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The Latest Evidence on Bempedoic Acid: Meta-Analysis of Safety and Efficacy in High Cardiovascular Risk Patients with Hypercholesterolemia

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RESEARCH ARTICLE

The Latest Evidence on Bempedoic Acid: Meta-Analysis of Safety and Efficacy in High Cardiovascular Risk Patients With Hypercholesterolemia☆

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Abstract

Background: **Bempedoic Acid (BA) is a novel drug that has a potential to serve as an alternative to statins to decrease lipid levels and improve cardiovascular disease (CVD) outcomes, particularly for statin-intolerant individuals. However, insufficient statistical power has limited our understanding of the efficacy and safety of BA. This meta-analysis utilizes the latest data to improve our knowledge of BA's effects on lipids and CVD with increased statistical power.**

Methods: **MEDLINE, Embase, Cochrane Central, Clinicaltrials.gov, abstracts of national and international conferences, and reference lists of studies were searched for relevant studies. Rayyan was used to screen the search results, and Revman 5.3 was used for the meta-analysis and sensitivity analysis.**

Results: **Our final analysis included seven randomized control trials (RCTs) with 17,782 participants, 53.6 % in the BA group (n = 9535) and 46.4 % in the placebo group (n = 8247). BA significantly decreased major adverse cardiovascular events (MACE) (OR: 0.86; 95 % CI 0.78−0.95; p = 0.03), non-fatal myocardial infarction (OR 0.72; 95 % CI 0.61−0.85; p = 0.0001), and new onset/worsening diabetes (OR:0.55; 95 % CI 0.30−0.98, p = 0.04), while reducing low-density lipoprotein cholesterol (LDL-C) levels by 22.5 % (MD: −22.53 %; 95 % CI -25.54 to −19.52, p < 0.00001).**

Conclusion: **The findings of this meta-analysis suggest that BA is a promising and effective alternative to statin therapy, particularly for statin-intolerant and high CVD-risk patients. However, further studies with diverse populations are needed to quantify the long-term efficacy and safety endpoints.**

Keywords: BA, High cardiovascular risk, LDL-C levels, Safety, Efficacy, Meta-analysis

1. Introduction

It is widely recognized that high cholesterol levels increase the chances of developing cardiovascular disease, the leading cause of death across the globe.[1] One of the primary therapeutic goals for preventing cardiovascular disease is lowering LDL-C (low-density lipoprotein cholesterol). The AHA (American Heart Association) and the ESC (European Society of Cardiology) guidelines advise high-risk individuals to aim for a 50−55 % reduction in LDL-C levels as a rule of thumb.[2-4] Statins are the

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primary class of drugs used for reducing LDL-C, however some patients experience adverse effects, insufficient response, or intolerance.[5] This led to a need for alternative treatments for example: ezetimibe (EZ), PCSK9 inhibitors, and bile acid resins.[6] However, these therapies also have limitations, including variable tolerance, resistance, and limited availability, which has led to a need for a new therapeutic option.[7]

Bempedoic Acid (BA) is a novel oral anti-cholesterol drug that can be taken once a day.[7,8] By inhibiting cholesterol synthesis, BA indirectly upregulates hepatic LDL uptake receptors, leading to improved clearance of LDL, and ultimately decreasing LDL-C levels.[7,9] Additionally, BA has been shown to increase the expression of AMP-activated protein kinase, reducing inflammation throughout the body.[9] These two mechanisms make BA an especially favorable treatment option for managing high cholesterol levels.

BA received FDA and European Union approval three years ago for the management of heterozygous familial hypercholesterolemia (HeFH), and high-risk patients with atherosclerotic cardiovascular disease (ASCVD).[10-12] With the increasing need for a safe and effective adjunct to statin therapy, BA emerged as a potential option for reducing LDL-C levels with minimal adverse effects.

In a recent meta-analysis by Lin Y et al., the effectiveness of BA as a treatment for lowering lipids was evaluated using pooled data from 3956 patients.[13] However, the study did not produce significant findings in relation to cardiovascular outcomes, notably cardiovascular mortality, nonfatal myocardial infarctions, major adverse cardiovascular events (MACE), and all-cause death.[13] Since the publication of the CLEAR Outcomes trial,[14] the biggest clinical trial to date that discusses the safety and efficacy of BA, there is a need for an updated meta-analysis. We aim to provide the most recent and largest meta-analysis on safety and efficacy of BA in high cardiovascular risk patients.

2. Methods

This systematic review & meta-analysis follows the 2020 (PRISMA) Preferred reporting items for systematic reviews and meta-analysis statement.[15] The PRISMA 2020 checklist is reported in supplementary appendix 2.

