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Bempedoic acid in the current era of lipid management

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Abstract

Bempedoic acid, a first-in-class adenosine triphosphate-citrate lyase inhibitor, significantly advances lipid management. This review examines the clinical evidence, efficacy, and safety profile of bempedoic acid based on major clinical trials and recent meta-analyses. The CLEAR trials program demonstrated significant low density lipoprotein cholesterol (LDL-C) reductions ranging from 17-28.5% across different patient populations, with the CLEAR outcomes trial showing a 13% reduction in major adverse cardiovascular events. Meta-analyses have confirmed these findings, showing consistent LDL-C reductions and cardiovascular benefits, particularly in statin-intolerant patients. The medication's unique liver-specific activation mechanism contributes to reduced muscle-related side effects compared to statins. Current guidelines from both the American College of Cardiology and the European Society of Cardiology position bempedoic acid as a valuable option for high-risk patients requiring additional LDL-C lowering, especially those who are statin-intolerant or unable to achieve goals with maximally tolerated statin therapy. Bempedoic acid demonstrates a generally favourable safety profile, monitoring is recommended for potential adverse effects including elevated uric acid levels and liver enzymes.

Keywords: Bempedoic Acid; Lipid Management; Cardiovascular Outcomes; Adenosine Triphosphate-Citrate Lyase (ACL)

1. Introduction

Bempedoic acid is a first-in-class adenosine triphosphate-citrate lyase (ACL) inhibitor that reduces cholesterol synthesis in the liver and lowers low density lipoprotein cholesterol (LDL-C) levels by upregulating LDL receptor expression. Bempedoic acid was first approved by the FDA in the United States in February 2020 [1] and received marketing authorisation in the European Union in April 2020 [2]. In India, it was launched in June 2023 under Bemacip [3]. Based on clinical evidence, bempedoic acid is indicated for adults with heterozygous familial hypercholesterolemia or established atherosclerotic cardiovascular disease (ASCVD) who require additional LDL-C lowering despite maximally tolerated statin therapy, making it particularly valuable for statin-intolerant patients or those who experience muscle-related side effects with statins [4].

1.1. Clinical Evidence

Following clinical trials have demonstrated the efficacy of bempedoic acid in reducing LDL-C levels. These studies have shown significant reductions in LDL-C, especially in patients who are intolerant to statins.

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Table 1 Phase III clinical trials on Bempedoic acid

Phase III Clinical trials	Trial details	Relative Risk (RR)
CLEAR Serenity (July 2016) [5]	A trial specifically studied 345 statin-intolerant patients. Demonstrated 21.4% LDL-C reduction with bempedoic acid vs placebo over 24 weeks.	RR reduction of about 23% in LDL-C levels at 12 weeks. The trial showed good tolerability in patients who previously couldn't take statins.
CLEAR Wisdom (July 2016) [6]	A 52-week trial included 779 high-risk patients with ASCVD or heterozygous FH on maximally tolerated statin therapy.	RR reduction of 17.4% in LDL-C levels compared to placebo at 12 weeks. The trial demonstrated sustained efficacy over 52 weeks.
CLEAR Tranquility (August 2016) [7]	Studied bempedoic acid in combination with ezetimibe in 269 patients with high LDL-C who were statin-intolerant. Showed 28.5% additional LDL-C reduction vs ezetimibe alone.	RR reduction of 28.5% in LDL-C compared to ezetimibe alone, demonstrating the additive benefit of combining these medications.
CLEAR Harmony (November 2016) [8]	A 52-week trial included 2,230 patients with ASCVD and/or heterozygous familial hypercholesterolemia on maximally tolerated statin therapy.	Reduction of 18.1% in LDL-C levels compared to placebo. The study demonstrated long-term safety and sustained efficacy over 52 weeks.
CLEAR Outcomes (December 2016) [9]	The most significant cardiovascular outcomes trial involved 13,970 statin-intolerant patients over 3.4 years.	Risk Ratio reduction of 13% in major adverse cardiovascular events (MACE) compared to placebo. This included a 23% reduction in heart attacks and a 19% reduction in coronary revascularization procedures. The trial was notable for being the first to demonstrate cardiovascular benefit with bempedoic acid in statin-intolerant patients.

