

PubMed search

Keywords	Number
	of results
(bempedoic acid OR ETC-1002)	54
(bempedoic acid OR ETC-1002) AND (cholesterol)	49
(bempedoic acid OR ETC-1002) AND (cholesterol OR hypercholesterolemia)	49
(bempedoic acid OR ETC-1002) AND (cholesterol OR hypercholesterolemia OR hypercholesterolemic)	49
(bempedoic acid OR ETC-1002) AND (cholesterol OR hypercholesterolemia OR hypercholesterolemic OR lipoprotein)	50
(bempedoic acid OR ETC-1002) AND (cholesterol OR hypercholesterolemia OR hypercholesterolemic OR lipoprotein OR LDL)	50

Table S1. Assessment of risk of bias in included studies.

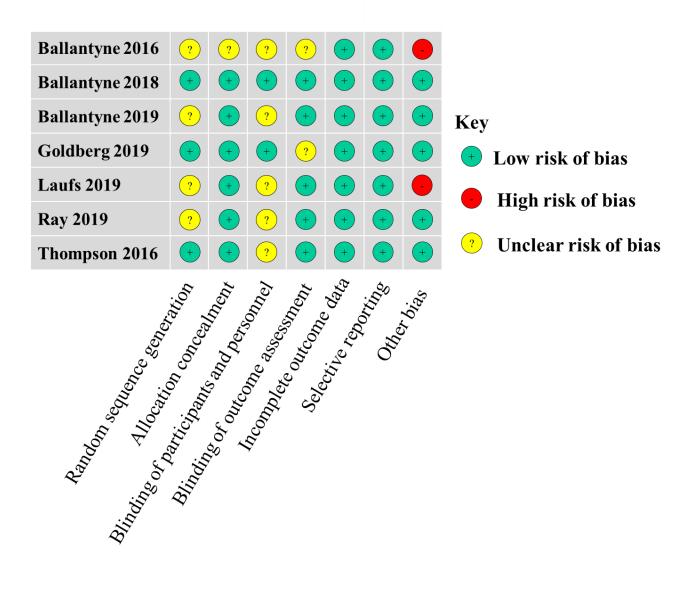


Table S2. Characteristics of included studies.

Study	Background lipid lowering therapy	Baseline LDL-c cut-off
Ray 2019	Maximally tolerated statin therapy±other LLT	\geq 70 mg/dl
Harmony ²⁶		
Goldberg 2019	Maximally tolerated statin therapy±other LLT	≥ 100 mg/dl at screening or
Wisdom ²³		\geq 70 mg/dl at randomization
Ballantyne 2019 ²⁴	Maximally tolerated statin therapy.	≥ 100 mg/dL for CAD/FH
		≥130 mg/dL for multiple
		VRFs
Ballantyne 2016 ²⁹	Maximally tolerated statin therapy	115-220 mg/dl
Thompson 2016 ²⁸	Maximally tolerated statin therapy	130-220 mg/dL
Ballantyne 2018	No statin or low-dose statin	$\geq 100 \text{ mg/dL}$
Tranquility ²⁷		
Laufs 2019	Maximally tolerated statin therapy	≥ 100 mg/dL for CAD/FH
Serenity ²⁵		≥130 mg/dL for primary
		prevention

^{*}LLT: lipid-lowering therapies

Table S3. Meta-regression analyses. Impact of Age, male gender, body Mass Index (BMI), diabetes and baseline LDL-C on the difference in the incidence of adverse events, serious adverse events, drug discontinuation, muscle-related side effects and new-onset diabetes, gout flare and changes in uric acid between patients receiving bempedoic acid and control treatment group.

Outcome				Covariat	te	
Outcome		Age	Male sex	BMI	Diabetes	Baseline LDL
Adverse events	z-value	0.02	-1.43	1.19	1.14	1.65
	p-value	0.983	0.151	0.233	0.251	0.098
Serious adverse events	z-value	0.42	0.17	0.22	-0.42	0.40
	p-value	0.677	0.860	0.824	0.670	0.690
Drug	z-value	1.92	1.43	-1.30	-1.31	-0.99
discontinuation	p-value	0.053	0.153	0.194	0.187	0.322
Muscle-related side effects	z-value	1.84	2.05	-1.00	-0.43	-1.77
	p-value	0.065	0.041	0.315	0.663	0.077
New-onset	z-value	-1.02	-0.50	1.21	-0.19	0.98
diabetes	p-value	0.307	0.618	0.225	0.846	0.328
Gout flare	z-value	0.47	0.64	-0.60	0.20	-0.64
	p-value	0.635	0.518	0.547	0.842	0.522
Uric acid	z-value	3.40	0.70	-0.95	-0.29	-0.31
	p-value	<0.001	0.481	0.343	0.770	0.759

Figure S1. PRISMA Flow Diagram.

