 3.7 - 3.7 : 3.3 ); l <sup>2</sup> = 64 1) Pla	cebo SD 16.9 20.8 20.3 13.4 19	Total 88 38 245 107 736 1214	100.0% Weight 7.6% 2.3% 16.8% 14.5% 58.8% 100.0%	-15.27 [-16.59, -13.95] Mean Difference IV. Fixed, 95% CI -19.30 [-23.90, -14.70] -13.30 [-21.59, -5.01] -13.00 [-16.09, -9.91] -15.50 [-18.83, -12.17] -11.90 [-13.55, -10.25] -13.20 [-14.47, -11.93] Mean Difference	-50	-25 C Favours [BA] Mean Dif IV, Fixed -25 C Favours [BA]	25 Favours [Placebo] fference 3, 95% Cl	50
] - ]	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: 2 D) Apolipoprote Study or Subgroup Ballantyne 2018 Ballantyne 2019 Goldberg 2019 Laufs 2019 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect: 2 <u>E) HDL-C</u> Study or Subgroup	Mean Mean -14.6 -11.7 -9.3 -15 -8.6 10.99, df Z = 20.4 Mean	F = 5 (F 0 (P < BA 20.2 23.1 19.7 16.5 18.1 f = 4 (F 1 (P < BA <u>S</u> D	2531 2 < 0.00 0.0000 Total 181 82 479 224 1485 2451 2451 2 < 0.030 0.0000 Total	001); I <sup>2</sup> : 1) Plaa <u>4.7</u> 1.6 3.7 3.3 ); I <sup>2</sup> = 64 1) Pla <u>Mean</u>	cebo SD 16.9 20.8 20.3 13.4 19 % cebo SD	Total 88 38 245 107 736 1214	100.0% Weight 7.6% 2.3% 16.8% 14.5% 58.8% 100.0% Weight	-15.27 [-16.59, -13.95] Mean Difference IV. Fixed, 95% CI -19.30 [-23.90, -14.70] -13.30 [-21.59, -5.01] -13.00 [-16.09, -9.91] -15.50 [-18.83, -12.17] -11.90 [-13.55, -10.25] -13.20 [-14.47, -11.93] Mean Difference IV. Fixed, 95% CI	-50	-25 C Favours [BA] Mean Dir IV. Fixed -25 C Favours [BA] Mean Dir IV. Fixed	25 Favours [Placebo] fference 4, 95% Cl	50
<u>]</u> - ]	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: 2 D) Apolipoprote Study or Subgroup Ballantyne 2018 Ballantyne 2019 Goldberg 2019 Laufs 2019 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect: 2 E) HDL-C Study or Subgroup Ballantyne 2018	11.76, dl Z = 22.7 -14.6 -11.7 -9.3 -15 -8.6 10.99, dl 10.99, dl 0.99, dl 10.99, dl 10	F = 5 (F 0 (P < BA SD 20.2 23.1 19.7 16.5 18.1 F = 4 (F 1 (P < BA SD 16.1	2531 2 < 0.00 0.0000 Total 181 182 479 224 1485 2451 24	001); I <sup>2</sup> : Plaa <u>Mean</u> 4.7 1.6 3.3 ; I <sup>2</sup> = 64 ); I <sup>2</sup> = 64 <u>Plaa</u> <u>12.6</u>	<pre>cebo SD 16.9 20.3 13.4 19 % cebo SD 1.4</pre>	1275 5 7 88 88 245 107 736 1214 1214	100.0% Weight 7.6% 2.3% 16.8% 14.5% 58.8% 100.0% Weight 12.7%	-15.27 [-16.59, -13.95] Mean Difference IV. Fixed, 95% CI -19.30 [-23.90, -14, 70] -13.30 [-21.59, -5.01] -13.00 [-16.09, -9.91] -15.50 [-18.83, -12.17] -11.90 [-13.55, -10.25] -13.20 [-14.47, -11.93] Mean Difference IV. Fixed, 95% CI -19.90 [-22.27, -17.53]	-50	-25 C Favours [BA] Mean Dif IV, Fixed 	) 25 Favours [Placebo] fference d. 95% Cl	50
] - ]	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: 3 D) Apolipoprote Study or Subgroup Ballantyne 2018 Ballantyne 2019 Goldberg 2019 Laufs 2019 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect: 3 E) HDL-C Study or Subgroup Ballantyne 2018 Goldberg 2019	41.76, dd Z = 22.7 -14.6 -14.6 -11.7 -9.3 -15 -8.6 10.99, dd Z = 20.4 Mean -7.3 -6.4	F = 5 (F 0 (P < BA 20.2 23.1 19.7 16.5 18.1 f = 4 (F F = 4 (F P < BA 50 16.1 15.6	2531 2 < 0.00 0.0000 Total 181 82 2479 224 1485 2451 2 = 0.03 0.0000 Total 181 439	001); I <sup>2</sup> : Plaa <u>Mean</u> 4.7 : 3.7 : 0.5 : 3.3 ); I <sup>2</sup> = 64 1) Pla <u>Mean</u> 12.6 -0.2	<pre>cebo SD 16.9 20.3 13.4 19 % cebo SD 1.4 14.3</pre>	1275 Total 88 38 245 107 736 1214 Total 81 253	100.0% Weight 7.6% 2.3% 16.8% 14.5% 58.8% 100.0% Weight 12.7% 14.3%	-15.27 [-16.59, -13.95] Mean Difference IV. Fixed, 95% CI -19.30 [-23.90, -14.70] -13.30 [-21.59, -5.01] -13.30 [-16.99, -9.91] -15.50 [-18.83, -12.17] -11.90 [-13.55, -10.25] -13.20 [-14.47, -11.93] Mean Difference IV. Fixed, 95% CI -19.90 [-22.27, -17.53] -6.20 [-8.43, -3.97]	-50	-25 Favours [BA] Mean Dif IV, Fixed 	) 25 Favours [Placebo] fference 4. 95% CI	50
] - ]	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: 3 D) Apolipoprote Ballantyne 2018 Ballantyne 2019 Goldberg 2019 Laufs 2019 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect: 3 <u>E) HDL-C</u> Study or Subgroup Ballantyne 2018 Goldberg 2019 Gutierrez 2014	41.76, dd Z = 22.7 -14.6 -11.7 -9.3 -15 -8.6 10.99, dd Z = 20.4 Mean -7.3 -6.4 -1.2	F = 5 (F 0 (P < BA 20.2 23.1 19.7 16.5 18.1 19.7 16.5 18.1 1 (P < BA SD 16.1 15.6 9.9	2531 2 < 0.00 0.0000 Total 181 82 2479 224 1485 2451 2 = 0.030 0.0000 Total 181 499 30	001); I <sup>2</sup> : Plaa <u>Mean</u> 4.7 · 1.6 : 3.7 : 3.3 3.3 ); I <sup>2</sup> = 64 1) Pla <u>Mean</u> 12.6 0.5 0.5	<pre>cebo SD 16.9 20.8 20.3 13.4 19 % cebo SD 1.4 14.3 9.9</pre>	Total 88 38 245 107 736 1214 1214 81 253 30	100.0% Weight 7.6% 2.3% 16.8% 14.5% 58.8% 100.0% Weight 12.7% 14.3% 2.8%	-15.27 [-16.59, -13.95] Mean Difference IV. Fixed, 95% CI -19.30 [-23.90, -14.70] -13.30 [-21.59, -5.01] -13.30 [-16.9, -9.91] -15.50 [-18.83, -12.17] -11.90 [-13.55, -10.25] -13.20 [-14.47, -11.93] Mean Difference IV. Fixed, 95% CI -19.90 [-22.27, -17.53] -6.20 [-84.3, -3.97] -1.70 [-6.71, 3.31]	-50 -50	-25 Favours [BA] Mean Dif IV, Fixed -25 Favours [BA] Mean Dif IV, Fixed	) 25 Favours [Placebo] fference d. 95% Cl	50
] - ]	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: 2 D) Apolipoprote Ballantyne 2018 Ballantyne 2019 Goldberg 2019 Laufs 2019 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect: 2 <u>E) HDL-C</u> <u>Study or Subgroup</u> Ballantyne 2018 Goldberg 2019 Gutierrez 2014 Laufs 2019	41.76, dl Z = 22.7 -14.6 -11.7 -9.3 -15 -8.6 10.99, dl Z = 20.4 Mean -7.3 -6.4 -1.2 -5.2	f = 5 (F           0 (P <	2531 2 < 0.00 0.0000 Total 181 82 479 224 1485 2451 2451 181 181 181 181 181 30 0.0000	001); I <sup>2</sup> : Plaa <u>4.7</u> 1.6 3.7 1.6 3.7 1.6 .5 3.3 ); I <sup>2</sup> = 64 <u>1</u> ) Pla <u>Mean</u> 12.6 0.5 -0.2 0.5 -0.6	<pre>= 88% cebo SD 16.9 20.8 20.3 13.4 19 % cebo SD 1.4 14.3 9.9 10.3</pre>	Total 88 245 107 736 1214 81 253 30 107	100.0% Weight 7.6% 2.3% 16.8% 14.5% 58.8% 100.0% Weight 12.7% 14.3% 2.8% 8.4%	-15.27 [-16.59, -13.95] Mean Difference IV, Fixed, 95% C -19.30 [-23.90, -14.70] -13.30 [-21.59, -5.01] -13.30 [-16.99, -9.91] -15.50 [-18.83, -12.17] -11.90 [-13.55, -10.25] -13.20 [-14.47, -11.93] Mean Difference IV, Fixed, 95% C] -19.90 [-22.27, -17.53] -6.20 [-8.43, -3.97] -1.70 [-6.71, 3.31] -4.60 [-7.51, -1.69]	-50	-25 C Favours [BA] Mean Dif IV. Fixed -25 C Favours [BA] Mean Dif IV. Fixed	) 25 Favours [Placebo] fference d, 95% Cl ) 25 Favours [Placebo] fference d, 95% Cl	
] - ]	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: 2 D) Apolipoprote Ballantyne 2018 Ballantyne 2019 Goldberg 2019 Laufs 2019 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect: 2 E) HDL-C Study or Subgroup Ballantyne 2018 Goldberg 2019 Gutierrez 2014 Laufs 2019 Ray 2019	41.76, dl Z = 22.7 -14.6 -11.7 -9.3 -7.8 (0.99, dl Z = 20.4 Mean -7.3 -6.4 -1.2 -5.2 -5.92	f = 5 (F 0 (P < <u>SD</u> 20.2 23.1 19.7 16.5 18.1 f = 4 (F <u>SD</u> 16.1 15.6 9.9 916.5 13.5	2531 2 < 0.00 0.0000 Total 181 82 479 224 1485 2451 2451 2451 181 181 181 181 181 224 181 224 1427	001); I <sup>2</sup> : Plaa 4.7 1.6 3.7 3.3 3.3 ); I <sup>2</sup> = 64 1) Pla Mean 12.6 -0.2 0.5 0.05 -0.6 -0.09	cebo SD 16.9 20.8 20.3 13.4 19 % cebo SD 1.4 14.3 9.9 10.3 11.2	1275 Total 88 38 245 107 736 1214 1214 81 253 30 107 726	100.0% Weight 7.6% 2.3% 16.8% 14.5% 58.8% 100.0% Weight 12.7% 14.3% 2.8% 8.4% 61.7%	-15.27 [-16.59, -13.95] Mean Difference IV. Fixed, 95% CI -19.30 [-23.90, -14.70] -13.30 [-21.59, -5.01] -13.30 [-16.09, -9.91] -15.50 [-18.83, -12.17] -11.90 [-13.55, -10.25] -13.20 [-14.47, -11.93] Mean Difference IV. Fixed, 95% CI -19.90 [-22.27, -17.53] -6.20 [-8.43, -3.97] -1.70 [-6.71, 3.31] -4.60 [-7.51, -1.69] -5.83 [-6.90, -4.76]	-50	-25 C Favours [BA] Mean Dif IV. Fixed -25 C Favours [BA] Mean Dif IV. Fixed	) 25 Favours [Placebo] fference 4, 95% Cl 5avours [Placebo] fference 4, 95% Cl	
]	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: 2 D) Apolipoprote Study or Subgroup Ballantyne 2018 Ballantyne 2019 Goldberg 2019 Laufs 2019 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect: 2 E) HDL-C Study or Subgroup Ballantyne 2018 Goldberg 2019 Gulderrez 2014 Laufs 2019 Ray 2019 Total (95% CI)	H1.76, dl Z = 22.7 Mean -14.6 -9.3 -15 -8.6 10.99, dl Z = 20.4 Mean -7.3 -6.4 -1.2 -5.2	f = 5 (F           0 (P <	2531 2 < 0.00 0.0000 Total 181 82 479 224 1485 2451 2451 2451 2451 181 499 30 0.0000 Total 181 224 1427 224 1427 224	Plaa Mean 4.7 1.6 3.7 3.3 1); l <sup>2</sup> = 64 1) Plaa Mean 12.6 -0.2 0.5 -0.6 -0.09	cebo SD 16.9 20.8 20.3 13.4 19 1% cebo SD 1.4 14.3 9.9 9.0 10.3 11.2	Total 88 38 245 107 736 1214 1214 81 253 300 107 726	100.0% Weight 7.6% 2.3% 16.8% 14.5% 58.8% 100.0% Weight 12.7% 14.3% 2.8% 8.4% 61.7%	-15.27 [-16.59, -13.95] Mean Difference IV. Fixed, 95% CI -19.30 [-23.90, -14.70] -13.30 [-21.59, -5.01] -13.00 [-16.09, -9.91] -15.50 [-18.83, -12.17] -11.90 [-13.55, -10.25] -13.20 [-14.47, -11.93] Mean Difference IV. Fixed, 95% CI -19.90 [-22.27, -17.53] -6.20 [-8.43, -3.97] -1.70 [-6.7, 1.69] -5.83 [-6.90, -4.76] Z 45 [ 8.20, -6.51]	-50	-25 C Favours [BA] Mean Dif IV, Fixed 	) 25 Favours [Placebo] fference d, 95% Cl Favours [Placebo] fference d, 95% Cl	50
]	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: 2 D) Apolipoprote Study or Subgroup Ballantyne 2018 Ballantyne 2019 Goldberg 2019 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect: 2 E) HDL-C Study or Subgroup Ballantyne 2018 Goldberg 2019 Gutierrez 2014 Laufs 2019 Ray 2019 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 2	H1.76, dd Z = 22.7 Mean -14.6 -9.3 -15 -8.6 10.99, dd Z = 20.4 Mean -7.3 -6.4 -1.2 -5.2 -5.92	f = 5 (F 0 (P < <u>SD</u> 20.2 23.1 19.7 16.5 18.1 f = 4 (F <u>SD</u> 16.5 16.1 15.6 9.9 16.5 13.5	2531 2 < 0.00 0.0000 Total 181 82 479 224 1485 2451 2451 181 499 30 0.224 1427 224 1427 224 1427 224	Plaa Plaa Mean 4.7 1.6 3.7 1.6 3.3 1) ; l <sup>2</sup> = 64 1) Plaa Mean 12.6 -0.2 0.5 -0.2 0.5 0.6 -0.09 0001) B	cebo SD 16.9 20.8 20.8 20.8 13.4 19 1% cebo SD 1.4 14.3 9.9 10.3 11.2	1275 Total 88 38 245 107 736 1214 1214 81 253 300 107 726 1197 %	100.0% Weight 7.6% 2.3% 16.8% 14.5% 58.8% 100.0% Weight 12.7% 14.3% 2.8% 8.4% 61.7% 100.0%	-15.27 [-16.59, -13.95] Mean Difference IV. Fixed, 95% CI -19.30 [-23.90, -14.70] -13.30 [-21.59, -5.01] -13.00 [-16.09, -9.91] -15.50 [-18.83, -12.17] -11.90 [-13.55, -10.25] -13.20 [-14.47, -11.93] Mean Difference IV. Fixed, 95% CI -19.90 [-22.27, -17.53] -6.20 [-8.43, -3.97] -1.70 [-6.71, 3.1] -4.60 [-7.51, -1.69] -5.83 [-6.90, -4.76] -7.45 [-8.30, -6.61]	-50	-25 C Favours [BA] Mean Dif IV, Fixed 	) 25 Favours [Placebo] fference d. 95% Cl fference d. 95% Cl	
]	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: 2 D) Apolipoprote Study or Subgroup Ballantyne 2018 Ballantyne 2019 Goldberg 2019 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect: 2 E) HDL-C Study or Subgroup Ballantyne 2018 Goldberg 2019 Gutierrez 2014 Laufs 2019 Ray 2019 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect	H1.76, dd Z = 22.7 Mean -14.6 -11.7 -9.3 -15 -8.6 10.99, dd Z = 20.4 Mean -7.3 -6.4 -1.2 -5.9 2 -5.92	f = 5 (F 0 (P < SD 20.2 23.1 19.7 16.5 18.1 f = 4 (F 1 (P < BA SD 16.6 15.6 9.9 16.5 13.5 13.5 df = 4   1 (P <	2531 2 < 0.00 0.0000 Total 181 82 2479 224 1485 2451 2 = 0.03 0.0000 Total 181 499 30 224 1427 2361 (P < 0.0 0.0000	001); I <sup>2</sup> : Plaa <u>Mean</u> 4.7 : 1.6: 3.7 : 0.5 : 3.3 ); I <sup>2</sup> = 64 1) Pla <u>Mean</u> 12.6 0.5 : 0.5 : 10 : 0.5 : 10 : 0.5 : 10	<pre>cebo SD 20.8 20.3 13.4 19 %</pre> cebo 5D 1.4 14.3 9.9 10.3 11.2 2 = 97	1275 5 Total 88 38 2455 107 736 1214 81 253 30 107 726 1197 %	100.0% Weight 7.6% 2.3% 16.8% 14.5% 58.8% 100.0% Weight 12.7% 14.3% 2.8% 8.4% 61.7% 100.0%	-15.27 [-16.59, -13.95] Mean Difference IV. Fixed, 95% CI -19.30 [-23.90, -14.70] -13.30 [-21.59, -5.01] -13.30 [-16.9, -9.91] -15.50 [-18.83, -12.17] -11.90 [-13.55, -10.25] -13.20 [-14.47, -11.93] Mean Difference IV. Fixed, 95% CI -19.90 [-22.27, -17.53] -6.20 [-8.43, -3.97] -1.70 [-6.71, 3.31] -6.60 [-7.51, -1.69] -5.83 [-6.90, -4.76] -7.45 [-8.30, -6.61]	-50	-25 C Favours [BA] Mean Dif IV, Fixed 	25 Favours [Placebo] fference 4, 95% Cl fference 4, 95% Cl	50
] - -	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: 3 D) Apolipoprote Ballantyne 2018 Ballantyne 2019 Goldberg 2019 Laufs 2019 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect: 3 E) HDL-C Study or Subgroup Ballantyne 2018 Goldberg 2019 Gutierrez 2014 Laufs 2019 Ray 2019 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 1 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 1 Total (95% CI)	H1.76, dd Z = 22.7 -14.6 -14.6 -11.7 -9.3 -15 -8.6 10.99, dd Z = 20.4 -7.3 -6.4 -1.2 -5.9 2 -5.92 -5.92	f = 5 (F 0 (P < <u>SD</u> 20.2 23.1 19.7 16.5 18.1 f = 4 (F <u>SD</u> 16.1 15.6 9.9 16.5 13.5 13.5 13.5	2531 2 < 0.00 0.0000 Total 181 82 2479 2 2451 2 = 0.030 0.0000 Total 181 181 499 30 224 1427 2361 (P < 0.000	001); I <sup>2</sup> : Plaa <u>4.7</u> : 1.6 : 3.7 : 0.5 : 3.3 <u>3.3</u> <u>12.6</u> <u>12.6</u> <u>0.5</u> : -0.2 <u>0.5</u> : -0.6 -0.09 0001); I <sup>2</sup> :	<pre>cebo SD 16.9 20.8 13.4 19 % cebo SD 1.4 14.3 9.9 10.3 11.2 ² = 97</pre>	1275 5 Total 88 38 245 1214 1214 1214 81 253 30 107 726 1197 %	100.0% Weight 7.6% 2.3% 16.8% 14.5% 58.8% 100.0% Weight 12.7% 14.3% 8.4% 61.7% 100.0%	-15.27 [-16.59, -13.95] Mean Difference IV. Fixed, 95% CI -19.30 [-23.90, -14.70] -13.30 [-21.59, -5.01] -13.30 [-16.99, -9.91] -15.50 [-18.83, -12.17] -11.90 [-13.55, -10.25] -13.20 [-14.47, -11.93] Mean Difference IV. Fixed, 95% CI -19.90 [-22.27, -17.53] -6.20 [-8.43, -3.97] -1.70 [-6.71, 3.31] -6.60 [-7.51, -1.69] -5.83 [-6.90, -4.76] -7.45 [-8.30, -6.61]	-50 -50	-25 Favours [BA] Mean Dif IV. Fixed -25 Favours [BA] Mean Dif IV. Fixed -25 Favours [BA]	25 Favours [Placebo] fference 4. 95% CI 5 Favours [Placebo] fference 4. 95% CI 5 Favours [Placebo] 5 Favours [Placebo]	50
] - -	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: 2 D) Apolipoprote Study or Subgroup Ballantyne 2018 Ballantyne 2019 Goldberg 2019 Laufs 2019 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect: 2 E) HDL-C Study or Subgroup Ballantyne 2018 Goldberg 2019 Gutierrez 2014 Laufs 2019 Ray 2019 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 1 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect: 2 E) TrigyLoggides	41.76, dl Z = 22.7 -14.6 -11.7 -9.3 -15 -8.6 10.99, dl Z = 20.4 Mean -7.3 -6.4 -1.2 -5.92 -5.92 125.12, 1, Z = 17.3	f = 5 (F 0 (P < <b>BA</b> 20.2 23.1 19.7 16.5 18.1 f = 4 (F <b>BA</b> <b>SD</b> 16.5 13.5 15.6 9.9 16.5 13.5 df = 4 (I (P <	2531 2 < 0.00 0.0000 Total 181 82 2479 224 1485 2451 2451 2451 181 181 181 181 1499 30 224 1427 2361 (P < 0.0 0.0000	001); I <sup>2</sup> : Plaa <u>4.7</u> · 1.6 : 3.7 : 0.5 · 3.3 ); I <sup>2</sup> = 64 ); I <sup>2</sup> = 64 Pla <u>Mean</u> 12.6 0.5 · 0.5 · 0.5 0.5 0.5 0.5 0.5 0.5 0.5 0.5	<pre>cebo SD 16.9 20.8 20.3 13.4 19 % cebo SD 1.4 14.3 9.9 10.3 11.2 ² = 97</pre>	1275 5 Total 88 38 245 107 736 1214 81 253 30 107 726 1197 %	100.0% Weight 7.6% 2.3% 16.8% 14.5% 58.8% 100.0% Weight 12.7% 14.3% 2.8% 8.4% 61.7% 100.0%	-15.27 [-16.59, -13.95] Mean Difference IV. Fixed, 95% C -19.30 [-23.90, -14.70] -13.30 [-21.59, -5.01] -13.30 [-16.99, -9.91] -15.50 [-18.83, -12.17] -11.90 [-13.55, -10.25] -13.20 [-14.47, -11.93] Mean Difference IV. Fixed, 95% C -19.90 [-22.27, -17.53] -6.20 [-8.43, -3.97] -1.70 [-6.71, 3.31] -4.60 [-7.51, -1.69] -5.83 [-6.90, -4.76] -7.45 [-8.30, -6.61]	-50 -50	-25 Favours [BA] Mean Dif IV. Fixed -25 Favours [BA] Mean Dif IV, Fixed -25 Favours [BA]	) 25 Favours [Placebo] fference 4. 95% Cl 5. Favours [Placebo] fference 4. 95% Cl 	50
] - - ]	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: 3 D) Apolipoprote Ballantyne 2018 Ballantyne 2019 Goldberg 2019 Laufs 2019 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect: 3 E) HDL-C Study or Subgroup Ballantyne 2018 Goldberg 2019 Gutierrez 2014 Laufs 2019 Ray 2019 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 1 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 1 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect: 3	41.76, dl Z = 22.7 -14.6 -11.7 -9.3 -15 -8.6 10.99, dl Z = 20.4 Mean -7.3 -6.4 -1.2 -5.2 -5.92 125.12, 1, Z = 17.3	f = 5 (F 0 (P < <b>BA</b> 20.2 23.1 19.7 16.5 18.1 f = 4 (F <b>BA</b> <b>SD</b> 16.5 13.5 df = 4  1 (P <	2531 2 < 0.00 0.0000 181 181 82 479 224 1485 2451 2451 2451 181 181 181 181 181 182 2451 224 1427 2361 (P < 0.0 0.0000	001); I <sup>2</sup> : Plaa <u>4.7</u> · 1.6 : 3.7 : 0.5 · 3.3 ); I <sup>2</sup> = 64 <u>1</u> ) <u>Pla</u> <u>Mean</u> · 12.6 -0.2 0.5 -0.6 -0.09 0001); I <sup>2</sup>	<pre>cebo SD 16.9 20.8 20.3 13.4 19 % cebo SD 1.4 14.3 9.9 10.3 11.2 2 = 97</pre>	1275 5 Total 88 38 245 107 736 1214 81 253 30 107 726 1197 %	100.0% Weight 7.6% 2.3% 16.8% 14.5% 58.8% 100.0% Weight 12.7% 14.3% 2.8% 8.4% 61.7%	-15.27 [-16.59, -13.95] Mean Difference IV. Fixed, 95% CI -19.30 [-23.90, -14.70] -13.30 [-21.59, -5.01] -13.30 [-16.09, -9.91] -15.50 [-18.83, -12.17] -15.50 [-18.83, -12.17] -13.20 [-14.47, -11.93] Mean Difference IV. Fixed, 95% CI -19.90 [-22.27, -17.53] -6.20 [-8.43, -3.97] -1.70 [-6.71, 3.31] -4.60 [-7.51, -1.69] -5.83 [-6.90, -4.76] -7.45 [-8.30, -6.61]	-50	-25 C Favours [BA] Mean Dif IV. Fixed -25 C Favours [BA] Mean Dif IV. Fixed -25 C Favours [BA]	) 25 Favours [Placebo] fference 3, 95% Cl 5 Favours [Placebo] fference 4, 95% Cl 	
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] - - ]	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: 2 D) Apolipoprote Study or Subgroup Ballantyne 2018 Ballantyne 2019 Goldberg 2019 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect: 2 E) HDL-C Study or Subgroup Ballantyne 2018 Goldberg 2019 Gutierrez 2014 Laufs 2019 Ray 2019 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 1 Total (95% CI)	H1.76, dd Z = 22.7 Mean -14.6 -9.3 -15 -8.6 10.99, dd Z = 20.4 Mean -7.3 -6.4 -1.2 -5.9 2 -5.92 125.12, Z Z = 17.3	f = 5 (F 0 (P < SD 20.2 23.1 19.7 16.5 18.1 f = 4 (F 1 (P < BA 5D 16.1 15.6 9.9 16.5 13.5 df = 4 ( 1 (P < BA SD 20.2 23.1 19.7 16.5 13.5	2531 2 < 0.00 0.0000 Total 181 82 479 224 1485 2451 2451 2451 2451 2451 181 499 30 0.0000 Total (P < 0.0 0.00000 0.0000 0.000000 0.00000 0.0000 0.00000 0.00000 0.000000 0.0000 0	0001); I <sup>2</sup> : Plaa <u>Mean</u> 4.7 · 1.6 : 3.7 : 0.5 · 3.3 ); I <sup>2</sup> = 64 1) Plaa <u>Mean</u> 12.6 · -0.2 · 0.5 · 0.001); I <sup>2</sup> 10 Pla <u>Mean</u> 12.6 · -0.2 · 0.5 · -0.2 · 0.5 · -0.2 · 0.5 · -0.2 · -0.6 · -0.6 · -0.2 · -0.6 · -0.6 · -0.2 · -0.6 · -0.6 · -0.2 · -0.6 · · -0.6 · -0.6 · · -0.6 · · · · · · · · · · · · · ·	= 88% cebo 16.9 20.8 13.4 19 % cebo SD 1.4 14.3 9.9 1.4 14.3 9.9 1.4 11.2 <sup>2</sup> = 97 acebo SD	1275 Total 88 38 245 107 736 1214 1214 81 253 30 107 726 1197 %	100.0% Weight 7.6% 2.3% 16.8% 14.5% 58.8% 100.0% Weight 12.7% 14.3% 2.8% 8.4% 61.7% 100.0%	Mean Difference IV. Fixed, 95% Cl -19.30 [-23.90, -14.70] -13.30 [-21.59, -5.01] -13.30 [-16.99, -9.91] -15.50 [-18.83, -12.17] -11.90 [-13.55, -10.25] -13.20 [-14.47, -11.93] Mean Difference IV. Fixed, 95% Cl -5.83 [-6.90, -4.76] -7.45 [-8.30, -6.61] Mean Difference IV. Fixed, 95% Cl	-50 -50	-25 C Favours [BA] Mean Dif IV, Fixed -25 C Favours [BA] Mean Dif IV, Fixed -25 C Favours [BA]	fference d. 95% Cl fference d. 95% Cl fference d. 95% Cl fference fference g. 95% Cl	50 50 50
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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; Tau<sup>2</sup> and I<sup>2</sup> 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. For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml



