

## RESEARCH ARTICLE

## Efficacy and safety of bempedoic acid for the treatment of hypercholesterolemia: A systematic review and meta-analysis

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## Abstract

## Background

Bempedoic acid is a first-in-class lipid-lowering drug recommended by guidelines for the treatment of hypercholesterolemia. Our objective was to estimate its average effect on plasma lipids in humans and its safety profile.

## Methods and findings

We carried out a systematic review and meta-analysis of phase II and III randomized controlled trials on bempedoic acid (PROSPERO: CRD42019129687). PubMed (Medline), Scopus, Google Scholar, and Web of Science databases were searched, with no language restriction, from inception to 5 August 2019. We included 10 RCTs ( $n = 3,788$ ) comprising 26 arms (active arm [ $n = 2,460$ ]; control arm [ $n = 1,328$ ]). Effect sizes for changes in lipids and high-sensitivity C-reactive protein (hsCRP) serum concentration were expressed as mean differences (MDs) and 95% confidence intervals (CIs). For safety analyses, odds ratios (ORs) and 95% CIs were calculated using the Mantel-Haenszel method. Bempedoic acid significantly reduced total cholesterol (MD  $-14.94\%$ ; 95% CI  $-17.31\%$ ,  $-12.57\%$ ;  $p < 0.001$ ), non-high-density lipoprotein cholesterol (MD  $-18.17\%$ ; 95% CI  $-21.14\%$ ,  $-15.19\%$ ;  $p < 0.001$ ), low-density lipoprotein cholesterol (MD  $-22.94\%$ ; 95% CI  $-26.63\%$ ,  $-19.25\%$ ;  $p < 0.001$ ), low-density lipoprotein particle number (MD  $-20.67\%$ ; 95% CI  $-23.84\%$ ,  $-17.48\%$ ;  $p < 0.001$ ), apolipoprotein B (MD  $-15.18\%$ ; 95% CI  $-17.41\%$ ,  $-12.95\%$ ;  $p < 0.001$ ), high-density lipoprotein cholesterol (MD  $-5.83\%$ ; 95% CI  $-6.14\%$ ,  $-5.52\%$ ;  $p < 0.001$ ), high-density lipoprotein particle number (MD  $-3.21\%$ ; 95% CI  $-6.40\%$ ,  $-0.02\%$ ;  $p = 0.049$ ), and hsCRP (MD  $-27.03\%$ ; 95% CI  $-31.42\%$ ,  $-22.64\%$ ;  $p < 0.001$ ). Bempedoic acid did not

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**Abbreviations:** ACLY, ATP citrate lyase; AE, adverse event; Apo, apolipoprotein; CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; MD, mean difference; OR, odds ratio; RCT, randomized controlled trial; SD, standard deviation; SUA, serum uric acid; TC, total cholesterol; TG, triglyceride; VLDL, very-low-density lipoprotein.

significantly modify triglyceride level (MD  $-1.51\%$ ; 95% CI  $-3.75\%$ ,  $0.74\%$ ;  $p = 0.189$ ), very-low-density lipoprotein particle number (MD  $3.79\%$ ; 95% CI  $-9.81\%$ ,  $17.39\%$ ;  $p = 0.585$ ), and apolipoprotein A-1 (MD  $-1.83\%$ ; 95% CI  $-5.23\%$ ,  $1.56\%$ ;  $p = 0.290$ ). Treatment with bempedoic acid was positively associated with an increased risk of discontinuation of treatment (OR  $1.37$ ; 95% CI  $1.06$ ,  $1.76$ ;  $p = 0.015$ ), elevated serum uric acid (OR  $3.55$ ; 95% CI  $1.03$ ,  $12.27$ ;  $p = 0.045$ ), elevated liver enzymes (OR  $4.28$ ; 95% CI  $1.34$ ,  $13.71$ ;  $p = 0.014$ ), and elevated creatine kinase (OR  $3.79$ ; 95% CI  $1.06$ ,  $13.51$ ;  $p = 0.04$ ), though it was strongly associated with a decreased risk of new onset or worsening diabetes (OR  $0.59$ ; 95% CI  $0.39$ ,  $0.90$ ;  $p = 0.01$ ). The main limitation of this meta-analysis is related to the relatively small number of individuals involved in the studies, which were often short or middle term in length.

## Conclusions

Our results show that bempedoic acid has favorable effects on lipid profile and hsCRP levels and an acceptable safety profile. Further well-designed studies are needed to explore its longer-term safety.

## Author summary

### Why was this study done?

- Lowering low-density lipoprotein cholesterol (LDL-C) is effective for reducing cardiovascular events over time.
- A number of phase II and phase III randomized controlled trials (RCTs) are already available showing encouraging results of bempedoic acid treatment on LDL-C.
- We aimed to perform a systematic review and meta-analysis on the clinical evidence available to date to better define the efficacy and tolerability profile of treatment with bempedoic acid.

### What did the researchers do and find?

- In this analysis of bempedoic acid that included 10 randomized clinical trials ( $n = 3,788$  patients) comprising 26 arms (active arm [ $n = 2,460$ ]; control arm [ $n = 1,328$ ]), we confirmed that bempedoic acid significantly reduced total cholesterol (by  $15\%$ ), non-high-density lipoprotein cholesterol (by  $18.2\%$ ), LDL-C (by  $22.9\%$ ), low-density lipoprotein particle number (by  $20.7\%$ ), apolipoprotein B (by  $15.2\%$ ), and high-sensitivity C-reactive protein (hsCRP) (by  $27\%$ ), while negatively affecting serum levels of high-density lipoprotein cholesterol ( $-5.8\%$ ) and high-density lipoprotein particle number ( $-3.2\%$ ).
- Our results also confirmed that the therapy is overall safe and well tolerated, with no significant increase of serious adverse effects.

### What do these findings mean?

- The current meta-analysis demonstrates the multiple positive effects of bempedoic acid on lipid profile and hsCRP serum levels, as well as acceptable safety profile.
- This could be relevant in a setting where statin intolerance is very frequent and the LDL-C target suggested by international guidelines for dyslipidemia management is hard to achieve with standard therapies.
- An ongoing long-term cardiovascular outcomes trial will answer questions on the effect of bempedoic acid on cardiovascular events and mortality as well as on the drug's safety issues.

## Introduction

Cardiovascular diseases (CVDs) are still the leading cause of disability and death in developed countries [1]. As reported by Mendelian randomization studies, a lifetime reduction of low-density lipoprotein cholesterol (LDL-C) of 1 mmol/l might reduce the potential risk of atherosclerotic CVDs by over 50% [2]. Controlled clinical studies successfully showed a consistent relationship between the reduction of LDL-C and cardiovascular (CV) risk decrease [3], such that lipid-lowering therapy became a cornerstone in CV risk reduction.

Bempedoic acid (8-hydroxy-2,2,14,14-tetramethylpentadecanedioic acid; ETC-1002; Esperion Therapeutics, Ann Arbor, MI) is a first-in-class small-molecule inhibitor of ATP citrate lyase (ACLY), a key enzyme that supplies substrate for cholesterol and fatty acid synthesis [4]. ACLY is essential for growth and development, such that homozygous knockout ( $Acly^{-/-}$ ) in mice is embryonic lethal, indicating non-redundancy during development [5]. By inhibiting ACLY, bempedoic acid induces LDL receptor upregulation and stimulates the uptake of LDL particles by the liver, which contributes to reduction of LDL-C concentration in the blood [6]. Bempedoic acid is administered orally once a day, is quickly absorbed in the small intestine, and has a half-life ranging from 15 to 24 hours [7]. It is a prodrug that is activated by very-long-chain acyl-CoA synthetase 1, an enzyme that is synthesized only in the liver [8]. Even though bempedoic acid acts on the same pathway as statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors), the lack of the activating enzyme in skeletal muscle may prevent the muscular adverse effects associated with statins [8]. For this reason, bempedoic acid may represent a novel treatment to reach LDL-C goals for statin-intolerant patients [9].

A number of phase II and phase III randomized controlled trials (RCTs) are already available, showing encouraging effects of bempedoic acid treatment on LDL-C. Consequently, we aimed to perform a systematic review and meta-analysis of the clinical evidence available to date to better define its efficacy and tolerability profile.

## Methods

The study is reported in accordance with the 2009 guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (S1 PRISMA Checklist) [10], and was registered in the PROSPERO database (registration code: CRD42019129687). Due to the study design (meta-analysis), neither institutional review board approval nor patient informed consent was required.

## Search strategy

PubMed (Medline), Web of Science, Google Scholar, and Scopus databases were searched, with no language restriction, using the following search terms: (“Bempedoic acid” OR “ETC-1002”) AND (“Trial” OR “Study”) [Search terms: ((“Bempedoic acid”) AND Study) OR ((Bempedoic acid) AND Trial) OR (ETC-1002 AND Study) OR (ETC-1002 AND Trial)]. The wild-card term “\*” was used to increase the sensitivity of the search strategy, which was limited to studies in humans. The reference lists of identified papers were manually checked for additional relevant articles. Additional searches for potential trials included the references of review articles on bempedoic acid, and the abstracts from selected scientific conferences on the subject of the meta-analysis. Literature was searched from inception to 5 August 2019.