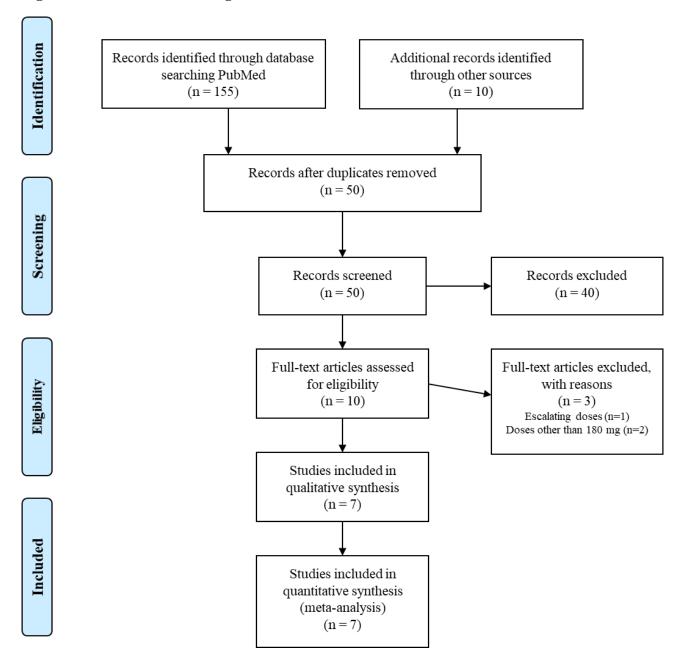
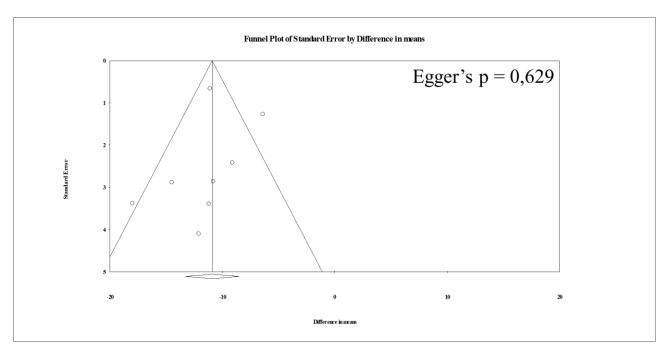


Figure S2. Changes in high sensitivity C reactive protein (hsCRP) after 12 weeks of treatment with bempedoic acid as compared to control treatment.

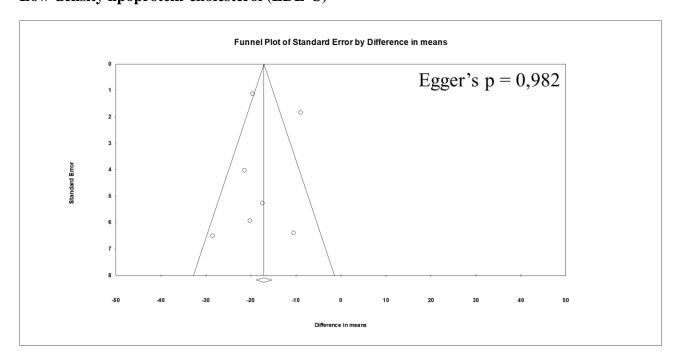
Study name	Sample	size	Stati	stics for (each stu	dy		Difference i	n mean	s and 95% C	
hsCRP	Bempedoic Acid	Placebo	Difference in means	Lower limit	Upper limit	p-Value					
Ballantyne 2016	43	43	-14,8	-25,6	-4,0	0,01			— I		
Ballantyne 2018	. 181	87	-23,6	-33,2	-14,0	0,00		- ■- -			
Ballantyne 2019 a	110	55	-13,1	-18,3	-7,9	0,00		-∎	⊪ │		
Ballantyne 2019 b ²	102	102	-19,0	-52,8	14,8	0,27	-			-	
Goldberg 2019 ²³ Laufs 2019 ²⁵	498	253	-10,8	-17,2	-4,4	0,00		⊣	■-		
Laufs 2019 ²⁵	234	111	-17,9	-24,5	-11,3	0,00		-■-	-		
Ray 2019 ²⁶	1488	742	-13,4	-15,1	-11,7	0,00					
Thompson 2016	99	98	-6,6	-9,8	-3,4	0,00					
<u>Overall</u>	2755	1491	-13,2	-16,7	-9,8	0,00		-)		
				I	2: 69,0%	p = 0.002	-55,00	-27,50	0,00	27,50	55,00
								Favours BA		Favours Control	

Figure S3. Funnel plots of effect size versus standard error for studies evaluating the changes in total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), non- high-density lipoprotein-cholesterol (non-HDL-C), Apolipoprotein B (Apo B) and high sensitivity C reactive protein (hsCRP) in subjects receiving bempedoic acid and in control treatment group.