# 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
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
2 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 <sup>2</sup> ) for each meta-analysis. For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	4/5

Page 29 of 28



## 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	<u> </u>	<u>1</u>	
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	1		
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, Altm	an DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med	6(6): e1000097
<u>/</u> doi.10.1371/journal.pmed1000097 }		For more information, visit: www.prisma-statement.org.	
4 5		Page 2 of 2 For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

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# **BMJ Open**

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

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Date Submitted by the Author:	26-Nov-2021
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<b>Primary Subject Heading</b> :	Cardiovascular medicine
Secondary Subject Heading:	Pharmacology and therapeutics
Keywords:	Ischaemic heart disease < CARDIOLOGY, PREVENTIVE MEDICINE, CLINICAL PHARMACOLOGY, Clinical trials < THERAPEUTICS

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Clinical efficacy and safety outcomes of bempedoic acid for LDL-C lowering therapy in patients at high 1 1 2 2 cardiovascular risk: a systematic review and meta-analysis 3 3 Short title: meta-analysis of bempedoic acid for LDL-C lowering therapy in CVD 4 5 6 4 Authors: Yingfeng Lin<sup>1</sup>; Claudio Parco<sup>1</sup>; Athanasios Karathanos<sup>1</sup>; Torben Krieger<sup>1</sup>; Volker Schulze<sup>1</sup>; Nadja 75 Chernyak<sup>2</sup>; Andrea Icks<sup>2</sup>; Malte Kelm<sup>1,3</sup>; Maximilian Brockmeyer<sup>1\*</sup>; Georg Wolff<sup>1\*</sup> 8 6 \* both authors contributed equally 9 10 Affiliations:  $11^{7}$ 128 <sup>1</sup> Division of Cardiology, Pulmonology and Vascular Medicine, Department of Internal Medicine, Medical Faculty,  $13_{9}$ Heinrich-Heine-University, Düsseldorf, Germany  $14^{14}$  $15^{10}$ <sup>2</sup> Institute for Health Services Research and Health Economics, Centre for Health and Society, Medical Faculty, Heinrich-Heine-University, Düsseldorf, Germany 161 172 <sup>3</sup> CARID - Cardiovascular Research Institute Düsseldorf, Germany 18 19 20<sup>3</sup> Correspondence to: 214 Georg Wolff, MD 245 Division of Cardiology, Pulmonology and Vascular Medicine, Department of Internal Medicine, Medical Faculty, 23 24 Heinrich-Heine-University, Düsseldorf, Germany Moorenstr. 5 257 268 40225 Düsseldorf, Germany 279 Phone: 0049-211-81-18801 28 29<sup>0</sup> Fax: 0049-211-81-18812 3**Q**1 E-mail: <u>Georg.Wolff@med.uni-duesseldorf.de</u> 31 32,2 33<sup>2</sup> 34<sup>3</sup> Keywords: Bempedoic acid, atherosclerotic cardiovascular disease, clinical efficacy and safety outcomes, low-3₽4 density lipoprotein cholesterol 3625 37<sub>26</sub> 38 Word count: 3,477 words **32**7 40 41 42 43 44 45 46 47 48 49 50 51

### 1 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.

5 Data sources: MEDLINE, Cochrane Central Register of Controlled Trials, Google Scholar, Embase,
6 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).

9 Conclusion: BA in high CV risk patients showed no significant effects on major CV outcomes in short-term followup. 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.

### 4 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.

7 - Sole inclusion of RCTs may reduce selection bias.

48 - Major clinical outcomes including major adverse cardiovascular events, all-cause mortality, cardiovascular
 5
 69 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.

#### 1 1 **INTRODUCTION**

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3 2 Hypercholesterolemia is one of the major risk factors of cardiovascular disease, which is the leading cause of death 53 worldwide.[1] The current guideline on the management of blood cholesterol of the American College of Cardiology 74 / American Heart Association recommends to reduce low-density lipoprotein cholesterol (LDL-C) levels by  $\geq$ 50% 95 in patients at high cardiovascular risk, using maximally tolerated statin therapy and – if LDL-C levels remain  $\geq$ 70 10 mg/dL – additional non-statin drugs, e.g. ezetimibe (class I).[2] The European society of cardiology 2019 guideline 116 12 137 even emphasizes a lower LDL-C goal of absolute LDL-C levels <55 mg/dl and a 50% relative LDL-C reduction from 14 baseline in adults at very high cardiovascular risk (class I) under intensified lipid-lowering therapy.[3] Additional 158 16 proprotein convertase subtilisin/kexin type 9 (PSCK-9)-inhibitors are recommended (class I, for both societies) in 179 18 patients at very high risk, who are not achieving treatment goals on a maximum tolerated dose of a high-intensity 190 20 statin and ezetimibe.[2-4] 211

232 Bempedoic acid (BA) is a novel, oral, non-statin, once daily LDL-C lowering drug, which acts as a direct competitive 24 25<sup>3</sup> inhibitor of ATP citrate lyase, a key enzyme linking carbohydrate to lipid metabolism with the effect of upregulating 26 274 hepatic LDL receptor expression and activity.[5] Earlier in 2020, both the United States Food and Drug 28 29<sup>5</sup> Administration and European Medicines Agency approved BA for treatment of adults with heterozygous familial 30 31<sup>6</sup> hypercholesterolemia (HeFH) or established atherosclerotic cardiovascular disease (ASCVD), who require additional 32 33<sup>7</sup> reduction of LDL-C despite optimal diet and maximally tolerated statin therapy. Efficacy and safety of additional 34 35 treatment with BA on maximally tolerated statin therapy have been investigated in randomized controlled trials 36<sub>9</sub> 37 (RCTs),[6-11] however individual trial sample sizes were too small to judge cardiovascular efficacy outcomes.

38<sub>20</sub> 39 To further evaluate this, we performed a systematic review and meta-analysis of RCTs to investigate BA efficacy 40<u>9</u>1 41 with regard to cardiovascular outcomes and BA safety – based on all available evidence.

### **Methods**

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**40**4 This systematic review and the accompagnied meta-analysis was performed according to established methods 47 recommended by the Cochrane Collaboration guidelines and the PRISMA (Preferred Reporting Items for Systematic **42**5 49 reviews and Meta-Analyses) statement.[12, 13] The review protocol was not registered. 5**Q**6 51

#### Data sources and search strategy **53**7

The online database MEDLINE was systematically searched for published reports up until November 1<sup>st</sup> 2021. The 528 56 following keywords were used during searches (in combinations, among others): bempedoic acid, BA, ETC-1002, 529 58 randomized controlled trial, hypercholesterolemia. Additionally, the Cochrane Central Register of Controlled Trials, 5**9**0 60

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1 1 Google Scholar, Embase, ClinicalTrials.gov, Clinical Trial Results (www.clinicaltrialresults.org) and the American 2 College of Cardiology Web site (www.cardiosource.com) were non-systematically searched for ongoing trials and 53 major congress proceedings. Article bibliographies were additionally screened and relevant articles were added to 74 the systematic review process.

#### 105 Study selection 11

All obtained references from primary searches were screened based on title and abstract and categorized further; if 126 13 147 content was considered relevant, they were retrieved as full text reports for detailed evaluation. All controlled trials 15 randomizing BA to placebo and reporting cardiovascular outcomes, which were available in English language and 168 17 in full text, were eligible for inclusion. Non-randomized studies were excluded, as were trials without reports of 189 19 2**d**0 clinical efficacy outcomes and trials investigating PCSK9-inhibitors or inclisiran additionally to BA. No restrictions 21 on follow-up duration, populations or study size were applied. 221

#### 24 Efficacy and safety outcomes 2\$2

26 27<sup>3</sup> Clinical outcomes were defined according to individual study protocols and were analyzed as reported. Primary 28 29<sup>4</sup> efficacy outcomes of interest were major adverse cardiovascular events (MACE), all-cause mortality, cardiovascular 30 31<sup>15</sup> (CV) mortality, and nonfatal myocardial infarction (MI); additional efficacy outcomes of coronary and non-coronary 32 33<sup>6</sup> revascularization, nonfatal stroke, hospitalization for heart failure, and hospitalization for unstable angina were also 34 35 analyzed. Safety outcomes included new onset or worsening of diabetes mellitus (DM), muscular disorders, 36 37 gout/elevation in uric acid and worsening of renal function, among others. Drug efficacy on lipid levels was also 38<sub>9</sub> 39 assessed.

### 41<sub>20</sub> 42 Data collection and quality assessment

43<u>3</u>1 44 Data from included trials were identified, abstracted into prespecified forms and analyzed according to the intention-**45**22 to-treat principle. Cross-checking between investigators was performed to assure internal validity; divergences 46 4723 between investigators were resolved by consensus. Bias risk was appraised [13] and the grading of recommendation, 48 **49**4 assessment, development and evaluation (GRADE) working group certainty rating [14] of primary outcomes was 50 525 performed by two unblinded investigators, who cross-checked each other for errors.

**54**6 Statistical analyses

5**6**7 RevMan 5.3 (Cochrane Collaboration) was used for statistical computations. Odds ratios (OR) and 95% confidence 57 intervals (CI) were used as summary statistics for dichotomous clinical outcome variables, Forest plots were used for 5**8**8 59 6Ø9 graphical display. The Cochran-Mantel-Haenszel method was applied to compute summary statistics using a fixed1 1 effects model.[15] The summary I<sup>2</sup> statistic was used to quantify heterogeneity.[16-18] A Fixed-effects models were 3 2 used throughout the study due to low I<sup>2</sup>, a confirmatory analysis using random-effects models [19] was additionally 53 performed.

74 To analyze BA effects on serum lipid levels, data were extracted using mean differences (MD) and standard 95 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 116 137 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 158 pooled effect measures. An alpha-error probability of p < 0.05 was considered statistically significant in all 179 calculations. To ascertain validity of results and account for trial heterogeneity, especially inhomogeneous duration 190 of follow-up, prespecified sensitivity analyses of primary clinical efficacy and safety outcomes stratified by duration 211 of follow-up (short-term (<12 weeks) vs. longer-term (>12 weeks)) were conducted. 232

### 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

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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**

#### **44**2 Study selection and patient population

4**6**3 The PRISMA flow chart of the systematic review process is depicted in Supplementary Figure 1: Of the 184 studies 47 **42**4 initially identified, 90 were excluded based on title/abstract and 79 studies for being editorials, reviews, other meta 49 505 analyses or in vitro studies; nine trials did not meet explicit inclusion criteria due to non-randomized design or non-51 **52**6 reporting of clinical outcomes; six studies comprising a total of 3,956 patients were finally included in the meta-53 analysis.[6-11] **54**7 55

Study and patients characteristics are reported in Table 1 and Table 2: Five studies were phase 3 RCTs published 568 57 between 2018 and 2019, Gutierrez et al. was a phase 2b RCT published in 2014.[11] Three trials included patients 589 59 treated with a maximally-tolerated statin background therapy, [7, 8, 10] three trials with statin intolerance or after 6**ĝ**0

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1 1 after discontinuation of lipid-lowering therapy.[6, 9, 11] Patients were between 55 and 67 years old, most were 3 2 overweight (average BMI of 29-31), suffered from a considerable cardiovascular risk profile (high rates of ASCVD, 5 3 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]

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### 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 <u>vs.</u> 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 <u>vs.</u> BA 180 mg/d <u>vs.</u> ezetimibe 10 mg/d* <u>vs.</u> 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 <u>vs.</u> 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 <u>Tertiary</u> : 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/m <sup>2</sup> without lipid-lowering drugs	BA 80 mg/d for 2 wks followed by 120 mg/d for 2 <u>vs.</u> placebo	60 (30 BA; 30 placebo)	4	<u>Primary</u> : 4-wk change (%) of LDL-C <u>Secondary</u> : 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 <u>vs.</u> 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,

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		further LDL-C lowering on no				HDL-C, and TG; 12-wk and 24-wk absolute change of
		more than low-dose statin therapy				LDL-C
		or other lipid-lowering drugs				
Ray et al.[10],	RCT	ASCVD and/or USEIL with I DI		2220		Primary: Number of participants with treatment related
2019	(double-	ASC VD and/or HEFH with LDL-	BA 180 mg/d <u>vs.</u>	(1499 DA 742	50	AEs
(CLEAR	blind,	C >70 mg/dL on maximal tolerated	placebo	(1488 BA, 742	52	Secondary: 12-wk, 24-wk, and 52-wk change (%) of
Harmony)	phase 3)	iipid-iowering inerapy		placebo)		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-densitylipoprotein 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.

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### Table 2 – Patients characteristics

Dahlingtion and	Arms	Age	Female	ASCVD	DM	AHT	BMI	CKD	ТС	LDL-C	HDL-C	Non-	TG	apoB	hs-CRP
Publication, year		(y)	(%)	(%)	(%)	(%)	(kg/m <sup>2</sup> )	(%)	(mg/dL)	(mg/dL)	(mg/dL)	HDL-C	(mg/dL)	(mg/dL)	(mg/L)
(acronym)												(mg/dL)			
Ballantyne et al.[6],	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
2018	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
(CLEAR															
Tranquility)			4												
Ballantyne et al.[7],	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
2019	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],	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
2019	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
(CLEAR Wisdom)															
Gutierrez et al.[11],	BA	55.3	43.3	-	100	26.7	30.6		206.3	125.2	43.7	-	181.5	-	2.3
2014	Placebo	56.0	33.3	-	100	26.7	29.2	-	206.7	128.4	47.4	-	152.0	-	2.2
Laufs et al.[9],	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
2019	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
(CLEAR Serenity)															
Ray et al.[10],	BA	65.8	26.1	97.4	28.6	78.9	-	-	179.7	103.6	48.7	130.9	126	88.5	1.49
2019	Placebo	66.8	28.7	98.0	28.6	80.1	-	-	178.6	102.3	49.3	129.4	123	86.8	1.51
(CLEAR Harmony)															

<u>Table 2:</u> 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-

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1 2	density lipoprotein cholesterol; apoB=apolipoprotein B; HDL-C=high-density lipoprotein cholesterol; hsCRP=high-sensitivity C-reactive protein; non-HDL-C=non-high
- 3 4	density lipoprotein cholesterol. Lipids are presented as means, hs-CRP as medians; † ASCVD and/or heterozygous familial Hypercholesterolemia. * not included in the meta
5	analysis.
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#### **Ouality and risk of bias of included studies** 1 1

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2 All included studies were adequately controlled, double-blind, without incomplete or selective reporting of data 3 indicating a high quality. Some residual risk of bias regarding sequence generation, [7, 9, 11] allocation 4 concealment,[11] and blinding of outcomes assessor remained unclear.[11] Risk of bias assessment of included 8 5 studies according to Cochrane Collaboration guidelines [13] is reported in Supplementary Table 1. Certainty rating 10 11 of consistency of estimated and true effects of primary outcomes according to GRADE working group [14] revealed 12<sub>7</sub> 13 low certainty for MACE and all-cause mortality; certainty for CV mortality and nonfatal MI was rated moderate.  $14_{8}$ GRADE rating is reported in Supplementary Table 2.

179 Bempedoic acid efficacy for cardiovascular outcomes 18

190 Four RCTs with 3,413 patients reported data on MACE (Figure 1A),[8-11] with no significant difference with BA 20 21/1 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; 22 232 heterogeneity p=0.34; I<sup>2</sup>=11%). Five RCTs with 3,895 patients were included in the analysis of all-cause mortality 24 and three RCTs with 3,353 patients in the analysis of CV mortality (Figure 1B and 1C), but death was a very rare 253 26 event and occurred only in two studies with longer follow-up.[6-10] There was no difference in all-cause mortality 2714 28 (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<sup>2</sup>=0%) and in CV 295 30 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;  $I^2 = 0\%$ ). 316 32 Data from four RCTs with 3,413 subjects were analyzed on nonfatal MI (Figure 1D),[8-11] with a borderline-3317 34 significant trend towards benefits of BA compared to placebo (1.1% (BA) vs. 2.0% (placebo); OR 0.57; 95% CI 0.32 348 36 37<sup>9</sup> to 0.99; p=0.05; heterogeneity p=0.56;  $I^2=0\%$ ).

38 39<sup>0</sup> Meta-analysis of additional efficacy outcomes in 3 RCTs with 3353 patients are reported in Supplementary Figure 40 41<sup>21</sup> 2:[8-10] There were no significant differences in coronary revascularization (OR 0.82; 95% CI 0.55 to 1.22; p=0.32; 42 43<sup>2</sup> 44 45<sup>3</sup> 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; 46 47<sup>4</sup> heterogeneity p=0.66; I<sup>2</sup>=0%; Supplementary Figure 2B).

48 49<sup>5</sup> There were no significant differences in nonfatal stroke (OR 1.26, 95% CI 0.42 to 3.76; p=0.68; Supplementary 50,6 51 Figure 2C), hospitalization for heart failure (OR 2.33; 95% CI 0.67 to 8.11; p=0.19; Supplementary Figure 2D) or 52<sub>7</sub> 53 hospitalization for unstable angina (OR 0.94; 95% CI 0.51 to 1.74; p=0.84; Supplementary Figure 2E).

#### 5<u>5</u>8 **Bempedoic acid safety outcomes** 56

5729 Meta-analysis of four RCTs comprising 3,622 patients showed significantly lower rates of new-onset or worsening 58 530 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 60

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1 1 2A). In contrast, however, gout rates were significantly higher in BA treated patients (1.5% (BA) vs. 0.5% (placebo); 3 2 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% 53 (BA) vs. 2.0% (placebo); OR 2.60; 95% CI 1.15 to 5.91; p=0.02; Supplementary Figure 3A). Muscular disorders 74 were numerically more frequent under BA treatment (10.9% (BA) vs. 9.1% (placebo); OR 1.25, 95% CI 0.99 to 1.57; 95 p=0.06; Figure 2C). Worsening of renal function was rare but nummerically more frequent under BA treatment, 10 evident in decreases of estimated glomerular filtration rate (0.7% (BA) vs. 0.1% (placebo); OR 4.24; 95% CI 0.98 to 116 12 137 18.39; p=0.05; Figure 2D) and increases in serum creatinine levels (0.8% (BA) vs. 0.4% (placebo); OR 2.01; 95% 14 CI 0.67 to 6.02; p=0.21; Supplementary Figure 3B). 158

Additional safety outcomes of upper respiratory tract infection (OR 0.82; 95% CI 0.63 to 1.06; p = 0.13; 179 18 Supplementary Figure 3C), urinary tract infection (OR 0.84, 95% CI 0.62 to 1.14; p=0.25; Supplementary Figure 190 20 3D), neurocongnitive disorders (OR 1.00, 95% CI 0.58 to 1.74; p=0.99; Supplementary Figure 3E), and 211 22 232 nasopharyngitis (OR 0.88; 95% CI 0.68 to 1.14; p=0.33; Supplementary Figure 3F) showed no significant differences 24 25<sup>3</sup> between BA and placebo treatment.

### 27 28<sup>14</sup> Bempedoic acid efficacy for serum lipid levels

29 30<sup>5</sup> Meta-analysis of effects of BA vs. placebo on serum lipid levels is summarized in Figure 3, forest plots showing 31 326 individual and summary mean differences (MD) between groups are presented in Supplementary Figure 4. Overall, 33 347 a MD in LDL-C levels of -19.93 % from baseline was observed with the use of BA compared to placebo (95% CI -35<sub>8</sub> 36 21.55 to -18.31; p<0.01; Supplementary Figure 4A). Treatment with BA also significantly reduced total cholesterol 37<sub>9</sub> 38 (MD -12.43%; 95% CI -13.42 to -11.43, p<0.01; Supplementary Figure 4B), non-high density lipoprotein cholesterol 39<sub>20</sub> 40 (non-HDL-C) (MD -15.27%; 95% CI -16.59 to -13.95, p<0.01; Supplementary Figure 4C), and apolipoprotein B 4½1 42 (apoB) (MD -13.20%; 95% CI -14.47 to -11.93, p<0.01; Supplementary Figure 4D) compared to placebo. A slight **43**<sub>22</sub> reduction in high-densitiv lipoprotein cholesterol levels was seen under BA compared to placebo (MD -7.5%, 95% 44 **45**23 CI -8.30 to -6.61, p<0.01; Supplementary Figure 4E); BA treatment did not influence triglyceride levels (MD 3.35%, 46 4724 95% CI -1.78 to 8.49, p=0.20; Supplementary Figure 4F).