2.1. Search and study selection

We performed a comprehensive search on April 29, 2023, using the following keywords: "Bempedoic acid," "nilemdo," "nexletol," "ETC-1002," "ESP55016," "ESP-55016," "cardiovascular disease," "Major Adverse Cardiac Events," "Cardiac Event*," and "Adverse Cardiac Event*." We searched Embase, Medline®, Clinicaltrials.gov, and Cochrane CENTRAL databases with no date restrictions. We also explored other grey literature databases and reviewed the references of relevant studies to identify any additional studies. There were no restrictions on article type or language in the initial search. The search results were uploaded to Rayyan®, and duplicates were removed.[16] Two reviewers (MAA and MA) screened the studies, and any conflicts were resolved by a senior reviewer (AAM). The complete search string for each individual database is given in supplementary appendix 1 (Table S1) (https://scholarlycommons.gbmc.org/cgi/editor.cgi?article=1305&window=additional_files&context=jchimp).

2.2. Eligibility criteria

In this study, we only included phase IIb and phase III randomized controlled trial (RCTs) discussing the efficacy as well as safety of BA. Patients 18 years & older with a history of hypercholesterolemia (fasting LDL-C at least more $\geq$ than 70 mg/dl) and either a high risk or history of cardiovascular disease, symptomatic peripheral arterial disease, and/or cerebrovascular disease were included. Trials with a minimum duration of one month and at least two arms of patients on lipid-modifying therapy were included. Observational studies, open label single arm studies and animal studies were excluded.

2.3. Data extraction and risk of bias assessment

Three reviewers (MAA, NK, AH) extracted data from the final included studies using a standardized data extraction table to ensure accuracy. Efficacy outcomes such as major adverse cardiovascular events (MACE), overall cardiovascular mortality, non-fatal myocardial infarction, change in LDL-C, as well as safety findings such as serious adverse events, muscular disorder, renal impairment, gout, and new onset or worsening of diabetes mellitus were extracted from the general study characteristics (author, year, participants, inclusion criteria, length of follow-up). Two reviewers (MAA and MA) used the Cochrane risk of bias tool (RoB 2) to assess bias regarding publication bias among the included RCTs.[17] As the number of studies included was less than 10, Egger's test and funnel plot were not

recommended.[18] A senior reviewer (RV) resolved any discrepancy in risk of bias.

2.4. Data synthesis and analysis

A fixed effect meta-analysis model with Mantel–Haenszel odds ratios (ORs) and the 95 % confidence intervals (CIs) was used for dichotomous efficacy and safety outcomes. One outcome (new advent or worsening diabetes mellitus), was analyzed using a random effects model because it had high heterogeneity.[19,20] We used odds ratio (OR) instead of relative risk (RR) for our results as the probability of the outcomes in treatment and control groups was less than 0.1 [21,22]. For the lipid level outcomes, a random effects models were used for the mean difference percent because of the high heterogeneity of studies.[19,20] Heterogeneity was assessed using the Higgins and Thompsons' I^2 and the Cochran's Q statistic. We also conducted a random-effects model analysis for each parameter in order to validate our findings. The Cochrane Collaboration Review Manager 5.3 (RevMan v.5.3) was used to perform all the analyses in our study.[23]

2.5. Sensitivity analyses

We anticipated that the variable follow-up of the included studies might offset the results. Thus, we classified studies with a follow-up period of three months or less as "short-term follow-up" and those with follow-up periods of more than 3 months as "long-term follow-up" and performed a predefined sensitivity analysis. One study Ballantyne, 2019[7] had four arms (BA, BA + ezetimibe, ezetimibe, and placebo). To avoid potential confounding of results, we excluded two of the four arms from our analysis, specifically the BA + EZ and EZ arms. These arms did not administer BA alone, which was the focus of our study.

2.6. Quality assessment

A GRADE assessment of the efficacy outcomes was conducted by two independent reviewers (AAM and HS) using GRADEpro GDT software.[24,25] Any discrepancies were resolved through mutual discussion.

3. Results

We retrieved 475 articles from searching the databases. Following identification and screening, the meta-analysis included 7 RCTs. The PRISMA flowchart depicted in Fig. S1 (https://scholarlycommons.gbmc.org/cgi/editor.cgi?article=1305&window=additional_files&context=jchimp) provides a full description of the search procedure.

3.1. General characteristics of included studies

This meta-analysis included a total of 17,782 individual participants from 7 RCTs, with 9535 individuals in the BA arm while 8247 individuals made up the control arm. The mean age ranged from 55.3 to 66.8 years, and the follow-up duration consisted of range 1 month–40.6 months. Of the total participants, 54.6 % (9710) were males, and 74.9 % (13,317) of participants completed their trials. The CLEAR Outcomes[14] (Nissen 2023) trial contributed the majority of participants (78.6 %, n = 13,970) in this meta-analysis. Six of the included trials were phase III ((CLEAR Tranquility[26] *(Ballantyne 2018)*; Clear Wisdom[27] *(Goldberg 2019)*; CLEAR serenity[28] (*Laufs 2019)*; CLEAR Harmony[8] (*Ray 2019)*; CLEAR Outcomes[14] *(Nissen 2023)*; Ballantyne,[7] 2019)), while one trial (Gutierrez et al.[29]) was a phase IIb trial. All trials were placebo controlled double-blind trials. All trials used a once daily dose of BA 180 mg except Gutierrez et al.[29] where BA was administered 80 mg per day for two weeks following which 120 mg per day was administered for two weeks. In two trials[26,28] (CLEAR Serenity and CLEAR Tranquility), the patients were placed on low-dose statin therapy. The population in five studies[7,8,14,27,28] (Ballantyne, 2019, CLEAR Harmony, CLEAR Outcomes, Clear Wisdom, and Gutierrez et al.) was high cardiovascular disease risk patients, and four studies[7,8,27,28] (Ballantyne, 2019, CLEAR Harmony, Clear Wisdom, and CLEAR Serenity) included patients with heterozygous familial hypercholesterolemia. Six trials had 2 arms (BA, placebo) while one trial[7] (Ballantyne, 2019) had 4 arms (BA, BA + EZ, EZ, Placebo). Details about general characteristics of included studies are given in Table 1 and details about participant characteristics are given in the supplementary appendix Table S2 (https://scholarlycommons.gbmc.org/cgi/editor.cgi?article=1305&window=additional_files&context=jchimp).