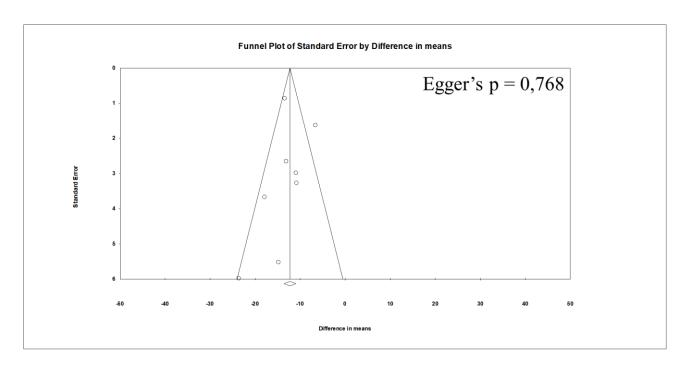
Total cholesterol (TC)



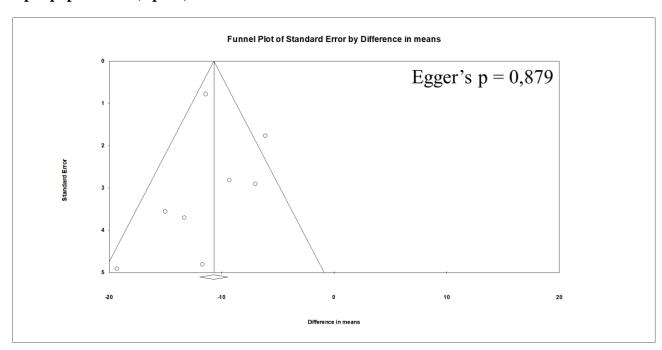
Low-density lipoprotein-cholesterol (LDL-C)



Non-high-density lipoprotein-cholesterol (HDL-C)



Apolipoprotein B (Apo B)



High sensitivity C reactive protein (hsCRP)

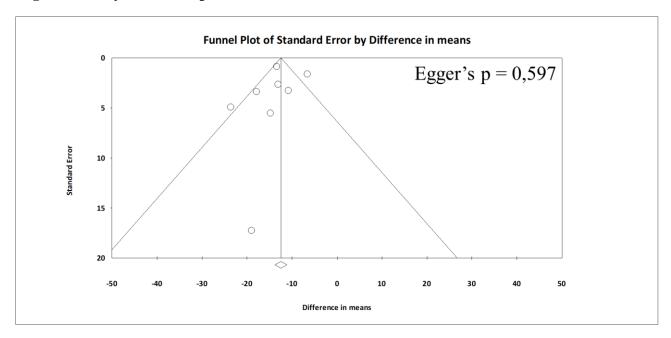


Figure S4. Incidence of adverse events, serious adverse events, drug discontinuation, musclerelated side effects, new-onset diabetes, gout flare and changes in uric acid during treatment with bempedoic acid as compared to control treatment group.

Study name	Expose	d / Total	Statistics for each study			study		<u>c</u>	dds rat	io and	95% (<u>CI</u>	
Adverse events	Cases	Controls	Odds ratio	Lower limit	Upper limit	p-Value							
Ballantyne 2016 ²⁹	28 / 45	28 / 45	1,0	0,4	2,3	1,00			+	+	+		
Ballantyne 2018 ²⁷	88 / 181	39 / 87	1,2	0,7	1,9	0,56			-	┵	_		
Ballantyne 2019 a	24 68 / 110	24 / 55	2,1	1,1	4,0	0,03				-	┿	-	
Ballantyne 2019 ba	24 63 / 107	58 / 109	1,3	0,7	2,2	0,40				┿	- -		
Goldberg 2019 ²³	366 / 522	182 / 257	1,0	0,7	1,3	0,84			-	-			
Laufs 2019 ²⁵	150 / 234	63 / 111	1,4	0,9	2,2	0,19				+-	\dashv		
Ray 2019 26	1167 / 1487	584 / 742	1,0	0,8	1,2	0,90				#			
Thompson 2016 ²⁸	55 / 100	53 / 99	1,1	0,6	1,9	0,84			-	┿	-		
<u>Overall</u>		1031 / 1505	1,1	0,9	1,3	0,25				•			
]	I ² : 0%	p= 0,495	0,1	0,2	0,5	1	2	5	10