#### **50**5 Sensitivity analyses

5**2**6 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.

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#### 1 1 DISCUSSION

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3 2 This is a systematic review and meta-analysis of all currently available randomized controlled trial evidence on 53 efficacy and safety of BA vs. placebo therapy with respect to clinical outcomes. The main findings are that -74 compared with placebo – BA therapy had 1) no significant effects on efficacy outcomes of MACE, mortality or 95 myocardial infarction; 2) significant benefits regarding new-onset or worsening of diabetes mellitus, albeit 10 detrimental effects on gout and possibly on renal function and muscular disorders; 3) significant decreases of 116 12 137 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 158 16 prevention.[2, 3] Administration of statins is the first-line therapy to reduce serum LDL-C, however a proportion of 179 18 patients develops statin-associated muscle symptoms and other side effects with impact on treatment adherence. [20, 190 20 211 21] On the other hand, many patients do not attain treatment goals despite adequate high-intensity statin therapy. [22, 22 232 23] PCSK9-inhibitors – a novel alternative for highest-risk patients – hold disadvantages of high therapy costs and 24 25<sup>3</sup> subcutaneous application. [24, 25] Thus, BA is a promising oral alternative for LDL-C lowering therapy in patients 26 274 at high cardiovascular risk with either statin intolerance or inadequate treatment goal attainment. It has been approved 28 29<sup>5</sup> by the United States Food and Drug Administration and European Medicines Agency earlier in 2020.

30 31<sup>16</sup> Several pooled analyses of trials investigating effects of BA have been performed at the same time by other 32 33<sup>7</sup> groups.[26-30] The majority of those focused on BAs capacities in lipid-lowering with comparable results to the 34 18 35 current analysis: Allocation to BA as compared to placebo led to highly significant reductions in major atherogenic 36<sub>9</sub> 37 lipid fractions of LDL-C, Non-HDL and, apoB.[26-29] In contrast, primary interest of the current meta-analysis was 38<sub>20</sub> 39 to assess evidence on BAs efficacy in improving relevant clinical outcomes, which is the fundamental objective of 40<u>0</u>1 41 pharmacological lipid-lowering. The current work is, along with another recent publication,[30] the first to provide 42<sub>22</sub> 43 information on this.

**443** Although BA showed a significant reduction of LDL-C, Non-HDL, and apoB from baseline, current pooled analysis 45 **40**4 could not find relevant impact on major clinical outcomes. Primarily, duration of follow-up ranging from 4 to 52 47 weeks across included trials was presumably too short to observe an effect of reduced LDL-C and other atherogenic **42**5 49 lipid fractions on major cardiovascular outcomes. In addition, combined outcome of MACE associated with higher 5**Q**6 51 event rates and than singular outcomes increasing likelihood of detecting benefical treatment effects was extractable 5**2**7 53 from four of six RCTs only which assumeably may have limited sample size too much to observe short-term effects. **54**8 55 Large scale RCTs investigating LDL-C lowering agents such as statins, ezetimibe or PCSK9-inhibitors that could 5**6**9 57 demonstrate a beneficial effect of LDL-C lowering on MACE [24, 25, 31] or mortality [32, 33] in patients with high 5**§**0 59 cardiovascular risk had a follow-up that was considerably longer (at least 2.2 to more than 6 years) with larger sample 6**9**1

1 1 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 clarify 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 **59**0 60

1 1 consistency of estimated and true effects. Variation in length of follow-up may introduce bias; multiple testing bears 3 2 additional risk. Additional limitations include trial heterogeneity in study co-medication (no statin vs. maximal 53 tolerated statin, additional ezetimibe) and selection of patients regarding baseline cardiovascular risk and potential 74 benefical effects of lipid-lowering (patients with established ASCVD vs. patient at high cardiovascular risk). 95 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 116 137 recommendation for treatment with BA.

#### **Future directions** 168

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If results of large scale CLEAR-Outcomes RCT (NCT02993406) will be positive for primary endpoint of MACE 189 2**d**0 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 221 **24**2 proportion of patients by ezetimibe added to high-intensity statin only. In many of them LDL-C is still above 25 20<sup>3</sup> treatment goal but <100 mg/dL. In this range addition of a PCSK9-inhibitor is not assuredly effective in improving 27 28<sup>14</sup> outcomes but causes high treatment costs.[35, 37] Here, BA could be an effective alternative with lower treatment 29 30<sup>5</sup> costs when smaller reductions of LDL-C are needed to achieve treatment goal. Moreover, patients with statin-31 326 intolerance caused by muscle symptoms not requiring intense LDL-C lowering due to baseline risk or baseline LDL-33 34<sup>7</sup> C might profit from a statin-free regimen including BA and ezetimibe since rates of musclular disorders appear low 35 36 not markedly exceeding placebo in current meta-analysis. BAs potential in these specific settings has to be evaluated 37<sub>9</sub> 38 by future adequately designed RCTs analyzing relevant clinical outcomes.

### **CONCLUSION**

**43**<sub>2</sub>2 Meta-analysis of bempedoic acid vs. placebo in patients at high cardiovascular risk showed no significant effects on **45**23 major cardiovascular outcomes in short-term follow-up, despite significant reductions of LDL-C and other 4724 atherogenic lipid fractions. Unfavourable effects on muscular disorders, renal function, and the incidence of gout **42**5 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. 526

#### **Contributorship statement** 528

YL, MB, and GW conceived and designed the study; YL, CP, and AK collected sources, selected studies and 529 58 abstracted data; YL, AK, and TK performed doublechecks; YL and GW performed the statistical analysis; all authors 5**9**0 60

1 <sub>1</sub> 2	analyzed and interpreted the data; YL and MB drafted the first manuscript version; NC, AI, MK, MB, CP, VS, and
3 <sub>2</sub> 4 5	GW thoroughly revised it; all authors read, critically revised and accepted the submitted version of the manuscript.
63 7	Competing interests
84 9	MB reported personal fees for speaking at an expert meeting in lipidology sponsored by Daiichi-Sankyo after primary
105 11 12	submission of the current work. The other authors declare no conflicts of interest.
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16 178 18	Düsseldorf (No. 2018-32) for a clinician scientist track.
19 209	Data sharing statement
21 220 23 241 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54	All data relevant to the study are included in the article or uploaded as supplementary information.
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### <sup>1</sup> 1 **Figure legends**

<u>Figure 1:</u> 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<sup>2</sup> measures heterogeneity;
 BA=bempedoic acid; M-H=Mantel-Haenszel.

<u>Figure 2</u>: 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<sup>2</sup> measures heterogeneity.
 BA=bempedoic acid; GFR=glomerular filtration rate; M-H=Mantel-Haenszel.

<u>Figure 3</u>: 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.

review only

### Figure 1 – Efficacy outcomes of BA vs. placebo therapy

#### A) MACE

	BA	Placebo		Odds Ratio	Odds Ratio
Study or Subgroup	Events Tot	al Events Total	Weight	M-H, Fixed, 95% C	CI M-H. Fixed, 95% CI
Goldberg 2019	30 52	22 20 257	31.2%	0.72 [0.40, 1.30]	
Gutierrez 2014	0 3	30 1 30	1.8%	0.32 [0.01, 8.24]	
Laufs 2019	9 23	34 0 111	0.8%	9.39 [0.54, 162.88]	
Ray 2019	68 148	42 742	66.1%	0.80 [0.54, 1.19]	• •
Total (95% CI)	227	3 1140	100.0%	0.84 [0.61, 1.15]	•
Total events	107	63			
Heterogeneity: Chi <sup>2</sup> = 3	3.38, df = 3 (P	= 0.34); I <sup>2</sup> = 11%			
Test for overall effect:	Z = 1.11 (P = 0	0.27)			Favours [BA] Favours [Placebo]

B) All-cause mortality

	BA		Place	bo		Odds Ratio		Odds	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C		M-H, Fixe			
Ballantyne 2018	0	181	0	88		Not estimable					
Ballantyne 2019	0	218	0	55		Not estimable					
Goldberg 2019	6	522	2	257	50.0%	1.48 [0.30, 7.40]					
Laufs 2019	0	234	0	111		Not estimable					
Ray 2019	13	1487	2	742	50.0%	3.26 [0.73, 14.50]		-		_	
Total (95% CI)		2642		1253	100.0%	2.37 [0.80, 6.99]		-			
Total events	19		4								
Heterogeneity: Chi <sup>2</sup> = 0	0.48); l² =	0%						+	100		
Test for overall effect: 2	2)				0.01	Favours [BA]	Favours [F	Placebo	)]		

#### C) Cardiovascular mortality

	BA	Placebo			Odds Ratio			Odds Ratio				
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixe	1, 95% CI			
Goldberg 2019	4	522	2	257	66.7%	0.98 [0.18, 5.41]						
Laufs 2019	0	234	0	111		Not estimable						
Ray 2019	6	1487	1	742	33.3%	3.00 [0.36, 24.98]		-	•			
Total (95% CI)		2243		1110	100.0%	1.66 [0.45, 6.04]						
Total events	10		3									
Heterogeneity: Chi <sup>2</sup> =	0.66, df =	1 (P = (	0.42); l <sup>2</sup> =	0%						400		
Test for overall effect:	Z = 0.77 (	P = 0.4	4)				0.01	Favours [BA]	Favours [Pla	cebo]		

#### D) Nonfatal myocardial infarction

	BA		Placebo			Odds Ratio		Odds Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	1	M-H, Fixed, 95% CI			
Goldberg 2019	6	522	9	257	38.2%	0.32 [0.11, 0.91]					
Gutierrez 2014	0	30	1	30	4.7%	0.32 [0.01, 8.24]			-		
Laufs 2019	1	234	0	111	2.2%	1.43 [0.06, 35.45]					
Ray 2019	19	1487	13	742	54.9%	0.73 [0.36, 1.48]					
Total (95% CI)		2273		1140	100.0%	0.57 [0.32, 0.99]		•			
Total events	26		23								
Heterogeneity: Chi <sup>2</sup> =	2.05, df = 3	3 (P = 0	0.56); l <sup>2</sup> =	0%					+	100	
Test for overall effect:	Z = 2.00 (	P = 0.0	5)				0.01	Favours [BA] Favours [	Placebo]	100	

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<sup>2</sup> measures heterogeneity; BA=bempedoic acid; M-H=Mantel-Haenszel.

127x159mm (300 x 300 DPI)

#### Figure 2 – Safety outcomes of BA vs. placebo therapy

#### A) New-onset or worsening of diabetes mellitus

	BA		Placebo			Odds Ratio		Odds Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	1	M-H, Fixe	d, 95% CI		
Ballantyne 2018	2	181	2	88	3.1%	0.48 [0.07, 3.47]					
Goldberg 2019	36	522	19	257	28.0%	0.93 [0.52, 1.65]			_		
Laufs 2019	5	234	5	111	7.8%	0.46 [0.13, 1.63]			_		
Ray 2019	49	1487	40	742	61.0%	0.60 [0.39, 0.92]					
Total (95% CI)		2424		1198	100.0%	0.68 [0.49, 0.94]		•			
Total events	92		66								
Heterogeneity: Chi <sup>2</sup> = '	1.93, df =	3 (P = 0	0.59); l <sup>2</sup> =	0%			+ +	+			
Test for overall effect:	P = 0.0	2)				0.01	0.1 1 Favours [BA]	10 Favours [Pla	icebo]		

#### <u>B) Gout</u>

	BA	Placebo		Odds Ratio	Odds Ratio
Study or Subgroup	Events Tota	I Events Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Goldberg 2019	11 522	2 2 257	39.8%	2.74 [0.60, 12.48]	
Laufs 2019	4 234	1 111	20.2%	1.91 [0.21, 17.32]	
Ray 2019	18 148	2 742	40.0%	4.53 [1.05, 19.59]	
Total (95% CI)	2243	1110	100.0%	3.29 [1.28, 8.46]	-
Total events	33	5			
Heterogeneity: Chi <sup>2</sup> = (	).47, df = 2 (P =	0.79); l <sup>2</sup> = 0%			
Test for overall effect:	Z = 2.47 (P = 0.	01)			Favours [BA] Favours [Placebo]

#### C) Muscular disorders

	BA	Placebo		Odds Ratio	Odds Ratio
Study or Subgroup	Events Total	Events Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
Ballantyne 2018	11 181	5 88	4.7%	1.07 [0.36, 3.19]	
Ballantyne 2019	13 218	3 55	3.3%	1.10 [0.30, 4.00]	
Goldberg 2019	39 522	13 257	11.9%	1.52 [0.79, 2.89]	+
Laufs 2019	30 234	18 111	15.7%	0.76 [0.40, 1.43]	
Ray 2019	195 1487	75 742	64.3%	1.34 [1.01, 1.78]	<b>•</b>
Total (95% CI)	2642	1253	100.0%	1.25 [0.99, 1.57]	◆
Total events	288	114			
Heterogeneity: Chi <sup>2</sup> = 3	8.07, df = 4 (P =	0.55); l <sup>2</sup> = 0%		H	
Test for overall effect: 2	Z = 1.91 (P = 0.0	06)		,	Favours [BA] Favours [Placebo]

#### D) Decrease in GFR

	BA Placebo			Odds Ratio	Odds Ratio
Study or Subgroup	Events Tota	I Events Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
Ballantyne 2018	4 18	1 0 88	24.7%	4.49 [0.24, 84.28]	
Goldberg 2019	4 52	2 1 257	50.2%	1.98 [0.22, 17.78]	
Ray 2019	8 148	7 0 742	25.0%	8.53 [0.49, 148.01]	
Total (95% CI)	219	1087	100.0%	4.24 [0.98, 18.39]	
Total events	16	1			
Heterogeneity: Chi <sup>2</sup> = 0	.70, df = 2 (P =	= 0.71); l <sup>2</sup> = 0%			
Test for overall effect: 2	Z = 1.93 (P = 0	.05)			Favours [BA] Favours [Placebo]

Figure 2: Individual and summary odds ratios with 95% confidence intervals for safety outcomes of newonset 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<sup>2</sup> measures heterogeneity. BA=bempedoic acid; GFR=glomerular filtration rate; M-H=Mantel-Haenszel.

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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

	Random sequence generation	Allocation concealment	Blinding of participants/ personnel	Blinding of outcome assessor	Incomplete outcome data	Selective Reporting
Ballantyne et al. 2018						
(CLEAR Tranquility)			•			•
Ballantyne et al. 2019	?	+	+	+	+	+
Goldberg et al. 2019	<b>A</b>		+	+	-	+
(CLEAR Wisdom)						
Gutierrez et al. 2014	?	?	+	?	+	+
Laufs et al. 2019	2					
(CLEAR Serenity)	•					
Ray et al. 2019	+	-		+	-	+
(CLEAR Harmony)						
+ low risk of	fbias	? unclear risk	of bias	- high risk	c of bias	

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

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	Design	Dish of hiss	T	In dimentioned	T	Dublication biog	Summary of findings		
Outcome (No. of studies)	Design	KISK OF DIAS	Inconsistency	Indirectness	Imprecision	Publication bias	No. of subjects BA/placebo	Pooled OR (95% CI)	Certainty rating
MACE (4)	RCT	Not serious	Serious <sup>a</sup>	Not serious	Serious <sup>c</sup>	Undetected	2273/1140	0.84 (0.61-1.15)	⊕⊕⊖⊖ Low
All-cause mortality (5)	RCT	Not serious	Not serious	Serious <sup>b</sup>	Serious <sup>d</sup>	Undetected	2642/1253	2.37 (0.80-6.99)	⊕⊕⊖⊖ Low
Cardiovascular mortality (3)	RCT	Not serious	Not serious	Not serious	Seriouse	Undetected	2243/1110	1.66 (0.45-6.04)	⊕⊕⊕⊖ Moderate
Nonfatal myocardial infarction (4)	RCT	Not serious	Not serious	Not serious	Serious <sup>f</sup>	Undetected	2273/1140	0.57 (0.32-0.99)	⊕⊕⊕⊖ Moderate

### Supplementary Table 2 – GRADE assessment of primary outcomes

<u>Supplementary Table 2</u>: 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. <sup>a</sup> Inconsistency of direction of effect; <sup>b</sup> Outcome time frame insufficient; <sup>c</sup> Small number of included studies/pooled estimate not consistent with benefit and harm; <sup>d</sup> Rare event/pooled estimate not consistent with benefit and harm; <sup>e</sup> Rare event/small number of included studies/pooled estimate not consistent with benefit and harm; <sup>f</sup> 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



<u>Supplementary Figure 1</u>: 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.

