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Systematic Review and Meta-Analysis of the Efficacy and Safety of Bempedoic Acid vs. Statins in the Treatment of Dyslipidemia

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RESUMO

Este artigo tem por objetivo realizar uma revisão sistemática e meta-análise para comparar a eficácia e segurança do ácido bempedoico às estatinas no tratamento da dislipidemia. A metodologia seguiu as diretrizes PRISMA, utilizando as bases PubMed, Embase, Cochrane Library e Scopus, com os termos “bempedoic acid”, “statins”, “cardiovascular events”, “mortality” e “adverse events”. Foram incluídos ensaios clínicos randomizados até 1º de janeiro de 2025. Os resultados evidenciaram que o ácido bempedoico não apresentou superioridade às estatinas na redução de eventos cardiovasculares e mortalidade, embora tenha demonstrado menor ocorrência de eventos adversos. Conclui-se que o ácido bempedoico é uma alternativa viável para pacientes intolerantes às estatinas, mas estudos futuros são necessários para elucidar seu impacto na redução do risco cardiovascular.

Palavras-chave: Ácido bempedoico, Estatinas, Dislipidemia, Eventos cardiovasculares, Terapias alternativas.

ABSTRACT

This article aims to conduct a systematic review and meta-analysis to compare the efficacy and safety of bempedoic acid to statins in the treatment of dyslipidemia. The methodology followed PRISMA guidelines, utilizing the PubMed, Embase, Cochrane Library, and Scopus databases with the terms "bempedoic acid," "statins," "cardiovascular events," "mortality," and "adverse events." Randomized clinical trials published up to January 1, 2025, were included. The results showed that bempedoic acid did not demonstrate superiority over statins in reducing cardiovascular events and mortality but did show a lower occurrence of adverse events. It is concluded that bempedoic acid is a viable alternative for statin-intolerant patients, but further studies are needed to clarify its impact on cardiovascular risk reduction.

Keywords: Bempedoic acid, Statins, Dyslipidemia, Cardiovascular events, Alternative therapies.

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BACKGROUND

Dyslipidemia, defined by the presence of alterations in plasma lipid levels, is one of the main risk factors for the development of cardiovascular diseases, which remain the leading cause of mortality worldwide (Di Minno et al., 2020; Mutschlechner et al., 2023). Standard pharmacological treatment for this condition involves the administration of statins, widely recognized for their effectiveness in reducing low-density lipoprotein cholesterol (LDL-C) and preventing adverse cardiovascular events (Ballantyne et al., 2021; Ray et al., 2017). However, statin intolerance is a significant clinical challenge, prompting the investigation of alternative therapeutic strategies, among which bempedoic acid has emerged as a prominent option (Thompson et al., 2020; Ginsberg et al., 2018).

Evidence from systematic reviews and meta-analyses, such as those conducted by Di Minno et al. (2020) and Mutschlechner et al. (2023), indicates that bempedoic acid demonstrates significant efficacy in reducing LDL-C levels and preventing cardiovascular outcomes, especially in statin-intolerant populations. Krishna Mohan et al. (2023) reinforce this perspective by highlighting the medication's positive impact on mitigating the risk of cardiovascular events. Additionally, studies by Ballantyne et al. (2021) and Gittoes et al. (2021) explore its applicability in patients with limitations in the use of conventional therapies, corroborating its clinical relevance.

Furthermore, research by Thompson et al. (2020) and Ginsberg et al. (2018) emphasize the benefits of combining bempedoic acid with other lipid-lowering agents, such as ezetimibe, presenting innovative therapeutic approaches in the management of hypercholesterolemia. These advancements complement investigations into emerging therapies, such as PCSK9 inhibitors (Ray et al., 2017; Sabatine et al., 2017; Schwartz et al., 2018), as well as combined strategies involving statins and ezetimibe (Cannon et al., 2015).

