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Bempedoic Acid Versus Ezetimibe in Statin-Intolerant Patients: A Comprehensive Review of Efficacy, Safety, and Cardiovascular Outcomes

Adilova Nargiza Orifovna[1,*], Mavlyanov Sarvar Iskandarovich[2], Ismailova Mukhbina Shavkatovna[3], Akbarova Gulnoza Pulatovna[4], Islomova Malika Sanjarovna[5]

[1]Senior Lecturer, Department of Clinical Pharmacology, Family Medicine №2, Tashkent State Medical University, Tashkent, Uzbekistan
[2]Head of the Department of Pediatrics, Kimyo International University in Tashkent, Uzbekistan
[3]Center for the Development of Professional Qualifications of Medical Personnel. 2nd year clinical ordinator of the Department of Folk Medicine, Tashkent, Uzbekistan
[4]Senior Lecturer, Department of Internal Medicine, Tashkent State Medical University, Tashkent, Uzbekistan
[5]PhD, Assistant, Department of Internal Medicine, Tashkent State Medical University, Tashkent, Uzbekistan

Abstract The pervasive challenge of statin intolerance, affecting a substantial portion of patients with atherosclerotic cardiovascular disease (ASCVD), creates a critical therapeutic gap, leaving individuals at high residual risk for recurrent major adverse cardiovascular events (MACE). This comprehensive review meticulously examines the evolving landscape of non-statin lipid-lowering therapy, with a focused comparison between two pivotal oral agents: ezetimibe, a well-established inhibitor of intestinal cholesterol absorption, and bempedoic acid, a novel, liver-specific inhibitor of cholesterol synthesis. We synthesize evidence from foundational mechanistic studies, pivotal randomized controlled trials (RCTs) such as IMPROVE-IT and CLEAR Outcomes, and emerging real-world evidence (RWE), including a recent prospective comparative study. Our analysis confirms that bempedoic acid consistently demonstrates superior efficacy in reducing low-density lipoprotein cholesterol (LDL-C), with reductions approximately 5% greater than those achieved with ezetimibe monotherapy. Both agents exhibit exemplary tolerability regarding statin-associated muscle symptoms (SAMS), validating their use in statin-intolerant populations. However, their safety profiles diverge, with bempedoic acid carrying a specific, dose-dependent risk of hyperuricemia and gout, necessitating pre-treatment screening and monitoring. Critically, both agents have demonstrated significant reductions in MACE—ezetimibe as an add-on therapy and bempedoic acid as monotherapy—though direct comparative long-term outcome data remain limited. This review concludes that bempedoic acid represents a potent first-line non-statin option for patients requiring substantial LDL-C reduction, while ezetimibe remains a valuable, well-tolerated alternative for moderate lowering or in patients with specific comorbidities like gout. The decision is not hierarchical but strategic, requiring individualized patient assessment to optimize cardiovascular risk reduction in this challenging clinical cohort.

Keywords Bempedoic Acid, Ezetimibe, Statin Intolerance, SAMS, Atherosclerotic Cardiovascular Disease, LDL Cholesterol

1. Introduction

Atherosclerotic cardiovascular disease (ASCVD) remains the principal cause of global mortality and a leading driver of healthcare costs worldwide [1]. The foundational role of elevated low-density lipoprotein cholesterol (LDL-C) in the initiation and progression of atherosclerosis is irrefutable, established through a convergence of genetic, epidemiologic, and interventional studies [2]. Consequently, aggressive LDL-C lowering constitutes the cornerstone of ASCVD risk reduction, a principle robustly validated by decades of clinical trial evidence [3].

3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, or statins, have long been the first-line pharmacologic agents for achieving this goal. Their efficacy in reducing major adverse cardiovascular events (MACE) across the spectrum of primary and secondary prevention is unparalleled [3]. However, a significant limitation in their real-world application is the high prevalence of statin intolerance, a clinical syndrome predominantly characterized by statin-associated muscle symptoms (SAMS). These range from benign myalgia to, in rare instances, life-threatening

* Corresponding author:
adilova.nargiza82@gmail.com (Adilova Nargiza Orifovna)
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rhabdomyolysis [4]. Large-scale observational registries and meta-analyses suggest that SAMS affect 7-29% of patients in clinical practice, with a consensus estimate of 10-15% being frequently cited [4,5]. This intolerance often leads to statin discontinuation, dose reduction, or non-adherence, resulting in a "therapeutic gap" where patients are exposed to persistently high levels of atherogenic lipoproteins and a consequently elevated residual cardiovascular risk [6].