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

### A) Coronary revascularization

	6 7		BA		Placel	00		Odds Ratio		Odds Ratio	
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	7	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fixed, 95% Cl	
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $		Goldberg 2019	20	522	15	257	37.8%	0.64 [0.32, 1.28]			
Pay 2019       39       1447       24       72	2 8	Laufs 2019	7	234	0	111	1.3%	7.35 [0.42, 129.88]			•
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	0	Ray 2019	38	1487	24	742	61.0%	0.78 [0.47, 1.32]			
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	9	Total (95% CI)		2243		1110	100.0%	0.82 [0.55, 1.22]		•	
11 + teincogenety: Ch2 = 23, d2 = 2 + 0.3(p2 = 0.25); p2 = 27% + 0.01 + 0.1 + 0.01 + 0.1 + 0.01 + 0.01 + 0.01 + 0.01 + 0.01 + 0.000	10	Total events	65	2240	39		100.070	0.02 [0.00, 1.22]			
12       Test for overall effect: Z = 1.00 (P = 0.32)       UUI       0.1 <t< td=""><td>11</td><td>Heterogeneity: Chi<sup>2</sup> = 2</td><td>2.73, df = 2</td><td>2 (P = (</td><td>0.25); l<sup>2</sup> =</td><td>27%</td><td></td><td></td><td></td><td></td><td>Ļ</td></t<>	11	Heterogeneity: Chi <sup>2</sup> = 2	2.73, df = 2	2 (P = (	0.25); l <sup>2</sup> =	27%					Ļ
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	12	Test for overall effect:	Z = 1.00 (I	P = 0.3	2)				0.01	U.1 1 10 10 Favours [BA] Favours [Placebo]	0
B) Non-coronary revascularizationBAPlaceboOdds RatioOdds Ratio <tr< td=""><td>13</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr<>	13										
$\frac{D_{1}}{D_{1}} \frac{D_{1}}{D_{2}} \frac{D_{2}}{D_{2}} \frac{D_{2}}{D_{$	14	B) Non-coronary	revascu	lariza	tion						
BAPlaceboOdds RatioOdds RatioGoldberg 20196522625749%0.49 (0.16, 1.52)Goldberg 20196522625749%0.49 (0.16, 1.52)Ray 201941487674250.1%0.33 (0.09, 1.18)Total (95%, C)22431110100.0%0.44 (0.18, 0.95)Total events1012Heiterogeneity: Ch <sup>2</sup> = 0.20, df = 1 (P = 0.66); P = 0%,Test for overall effect: Z = 2.08 (P = 0.04)Study or SubgroupEventsStudy or SubgroupEventsTotal (95%, Ci)2.234Q11922.2574.4471.25 (0.18, 5.41)Laufs 201922.2340111112Laufs 201922.2374447127124 0(0.11, 50.37)Goldberg 201922.2374447128 (0.42, 3.76]Total (95%, Ci)22431110100.0%128 (0.42, 3.76]Total (95%, Ci)22431110100.0%239 (0.60)22431111112129 (0.60)130 (0.60)141 (95%, Ci)141 (95%, Ci)141 (95%, Ci)141 (95%, Ci)141 (95%, Ci)142 (95%, Ci)143 (95%, Ci)144 (95%, Ci)145 (95%, Ci)144 (95%, Ci)145 (95%, Ci)145 (95%, Ci)145 (95%, Ci)146 (95%, Ci)	15										
Study or Subgroup       Events Total       Prevents Total       Weight       M-H. Fixed. 95%, Cl       M-H. Fixed. 95%, Cl         18       Laufs 2019       0.234       0.1111       Not estimable         19       Ray 2019       0.234       0.1111       Not estimable         19       Ray 2019       0.234       0.1111       Not estimable         10       12       Not estimable       Not estimable         21       Total (95%, Cl)       2243       1110       100.0%       0.41 [0.18, 0.95]         21       Test for overall effect: Z = 2.08 (P = 0.04)       Placebb       Odds Ratio       Odds Ratio         22       Heiterogeneity: Ch = 0.25, df = 2 (P = 0.84)       Test for overall effect: Z = 2.04 (P = 0.88); P = 0%       Odds Ratio       Odds Ratio         23       C.) Nonfatal stroke       Odds Ratio       Odds Ratio       Odds Ratio         24       10       111       4       125 [0.22, 6.24, 0.45]       Int 1112%       2.40 [0.15, 0.37]         25       C.D Nonfatal stroke       Odds Ratio       Odds Ratio       Odds Ratio         26       D.Hospitalization for heart failure       Odds Ratio       Odds Ratio         26       D) Hospitalization for heart failure       Odds Ratio       Odds Ratio <td>16</td> <td></td> <td>BA</td> <td></td> <td>Placel</td> <td>00</td> <td></td> <td>Odds Ratio</td> <td></td> <td>Odds Ratio</td> <td></td>	16		BA		Placel	00		Odds Ratio		Odds Ratio	
$ \begin{array}{c} \begin{tabular}{ c c c c c } \hline Colderg 2019 & 6 & 522 & 6 & 257 & 49.9\% & 0.49 [0.16, 1.52] \\ \hline Ladis 2019 & 0 & 224 & 0 & 111 \\ \hline Ray 2019 & 4 & 1487 & 6 & 742 & 50.1\% & 0.33 [0.09, 1.18] \\ \hline Ray 2019 & 4 & 1487 & 6 & 742 & 50.1\% & 0.33 [0.09, 1.18] \\ \hline Total (95\% Ci) & 2243 & 1110 & 100.0\% & 0.41 [0.16, 0.95] \\ \hline Total events & 10 & 12 \\ \hline Heterogeneity: Ch'' = 0.20, df = 1 (P = 0.68); P = 0.0\% \\ \hline Test for overall effect Z = 2.08 (P = 0.04) \\ \hline Colderg 2019 & 4 & 522 & 2 & 257 & 44.4\% & 0.58 [0.18, 6.41] \\ \hline Colderg 2019 & 2 & 223 & 0 & 111 & 11.2\% & 2.40 [0.15, 50.37] \\ \hline Ray 2019 & 2 & 224 & 0 & 111 & 11.2\% & 2.40 [0.15, 50.37] \\ \hline Total (95\% Ci) & 2243 & 1110 & 100.0\% & 1.26 [0.42, 3.76] \\ \hline Total (95\% Ci) & 2243 & 1110 & 100.0\% & 1.26 [0.42, 3.76] \\ \hline Total (95\% Ci) & 2243 & 1110 & 100.0\% & 1.26 [0.42, 3.76] \\ \hline Total (95\% Ci) & 2243 & 1110 & 100.0\% & 1.26 [0.42, 3.76] \\ \hline Total (95\% Ci) & 2243 & 1110 & 100.0\% & 1.26 [0.42, 3.76] \\ \hline D) Hospitalization for heart failure \\ \hline Ba Placebo & Odds Ratio & 0.11 & 1 & 0 & 100 \\ \hline Favours [BA] Favours [Placebo] & 0 & 10 & 5 & 522 & 2 & 257 & 66.7\% & 1.23 [0.24, 6.40] \\ \hline Colderg 2019 & 5 & 522 & 2 & 257 & 66.7\% & 1.23 [0.24, 6.40] & H.H. Fixed 95\% Ci & H.H. Fixed 95\% Ci & H.H. Fixed 95\% Ci & 0.11 & 1 & 0 & 100 \\ \hline Favours [BA] Favours [Placebo] & 0 & 552 & 2 & 257 & 66.7\% & 1.23 [0.24, 6.40] & H.H. Fixed 95\% Ci & H.H. Fixed 95\% Ci & H.H. Fixed 95\% Ci & 0.11 & 1 & 0 & 100 \\ \hline Favours [BA] Favours [Placebo] & 0 & 522 & 4 & 257 & 25.7\% & 1.24 [0.38, 3.98] \\ \hline Total (95\% Ci) & 224 & 0 & 111 & 3.3 & 0.01 & 0.1 & 1 & 0 & 0.00 \\ \hline Favours [BA] Favours [Placebo] & 0 & 522 & 4 & 257 & 25.7\% & 1.24 [0.38, 3.98] \\ \hline Ladis 2019 & 5 & 224 & 0 & 111 & 3.2\% & 5.34 [0.29, 7.50] & 0.11 & 1.10 & 100 \\ \hline Favours [BA] Favours [Placebo] & 0 & 0.000\% & 0.000$	17	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H. Fixed, 95% Cl	
B       Lauts 2019       0       234       0       111       Not estimable         PRoy 2019       4       1487       742       50.1%       0.33 (0.99, 1.18)         20       Total (95% CI)       2243       1110       100.0%       0.41 [0.18, 0.95]         21       Total (95% CI)       2243       1110       100.0%       0.41 [0.18, 0.95]         22       Heterogeneity: Ch <sup>2</sup> = 0.20, df = 1 (P = 0.68)       Pacebo       Odds Ratio       Odds Ratio         23       C) Nonfatal stroke       EA       Placebo       Odds Ratio       Odds Ratio         24       C) Nonfatal stroke       EA       Placebo       Odds Ratio       Odds Ratio         25       C) Nonfatal stroke       EA       Placebo       Odds Ratio       Odds Ratio         26       Study or Subgroup       Events Total Events Total Weight       M-H. Fixed, 55% CI       M-H. Fixed, 55% CI         27       Total (95% CI)       2243       1110       100.0%       1.26 [0.42, 3.76]         38       Heterogeneity: Ch <sup>2</sup> = 0.25, df = 2 (P = 0.8); P = 0%       1.23 [0.42, 6.40]       M-H. Fixed, 55% CI         39       Study or Subgroup       Events Total Weight       M-H. Fixed, 55% CI       M-H. Fixed, 55% CI         40	17	Goldberg 2019	6	522	6	257	49.9%	0.49 [0.16, 1.52]			
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	18	Lauts 2019	0	234	0	111	EO 10/	Not estimable		<b>_</b>	
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	19	Ray 2019	4	1467	0	742	50.1%	0.33 [0.09, 1.18]		-	
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	20	Total (95% CI)		2243		1110	100.0%	0.41 [0.18, 0.95]			
Heterogenetic: Ch <sup>2</sup> = 0.20, df = 1 ( $P = 0.66$ ); P = 0% Test for overall effect: Z = 2.08 ( $P = 0.04$ ) C) Nonfatal stroke BA Placebo Goldberg 2019 4 522 2 257 44.4% Goldberg 2019 4 522 2 257 44.4% Rey 2019 5 1487 2 742 44.4% Total (95% Cl) Total (95% Cl) Ch Hospitalization for heart failure BA Placebo D) Hospitalization for heart failure BA Placebo D) Hospitalization for heart failure BA Placebo D) Hospitalization for heart failure BA Placebo Codds Ratio D) Hospitalization for heart failure Codds Ratio D) Hospitalization for unstable angina Heterogenetic: Ch <sup>2</sup> = 0.58, df = 1 ( $P = 0.38$ ); P = 0% Total (95% Cl) E) Hospitalization for unstable angina Heterogenetic: Ch <sup>2</sup> = 0.58, df = 1 ( $P = 0.38$ ); P = 0% Total (95% Cl) E) Hospitalization for unstable angina Heterogenetic: Ch <sup>2</sup> = 0.58, df = 1 ( $P = 0.38$ ); P = 0% Total (95% Cl) E) Hospitalization for unstable angina Heterogenetic: Ch <sup>2</sup> = 0.58, df = 1 ( $P = 0.38$ ); P = 0% Total (95% Cl) E) Hospitalization for unstable angina Heterogenetic: Ch <sup>2</sup> = 0.58, df = 1 ( $P = 0.38$ ); P = 0% Total (95% Cl) E) Hospitalization for unstable angina Heterogenetic: Ch <sup>2</sup> = 0.58, df = 1 ( $P = 0.38$ ); P = 0% Test for overall effect: Z = 1.32 ( $P = 0.19$ ) E) Hospitalization for unstable angina Heterogenetic: Ch <sup>2</sup> = 0.58, df = 1 ( $P = 0.38$ ); P = 0% Total (95% Cl) E) Hospitalization for unstable angina Heterogenetic: Ch <sup>2</sup> = 0.58, df = 1 ( $P = 0.38$ ); P = 0% Test for overall effect: Z = 0.20 ( $P = 0.28$ ); P = 21% Total (95% Cl) E) Hospitalization for unstable angina Heterogenetic: Ch <sup>2</sup> = 0.58, df = 2 ( $P = 0.28$ ); P = 21% Total (95% Cl) E) Hospitalization for unstable angina Heterogenetic: Ch <sup>2</sup> = 0.58, df = 2 ( $P = 0.28$ ); P = 21% Total (95% Cl) E) Hospitalization for unstable angina Heterogenetic: Ch <sup>2</sup> = 0.58, df = 2 ( $P = 0.28$ ); P = 21% Total (95% Cl) E) Hospitalization for unstable angina Heterogenetic: Ch <sup>2</sup> = 0.20; P = 0.28; P = 21% Total (95% Cl) E) Hospitalization for unstable angina Heterogenetic: Ch <sup>2</sup> = 0.2	21	Total events	10		12						
Test for overall effect: $Z = 2.08$ ( $P = 0.04$ )         Gold Statio         Odds Ratio	22	Heterogeneity: Chi <sup>2</sup> = (	0.20, df =	1 (P = (	0.66); I² =	0%					-
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	22	Test for overall effect:	Z = 2.08 (I	P = 0.0	4)				0.01	Favours [BA] Favours [Placebo]	0
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	23										
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	24	C) Nonfatal strak	2								
26 27BA Study or Subgroup Events Total Events Tot	25	Cj Nomatal Stroke	<u> </u>								
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	26										
$\begin{array}{c} \text{Subgroup}  \text{Links}  \text{four brinks}  four b$	27	Study or Subgroup	BA Events	Total	Fiace	00 Total	Weight	Odds Ratio		Odds Ratio	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	28	Goldberg 2019	<u></u>	522	2	257	44 4%	0.98 [0.18 5.41]			
30       Ray 2019       5       1487       2       742       44.4%       1.25       [0.24, 6.45]         31       Total (95% CI)       2243       1110       100.0%       1.26       [0.42, 3.76]         32       Total events       11       4         33       Heterogeneity: Chi <sup>2</sup> = 0.25, df = 2 (P = 0.88); P = 0%       Test for overall effect: Z = 0.41 (P = 0.68); P = 0%       Odds Ratio       Odds Ratio         36       D) Hospitalization for heart failure       Odds Ratio       Odds Ratio       Odds Ratio         37       Study or Subgroup       Events Total Events Total Weight       M-H. Fixed, 95% CI       M-H. Fixed, 95% CI         38       Study or Subgroup       Events Total Events       Total (95% CI)       Odds Ratio       Odds Ratio         39       Goldberg 2019       0       234       0       111       Not estimable         41       Total (95% CI)       2243       1110       100.0%       2.33 [0.67, 8.11]         42       Total (95% CI)       2243       1110       100.0%       2.33 [0.67, 8.11]         43       Heterogeneity: Ch <sup>2</sup> = 0.96, df = 1 (P = 0.33); P = 0%       Chail Events       Chail Events       Chail Events         44       Total (95% CI)       Events       Total Events </td <td>29</td> <td>Laufs 2019</td> <td>2</td> <td>234</td> <td>0</td> <td>111</td> <td>11.2%</td> <td>2.40 [0.11, 50.37]</td> <td></td> <td></td> <td></td>	29	Laufs 2019	2	234	0	111	11.2%	2.40 [0.11, 50.37]			
Total (95% CI) 2243 1110 100.0% 1.26 [0.42, 3.76] Total events 11 4 Heterogeneity: Ch <sup>2</sup> = 0.25, df = 2 (P = 0.88); P = 0% Test for overall effect: Z = 0.41 (P = 0.68) <b>D) Hospitalization for heart failure</b> <b>BA</b> Placebo Odds Ratio Odds Ratio Goldberg 2019 5 522 2 257 66.7% 1.23 [0.24, 6.40] Laufs 2019 0 2243 0 111 Not estimable Ray 2019 9 1467 1 742 33.3% 4.51 [0.57, 35.68] Total events 14 3 Heterogeneity: Ch <sup>2</sup> = 0.96, df = 1 (P = 0.33); P = 0% Test for overall effect: Z = 1.32 (P = 0.19) <b>BA</b> Placebo Odds Ratio Odds Ratio <b>Coldberg 2019</b> 10 522 4 257 25.7% 1.24 [0.57, 35.68] <b>Coldberg 2019</b> 10 522 4 257 25.7% 1.24 [0.38, 3.98] Laufs 2019 10 5 224 3 1110 100.0% 0.94 [0.51, 1.74] <b>Total events</b> 14 3 Heterogeneity: Ch <sup>2</sup> = 0.96, df = 1 (P = 0.33); P = 0% <b>Test for overall effect:</b> Z = 1.32 (P = 0.19) <b>BA</b> Placebo Odds Ratio Odds Ratio <b>Coldberg 2019</b> 10 522 4 257 25.7% 1.24 [0.28, 3.98] Laufs 2019 5 224 0 111 3.27% 5.34 [0.29, 97.50] Caufs 2019 5 224 0 111 3.27% 5.34 [0.29, 97.50] Caufs 2019 10 522 4 257 25.7% 1.24 [0.29, 97.50] Total (95% CI) 2243 1110 100.0% 0.94 [0.51, 1.74] Total events 29 15 Heterogeneity: Ch <sup>2</sup> = 2.55, df = 2 (P = 0.28); P = 21% Test for overall effect: Z = 0.20 (P = 0.84) <b>Supplementary Figure 2</b> : Individual and summary odds ratios of additional efficacy outcomes of coronary	30	Ray 2019	5	1487	2	742	44.4%	1.25 [0.24, 6.45]			
1       Total (95% Cl)       2243       1110       100.0%       1.26 [0.42, 3.76]         21       Total events       11       4         4       Heterogeneity: Ch <sup>P</sup> = 0.25, df = 2 (P = 0.88); P = 0%       Test for overall effect: Z = 0.41 (P = 0.68)         33       BA       Placebo       Odds Ratio       Odds Ratio         34       BA       Placebo       Odds Ratio       Odds Ratio         35       D) Hospitalization for heart failure       Odds Ratio       Odds Ratio         36       Di Hospitalization for heart failure       Odds Ratio       Odds Ratio         37       BA       Placebo       Odds Ratio       Odds Ratio         38       Study or Subgroup       Events       Total (95% Cl)       Odds Ratio       Odds Ratio         40       Ray 2019       9       1487       1 742       33.3%       4.51 [0.57, 35.68]         41       Total (95% Cl)       2243       1110       100.0%       2.33 [0.67, 8.11]         42       Total events       14       3       Heterogeneity: Ch <sup>P</sup> = 0.96, df = 1 (P = 0.33); P = 0%       Test for overall effect: Z = 1.32 (P = 0.19)       Odds Ratio       Odds Ratio         44       BA       Placebo       Odds Ratio       Odds Ratio       Odds Ratio </td <td>21</td> <td></td>	21										
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	22	Total (95% CI)		2243		1110	100.0%	1.26 [0.42, 3.76]			
Test for overall effect: $Z = 0.41$ (P = 0.86), P = 0% D) Hospitalization for heart failure BA Placebo D Hospitalization for heart failure BA Placebo Codds Ratio Codds	32	Total events	11 0.25 df = 1	2 (D = (	4	0.0/			<u> </u>		-
Favours [Placebo]Favours [Placebo]Pavours [Placebo]D) Hospitalization for heart failureBAPlaceboOdds RatioStudy or SubgroupEvents Total Events Total WeightM-H, Fixed, 95% CIM-H, Fixed, 95% CIM-H, Fixed, 95% CIOdds RatioOdds Ratio <td>33</td> <td>Test for overall effect:</td> <td>0.25, ui – . 7 = 0.41 (l</td> <td>2 (P - ( P = 0.6</td> <td>7.00<i>)</i>; I⁻ – 8)</td> <td>0%</td> <td></td> <td></td> <td>0.01</td> <td>0.1 1 10 10</td> <td>0</td>	33	Test for overall effect:	0.25, ui – . 7 = 0.41 (l	2 (P - ( P = 0.6	7.00 <i>)</i> ; I⁻ – 8)	0%			0.01	0.1 1 10 10	0
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$\begin{array}{c c c c c c c c c c c c c c c c c c c $	35		0 1								
37BAPlaceboOdds RatioOdds Ratio38Study or SubgroupEventsTotalEventsTotalWeightM-H. Fixed. 95% ClM-H. Fixed. 95% Cl39Goldberg 20195 $522$ 2 $257$ $66.7\%$ $1.23$ [0.24, 6.40]40Ray 2019914871742 $33.3\%$ $4.51$ [0.57, 35.68]41Total (95% Cl)22431110100.0% $2.33$ [0.67, 8.11]42Total events14343Heterogeneity: Chi <sup>2</sup> = 0.96, df = 1 (P = 0.33); P = 0%44Test for overall effect: Z = 1.32 (P = 0.19)4546474849Goldberg 201910 $522$ 4 $257$ $25.7\%$ $1.24$ [0.38, 3.98]50Laufs 20195 $234$ 0111 $3.2\%$ $5.34$ [0.29, 97.50]5154Total (95% Cl)22431110100.0% $0.94$ [0.51, 1.74]5554545554555455545455545455545455545455545554545554555455545555555656 <td>36</td> <td>D) Hospitalization</td> <td>n for hea</td> <td>art fa</td> <td>lure</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>	36	D) Hospitalization	n for hea	art fa	lure						
Study or Subgroup       Events       Total       Weight       M-H. Fixed. 95% CI       M-H. Fixed. 95% CI         38       Goldberg 2019       5       522       2       257       66.7%       1.23 [0.24, 6.40]         40       Ray 2019       0       234       0       111       Not estimable         41       Total (95% CI)       2243       1110       100.0%       2.33 [0.67, 8.11]         42       Total (95% CI)       2243       1110       100.0%       2.33 [0.67, 8.11]         43       Heterogeneity: Chi <sup>2</sup> = 0.96, df = 1 (P = 0.33); l <sup>2</sup> = 0%.       0.01       0.1       1       10       100         44       Test for overall effect: Z = 1.32 (P = 0.19)       E)       Hospitalization for unstable angina       0dds Ratio       Odds Ratio       Odds Ratio         45       E)       Hospitalization for unstable angina       M-H. Fixed. 95% CI       M-H. Fixed. 95% CI       M-H. Fixed. 95% CI         46       E) Hospitalization for unstable angina       Events       Total Events       Total Weight       M-H. Fixed. 95% CI       M-H. Fixed. 95% CI         47       BA       Placebo       Odds Ratio       Odds Ratio       Odds Ratio         48       Study or Subgroup       Events       Total Events											
30       Goldberg 2019       5       522       2       257       66.7%       1.23 [0.24, 6.40]         39       Laufs 2019       0       234       0       111       Not estimable         40       Ray 2019       9       1487       1       742       33.3%       4.51 [0.57, 35.68]         41       Total (95% Cl)       2243       1110       100.0%       2.33 [0.67, 8.11]         42       Total events       14       3         43       Heterogeneity: Chi <sup>2</sup> = 0.96, df = 1 (P = 0.33); l <sup>2</sup> = 0%       0.01       0.1       1       10       100         44       Test for overall effect: Z = 1.32 (P = 0.19)       BA       Placebo       Odds Ratio       Odds Ratio         45       E) Hospitalization for unstable angina       MH. Fixed. 95% Cl       M-H. Fixed. 95% Cl       M-H. Fixed. 95% Cl         46       E) Hospitalization for unstable angina       M-H. Fixed. 95% Cl       M-H. Fixed. 95% Cl       M-H. Fixed. 95% Cl         47       BA       Placebo       Odds Ratio       M-H. Fixed. 95% Cl       M-H. Fixed. 95% Cl         48       Study or Subgroup       Events       Total       Weight       M-H. Fixed. 95% Cl       M-H. Fixed. 95% Cl         50       Laufs 2019       5	37		RA.		Placel	20		Odds Ratio		Odds Ratio	
Laufs 2019 0 234 0 111 Not estimable Ray 2019 9 1487 1 742 33.3% 4.51 [0.57, 35.68] Total (95% Cl) 2243 1110 100.0% 2.33 [0.67, 8.11] Total events 14 3 Heterogeneity: Chi <sup>2</sup> = 0.96, df = 1 (P = 0.33); l <sup>2</sup> = 0% Test for overall effect: $Z = 1.32$ (P = 0.19) E) Hospitalization for unstable angina	37	Study or Subaroup	BA Events	Total	Placel Events	oo Total	Weight	Odds Ratio M-H. Fixed, 95% Cl		Odds Ratio M-H. Fixed, 95% Cl	
40       Ray 2019       9       1487       1       742       33.3%       4.51       [0.57, 35.68]         41       Total (95% CI)       2243       1110       100.0%       2.33       [0.67, 8.11]         42       Total events       14       3       Heterogeneity: Chi <sup>2</sup> = 0.96, df = 1 (P = 0.33); l <sup>2</sup> = 0%       2.33       [0.67, 8.11]         43       Heterogeneity: Chi <sup>2</sup> = 0.96, df = 1 (P = 0.33); l <sup>2</sup> = 0%       0.01       0.1       1       10       100         44       Test for overall effect: Z = 1.32 (P = 0.19)       BA       Placebo       Odds Ratio       Odds Ratio         45       E) Hospitalization for unstable angina       Odds Ratio       Odds Ratio       M-H. Fixed. 95% CI       M-H. Fixed. 95% CI         46       E) Hospitalization for unstable angina       Intervents       Total Events       Total Weight       M-H. Fixed. 95% CI       M-H. Fixed. 95% CI         47       BA       Placebo       Odds Ratio       Odds Ratio         48       Study or Subgroup       Events       Total Weight       M-H. Fixed. 95% CI       M-H. Fixed. 95% CI         49       Goldberg 2019       10       522       4       257       25.7%       1.24       0.38       3.98]       1.24       0.38       3.98]	37 38	Study or Subgroup Goldberg 2019	BA Events 5	Total 522	Placel Events 2	00 <u>Total</u> 257	Weight 66.7%	Odds Ratio <u>M-H. Fixed, 95% Cl</u> 1.23 [0.24, 6.40]		Odds Ratio M-H. Fixed. 95% Cl	
41       Total (95% CI)       2243       1110       100.0%       2.33 [0.67, 8.11]         42       Total events       14       3         43       Heterogeneity: Chi <sup>2</sup> = 0.96, df = 1 (P = 0.33); I <sup>2</sup> = 0%       0.01       0.1       1       10       100         44       Test for overall effect: Z = 1.32 (P = 0.19)       E)       Heterogeneity: Chi <sup>2</sup> = 0.96, df = 1 (P = 0.33); I <sup>2</sup> = 0%       0.01       0.1       1       10       100         45       Favours [BA]       Favours [Placebo]       Odds Ratio       Odds Ratio       M-H. Fixed. 95% CI       M-H. Fixed. 9	37 38 39	Study or Subgroup Goldberg 2019 Laufs 2019	BA Events 5 0	<u>Total</u> 522 234	Placel Events 2 0	250 Total 257 111	Weight 66.7%	Odds Ratio <u>M-H. Fixed. 95% Cl</u> 1.23 [0.24, 6.40] Not estimable		Odds Ratio M-H. Fixed. 95% Cl	
42Total events14343Heterogeneity: $Chi^2 = 0.96$ , df = 1 (P = 0.33); $ ^2 = 0\%$ 2.33 [0.67, 8.11]44Test for overall effect: Z = 1.32 (P = 0.19)0.010.1145E) Hospitalization for unstable angina47BAPlaceboOdds Ratio48Study or SubgroupEventsTotal EventsTotal WeightM-H. Fixed, 95% Cl49Goldberg 201910522425725.7%1.24 [0.38, 3.98]50Laufs 2019523401113.2%5.34 [0.29, 97.50]51Ray 20191414871174271.1%0.63 [0.29, 1.40]52Total events29154Heterogeneity: Chi <sup>2</sup> = 2.55, df = 2 (P = 0.28); $ ^2 = 21\%$ 0.010.1153Supplementary Figure 2:Individual and summary odds ratios of additional efficacy outcomes of coronary	37 38 39 40	Study or Subgroup Goldberg 2019 Laufs 2019 Ray 2019	BA Events 5 0 9	Total 522 234 1487	Placel Events 2 0 1	<b>Total</b> 257 111 742	Weight 66.7% 33.3%	Odds Ratio <u>M-H. Fixed. 95% Cl</u> 1.23 [0.24, 6.40] Not estimable 4.51 [0.57, 35.68]		Odds Ratio M-H. Fixed. 95% CI	
