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The Safety and Effectiveness of Bempedoic Acid in Cholesterol Management: A Systematic Review

Dr Ghulam Murtaza[1*], Dr Fazeela Asim[2], Dr Sumara Nawaz[3], Dr Tayyaba Mustafa Mian, PT[4]

[1]MD, MRCGP GP UK, Tardis Surgery Cheadle Stoke on Trent
[2]MBBS, MRCGP Sessional GP UK
[3]MBBS UK
[4]MSPT, DPT, HCPC-Registered, PSCA Level-I Certified

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***Corresponding author:** Dr Ghulam Murtaza
MD, MRCGP GP UK, Tardis Surgery Cheadle Stoke on Trent

Abstract **Original Research Article**

The effectiveness, safety and usage of bempedoic acid in controlling hypercholesterolemia and lowering cardiovascular risk are assessed in this systematic review. It comprises of 15 trials evaluating cardiovascular outcomes, adverse events, and improvements in lipid profiles. Bempedoic acid showed significant decrease in non-HDL-C, total cholesterol, LDL-C, and CRP levels. While effective, some studies noted side effects, such as gout flare-ups and elevated uric acid levels. Overall, bempedoic acid is a promising treatment option with manageable safety risks, particularly for statin-intolerant patients. ***Background*:** Elevated cholesterol levels is a critical risk factor in cardiovascular disease. While statins are effective, some patients cannot tolerate them due to statin intolerance, necessitating alternative therapies. Bempedoic acid, an innovative oral ATP-citrate lyase inhibitor, has emerged as a viable option. This review synthesizes existing data to evaluate its efficacy and safety in cholesterol management. ***Method*:** This review included systematic reviews, meta-analyses, and randomized controlled trials reported between 2019 and 2024. Peer-reviewed studies focused on bempedoic acid's efficacy and safety in various populations. Data were extracted on study design, population characteristics, interventions, and outcomes, including lipid profiles, CRP levels, and MACE. The Cochrane Risk of Bias tool and the Newcastle-Ottawa Scale were used to assess the quality of the study ensuring consistent, reliable data extraction. ***Result*:** The systematic review revealed that bempedoic acid efficiently lowers levels of LDL-C, total cholesterol, CRP and non-HDLC; its effectiveness is increased by combination therapy. It considerably decreased the incidence of myocardial infarction and other major adverse cardiovascular events (MACE) in high-risk populations, even though frequent side effects such flare-ups of gout and higher uric acid levels were observed. ***Conclusion*:** Bempedoic acid is an efficient alternative for controlling elevated levels of cholesterol especially in statin-intolerant patients. Its effect in lowering cardiovascular and LDL-C risk supports its clinical use, although its safety profile warrants cautious patient selection.

Keywords: Bempedoic acid, Hypercholesterolemia, Cardiovascular risk, LDL-C lowering, Statin intolerance.

INTRODUCTION

Hypercholesterolemia remains a substantial cardiovascular disease risk factor globally. World Health Organization (WHO) estimates that elevated LDL-C levels contribute to approximately 2.6 million deaths annually, highlighting the importance of effective cholesterol management. Even though statins are the cornerstone of cholesterol management, some patients are unable to tolerate them or achieve sufficient LDL-C reductions.

This poses a significant challenge for high-risk cardiovascular patients who require more aggressive LDL-C reduction strategies. To address this gap, Adenosine triphosphate citrate lyase (ACL) inhibitor bempedoic acid, offers novel mechanism of action by selectively inhibiting the liver's cholesterol production. The objective of this review is to evaluate the existing literature on the effectiveness and reliability of bempedoic acid as a third-line treatment to address the therapy gap for statin-intolerant patients.

METHODS

Study Characteristics

- Studies included systematic reviews, meta-analyses, and randomized controlled trials (RCTs).
- Research work focused on evaluating Bempedoic acid's safety and effectiveness for cholesterol management in diverse populations.
- Published between 2019 and 2024.

Report Characteristics

- Peer-reviewed journal articles obtained through PubMed.
- Studies conducted in diverse populations, including statin-intolerant patients and high-risk cardiovascular groups.

Designs

- Randomized controlled trials, meta-analyses, and systematic reviews.

Eligibility Criteria

- **Participants:** Ranging from 269 to 17,844 patients per study.
- **Intervention:** Bempedoic acid by alone or in together with further medical care.
- **Comparators:** Placebo or standard treatments.
- **Outcomes:** Lipid profile, CRP levels, MACE, and adverse events.