The management of statin-intolerant patients thus represents a critical frontier in contemporary cardiology. Among the available non-statin options, two oral therapies have garnered significant attention: ezetimibe, an established agent with a well-defined mechanism and safety profile, and bempedoic acid, a novel therapeutic with a unique, liver-specific mode of action. While both are endorsed by international guidelines [7], their direct comparison in terms of efficacy, safety, and impact on clinical outcomes is a subject of ongoing research and clinical inquiry. This in-depth review aims to synthesize the current body of evidence, from molecular mechanisms to hard clinical endpoints, to provide a nuanced and comprehensive comparison of bempedoic acid and ezetimibe, thereby guiding evidence-based therapeutic decision-making for the challenging population of statin-intolerant ASCVD patients.

2. Fundamental Mechanisms of Action: Divergent Pathways to LDL-C Reduction

Understanding the distinct pharmacological targets of ezetimibe and bempedoic acid is essential to appreciating their differing efficacies, safety profiles, and potential for combination therapy.

2.1. Ezetimibe

Peripheral Inhibition of Cholesterol Absorption Ezetimibe operates through a highly selective and localized mechanism. It potently inhibits the Niemann-Pick C1-Like 1 (NPC1L1) protein, a sterol transporter located on the brush border of enterocytes in the small intestine [8]. By blocking this transporter, ezetimibe significantly reduces the absorption of both dietary and, crucially, biliary cholesterol. This reduction in cholesterol delivery to the enterocyte leads to a decrease in the incorporation of cholesterol into chylomicrons. The net effect is a diminished flow of intestinal cholesterol to the liver.

This hepatic cholesterol depletion triggers a compensatory response: the upregulation of hepatic LDL receptor (LDL-R) expression on the surface of hepatocytes. Increased LDL-R activity enhances the clearance of atherogenic LDL particles from the circulation, thereby lowering plasma LDL-C levels [8]. It is important to note that ezetimibe's action is entirely peripheral; it does not directly affect hepatic cholesterol synthesis. Its efficacy is therefore intrinsically linked to this indirect, compensatory upregulation of LDL-R.

2.2. Bempedoic Acid

Central Inhibition of Hepatic Cholesterol Synthesis Bempedoic acid employs a fundamentally different, liver-centric strategy. It is an oral prodrug that requires enzymatic conversion to its active form, ESP-15228. This activation is mediated by very-long-chain acyl-CoA synthetase 1 (ACSVL1), an enzyme that is abundantly expressed in hepatocytes but has minimal presence in skeletal muscle cells [9,10]. This tissue-selective activation is the foundational principle behind its favorable muscle safety profile.

Once activated, ESP-15228 inhibits adenosine triphosphate-citrate lyase (ACL), a key cytosolic enzyme in the cholesterol and fatty acid biosynthesis pathway. ACL catalyzes the conversion of citrate and CoA to oxaloacetate and acetyl-CoA. Acetyl-CoA serves as the essential building block for the entire mevalonate pathway, including the synthesis of cholesterol by HMG-CoA reductase (the statin target) and fatty acids [9]. By inhibiting ACL, bempedoic acid effectively reduces the pool of acetyl-CoA available for de novo cholesterol synthesis within the hepatocyte, acting at a step upstream of HMG-CoA reductase.

Similar to the effect of statins and the indirect effect of ezetimibe, this intracellular cholesterol depletion leads to a potent upregulation of LDL-R expression and a subsequent increase in the catabolism of circulating LDL-C [10]. Because its mechanism is complementary to that of ezetimibe and targets a different step in the cholesterol homeostasis pathway, bempedoic acid exhibits synergistic effects when combined with other lipid-lowering agents.