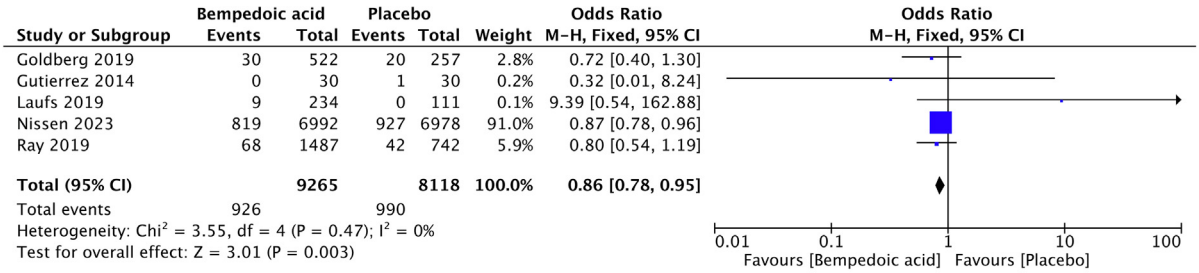
3.2. Efficacy outcomes of bempedoic acid

Efficacy of bempedoic acid was determined by analyzing the odds of primary RCT endpoints, in the bempedoic acid as compared to placebo group. Five RCTs (n = 17,383) reported MACE (major adverse cardiovascular events). BA a significantly reduced the odds of MACE vs placebo with an OR of 0.86; 95 % CI 0.78–0.95; p = 0.03; I^2 = 0 %. (Fig. 1 (i)).

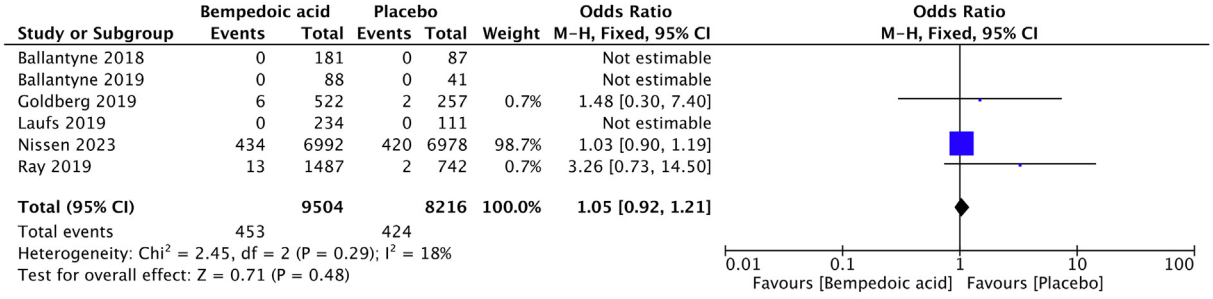
Table 1. General characteristics of included studies.