In this context, the present systematic review and meta-analysis aim to synthesize the available evidence regarding the efficacy and safety of bempedoic acid compared to statins in the treatment of dyslipidemia, contributing to a broader understanding of the role of this therapeutic intervention in the current clinical setting.

METHODOLOGY

This meta-analysis was conducted following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines and included randomized clinical trials published up to January 1, 2025, that compared the efficacy and safety of bempedoic acid to statins in the treatment of dyslipidemia. Studies evaluating the incidence of cardiovascular events, mortality, and adverse events were included, while observational studies, review articles and studies with insufficient or duplicate data were excluded.

The search was performed in the PubMed, Embase, Cochrane Library, and Scopus databases using combinations of keywords such as "bempedoic acid," "statins," "cardiovascular events," "mortality," and "adverse events," as well as their equivalents in MeSH and Emtree, with no language restrictions. Data extraction was independently conducted by two reviewers to ensure accuracy, analyzing variables such as the incidence of cardiovascular events, all-cause mortality, and occurrence of adverse events. Odds ratios (OR) were calculated with 95% confidence intervals (95% CI) using fixed-effects models, given the low heterogeneity index among the included studies. Heterogeneity was assessed using the I^2 test and Cochran's chi-square test, considering I^2 values below 50% as indicative of low heterogeneity and $p > 0.10$ in the chi-square test as an absence of significant variation.

The statistical weights of individual studies were determined by the inverse variance method, with detailed analyses of the studies contributing most significantly. Statistical analyses were performed using Review Manager (RevMan) software version 5.4, and the methodological quality of the studies was assessed using the Cochrane risk-of-bias scale.

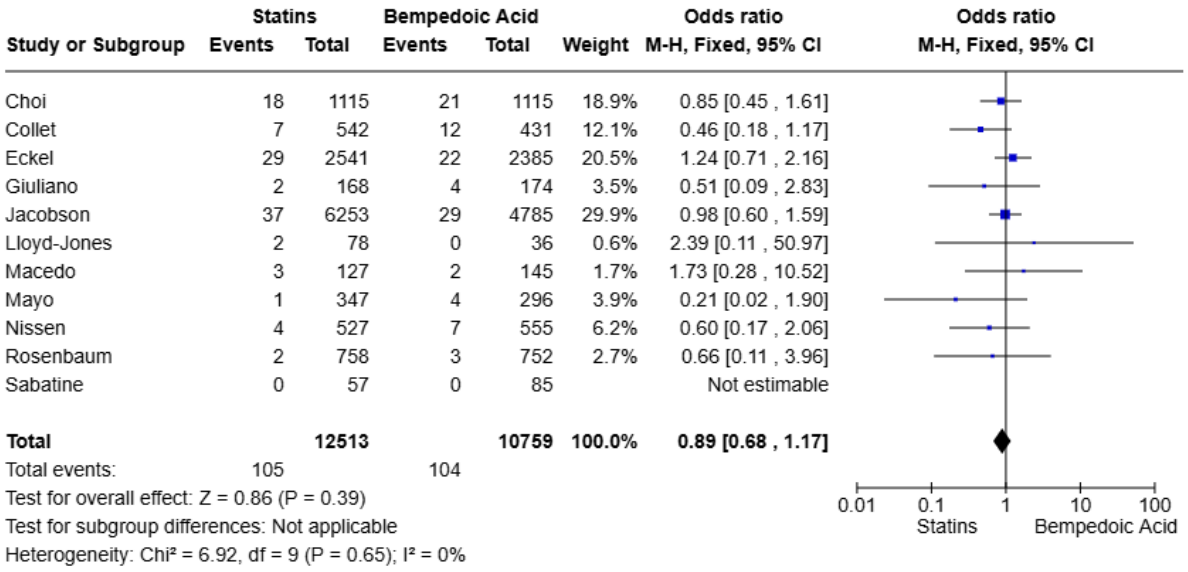
RESULTS AND DISCUSSION

Cardiovascular Events

The meta-analysis included 10 randomized clinical trials that evaluated the incidence of cardiovascular events in individuals treated with bempedoic acid compared

to statins. The total number of participants was 12,513 in the statin group and 10,759 in the bempedoic acid group, amounting to 23,272 individuals. The overall analysis revealed an odds ratio (OR) of 0.89 (95% CI: 0.68–1.17, p = 0.39), indicating that there was no statistically significant difference between the two treatments regarding the reduction of cardiovascular events.