All abstracts were screened by 2 reviewers (FF and AFGC) in an initial process to remove ineligible articles. The remaining articles were obtained in full-text and assessed again by the same 2 researchers, who evaluated each article independently and carried out data extraction and quality assessment. Disagreements were resolved by discussion with a third party (MB).

## Study selection criteria

Original studies were included if they met the following criteria: (i) were a phase II or III RCT with either multicenter or single-center design, (ii) investigated the effect of bempedoic acid on plasma lipids or high-sensitivity C-reactive protein (hsCRP), (iii) tested the safety of bempedoic acid in short- and middle-term administration, and (iv) reported all the adverse events (AEs) that occurred during the treatment.

Studies that lacked a control-treated group for comparison with bempedoic acid were excluded.

## Data extraction

Data abstracted from the eligible studies were the following: (i) study registration code; (ii) first author’s name; (iii) publication year; (iv) study phase; (v) main inclusion criteria and underlying disease; (vi) treatment duration; (vii) study arms; (viii) number of participants in the active and control group; (ix) age and sex of study participants, (x) baseline and outcome data of total cholesterol (TC), LDL-C, high-density lipoprotein cholesterol (HDL-C), very-low-density lipoprotein (VLDL), non-HDL-C, triglycerides (TGs), apolipoprotein (Apo) B, Apo A-1, and hsCRP; and (xi) discontinuation of treatment and AEs that occurred during the trials. Safety outcomes included: AEs, serious AEs, study-drug-related AEs, AEs leading to discontinuation of treatment, death, major adverse cardiac events, muscle-related AEs, arthralgia, gout, back pain, pain in extremity, pruritus, rash, new onset hypertension, headache, fatigue, dizziness, dyspepsia, abdominal pain, nausea, constipation, diarrhea, nasopharyngitis, sinusitis, cough, dyspnea, upper respiratory tract infection, bronchitis, urinary tract infection, vulvo-vaginal mycotic infection, new onset or worsening diabetes, neurocognitive disorders, vertigo, increase in blood creatinine level, decrease in glomerular filtration rate, creatine kinase (CK) elevation serum uric acid (SUA) elevation, and liver enzyme (transaminase and gamma-glutamyl transferase) elevation. All the verbatim terms for the AEs were coded to preferred term and System Organ Class with the use of the Medical Dictionary for Regulatory Activities (MedDRA).

Missing or unpublished data were sought by trying to contact authors or sponsors via e-mail, and, in cases of no response, repeated messages were sent. Data extraction and database typing were performed by 2 authors (AFGC and FF) and reviewed by a third author (MB) before the final analysis. Doubts were resolved by mutual agreement among the authors.

## Risk of bias evaluation

A systematic evaluation of risk of bias in the included studies was performed using the Cochrane tool [11]. The items used were the following: adequacy of sequence generation, blinding, addressing of dropouts (incomplete outcome data), allocation concealment, selective outcome reporting, and other probable sources of bias [12]. Risk of bias assessment was performed by 2 reviewers (FF and AFGC) independently; disagreements were resolved by a consensus-based discussion. Each item was judged as high, low, or unclear risk of bias. A trial with high risk of bias in the randomization or blinding items was judged as having high risk of bias overall.

## Data synthesis

All analyses were performed with Comprehensive Meta-Analysis (CMA) version 3 software (Biostat, Englewood, NJ) [13]. Changes in continuous outcomes were calculated for each study arm by subtracting the value at baseline from the one after intervention. All values were expressed as percent change from baseline. Standard deviations (SDs) of the mean differences (MDs) were obtained as follows, per Follmann and colleagues [14]:  $SD = \sqrt{[SD_{pre}^2 + SD_{post}^2 - (2R \times SD_{pre} \times SD_{post})]}$ , assuming a correlation coefficient ( $R$ ) of 0.5. If the outcome measures were reported in the original articles as median and interquartile range (or 95% confidence interval [CI]), mean and SD values were obtained as described by Wan et al. [15]. In case standard error of the mean (SEM) was only reported as a dispersion measure, SD was estimated using the following formula:  $SD = SEM \times \sqrt{n}$ , with  $n$  being the number of individuals. To handle the double-counting problem in trials comparing different treatments against a single control group, individuals within the control group were divided by the required comparisons.

Meta-analyses were conducted using a fixed-effect model or a random-effect model (using the DerSimonian–Laird method) and the generic inverse variance method based on the moderately low (<50%) or high ( $\geq$ 50%) inter-study heterogeneity, which was quantitatively assessed using the Higgins index ( $I^2$ ) [16]. Effect sizes for lipid and hsCRP changes were expressed as MDs and 95% CIs. For safety analyses, odds ratios (ORs) and 95% CIs were calculated using the Mantel–Haenszel method [17]. If 1 or more outcomes could not be extracted from a study, the study was removed from the analysis involving those outcomes. AEs were included in the analysis only if occurring in at least 2 of the selected clinical trials. The efficacy analysis was performed on the safety population; the analysis of safety data was based on the intention-to-treat population.

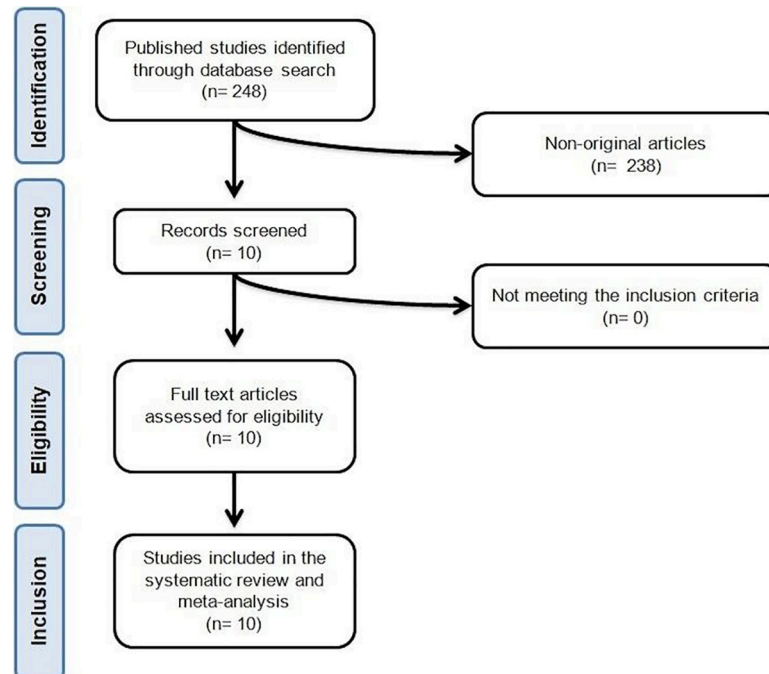
For the purpose of evaluating the influence of each study on the overall effect size, sensitivity analysis was conducted using the leave-one-out method (i.e., repeating the analysis after omitting 1 study at a time) [18]. Two-sided  $p$ -values  $\leq 0.05$  were considered statistically significant for all tests.

If statistical heterogeneity was detected, attempts to identify the sources of heterogeneity and potential publication biases were made through the visual inspection of Begg’s funnel plot asymmetry, and carrying out the Begg’s rank correlation test and Egger’s linear regression test [19]. The Duval and Tweedie “trim and fill” method was used to adjust the analysis for the effects of publication bias [20]. In case of a significant result, the number of potentially missing studies required to make the  $p$ -value non-significant was estimated by using the classical fail-safe  $N$  method as another marker of publication bias. Two-sided  $p$ -values  $\leq 0.05$  were considered statistically significant.

## Results

### Flow and characteristics of the included studies

We identified 248 published abstracts. Of these, 238 were excluded because they were not original articles. All the other 10 studies met the inclusion criteria and were carefully assessed and



**Fig 1. Flow chart of the number of studies identified and included in the meta-analysis.** Data were pooled from 10 trials comprising 26 treatment arms, which included overall 3,788 individuals, with 2,460 in the active arm and 1,328 in the control arm.

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reviewed. On the basis of the established eligibility criteria, all 10 RCTs were included in the meta-analysis [9,21–29]. The study selection process is shown in Fig 1.

Eligible studies were published between 2013 and 2019. Follow-up periods ranged between 4 and 52 weeks, and several treatment schedules were tested. All trials were parallel and multi-center [9,21–26,28,29] or single-center [27]. Enrolled individuals were statin-intolerant individuals [9,21,24,28], patients with type 2 diabetes [21,27], or patients affected by hypercholesterolemia despite statin treatment [21–23,25,26,29]. The main characteristics of the selected studies are summarized in Table 1.

### Risk of bias evaluation

The studies reported sufficient information regarding sequence generation, allocation concealment, blinding of participants, personnel, and outcome assessment. Details of the risk of bias evaluation are reported in Table 2.