Study ID (Acronym)	First author, year	Study design	Phase	Centers	Follow-up (weeks)	Outcomes	Study arms	Sample size, n
NCT03001076 (CLEAR Tranquility)	Ballantyne, 2018 [26]	RCT (double-blind, placebo- controlled, parallel-group)	III	Multi center in USA	12	Primary: % Change From Baseline to Week 12 in LDL-C; Secondary: % Change From Baseline to Week 12 in TC, non-HDL-C, apoB, hs- CRP, TG and HDL-C	BA: 180 mg/day Placebo	181 88
NCT03337308	Ballantyne, 2019 [7]	RCT (double-blind, placebo- controlled, parallel-group)	III	Multi center in USA	12	Primary: % Change From Baseline to Week 12 in LDL-C; Secondary: % Change From Baseline to Week 12 in TC, non-HDL-C, apoB, hs-CRP	BA + EZE: 180 mg/day + 10 mg/day BA: 180 mg/day EZE: 10 mg/day Placebo	86 88 86 41
NCT02991118 (CLEAR Wisdom)	Goldberg, 2019 [27]	RCT (double-blind, placebo- controlled, parallel-group)	III	Multi-center in North America and Europe	52	Primary: % Change From Baseline to Week 12 in LDL-C; Secondary: % Change From Baseline to Week 24 in LDL-C; % Change From Baseline to Week 12 in TC, non-HDL-C, apoB and hs-CRP; 12 Week and 24 Week absolute change of LDL-C	BA: 180 mg/day Placebo	522 257
NCT01607294	Gutierrez, 2014 [29]	RCT (double-blind, placebo- controlled, parallel-group)	IIb	Single Center in USA	4	Primary: % change from baseline to week 4 in LDL-C; Secondary: % change from baseline to week 4 in TC, non-HDL-C, HDL-C and TG	BA: 80 mg/day for 2 weeks followed by BA: 120 mg/day for 2 weeks Placebo	30 30
NCT02988115 (CLEAR Serenity)	Laufs, 2019 [28]	RCT (double-blind, placebo- controlled, parallel-group)	III	Multicenter in USA and Canada	24	Primary: % change from baseline to week 12 in LDL-C; Secondary: % change from baseline to week 24 in LDL-C; % change from baseline to week 12 and 24 in TC, non-HDL-C, apoB, hs-CRP, HDL-C and TG; week 12 and week 24 absolute change of LDL-C	BA: 180 mg/day Placebo	234 111
NCT02993406 (CLEAR Outcome)	Nissen, 2023 [14]	RCT (double-blind, placebo- controlled, parallel-group)	III	Multi center in 32 countries	176	Primary: Four component MACE, Secondary: Three-component MACE, Fatal or non fatal MI, coronary revascularization, fatal oe non-fatal stroke, Death from CV causes, Death from any cause, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization, Five-component MACE, Hospitalization for unstable angina, New-onset type 2 diabetes mellitus	BA: 180 mg/day Placebo	6992 6978
NCT02666664 (CLEAR Harmony)	Ray, 2019 [11]	RCT (double-blind, placebo- controlled, parallel-group)	III	Multi Center in North America and Europe	52	Primary: Number of participants with treatment-related AEs; Secondary: % change from baseline to Week 12, 24 and 52 in LDL-C, non-HDL-C, TC, apoB and hs-CRP	BA: 180 mg/day Placebo	1488 742

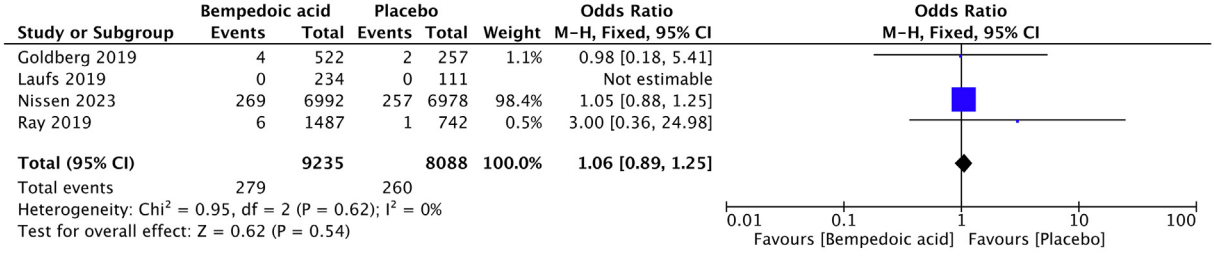
AEs: adverse events; apoB: apolipoprotein B; BA:Bempedoic acid; CV: cardiovascular; EZE: Ezetimibe; HDL-C: high-density lipoprotein cholesterol; hs-CRP: C-reactive protein high sensitivity; low-density lipoprotein cholesterol; MACE: major adverse cardiovascular events; RCT: randomized control trials; TC: total cholesterol; TG: triglycerides.



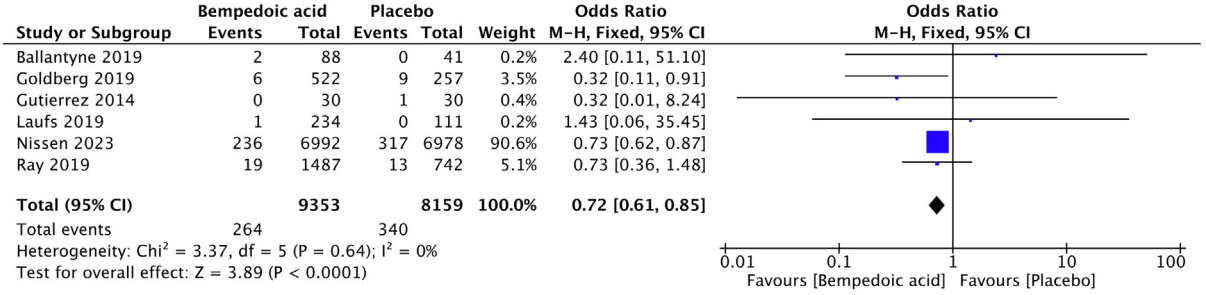
i) MACE



ii) All-cause mortality



iii) Cardiovascular mortality



iv) Non-fatal MI

Fig. 1. Pooled Odds ratio (OR) for efficacy outcomes of BA vs placebo.