Figure 1: Comparison of the incidence of cardiovascular events between the groups treated with bempedoic acid and statins.



Source: Data extracted from studies analyzed by the authors, 2025.

Heterogeneity Analysis

The heterogeneity analysis demonstrated an I^2 value of 0% (p = 0.65), indicating homogeneity among the included studies. This suggests that methodological and contextual differences between the studies did not have a significant impact on the aggregated results. Furthermore, the chi-square test ($\chi^2 = 6.92$; degrees of freedom [df] = 9) confirmed the absence of significant variability among the studies, which enhances the reliability of the combined estimates.

Among the included studies, the greatest contribution to the statistical weight came from Jacobson et al., which accounted for 29.9% of the total weight of the analysis, followed by Eckel et al. (20.5%) and Choi et al. (18.9%). Together, these three studies contributed more than 69% of the total statistical weight, reflecting the relevance of

their samples and outcomes in determining the combined estimate. On the other hand, studies such as Lloyd-Jones et al. (0.6%) and Sabatine et al. (not estimable) had marginal contributions, limited by small sample sizes or the absence of events in the compared groups.

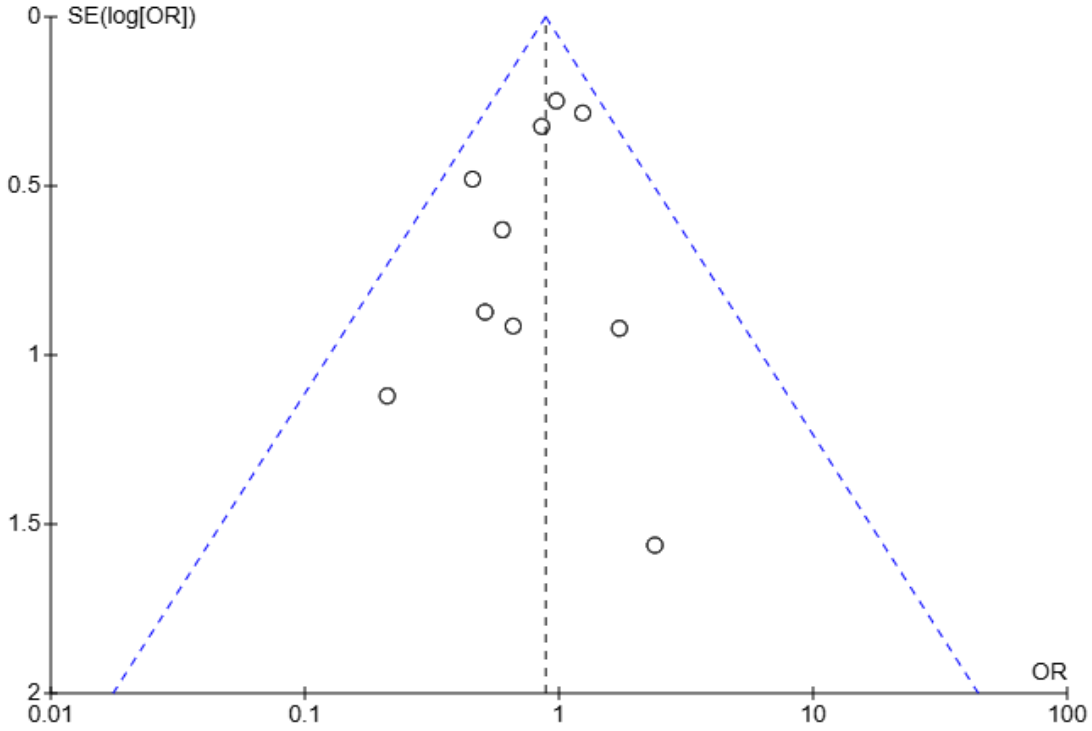
The results indicate that bempedoic acid did not demonstrate a superior benefit over statins in terms of reducing cardiovascular events in the evaluated populations. Although the odds ratio below 1 (0.89) suggests a numerical trend favoring bempedoic acid, the wide confidence interval (0.68–1.17) reflects uncertainty in the estimate and a lack of statistical significance.