### Effect of bempedoic acid on selected laboratory parameters

Meta-analysis of available data showed that bempedoic acid significantly reduced TC ( $n = 3,485$ ; MD  $-14.94\%$ ; 95% CI  $-17.31\%$ ,  $-12.57\%$ ;  $p < 0.001$ ;  $I^2 = 76.1\%$ ) (Fig 2), non-HDL-C ( $n = 3,485$ ; MD  $-18.17\%$ ; 95% CI  $-21.14\%$ ,  $-15.19\%$ ;  $p < 0.001$ ;  $I^2 = 87.2\%$ ) (Fig 3), LDL-C ( $n = 3,483$ ; MD  $-22.94\%$ ; 95% CI  $-26.63\%$ ,  $-19.25\%$ ;  $p < 0.001$ ;  $I^2 = 77.3\%$ ) (Fig 4), LDL particle number ( $n = 441$ ; MD  $-20.67\%$ ; 95% CI  $-23.84\%$ ,  $-17.48\%$ ;  $p < 0.001$ ;  $I^2 = 0\%$ ) (Fig 5), Apo B ( $n = 3,402$ ; MD  $-15.18\%$ ; 95% CI  $-17.41\%$ ,  $-12.95\%$ ;  $p < 0.001$ ;  $I^2 = 81.4\%$ ) (Fig 6), HDL-C ( $n = 3,453$ ; MD  $-5.83\%$ ; 95% CI  $-6.14\%$ ,  $-5.52\%$ ;  $p < 0.001$ ;  $I^2 = 33.4\%$ ) (Fig 7), and hsCRP ( $n = 3,179$ ; MD  $-27.03\%$ ; 95% CI  $-31.42\%$ ,  $-22.64\%$ ;  $p < 0.001$ ;  $I^2 = 0\%$ ) (Fig 8). Furthermore,

Table 1. Main characteristics of the selected studies.

Study	First author, year [reference]	Study design	Main inclusion criteria	Primary outcomes	Treatment duration	Study groups	Patients, n	Age (years), mean $\pm$ SD	Female, n (%)	Average change in LDL-C from baseline
NCT03337308	Ballantyne, 2019 [21]	Multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase III clinical study	$\geq 18$ years of age; high risk for CVD; LDL-C $\geq 2.4$ mmol/l for ASCVD or HeFH patients and LDL-C $\geq 3.4$ mmol/l for patients with multiple CVD risk factors; TGs $< 5.6$ mmol/l; maximally tolerated lipid-lowering therapy	Percent change in LDL-C	12 weeks	Bempedoic acid 180 mg/day and ezetimibe 10 mg/day	86	62.2 $\pm$ 9.5	44 (51.2%)	-36.2%
						Ezetimibe 10 mg/day	86	65.1 $\pm$ 8.4	43 (50.0%)	-23.2%
						Bempedoic acid 180 mg/day	88	65.2 $\pm$ 9.8	48 (54.5%)	-17.2%
						Placebo	41	65.4 $\pm$ 10.8	17 (41.5%)	+1.8%
NCT02659397	Lalwani, 2019 [22]	Multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase II clinical study	18–70 years of age; BMI $\geq 18$ kg/m <sup>2</sup> and $\leq 40$ kg/m <sup>2</sup> ; no history of CVD; treatment with atorvastatin 80 mg/day	Percent change in LDL-C from baseline to week 4; fold change in C <sub>max</sub> from baseline to week 2; fold change in AUC from baseline to week 2	4 weeks	Bempedoic acid 180 mg/day	45	58 (10)*	21 (51.2%)	-13.3%
						Placebo	23	58 (8)*	10 (43.5%)	+9.2%
CLEAR Serenity (NCT02988115)	Laufs, 2019 [9]	Multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase III clinical study	Men and postmenopausal or surgically sterile women; $\geq 18$ years of age; history of intolerance of $\geq 2$ statins; LDL-C $\geq 3.4$ mmol/l for primary prevention patients and $\geq 2.4$ mmol/l for HeFH patients	Percent change in LDL-C from baseline to week 12	24 weeks	Bempedoic acid 180 mg/day	234	65.2 $\pm$ 9.7	133 (56.8%)	-23.6%*
						Placebo	111	65.1 $\pm$ 9.2	61 (55%)	-1.3%*
CLEAR Harmony (NCT02666664)	Ray, 2019 [23]	Multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase III clinical study	Men and postmenopausal or surgically sterile women; $\geq 18$ years of age; high CV risk; maximally tolerated lipid-lowering therapy; LDL-C $\geq 1.8$ mmol/l	Overall safety, assessed according to the incidence of adverse events and changes in safety laboratory variables	52 weeks	Bempedoic acid 180 mg/day	1,487	65.8 $\pm$ 9.1	389 (26.1%)	-12.6%
						Placebo	742	66.8 $\pm$ 8.6	213 (28.7%)	+1.1%
CLEAR Tranquility (NCT03001076)	Ballantyne, 2018 [24]	Multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase III clinical study	$\geq 18$ years of age; history of intolerance to statin; low-dose statin therapy or no statin therapy; LDL-C $\geq 2.4$ mmol/l	Percent change in LDL-C	12 weeks	Bempedoic acid 180 mg/day	181	63.8 $\pm$ 10.8	109 (60.2%)	-23.5%
						Placebo	88	63.7 $\pm$ 11.3	56 (63.6%)	+5.2%

(Continued)

Table 1. (Continued)

Study	First author, year [reference]	Study design	Main inclusion criteria	Primary outcomes	Treatment duration	Study groups	Patients, n	Age (years), mean $\pm$ SD	Female, n (%)	Average change in LDL-C from baseline
NCT02072161	Ballantyne, 2016 [25]	Multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase IIb clinical study	18–80 years of age; BMI $\geq$ 18 kg/m <sup>2</sup> and $\leq$ 45 kg/m <sup>2</sup> ; statin therapy; LDL-C $\geq$ 3 mmol/l and $\leq$ 5.7 mmol/l; TGs $\leq$ 4.5 mmol/l	Percent change in LDL-C	12 weeks	Bempedoic acid 180 mg/day	45	57 $\pm$ 10	31 (69%)	-24.3%
						Bempedoic acid 120 mg/day	44	59 $\pm$ 9	26 (61%)	-17.3%
						Placebo	45	56 $\pm$ 10	22 (49%)	-4.2%
NCT01941836	Thompson, 2016 [26]	Multicenter, randomized, double-blind, controlled, parallel-group, phase IIb clinical study	18–80 years of age; LDL-C $\geq$ 3.4 mmol/l and $\leq$ 5.7 mmol/l; TGs $\leq$ 4.5 mmol/l; BMI $\geq$ 18 kg/m <sup>2</sup> and $\leq$ 45 kg/m <sup>2</sup>	Percent change in LDL-C	12 weeks	Bempedoic acid 180 mg/day and ezetimibe 10 mg/day	24	59 $\pm$ 9	13 (54.2%)	-48.2%
						Bempedoic acid 120 mg/day and ezetimibe 10 mg/day	26	59 $\pm$ 10	14 (54%)	-43.3%
						Ezetimibe 10 mg/day	99	60 $\pm$ 10	52 (51.5%)	-21.2%
NCT01607294	Gutierrez, 2014 [27]	Single-center, randomized, double-blind, placebo-controlled, parallel-group, phase II clinical study	Type 2 diabetes; low risk for CVD; 18–70 years of age; LDL-C $\geq$ 2.4 mmol/l; BMI $\geq$ 25 kg/m <sup>2</sup> and $\leq$ 35 kg/m <sup>2</sup>	Percent change in LDL-C	4 weeks	Bempedoic acid 80 mg/day for 2 weeks followed by bempedoic acid 120 mg/day for 2 weeks	30	55.3 $\pm$ 6.9	13 (43.4%)	-42.9%
						Placebo	30	56.0 $\pm$ 9.9	10 (33.3%)	-4.3%
NCT01751984	Thompson, 2015 [28]	Multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase II clinical study	Men and postmenopausal or surgically sterile women; 18–80 years of age; history of intolerance $\geq$ 1 statin; LDL-C $\geq$ 2.4 mmol/l and $\leq$ 5.7 mmol/l; TGs $<$ 4 mmol/l; BMI $\geq$ 18 kg/m <sup>2</sup> and $\leq$ 40 kg/m <sup>2</sup>	Percent change in LDL-C	8 weeks	Bempedoic acid 60 mg/day for 2 weeks followed by increasing dose at 2-week intervals to 120, 180, and 240 mg/day	37	64 $\pm$ 5	17 (46%)	-32.5%
						Placebo	19	60 $\pm$ 8	11 (58%)	-3.3%

(Continued)



Table 1. (Continued)

Study	First author, year [reference]	Study design	Main inclusion criteria	Primary outcomes	Treatment duration	Study groups	Patients, n	Age (years), mean $\pm$ SD	Female, n (%)	Average change in LDL-C from baseline
NCT01262638	Ballantyne, 2013 [29]	Multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase II clinical study	18–80 years of age; LDL-C $\geq$ 3.4 mmol/l and $\leq$ 5.2 mmol/l; TGs $<$ 4.5 mmol/l; BMI $\geq$ 18 kg/m <sup>2</sup> and $\leq$ 35 kg/m <sup>2</sup>	Percent change in LDL-C	12 weeks	Bempedoic acid 120 mg/day	44	57 $\pm$ 10	19 (43%)	-26.6%
						Bempedoic acid 80 mg/day	44	59 $\pm$ 9	21 (48%)	-25.4%
						Bempedoic acid 40 mg/day	45	58 $\pm$ 9	26 (58%)	-17.9%
						Placebo	44	56 $\pm$ 10	13 (30%)	-2.1%

\*Expressed as median (standard deviation).