The all-cause mortality and cardiovascular mortality outcomes of BA vs Placebo were not significant ((OR 1.05; 95 % CI 0.92–1.21; p = 0.48; I^2 = 18 %; 6 RCTS; 17,720 participants) (OR 1.06; 95 % CI 0.89–1.25; p = 0.54 I^2 = 0 %; 4 RCTs; 17,323 participants) respectively). (Fig. 1 (ii) (iii))

When compared to placebo, the risks of a non-fatal myocardial infarction were statistically

significantly lower after BA administration in the six RCTs with a total of 17,512 individuals. (OR 0.72; 95 % CI 0.61–0.85; p < 0.0001; I^2 = 0 %) (Fig. 1 (iv))

3.3. Safety outcomes of bempedoic acid

The incidence of certain side effects was evaluated in this meta-analysis. Between the BA and placebo groups, there were no discernible differences in the frequency of major adverse events. (OR 1.03; 95 % CI 0.96–1.10; p = 0.45; I^2 = 0 %; 6 RCTs; 17,715 participants) (Fig. 2 (i)).

BA demonstrated a significant reduction in the odds of new-onset or worsening diabetes mellitus in comparison to placebo (OR 0.55; 95 % CI 0.30–0.98; p = 0.04; I^2 = 84 %) across 5 RCTs, involving 17,568 participants. (Fig. 2 (ii)) The high heterogeneity observed (I^2 = 84 %) in this study, necessitated the use of a random-effects model to compute the odds ratio in this outcome.

Results showed that gout (OR 1.59; 95 % CI 1.29–1.96; p < 0.0001; I^2 = 0 %; 5 RCTs; 17,568 participants), elevated transaminases (OR 1.56; 95 % CI 1.31–1.86; p = <0.00001; I^2 = 0 %; 7 RCTs; 17,775 participants), and renal impairment (OR 1.38; 95 % CI 1.23–1.54; p = <0.00001; I^2 = 0 %; 5 RCTs; 17,568 participants) had a significantly higher probability of occurring in the BA group as compared to placebo (Fig. 2 (iii) (v) (vi)). Further analysis indicated that these effects did not differ significantly between studies, as indicated by an I^2 value of 0 % for each outcome. However, muscle-related adverse events did not differ significantly between participants receiving BA and those receiving placebo as shown in (Fig. 3(iv)).

3.4. Bempedoic acid vs placebo effects on lipid levels

The pooled mean difference in LDL-C for BA compared to placebo was found to be significant in 7 RCTs (MD = −22.53 %; 95 % CI -25.54 to −19.52, p < 0.00001; I^2 = 84 %; 17,781 participants). Similarly, in 7 RCTs (n = 17,741), the mean difference in total cholesterol was significant for BA compared to placebo (MD = −16.90 %; 95 % CI -19.62 to −14.18, p < 0.00001; I^2 = 87 %) (Fig. 4 (i)).

In terms of other lipid parameters, BA also showed a significant effect on apolipoprotein B showing a mean difference change of −14.6 %; 95 % CI -17.43 to −11.95, p < 0.00001; I^2 = 70 % in 5 RCTs (n = 3683) (Fig. 3 (iii)). For high density lipoprotein (HDL-C), the mean difference was −6.12 %; 95 % CI -6.76 to −5.48, p < 0.00001; I^2 = 14 % in 6 RCTs (n = 17,535) (Fig. 3 (iv)). Finally, in 7 RCTs (n = 17,747), the mean difference change in Non HDL-C cholesterol was −18.87 %; 95 % CI -21.70 to −16.04, p < 0.00001; I^2 = 82 % (Fig. 3 (v)).

3.5. Sensitivity analyses

Three studies (Ballantyne,[26] 2018; Ballantyne,[7] 2019; Gutierrez,[29] 2014) were identified as having a short-term follow-up and were subsequently removed from the sensitivity analysis. The remaining four studies included in the sensitivity analysis yielded identical results, thereby confirming that those three short-term studies did not significantly affect our results. The supplemental appendix 1's Fig. S2 (https://scholarlycommons.gbmc.org/cgi/editor.cgi?article=1305&window=additional_files&context=jchimp) contains specific figures outlining the outcomes of the sensitivity analysis.

3.6. Risk of bias

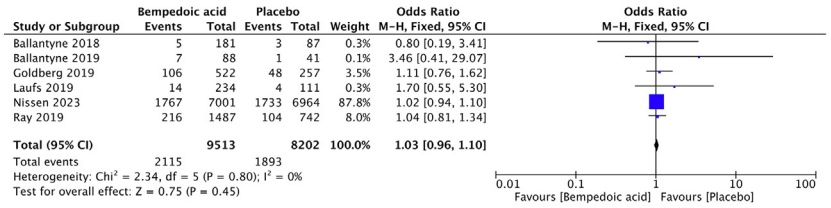
Three studies[8,14,26] were at low risk of bias for all categories. Selection bias was assess in all studies and revealed that three studies[7,28,29] had an unclear risk for random sequence generation and two studies[7,29] were at an unclear risk of allocation concealment. The study by Gutierez et al.[29] was at an unclear risk of bias in four category divisions (allocation concealment, Random sequence generation, blinding of outcome assessments and other bias. This study was removed from the sensitivity analysis on account of short follow-up. The figure for risk of bias is given in supplementary appendix in Fig. S3 (https://scholarlycommons.gbmc.org/cgi/editor.cgi?article=1305&window=additional_files&context=jchimp).