Table 2 Recent systematic review and meta-analysis on Bempedoic acid

Author Name (year)	Results
Li et al (2024) [10] Included 16 Randomized Controlled Trials (RCTs)	Bempedoic acid treatment reduced low-density lipoprotein cholesterol levels more than placebo (mean difference -2.97%, 95% confidence interval [CI] -5.89% to -0.05%) The risk of death (Odds ratio [OR] 1.18, 95% CI 0.70 to 1.98) and muscle-associated occurrences (OR 1.00, 95% CI 0.77 to 1.31) was not impacted by bempedoic acid. Discontinuation of treatment was more frequently caused by adverse events in the bempedoic acid group (OR 1.13, 95% CI 1.01 to 1.27).
Afzal et al (2024) [11] 17,782 participants from 7 RCTs, 53.6 % in the Bempedoic acid (BA) group (n = 9535) and 46.4 % in the placebo group (n = 8247).	Decreased 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 LDL-C levels by 22.5 % (mean difference [MD]: −22.53 %; 95 % CI -25.54 to −19.52, p < 0.00001)
Goyal et al (2023) [12] 5 RCTs with a total of 18,848 participants.	Bempedoic acid showed a significant reduction in LDL-C [Least-square mean (LSM) difference in %: -25.24; 95 % CI: -30.79 to -19.69; p < 0.00001], total cholesterol [LSM difference in %:-21.28; 95 % CI:-30.58 to-11.98; p < 0.00001], non-HDL-C [LSM difference in %: -23.27; 95 % Cl: -29.80 to -16.73 p < 0.00001], and HDL-C [LSM difference in %:-3.37, 95 % CI:-3.73 to-3.01, p < 0.00001] compared to placebo. Associated with a lower risk of coronary revascularization [RR:0.81; 95 % CI:0.66 to 0.99; p = 0.04], hospitalization for unstable angina [RR:0.67; 95

	% CI:0.50 to 0.88; p = 0.005], and myocardial infarction [RR:0.76; 95 % CI:0.66 to 0.88; p = 0.0004].
Cordero et al (2023) [13] 4 clinical trials evaluated 17,324 patients; 9,236 received bempedoic acid for a median of 46.6 months. The mean baseline LDL was 129.4 (22.8) mg/100 ml	Treatment with bempedoic acid significantly reduced the incidence of MACE (hazard ratio [HR] 0.88, 95% CI 0.81 to 0.96), myocardial infarction (HR 0.76, 95% CI 0.66 to 0.89) and myocardial revascularization (HR 0.82, 95% CI 0.73 to 0.92) The crude incidence of stroke, cardiovascular or all-cause mortality was lower in patients in the bempedoic acid groups although no significant risk reduction was observed.
Bhagavathula (2023) [14] 3 phase II and III RCTs, included 388 patients. 49.2% were treated with bempedoic acid and ezetimibe, and 197 controls, were identified. The duration of treatment was 12 weeks.	Bempedoic acid and ezetimibe significantly reduced low-density lipoprotein cholesterol (MD - 29.14%, 95% CI - 39.52 to - 18.76; p < .001), total cholesterol (MD - 15.78%, 95% CI - 20.84 to - 10.72; p = 0.01), non-high-density lipoprotein cholesterol (MD - 18.36%, 95% CI - 24.60 to - 12.12; p = 0.01), and hs-C-reactive protein (CRP) levels (MD - 30.48%, 95% CI - 44.69 to - 16.28; p = 0.04). No significant effects on triglycerides (MD - 8.35%, 95% CI - 16.08 to - 0.63; p = 0.72) and improvement in high-density lipoprotein cholesterol (MD 1.63%, 95% CI - 4.03 to 7.28; p = 0.92) were observed with the fixed-dose combination therapy.
Filippo et al. (2022) [15] 11 studies, including 18,315 patients (9854 on BA vs 8461 on placebo/no treatment)	BA was associated with a reduced risk of MACE (OR 0.86, 95% CI 0.79-0.95), myocardial infarction (OR 0.76, 95% CI 0.64-0.88) and unstable angina (OR 0.69, 95% CI 0.54-0.88) compared to control, over a median follow up of 87 (15-162) weeks. BA was associated with a reduction of LDL-C (MD-22.42,95% CI - 24.02% to - 20.82%), total cholesterol (- 16.50%,95% - 19.21% to - 13.79%), Apo-B lipoprotein (- 19.55%, - 22.68% to - 16.42%) and high-sensitivity CRP (- 27.83%, - 31.71% to - 23.96%) at 12 weeks. BA was associated with a higher risk of gout (OR 1.55, 95% CI 1.27-1.90) as compared with placebo.