<sup>†</sup>After 12 weeks of treatment.

ASCVD, atherosclerotic cardiovascular disease; AUC, area under the curve; BMI, body mass index;  $C_{max}$ , peak plasma concentration; CV, cardiovascular; CVD, cardiovascular disease; HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride.

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bempedoic acid had a barely detectable significant effect on HDL-C particle number ( $n = 271$ ; MD  $-3.21\%$ ; 95% CI  $-6.40\%$ ,  $-0.02\%$ ;  $p = 0.049$ ;  $I^2 = 43.3\%$ ) (Fig 9).

There were no significant effects on TGs ( $n = 2,954$ ; MD  $-1.51\%$ ; 95% CI  $-3.75\%$ ,  $0.74\%$ ;  $p = 0.189$ ;  $I^2 = 15.1\%$ ) (Fig 10), VLDL particle number ( $n = 271$ ; MD  $3.79\%$ ; 95% CI  $-9.81\%$ ,  $17.39\%$ ;  $p = 0.585$ ;  $I^2 = 35.1\%$ ) (Fig 11), and Apo A-1 ( $n = 382$ ; MD  $-1.83\%$ ; 95% CI  $-5.23\%$ ,  $1.56\%$ ;  $p = 0.290$ ;  $I^2 = 50.1\%$ ) (Fig 12). When the largest study (the CLEAR Harmony trial) [23] was excluded from the meta-analysis, all the effect sizes were similar (S1 Table). Furthermore,

Table 2. Risk of bias evaluation of the studies according to Cochrane guidelines.

First author, year [reference]	Sequence generation	Allocation concealment	Blinding of participants, personnel, and outcome assessment	Incomplete outcome data	Selective outcome reporting	Other potential threats to validity
Ballantyne, 2019 [21]	L	L	L	H	U	U
Lalwani, 2019 [22]	L	L	L	L	L	L
Laufs, 2019 [9]	L	L	L	L	L	L
Ray, 2019 [23]	L	L	L	L	L	L
Ballantyne, 2018 [24]	L	L	L	L	L	L
Ballantyne, 2016 [25]	L	L	L	L	L	L
Thompson, 2016 [26]	L	L	L	L	L	L
Gutierrez, 2014 [27]	L	L	L	L	L	L
Thompson, 2015 [28]	L	L	L	L	L	L
Ballantyne, 2013 [29]	L	L	L	L	L	L

H, high risk of bias; L, low risk of bias; U, unclear risk of bias.

<https://doi.org/10.1371/journal.pmed.1003121.t002>

### Total Cholesterol

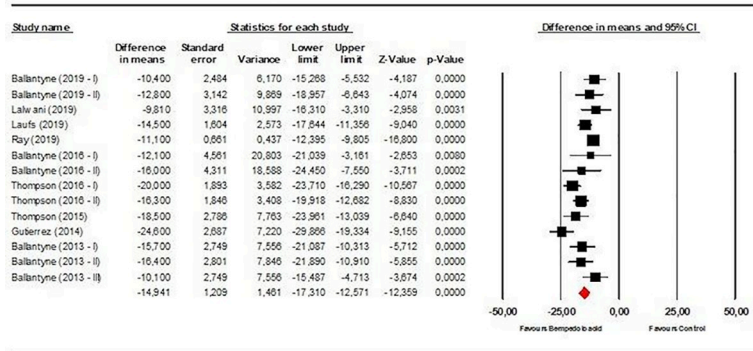


Fig 2. Forest plot displaying mean difference and 95% confidence intervals for the effect of bempedoic acid on plasma levels of total cholesterol.

<https://doi.org/10.1371/journal.pmed.1003121.g002>

the effect sizes were robust in the leave-one-out sensitivity analysis (S1–S4 Figs) and not mainly driven by a single study.

Visual inspection of Begg’s funnel plots did not reveal any asymmetry, suggesting no publication bias for the effect of bempedoic acid on the investigated parameters (S6 Fig).

Duval and Tweedie’s “trim and fill” method yielded 1 potentially missing study on the left side of the plot for TC, increasing the effect size to  $-15.27\%$  (95% CI  $-17.61\%$ ,  $-12.92\%$ ); 4 potentially missing studies on the left side of the plot for HDL-C, lowering the effect size to  $-5.88\%$  (95% CI  $-6.18\%$ ,  $-5.57\%$ ); 1 potentially missing study on the right side of the plot for HDL particle number, lowering the effect size to  $-1.86\%$  (95% CI  $-4.86\%$ ,  $1.13\%$ ); 4 potentially missing studies on the left side of the plot for non-HDL-C, increasing the effect size to  $-20.15\%$  (95% CI  $-23.73\%$ ,  $-16.57\%$ ); 3 potentially missing studies on the left side of the plot for LDL-C, increasing the effect size to  $-25.17\%$  (95% CI  $-29.55\%$ ,  $-20.79\%$ ); 2 potentially missing studies on the left side of the plot for LDL particle number, lowering the effect size to  $-21.85\%$  (95% CI  $-24.74\%$ ,  $-18.96\%$ ); 1 potentially missing study on the right side of the funnel for VLDL particle number, increasing the effect size to  $8.55\%$  (95% CI  $-4.01\%$ ,  $21.11\%$ ); 2 potentially missing studies on the left side of the plot for Apo A-1, lowering the effect size to  $-3.77\%$  (95% CI  $-7.33\%$ ,  $-0.21\%$ ); and 3 potentially missing studies on the right side of the

### Non HDL-Cholesterol

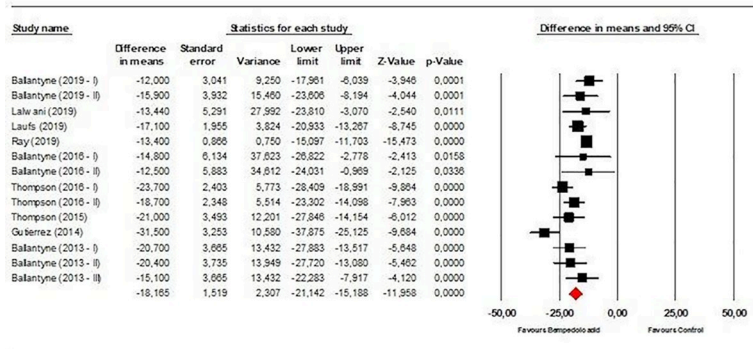
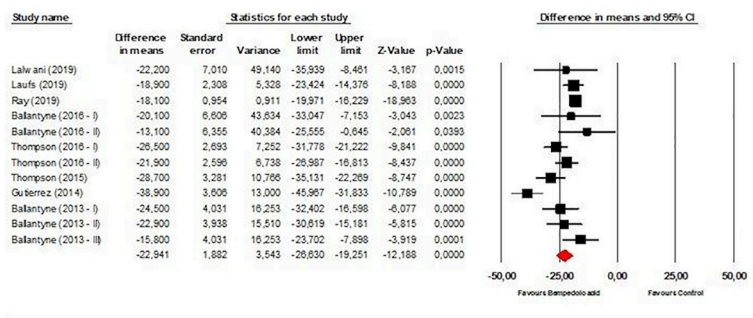


Fig 3. Forest plot displaying mean difference and 95% confidence intervals for the effect of bempedoic acid on plasma levels of non-high-density lipoprotein (HDL) cholesterol.

<https://doi.org/10.1371/journal.pmed.1003121.g003>

### LDL-Cholesterol



**Fig 4.** Forest plot displaying mean difference and 95% confidence intervals for the effect of bempedoic acid on plasma levels of low-density lipoprotein (LDL) cholesterol.

<https://doi.org/10.1371/journal.pmed.1003121.g004>

plot for hsCRP, lowering the effect size to -25.69% (95% CI -29.89%, -21.48%). However, neither Begg’s rank correlation nor Egger’s linear regression confirmed the presence of publication bias for the analyses ( $p > 0.05$  for all) (S2 Table).

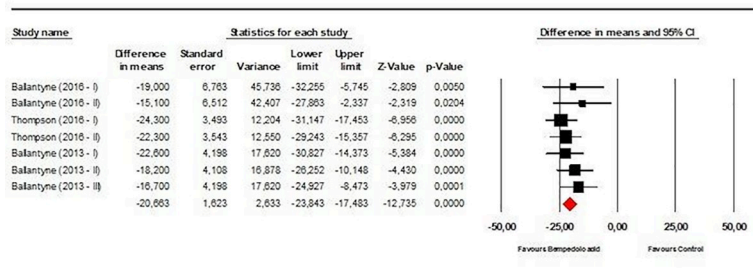
The classic fail-safe  $N$  test suggested that the following number of studies with negative results would be needed to bring the estimated effect size for each outcome to a non-significant level: 2,280 studies for TC ( $p < 0.001$  for the test), 838 studies for HDL-C ( $p < 0.001$  for the test), 2 studies for HDL particle number ( $p = 0.017$  for the test), 2,004 studies for non-HDL-C ( $p < 0.001$  for the test), 2,053 studies for LDL-C ( $p < 0.001$  for the test), 263 studies for LDL particle number ( $p < 0.001$  for the test), 1,308 studies for Apo B ( $p < 0.001$  for the test), and 188 studies for hsCRP ( $p < 0.001$  for the test). The individual analyses are included in S3 Table.