3.7. Quality assessment

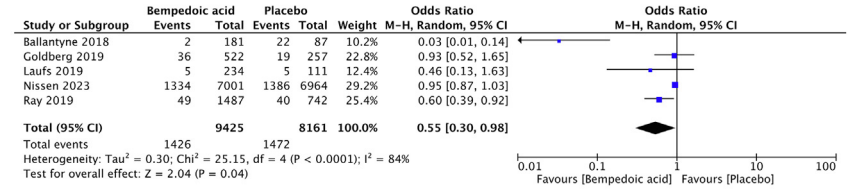
GRADE assessment for the efficacy outcomes showed a high certainty of evidence for MACE and non-fatal MI, moderate certainty of evidence for cardiovascular mortality, and low certainty of evidence for mortality. The GRADE certainty of evidence for clinicians is given in Fig. 4 and a detailed table is given in the supplementary appendix 1 (Tables S2a and S2b) (https://scholarlycommons.gbmc.org/cgi/editor.cgi?article=1305&window=additional_files&context=jchimp).

4. Discussion

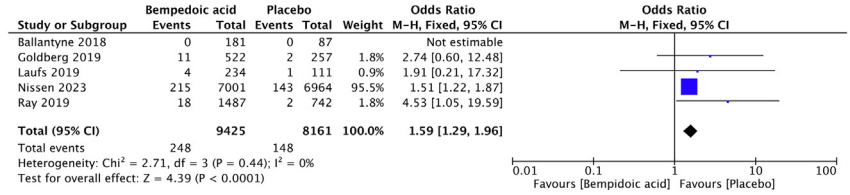
We conducted this meta-analysis of 7 RCTs to examine the safety and efficacy of BA in patients who have hypercholesterolemia and are either



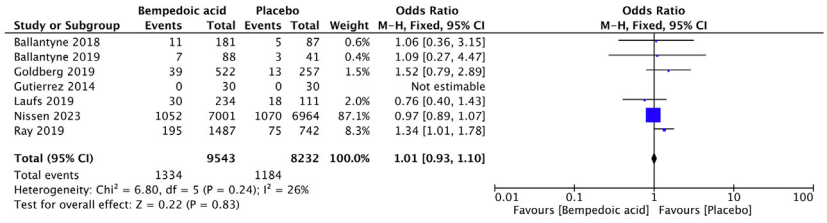
i) Serious adverse events



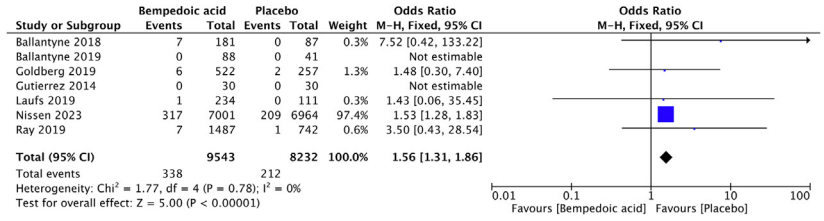
ii) New-onset and worsening of diabetes mellitus