Study name	Expose	d / Total	Statistics for each study					Odds rat	tio and	95% (
<u>Serious</u> <u>Adverse events</u>	Cases	Controls	Odds ratio	Lower limit	Upper limit	p-Value						
Ballantyne 2016 ²⁹	1 / 45	2/45	0,5	0,0	5,6	0,56	k 	-	_	_	\rightarrow	
Ballantyne 2018 ²⁷	5 / 181	3 / 87	0,8	0,2	3,4	0,76	+		•	_	-	
Ballantyne 2019 a 24	7 / 110	1 / 55	3,7	0,4	30,6	0,23		+		_	•	\rightarrow
Ballantyne 2019 b 24	8 / 107	10 / 109	0,8	0,3	2,1	0,65		-	-	\dashv		
Goldberg 2019 ²³	106 / 522	48 / 257	1,1	0,8	1,6	0,59			-	-		
Laufs 2019 25	14 / 234	4 / 111	1,7	0,5	5,3	0,36		-		•	$\overline{}$	
Ray 2019 ²⁶	216 / 1487	104 / 742	1,0	0,8	1,3	0,75			#			
Thompson 2016 ²⁸	1 / 100	1 / 99	1,0	0,1	16,0	0,99	(_	+	_	+	\rightarrow
<u>Overall</u>	358 / 2786	173 / 1505	1,1	0,9	1,3	0,53			*			
					I ² : 0%	p = 0.892	0,1 0,2	0,5	1	2	5	10

Study name	Exposed / Total			atistics fo	or each s	tudy	Odd	ds ratio a	ratio and 95% Cl			
<u>Drug</u> discontinuation	Cases	Controls	Odds ratio	Lower limit	Upper limit	p-Value						
Ballantyne 2016 ²⁹	2/45	3 / 45	0,7	0,1	4,1	0,65	 	+•+	\rightarrow	— [
Ballantyne 2018 ²⁷	11 / 181	5 / 87	1,1	0,4	3,2	0,91		┿	\rightarrow	-		
Ballantyne 2019 a ²⁴	9 / 110	2/55	2,4	0,5	11,3	0,28		\vdash	\rightarrow		_	
Ballantyne 2019 b ²⁴	7 / 107	10 / 109	0,7	0,3	1,9	0,47	—	 • 	—			
Goldberg 2019 ²³	57 / 522	22 / 257	1,3	0,8	2,2	0,31		\perp	▄			
Laufs 2019 ²⁵	43 / 234	13 / 111	1,7	0,9	3,3	0,12		\perp		—		
Ray 2019 ²⁶	162 / 1487	53 / 742	1,6	1,2	2,2	0,00		1 1	╼			
Thompson 2016 ²⁸	6 / 100	8 / 99	0,7	0,2	2,2	0,57	—	 - 	\rightarrow			
Overall	297 / 2786	116 / 1505	1,4	1,1	1,8	0,00		-				
					I ² : 0%	p = 0,591	0,1 0,2	0,5 1	2	5	j	

Study name	Expose	St	atistics fo	or each s	tudy	Odds ratio and 95°			d 95% (
Muscle-related side effects	Cases	Controls	Odds ratio	Lower limit	Upper limit	p-Value						
Ballantyne 2016 ²⁹	1 / 45	6 / 45	0,1	0,0	1,3	0,08	- 	-+	+			
Ballantyne 2018 ²⁷	11 / 181	5 / 87	1,1	0,4	3,2	0,91		+	-	+	.	
Ballantyne 2019 a 24	7 / 110	3 / 55	1,2	0,3	4,7	0,82		-		+	—	
Ballantyne 2019 b 24	6 / 107	7 / 109	0,9	0,3	2,7	0,80		\rightarrow		+		
Goldberg 2019 ²³	39 / 522	13 / 257	1,5	0,8	2,9	0,21			+	▄┼╴		
Laufs 2019 25	30 / 234	18 / 111	0,8	0,4	1,4	0,40		+	■	.		
Ray 2019 26	195 / 1487	75 / 742	1,3	1,0	1,8	0,04			H	⊩ │		
<u>Overall</u>	289 / 2686	127 / 1406	1,1	0,9	1,5	0,38				•		
				I^2 :	15,4%	p = 0.313	0,1 0,2	0,5	1	2	5	10