1.2. Position of Bempedoic Acid in Guidelines

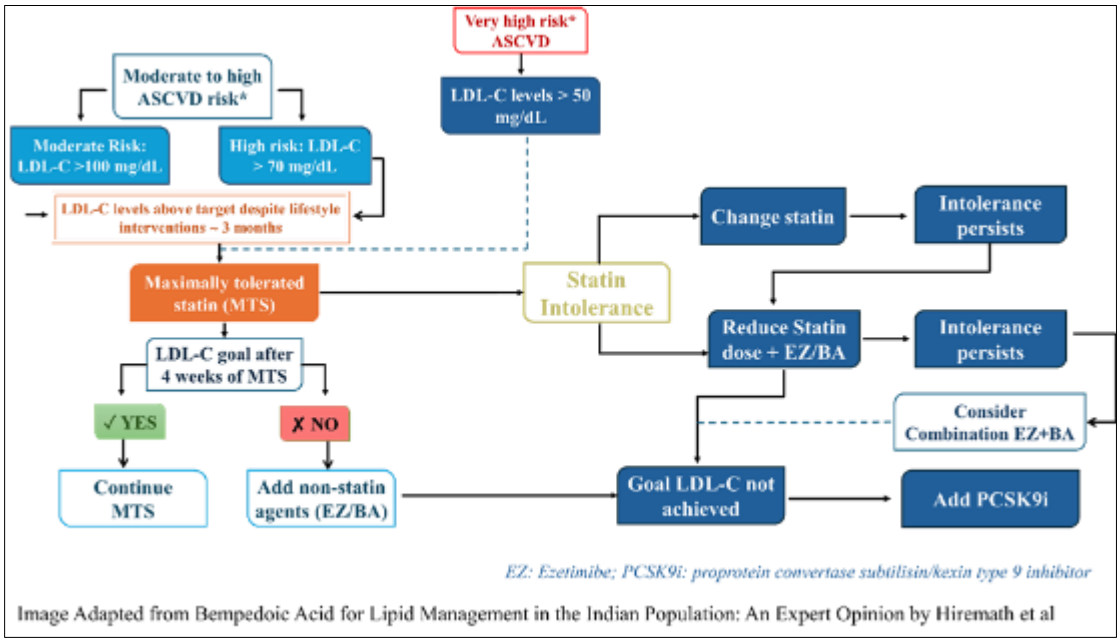

Figure 1 Diagram of managing LDL levels by statin and non-statin [16]

The American College of Cardiology (ACC) Expert Consensus Decision Pathway on novel therapies for cardiovascular risk reduction [17] and the 2023 European Society of Cardiology (ESC) [18] Guidelines on the management of dyslipidemia recommends the use of bempedoic acid. In the ACC pathway, bempedoic acid is recommended as an additional option for high-risk patients who require further LDL-C lowering despite maximally tolerated statin therapy, particularly in those who are statin-intolerant. The ACC acknowledges its role as an adjunct therapy, especially when used in combination with ezetimibe. The ESC guidelines position bempedoic acid as a treatment option for patients who are statin-intolerant or those who cannot achieve LDL-C goals with maximally tolerated statin therapy and ezetimibe. The guidelines particularly note its utility in patients with high cardiovascular risk who need additional LDL-C lowering.

1.3. Lipid profile with Bempedoic acid

Bempedoic acid demonstrates consistent efficacy in reducing LDL-C levels across various patient populations. It works by inhibiting ATP citrate lyase, an enzyme involved in cholesterol synthesis, effectively reducing LDL-C levels. As a, Monotherapy 15-25% reduction in LDL-C [19]; Addition to statins: 15-20% additional LDL-C reduction [20]; Combination with Ezetimibe: Up to 38% reduction in LDL-C [21]. Effects on other lipid parameters: Modest reduction in triglycerides (5-10%) [22]; Small decrease in high-sensitivity C-reactive protein (hs-CRP) [19]; Minimal effect on HDL-C [19]. One of its key advantages is providing an alternative treatment option for patients who cannot tolerate statins due to side effects. The drug's unique activation mechanism in the liver may contribute to reduced muscle-related side effects compared to statins. Furthermore, it can be used as a standalone treatment or in combination with other cholesterol-lowering medications, including a convenient combination pill with ezetimibe for enhanced efficacy.

1.4. Adverse Events and Contraindications

Like all medications, bempedoic acid comes with potential risks and side effects that need careful consideration. Patients may experience upper respiratory tract infections, back pain, abdominal pain, and bronchitis. More concerning risks include elevated uric acid levels, which could increase the risk of gout, and the potential for tendon rupture, particularly in older patients. The medication can also cause elevated liver enzymes, necessitating regular monitoring of liver function [23]. Bempedoic acid is contraindicated during pregnancy and breastfeeding, and its long-term safety profile is still being established through ongoing clinical trials [24]. While the drug shows promise in cholesterol management, its effects on cardiovascular outcomes are still under investigation.

1.5. Recommended Dose

Bempedoic acid is available in 180 mg of daily dose. The liver is the primary site of metabolism. Excretion happens mainly via kidneys (70% of parent drug and metabolites) whereas 30% is via the faecal route [25].

1.6. Ongoing Research

Ongoing research in bempedoic acid encompasses several exciting avenues that aim to expand our understanding of this medication's therapeutic potential. The drug's efficacy in the primary prevention of cardiovascular events in statin-intolerant patients, suggests potential benefits in reducing major adverse cardiovascular events [26]. Research has also examined the impact of bempedoic acid on cardiovascular outcomes by sex, indicating similar reductions in cardiovascular risk and LDL-C levels in both females and males [27]. Real-world evidence studies are collecting data on medication adherence, patient satisfaction, and clinical outcomes outside the controlled trial environment.

2. Conclusion

Bempedoic acid has emerged as a valuable addition to the therapeutic arsenal for lipid management. Clinical trials and systematic reviews consistently demonstrate its efficacy in lowering LDL-C, total cholesterol, and inflammatory markers, with additional cardiovascular benefits in reducing events such as myocardial infarction and coronary revascularization. These findings are reflected in major guidelines, positioning bempedoic acid as a key adjunctive therapy in high-risk patients. Bempedoic acid stands as a testament to the evolving landscape of lipid-lowering therapies, offering hope for better-managing hypercholesterolemia and associated cardiovascular risks in patients with unmet needs.

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