3. Comparative Efficacy in Lipid-Lowering: A Hierarchy of Potency

A substantial body of evidence from both controlled trials and real-world studies has established a clear hierarchy in the LDL-C-lowering potency of these two agents.

3.1. The Established Profile of Ezetimibe

As monotherapy, ezetimibe produces a consistent and reliable LDL-C reduction, typically in the range of 15-20% from baseline, with a favorable dose-response curve that plateaus at 10 mg daily [8]. Its efficacy is additive to that of statins, as demonstrated in numerous trials. The landmark IMProvement of Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) solidified its role in secondary prevention, showing that adding ezetimibe to simvastatin in post-acute coronary syndrome patients led to a significant incremental LDL-C reduction (from a median of 69.9 mg/dL to 53.2 mg/dL) and a corresponding 6.4% relative risk reduction in the primary composite cardiovascular endpoint over 7 years [11].

3.2. The Potent Effect of Bempedoic Acid

The clinical development program for bempedoic acid (the CLEAR trials) established its potency as a monotherapy.

In statin-intolerant patients, bempedoic acid 180 mg/day consistently achieved LDL-C reductions of 17% to 28% versus placebo [12]. This positions it as a more potent LDL-C-lowering agent than ezetimibe monotherapy.

3.3. Head-to-Head and Real-World Evidence

Direct comparative data, while still emerging, robustly support this efficacy gap. A recent prospective, observational cohort study provided a direct, real-world comparison [13]. The study followed 180 rigorously defined statin-intolerant ASCVD patients for 12 months, allocated to either bempedoic acid 180 mg/day (n=90) or ezetimibe 10 mg/day (n=90). The results were unequivocal: bempedoic acid demonstrated significantly greater LDL-C reduction at both 6 months (-21.5% ± 6.8% vs. -16.2% ± 7.1%, $p<0.01$) and 12 months (-20.8% ± 7.0% vs. -15.9% ± 6.5%, $p<0.01$) [13].

This approximate 5% absolute difference is not merely statistically significant but is clinically meaningful. According to the Cholesterol Treatment Trialists' (CTT) collaboration meta-analysis, a 1 mmol/L (≈39 mg/dL) reduction in LDL-C is associated with a 22% relative reduction in the annual rate of major vascular events [3]. Extrapolating from this, the additional LDL-C lowering achieved with bempedoic acid has the potential to translate into substantial long-term cardiovascular risk reduction, adhering to the "lower is better" principle that is central to modern lipid management guidelines [7].

Furthermore, bempedoic acid has demonstrated beneficial effects on other atherogenic lipid parameters, including non-HDL cholesterol and apolipoprotein B (ApoB), often to a greater extent than ezetimibe, suggesting a broader anti-atherogenic impact [12,13].

4. Safety and Tolerability

Both agents are celebrated for their excellent overall tolerability in statin-intolerant populations, but they possess distinct safety considerations that are crucial for clinical decision-making.

4.1. Musculoskeletal Safety: The Core Advantage

The most significant shared feature of ezetimibe and bempedoic acid is their minimal risk of causing SAMS. In the comparative study by Adilova et al., and across larger RCTs, the incidence of myalgia and clinically significant elevations in creatine kinase (CK) with either agent was no different from placebo and did not lead to therapy discontinuation at a higher rate [11,13,14]. This validates their core indication: providing effective lipid-lowering for patients who cannot tolerate statins.

4.2. The Bempedoic Acid Specificity: Hyperuricemia and Gout

A recognized and mechanism-based side effect of bempedoic acid is an increase in serum uric acid levels. This occurs because bempedoic acid and its active metabolite compete with uric acid for renal tubular excretion via organic anion transporter 2 (OAT2) and the urate transporter 1 (URAT1) [15]. This competition reduces uric acid excretion, leading to hyperuricemia.