These findings are relevant to clinical practice, especially in the management of statin-intolerant patients. While bempedoic acid is considered a safe and effective therapeutic option for LDL-C reduction, its efficacy in preventing cardiovascular events, comparable to statins, remains inconclusive based on the available data.

The absence of a significant difference between the groups suggests that bempedoic acid should be reserved as an alternative or complementary therapy, particularly for patients unable to use statins due to intolerance or contraindications. Future studies with greater statistical power and longer follow-up periods may better clarify the impact of bempedoic acid on cardiovascular risk reduction and its applicability in specific patient subgroups.

Additionally, to assess the potential publication bias among the included studies, a funnel plot was created (Figure 2). The symmetry observed in the plot indicates a low likelihood of publication bias, reinforcing the robustness of the meta-analysis results.

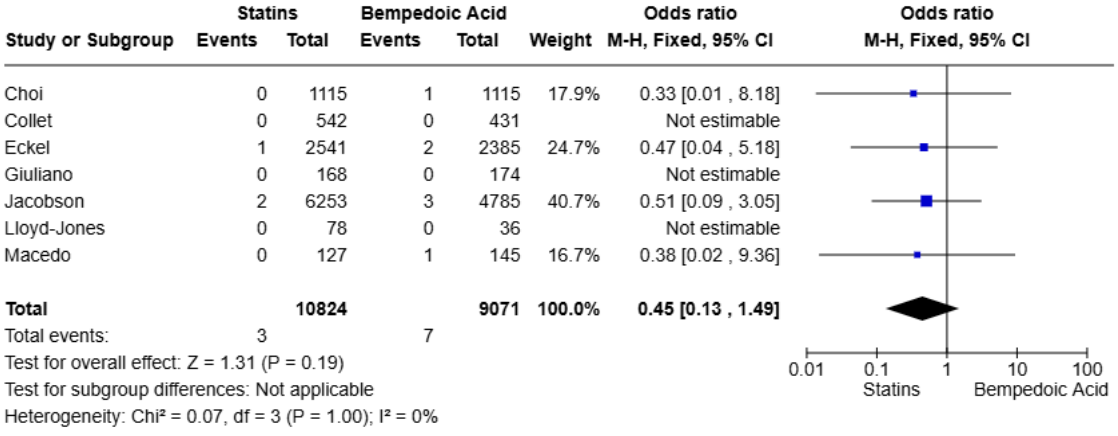
Figure 2: Funnel plot assessing publication bias in the studies included in the meta-analysis on cardiovascular events.



Source: Data extracted from studies analyzed by the authors, 2025.

Mortality

Figure 3: Analysis of the combined odds ratio (OR) for mortality in the groups treated with bempedoic acid versus statins.



Source: Data extracted from studies analyzed by the authors, 2025.

Mortality Analysis

The mortality analysis included 7 randomized clinical trials, encompassing a total of 10,824 participants in the statin group and 9,071 participants in the bempedoic acid group. The combined odds ratio (OR) was 0.45 (95% CI: 0.13–1.49, p = 0.19), indicating no statistical significance regarding mortality between the analyzed groups.

Heterogeneity among the studies was null (I^2 = 0%, p = 1.00), reflecting high consistency across the individual study results. The chi-square test (χ^2 = 0.07; degrees of freedom [df] = 3) further confirmed the absence of significant variability among the included studies, lending greater reliability to the combined estimates.