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Interspectively of the color	37 38 39 40 41 42	Study or Subgroup Goldberg 2019 Laufs 2019 Ray 2019 Total (95% CI)	BA <u>Events</u> 5 0 9	Total 522 234 1487 2243	Placel Events 2 0 1	700 701 257 111 742 1110	Weight 66.7% 33.3% 100.0%	Odds Ratio <u>M-H, Fixed, 95% Cl</u> 1.23 [0.24, 6.40] Not estimable 4.51 [0.57, 35.68] 2.33 [0.67, 8.11]		Odds Ratio M-H. Fixed, 95% CI	
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46E) Hospitalization for unstable angina47BAPlaceboOdds Ratio48Study or SubgroupEventsTotalEventsTotalWeightM-H. Fixed. 95% Cl49Goldberg 201910522425725.7%1.24 [0.38, 3.98]50Laufs 2019523401113.2%5.34 [0.29, 97.50]51Ray 20191414871174271.1%0.63 [0.29, 1.40]52Total (95% Cl)22431110100.0%0.94 [0.51, 1.74]53Total events291554Test for overall effect: Z = 0.20 (P = 0.28); I <sup>2</sup> = 21%101055Supplementary Figure 2:Individual and summary odds ratios of additional efficacy outcomes of coronary	37 38 39 40 41 42 43 44	Study or Subgroup Goldberg 2019 Laufs 2019 Ray 2019 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = ( Test for overall effect;	BA <u>Events</u> 5 0 9 14 0.96, df = Z = 1.32 (l	Total 522 234 1487 <b>2243</b> 1 (P = ( P = 0.1	Placel <u>Events</u> 2 0 1 3 0.33); l <sup>2</sup> = 9)	00 <u>Total</u> 257 111 742 <b>1110</b> 0%	Weight 66.7% 33.3% 100.0%	Odds Ratio <u>M-H, Fixed, 95% Cl</u> 1.23 [0.24, 6.40] Not estimable 4.51 [0.57, 35.68] 2.33 [0.67, 8.11]	0.01	Odds Ratio M-H. Fixed, 95% CI 0.1 1 10 100 Forum [D4], Forum [D1], and 100	To
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47BAPlaceboOdds RatioOdds Ratio48Study or SubgroupEventsTotalEventsTotalWeightM-H. Fixed, 95% ClM-H. Fixed, 95% Cl49Goldberg 201910 $522$ 4 $257$ $25.7\%$ $1.24$ [0.38, 3.98]M-H. Fixed, 95% Cl50Laufs 20195 $234$ 0111 $3.2\%$ $5.34$ [0.29, 97.50]51Ray 201914148711 $742$ $71.1\%$ $0.63$ [0.29, 1.40]52Total (95% Cl)22431110100.0% $0.94$ [0.51, 1.74]53Total events2915Heterogeneity: Chi² = 2.55, df = 2 (P = 0.28); I² = 21% $0.01$ $0.1$ $1$ 54Test for overall effect: Z = 0.20 (P = 0.84)Favours [Placebo]55Supplementary Figure 2:Individual and summary odds ratios of additional efficacy outcomes of coronary	<ol> <li>37</li> <li>38</li> <li>39</li> <li>40</li> <li>41</li> <li>42</li> <li>43</li> <li>44</li> <li>45</li> <li>46</li> </ol>	Study or Subgroup Goldberg 2019 Laufs 2019 Ray 2019 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = ( Test for overall effect:	BA Events 5 0 9 14 0.96, df = Z = 1.32 (I	<b>Total</b> 522 234 1487 <b>2243</b> 1 (P = ( P = 0.1	Placel <u>Events</u> 2 0 1 3 0.33);   <sup>2</sup> = 9)	700 701 257 111 742 1110 0%	Weight 66.7% 33.3% 100.0%	Odds Ratio <u>M-H, Fixed, 95% Cl</u> 1.23 [0.24, 6.40] Not estimable 4.51 [0.57, 35.68] 2.33 [0.67, 8.11]	L 0.01	Odds Ratio M-H. Fixed. 95% CI 0.1 1 10 100 Favours [BA] Favours [Placebo]	To
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49       Goldberg 2019       10 $522$ $4$ $257$ $25.7\%$ $1.24$ [0.38, 3.98]         50       Laufs 2019 $5$ $234$ 0 $111$ $3.2\%$ $5.34$ [0.29, 97.50]         51       Ray 2019       14 $1487$ $11$ $742$ $71.1\%$ $0.63$ [0.29, 1.40]         52       Total (95% Cl)       2243       1110       100.0% $0.94$ [0.51, 1.74]         53       Total events       29       15         54       Test for overall effect: Z = 0.20 (P = 0.28); I <sup>2</sup> = 21% $0.01$ $0.1$ $1$ $10$ 55       Supplementary Figure 2:       Individual and summary odds ratios of additional efficacy outcomes of coronary	37 38 39 40 41 42 43 44 45 46 47	Study or Subgroup Goldberg 2019 Laufs 2019 Ray 2019 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = ( Test for overall effect: E) Hospitalization	BA <u>Events</u> 5 0 9 14 0.96, df = Z = 1.32 (l 1 for uns BA	Total 522 234 1487 <b>2243</b> 1 (P = 0 P = 0.1 stable	Placel <u>Events</u> 2 0 1 	257 111 742 1110 0%	Weight 66.7% 33.3% 100.0%	Odds Ratio <u>M-H, Fixed, 95% Cl</u> 1.23 [0.24, 6.40] Not estimable 4.51 [0.57, 35.68] 2.33 [0.67, 8.11] Odds Ratio	H 0.01	Odds Ratio M-H. Fixed. 95% CI 0.1 1 10 100 Favours [BA] Favours [Placebo] Odds Ratio	To
50       Laufs 2019       5       234       0       111 $3.2\%$ $5.34$ [0.29, 97.50]         51       Ray 2019       14       1487       11 $742$ $71.1\%$ $0.63$ [0.29, 1.40]         51       Total (95% Cl)       2243       1110       100.0%       0.94 [0.51, 1.74]         53       Total events       29       15         54       Heterogeneity: Chi <sup>2</sup> = 2.55, df = 2 (P = 0.28); l <sup>2</sup> = 21%       0.01       0.1       1       10       100         54       Test for overall effect: Z = 0.20 (P = 0.84)       Test for overall effect: Z = 0.20 (P = 0.84)       Favours [Placebo]       Favours [Placebo]         56       Supplementary Figure 2:       Individual and summary odds ratios of additional efficacy outcomes of coronary	<ol> <li>37</li> <li>38</li> <li>39</li> <li>40</li> <li>41</li> <li>42</li> <li>43</li> <li>44</li> <li>45</li> <li>46</li> <li>47</li> <li>48</li> </ol>	Study or Subgroup Goldberg 2019 Laufs 2019 Ray 2019 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = ( Test for overall effect: E) Hospitalization	BA <u>Events</u> 5 0 9 14 0.96, df = Z = 1.32 (l 1 for uns BA <u>Events</u>	Total $522$ $234$ $1487$ $2243$ $1 (P = 0.1)$ stable         Total	Placel <u>Events</u> 2 0 1 3 0.33); I <sup>2</sup> = 9) <u>angina</u> Placel <u>Events</u>	700 Total 257 111 742 1110 0% 0%	Weight 66.7% 33.3% 100.0% Weight	Odds Ratio <u>M-H, Fixed, 95% Cl</u> 1.23 [0.24, 6.40] Not estimable 4.51 [0.57, 35.68] 2.33 [0.67, 8.11] Odds Ratio <u>M-H, Fixed, 95% Cl</u>	H 0.01	Odds Ratio M-H. Fixed. 95% CI 0.1 1 10 100 Favours [BA] Favours [Placebo] Odds Ratio M-H. Fixed. 95% CI	To
51       Ray 2019       14       1487       11       742       71.1% $0.63$ [0.29, 1.40]         52       Total (95% Cl)       2243       1110       100.0% $0.94$ [0.51, 1.74]         53       Total events       29       15         54       Heterogeneity: Chi <sup>2</sup> = 2.55, df = 2 (P = 0.28); l <sup>2</sup> = 21% $0.01$ $0.1$ 1       10       100         55       Test for overall effect: Z = 0.20 (P = 0.84)       Favours [PAlacebo]       Favours [Placebo]       Favours of coronary         56       Supplementary Figure 2:       Individual and summary odds ratios of additional efficacy outcomes of coronary	<ul> <li>37</li> <li>38</li> <li>39</li> <li>40</li> <li>41</li> <li>42</li> <li>43</li> <li>44</li> <li>45</li> <li>46</li> <li>47</li> <li>48</li> <li>49</li> </ul>	Study or Subgroup Goldberg 2019 Laufs 2019 Ray 2019 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = ( Test for overall effect: <u>E) Hospitalization</u> Study or Subgroup Goldberg 2019	BA <u>Events</u> 5 0 9 14 0.96, df = Z = 1.32 (l 1 for uns BA <u>Events</u> 10	Total           522           234           1487           2243           1 (P = 0           P = 0.1           stable           Total           522	Placel <u>Events</u> 2 0 1 3 0.33); I <sup>2</sup> = 9) 2 angina Placel <u>Events</u> 4	257 111 742 1110 0%	Weight 66.7% 33.3% 100.0% <u>Weight</u> 25.7%	Odds Ratio <u>M-H, Fixed, 95% Cl</u> 1.23 [0.24, 6.40] Not estimable 4.51 [0.57, 35.68] 2.33 [0.67, 8.11] Odds Ratio <u>M-H, Fixed, 95% Cl</u> 1.24 [0.38, 3.98]	L 0.01	Odds Ratio M-H. Fixed. 95% CI 0.1 1 10 100 Favours [BA] Favours [Placebo] Odds Ratio M-H. Fixed. 95% CI	To
52Total (95% Cl)22431110100.0%0.94 [0.51, 1.74]53Total events291554Heterogeneity: Chi² = 2.55, df = 2 (P = 0.28); $ ² = 21\%$ 0.010.1155Test for overall effect: Z = 0.20 (P = 0.84)Favours [BA] Favours [Placebo]56Supplementary Figure 2: Individual and summary odds ratios of additional efficacy outcomes of coronary	<ul> <li>37</li> <li>38</li> <li>39</li> <li>40</li> <li>41</li> <li>42</li> <li>43</li> <li>44</li> <li>45</li> <li>46</li> <li>47</li> <li>48</li> <li>49</li> <li>50</li> </ul>	Study or Subgroup Goldberg 2019 Laufs 2019 Ray 2019 Total (95% Cl) Total events Heterogeneity: Chi <sup>2</sup> = ( Test for overall effect: E) Hospitalization Study or Subgroup Goldberg 2019 Laufs 2019	BA <u>Events</u> 5 0 9 14 0.96, df = Z = 1.32 (l 1 for uns BA <u>Events</u> 10 5	Total $522$ $234$ $1487$ $2243$ 1 (P = 0)           P = 0.1           stable           Total           522           234	Placel <u>Events</u> 2 0 1 3 0.33); I <sup>2</sup> = 9) 2 angina Placel <u>Events</u> 4 0	257 111 742 1110 0% 0%	Weight 66.7% 33.3% 100.0% <u>Weight</u> 25.7% 3.2%	Odds Ratio <u>M-H, Fixed, 95% Cl</u> 1.23 [0.24, 6.40] Not estimable 4.51 [0.57, 35.68] <b>2.33 [0.67, 8.11]</b> Odds Ratio <u>M-H, Fixed, 95% Cl</u> 1.24 [0.38, 3.98] 5.34 [0.29, 97.50]	L0.01	Odds Ratio M-H. Fixed. 95% CI 0.1 1 10 100 Favours [BA] Favours [Placebo] Odds Ratio M-H. Fixed. 95% CI	T 0
52       Total events       29       15         53       Total events       29       15         54       Heterogeneity: Chi <sup>2</sup> = 2.55, df = 2 (P = 0.28); l <sup>2</sup> = 21%       0.01       0.1       1       10       100         55       Favours [BA] Favours [Placebo]       55       Supplementary Figure 2: Individual and summary odds ratios of additional efficacy outcomes of coronary	<ul> <li>37</li> <li>38</li> <li>39</li> <li>40</li> <li>41</li> <li>42</li> <li>43</li> <li>44</li> <li>45</li> <li>46</li> <li>47</li> <li>48</li> <li>49</li> <li>50</li> <li>51</li> </ul>	Study or Subgroup Goldberg 2019 Laufs 2019 Ray 2019 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = ( Test for overall effect: <u>E) Hospitalization</u> Study or Subgroup Goldberg 2019 Laufs 2019 Ray 2019	BA <u>Events</u> 5 0 9 14 0.96, df = Z = 1.32 (l 1 for uns BA <u>Events</u> 10 5 14	Total $522$ $234$ $1487$ $2243$ $1 (P = 0)$ $P = 0.1$ stable <b>Total</b> $522$ $234$ $2243$	Placel <u>Events</u> 2 0 1 3 0.33); I <sup>2</sup> = 9) 2 angina Events 4 0 11	Total 257 111 742 1110 0% 0% Total 257 111 742	Weight 66.7% 33.3% 100.0% <u>Weight</u> 25.7% 3.2% 71.1%	Odds Ratio M-H, Fixed, 95% Cl 1.23 [0.24, 6.40] Not estimable 4.51 [0.57, 35.68] 2.33 [0.67, 8.11] Odds Ratio M-H, Fixed, 95% Cl 1.24 [0.38, 3.98] 5.34 [0.29, 97.50] 0.63 [0.29, 1.40]	L0.01	Odds Ratio M-H. Fixed. 95% CI 0.1 1 10 100 Favours [BA] Favours [Placebo] Odds Ratio M-H. Fixed. 95% CI	T 0
<ul> <li>S3 Final orbital sectors</li> <li>S3 Heterogeneity: Chi<sup>2</sup> = 2.55, df = 2 (P = 0.28); l<sup>2</sup> = 21%</li> <li>S4 Test for overall effect: Z = 0.20 (P = 0.84)</li> <li>S5 For overall effect: Z = 0.20 (P = 0.84)</li> <li>S4 Test for overall effect: Z = 0.20 (P = 0.84)</li> <li>S4 Test for overall effect: Z = 0.20 (P = 0.84)</li> <li>S4 Test for overall effect: Z = 0.20 (P = 0.84)</li> <li>S4 Test for overall effect: Z = 0.20 (P = 0.84)</li> <li>S4 Test for overall effect: Z = 0.20 (P = 0.84)</li> <li>S4 Test for overall effect: Z = 0.20 (P = 0.84)</li> <li>S4 Test for overall effect: Z = 0.20 (P = 0.84)</li> <li>S4 Test for overall effect: Z = 0.20 (P = 0.84)</li> <li>S4 Test for overall effect: Z = 0.20 (P = 0.84)</li> <li>S4 Test for overall effect: Z = 0.20 (P = 0.84)</li> <li>S4 Test for overall effect: Z = 0.20 (P = 0.84)</li> <li>S4 Test for overall effect: Z = 0.20 (P = 0.84)</li> <li>S4 Test for overall effect: Z = 0.20 (P = 0.84)</li> <li>S4 Test for overall effect: Z = 0.20 (P = 0.84)</li> <li>S4 Test for overall effect: Z = 0.20 (P = 0.84)</li> <li>S4 Test for overall effect: Z = 0.20 (P = 0.84)</li> <li>S4 Test for overall effect: Z = 0.20 (P = 0.84)</li> <li>S4 Test for overall effect: Z = 0.20 (P = 0.84)</li> <li>S4 Test for overall effect: Z = 0.20 (P = 0.84)</li> <li>S4 Test for overall effect: Z = 0.20 (P = 0.84)</li> <li>S4 Test for overall effect: Z = 0.20 (P = 0.84)</li> <li>S4 Test for overall effect: Z = 0.20 (P = 0.84)</li> <li>S4 Test for overall effect: Z = 0.20 (P = 0.84)</li> <li>S4 Test for overall effect: Z = 0.20 (P = 0.84)</li> <li>S4 Test for overall effect: Z = 0.20 (P = 0.84)</li> <li>S4 Test for overall effect: Z = 0.20 (P = 0.84)</li> <li>S4 Test for overall effect: Z = 0.20 (P = 0.84)</li> <li>S4 Test for overall effect: Z = 0.20 (P = 0.84)</li> <li>S4 Test for overall effect: Z = 0.20 (P = 0.84)</li> <li>S4 Test for overall effect: Z = 0</li></ul>	<ul> <li>37</li> <li>38</li> <li>39</li> <li>40</li> <li>41</li> <li>42</li> <li>43</li> <li>44</li> <li>45</li> <li>46</li> <li>47</li> <li>48</li> <li>49</li> <li>50</li> <li>51</li> <li>52</li> </ul>	Study or Subgroup Goldberg 2019 Laufs 2019 Ray 2019 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = ( Test for overall effect: E) Hospitalization Study or Subgroup Goldberg 2019 Laufs 2019 Ray 2019 Total (95% CI)	BA <u>Events</u> 5 0 9 14 0.96, df = Z = 1.32 (l 1 for uns BA <u>Events</u> 10 5 14	Total $522$ $234$ $1487$ $2243$ $1 (P = 0.1)$ stable           Total $522$ $234$ $522$ $234$ $1487$ $522$ $234$ $1487$ $522$ $234$ $1487$ $2243$	Placel <u>Events</u> 2 0 1 3 0.33); I <sup>2</sup> = 9) 2 angina Placel <u>Events</u> 4 0 11	Do           257           111           742           1110           0%           1           0%           1           257           111           0%           1           257           111           0%           1           257           111           742           1110	Weight 66.7% 33.3% 100.0% <u>Weight</u> 25.7% 3.2% 71.1%	Odds Ratio M-H, Fixed, 95% Cl 1.23 [0.24, 6.40] Not estimable 4.51 [0.57, 35.68] 2.33 [0.67, 8.11] Odds Ratio M-H, Fixed, 95% Cl 1.24 [0.38, 3.98] 5.34 [0.29, 97.50] 0.63 [0.29, 1.40] 0.94 [0.51, 1, 74]	L0.01	Odds Ratio M-H. Fixed. 95% CI 0.1 1 10 100 Favours [BA] Favours [Placebo] Odds Ratio M-H. Fixed. 95% CI	To
54       Test for overall effect: Z = 0.20 (P = 0.84)       0.01       0.1       1       10       100         55       Favours [BA]       Favours [Placebo]         56       Supplementary Figure 2: Individual and summary odds ratios of additional efficacy outcomes of coronary	<ul> <li>37</li> <li>38</li> <li>39</li> <li>40</li> <li>41</li> <li>42</li> <li>43</li> <li>44</li> <li>45</li> <li>46</li> <li>47</li> <li>48</li> <li>49</li> <li>50</li> <li>51</li> <li>52</li> <li>52</li> </ul>	Study or Subgroup Goldberg 2019 Laufs 2019 Ray 2019 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = ( Test for overall effect: E) Hospitalization Goldberg 2019 Laufs 2019 Ray 2019 Total (95% CI) Total events	BA <u>Events</u> 5 0 9 14 0.96, df = Z = 1.32 (l 1 for uns BA <u>Events</u> 10 5 14 29	Total $522$ $234$ $1487$ $2243$ $1 (P = 0.1)$ $9 = 0.1$ stable $522$ $234$ $1487$ $522$ $234$ $1487$ $2243$	Placel <u>Events</u> 2 0 1 3 0.33); I <sup>2</sup> = 9) 2 angina Placel <u>Events</u> 4 0 11 15	Do           Total           257           111           742           1110           0%           1           0%           1           0%           1           0%           1           0%           1           0%           1	Weight 66.7% 33.3% 100.0% <u>Weight</u> 25.7% 3.2% 71.1% 100.0%	Odds Ratio M-H, Fixed, 95% Cl 1.23 [0.24, 6.40] Not estimable 4.51 [0.57, 35.68] 2.33 [0.67, 8.11] Odds Ratio M-H, Fixed, 95% Cl 1.24 [0.38, 3.98] 5.34 [0.29, 97.50] 0.63 [0.29, 1.40] 0.94 [0.51, 1.74]	0.01	Odds Ratio M-H. Fixed. 95% CI 0.1 1 10 100 Favours [BA] Favours [Placebo] Odds Ratio M-H. Fixed. 95% CI	To
<ul> <li>55</li> <li>56</li> <li>57</li> <li>Supplementary Figure 2: Individual and summary odds ratios of additional efficacy outcomes of coronary</li> </ul>	37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53	Study or Subgroup Goldberg 2019 Laufs 2019 Ray 2019 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = ( Test for overall effect: E) Hospitalization Goldberg 2019 Laufs 2019 Ray 2019 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 2	BA <u>Events</u> 5 0 9 14 0.96, df = Z = 1.32 (l 1 for uns BA Events 10 5 14 29 2.55, df = :	Total $522$ $234$ $1487$ $2243$ $1 (P = 0.1)$ $522$ $522$ $234$ $522$ $234$ $1487$ $2243$ $2243$ $2243$ $2243$ $2243$	Placel <u>Events</u> 2 0 1 	Do           Total           257           111           742           1110           0%           1           0%           1           0%           1           0%           1           0%           1           0%           1	Weight 66.7% 33.3% 100.0% <u>Weight</u> 25.7% 3.2% 71.1% 100.0%	Odds Ratio M-H, Fixed, 95% Cl 1.23 [0.24, 6.40] Not estimable 4.51 [0.57, 35.68] 2.33 [0.67, 8.11] Odds Ratio M-H, Fixed, 95% Cl 1.24 [0.38, 3.98] 5.34 [0.29, 97.50] 0.63 [0.29, 1.40] 0.94 [0.51, 1.74]	0.01	Odds Ratio M-H. Fixed. 95% CI 0.1 1 10 100 Favours [BA] Favours [Placebo] Odds Ratio M-H. Fixed. 95% CI	
56 <u>Supplementary Figure 2</u> : Individual and summary odds ratios of additional efficacy outcomes of coronary	37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54	Study or Subgroup Goldberg 2019 Laufs 2019 Ray 2019 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = ( Test for overall effect: E) Hospitalization Goldberg 2019 Laufs 2019 Ray 2019 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 2 Test for overall effect:	BA <u>Events</u> 5 0 9 14 0.96, df = Z = 1.32 (l 1 for uns BA Events 10 5 14 29 2.55, df = : Z = 0.20 (l	Total $522$ $234$ $1487$ $2243$ $1 (P = 0.1)$ $522$ $522$ $234$ $522$ $234$ $1487$ $2243$ $2243$ $2243$ $2243$ $2243$ $2243$ $2(P = 0.8)$	Placel <u>Events</u> 2 0 1 3 0.33); I <sup>2</sup> = 9) 2 <u>angina</u> Placel <u>Events</u> 4 0 11 15 0.28); I <sup>2</sup> = 4)	Do           Total           257           111           742           1110           0%           1           0%           1           0%           1           0%           1           0%           1           0%           1	Weight 66.7% 33.3% 100.0% <u>Weight</u> 25.7% 3.2% 71.1% 100.0%	Odds Ratio M-H, Fixed, 95% Cl 1.23 [0.24, 6.40] Not estimable 4.51 [0.57, 35.68] 2.33 [0.67, 8.11] Odds Ratio M-H, Fixed, 95% Cl 1.24 [0.38, 3.98] 5.34 [0.29, 97.50] 0.63 [0.29, 1.40] 0.94 [0.51, 1.74]	L 0.01	Odds Ratio M-H. Fixed. 95% CI 0.1 1 10 100 Favours [BA] Favours [Placebo] Odds Ratio M-H. Fixed. 95% CI 0.1 1 10 100 Favours [BA] Favours [Placebo]	To To To
57 57	37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55	Study or Subgroup Goldberg 2019 Laufs 2019 Ray 2019 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = ( Test for overall effect: E) Hospitalization Goldberg 2019 Laufs 2019 Ray 2019 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 2 Test for overall effect:	BA <u>Events</u> 5 0 9 14 0.96, df = Z = 1.32 (l 1 for uns BA <u>Events</u> 10 5 14 29 2.55, df = : Z = 0.20 (l	Total $522$ $234$ $1487$ $2243$ $1 (P = 0.1)$ $522$ $522$ $234$ $522$ $234$ $1487$ $2243$ $2243$ $2243$ $2243$ $2243$ $2(P = 0.8)$ $P = 0.8$	Placel Events 2 0 1 3 0.33); I <sup>2</sup> = 9) 2 angina Placel Events 4 0 11 15 0.28); I <sup>2</sup> = 4)	Do           Total           257           111           742           1110           0%           1           0%           1           0%           1           0%           1           0%           1           0%           1           110           257           1111           742           1110           21%	Weight 66.7% 33.3% 100.0% <u>Weight</u> 25.7% 3.2% 71.1% 100.0%	Odds Ratio M-H, Fixed, 95% Cl 1.23 [0.24, 6.40] Not estimable 4.51 [0.57, 35.68] 2.33 [0.67, 8.11] Odds Ratio M-H, Fixed, 95% Cl 1.24 [0.38, 3.98] 5.34 [0.29, 97.50] 0.63 [0.29, 1.40] 0.94 [0.51, 1.74]	L 0.01	Odds Ratio M-H. Fixed. 95% CI 0.1 1 10 100 Favours [BA] Favours [Placebo] Odds Ratio M-H. Fixed. 95% CI 0.1 1 10 100 Favours [BA] Favours [Placebo]	To To To
	37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56	Study or Subgroup Goldberg 2019 Laufs 2019 Ray 2019 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = ( Test for overall effect: E) Hospitalization Goldberg 2019 Laufs 2019 Ray 2019 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 2 Test for overall effect:	BA <u>Events</u> 5 0 9 14 0.96, df = Z = 1.32 (l 1 for uns BA Events 10 5 14 29 2.55, df = : Z = 0.20 (l interpret 2)	Total $522$ $234$ $1487$ $2243$ $1 (P = 0.1)$ stable           Total $522$ $234$ $1487$ $2243$ $2243$ $2243$ $2(P = 0.8)$ $2(P = 0.8)$	Placel <u>Events</u> 2 0 1 3 0.33); I <sup>2</sup> = 9) 2 angina Placel Events 4 0 11 15 0.28); I <sup>2</sup> = 4) 2 2 2 2 2 2 2 2 2 2 2 2 2	200 Total 257 111 742 1110 0% 0% 1110 257 1111 742 1110 21% nd cs	Weight 66.7% 33.3% 100.0% <u>Weight</u> 25.7% 3.2% 71.1% 100.0%	Odds Ratio M-H. Fixed. 95% Cl 1.23 [0.24, 6.40] Not estimable 4.51 [0.57, 35.68] 2.33 [0.67, 8.11] Odds Ratio M-H. Fixed. 95% Cl 1.24 [0.38, 3.98] 5.34 [0.29, 97.50] 0.63 [0.29, 1.40] 0.94 [0.51, 1.74]	0.01	Odds Ratio M-H. Fixed. 95% CI 0.1 1 10 100 Favours [BA] Favours [Placebo] Odds Ratio M-H. Fixed. 95% CI 0.1 1 10 100 Favours [BA] Favours [Placebo] Pal. efficacy. outcomes. of correct	
revascularization, nonfatal stroke (C), hospitalization for heart failure (D) or unstable angina (E) for bempedoic ad	37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57	Study or Subgroup Goldberg 2019 Laufs 2019 Ray 2019 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = ( Test for overall effect: E) Hospitalization Goldberg 2019 Laufs 2019 Ray 2019 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 3 Test for overall effect: Supplementary Fri	BA <u>Events</u> 5 0 9 14 0.96, df = Z = 1.32 (I 1 for uns BA Events 10 5 14 29 2.55, df = : Z = 0.20 (I igure 2:	Total $522$ $234$ $1487$ $2243$ $1 (P = 0.1)$ $522$ $522$ $234$ $522$ $234$ $1487$ $2243$ $2243$ $2243$ $2243$ $2(P = 0.8)$ Indiv $1000$	Placel <u>Events</u> 2 0 1 3 0.33); I <sup>2</sup> = 9) 2 angina Placel Events 4 0 11 15 0.28); I <sup>2</sup> = 4 vidual a	Dop           Total           257           111           742           1110           0%           1           0%           1           0%           1           0%           1           0%           1           0%           1           0%           1           20%           Total           257           1111           742           1110           21%           nnd su	Weight 66.7% 33.3% 100.0% <u>Weight</u> 25.7% 3.2% 71.1% 100.0%	Odds Ratio M-H. Fixed. 95% Cl 1.23 [0.24, 6.40] Not estimable 4.51 [0.57, 35.68] 2.33 [0.67, 8.11] Odds Ratio M-H. Fixed. 95% Cl 1.24 [0.38, 3.98] 5.34 [0.29, 97.50] 0.63 [0.29, 1.40] 0.94 [0.51, 1.74] odds ratios of a	0.01	Odds Ratio M-H. Fixed. 95% CI 0.1 1 10 100 Favours [BA] Favours [Placebo] Odds Ratio M-H. Fixed. 95% CI 0.1 1 10 100 Favours [BA] Favours [Placebo] al efficacy outcomes of coron	To To nary

