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	+	+	+	+	+	+
(CLEAR Wisdom)						
Gutierrez et al. 2014	?	?	+	?	+	+
Laufs et al. 2019	?	+	+	+	+	+
(CLEAR Serenity)						
Ray et al. 2019	_	_	-	+	+	+
(CLEAR Harmony)						

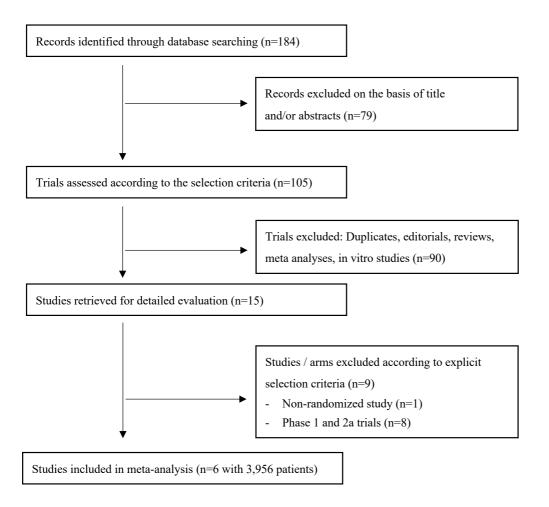
Supplementary Table 1: Risk of bias assessment of all included trials, according to the Cochrane collaboration guidelines.

Supplementary Table 2 – GRADE assessment of primary outcomes

Outcome (No. of studies)	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Sun	nmary of findings	
Outcome (No. of studies)	Design	RISK OF DIAS	inconsistency	munectness	mprecision	r ublication bias	No. of subjects BA/placebo	Pooled OR (95% CI)	Certainty rating
MACE (4)	RCT	Not serious	Seriousª	Not serious	Serious ^e	Undetected	2273/1140	0.84 (0.61-1.15)	⊕⊕⊖⊖ Low
All-cause mortality (5)	RCT	Not serious	Not serious	Serious ^b	Serious ^d	Undetected	2642/1253	2.37 (0.80-6.99)	⊕⊕⊖⊖ Low
Cardiovascular mortality (3)	RCT	Not serious	Not serious	Not serious	Serious ^e	Undetected	2243/1110	1.66 (0.45-6.04)	⊕⊕⊕⊖ Moderate
Nonfatal myocardial infarction (4)	RCT	Not serious	Not serious	Not serious	Serious ^f	Undetected	2273/1140	0.57 (0.32-0.99)	⊕⊕⊕⊖ Moderate

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

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



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

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

A) Coronary revascularization

	BA		Place	bo		Odds Ratio		Odds	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fixe	ed, 95% Cl	
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 ² =	2.73, df =	2 (P = 0	0.25); I ² =	27%						100
Test for overall effect	: Z = 1.00 (P = 0.3	2)				0.01	0.1 Favours [BA]	1 10 Favours [Plac	100 ebo]

B) Non-coronary revascularization

	BA		Place	bo		Odds Ratio		c	Odds Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C		M-H	Fixed, 95	% CI	
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								
Heterogeneity: Chi ² =	0.20, df =	1 (P = 0	0.66); I ² =	0%						10	
Test for overall effect:	Z = 2.08 (P = 0.0	4)				0.01	0.1 Favours	1 [BA] Favo	10 urs [Placeb	100 o]

C) Nonfatal stroke

	BA		Place	bo		Odds Ratio		Odds	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C		M-H, Fix	ed, 95% Cl		
Goldberg 2019	4	522	2	257	44.4%	0.98 [0.18, 5.41]			•		
Laufs 2019	2	234	0	111	11.2%	2.40 [0.11, 50.37]					
Ray 2019	5	1487	2	742	44.4%	1.25 [0.24, 6.45]					
Total (95% CI)		2243		1110	100.0%	1.26 [0.42, 3.76]					
Total events	11		4								
Heterogeneity: Chi ² =	0.25, df =	2 (P = 0).88); I² =	0%					1	+	100
Test for overall effect:	Z = 0.41 (P = 0.6	8)				0.01	0.1 Favours [BA]	Favours [10 Placebo	100 o]