### Safety analysis

Bempedoic acid was positively associated with an increased risk of discontinuation of treatment ( $n = 3,731$ ; OR 1.37; 95% CI 1.06, 1.76;  $p = 0.015$ ;  $I^2 = 0\%$ ), elevated SUA ( $n = 569$ ; OR 3.55; 95% CI 1.03, 12.27;  $p = 0.045$ ;  $I^2 = 0\%$ ), elevated liver enzymes ( $n = 2,363$ ; OR 4.28; 95% CI 1.34, 13.71;  $p = 0.014$ ;  $I^2 = 0\%$ ), and elevated CK ( $n = 2,718$ ; OR 3.79; 95% CI 1.06, 13.51;  $p = 0.04$ ;  $I^2 = 0\%$ ), but it was strongly associated with a decreased risk of new onset or worsening diabetes ( $n = 2,498$ ; OR 0.59; 95% CI 0.39, 0.90;  $p = 0.01$ ;  $I^2 = 0\%$ ) (Fig 13).

These findings were robust in the leave-one-out sensitivity analyses (S6 Fig). However, when the data from the largest study (the CLEAR Harmony trial) [23] were excluded from the

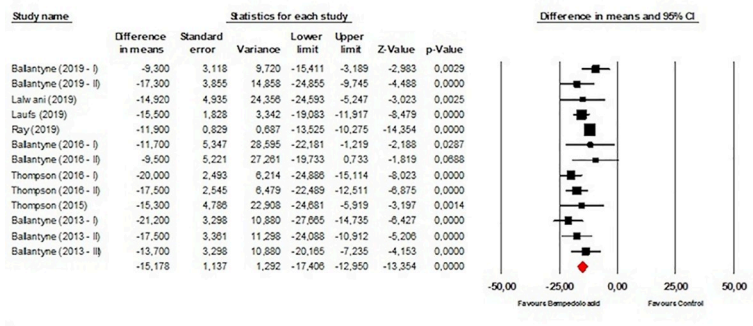
### LDL Particle Number



**Fig 5.** Forest plot displaying mean difference and 95% confidence intervals for the effect of bempedoic acid on plasma levels of low-density lipoprotein (LDL) particle number.

<https://doi.org/10.1371/journal.pmed.1003121.g005>

### Apolipoprotein B



**Fig 6.** Forest plot displaying mean difference and 95% confidence intervals for the effect of bempedoic acid on plasma levels of apolipoprotein B.

<https://doi.org/10.1371/journal.pmed.1003121.g006>

meta-analysis, the effect sizes for the safety outcomes lost their statistical significance (S1 Table).

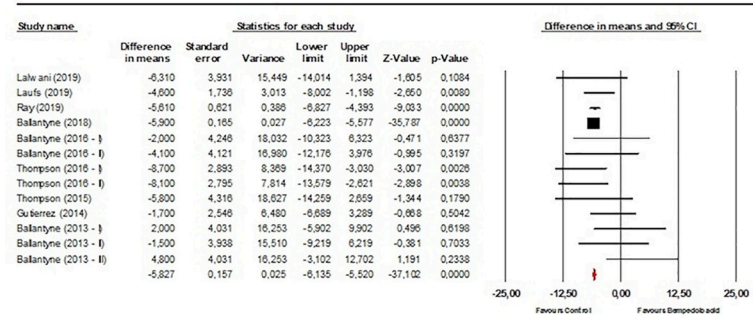
The incidence of the other AEs did not differ between groups (S4 Table). Considering the reasons for treatment discontinuation in included trials that reported all or part of them (S5 Table), it was not possible to identify the responsible reasons of the effect size of Fig 6 (S7 Fig).

Visually, the funnel plot of standard error by log OR was slightly asymmetric only for risk of discontinuation of treatment. This asymmetry was imputed to 6 potentially missing studies on the right side of the funnel plot, increasing the estimated risk to 1.55 (95% CI 1.22, 1.97) (S8 Fig). The presence of publication bias for the analysis was confirmed by Egger’s linear regression ( $p = 0.005$ ), but not by Begg’s rank correlation ( $p = 0.298$ ). The classic fail-safe  $N$  test suggested that 1 study with a negative result would be needed to bring the estimated risk of CK elevation to a non-significant level ( $p = 0.042$  for the test), and 2 studies with negative results would be needed to bring the estimated risk of transaminase elevation to a non-significant level ( $p = 0.021$  for the test). The individual analyses are included in S6 Table.

### Discussion

Inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase (statins) represent the first-line treatment for dyslipidemia, being able to reduce LDL-C by 30%–50% and subsequently

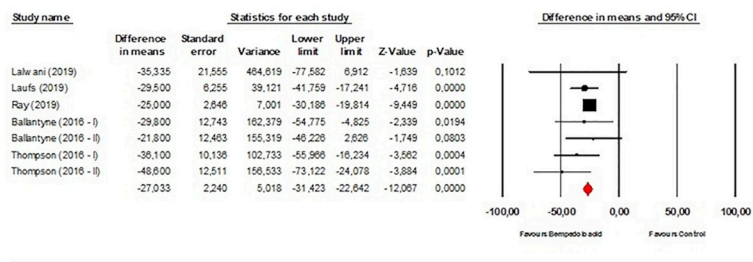
### HDL-Cholesterol



**Fig 7.** Forest plot displaying mean difference and 95% confidence intervals for the effect of bempedoic acid on plasma levels of high-density lipoprotein (HDL) cholesterol.

<https://doi.org/10.1371/journal.pmed.1003121.g007>

### High sensitivity-C Reactive Protein



**Fig 8. Forest plot displaying mean difference and 95% confidence intervals for the effect of bempedoic acid on plasma levels of high-sensitivity C-reactive protein.**

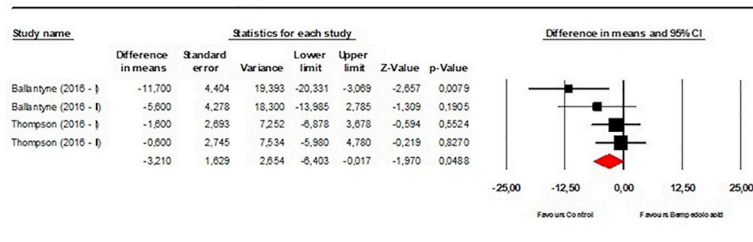
<https://doi.org/10.1371/journal.pmed.1003121.g008>

decrease the incidence of CV events [30]. Despite the highly favorable benefit/risk profile of statins, a large number of patients are statin intolerant or need additional lipid-lowering drugs to reach optimal LDL-C levels [3]. The current meta-analysis shows that bempedoic acid safely reduces LDL-C levels by about 23%, suggesting that it might be considered as an effective alternative or add-on therapy to statins or ezetimibe.

About 31%–49% or more of patients with hyperlipidemia do not achieve LDL-C goals with current lipid-lowering therapies [31,32], and more than half of patients stop statin treatment within 1 year of initiation [33]. Sixty percent of patients who discontinue statins report different symptoms of drug intolerance as the main reason for discontinuation [34]. Statin intolerance, usually characterized by myalgia, myositis, and/or myopathy, occurs in 2%–15% of users, the estimate being strongly variable in epidemiological and rechallenging studies [35,36]. Furthermore, large meta-analyses showed that statin treatment is associated with a 9%–13% increase in risk of developing diabetes [37]. However, scientifically unsupported concerns about statin safety spread by mass media lead to the formation of a negative image of these drugs and increase of their cessation rate [38].

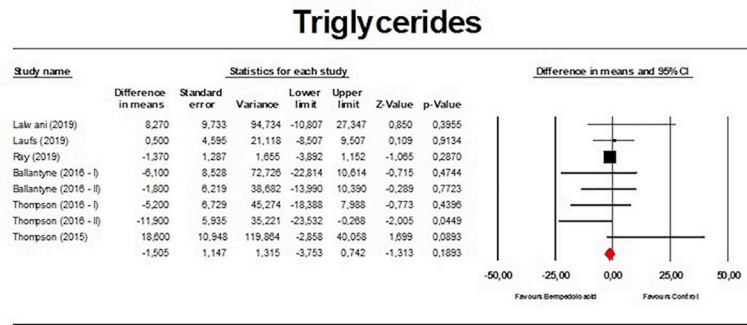
Additional treatments of dyslipidemia include ezetimibe (second-line) and fenofibrate (third-line). Ezetimibe, in combination with statin therapy, lowers LDL-C by an additional 20% or so [39] and significantly reduces the risk of major adverse CV events, non-fatal myocardial infarction, and non-fatal stroke compared with statins alone, with less or no effect on fatal endpoints [40]. A simulation based on adding ezetimibe in a huge statin-treated cohort suggests that the percentage of patients with LDL-C > 1.8 mmol/l and >2.4 mmol/l would fall from 65% to 38% and from 25% to 12%, respectively [41].