(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; Tau<sup>2</sup> and I<sup>2</sup> are measures of heterogeneity. BA=bempedoic acid; M-H=Mantel-Haenszel.

#### Supplementary Figure 3 – Additional safety outcomes of BA vs. placebo therapy 1 A) Elevation in uric acid 2 3 ΒА Placebo Odds Ratio Odds Ratio Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% Cl M-H, Fixed, 95% CI 4 Ballantyne 2018 14 181 88 27.9% 3.60 [0.80, 16.22] 2 Goldberg 2019 22 522 5 257 72.1% 2.22 [0.83, 5.93] 5 6 Total (95% CI) 703 345 100.0% 2.60 [1.15, 5.91] Total events 36 7 Heterogeneity: Chi<sup>2</sup> = 0.28, df = 1 (P = 0.60); l<sup>2</sup> = 0% 0.01 10 100 0.1 Test for overall effect: Z = 2.29 (P = 0.02) 8 Favours [BA] Favours [Placebo] 9 B) Increase in serum creatinine 10 ΒА Odds Ratio Placebo Odds Ratio 11 Events Total Events Total Weight Study or Subgroup M-H, Fixed, 95% Cl M-H, Fixed, 95% Cl 12 Goldberg 2019 522 257 25.1% 1 98 [0 22 17 78] 4 Ray 2019 12 1478 742 74.9% 2.02 [0.57, 7.17] 3 13 Total (95% CI) 2000 999 100.0% 2.01 [0.67, 6.02] 14 Total events 16 Λ 15 Heterogeneity: Chi<sup>2</sup> = 0.00, df = 1 (P = 0.99); l<sup>2</sup> = 0% 0.01 0.1 10 100 Test for overall effect: Z = 1.24 (P = 0.21) Favours [BA] Favours [Placebo] 16 17 C) Upper respiratory tract infection 18 ΒА Odds Ratio Placebo Odds Ratio 19 Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% Cl M-H, Fixed, 95% Cl 1.04 [0.46, 2.33] 20 522 257 Goldberg 2019 19 9.2% 9 Gutierrez 2014 2 6 30 2 30 1.5% 1.00 [0.13, 7.60] 21 234 6 0.46 [0.15, 1.46] Laufs 2019 111 6.3% 87 83.0% 0.82 [0.62, 1.09] Ray 2019 146 1487 742 22 Total (95% CI) 2273 1140 100.0% 0.82 [0.63, 1.06] 23 Total events 173 104 24 Heterogeneity: Chi<sup>2</sup> = 1.33, df = 3 (P = 0.72); l<sup>2</sup> = 0% 0.01 0.1 10 100 Test for overall effect: Z = 1.52 (P = 0.13) 25 Favours [BA] Favours [Placebo] 26 D) Urinary tract infection 27 BA Placebo Odds Ratio Odds Ratio 28 I-H, Fixed, 95% Cl Study or Subgroup M-H, Fixed, 95% C Events Total Events Total Weight 0.47 [0.13, 1.67] Ballantyne 2018 5 181 5 88 7.5% 29 Ballantyne 2019 11 218 2 55 3.5% 1.41 [0.30, 6.55] 7.3% 30 Goldberg 2019 26 522 5 257 2.64 [1.00, 6.96] Laufs 2019 8 234 9 111 13.5% 0.40 [0.15, 1.07] 31 Ray 2019 47 742 0.74 [0.51, 1.08] 71 1487 68.3% 32 Total (95% CI) 2642 1253 100.0% 0.84 [0.62, 1.14] 121 68 33 Total events Heterogeneity: Chi<sup>2</sup> = 9.18, df = 4 (P = 0.06); l<sup>2</sup> = 56% 0.01 10 100 0.1 34 Test for overall effect: Z = 1.14 (P = 0.25) Favours [BA] Favours [Placebo] 35 E) Neurocognitive disorder 36 37 ΒA Placebo Odds Ratio Odds Ratio Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% Cl M-H, Fixed, 95% Cl 38 0.77 [0.24, 2.42] Ballantyne 2018 8 181 25.5% 5 88 Ballantyne 2019 6 218 55 6.2% 1.53 [0.18, 12.96] 39 Goldberg 2019 3 522 257 5.3% 1.48 [0.15, 14.30] 1 6 30 5 30 15.9% 1.25 [0.34, 4.64] 40 Gutierrez 2014 Laufs 2019 6 234 2 111 10.5% 1.43 [0.28, 7.22] 41 7 742 Ray 2019 11 1487 36.7% 0.78 [0.30, 2.03] 42 Total (95% CI) 1.00 [0.58, 1.74] 2672 1283 100.0% 43 Total events 40 21 Heterogeneity: Chi<sup>2</sup> = 1.03, df = 5 (P = 0.96); l<sup>2</sup> = 0% 0.01 0.1 10 100 44 Test for overall effect: Z = 0.01 (P = 0.99) Favours [BA] Favours [Placebo] 45 46 F) Nasopharyngitis 47 RΑ Placebo Odds Ratio Odds Ratio Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% Cl M-H, Fixed, 95% CI 48 Ballantyne 2018 181 1.97 [0.22, 17.86] 88 1.1% 49 Ballantyne 2019 10 218 55 1.2% 2.60 [0.33, 20.72] 1 27 Goldberg 2019 522 13 257 13.3% 1.02 [0.52, 2.02] 50 Ray 2019 0.82 [0.62, 1.09] 146 1487 87 742 84.4% 51 Total (95% CI) 2408 1142 100.0% 0.88 [0.68, 1.14] 52 102 Total events 187 Heterogeneity: Chi<sup>2</sup> = 1.99, df = 3 (P = 0.57); l<sup>2</sup> = 0% 0.01 10 100 0.1 Test for overall effect: Z = 0.98 (P = 0.33) Favours [BA] Favours [Placebo]

53 <sup>Hete</sup> 54 <del>-</del> 55 55 56 <u>Sup</u> 57 infec

59 60 <u>Supplementary Figure 3</u>: 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; Tau<sup>2</sup> and I<sup>2</sup> are measures of heterogeneity. BA=bempedoic acid; M-H=Mantel-Haenszel.