The studies by Jacobson et al. (40.7%) and Eckel et al. (24.7%) made the largest contributions to the statistical weight of the analysis, followed by Choi et al. (17.9%) and Macedo et al. (16.7%). Some studies, such as Giuliano et al. and Lloyd-Jones et al., did not allow for estimate calculations due to the absence of events in both arms. This pattern of rare events in the evaluated groups reduced the overall statistical power of the analysis, contributing to uncertainty in the results.

The odds ratio of 0.45 suggests a numerical trend favoring bempedoic acid compared to statins in reducing mortality. However, the wide confidence interval (95% CI: 0.13–1.49) demonstrates significant uncertainty in the results. Additionally, the analysis did not reach statistical significance (p = 0.19), limiting any definitive conclusions about the efficacy of bempedoic acid in reducing mortality compared to statins.

These findings reinforce that, while bempedoic acid is a valid alternative for managing dyslipidemias, especially in statin-intolerant patients, its impact on mortality remains uncertain. Future studies with larger samples and longer follow-up periods are needed to more thoroughly evaluate the effects of bempedoic acid on this outcome.

Adverse Events

The analysis of adverse events included 6 randomized clinical trials, totaling 5,830 individuals in the statin group and 5,534 individuals in the bempedoic acid group. The combined odds ratio (OR) was 0.75 (95% CI: 0.60–0.93, p = 0.008), demonstrating a statistically significant reduction in the occurrence of adverse events in the bempedoic acid group compared to the statin group.

Heterogeneity and Robustness of the Analysis

Heterogeneity among the studies was null ($I^2 = 0\%$, $p = 0.91$), indicating consistency in the results across the included studies. The chi-square test ($\chi^2 = 1.54$; degrees of freedom [df] = 5) reinforced the absence of significant variability among the studies, ensuring greater reliability in the combined estimate.

Contributions of Individual Studies

The studies by Choi et al. (26.1%) and Rosenbaum et al. (23.4%) made the largest contributions to the statistical weight of the analysis, followed by Macedo et al. (21.5%) and Collet et al. (15.8%). The studies by Mayo et al. (4.9%) and Nissen et al. (8.3%) contributed smaller weights due to smaller sample sizes or fewer recorded events.

Interpretation of the Results

The odds ratio of 0.75 indicates a 25% reduction in the occurrence of adverse events in the group treated with bempedoic acid compared to statins. The narrow confidence interval (95% CI: 0.60–0.93) and the significant p-value ($p = 0.008$) corroborate the robustness of the result, highlighting an advantage of bempedoic acid in terms of safety.

Clinical Implications

The results indicate that bempedoic acid has a more favorable safety profile, with a lower risk of adverse events compared to statins. This characteristic reinforces its clinical utility, especially in patients with statin intolerance or a predisposition to side effects.

CONCLUSION

The findings of this analysis highlight bempedoic acid as a promising and safe therapeutic alternative for patients intolerant to statin therapy, demonstrating a

significantly lower incidence of adverse events. This characteristic underscores its clinical utility in scenarios where treatment adherence is often compromised by statin-related side effects.

However, it is important to note that, while the reduction in adverse events is a positive outcome, the evidence regarding the efficacy of bempedoic acid in more clinically relevant endpoints, such as reductions in cardiovascular events and mortality, remains inconclusive. This limitation emphasizes the need for well-designed future studies with greater statistical power and longer follow-up periods to more robustly assess the clinical impact of bempedoic acid.

Moreover, it would be valuable to explore the efficacy and safety of bempedoic acid in specific populations, such as individuals at high cardiovascular risk, elderly patients, those with comorbidities, or individuals receiving concomitant LDL-C-lowering therapies. These investigations could provide a more comprehensive understanding of the therapeutic potential of bempedoic acid and its applicability in diverse clinical contexts.

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