Study name	Expose	d / Total	Statistics for each study					_(Odds rat	io an	d 95% C	1	
New-onset diabetes	Cases	Controls	Odds ratio	Lower limit	Upper limit	p-Value							
Ballantyne 2018	2 / 181	2/87	0,5	0,1	3,4	0,46		+	-	+	+	-	
Goldberg 2019 ²³	36 / 522	19 / 257	0,9	0,5	1,7	0,80			-	=	-		
Ray 2019 ²⁶	49 / 1487	40 / 742	0,6	0,4	0,9	0,02				-			
Overall	87 / 2190	61 / 1086	0,7	0,5	1,0	0,03			•				
					I ² : 0%	p= 0,454	0,1	0,2	0,5	1	2	5	10

Study name	Exposed	d / Total	Statistics for each study					0	dds rat	io an	d 95%	CI	
Gout flare	Cases	Controls		Lower limit	Upper limit	p-Value							
Goldberg 2019	²³ 11 / 522	2/257	2,7	0,6	12,5	0,19			-	+		\vdash	\rightarrow
Laufs 2019 ²⁵	4/234	1 / 111	1,9	0,2	17,3	0,56		-	_	+	-	_	\rightarrow
Ray 2019 ²⁶	18 / 1487	2/742	4,5	1,0	19,6	0,04				-		-	\rightarrow
<u>Overall</u>	33 / 2243	5 / 1110	3,2	1,2	8,2	0,02				-			-
					I ² : 0%	p = 0.792	0,1	0,2	0,5	1	2	5	10

Study name	Sample	size	Statistics for each study					Difference i	Difference in means and 95% Cl				
Uric acid	Bempedoic Acid	Placebo	Difference in means	Lower limit	Upper limit	p-Value							
Ballantyne 2019 a ²	4 110	55	0,9	0,6	1,2	0,00	- [1	1	+=-	-		
Ballantyne 2019 b ²	4 107	109	0,5	0,2	0,7	0,00			-	■-			
Goldberg 2019 ²³	522	257	0,5	0,3	0,7	0,00			-	-			
Ray 2019 ²⁶	1487	742	0,8	0,7	0,9	0,00							
Overall	2226	1163	0,7	0,5	0,9	0,00	l						
				I ² : 7	7,69%	p = 0,004	-1,50	-0,75	0,00	0,75	1,50		

Figure S5. Funnel plots of effect size versus standard error for studies evaluating the incidence of adverse events in subjects receiving bempedoic acid and in control treatment group (upper panel); adjustment of results by means of the Duval and Tweedie's trim and fill method (lower panel)

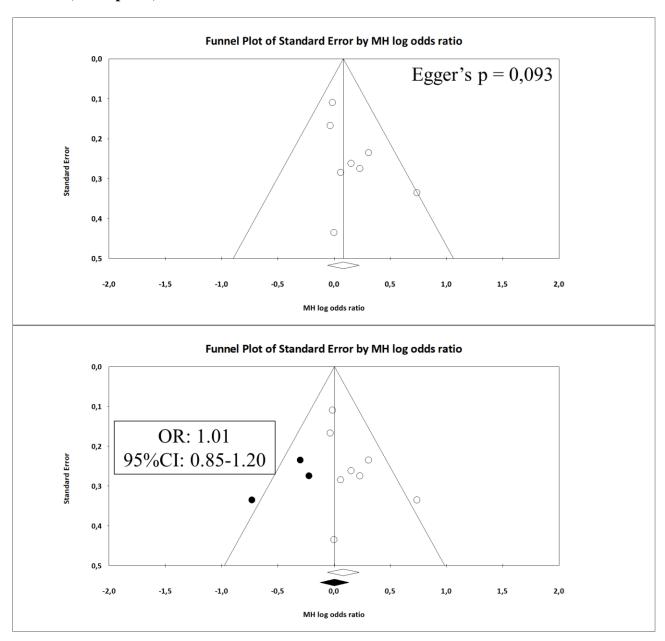


Figure S6. Funnel plots of effect size versus standard error for studies evaluating the incidence of serious adverse events (Panel A), drug discontinuation (Panel B); muscle-related side effects (Panel C); new-onset diabetes (Panel D); gout flare (Panel E); changes in uric acid (Panel F) in subjects receiving bempedoic acid and in control treatment group.