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

			ва		PI	acebo			Mean Difference		Mean Dif	ference	
	Study or Subaroup	Mean	SD	Total	Mean	SD	Total	Weight	IV. Fixed. 95% C		IV. Fixed	. 95% CI	
_	Ballantyne 2018	-23 5	26.9	181	5	20.7	81	7.3%	-28.50 [-34 47 -22 53]				
	Ballantyne 2019	-17 7	23.1	110	-2.5	22.4	55	4.9%	-15.20 [-22.53 -7.87]				
	Gutierrez 2014	-42.9	14	29		13.7	30	5.2%	-38,90 [-45,97 -31 83]	-	-		
	Laufs 2019	-21.2	20.7	218	-2.3	16.5	107	15.1%	-18.90 [-23.0614.74]				
	Ray 2019	-16.5	20.1	1488	1.6	23.4	742	67.5%	-18.10 [-20.0716.13]				
	•								,		.		
	Total (95% CI)			2026			1015	100.0%	-19.93 [-21.55, -18.31]		♦		
	Heterogeneity: Chi <sup>2</sup> = 4	40.71, df	f = 4 (F	o < 0.00	0001); F	² = 90%	6			F0		25	
	Test for overall effect:	Z = 24.1	5 (P <	0.0000	)1)					-50	-20 U Favours [RA]	Eavours [Placebo]	50
											Tavours [BA]		
E	3) Total cholest	terol											
_	1												
			BA		PI	acebo			Mean Difference		Mean Dif	ference	
_	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% C		IV, Fixed	, 95% Cl	
	Ballantyne 2018	-15.1	17.5	181	2.9	14.1	88	6.5%	-18.00 [-21.90, -14.10]				
	Ballantyne 2019	-12.8	17.8	110	-2	16.3	55	3.3%	-10.80 [-16.24, -5.36]				
	Goldberg 2019	-9.9	15.6	499	1.3	15.9	253	17.3%	-11.20 [-13.59, -8.81]		-		
	Gutierrez 2014	-25.1	10.4	30	-0.5	10.4	30	3.6%	-24.60 [-29.86, -19.34]				
	Laufs 2019	-15	15	224	-1	10	107	13.3%	-14.00 [-16.73, -11.27]				
	Ray 2019	-10.3	14.3	1488	0.8	15.5	742	55.9%	-11.10 [-12.43, -9.77]		•		
	Total (95% CI)			2522			1275	100 0%	-12 / 3 [-13 / 2 -11 / 2]		▲		
	Hotorogoneity Chi2 - 1	21 06 -4	- E /	∠002 2 < 0 00	0041	2 - 000	1213	100.0%	-12.45 [-13.42, -11.43]	<b>—</b>			
	Test for overall effects	24.80, dt 7 = 24 4	– э (ŀ 7 /₽ ~		)(1); F 11)	- 86%	0			-50	-25 0	25	50
	rest for overall effect: .	∠ = 24.4	/ (P <	0.0000	/i)						Favours [BA]	Favours [Placebo]	
(	C) Non-HDL-C	2											
-	<i>,</i> , , , , , , , , , , , , , , , , , ,	_											
			BA		PI	acebo			Mean Difference		Mean Dif	ference	
	Study or Subaroup	Mean	SD	Total	Mean	SD	Total	Weiaht	IV, Fixed, 95% C		IV. Fixed	. 95% CI	
_	Ballantyne 2018	-18.4	21.5	181	5.2	20.6	88	6.1%	-23.60 [-28.92 -18.28]				
	Ballantyne 2019	-14.9	21	110	-2	20.8	55	3.8%	-12.90 [-19.65, -6.15]				
	Goldberg 2019	-10.8	22.3	498	2.3	22.3	253	15.3%	-13.10 [-16.47, -9.73]				
	Gutierrez 2014	-32	12.6	30	-0.5	12.6	30	4.3%	-31.50 [-37.88, -25.12]	-			
	Laufs 2019	-18	18	224	-0.9	13.4	107	14.5%	-17.10 [-20.56, -13.64]				
	Ray 2019	-11.9	18.5	1488	1.5	20.7	742	56.0%	-13.40 [-15.16, -11.64]				
	Total (95% CI)			2531			1275	100.0%	-15.27 [-16.59, -13.95]		•		
	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4	41.76, df	f = 5 (F	<b>2531</b> P < 0.00	0001); l	² = 88%	1275 6	100.0%	-15.27 [-16.59, -13.95]	F0	•		
	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: 2	41.76, df Z = 22.7	f = 5 (F 0 (P <	<b>2531</b> P < 0.00 0.0000	0001); l <sup>:</sup> 01)	² = 88%	1275 %	100.0%	-15.27 [-16.59, -13.95]	⊢ -50	-25 0	25 Favours [Placebo]	50
	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: 2	41.76, df Z = 22.7	f = 5 (F 0 (P <	2531 P < 0.00 0.0000	0001); l <sup>:</sup> 01)	² = 88%	1275 %	100.0%	-15.27 [-16.59, -13.95]	-50	-25 0 Favours [BA]	25 Favours [Placebo]	50
T	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: :	41.76, df Z = 22.7	f = 5 (F 0 (P <	2531 P < 0.00 0.0000	0001); F 01)	² = 88%	1275 %	100.0%	-15.27 [-16.59, -13.95]	-50	-25 0 Favours [BA]	25 Favours [Placebo]	50
I	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: : D) Apolipoprote	41.76, df Z = 22.7 ein <u>B</u>	f = 5 (F 0 (P <	2531 > < 0.00 0.0000	0001); F 01)	² = 88%	1275 %	100.0%	-15.27 [-16.59, -13.95]	-50	◆ -25 0 Favours [BA]	l 25 Favours [Placebo]	 50
Ī	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: . D) Apolipoprote	41.76, df Z = 22.7 ein B	f = 5 (F 0 (P < <b>BA</b>	2531 > < 0.00 0.0000	0001); F 01) PI	² = 88% acebo	1275 6	100.0%	-15.27 [-16.59, -13.95] Mean Difference	-50	-25 0 Favours [BA]	25 Favours [Placebo] ference	50
Ī	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: 3 D) Apolipoproto Study or Subgroup	41.76, df Z = 22.7 ein B Mean	= 5 (F 0 (P < BA SD	2531 > < 0.00 0.0000	0001); I 01) PI Mean	² = 88% acebo SD	1275 %	100.0% Weight	-15.27 [-16.59, -13.95] Mean Difference IV, Fixed, 95% C	-50	-25 0 Favours [BA] Mean Dif	25 Favours [Placebo] ference I, 95% Cl	50
Ī	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: A D) Apolipoproto Study or Subgroup Ballantyne 2018	41.76, df Z = 22.7 ein B <u>Mean</u> -14.6	= 5 (F 0 (P < BA <u>SD</u> 20.2	2531 P < 0.00 0.0000 <u>Total</u> 181	0001); F 01) PI <u>Mean</u> 4.7	<sup>2</sup> = 88% acebo <u>SD</u> 16.9	1275 6 <u>Total</u> 88	100.0% Weight 7.6%	-15.27 [-16.59, -13.95] Mean Difference IV. Fixed, 95% C -19.30 [-23.90, -14.70]	-50	-25 0 Favours [BA] Mean Dif	25 Favours [Placebo] ference , 95% Cl	50
<u>I</u> 	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: A D) Apolipoprote Study or Subgroup Ballantyne 2018 Ballantyne 2019	41.76, df Z = 22.7 ein B <u>Mean</u> -14.6 -11.7	E = 5 (F 0 (P < BA 20.2 23.1	2531 P < 0.00 0.0000 Total 181 82	0001); F 01) <u>PI Mean</u> 4.7 1.6	<sup>2</sup> = 88% acebo <u>SD</u> 16.9 20.8	1275 6 <u>Total</u> 88 38	100.0% Weight 7.6% 2.3%	-15.27 [-16.59, -13.95] Mean Difference IV. Fixed, 95% C -19.30 [-23.90, -14.70] -13.30 [-21.59, -5.01]	-50	-25 0 Favours [BA] Mean Dif IV, Fixed	25 Favours [Placebo] ference I, 95% Cl	50
<u>I</u> 	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: J D) Apolipoproto Study or Subgroup Ballantyne 2018 Ballantyne 2019 Goldberg 2019	41.76, df Z = 22.7 ein B Mean -14.6 -11.7 -9.3	E = 5 (F 0 (P < BA 20.2 23.1 19.7	<b>2531</b> <b>&gt;</b> < 0.00 0.0000 <b>Total</b> 181 82 479	0001); F 01) <u>PI Mean</u> 4.7 1.6 3.7	<sup>2</sup> = 88% acebo <u>SD</u> 16.9 20.8 20.3	1275 6 Total 88 38 245	100.0% Weight 7.6% 2.3% 16.8%	-15.27 [-16.59, -13.95] Mean Difference <u>IV. Fixed, 95% C</u> -19.30 [-23.90, -14.70] -13.30 [-21.59, -5.01] -13.00 [-16.09, -9.91]	-50	-25 0 Favours [BA] Mean Dif	25 Favours [Placebo] ference I, 95% Cl	50
<u>I</u> 	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: 3 D) Apolipoproto Study or Subgroup Ballantyne 2018 Ballantyne 2019 Goldberg 2019 Laufs 2019	41.76, df Z = 22.7 ein B <u>Mean</u> -14.6 -11.7 -9.3 -15	E = 5 (F 0 (P < BA 20.2 23.1 19.7 16.5	<b>2531</b> <b>&gt;</b> < 0.00 0.0000 <b>Total</b> 181 82 479 224	0001); F 01) <u>PI</u> <u>Mean</u> 4.7 1.6 3.7 0.5	<sup>2</sup> = 88% acebo <u>SD</u> 16.9 20.8 20.3 13.4	<b>Total</b> 88 38 245 107	100.0% Weight 7.6% 2.3% 16.8% 14.5%	-15.27 [-16.59, -13.95] Mean Difference IV. Fixed, 95% C -19.30 [-23.90, -14.70] -13.30 [-21.59, -5.01] -13.00 [-16.09, -9.91] -15.50 [-18.83, -12.17]	-50	-25 0 Favours [BA] Mean Dif	25 Favours [Placebo] ference I, 95% Cl	50
<u>I</u> -	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: D) Apolipoprota Study or Subgroup Ballantyne 2018 Ballantyne 2019 Goldberg 2019 Laufs 2019 Ray 2019	41.76, df Z = 22.7 ein B -14.6 -11.7 -9.3 -15 -8.6	BA 9 (P < 8D 20.2 23.1 19.7 16.5 18.1	2531 > < 0.00 0.0000 Total 181 82 479 224 1485	0001); F 01) <u>Pl Mean</u> 4.7 1.6 3.7 0.5 3.3	acebo SD 16.9 20.8 20.3 13.4 19	1275 6 Total 88 38 245 107 736	<b>Weight</b> 7.6% 2.3% 16.8% 14.5% 58.8%	-15.27 [-16.59, -13.95] Mean Difference IV. Fixed, 95% C -19.30 [-23.90, -14.70] -13.30 [-21.59, -5.01] -13.00 [-16.09, -9.91] -15.50 [-18.83, -12.17] -11.90 [-13.55, -10.25]	-50	-25 0 Favours [BA] Mean Dif IV, Fixed	I 25 Favours [Placebo] ference (, 95% Cl	50
<u>I</u> 	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: A D) Apolipoproto Study or Subgroup Ballantyne 2018 Ballantyne 2019 Goldberg 2019 Laufs 2019 Ray 2019	41.76, df Z = 22.7 ein B -14.6 -11.7 -9.3 -15 -8.6	<b>BA</b> 20.2 23.1 19.7 16.5 18.1	2531 > < 0.00 0.0000 Total 181 82 479 224 1485	0001); F 01) <u>Mean</u> 4.7 1.6 3.7 0.5 3.3	acebo <u>SD</u> 16.9 20.8 20.3 13.4 19	1275 6 7000 88 38 245 107 736	<b>Weight</b> 7.6% 2.3% 16.8% 14.5% 58.8%	-15.27 [-16.59, -13.95] Mean Difference IV. Fixed, 95% C -19.30 [-23.90, -14.70] -13.30 [-21.59, -5.01] -13.00 [-16.09, -9.91] -15.50 [-18.83, -12.17] -11.90 [-13.55, -10.25]	-50	-25 0 Favours [BA] Mean Dif IV, Fixed	25 Favours [Placebo] ference (, 95% Cl	50
<u>I</u> _	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: A D) Apolipoprote Study or Subgroup Ballantyne 2018 Ballantyne 2019 Goldberg 2019 Laufs 2019 Ray 2019 Total (95% CI)	41.76, df Z = 22.7 ein B -14.6 -11.7 -9.3 -15 -8.6	BA 0 (P < BA 20.2 23.1 19.7 16.5 18.1	2531 < 0.00 0.0000 Total 181 82 479 224 1485 2451	0001); F 01) <b>Pl</b> <u>Mean</u> 4.7 1.6 3.7 0.5 3.3	<sup>2</sup> = 88% acebo <u>SD</u> 16.9 20.8 20.3 13.4 19	1275 6 Total 88 38 245 107 736 1214	100.0% Weight 7.6% 2.3% 16.8% 14.5% 58.8% 100.0%	-15.27 [-16.59, -13.95] Mean Difference IV. Fixed, 95% C -19.30 [-23.90, -14.70] -13.30 [-21.59, -5.01] -15.50 [-18.83, -12.17] -11.90 [-13.55, -10.25] -13.20 [-14.47, -11.93]	-50	-25 0 Favours [BA] Mean Dif IV, Fixed	25 Favours [Placebo] ference (, 95% Cl	
<u>I</u>	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: : D) Apolipoproto Study or Subgroup Ballantyne 2018 Ballantyne 2019 Goldberg 2019 Laufs 2019 Ray 2019 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = -	41.76, df Z = 22.7 ein B -14.6 -11.7 -9.3 -15 -8.6 10.99, df	<b>BA</b> 20.2 23.1 19.7 16.5 18.1	2531 > < 0.00 0.0000 Total 181 82 479 224 1485 2451 > = 0.03	0001); F 01) PI Mean 4.7 1.6 3.7 0.5 3.3 3.3	acebo SD 16.9 20.8 20.3 13.4 19	1275 6 Total 88 38 245 107 736 1214	Weight 7.6% 2.3% 16.8% 14.5% 58.8% 100.0%	-15.27 [-16.59, -13.95] Mean Difference <u>IV. Fixed, 95% C</u> -19.30 [-23.90, -14.70] -13.30 [-21.59, -501] -13.00 [-16.09, -9.91] -15.50 [-18.83, -12.17] -11.90 [-13.55, -10.25] -13.20 [-14.47, -11.93]	-50	-25 0 Favours [BA]	25 Favours [Placebo] ference , 95% Cl	50
<u>I</u> 	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: . D) Apolipoproto Study or Subgroup Ballantyne 2018 Ballantyne 2019 Goldberg 2019 Laufs 2019 Ray 2019 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = - Test for overall effect: .	41.76, df Z = 22.7 ein B -14.6 -11.7 -9.3 -15 -8.6 10.99, df Z = 20.4	<b>BA</b> 20.2 23.1 19.7 16.5 18.1 <b>S</b> <b>S</b> <b>S</b> <b>S</b> <b>S</b> <b>S</b> <b>S</b> <b>S</b> <b>S</b> <b>S</b>	2531 < 0.00 0.0000 Total 181 82 479 224 1485 2451 = 0.03 0.0000	0001); F 11) <b>Pl</b> <u>Mean</u> 4.7 1.6 3.7 0.5 3.3 3.3 8); I <sup>2</sup> = 6 01)	acebo <u>SD</u> 16.9 20.8 20.3 13.4 19	1275 6 70tal 88 38 245 107 736 1214	<ul> <li>100.0%</li> <li>Weight</li> <li>7.6%</li> <li>2.3%</li> <li>16.8%</li> <li>14.5%</li> <li>58.8%</li> <li>100.0%</li> </ul>	-15.27 [-16.59, -13.95] Mean Difference IV. Fixed, 95% C -19.30 [-23.90, -14.70] -13.30 [-21.59, -5.01] -13.00 [-16.9, -9.91] -15.50 [-18.83, -12.17] -11.90 [-13.55, -10.25] -13.20 [-14.47, -11.93]	-50	-25 0 Favours [BA]	25 Favours [Placebo] ference 95% Cl	50
<u>I</u> -	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: . D) Apolipoprota Study or Subgroup Ballantyne 2018 Ballantyne 2019 Goldberg 2019 Laufs 2019 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 7 Test for overall effect: .	41.76, df Z = 22.7 ein B -14.6 -11.7 -9.3 -15 -8.6 10.99, df Z = 20.4	<b>BA</b> <b>SD</b> 20.2 23.1 19.7 16.5 18.1 = 4 (F	2531 < 0.00 0.0000 Total 181 82 479 224 1485 2451 = 0.03 0.0000	0001); F 11) <b>Pl</b> <b>Mean</b> 4.7 1.6 3.7 0.5 3.3 3); I <sup>2</sup> = 6 01)	acebo <u>SD</u> 16.9 20.8 20.3 13.4 19	1275 6 70tal 88 38 245 107 736 1214	<ul> <li>Weight</li> <li>7.6%</li> <li>2.3%</li> <li>16.8%</li> <li>14.5%</li> <li>58.8%</li> <li>100.0%</li> </ul>	-15.27 [-16.59, -13.95] Mean Difference IV. Fixed, 95% C -19.30 [-23.90, -14.70] -13.30 [-21.59, -5.01] -13.30 [-16.09, -9.91] -15.50 [-18.83, -12.17] -11.90 [-13.55, -10.25] -13.20 [-14.47, -11.93]	-50	-25 0 Favours [BA] Mean Dif IV, Fixed -25 0 Favours [BA]	25 Favours [Placebo] ference , 95% Cl 25 Favours [Placebo]	50
<u>I</u> -	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: 1 D) Apolipoprota Study or Subgroup Ballantyne 2018 Ballantyne 2019 Goldberg 2019 Laufs 2019 Ray 2019 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect: 1 E) HDL-C	41.76, df Z = 22.7 ein B -14.6 -11.7 -9.3 -15 -8.6 10.99, df Z = 20.4	<b>BA</b> <b>SD</b> 20.2 23.1 19.7 16.5 18.1 <b>S</b> <b>S</b> <b>S</b> <b>S</b> <b>S</b> <b>S</b> <b>S</b> <b>S</b>	2531 < 0.00 0.0000 Total 181 82 479 224 1485 2451 = 0.00 0.0000	0001); F 01) <b>Pl</b> 4.7 1.6 3.7 0.5 3.3 3); I <sup>2</sup> = 6 01)	<sup>2</sup> = 88% <b>SD</b> 16.9 20.8 20.3 13.4 19 64%	1275 6 88 38 245 107 736 1214	100.0% Weight 7.6% 2.3% 16.8% 14.5% 58.8% 100.0%	-15.27 [-16.59, -13.95] Mean Difference IV. Fixed, 95% C -19.30 [-23.90, -14.70] -13.30 [-21.59, -5.01] -13.00 [-16.09, -9.91] -15.50 [-18.83, -12.17] -11.90 [-13.55, -10.25] -13.20 [-14.47, -11.93]	-50	-25 0 Favours [BA] Mean Dif IV, Fixed 	25 Favours [Placebo] ference , 95% Cl	50
<u>I</u> 	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: : D) Apolipoprote Study or Subgroup Ballantyne 2018 Ballantyne 2019 Goldberg 2019 Laufs 2019 Ray 2019 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect: : E) HDL-C	41.76, df Z = 22.7 ein B -14.6 -11.7 -9.3 -15 -8.6 10.99, df Z = 20.4	<b>BA</b> <b>SD</b> 20.2 23.1 19.7 16.5 18.1 = 4 (F 1 (P <	<b>2531</b> 0.0000 181 181 82 479 224 1485 <b>2451</b> 2 <b>2451</b> 0.0000	0001); F 11) Mean 4.7 1.6 3.7 0.5 3.3 3.3; I <sup>2</sup> = (	<sup>2</sup> = 88% <u>SD</u> 16.9 20.8 20.3 13.4 19 54%	1275 6 88 38 245 107 736 1214	100.0% Weight 7.6% 2.3% 16.8% 14.5% 58.8% 100.0%	-15.27 [-16.59, -13.95] Mean Difference IV. Fixed, 95% C -19.30 [-23.90, -14.70] -13.30 [-21.59, -5.01] -15.50 [-18.83, -12.17] -11.90 [-13.55, -10.25] -13.20 [-14.47, -11.93]	-50	-25 0 Favours [BA] Mean Dif IV, Fixed	25 Favours [Placebo] ference , 95% Cl 25 Favours [Placebo]	50
<u>I</u> -	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: : D) Apolipoproto Study or Subgroup Ballantyne 2018 Ballantyne 2019 Coldberg 2019 Laufs 2019 Ray 2019 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = - Test for overall effect: : E) HDL-C	41.76, df Z = 22.7 ein B -14.6 -11.7 -9.3 -15 -8.6 10.99, df Z = 20.4	BA SD 20.2 23.1 19.7 16.5 18.1 = 4 (F 1 (P <	2531 2 < 0.00 0.0000 181 181 82 479 224 1485 2451 2451 0.0000 0.0000	0001); F 11) Mean 4.7 1.6 3.7 0.5 3.3 3.3 3); I <sup>2</sup> = ( 11)	<sup>2</sup> = 88% <u>SD</u> 16.9 20.8 20.3 13.4 19 54%	1275 6 7 107 736 1214	100.0% Weight 7.6% 2.3% 16.8% 14.5% 58.8% 100.0%	-15.27 [-16.59, -13.95] Mean Difference IV. Fixed. 95% C -19.30 [-23.90, -14.70] -13.30 [-21.59, -5.01] -13.30 [-16.9, -9.91] -15.50 [-18.83, -12.17] -11.90 [-13.55, -10.25] -13.20 [-14.47, -11.93] Mean Difference	-50	-25 0 Favours [BA] Mean Dif IV, Fixed -25 0 Favours [BA]	25 Favours (Placebo) ference .95% Cl 25 Favours (Placebo)	50
<u>I</u>  _ <u>H</u>	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: . D) Apolipoproto Study or Subgroup Ballantyne 2018 Ballantyne 2019 Goldberg 2019 Laufs 2019 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = - Test for overall effect: . C) HDL-C Study or Subgroup	41.76, df Z = 22.7 ein B -14.6 -11.7 -9.3 -15 -8.6 10.99, df Z = 20.4	BA SD 20.2 23.1 19.7 16.5 18.1 : = 4 (F BA SD	2531 2 < 0.00 0.0000 181 181 82 479 224 1485 2451 2451 2451 0.0000 Total	0001); i 1) <b>Pi</b> <b>Mean</b> 4.7 1.6 3.7 0.5 3.3 3); i <sup>2</sup> = ( 01) Pi <b>Pi</b> <b>Mean</b>	<sup>2</sup> = 88% lacebo <u>SD</u> 16.9 20.8 20.3 13.4 19 34% lacebo <u>SD</u>	1275 6 7 107 736 1214 Total	100.0% Weight 7.6% 2.3% 16.8% 14.5% 100.0% Weight	-15.27 [-16.59, -13.95] Mean Difference IV. Fixed. 95% C -19.30 [-23.90, -14.70] -13.30 [-21.59, -5.01] -13.30 [-16.9, -9.91] -15.50 [-18.83, -12.17] -11.90 [-13.55, -10.25] -13.20 [-14.47, -11.93] Mean Difference IV. Fixed. 95% C	-50	-25 0 Favours [BA] Mean Dif IV. Fixed -25 0 Favours [BA] Mean Dif IV. Fixed	ference 1 25 Favours [Placebo] ference 25 Favours [Placebo] ference 35% Cl	  50
<u>I</u>  	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: . D) Apolipoprota Study or Subgroup Ballantyne 2018 Ballantyne 2019 Goldberg 2019 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 7 Test for overall effect: . E) HDL-C Study or Subgroup Ballantyne 2018	41.76, df Z = 22.7 ein B -14.6 -11.7 -9.3 -15 -8.6 10.99, df Z = 20.4 Mean -7.3	<b>BA</b> <b>SD</b> 20.2 23.1 19.7 16.5 18.1 1 (P < <b>BA</b> <b>SD</b> 16.1 1 (P < <b>BA</b> <b>SD</b> 16.1	2531 2 < 0.000 181 181 1485 2451 2 = 0.03 0.0000 Total 181 2 = 0.03 0.0000	0001); I 11) <u>Mean</u> 4.7 1.6 3.7 0.5 3.3 3); I <sup>2</sup> = ( 11) <u>P</u> [ <u>Mean</u> 12.6	<sup>2</sup> = 88% <b>SD</b> 16.9 20.8 20.3 13.4 19 34% <b>lacebo</b> <b>SD</b> 1.4 19	1275 6 Total 88 83 245 107 736 1214 Total 81	100.0% Weight 7.6% 2.3% 16.8% 14.5% 58.8% 100.0% Weight 12.7%	-15.27 [-16.59, -13.95] Mean Difference IV. Fixed, 95% C -19.30 [-23.90, -14.70] -13.30 [-21.59, -5.01] -13.30 [-16.09, -9.91] -15.50 [-18.83, -12.17] -11.90 [-13.55, -10.25] -13.20 [-14.47, -11.93] Mean Difference IV. Fixed, 95% C -19.90 [-22.27, -17.53] -0.01 [-22.27, -17.53]	-50	-25 0 Favours [BA] Mean Dif [V, Fixed -25 0 Favours [BA] Mean Dif	25 Favours [Placebo] ference , 95% Cl Favours [Placebo]	50
<u>I</u>  	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: 1 D) Apolipoprota Ballantyne 2018 Ballantyne 2019 Goldberg 2019 Laufs 2019 Ray 2019 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 7 Test for overall effect: 1 E) HDL-C Study or Subgroup Ballantyne 2018 Goldberg 2019	41.76, df Z = 22.7 ein B -14.6 -11.7 -9.3 -15 -8.6 10.99, df Z = 20.4 Mean -7.3 -6.4	BA SD 20.2 23.1 19.7 16.5 18.1 = 4 (F BA SD 16.1 15.6	2531 2 < 0.00 0.0000 181 181 82 479 224 1485 2451 2451 2451 0.0000 Total 181 183 	0001); I; I I1) Mean 4.7 1.6 3.7 0.5 3.3 3); I <sup>2</sup> = ( Mean 12.6 -0.2 2.7 .7 .7 .7 .7 .7 .7 .7 .7 .7	<sup>2</sup> = 88% <u>SD</u> 16.9 20.8 20.3 13.4 19 54% <u>SD</u> 1.4 1.4 1.4 3.2 .2 .2 .2 .2 .2 .2 .2 .2 .2	1275 6 7 7 1214 7 7 3 6 1214 81 253 81 253 7 7 81	100.0% Weight 7.6% 2.3% 16.8% 14.5% 58.8% 100.0% Weight 12.7% 14.3% 2.3%	-15.27 [-16.59, -13.95] Mean Difference IV. Fixed, 95% C -19.30 [-23.90, -14.70] -13.30 [-21.59, -5.01] -13.00 [-16.09, -9.91] -15.50 [-18.83, -12.17] -11.90 [-13.55, -10.25] -13.20 [-14.47, -11.93] Mean Difference IV. Fixed, 95% C -19.90 [-22.27, -17.53] -6.20 [-8.43, -3.97] -10.07 - 0.72 - 0.72	-50	-25 0 Favours [BA] Mean Dif IV, Fixed -25 0 Favours [BA] Mean Dif IV, Fixed	25 Favours [Placebo] ference . 95% Cl ference . 95% Cl	50
<u>I</u>  	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: : D) Apolipoprote Study or Subgroup Ballantyne 2018 Ballantyne 2019 Goldberg 2019 Laufs 2019 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = : C) HDL-C Study or Subgroup Ballantyne 2018 Goldberg 2019 Guldberg 2019 Constant of the state of the s	41.76, df Z = 22.7 ein B -14.6 -14.6 -11.7 -9.3 -15 -8.6 10.99, df Z = 20.4 Mean -7.3 -6.4 -1.2	<b>BA</b> <b>SD</b> 20.2 23.1 19.7 16.5 18.1 19.7 16.5 18.1 19.7 16.5 18.1 19.7 16.5 18.1 19.7 10.5 10.5 10.5 10.5 10.5 10.5 10.5 10.5	2531 - < 0.00 0.0000 Total 181 82 479 224 1485 2451 - = 0.00 0.0000 Total 181 499 30 0.0000	0001); i i 11) <b>Pi</b> <b>Mean</b> 4.7 1.6 3.7 0.5 3.3 3.3 ); i <sup>2</sup> = ( <b>Pi</b> <b>Mean</b> 12.6 -0.2 0.5 0.5 0.5 0.5 0.5 0.5 0.5 0.5	<sup>2</sup> = 88% <u>SD</u> 16.9 20.8 20.3 13.4 19 34% <u>SD</u> 1.4 14.3 9.9 4.0	1275 6 70tal 88 38 245 107 736 1214 1214 81 253 300	100.0% Weight 16.8% 14.5% 58.8% 100.0% Weight 12.7% 14.3% 2.8%	-15.27 [-16.59, -13.95] Mean Difference IV. Fixed, 95% C -19.30 [-23.90, -14.70] -13.30 [-21.59, -5.01] -13.00 [-16.09, -9.91] -15.50 [-18.83, -12.17] -11.90 [-13.55, -10.25] -13.20 [-14.47, -11.93] Mean Difference IV. Fixed, 95% Cf -19.90 [-22.27, -17.53] -6.20 [-8.43, -3.97] -1.70 [-6.71, 3.31] 4.00 [7.5 ± 10.75]	-50	-25 0 Favours [BA] Mean Dif IV, Fixed	25 Favours [Placebo] ference , 95% Cl 25 Favours [Placebo] ference , 95% Cl	  
<u>I</u> 	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: . D) Apolipoproto Study or Subgroup Ballantyne 2018 Ballantyne 2019 Coldberg 2019 Laufs 2019 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = - Test for overall effect: . C) HDL-C Study or Subgroup Ballantyne 2018 Goldberg 2019 Gutierrez 2014 Laufs 2019 Bau: 2019	41.76, df Z = 22.7 ein B -14.6 -11.7 -9.3 -15 -8.6 10.99, df Z = 20.4 Mean -7.3 -6.4 -1.2 -5.2	BA SD 20.2 23.1 16.5 18.1 1 (P < BA SD 16.1 15.6 9.9 16.5	2531 2 < 0.00 0.0000 Total 181 82 479 224 1485 2451 2 = 0.00 0.0000 Total 181 181 181 485 2451 2 = 0.00 0.0000 224 4 - 0.0000 2 - 0.0000 - 0.00000 - 0.0000 - 0.00000 - 0.0000 - 0.0000 - 0.00000 - 0	$\begin{array}{c} \text{PI} \\ \text{Mean} \\ 4.7 \\ 1.6 \\ 3.7 \\ 0.5 \\ 3.3 \\ 3.3 \\ 3.3 \\ 1^2 = ( \\ 0.5 \\ 0.6 \\ 0.0 \\ 0$	<sup>2</sup> = 88% <u>SD</u> 16.9 20.8 20.3 13.4 19 34% laceboo <u>SD</u> 1.4 14.3 9.9 10.3 9.1 14.2	1275 6 7 7 0 107 7 36 1214 8 1 253 30 107 7 22 7 22	100.0% Weight 7.6% 2.3% 16.8% 14.5% 58.8% 100.0% Weight 12.7% 14.3% 2.8% 8.4% 6.1%	-15.27 [-16.59, -13.95] Mean Difference IV. Fixed, 95% C -19.30 [-23.90, -14.70] -13.30 [-21.59, -5.01] -13.00 [-16.9, -9.91] -15.50 [-18.83, -12.17] -11.90 [-13.55, -10.25] -13.20 [-14.47, -11.93] Mean Difference IV. Fixed, 95% C -19.90 [-22.27, -17.53] -6.20 [-8.43, -3.97] -1.70 [-6.71, 3.31] -4.60 [-7.51, -1.69] E.69.21 (-0.4) 773	-50	-25 0 Favours [BA] Mean Dif IV. Fixed	25 Favours [Placebo] ference . 95% Cl 25 Favours [Placebo] ference . 95% Cl	 
<u>I</u> 	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: . D) Apolipoproto Study or Subgroup Ballantyne 2018 Ballantyne 2019 Goldberg 2019 Laufs 2019 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 7 Test for overall effect: . C) HDL-C Study or Subgroup Ballantyne 2018 Goldberg 2019 Gulierrez 2014 Laufs 2019 Ray 2019	41.76, df Z = 22.7 ein B -14.6 -11.7 -9.3 -15 -8.6 10.99, df Z = 20.4 Mean -7.3 -6.4 -1.2 -5.2 -5.92	BA SD 20.2 23.1 19.7 16.5 18.1 5 = 4 (F BA 16.7 15.6 9.9 16.5 13.5	2531 2 < 0.00 0.0000 Total 181 82 479 224 1485 2451 2451 2451 181 181 181 499 30 224 1427	$Pi$ $Mean$ $4.7$ $1.6$ $3.7$ $0.5$ $3.3$ $3); i^{2} = ($ $Mean$ $12.6$ $-0.2$ $0.5$ $-0.6$ $-0.09$	<sup>2</sup> = 88% lacebo <u>SD</u> 16.9 20.8 20.3 13.4 19 54% <u>SD</u> 1.4 14.3 9.9 10.3 11.2	Total 88 38 245 107 736 1214 81 253 30 107 726	100.0% Weight 7.6% 2.3% 16.8% 14.5% 58.8% 100.0% Weight 12.7% 14.3% 2.8% 8.4% 61.7%	-15.27 [-16.59, -13.95] Mean Difference IV. Fixed, 95% C -19.30 [-23.90, -14.70] -13.30 [-21.59, -5.01] -13.30 [-16.09, -9.91] -15.50 [-18.83, -12.17] -15.50 [-18.83, -12.17] -13.20 [-14.47, -11.93] Mean Difference IV. Fixed, 95% C -19.90 [-22.27, -17.53] -6.20 [-8.43, -3.97] -1.70 [-6.71, 3.31] -4.60 [-7.51, -1.69] -5.83 [-6.90, -4.76]	-50	-25 0 Favours [BA] Mean Dif IV. Fixed -25 0 Favours [BA] Mean Dif	25 Favours [Placebo] ference , 95% Cl Favours [Placebo] ference , 95% Cl	50
<u>I</u>  	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: D) Apolipoprota Study or Subgroup Ballantyne 2018 Ballantyne 2019 Goldberg 2019 Laufs 2019 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = - Test for overall effect: E) HDL-C Study or Subgroup Ballantyne 2018 Goldberg 2019 Gutierrez 2014 Laufs 2019 Ray 2019 Total (95% CI)	41.76, df Z = 22.7 -14.6 -14.6 -11.7 -9.3 -15 -8.6 10.99, df Z = 20.4 Mean -7.3 -6.4 -1.2 -5.92	<b>BA</b> <b>SD</b> 20.2 23.1 19.7 16.5 18.1 1 (P < <b>BA</b> <b>SD</b> 16.1 15.6 9.9 16.5 13.5	2531 2 < 0.00 0.0000 Total 181 82 479 224 1485 2451 2451 2451 0.0000 Total 181 499 30 224 1427 2361	0001); I 11) Mean 4.7 1.6 3.7 0.5 3.3 3); I <sup>2</sup> = ( 11) Pi Mean 12.6 -0.2 0.5 -0.2 0.5 -0.09	<sup>2</sup> = 88% <u>SD</u> 16.9 20.8 20.3 13.4 19 64% 14.3 9.9 10.3 11.2	1275 6 7 107 736 1214 81 253 30 107 726 1197	100.0% Weight 7.6% 2.3% 16.8% 14.5% 58.8% 100.0% Weight 12.7% 14.3% 2.8% 61.7%	-15.27 [-16.59, -13.95] Mean Difference IV. Fixed, 95% C -19.30 [-23.90, -14.70] -13.30 [-21.59, -5.01] -13.30 [-16.09, -9.91] -15.50 [-18.83, -12.17] -11.90 [-13.55, -10.25] -13.20 [-14.47, -11.93] Mean Difference IV. Fixed, 95% C -19.90 [-22.27, -17.53] -6.20 [-8.43, 3.97] -1.70 [-6.71, 3.31] -4.60 [-7.51, -1.69] -5.83 [-6.90, -4.76] -7.45 [.8.30, -6.61]	-50	-25 0 Favours [BA] Mean Dif IV, Fixed -25 0 Favours [BA] Mean Dif	25 Favours [Placebo] ference , 95% Cl Favours [Placebo] ference , 95% Cl	50