D) Hospitalization for heart failure

	BA		Placel	bo		Odds Ratio		Odds	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C		M-H, Fixe	ed. 95% C	1	
Goldberg 2019	5	522	2	257	66.7%	1.23 [0.24, 6.40]					
Laufs 2019	0	234	0	111		Not estimable					
Ray 2019	9	1487	1	742	33.3%	4.51 [0.57, 35.68]		_			-
Total (95% CI)		2243		1110	100.0%	2.33 [0.67, 8.11]		-		•	
Total events	14		3								
Heterogeneity: Chi ² = 0	0.96, df =	1 (P = 0	0.33); I ² =	0%						10	
Test for overall effect: 2	Z = 1.32 (P = 0.1	9)				0.01	0.1 Favours [BA]	Favours	10 [Placeb	100 o]

E) Hospitalization for unstable angina

	ВА		Place	bo		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fixed, 95% Cl
Goldberg 2019	10	522	4	257	25.7%	1.24 [0.38, 3.98]		
Laufs 2019	5	234	0	111	3.2%	5.34 [0.29, 97.50]		
Ray 2019	14	1487	11	742	71.1%	0.63 [0.29, 1.40]		
Total (95% CI)		2243		1110	100.0%	0.94 [0.51, 1.74]		•
Total events	29		15					
Heterogeneity: Chi ² = 2	2.55, df =	2 (P = 0	0.28); I ² =	21%				
Test for overall effect:	Z = 0.20 (P = 0.8	4)				0.01	0.1 1 10 100 Favours [BA] Favours [Placebo]

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

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

A) Elevation in uric acid

	BA		Placel	00		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C		M-H, Fixed, 95% Cl
Ballantyne 2018	14	181	2	88	27.9%	3.60 [0.80, 16.22]		+_ -
Goldberg 2019	22	522	5	257	72.1%	2.22 [0.83, 5.93]		⊢∎ −
Total (95% CI)		703		345	100.0%	2.60 [1.15, 5.91]		◆
Total events	36		7					
Heterogeneity: Chi ² =	0.28, df =	1 (P = 0	0.60); I ² =	0%			0.01	0.1 1 10 10
Test for overall effect:	Z = 2.29 (P = 0.0	2)				0.01	0.1 1 10 10 Favours [BA] Favours [Placebo]

B) Increase in serum creatinine

	BA		Place	bo		Odds Ratio		Odd	s Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C		M-H, Fix	ed, 95%	CI	
Goldberg 2019	4	522	1	257	25.1%	1.98 [0.22, 17.78]			<u> </u>		
Ray 2019	12	1478	3	742	74.9%	2.02 [0.57, 7.17]		_	╞╴┻╴╴	_	
Total (95% CI)		2000		999	100.0%	2.01 [0.67, 6.02]		-			
Total events	16		4								
Heterogeneity: Chi ² =	0.00, df =	1 (P = 0	0.99); I ² =	0%			0.01		+	1	
Test for overall effect:	Z = 1.24 (P = 0.2	1)				0.01	0.1 Favours [BA]	Favours	10 Placel	100 [00

C) Upper respiratory tract infection

	BA		Place	bo		Odds Ratio			Odds Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C		M-H	, Fixed, 95	% CI	
Goldberg 2019	19	522	9	257	9.2%	1.04 [0.46, 2.33]			-		
Gutierrez 2014	2	30	2	30	1.5%	1.00 [0.13, 7.60]					
Laufs 2019	6	234	6	111	6.3%	0.46 [0.15, 1.46]			-		
Ray 2019	146	1487	87	742	83.0%	0.82 [0.62, 1.09]			-		
Total (95% CI)		2273		1140	100.0%	0.82 [0.63, 1.06]			•		
Total events	173		104								
Heterogeneity: Chi ² =	1.33, df =	3 (P = 0).72); l ² =	0%				-		-	400
Test for overall effect:							0.01	0.1 Favours	1 [BA] Favo	10 urs [Placet	100 [00

