Indications of Bempedoic Acid

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Abstract: Cardiovascular disease remains the leading global cause of mortality, with projections indicating a steep rise in prevalence and deaths by 2050. Elevated low-density lipoprotein cholesterol (LDL-C) is a central driver of atherosclerotic cardiovascular disease, and lowering LDL-C consistently reduces major adverse cardiovascular events without an apparent threshold. Recent guidelines underscore both early and durable LDL-C reduction through sequential and combination therapies. Bempedoic acid, an oral first-in-class adenosine triphosphate-citrate lyase inhibitor, offers hepatoselective LDL-C lowering with reduced risk of myotoxicity. Randomized controlled trials demonstrate LDL-C reductions of 15–20% with monotherapy and up to 40% with ezetimibe combination, alongside cardiovascular event reduction in statin-intolerant patients. Regulatory approvals in the United States, European Union, and United Kingdom converge on its role in patients unable to tolerate statins or inadequately controlled on standard therapy. This review synthesizes current evidence and guideline positioning, situating bempedoic acid within contemporary lipid management strategies that emphasize earlier combination therapy, achievement of lower LDL-C thresholds, and long-term maintenance of treatment goals.

Key Words: bempedoic acid, low-density lipoprotein cholesterol, major adverse cardiovascular event, atherosclerotic cardiovascular disease

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Cardiovascular disease (CVD) remains the leading cause of death worldwide. Forecasts from the Global Burden of Disease study predict that the global prevalence of CVD will nearly double between 2025 and 2050, with crude mortality rising from 20.5 million to 35.6 million during this period, reflecting a 73.4% increase.[1] This anticipated rise underscores the urgency of optimizing preventive and therapeutic strategies.

A key driver of atherosclerotic cardiovascular disease (ASCVD) is elevated low-density lipoprotein cholesterol (LDL-C). Evidence from genetic studies, epidemiology, and randomized controlled trials consistently demonstrates a causal relationship between LDL-C and ASCVD risk.[2] A meta-analysis of 27 randomized trials involving 134,000 participants established that each 1.0 mmol/L (≈39 mg/dL) reduction in LDL-C reduces major adverse cardiovascular events (MACE) by 21%, with proportional benefits across age, sex, and baseline LDL-C levels. Importantly, no threshold for benefit was observed, suggesting that reductions of 2–3 mmol/L may decrease MACE by 40–50%.[3] Thus, sustained LDL-C lowering remains a foundational strategy in ASCVD prevention.[4,5]

GUIDELINE-BASED LDL-C LOWERING STRATEGIES

The 2023 American Heart Association/American College of Cardiology guideline on chronic coronary disease reaffirmed high-intensity statins as the cornerstone of therapy, with lipid reassessment recommended 4–12 weeks after initiation or dose adjustment, and every 3–12 months thereafter. For patients at very high risk who remain ≥70 mg/dL (≥1.8 mmol/L) on maximally tolerated statin therapy, ezetimibe is recommended. If LDL-C remains above threshold on combination therapy, the addition of a PCSK9 monoclonal antibody is appropriate. In patients who are not at very high risk but fail to achieve target levels, ezetimibe remains a reasonable next step. Where statins and ezetimibe are insufficient or not tolerated, bempedoic acid or inclisiran may be considered.[6]

The 2025 ACC/AHA acute coronary syndrome (ACS) guideline represents an important evolution, endorsing earlier intensification of lipid-lowering therapy. In patients with LDL-C between 55 and 69 mg/dL despite maximally tolerated statin therapy, the guideline recommends the addition of a nonstatin agent such as ezetimibe, bempedoic acid, a PCSK9 inhibitor, or inclisiran.[7] In parallel, the 2025 European Society of Cardiology/European Atherosclerosis Society Focused Update maintained LDL-C targets of <55 mg/dL for very-high-risk patients, with <40 mg/dL for those with recurrent events, and explicitly supports early combination therapy at the index ACS admission when statin monotherapy is unlikely to suffice.[8] Collectively, these documents outline a continuum of care: aggressive LDL-C lowering in the acute phase following ACS, followed by structured long-term maintenance in the stable phase.