In clinical practice, this translates to a higher incidence of new-onset gout. In the CLEAR Outcomes trial, gout was reported in 3.1% of patients in the bempedoic acid group versus 2.1% in the placebo group [14]. The real-world comparative study reported a more pronounced difference, with a 5.6% incidence in the bempedoic acid group versus 0% in the ezetimibe group ($p<0.05$) [13]. This highlights the importance of pre-treatment screening for a history of gout or hyperuricemia and periodic monitoring of serum uric acid levels. However, it is noteworthy that in most cases, these events can be managed with standard urate-lowering therapy or analgesics without necessitating the discontinuation of bempedoic acid.

4.3. Other Safety Considerations

Both agents have demonstrated favorable profiles regarding hepatic and renal safety. No significant differences in the incidence of elevated liver transaminases or serum creatinine have been consistently observed between either drug and placebo or between the two drugs directly [11,13,14]. Ezetimibe has a long-term safety record spanning nearly two decades, while bempedoic acid's safety data from trials and medium-term follow-up are similarly reassuring.

5. Impact on Cardiovascular Outcomes: From Surrogates to Hard Endpoints

The ultimate validation for any lipid-lowering therapy is its ability to reduce MACE.

5.1. Ezetimibe: Proof of Concept for Non-Statin Therapy

The IMPROVE-IT trial was a watershed moment, proving for the first time that a non-statin agent, when added to a statin, could provide incremental cardiovascular benefit [11]. This established that LDL-C lowering through intestinal cholesterol absorption inhibition is an effective strategy for reducing cardiovascular risk, moving ezetimibe beyond a mere surrogate marker drug.

5.2. Bempedoic Acid: A Landmark for Monotherapy

The CLEAR Outcomes trial fundamentally advanced the field for statin-intolerant patients [14]. This large, randomized, placebo-controlled trial enrolled 13,970 patients who were unable or unwilling to take statins. Over a median follow-up of 40.6 months, bempedoic acid monotherapy not only significantly reduced LDL-C (by 21.1%) but also demonstrated a 13% relative risk reduction in the primary composite MACE endpoint (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization) [14]. This provided Level A evidence for the cardiovascular benefit of bempedoic acid as a standalone therapy.

5.3. Comparative Outcomes Data

Direct, long-term comparative data on MACE between bempedoic acid and ezetimibe are not yet available from large RCTs. However, the real-world comparative study offers an early, albeit underpowered, glimpse [13]. Over 12 months, the study reported a numerical trend favoring bempedoic acid, with a MACE incidence of 5.6% compared to 8.9% in the ezetimibe group (p=0.38). While this difference was not statistically significant, the directional signal is biologically plausible given the greater magnitude of LDL-C reduction achieved with bempedoic acid and is consistent with the principle established by the CTT collaboration.

6. Discussion

The synthesis of current evidence allows for a sophisticated, patient-centered approach to managing statin intolerance.

6.1. Positioning the Therapies in the Treatment Algorithm

Bempedoic acid, with its superior LDL-C-lowering efficacy and proven MACE benefit as monotherapy, has a strong claim as a first-line non-statin option for statin-intolerant patients who require substantial LDL-C reduction to meet stringent secondary prevention targets (e.g., ≥50% reduction from baseline and an LDL-C level <1.4 mmol/L or <55 mg/dL) [7]. Its potency makes it particularly valuable for high- and very-high-risk patients with significant residual risk.

Ezetimibe remains an indispensable agent in the therapeutic arsenal. Its role is multifaceted:

- First-line for moderate risk reduction: For patients requiring less aggressive LDL-C lowering.
- In patients with gout/hyperuricemia: Where bempedoic acid may be relatively contraindicated or require careful co-management with a rheumatologist.

As part of combination therapy: The synergistic mechanisms of bempedoic acid and ezetimibe make their combination a highly effective oral regimen for patients who need intensive lipid-lowering but cannot tolerate statins or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are not accessible.

Based on availability and cost: In many healthcare systems, ezetimibe is more readily available and less expensive, making it a pragmatic choice.