D) Urinary tract infection

	BA		Place	bo		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Ballantyne 2018	5	181	5	88	7.5%	0.47 [0.13, 1.67]	
Ballantyne 2019	11	218	2	55	3.5%	1.41 [0.30, 6.55]	
Goldberg 2019	26	522	5	257	7.3%	2.64 [1.00, 6.96]	
Laufs 2019	8	234	9	111	13.5%	0.40 [0.15, 1.07]	
Ray 2019	71	1487	47	742	68.3%	0.74 [0.51, 1.08]	
Total (95% CI)		2642		1253	100.0%	0.84 [0.62, 1.14]	•
Total events	121		68				
Heterogeneity: Chi ² =	9.18, df =	4 (P = (0.06); I ² =	56%		H	
Test for overall effect:	Z = 1.14 (P = 0.2	5)			0.0	01 0.1 1 10 100 Favours [BA] Favours [Placebo]

E) Neurocognitive disorder

	BA		Place	bo		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Ballantyne 2018	8	181	5	88	25.5%	0.77 [0.24, 2.42]	
Ballantyne 2019	6	218	1	55	6.2%	1.53 [0.18, 12.96]	
Goldberg 2019	3	522	1	257	5.3%	1.48 [0.15, 14.30]	
Gutierrez 2014	6	30	5	30	15.9%	1.25 [0.34, 4.64]	
Laufs 2019	6	234	2	111	10.5%	1.43 [0.28, 7.22]	
Ray 2019	11	1487	7	742	36.7%	0.78 [0.30, 2.03]	
Total (95% CI)		2672		1283	100.0%	1.00 [0.58, 1.74]	+
Total events	40		21				
Heterogeneity: Chi ² =	1.03, df =	5 (P = 0	0.96); I ² =	0%		H	
Test for overall effect:	Z = 0.01 (P = 0.9	9)				0.01 0.1 1 10 100 Favours [BA] Favours [Placebo]
<u>F) Nasopharyng</u>	<u>titis</u>						
	BA		Place	bo		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Ballantyne 2018	4	181	1	88	1.1%	1.97 [0.22, 17.86]	
Ballantyne 2019	10	218	1	55	1.2%	2.60 [0.33, 20.72]	

Ballantyne 2019	10	218	1	55	1.2%	2.60 [0.33, 20.72]				
Goldberg 2019	27	522	13	257	13.3%	1.02 [0.52, 2.02]			_	
Ray 2019	146	1487	87	742	84.4%	0.82 [0.62, 1.09]				
Total (95% CI)		2408		1142	100.0%	0.88 [0.68, 1.14]		•		
Total events	187		102							
Heterogeneity: Chi ² =	= 1.99, df = 3	3 (P = 0.	57); I² =	0%			0.01	0.1 1	10	100
Test for overall effect	:: Z = 0.98 (F	P = 0.33)					0.01	Favours [BA]		

<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; Tau² and I² are measures of heterogeneity. BA=bempedoic acid; M-H=Mantel-Haenszel.

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

<u>A) LDL-C</u>	<u>A)</u>	LI	DL-	·C
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	BA Placebo				•		Mean Difference	Mean Difference				
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	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	-4	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 [-23.06, -14.74]				
Ray 2019	-16.5	20.1	1488	1.6	23.4	742	67.5%	-18.10 [-20.07, -16.13]	•			
Total (95% CI)			2026			1015	100.0%	-19.93 [-21.55, -18.31]	•			
Heterogeneity: Chi ² =	40.71, d	f = 4 (f	> < 0.00	0001); F	2 = 909	%						
Test for overall effect:									-50 -25 0 25 50 Favours [BA] Favours [Placebo]			