MECHANISM OF ACTION

Bempedoic acid is a once-daily oral lipid-lowering therapy that inhibits adenosine triphosphate-citrate lyase (ACLY), an enzyme upstream of 3-hydroxy -3-methylglutaryl coenzyme A reductase in the cholesterol synthesis pathway. In hepatocytes, it is converted by very-long-chain ACYL-CoA synthetase-1 (ACSVL1/SLC27A2) to bempedoyl-CoA, which directly inhibits ACLY. This reduces acetyl-CoA availability for cholesterol biosynthesis, upregulates hepatic LDL receptors, and lowers circulating LDL-C.[9] The absence of ACSVL1 in skeletal muscle prevents drug activation in muscle tissue, explaining its lower risk of myalgia compared with statins.[9] Experimental studies further suggest potential pleiotropic effects through activation of the AMP-activated protein kinase pathway, leading to downstream anti-inflammatory and metabolic effects such as reductions in high-sensitivity C-reactive protein. However, these are considered ancillary rather than primary mechanisms.[10]

CLINICAL EVIDENCE

Randomized controlled trials and meta-analyses demonstrate that bempedoic acid lowers LDL-C by approximately 15–20% as monotherapy. In fixed-dose combination with ezetimibe, reductions of 35–40% are observed, offering an entirely oral strategy for more substantial lipid lowering.[11] The medically cleared (CLEAR)

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Outcomes trial, the largest study of bempedoic acid to date, enrolled statin-intolerant patients and showed a significant reduction in MACE (hazard ratio 0.87, 95% confidence interval 0.79–0.96), supporting the use of bempedoic acid in patients unable to tolerate statins at recommended intensity.[12]

The safety profile is generally favorable, although clinicians should be mindful of increased risk of hyperuricemia, gout, and rare tendon rupture. Co-administration with simvastatin at doses >20 mg/day or pravastatin >40 mg/day is discouraged due to elevated statin exposure. Use during pregnancy and breastfeeding is not recommended.[13]

REGULATORY INDICATIONS

In the United States, bempedoic acid is approved for 2 major indications. First, it is indicated to reduce the risk of myocardial infarction and coronary revascularization in adults with ASCVD or at high risk who are unable to take recommended statin therapy, including those not taking any statin. Second, it is approved as an adjunct to diet for LDL-C reduction in adults with primary hyperlipidemia, including heterozygous familial hypercholesterolemia, either as monotherapy (180 mg once daily) or in a fixed-dose combination with ezetimibe (180/10 mg once daily). Lipid panels should be reassessed 8–12 weeks after initiation or dose adjustments.[13–15]

In the European Union, bempedoic acid is indicated for adults with primary hypercholesterolemia (familial or nonfamilial) or mixed dyslipidemia, in combination with statins when targets are unmet, or as monotherapy when statins are contraindicated or not tolerated. The fixed-dose combination with ezetemibe is indicated for patients requiring intensified oral LDL-C reduction.[16,17] In the United Kingdom, NICE Technology Appraisal 694 recommends bempedoic

TABLE 1. Global Regulatory Indications and Prescribing Guidance for Bempedoic Acid.