### HDL Particle Number



**Fig 9. Forest plot displaying mean difference and 95% confidence intervals for the effect of bempedoic acid on plasma levels of high-density lipoprotein (HDL) particle number.**

<https://doi.org/10.1371/journal.pmed.1003121.g009>



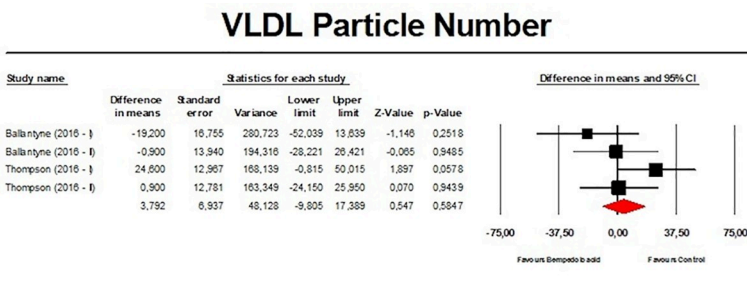
**Fig 10. Forest plot displaying mean difference and 95% confidence intervals for the effect of bempedoic acid on plasma levels of triglycerides.**

<https://doi.org/10.1371/journal.pmed.1003121.g010>

Fibrates are less effective on LDL-C levels, with their main indication being moderate-to-severe hypertriglyceridemia, such that they are rarely used in cardiology settings. However, a large meta-analysis of 16,112 patients showed evidence for a protective effect compared to placebo for the primary composite outcome of non-fatal myocardial infarction, non-fatal stroke, and vascular death [42]. Besides, patients with very high baseline LDL-C level or very high or extreme global CV risk need additional lipid-lowering drugs to optimize the lipid profile [43], especially in light of the most recent international recommendations [44,45]. Monoclonal antibodies that target proprotein convertase subtilisin/kexin type 9 (PCSK9) have recently been demonstrated to dramatically reduce LDL-C level (even over 60%) in the majority of cases, while significantly reducing CV risk; however, their cost–benefit ratio is yet under discussion, and in many countries their use is limited due to strict reimbursement rules [46]. In this context, there is yet place for the development of new less-expensive, effective/safe lipid-lowering drugs.

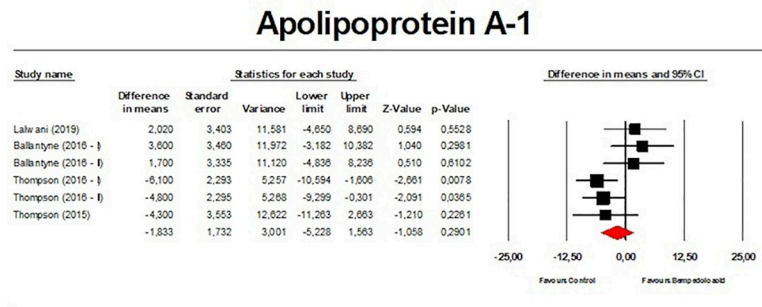
By analyzing data from 10 phase II and phase III RCTs including a total of 3,788 patients, we confirmed that bempedoic acid significantly reduced TC (by 15%), non-HDL-C (by 18.2%), LDL-C (by 22.9%), LDL particle number (by 20.7%), Apo B (by 15.2%), and hsCRP (by 27%), while negatively affecting serum levels of HDL-C (–5.8%) and HDL particle number (–3.2%). These findings strengthen the unpowered data previously reported by Wang et al., based on only 625 patients [47]. These findings could also be quantitatively relevant, since they have usually been obtained when bempedoic acid is administered on top of an effective lipid-lowering treatment, with a quite good safety and tolerability profile.

Our results also confirmed that bempedoic acid therapy is overall safe and well tolerated, with no significant increase of serious AEs. However, an increase of drug discontinuation and



**Fig 11. Forest plot displaying mean difference and 95% confidence intervals for the effect of bempedoic acid on plasma levels of very-low-density lipoprotein (VLDL) particle number.**

<https://doi.org/10.1371/journal.pmed.1003121.g011>



**Fig 12. Forest plot displaying mean difference and 95% confidence intervals for the effect of bempedoic acid on plasma levels of apolipoprotein A-1.**

<https://doi.org/10.1371/journal.pmed.1003121.g012>

elevations of SUA, transaminase, and CK were observed. The detailed analysis of the reasons for discontinuation (see [S5 Table](#)) reported in the available trials does not give any clear pattern that could explain the 37% increased risk of discontinuation of bempedoic acid in comparison to placebo; this issue, however, needs to be further investigated. As for the other adverse effects possibly related to bempedoic acid, it is important to emphasize that in the 4 trials where CK increase was reported, it was observed in only 16 patients (of 1,792 investigated; 0.9%), and only single patients had a repeated and confirmed CK elevation greater than 5 times the upper limit of normal. More data with longer follow-up are also necessary to confirm the risk of SUA increase with bempedoic acid (observed in only 3 trials, where SUA increase was observed in 18/354 [5%]), as well as the risk of transaminase increase (observed in 5 trials, where transaminase increase was observed in only 1.1% of patients [20/1,823] in active-treated group). It is also worth emphasizing that bempedoic acid, due to its mechanism of action, does not increase the risk muscle-related side-effects and significantly reduces the risk of worsening or new onset diabetes by about 40% (however, based only on 2 available studies)—AEs that might be relatively often observed in statin trials, especially for high- and very-high-risk patients requiring intense therapy.

In this context, bempedoic acid seems to be an interesting option as an overall safe drug to be easily associated to statins and ezetimibe. In particular, the drug will be marketed as monotherapy or in a single pill with ezetimibe for the management of statin-intolerant patients. Considering the different mechanism of action of bempedoic acid and ezetimibe, the high safety profile of both drugs, and the lack of interaction risk between them, it is expected that this association will be a relatively effective and safe lipid-lowering treatment.

The main limitation of this meta-analysis is related to the relatively small number of patients involved in the studies, which were often short or middle term, as well as their heterogeneity (including different populations that were investigated, i.e., patients with type 2 diabetes, hypercholesterolemia, or statin intolerance). Moreover, heterogeneity of effects is moderate to large across most of the biochemical outcomes. Data on decreased CV events and mortality are lacking for bempedoic acid as well [\[48\]](#).

In conclusion, the current meta-analysis demonstrates an acceptable safety profile and multiple positive effects of bempedoic acid on lipid profile and hsCRP serum levels.

Further data on the cost-benefit efficacy of bempedoic acid treatment will come from the CLEAR Outcomes study, a phase III, event-driven, randomised, multicenter, double-blind, placebo-controlled trial designed to evaluate whether treatment with bempedoic acid reduces the risk of CV events. The primary endpoint of the study is the effect of bempedoic acid on major adverse CV events (CV death, non-fatal myocardial infarction, non-fatal stroke, and coronary revascularization). The enrollment ended in November 2019 [\[49\]](#).

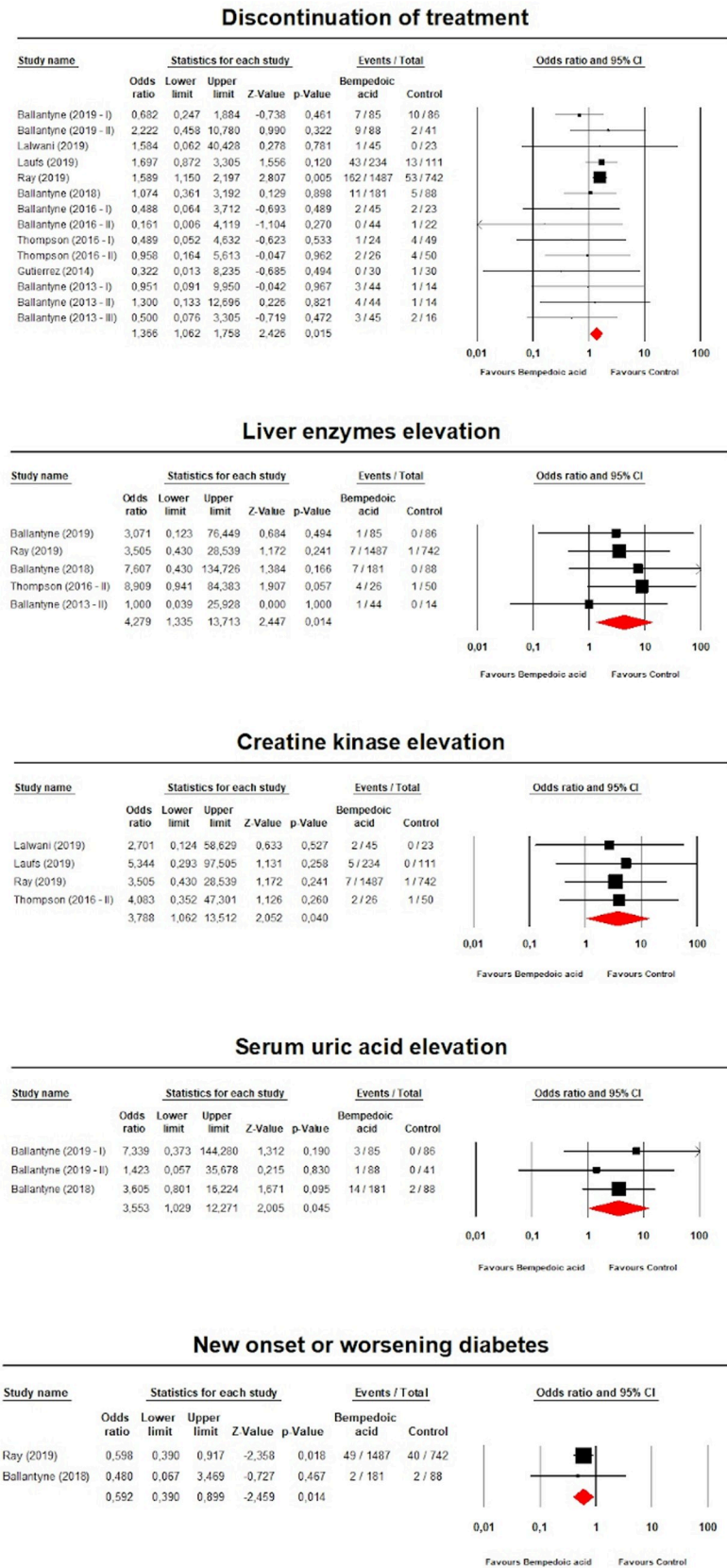


Fig 13. Forest plot comparing the risk of adverse events statistically associated with bempedoic acid treatment.