B) Total cholesterol

	BA Placebo					,		Mean Difference	Mean Difference				
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% C		IV, Fixe	d, 95% CI		
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)			2532			1275	100.0%	-12.43 [-13.42, -11.43]		•			
Heterogeneity: Chi ² = 34.86, df = 5 (P < 0.00001); l ² = 86%										-25	<u> </u>	25	50
Test for overall effect:	Z = 24.4	7 (P <	0.000	01)					-50	-25 Favours [BA]	U Favours [50

C) Non-HDL-C

		вА		PI	acebo	,		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% C	I 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]	•
Heterogeneity: Chi ² =	41.76, d	f = 5 (F	o < 0.00	0001); l ^a	2 = 889	%			
Test for overall effect:	Z = 22.7	'0 (P <	0.0000	01)					-50 -25 0 25 50 Favours [BA] Favours [Placebo]

D) Apolipoprotein B

		вА	Placebo					Mean Difference	Mean Difference				
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% C		IV, Fixe	<u>ed, 95%</u>	CI	
Ballantyne 2018	-14.6	20.2	181	4.7	16.9	88	7.6%	-19.30 [-23.90, -14.70]					
Ballantyne 2019	-11.7	23.1	82	1.6	20.8	38	2.3%	-13.30 [-21.59, -5.01]					
Goldberg 2019	-9.3	19.7	479	3.7	20.3	245	16.8%	-13.00 [-16.09, -9.91]					
Laufs 2019	-15	16.5	224	0.5	13.4	107	14.5%	-15.50 [-18.83, -12.17]					
Ray 2019	-8.6	18.1	1485	3.3	19	736	58.8%	-11.90 [-13.55, -10.25]					
Total (95% CI)			2451			1214	100.0%	-13.20 [-14.47, -11.93]		۲			
Heterogeneity: Chi ² =	-50	-25	+	25	50								
Test for overall effect:	Z = 20.4	1 (P <	0.000	01)					-50] Favo	urs [Placebo]	50

E) HDL-C

		BA		Placebo				Mean Difference	Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% Cl		IV, Fixed	95% CI	
Ballantyne 2018	-7.3	16.1	181	12.6	1.4	81	12.7%	-19.90 [-22.27, -17.53]		-		
Goldberg 2019	-6.4	15.6	499	-0.2	14.3	253	14.3%	-6.20 [-8.43, -3.97]		-		
Gutierrez 2014	-1.2	9.9	30	0.5	9.9	30	2.8%	-1.70 [-6.71, 3.31]		-+	-	
Laufs 2019	-5.2	16.5	224	-0.6	10.3	107	8.4%	-4.60 [-7.51, -1.69]		-		
Ray 2019	-5.92	13.5	1427	-0.09	11.2	726	61.7%	-5.83 [-6.90, -4.76]		•		
Total (95% CI)			2361			1197	100.0%	-7.45 [-8.30, -6.61]		•		
Heterogeneity: Chi ² =	125.12,	df = 4	(P < 0.0	00001);	l² = 97	7%			F			
Test for overall effect:	Z = 17.3	81 (P <	0.0000	01)					-50	-25 0 Favours [BA]	25 Favours [Placel	50 bo]

F) Trigylcerides

		BA		PI	acebo		Mean Difference			Mean Difference				
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IN IN	V. Fixed, 95% Cl			
Goldberg 2019	11	51.4	499	6.1	36.6	253	64.8%	4.90 [-1.48, 11.28]			+=-			
Laufs 2019	7.9	40.4	224	7.4	36.2	107	35.2%	0.50 [-8.16, 9.16]						
Total (95% CI)			723			360	100.0%	3.35 [-1.78, 8.49]			•			
Heterogeneity: Chi ² = Test for overall effect:			-50	-25 Favou	0 rs [BA] Favours	25 [Placebo]	50							

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