Region/ Regulator	Product	LDL-C-Lowering Indication	CV Risk-Reduction Indication	Eligible Population/Co-Therapy Expectations	Dosing & Key Monitoring/ Contraindications/DDIs
U.S. (FDA)	Nexletol (bempedoic acid 180 mg)	Adjunct to diet, with other LDL-C–lowering therapies or alone when concomitant therapy is not possible, to reduce LDL-C in adults with primary hyperlipidemia (incl. HeFH).	Reduce risk of MI and coronary revascularization in adults unable to take recommended statin therapy (incl. not on a statin) with established CVD or at high risk without established CVD.	Adults with primary hyperlipidemia; outcomes use specifies unable to take recommended statin therapy and CVD/high-risk status. Typically used after statin ± ezetimibe or in statin intolerance.	Dose: 180 mg once-daily; check lipids 8–12 weeks after start. Warnings: hyperuricemia/ gout; tendon rupture. DDIs: avoid simvastatin > 20 mg or pravastatin > 40 mg; pregnancy: may cause fetal harm; lactation: not recommended.
U.S. (FDA)	Nexlizet (bempedoic acid 180 mg/ ezetimibe 10 mg)	Reduce LDL-C in adults with primary hyperlipidemia (incl. HeFH), as adjunct to diet, alone or with other LLTs.	Bempedoic-acid component carries the same outcomes indication as Nexletol (MI/ revascularization reduction in adults unable to take recommended statin therapy with CVD or high risk).	Use when a larger oral LDL-C reduction is needed vs monotherapy; appropriate in statin-intolerant or not-at-goal patients. Separate timing if used with bile-acid sequestrants.	Dose: 180/10 mg once-daily; lipids 8–12 wks. Warnings (from BA component): hyperuricemia/gout; tendon rupture. Pregnancy/lactation: as per BA; BAS timing: ≥2 h before or ≥4 h after.
EU (EMA)	Nilemdo (bempedoic acid 180 mg)	Adults with primary hypercholesterolemia (HeFH or nonfamilial) or mixed dyslipidaemia: with a statin (± other LLTs) if goals unmet; or alone/with other LLTs if statin-intolerant/contraindicated.	Reduce cardiovascular risk by lowering LDL-C in adults with established or high-risk ASCVD, as an adjunct to correction of other risk factors (with statin if tolerated; or alone/ with ezetimibe if statin-intolerant/contraindicated).	Same adult populations as above; co-therapy with statin preferred when tolerated; statin-intolerant/ contraindicated patients may use BA ± ezetimibe.	Dose: 180 mg qd. Warnings: hyperuricemia/gout; ↑LFTs; contraindicated in pregnancy & breastfeeding. Simvastatin limit: ≤20 mg (≤40 mg only in select severe cases); caution for myopathy with statins.
EU (EMA)	Nustendi (bempedoic acid/ ezetimibe 180/10 mg)	Adults with primary hypercholesterolemia or mixed dyslipidaemia: with a statin when goals unmet or alone if statin-intolerant/contraindicated (mirrors Nilemdo LDL-C lowering).	EU indication framed via CV risk-reduction by lowering LDL-C in established/ high-risk ASCVD (as for Nilemdo).	Use for greater oral LDL-C reduction when statin alone is insufficient or statin-intolerant; aligns with EU pathways favoring early combination in very-high-risk.	Dose: 180/10 mg qd. Pregnancy/breastfeeding: contraindicated (per EU labels). Statin interactions/ limits follow Nilemdo principles; monitor LFTs/ urate as clinically indicated.
UK (NICE)	BA + ezetimibe (TA694)	Recommended as an option for adults with primary hypercholesterolemia or mixed dyslipidaemia when statins are contraindicated or not tolerated, and ezetimibe alone is insufficient. (NHS access/ coverage recommendation that mirrors EU license.)	— (NICE positions use within treatment pathways; it does not create outcomes label language.)	Used when statins cannot be used/tolerated and LDL-C remains above goal on ezetimibe; applicable with or without a statin where appropriate and consistent with SmPC.	Local formularies add practical notes (eg, monitoring urate/LFTs; pathway fit); TA694 is the basis for NHS reimbursement.

ASCVD indicates atherosclerotic cardiovascular disease; BA, bempedoic acid; CVD, cardiovascular disease; DDI, drug-drug interaction; HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; LFT, liver function test; LLT, lipid lowering therapy; MACE, major adverse cardiovascular events; MI, myocardial infarction; NHS, National Health service; smPC, summary of product characteristics.

acid plus ezetimibe for adults with hypercholesterolemia or mixed dyslipidemia when statins are contraindicated or not tolerated and ezetimibe alone is insufficient.[18] These indications are summarized in Table 1.

PATIENT SELECTION AND CLINICAL APPLICATION

Across jurisdictions, the key clinical role for bempedoic acid is in patients who are statin-intolerant or who fail to achieve LDL-C targets despite maximally tolerated statin and ezetimibe therapy. Documentation of intolerance, typically defined as symptoms on at least 2 different statins, one at the lowest approved dose, with symptom resolution on discontinuation and recurrence on re-challenge, is essential. In the United States, explicit documentation that a patient is "unable to take recommended statin therapy" is required for use as an outcomes-reduction therapy. Contemporary expert consensus supports bempedoic acid as a practical oral alternative in situations where injectable therapies are not acceptable or accessible.[19]

CONCLUSIONS

Bempedoic acid has emerged as an important addition to the lipid-lowering armamentarium. Its hepatoselective mechanism confers efficacy in reducing LDL-C with a favorable tolerability profile, particularly for patients with statin intolerance. The CLEAR Outcomes trial has provided cardiovascular event reduction data, and regulatory agencies in the United States, Europe, and the United Kingdom have aligned in recognizing its role. Positioned within 2025-era lipid management strategies, bempedoic acid enables earlier combination therapy, achievement of ambitious LDL-C thresholds, and long-term maintenance of lipid control. This convergence of trial evidence, guideline endorsement, and regulatory approval situates bempedoic acid as a flexible, evidence-based option to address residual LDL-C risk and reduce ASCVD burden in clinical practice.

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