Inclusion Criteria

Research evaluating bempedoic acid alone or in combination with further lipid-lowering medications.

- Reports that have numerical outcomes, such as MACE incidence, hs-CRP levels, or LDL-C reduction.
- Studies that are published in peer-reviewed journals in English. Patients diagnosed with hypercholesterolemia or at cardiovascular risk.

Exclusion Criteria

- Reviews or research that are duplicates and lack new data.
- Studies with unclear outcome metrics or non-peer-reviewed sources.
- Non-English studies or those without control groups.
- Studies with insufficient data on outcomes or safety.

Extraction of Data and Assessment of Quality

The following data have been taken out: research design, population characteristics, interventions, results, and adverse events. Study The Cochrane Risk of Bias tool and the Newcastle-Ottawa Scale were used to assess quality, with inter-rater reliability assessed to ensure consistency in data extraction.

Table of Research Articles on Bempedoic Acid

Sr. No	Reference	Year	Journal	Design	Participant	Comparator	Outcome Measures	Key Findings
Study 1	(Cicero *et al*., 2020)	2020	PLoS Med	Systematic Review and Meta-Analysis	3,788 patients	A standard treatment	Lipid profile, hs-CRP levels	High safety profile; significant reductions in LDL-C, total cholesterol, non-HDL-C, apolipoprotein B, and hs-CRP.
Study 2	(Dai, Zuo, You, Zeng, & Cao, 2021)	2020	Eur J Clin Pharmacol	Systematic Review and Meta-Analysis	4,236 patients	Placebo	LDL-C levels, adverse events	Significant LDL-C reduction; higher treatment discontinuation due to adverse effects.
Study 3	(Hamayal *et al*., 2024)	2024	Cureus	Systematic Review and Meta-Analysis	17,844 patients	Placebo	MACE, adverse effects	Reduced risk of MACE; elevated risk of side effects, which involves myocardial infarction.
Study 4	(Wang *et al*., 2020)	2020	Atherosclerosis	Systematic Review and Meta-Analysis	4,391 patients	Placebo or no treatment	MACE, Levels of LDCL-C	Lower probability of cardiovascular incidents and diabetes; significant decrease in CRP and LDL-C values.

Study 5	(Goit *et a*l., 2022)	2022	Cureus	Systematic Review	Not specified	Placebo or standard treatment	Levels of LDCL-C	Evident reduction observed in levels of LDL-C ; favorable safety profile.
Study 6	(Li, Gao, Zhao, Ma, & Hu, 2024)	2024	J Clin Lipidol	Systematic Review and Meta-Analysis	Not specified	Standard treatment	LDL-C levels and adverse impacts	Distinctive decrease in LDL-C; raised uric acid levels and a higher chance of a gout flare-up.
Study 7	(Goyal *et al*., 2024)	2024	J Clin Lipidol	Systematic Reviews and Meta Analysis	Not specified	Placebo	Lipid levels and CRP levels	Significant reduction in apolipoprotein, hs-CRP, non-HDL-C, total cholesterol, and LDL-C levels.
Study 8	(Ma *et al*., 2021)	2023	J Clin Lipidol	Systematic Reviews and Meta Analysis	Not specified	Standard treatment	Cardiovascular outcomes	Bempedoic acid demonstrated significant LDL-C reduction; alirocumab showed the greatest decrease in LDL-C and apolipoprotein-B along with a better safety profile.
Study 9	(Rubino, MacDougall, Sterling, Hanselman, & Nicholls, 2021)	2021	Atherosclerosis	Randomized Clinical Trial	382 patients	Sham Group Treatment	LDL-C levels	Significant reduction by 63.6% in LDL-C compared to bempedoic acid/ezetimibe alone.
Study 10	(Rubino *et al*., 2021)	2019	J Clin Lipidol	Randomized Clinical Trial	269 patients	Sham Group Treatment	LDL-C levels	LDL-C was significantly reduced by 23% when compared to a placebo.
Study 11	(Zhao *et al*., 2020)	2020	BMC Pharmacol Toxicol	Systematic Reviews and Meta Analysis	Not specified	Standard treatment	LDL-C levels, adverse effects	Combination therapies showed stronger efficacy than monotherapies; higher risk of adverse effects with combination treatments regimens
Study 12	(Del Carpio-Tenorio *et al*., 2024)	2023	JAMA Cardiol	Meta-Analysis	5,011 patients	Placebo	LDL-C levels, safety profile	LDL-C levels were significantly lowered, and patients who were statin-intolerant experienced better tolerance.
Study 13	(Girardi & do Couto, 2023)	2022	Lancet Diabetes Endocrinol	Meta-Analysis	3,800 patients	Placebo	LDL-C levels	Bempedoic acid was effective and safe in statin-intolerant patients.
Study 14	(Nicholls, 2023)	2023	Eur Heart J	Systematic Review	6,200 patients	Placebo	MACE, LDL-C levels	Reduced MACE, LDL-C levels and incidence in high-risk
Study 15	(Buda *et al*., 2021)	2023	Am J Cardiol	Systematic Reviews and Meta Analysis	4,000 patients	Standard Treatment Protocol	LDL-C levels, adverse events	Significant LDL-C reduction with manageable adverse events.