<https://doi.org/10.1371/journal.pmed.1003121.g013>



## Supporting information

**S1 PRISMA Checklist. PRISMA Checklist.**

(DOC)

**S1 Data. Summary data for all included studies.**

(XLS)

**S1 Fig. Forest plots showing leave-one-out for TC, non-HDL-C, and TG.**

(TIF)

**S2 Fig. Forest plots showing leave-one-out for LDL-C, LDL particle number, VLDL particle number, and Apo B.**

(TIF)

**S3 Fig. Forest plots showing leave-one-out for HDL-C, HDL particle number and Apo A-1.**

(TIF)

**S4 Fig. Forest plots showing leave-one-out for hsCRP.**

(TIF)

**S5 Fig. Funnel plots detailing publication bias in the studies reporting the effect of ETC-1002 treatment on serum lipids and hsCRP concentrations.**

(TIF)

**S6 Fig. Plot showing leave-one-out sensitivity analysis for safety analysis.**

(TIF)

**S7 Fig. Plot showing reasons for discontinuation to treatment as reported in the studies.**

\*Data referring to statin-intolerant patients; <sup>§</sup> Data referring to statin-tolerant patients.

(TIF)

**S8 Fig. Funnel plot detailing publication bias in the safety analysis.**

(TIF)

**S1 Table. Meta-analysis' findings after excluding the CLEAR Harmony study.**

(DOC)

**S2 Table. Begg's rank correlation nor Egger's linear regression tests.**

(DOC)

**S3 Table. Classic fail-safe N results for the efficacy analyses.**

(DOC)

**S4 Table. Adverse events occurred in at least 2 clinical trials. AEs = Adverse events.**

(DOC)

**S5 Table. Reasons of discontinuation to treatments as reported by the studies.**

(DOC)

**S6 Table. Classic fail-safe N results for the safety analyses.**

(DOC)

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**Writing – original draft:** Arrigo F. G. Cicero, Federica Fogacci, Maciej Banach.

**Writing – review & editing:** Arrigo F. G. Cicero, Federica Fogacci, Adrian V. Hernandez, Maciej Banach.

## References

1. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart disease and stroke statistics—2015 update: a report from the American Heart Association. *Circulation*. 2015; 131:e29–322. <https://doi.org/10.1161/CIR.000000000000152> PMID: 25520374
2. Ference BA, Yoo W, Alesh I, Mahajan N, Mirowska KK, Mewada A, et al. Effect of long-term exposure to lower low-density lipoprotein cholesterol beginning early in life on the risk of coronary heart disease: a Mendelian randomization analysis. *J Am Coll Cardiol*. 2012; 60:2631–9. <https://doi.org/10.1016/j.jacc.2012.09.017> PMID: 23083789
3. Strilchuk L, Fogacci F, Cicero AF. Safety and tolerability of injectable lipid-lowering drugs: an update of clinical data. *Expert Opin Drug Saf*. 2019; 18:611–21. <https://doi.org/10.1080/14740338.2019.1620730> PMID: 31100030
4. Ruscica M, Banach M, Sahebkar A, Corsini A, Sirtori CR. ETC-1002 (bempedoic acid) for the management of hyperlipidemia: from preclinical studies to phase 3 trials. *Expert Opin Pharmacother*. 2019; 20:791–803. <https://doi.org/10.1080/14656566.2019.1583209> PMID: 30810432
5. Beigneux AP, Kosinski C, Gavino B, Horton JD, Skarnes WC, Young SG. ATP-citrate lyase deficiency in the mouse. *J Biol Chem*. 2004; 279:9557–64. <https://doi.org/10.1074/jbc.M310512200> PMID: 14662765
6. Berkhout TA, Havekes LM, Pearce NJ, Groot PH. The effect of (-)-hydroxycitrate on the activity of the low-density-lipoprotein receptor and 3-hydroxy-3-methylglutaryl-CoA reductase levels in the human hepatoma cell line Hep G2. *Biochem J*. 1990; 272:181–6. <https://doi.org/10.1042/bj2720181> PMID: 2176080
7. Saeed A, Ballantyne CM. Bempedoic acid (ETC-1002): a current review. *Cardiol Clin*. 2018; 36:257–64. <https://doi.org/10.1016/j.ccl.2017.12.007> PMID: 29609755
8. Pinkosky SL, Newton RS, Day EA, Ford RJ, Lhotak S, Austin RC, et al. Liver-specific ATP-citrate lyase inhibition by bempedoic acid decreases LDL-C and attenuates atherosclerosis. *Nat Commun*. 2016; 7:13457. <https://doi.org/10.1038/ncomms13457> PMID: 27892461
9. Laufs U, Banach M, Mancini GBJ, Gaudet D, Bloedon LT, Sterling LR, et al. Efficacy and safety of bempedoic acid in patients with hypercholesterolemia and statin intolerance. *J Am Heart Assoc*. 2019; 8:e011662. <https://doi.org/10.1161/JAHA.118.011662> PMID: 30922146

10. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009; 339:b2535. <https://doi.org/10.1136/bmj.b2535> PMID: 19622551
11. Higgins JPT, Green S, editors. *Cochrane handbook for systematic reviews of interventions*. Chichester (UK): John Wiley & Sons; 2008.
12. Sahebkar A, Pirro M, Banach M, Mikhailidis DP, Atkin SL, Cicero AFG. Lipid-lowering activity of artichoke extracts: a systematic review and meta-analysis. *Crit Rev Food Sci Nutr*. 2018; 58:2549–56. <https://doi.org/10.1080/10408398.2017.1332572> PMID: 28609140
13. Borenstein M, Hedges L, Higgins J, Rothstein H. *Comprehensive meta-analysis*. Version 3. Englewood (NJ): Biostat; 2013.
14. Follmann D, Elliott P, Suh I, Cutler J. Variance imputation for overviews of clinical trials with continuous response. *J Clin Epidemiol*. 1992; 45:769–73. [https://doi.org/10.1016/0895-4356\(92\)90054-q](https://doi.org/10.1016/0895-4356(92)90054-q) PMID: 1619456
15. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol*. 2014; 14:135. <https://doi.org/10.1186/1471-2288-14-135> PMID: 25524443
16. Melsen WG, Bootsma MC, Rovers MM, Bonten MJ. The effects of clinical and statistical heterogeneity on the predictive values of results from meta-analyses. *Clin Microbiol Infect*. 2014; 20:123–9. <https://doi.org/10.1111/1469-0691.12494> PMID: 24320992
17. Haenszel W, Hon NB. Statistical approaches to the study of cancer with particular reference to case registers. *J Chronic Dis*. 1956; 4:589–99. [https://doi.org/10.1016/0021-9681\(56\)90049-2](https://doi.org/10.1016/0021-9681(56)90049-2) PMID: 13376690
18. Fogacci F, Banach M, Cicero AF. Resveratrol effect on patients with non-alcoholic fatty liver disease: a matter of dose and treatment length. *Diabetes Obes Metab*. 2018; 20:1798–9. <https://doi.org/10.1111/dom.13324> PMID: 29656521
19. Sahebkar A, Pirro M, Reiner Ž, Cicero A, Ferretti G, Simental-Mendía M, et al. A systematic review and meta-analysis of controlled trials on the effects of statin and fibrate therapies on plasma homocysteine levels. *Curr Med Chem*. 2016; 23:4490–503. <https://doi.org/10.2174/0929867323666161007155310> PMID: 27748179
20. Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics*. 2000; 56:455–63. <https://doi.org/10.1111/j.0006-341x.2000.00455.x> PMID: 10877304
21. Ballantyne CM, Laufs U, Ray KK, Leiter LA, Bays HE, Goldberg AC, et al. Bempedoic acid plus ezetimibe fixed-dose combination in patients with hypercholesterolemia and high CVD risk treated with maximally tolerated statin therapy. *Eur J Prev Cardiol*. 2020; 27:593–603. <https://doi.org/10.1177/2047487319864671> PMID: 31357887
22. Lalwani ND, Hanselman JC, MacDougall DE, Sterling LR, Cramer CT. Complementary low-density lipoprotein-cholesterol lowering and pharmacokinetics of adding bempedoic acid (ETC-1002) to high-dose atorvastatin background therapy in hypercholesterolemic patients: a randomized placebo-controlled trial. *J Clin Lipidol*. 2019; 13:568–79. <https://doi.org/10.1016/j.jacl.2019.05.003> PMID: 31202641
23. Ray KK, Bays HE, Catapano AL, Lalwani ND, Bloedon LT, Sterling LR, et al. Safety and efficacy of bempedoic acid to reduce LDL cholesterol. *N Engl J Med*. 2019; 380:1022–32. <https://doi.org/10.1056/NEJMoa1803917> PMID: 30865796
24. Ballantyne CM, Banach M, Mancini GBJ, Lepor NE, Hanselman JC, Zhao X, et al. Efficacy and safety of bempedoic acid added to ezetimibe in statin-intolerant patients with hypercholesterolemia: a randomized, placebo-controlled study. *Atherosclerosis*. 2018; 277:195–203. <https://doi.org/10.1016/j.atherosclerosis.2018.06.002> PMID: 29910030
25. Ballantyne CM, McKenney JM, MacDougall DE, Margulies JR, Robinson PL, Hanselman JC, et al. Effect of ETC-1002 on serum low-density lipoprotein cholesterol in hypercholesterolemic patients receiving statin therapy. *Am J Cardiol*. 2016; 117:1928–33. <https://doi.org/10.1016/j.amjcard.2016.03.043> PMID: 27138185
26. Thompson PD, MacDougall DE, Newton RS, Margulies JR, Hanselman JC, Orloff DG, et al. Treatment with ETC-1002 alone and in combination with ezetimibe lowers LDL cholesterol in hypercholesterolemic patients with or without statin intolerance. *J Clin Lipidol*. 2016; 10:556–67. <https://doi.org/10.1016/j.jacl.2015.12.025> PMID: 27206943
27. Gutierrez MJ, Rosenberg NL, Macdougall DE, Hanselman JC, Margulies JR, Strange P, et al. Efficacy and safety of ETC-1002, a novel investigational low-density lipoprotein-cholesterol-lowering therapy for the treatment of patients with hypercholesterolemia and type 2 diabetes mellitus. *Arterioscler Thromb Vasc Biol*. 2014; 34:676–83. <https://doi.org/10.1161/ATVBAHA.113.302677> PMID: 24385236