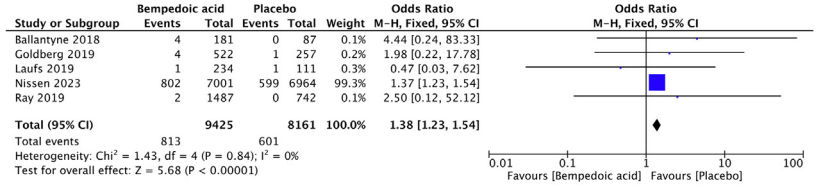
iii) Gout



iv) Muscle related adverse effects

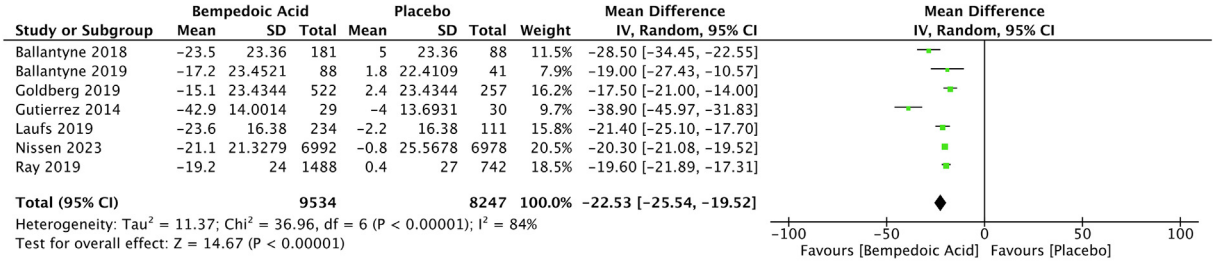


v) Elevated LFTs

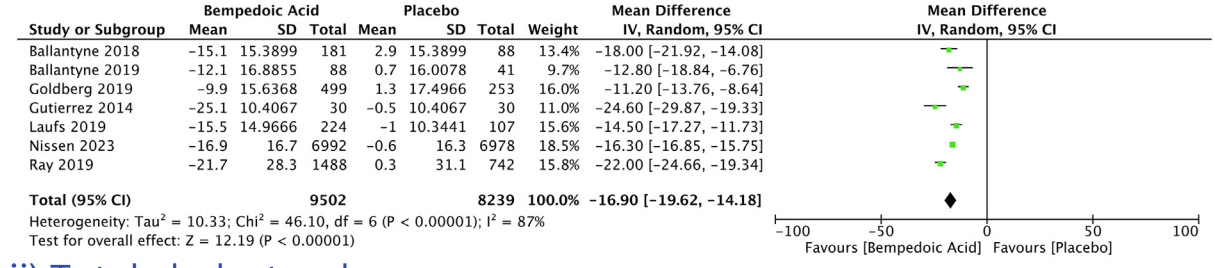


vi) Renal impairment

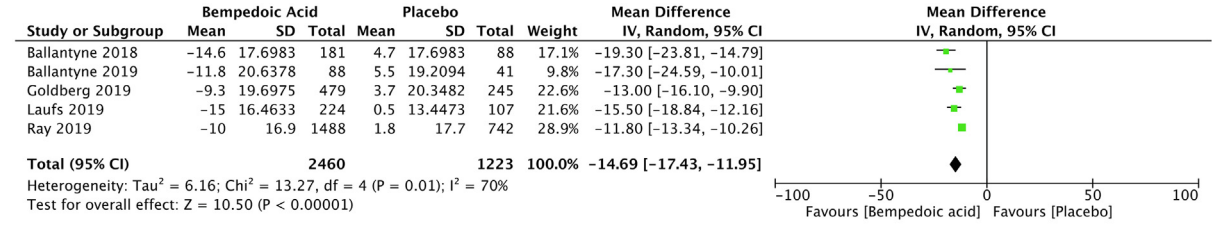
Fig. 2. Pooled Odds ratio (OR) for safety outcomes of BA vs placebo.



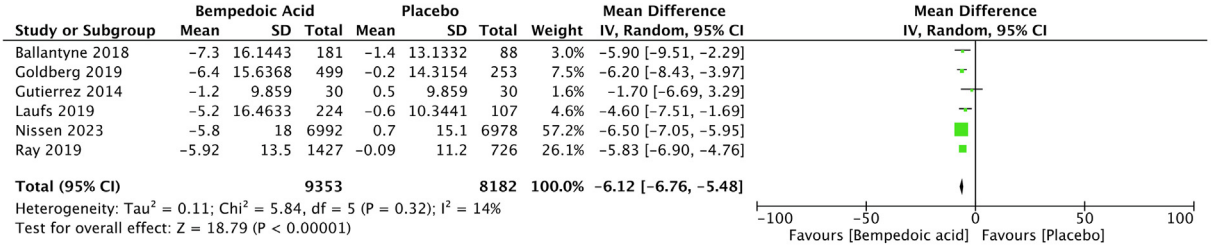
i) LDL-C



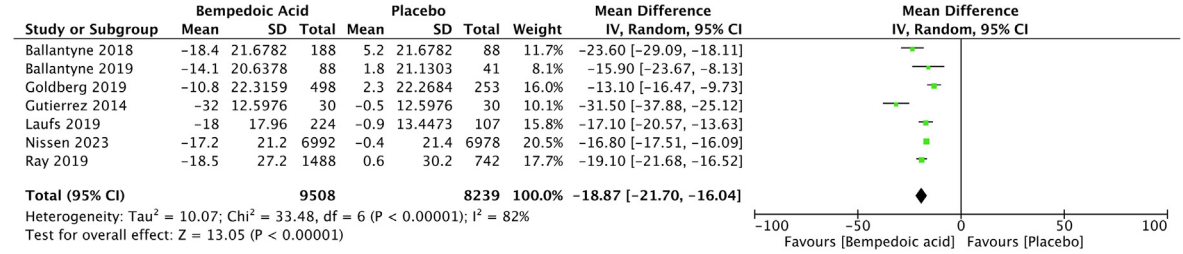
ii) Total cholesterol



iii) ApolIprotien B



iv) HDL-C



v) Non HDL-C

Fig. 3. Pooled % mean difference in lipid levels for BA vs Placebo.

statin intolerant or taking maximum dose statins and still require further control of their LDL-C levels. Our results showed that BA was able to lower LDL-C levels successfully compared to placebo. Moreover, we found that BA significantly reduced the odds of MACE and non-fatal MI. While BA was

Fig. 4. GRADE certainty of evidence for clinicians for BA vs placebo.

known to cause side effects, including gout, elevated transaminases, and renal impairment, we found no associations with serious adverse effects.