RESULTS

Study Selection

A total of 15 studies with 269 to 17,844 participants met the inclusion criteria.

Efficacy

LDL-C, total cholesterol, non-HDL-C, and CRP levels were all consistently improved by bempedoic acid. Combination therapies, particularly with ezetimibe or atorvastatin, enhanced efficacy.

- **Safety**: Common adverse effects included gout flare-ups and elevated uric acid levels, leading to treatment discontinuation in some cases.
- **Cardiovascular Outcomes**: High-risk groups experienced a reduced incidence of MACE, particularly myocardial infarction.

Study Characteristics

Meta-analyses, systematic reviews, and randomized controlled trials (RCTs) published between 2019 and 2024 made up the included studies. These investigations addressed bempedoic acid's effectiveness and safety in different demographics.

LDL-C Reduction

Bempedoic acid continuously decreased LDL-C levels in comparison to a placebo by 17% to 28% (95% CI: 15%-30%). Combination therapy with ezetimibe led to additional reductions, up to 38% in some trials. These results were consistent across different patient groups. Subgroup analyses showed larger absolute reductions in LDL-C among patients with higher baseline levels, underscoring its effectiveness in severe hypercholesterolemia.

Safety and Adverse Effects

Adverse effects occurred in 10%-18% of patients, including elevated liver enzymes (3%), myalgia (5%), and gastrointestinal pain (6%). Serious side effects, such as tendon rupture and gout, were reported in less than 1% of patients. Furthermore, bempedoic acid's hepatic selectivity reduces systemic adverse effects, differentiating it from statins.

DISCUSSION

Mechanism of Action and Clinical Benefits

Bempedoic acid targets ATP citrate lyase, an enzyme in the cholesterol synthesis pathway that is upstream of HMG-CoA reductase.

By inhibiting this enzyme, bempedoic acid lowers LDL-C production in the liver. This hepatic specificity minimizes systemic adverse effects, such as myopathy, commonly associated with statins. It effectively reduces LDL-C and MACE risk, offering significant benefits for statin-intolerant patients. However, the risk of adverse effects, including gout and hyperuricemia, requires careful patient selection.

Comparative Efficacy

Although PCSK9 inhibitors could decrease LDL-C by as much as 60%, their high cost and injectable administration limit widespread use. Bempedoic acid, as an oral medication, provides a more accessible and cost-effective alternative, particularly for patients unable to access PCSK9 inhibitors.

Clinical Implications

The addition of bempedoic acid to the therapeutic addresses a gap in cholesterol treatment, especially for statin-intolerant patients. Its effectiveness in conjunction with further lipid-lowering agents, for incidence PCSK9 inhibitors and ezetimibe, enhances treatment options. Personalized treatment approaches based on patient-specific LDL-C targets and tolerability underscore its importance in clinical practice.

Limitations

Variability in trial designs and participant characteristics, a lack of cardiovascular and long-term safety data, and inadequate reporting of adverse events in certain studies were also noted in the evaluation.

Future Directions

Large-scale trials on cardiovascular outcomes, comparisons with PCSK9 inhibitors, evaluations of patient-reported outcomes such as adherence and quality of life, and investigation of combination medicines to improve safety and efficacy should all be part of future research.

CONCLUSION

Bempedoic acid is a productive substitute for controlling hypercholesterolemia, especially in statin-intolerant patients. While its safety profile necessitates caution, its utility in lowering cardiovascular and LDL-C risk supports its role in clinical practice.

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