28. Thompson PD, Rubino J, Janik MJ, MacDougall DE, McBride SJ, Margulies JR, et al. Use of ETC-1002 to treat hypercholesterolemia in patients with statin intolerance. *J Clin Lipidol*. 2015; 9:295–304. <https://doi.org/10.1016/j.jacl.2015.03.003> PMID: 26073387
29. Ballantyne CM, Davidson MH, Macdougall DE, Bays HE, Dicarlo LA, Rosenberg NL, et al. Efficacy and safety of a novel dual modulator of adenosine triphosphate-citrate lyase and adenosine monophosphate-activated protein kinase in patients with hypercholesterolemia: results of a multicenter, randomized, double-blind, placebo-controlled, parallel-group trial. *J Am Coll Cardiol*. 2013; 62:1154–62. <https://doi.org/10.1016/j.jacc.2013.05.050> PMID: 23770179
30. Cholesterol Treatment Trialists' (CTT) Collaboration, Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet*. 2010; 376:1670–81. [https://doi.org/10.1016/S0140-6736\(10\)61350-5](https://doi.org/10.1016/S0140-6736(10)61350-5) PMID: 21067804
31. Gitt AK, Lautsch D, Ferrieres J, Kastelein J, Drexel H, et al. Low-density lipoprotein cholesterol in a global cohort of 57,885 statin-treated patients. *Atherosclerosis*. 2016; 255:200–9. <https://doi.org/10.1016/j.atherosclerosis.2016.09.004> PMID: 27667299
32. Ferrieres J, De Ferrari GM, Hermans MP, Elisaf M, Toth PP, Horack M, et al. Predictors of LDL-cholesterol target value attainment differ in acute and chronic coronary heart disease patients: Results from DYSIS II Europe. *Eur J Prev Cardiol*. 2018; 25(18):1966–76. <https://doi.org/10.1177/2047487318806359> PMID: 30335504
33. Lemstra M, Blackburn D, Crawley A, Fung R. Proportion and risk indicators of nonadherence to statin therapy: a meta-analysis. *Can J Cardiol*. 2012; 28:574–80. <https://doi.org/10.1016/j.cjca.2012.05.007> PMID: 22884278
34. Wei MY, Ito MK, Cohen JD, Brinton EA, Jacobson TA. Predictors of statin adherence, switching, and discontinuation in the USAGE survey: understanding the use of statins in America and gaps in patient education. *J Clin Lipidol*. 2013; 7:472–83. <https://doi.org/10.1016/j.jacl.2013.03.001> PMID: 24079289
35. Taylor BA, Thompson PD. Statin-associated muscle disease: advances in diagnosis and management. *Neurotherapeutics*. 2018; 15:1006–17. <https://doi.org/10.1007/s13311-018-0670-z> PMID: 30251222
36. Stroses ES, Thompson PD, Corsini A, Vladutiu GD, Raal FJ, Ray KK, et al. Statin-associated muscle symptoms: impact on statin therapy—European Atherosclerosis Society consensus panel statement on assessment. Aetiology and management. *Eur Heart J*. 2015; 36:1012–22. <https://doi.org/10.1093/eurheartj/ehv043> PMID: 25694464
37. Sattar N, Preiss D, Murray HM, Welsh P, Buckley BM, de Craen AJ, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *Lancet*. 2010; 375:735–42. [https://doi.org/10.1016/S0140-6736\(09\)61965-6](https://doi.org/10.1016/S0140-6736(09)61965-6) PMID: 20167359
38. Nielsen SF, Nordestgaard BG. Negative statin-related news stories decrease statin persistence and increase myocardial infarction and cardiovascular mortality: a nationwide prospective cohort study. *Eur Heart J*. 2016; 37:908–16. <https://doi.org/10.1093/eurheartj/ehv641> PMID: 26643266
39. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, et al. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med*. 2015; 372:2387–97. <https://doi.org/10.1056/NEJMoa1410489> PMID: 26039521
40. Zhan S, Tang M, Liu F, Xia P, Shu M, Wu X. Ezetimibe for the prevention of cardiovascular disease and all-cause mortality events. *Cochrane Database Syst Rev*. 2018; 11:CD012502. <https://doi.org/10.1002/14651858.CD012502.pub2> PMID: 30480766
41. De Ferrari GM, Perna GP, Nicosia A, Guasti L, Casu G, et al. Available oral lipid-lowering agents could bring most high-risk patients to target: an estimate based on the Dyslipidemia International Study II—Italy. *J Cardiovasc Med*. 2018; 19:485–90.
42. Wang D, Liu B, Tao W, Hao Z, Liu M. Fibrates for secondary prevention of cardiovascular disease and stroke. *Cochrane Database Syst Rev*. 2015; 10:CD009580.
43. Cicero AFG, Landolfo M, Ventura F, Borghi C. Current pharmacotherapeutic options for primary dyslipidemia in adults. *Expert Opin Pharmacother*. 2019; 20:1277–88. <https://doi.org/10.1080/14656566.2019.1604687> PMID: 31059312
44. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J*. 2019; 41:111–88. <https://doi.org/10.1093/eurheartj/ehz455> PMID: 31504418
45. Jellinger PS, Handelsman Y, Rosenblit PD, Bloomgarden ZT, Fonseca VA, Garber AJ, et al. American Association of Clinical Endocrinologists and American College of Endocrinology guidelines for management of dyslipidemia and prevention of cardiovascular disease—executive summary. *Endocr Pract*. 2017; 23(4):479–97. <https://doi.org/10.4158/EP171764.GL> PMID: 28156151

46. Pucci G, Cicero AF, Borghi C, Schillaci G. Emerging biologic therapies for hypercholesterolaemia. *Expert Opin Biol Ther.* 2017; 17:1077–87. <https://doi.org/10.1080/14712598.2017.1341485> PMID: [28617192](https://pubmed.ncbi.nlm.nih.gov/28617192/)
47. Wang X, Luo S, Gan X, He C, Huang R. Safety and efficacy of ETC-1002 in hypercholesterolaemic patients: a meta-analysis of randomised controlled trials. *Kardiol Pol.* 2019; 77:207–16. <https://doi.org/10.5603/KP.a2019.0013> PMID: [30740643](https://pubmed.ncbi.nlm.nih.gov/30740643/)
48. Ruscica M, Reiner Z, Sirtori CR. Can we further optimize statin therapy to increase tolerability? *Expert Opin Drug Discov.* 2019; 14(9):843–7. <https://doi.org/10.1080/17460441.2019.1615436> PMID: [31096808](https://pubmed.ncbi.nlm.nih.gov/31096808/)
49. Evaluation of major cardiovascular events in patients with, or at high risk for, cardiovascular disease who are statin intolerant treated with bempedoic acid (ETC-1002) or placebo (CLEAR Outcomes). NCT02993406. *ClinicalTrials.gov.* 2016 Dec 15 [cited 2020 Jun 12]. Available from: <https://clinicaltrials.gov/ct2/show/NCT02993406>.