With our study, we hope to add to the existing literature on the clinical effectiveness and safety profile of BA. In comparison to a past meta-analysis conducted by Lin et al.,[13] which included six trials and 3956 participants, our meta-analysis analyzed data from 7 trials, including the recently published CLEAR Outcomes trial (Nissen 2023).[14] The CLEAR Outcomes is the largest trial of BA to date with a sample size of 17, 868 participants. Our study found a significant decrease in the odds of MACE in the BA group as opposed to the placebo, whereas Lin et al. could not demonstrate a significant reduction in MACE. We also found a more significant reduction in the odds of non-fatal MI with BA than the previous meta-analysis ($p < 0.0001$ vs $p = 0.05$, respectively). Both studies showed similar outcomes for new onset or worsening of DM and increased odds of side effects such as gout, elevated transaminases, and renal impairment with BA. However, our study had greater statistical power and significance in these outcomes due to the larger pooled sample size.

Furthermore, our meta-analysis showed highly significant results for the mean decrease in levels of LDL-C in the participants taking BA (BA) compared to the placebo. We found a 22.3 % reduction in the LDL-C levels with a p-value less than 0.00001. This result is more significant than the previous meta-analysis, which reported a 19.93 % reduction with a p-value of less than 0.01. This further strengthens the notion that BA is an effective adjunct/alternative to statins, especially in statin-intolerant or statin-resistant individuals and other anti-lipid medication. This LDL-C lowering effect is further augmented when used in combination with ezetimibe, as demonstrated by Ballantyne 2019.[7]

BA has been an emerging treatment for hypercholesterolemia for patients particularly susceptible to developing cardiovascular disease as a sequel of ASCVD or HeFH.[30] Our meta-analysis further confirms and acknowledges this concept as the common risk factor in most of the included RCTs was ASCVD or HeFH.

Muscle-related side effects are the most common reason for cessation of statin therapy in most patients.[31] Our meta-analysis shows that BA does not lead to increased chances of developing muscular

adverse effects compared to placebo, suggesting that it could be a viable option for patients who are intolerant to statins. While statins are associated with increasing the risk of developing diabetes mellitus,[31] our analysis suggests that BA may offer a more favorable safety profile. Specifically, our findings indicate that BA is associated with decreased odds of initial development or progression of diabetes mellitus, making this drug a potential alternative therapy for patients with hypercholesterolemia who are intolerant to statins or have comorbidities such as diabetes. These findings indicate that BA could have potential use in managing cardiovascular risk in high-risk patient populations and therefore warrants further investigation in future clinical studies. A recent meta-analysis by Mutschlechner et al. on the efficacy of BA in hypercholesterolemia patients showed similar reductions in cardiovascular events.[32] However, this meta-analysis did not discuss the safety profile or the effect of BA on lipid levels, unlike our study.

Combination lipid-lowering therapy is shown to play a role in treating patients more prone to developing cardiovascular complications, starting with the prescription of statin and ezetimibe.[33] If LDL-C levels are not sufficiently (<50 %) reduced, PCSK-9 targeted therapy or BA can be added.[33] For patient's intolerant to statins, ezetimibe in combination with PCSK-9 targeted therapy or BA is recommended.[33] Thus, BA has a role in high CVD-risk patients and patients intolerant to statins. Therefore, this study will help guide further evidence-based decision-making for using BA in specific high-risk populations.

Our study had some limitations such as the limited number of RCTs included in the analysis and the variable follow-up period among studies.[14] However, our sensitivity analyses were successful in addressing the issue of heterogeneity in the follow-up period and instead confirmed the robustness of our results. Another limitation of our study is that all the trials included were conducted in North America or Europe and predominantly on the white race (92 %), thus making it difficult to generalize the results for recommendations on a diverse population. The strength of our study lies in its large, pooled sample size, making it the most extensive meta-analysis to date regarding the safety and efficacy of BA.

5. Conclusion

This meta-analysis provides valuable insights into the efficacy and safety of BA for controlling the LDL-C levels in patients who have hypercholesterolemia in addition to being either statin-intolerant or requiring additional therapy. The significant reduction in LDL-C levels and the decreased odds of MACE and non-fatal MI with BA compared to placebo highlights its potential as a treatment option in these patient populations. Additionally, the absence of an increased risk of muscle-related adverse effects with BA is a significant advantage for patient's intolerant to statins. This absence of muscle-related side effects may also play a role in helping reduce non-compliance among patients who report muscle aches as a primary cause of non-compliance to statin therapy. Our meta-analysis provides a basis for future research and clinical decision-making and supports using BA in high-risk populations. However, it is important to look out for the results of ongoing trials (Europe, Japan and the USA) and conduct further RCTs with ethnically diverse populations, larger sample sizes and longer follow-ups to confirm the efficacy and safety of BA in diverse patient populations.

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