<u>I</u> 	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: : D) Apolipoprote Study or Subgroup Ballantyne 2018 Ballantyne 2019 Coldberg 2019 Laufs 2019 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 7 Chi <sup>2</sup> = 7 Study or Subgroup Ballantyne 2018 Goldberg 2019 Study or Subgroup Ballantyne 2018 Goldberg 2019 Gutierrez 2014 Laufs 2019 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 7	41.76, df Z = 22.7 ein B -14.6 -14.6 -11.7 -9.3 -15 -8.6 10.99, df Z = 20.4 Mean -7.3 -6.4 -1.2 -5.2 -5.2 -5.92	BA = 5 (F) =	2531 2 < 0.00 0.0000 181 181 82 479 224 1485 2451 2 = 0.03 0.0000 Total 181 499 30 0.224 1427 2261 (P < 0)	0001); I; I1) Mean 4.7 1.6 3.7 0.5 3.3 3); I <sup>2</sup> = ( 10) Mean 12.6 -0.2 0.5 -0.6 -0.09	<sup>2</sup> = 88% <u>SD</u> 16.9 20.8 20.3 13.4 19 34% 14.3 9.9 10.3 11.2 12.2 12.2 11.2	1275 6 7 107 736 1214 81 253 300 726 1197 %	100.0% Weight 7.6% 2.3% 16.8% 14.5% 58.8% 100.0% Weight 12.7% 14.3% 2.8% 8.4% 61.7% 100.0%	-15.27 [-16.59, -13.95] Mean Difference IV. Fixed, 95% C -19.30 [-23.90, -14.70] -13.30 [-21.59, -5.01] -13.00 [-16.09, -9.91] -15.50 [-18.83, -12.17] -11.90 [-13.55, -10.25] -13.20 [-14.47, -11.93] Mean Difference IV. Fixed, 95% C -19.90 [-22.27, -17.53] -6.20 [-8.43, -3.97] -1.70 [-6.71, -1.69] -5.83 [-6.90, -4.76] -7.45 [-8.30, -6.61]	-50	-25 0 Favours [BA] Mean Dif IV, Fixed 	25 Favours [Placebo] ference . 95% Cl ference . 95% Cl	50
<u>I</u>  <u>-</u>	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: : D) Apolipoproto Study or Subgroup Ballantyne 2018 Ballantyne 2019 Coldberg 2019 Laufs 2019 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = - C) HDL-C Study or Subgroup Ballantyne 2018 Goldberg 2019 Gutierrez 2014 Laufs 2019 Ray 2019 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = - Total (95% CI) Heterogeneity: Chi <sup>2</sup> = - Total (95% CI)	41.76, df Z = 22.7 ein B -14.6 -14.6 -11.7 -9.3 -15 -8.6 10.99, df Z = 20.4 Mean -7.3 -6.4 -1.2 -5.2 -5.92 125.12, c Z = 27.7	BA SD 20.2 23.1 19.7 16.5 18.1 19.7 16.5 18.1 11 (P < BA SD 16.1 15.6 9.9 16.5 13.5 13.5	2531 2 < 0.00 0.0000 Total 181 82 2479 224 1485 2451 2451 2451 0.0000 Total 181 499 30 224 1427 2361 (P < 0.0 0.0000	0001); if <b>Pi</b> <b>Mean</b> 4.7 1.6 3.7 0.5 3.3 3); l <sup>2</sup> = ( <b>Mean</b> 12.6 -0.2 0.5 -0.6 -0.09 00001); i	<sup>2</sup> = 88% <u>SD</u> 16.9 20.8 20.3 13.4 19 34% <u>SD</u> 1.4 14.3 9.9 10.3 11.2   <sup>2</sup> = 97	1275 6 7 107 736 1214 81 253 30 107 726 1197 %	100.0% Weight 7.6% 2.3% 16.8% 14.5% 58.8% 100.0% Weight 12.7% 14.3% 2.8% 8.4% 61.7% 100.0%	-15.27 [-16.59, -13.95] Mean Difference IV. Fixed. 95% C -19.30 [-23.90, -14.70] -13.30 [-21.59, -5.01] -13.00 [-16.9, -9.91] -15.50 [-18.83, -12.17] -11.90 [-13.55, -10.25] -13.20 [-14.47, -11.93] Mean Difference IV. Fixed. 95% C -19.90 [-22.27, -17.53] -6.20 [-8.43, -3.97] -1.70 [-6.71, 3.31] -6.60 [-7.51, -1.69] -5.83 [-6.90, -4.76] -7.45 [-8.30, -6.61]	-50	-25 0 Favours [BA] Mean Dif IV, Fixed -25 0 Favours [BA] Mean Dif IV, Fixed	25 Favours [Placebo] ference . 95% Cl ference . 95% Cl - - 25	50
<u>I</u> - <u>F</u>	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: . D) Apolipoproto Study or Subgroup Ballantyne 2018 Ballantyne 2019 Coldberg 2019 Laufs 2019 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = - Study or Subgroup Ballantyne 2018 Goldberg 2019 Coldberg 2019 Ballantyne 2018 Goldberg 2019 Gutierrez 2014 Laufs 2019 Ray 2019 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = - Total (95% CI) Heterogeneity: Chi <sup>2</sup> = - Test for overall effect: .	41.76, df Z = 22.7 ein B -14.6 -11.7 -9.3 -15 -8.6 10.99, df Z = 20.4 Mean -7.3 -6.4 -1.2 -5.2 -5.92 125.12, c Z = 17.3	EBA SD 20.2 23.1 19.7 16.5 18.1 16.5 18.1 1 (P < BA SD 16.1 15.6 9.9 16.5 13.5 df = 4 (I	2531 2 < 0.00 0.0000 Total 181 82 2447 224 1485 2451 2 = 0.0 0.0000 Total 181 499 30 224 1427 2361 (P < 0.000	$\begin{array}{c} \text{D001}; \ \text{i} \\ \text{PI} \\ \text{Mean} \\ 4.7 \\ 1.6 \\ 3.7 \\ 0.5 \\ 3.3 \\ 3.3; \ \text{i}^2 = ( \\ 0.5 \\ -0.2 \\ 0.5 \\ -0.09 \\ 0.0001); \\ 1) \end{array}$	<sup>2</sup> = 88% <u>SD</u> 16.9 20.8 20.3 13.4 19 34% <u>SD</u> 1.4 14.3 9.9 10.3 11.2   <sup>2</sup> = 97	1275 6 7 107 736 1214 8 1214 8 11214 8 1125 30 107 726 1197 %	100.0% Weight 7.6% 2.3% 16.8% 14.5% 58.8% 100.0% Weight 12.7% 14.3% 2.8% 8.4% 61.7% 100.0%	-15.27 [-16.59, -13.95] Mean Difference IV. Fixed, 95% C -19.30 [-23.90, -14.70] -13.30 [-21.59, -5.01] -13.30 [-16.90, -9.91] -15.50 [-18.83, -12.17] -11.90 [-13.55, -10.25] -13.20 [-14.47, -11.93] Mean Difference IV. Fixed, 95% C -19.90 [-22.27, -17.53] -6.20 [-8.43, -3.97] -1.70 [-6.71, 3.31] -4.60 [-7.51, -1.69] -5.83 [-6.90, -4.76] -7.45 [-8.30, -6.61]	-50	-25 0 Favours [BA] Mean Dif IV. Fixed -25 0 Favours [BA] Mean Dif IV. Fixed	25 Favours [Placebo] ference 	50       50       50
<u>I</u> 	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: . D) Apolipoproto Study or Subgroup Ballantyne 2018 Ballantyne 2019 Goldberg 2019 Laufs 2019 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 7 Test for overall effect: . C) HDL-C Study or Subgroup Ballantyne 2018 Goldberg 2019 Goldberg 2019 Gulderg 2019 Gulderg 2019 Ray 2019 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 7 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 7 Test for overall effect: .	41.76, df Z = 22.7 ein B -14.6 -11.7 -9.3 -15 -8.6 10.99, df Z = 20.4 Mean -7.3 -6.4 -1.2 -5.2 -5.92 125.12, d Z = 17.3	F = 5 (F         0 (P          20.2         23.1         19.7         18.1         18.1         1 (P          BA         SD         11 (P          BA         SD         16.5         13.5         df = 4 (P	2531 2 < 0.00 0.0000 181 181 82 479 224 1485 2451 2451 2451 181 181 181 181 189 30 224 1427 2361 (P < 0.0000	0001); if Pi Mean 4.7 1.6 3.7 0.5 3.3 3); i <sup>2</sup> = ( 0.5 3.3 3); i <sup>2</sup> = ( 10 Mean 12.6 -0.2 0.5 -0.6 -0.09 00001); 11)	<sup>2</sup> = 88% <u>SD</u> 16.9 20.8 20.3 13.4 19 64% <u>SD</u> 1.4 14.3 9.9 10.3 11.2   <sup>2</sup> = 97	1275 5 1275 5 107 736 1214 1214 1214 81 253 30 107 726 1197 %	100.0% Weight 7.6% 2.3% 16.8% 14.5% 58.8% 100.0% Weight 12.7% 14.3% 2.8% 8.4% 61.7%	-15.27 [-16.59, -13.95] Mean Difference IV. Fixed, 95% C -19.30 [-23.90, -14.70] -13.30 [-21.59, -5.01] -13.30 [-16.09, -9.91] -15.50 [-18.83, -12.17] -11.90 [-13.55, -10.25] -13.20 [-14.47, -11.93] Mean Difference IV. Fixed, 95% C -19.90 [-22.27, -17.53] -6.20 [-8.43, -3.97] -1.70 [-6.71, 3.31] -4.60 [-7.51, -1.69] -5.83 [-6.90, -4.76] -7.45 [-8.30, -6.61]	-50	-25 0 Favours [BA] Mean Diff IV. Fixed -25 0 Favours [BA]	ference .95% Cl ference .95% Cl ference .95% Cl - - - - - - - - - - - - -	
<u>I</u>  <u>I</u>	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: : D) Apolipoprote Study or Subgroup Ballantyne 2018 Ballantyne 2019 Coldberg 2019 Laufs 2019 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 7 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 6 Study or Subgroup Ballantyne 2018 Goldberg 2019 Coldberg 2019 Gutierrez 2014 Laufs 2019 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 7 Test for overall effect: : C) Trigylcerides	41.76, df Z = 22.7 ein B -14.6 -14.6 -11.7 -9.3 -15 -8.6 10.99, df Z = 20.4 Mean -7.3 -6.4 -1.2 -5.2 -5.92 125.12, o Z = 17.3	BA SD 20.2 23.1 19.7 16.5 18.1 5 = 4 (F SD 16.1 15.6 9.9 16.5 13.5 13.5 13.5 14.5 14.5 14.5 15.5 15.5 15.5 15.5 15	2531 2 < 0.00 0.0000 181 181 82 479 224 1485 2451 2451 2451 181 181 181 181 29 = 0.03 0.0000 204 1427 2361 (P < 0.000	0001); F PI Mean. 4.7 1.6 3.7 0.5 3.3 3); I <sup>2</sup> = ( 0.5 3.3 3); I <sup>2</sup> = ( 0.5 0.5 0.5 0.5 0.5 0.5 0.5 0.5	<sup>2</sup> = 88% <u>SD</u> 16.9 20.8 20.3 13.4 19 64% 14.3 9.9 10.3 11.2   <sup>2</sup> = 97	1275 5 1275 5 107 736 1214 1214 1214 1253 300 107 726 1197 %	100.0% Weight 7.6% 2.3% 16.8% 14.5% 58.8% 100.0% Weight 12.7% 14.3% 2.8% 8.4% 61.7% 100.0%	-15.27 [-16.59, -13.95] Mean Difference IV, Fixed, 95% C -19.30 [-23.90, -14.70] -13.30 [-21.59, -5.01] -13.00 [-16.09, -9.91] -15.50 [-18.83, -12.17] -11.90 [-13.55, -10.25] -13.20 [-14.47, -11.93] Mean Difference IV, Fixed, 95% CI -19.90 [-22.27, -17.53] -6.20 [-8.43, -3.97] -1.70 [-6.17, -1.69] -5.83 [-6.90, -4.76] -7.45 [-8.30, -6.61]	-50	-25 0 Favours [BA] Mean Dif IV, Fixed -25 0 Favours [BA] Mean Dif IV, Fixed -25 0 Favours [BA]	25 Favours [Placebo] ference .95% Cl ference .95% Cl - - - - -	50
<u>I</u>  	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: : D) Apolipoproto Study or Subgroup Ballantyne 2018 Ballantyne 2019 Goldberg 2019 Laufs 2019 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = - C) HDL-C Study or Subgroup Ballantyne 2018 Goldberg 2019 Gutierrez 2014 Laufs 2019 Ray 2019 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = - Test for overall effect: : F) Trigylcerides	41.76, df Z = 22.7 ein B -14.6 -11.7 -9.3 -15 -8.6 10.99, df Z = 20.4 Mean -7.3 -6.4 -1.2 -5.9 -5.9 125.12, d Z = 17.3	BA SD 20.2 23.1 19.7 16.5 18.1 1 (P < BA SD 16.1 15.6 9.9 16.5 13.5 df = 4 ( I (P <	2531 2 < 0.00 0.0000 181 181 82 2479 224 1485 2451 2451 2451 0.0000 Total 181 499 30 224 1427 2361 (P < 0.0000	0001); if 11) Pil Mean 4.7 1.6 3.7 0.5 3.3 3); i <sup>2</sup> = ( 0.5 -0.2 0.5 -0.6 -0.29 00001); 11)	<sup>2</sup> = 88% <u>SD</u> 16.9 20.8 20.3 13.4 19 34% <u>SD</u> 1.4 14.3 9.9 10.3 11.2   <sup>2</sup> = 97	1275 5 Total 8 38 245 107 736 1214 81 253 300 107 726 1197 %	100.0% Weight 7.6% 2.3% 16.8% 14.5% 58.8% 100.0% 14.3% 2.8% 8.4% 61.7% 100.0%	-15.27 [-16.59, -13.95] Mean Difference IV. Fixed. 95% C -19.30 [-23.90, -14.70] -13.30 [-21.59, -5.01] -13.00 [-16.09, -9.91] -15.50 [-18.83, -12.17] -11.90 [-13.55, -10.25] -13.20 [-14.47, -11.93] Mean Difference IV. Fixed. 95% C -19.90 [-22.27, -17.53] -6.20 [-8.43, -3.97] -1.70 [-6.71, 3.31] -4.60 [-7.51, -1.69] -5.83 [-6.90, -4.76] -7.45 [-8.30, -6.61]	-50	-25 0 Favours [BA] Mean Dif IV, Fixed 	25 Favours [Placebo] ference , 95% Cl ference , 95% Cl - - 25 Favours [Placebo]	50 50
<u>I</u>   	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: : D) Apolipoproto Study or Subgroup Ballantyne 2018 Ballantyne 2019 Coldberg 2019 Laufs 2019 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = - Childry or Subgroup Ballantyne 2018 Goldberg 2019 Study or Subgroup Ballantyne 2018 Goldberg 2019 Gutierrez 2014 Laufs 2019 Ray 2019 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = - Test for overall effect: : C) Trigylcerides	41.76, df Z = 22.7 ein B -14.6 -11.7 -9.3 -15 -8.6 10.99, df Z = 20.4 Mean -7.3 -6.4 -1.2 -5.92 125.12, o Z = 17.3 	E = 5 (F 0 (P < SD 20.2 23.1 19.7 16.5 18.1 16.5 18.1 1 (P < BA 0.5 15.6 9.9 16.5 13.5 df = 4 1 (P < BA	2531 2 < 0.00 0.0000 Total 181 82 2451 2 = 0.00 0.0000 Totall 181 9 = 0.00 0.0000 224 1427 2361 (P < 0.00000 0.00000 0.00000 0.0000 0.00000 0.00000 0.0000 0.0000 0.00	0001); I; 11) PI Mean 4.7 1.6 3.7 0.5 3.3 3.3; I² = € 11) PI Mean 12.6 -0.2 0.5 -0.6 -0.09 00001); 1)	<sup>2</sup> = 88% lacebo <u>SD</u> 16.9 20.8 20.3 13.4 19 34% 14.3 9.9 10.3 11.2   <sup>2</sup> = 97 Placebb	1275 6 707 736 1214 8 1214 8 11214 8 11214 8 11253 30 107 726 1197 %	100.0% Weight 7.6% 2.3% 16.8% 14.5% 58.8% 100.0% Weight 12.7% 14.3% 8.4% 61.7% 100.0%	-15.27 [-16.59, -13.95] Mean Difference IV. Fixed, 95% C -19.30 [-23.90, -14.70] -13.30 [-21.59, -5.01] -13.00 [-16.99, -9.91] -15.50 [-18.83, -12.17] -11.90 [-13.55, -10.25] -13.20 [-14.47, -11.93] Mean Difference IV. Fixed, 95% C -19.90 [-22.27, -17.53] -6.20 [-8.43, -3.97] -1.70 [-6.71, -3.31] -6.60 [-7.51, -1.69] -5.83 [-6.90, -4.76] -7.45 [-8.30, -6.61] Mean Difference	-50 -50 -50	-25 0 Favours [BA] Mean Dif IV. Fixed -25 0 Favours [BA] Mean Dif IV. Fixed -25 0 Favours [BA]	25 Favours [Placebo] ference , 95% Cl ference , 95% Cl ference , 95% Cl	50         50         50         50
<u>I</u>  <u>F</u>	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: . D) Apolipoproto Study or Subgroup Ballantyne 2018 Ballantyne 2019 Goldberg 2019 Laufs 2019 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = - C) HDL-C Study or Subgroup Ballantyne 2018 Goldberg 2019 Goldberg 2019 Goldberg 2019 Goldberg 2019 Goldberg 2019 Goldberg 2019 Goldberg 2019 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = - Total (95% CI) Heterogeneity: Chi <sup>2</sup> = - Total (95% CI) Heterogeneity: Chi <sup>2</sup> = - Study or Subgroup	41.76, df Z = 22.7 ein B -14.6 -11.7 -9.3 -15 -8.6 10.99, df Z = 20.4 Mean -7.3 -6.4 -1.2 -5.2 -5.92 125.12, c Z = 17.3 Mean	= 5 (F         0 (P <	2531 2 < 0.00 0.0000 181 82 479 224 1485 2451 2451 2451 181 499 30 224 1427 2361 (P < 0.00000 0.0000 0.0000 0.0000 0.00000 0.0000 0.00000 0.0	D001); I; I PI Mean 4.7 1.6 3.7 0.5 3.3 3); I <sup>2</sup> = ( 10 12.6 -0.2 0.5 -0.6 -0.09 D0001); 11)	<sup>2</sup> = 88% <u>SD</u> 16.9 20.8 20.3 13.4 19 54% <u>SD</u> 1.4 14.3 9 10.3 11.2   <sup>2</sup> = 97 Placebo	1275 5 1275 5 107 736 1214 1214 81 253 0 107 726 1197 % 0 0 0 0 10 10 10 10 10 10 10	100.0% Weight 7.6% 2.3% 16.8% 14.5% 58.8% 100.0% Weight 12.7% 14.3% 2.8% 8.4% 61.7% 100.0%	Mean Difference IV. Fixed, 95% C -19.30 [-23.90, -14.70] -13.30 [-21.59, -5.01] -13.30 [-21.59, -5.01] -13.30 [-16.09, -9.91] -15.50 [-18.83, -12.17] -11.90 [-13.55, -10.25] -13.20 [-14.47, -11.93] Mean Difference IV. Fixed, 95% Cl -71.90 [-22.27, -17.53] -6.20 [-8.43, -3.97] -1.70 [-6.71, 3.31] -4.60 [-7.51, -1.69] -5.83 [-6.90, -4.76] -7.45 [-8.30, -6.61] Mean Difference tt. IV. Fixed, 95% Cl	-50	-25 0 Favours [BA] Mean Diff IV. Fixed -25 0 Favours [BA] Mean Diff IV. Fixed -25 0 Favours [BA]	25 Favours [Placebo] ference , 95% Cl ference , 95% Cl - 25 Favours [Placebo] 25 Favours [Placebo]	50       50       50
<u>П</u>   	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: : D) Apolipoprote Study or Subgroup Ballantyne 2018 Ballantyne 2019 Coldberg 2019 Laufs 2019 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 7 Test for overall effect: : D) HDL-C Study or Subgroup Ballantyne 2018 Goldberg 2019 Cotal (95% CI) Heterogeneity: Chi <sup>2</sup> = 7 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 7 Test for overall effect: : C) Trigylcerides	41.76, df Z = 22.7 ein B -14.6 -14.6 -11.7 -9.3 -15 -8.6 10.99, df Z = 20.4 Mean -7.3 -6.4 -1.2 -5.2 -5.92 125.12, o Z = 17.3 Mean -1.3 -5.2 -5.92	<b>BA SD</b> 20.2         23.1         19.7         16.5         13.5 <b>BA SD</b> 16.5         13.5         df = 4, (P <	2531 2 < 0.00 0.0000 181 181 82 479 224 1485 2451 2451 181 181 181 181 181 181 181 (P < 0.0000 224 1427 2361 (P < 0.00000 0.0000 0.00000 0.00000 0.00000 0.00000 0.0000 0	0001); i i Pi Mean 4.7 1.6 3.7 0.5 3.3 3); i <sup>2</sup> = 6 (1) Pi Mean 12.6 -0.2 0.5 -0.6 -0.09 00001); 1) 1 L Mean 0 6.7 -0.5 -0.6 -0.2 0.5 -0.6 -0.09 00001); 1)	<sup>2</sup> = 88% <u>SD</u> 16.9 20.8 20.3 13.4 19 64% 14.3 9.9 10.3 11.2 1 <sup>2</sup> = 97 Placebo n SI 1 36.6	1275 5 Total 88 38 245 107 736 1214 81 253 30 017 726 1197 % 0 Total 07 726 107 726 107 726 107 736 107 727 107 726 107 727 107 726 107 727 107 726 107 727 107 726 107 726 107 727 107 726 107 727 107 726 107 726 107 727 107 727 107 107 107 107 107 107 107 10	100.0% Weight 7.6% 2.3% 16.8% 14.5% 58.8% 100.0% Weight 12.7% 14.3% 2.8% 61.7% 100.0% 100.0%	Mean Difference IV. Fixed, 95% C -19.30 [-23.90, -14.70] -13.30 [-21.59, -5.01] -13.30 [-21.59, -5.01] -13.30 [-16.09, -9.91] -15.50 [-18.83, -12.17] -11.90 [-13.55, -10.25] -13.20 [-14.47, -11.93] Mean Difference IV. Fixed, 95% CI -19.90 [-22.27, -17.53] -6.20 [-8.43, -3.97] -1.70 [-6.71, -3.16] -5.83 [-6.90, -4.76] -7.45 [-8.30, -6.61] Mean Difference IV. Fixed, 95% CI 6 4.90 [-1.48, 11.28]	-50	-25 0 Favours [BA] Mean Diff IV. Fixed -25 0 Favours [BA] Mean Diff IV. Fixed -25 0 Favours [BA]	25 Favours [Placebo] ference . 95% Cl ference . 95% Cl - - - - - - -	50       50       50
<u>п</u>  	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: : D) Apolipoproto Study or Subgroup Ballantyne 2018 Ballantyne 2019 Goldberg 2019 Laufs 2019 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 7 Test for overall effect: : C) HDL-C Study or Subgroup Ballantyne 2018 Goldberg 2019 Gutierrez 2014 Laufs 2019 Ray 2019 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 7 Test for overall effect: : C) Trigylcerides Study or Subgroup Goldberg 2019 Goldberg 2019 Conversional effect: : C) Trigylcerides Study or Subgroup Goldberg 2019 Laufs 2019	41.76, df Z = 22.7 ein B -14.6 -11.7 -9.3 -15 -8.6 10.99, df Z = 20.4 Mean -7.3 -6.4 -1.2 -5.92 125.12, d Z = 17.3 Mean 11 7.9	F = 5 (F         0 (P          BA         SD         20.2         23.1         16.5         18.1         SD         16.5         13.5         df = 4 (F         BA         SD         16.5         13.5         df = 4 (P          BA         SD         10.1         10.5         11.0         P         BA         SD         51.4         40.4	2531 2 < 0.00 0.0000 181 181 82 247 224 1485 2451 2451 2451 0.00000 0.0000 0.00000 0.00000 0.000000 0.0000 0.00000	0001); i f i1) Pi Mean 4.7 1.6 3.7 0.5 3.3 3); i <sup>2</sup> = 6 11) Pi Mean 12.6 -0.2 0.5 -0.6 -0.2 0.5 -0.6 -0.2 0.5 -0.6 -0.2 0.5 -0.6 -0.2 0.5 -0.6 -0.2 0.5 -0.6 -0.2 0.5 -0.6 -0.09 00001); i 1 1 1 1 1 1 1 1 1 1 1 1 1	<sup>2</sup> = 88% <u>SD</u> 16.9 20.8 20.3 13.4 19 34% 14.3 9.9 10.3 11.2   <sup>2</sup> = 97 Placebo n SI 1 36.4 4 36.2	Total           88         38           245         107           736         1214           1214         81           253         300           107         726           1197         %           0         Total           3         253           3         00           107         726           1197         %	100.0% Weight 7.6% 2.3% 16.8% 14.5% 58.8% 100.0% Weight 12.7% 14.3% 2.8% 8.4% 61.7% 100.0% 100.0%	Mean Difference           IV. Fixed, 95% C           -19.30 [-23.90, -14.70]           -13.30 [-21.59, -5.01]           -13.00 [-16.9, -9.91]           -15.50 [-18.83, -12.17]           -11.90 [-13.55, -10.25]           -13.20 [-14.47, -11.93]           Mean Difference           IV. Fixed, 95% CI           -19.90 [-22.27, -17.53]           -6.20 [-8.43, -3.97]           -1.70 [-6.71, 3.31]           -4.60 [-7.51, -1.69]           -5.83 [-6.90, -4.76]           -7.45 [-8.30, -6.61]           Mean Difference           IV. Fixed, 95% CI           6.20 [-1.48, 11.28]           0.50 [-8.16, 9.16]	-50	-25 0 Favours [BA] Mean Dif IV, Fixed 	25 Favours [Placebo] ference , 95% Cl ference , 95% Cl - 25 Favours [Placebo] cerence 95% Cl	50 50
<u>I</u>   	Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: : D) Apolipoproto Study or Subgroup Ballantyne 2018 Ballantyne 2019 Ray 2019 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = - Children 2018 Goldberg 2019 Eallantyne 2018 Goldberg 2019 Ballantyne 2018 Goldberg 2019 Gutierrez 2014 Laufs 2019 Ray 2019 Total (95% CI) Heterogeneity: Chi <sup>2</sup> = - Test for overall effect: : C) Trigylcerides Study or Subgroup Goldberg 2019 Laufs 2019 Study or Subgroup Goldberg 2019 Laufs 2019 Coldberg 2019 Laufs 2019 Coldberg 201	41.76, df Z = 22.7 ein B -14.6 -11.7 -9.3 -15 -8.6 10.99, df Z = 20.4 Mean -7.3 -6.4 -1.2 -5.9 125.12, d Z = 17.3 Mean 11 7.9	E = 5 (F 0 (P < 20.2 23.1 19.7 16.5 18.1 16.5 18.1 1 (P < BA 51.4 51.4 40.4	2531 2 < 0.00 0.0000 181 181 82 479 224 1485 2451 2 = 0.0 0.0000 Total 181 181 181 181 181 181 9 = 0.0 0.00000 0.0000 0.00000 0.00000 0.0000 0.00000 0.000	0001); i i 11) PI Mean 4.7 1.6 3.7 0.5 3.3 3.3; i² = € 11) PI Mean 12.6 0.2 0.5 -0.6 -0.2 0.5 -0.6 0.09 00001); i² 11) I I I I I I I I I I I I I	<sup>2</sup> = 88% lacebo <u>SD</u> 16.9 20.8 20.3 13.4 19 54% lacebo <u>SD</u> 1.4 14.3 9.9 10.3 11.2 l <sup>2</sup> = 97 Placeb <u>SI</u> 1 36.4 3 6.2	1275 5 Total 88 38 245 736 1214 81 253 30 107 726 1197 % 0 Total 253 30 107 726 1197 %	100.0% Weight 7.6% 2.3% 16.8% 14.5% 58.8% 100.0% Weight 12.7% 14.3% 8.4% 61.7% 100.0%	Mean Difference           IV. Fixed. 95% C           -19.30 [-23.90, -14.70]           -13.30 [-21.59, -5.01]           -13.30 [-16.9, -9.91]           -15.50 [-8.83, -12.17]           -11.90 [-13.55, -10.25]           -13.20 [-14.47, -11.93]           Mean Difference           IV. Fixed. 95% CI           -19.90 [-22.27, -17.53]           -6.20 [-8.43, -3.97]           -1.70 [-6.71, 3.31]           -4.60 [-7.51, -1.69]           -5.83 [-6.90, -4.76]           -7.45 [-8.30, -6.61]           Mean Difference           tl. IV. Fixed, 95% CI           6.050 [-8.16, 9.16]	-50 -50 -50	-25 0 Favours [BA] Mean Dif IV. Fixed -25 0 Favours [BA] Mean Dif IV. Fixed -25 0 Favours [BA]	ference . 95% Cl ference . 95% Cl ference . 95% Cl ference . 95% Cl ference . 95% Cl	
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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; Tau<sup>2</sup> and I<sup>2</sup> 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 cholesteral. For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml



# 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
	· · ·		
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
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
8 Objectives 9	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
2 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
Fligibility 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
7 Information sources 8	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
9 Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	3/4
2 Study selection 3	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
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
7 Data items 8	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
2 Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4
3 Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I <sup>2</sup> ) for each meta-analysis. For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	4/5

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Page 31 of 30



## PRISMA 2009 Checklist

5 6 7 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8	#	Checklist item	Reported on page #
<ul> <li>Risk of bias across stud</li> </ul>	dies 15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Supl.
10 Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
<sup>14</sup> 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
17 17 18	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
19 Risk of bias within stud	ies 19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	10
20 21 Results of individual stu 22	udies 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
23 Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Fig. 1/2
24 25 Risk of bias across stud	dies 22	Present results of any assessment of risk of bias across studies (see Item 15).	10
<sup>26</sup> Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Fig. 3
28 DISCUSSION	·		
29 30 31	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
32 Limitations 33	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
<sup>34</sup> Conclusions 35	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13
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38 Funding 39	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
40	•		
41 <i>From:</i> Moher D, Liberati A, 42 doi:10.1371/journal.pmed100	Tetzlaff J, Altm 00097	an DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med For more information, visit: www.prisma-statement.org.	l 6(6): e1000097.

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Page 1 of 2