6.2. Guidance for the Practicing Clinician

The choice between these agents should be guided by a structured decision-making process:

- Calculate the absolute and percentage LDL-C reduction required to reach the patient's guideline-directed target.
- Screen for a history of gout, hyperuricemia, or renal impairment, which may sway the decision towards ezetimibe.
- Discuss the evidence for MACE reduction with the patient, acknowledging the robust data for both agents (ezetimibe as add-on, bempedoic acid as monotherapy).

Engage the patient in the conversation, discussing the efficacy expectations, the specific monitoring required for bempedoic acid (uric acid), and cost/access considerations.

Despite the robust data, gaps remain. There is a pressing need for a large, randomized, head-to-head trial comparing bempedoic acid directly against ezetimibe (and their combination) with long-term MACE as the primary endpoint. Furthermore, more RWE from diverse ethnic and geographic populations, including from regions like Central Asia, will help generalize the findings. Research is also needed to better identify patient factors that predict a superior response or a higher risk of adverse events with either agent.

7. Conclusions

The management of statin-intolerant patients with ASCVD has been profoundly enhanced by the availability of ezetimibe and bempedoic acid. This in-depth review confirms that bempedoic acid is a more potent LDL-C-lowering agent than ezetimibe, with a distinct, liver-specific mechanism that confers an excellent muscle safety profile but requires vigilance for hyperuricemia. Both agents have demonstrated the capacity to improve cardiovascular outcomes, solidifying their roles in evidence-based medicine. Ezetimibe should not be seen as being superseded by bempedoic acid, but rather, the two agents offer complementary strategies. The modern clinician, armed with an understanding of their comparative pharmacology, efficacy, and safety, is now better equipped than ever to individually tailor therapy, close the therapeutic gap in statin-intolerant patients, and effectively reduce the enduring burden of ASCVD.

REFERENCES

[1] Libby P, Buring JE, Badimon L, et al. Atherosclerosis. Nat Rev Dis Primers. 2019; 5(1): 56.

[2] Ference BA, Ginsberg HN, Graham I, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J. 2017; 38(32): 2459-2472.

[3] Cholesterol Treatment Trialists' (CTT) Collaboration. 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(9753): 1670-1681.

[4] Stroes ES, Thompson PD, Corsini A, 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(17): 1012-1022.

[5] Ganga HV, Slim HB, Thompson PD. A systematic review of statin-induced muscle problems in clinical trials. Am Heart J. 2014; 168(1): 6-15.

[6] Serban MC, Colantonio LD, Manthripragada AD, et al. Statin Intolerance and Risk of Coronary Heart Events and All-Cause Mortality Following Myocardial Infarction. J Am Coll Cardiol. 2017; 69(11): 1386-1395.

[7] Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020; 41(1): 111-188.

[8] Knopp RH, Gitter H, Truitt T, et al. Effects of ezetimibe, a new cholesterol absorption inhibitor, on plasma lipids in patients with primary hypercholesterolemia. Eur Heart J. 2003; 24(8): 729-741.

[9] Pinkosky SL, Newton RS, Day EA, et al. Liver-specific ATP-citrate lyase inhibition by bempedoic acid decreases LDL-C and attenuates atherosclerosis. Nat Commun. 2016; 7: 13457.

[10] Lalwani ND, Goldberg DI, Ason BL, et al. Bempedoic acid: A novel molecule for LDL-C lowering. Atherosclerosis. 2019; 287: e18.

[11] Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. N Engl J Med. 2015; 372(25): 2387-2397.

[12] Ballantyne CM, Banach M, Mancini GBJ, 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.

[13] Adilova NO. Comparative Analysis of the Efficacy and Cardiovascular Outcomes of Bempedoic Acid versus Ezetimibe in Statin-Intolerant Patients with Atherosclerotic Cardiovascular Disease in a Tertiary Care Center. [Unpublished Manuscript]. Tashkent: Tashkent State Medical University; 2024.

[14] Nissen SE, Lincoff AM, Brennan D, et al. Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients. N Engl J Med. 2023; 388(15): 1353-1364.

[15] Liu L, Liu S, Cai G, et al. The effects of bempedoic acid and its active metabolite on OAT2 and URAT1 and the potential for drug-drug interactions. Eur J Pharm Sci. 2021; 157: 105621.