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The role of bempedoic acid in the management of dyslipidaemia in people with diabetes: an expert opinion of Italian diabetologists

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Abstract

Diabetes mellitus is a rapidly growing global health challenge and a major driver of atherosclerotic cardiovascular disease (ASCVD). Dyslipidaemia, highly prevalent in both type 1 and type 2 diabetes, plays a central role in this excess cardiovascular risk and often persists despite statin therapy. Although statins remain the cornerstone of lipid management, many patients with diabetes do not achieve recommended low-density lipoprotein cholesterol (LDL-C) goals. Therefore, there is a need for effective, safe, and practical adjunctive therapies. Bempedoic acid is a first-in-class oral ATP-citrate lyase inhibitor with liver-specific activation, resulting in significant LDL-C reduction without relevant muscle-related adverse effects. Across clinical trials, including the CLEAR programme, bempedoic acid has demonstrated consistent LDL-C lowering, as well as reductions in apolipoprotein B and non-HDL-C, and favourable effects on the inflammatory marker high-sensitivity C-reactive protein (hs-CRP), with similar efficacy in patients with and without diabetes. Importantly, the CLEAR Outcomes trial showed a significant reduction in major adverse cardiovascular events in statin-intolerant patients, almost half of whom had diabetes, without adverse effects on glycaemic control. This article summarises the evidence supporting the use of bempedoic acid in people with diabetes, proposes its therapeutic positioning within contemporary lipid-lowering algorithms, and highlights its role as an effective oral option, aiming to provide practical and nationally relevant guidance for lipid management in people with diabetes. By helping to reduce residual cardiovascular risk and bridge treatment gaps in patients who may not be eligible for or have access to PCSK9 inhibitors, bempedoic acid represents a valuable addition to personalised lipid management strategies aimed at lowering cardiovascular morbidity and mortality in this high-risk population.

Keywords Diabetes, Dyslipidaemia, Cardiovascular risk, Lipid-lowering therapy, Bempedoic acid

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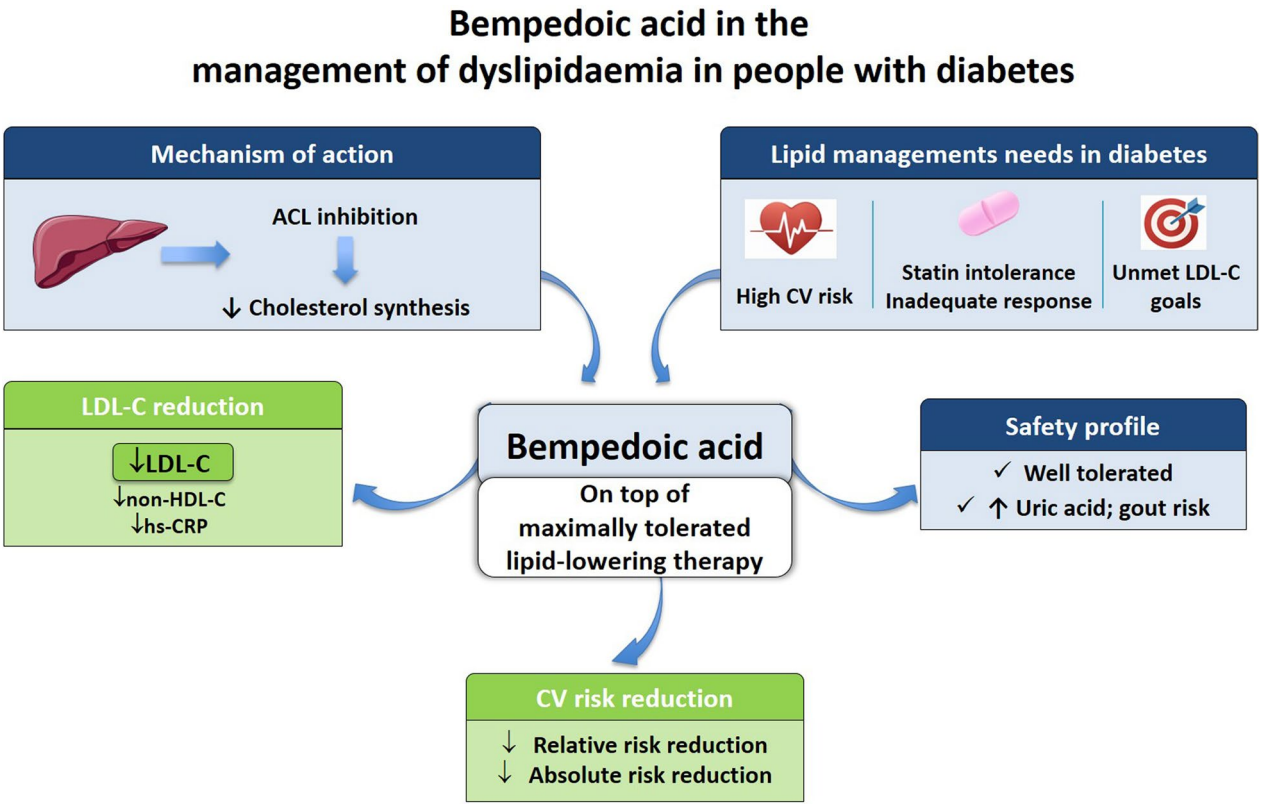
Graphical abstract



Research insights

What is currently known about this topic?

Diabetes confers a high cardiovascular risk, making LDL-C reduction essential. Many patients do not achieve LDL-C goals or are statin intolerant. Bempedoic acid lowers LDL-C and reduces cardiovascular events in statin-intolerant patients.

What is the key research question?

What is the optimal role of bempedoic acid in diabetes care? Which patients benefit most from its use? How can it be integrated into routine clinical practice?

What is new?

This expert opinion provides a diabetologist-led, Italy-specific framework. It defines practical treatment algorithms that include bempedoic acid. It positions bempedoic acid as an oral option between statins and PCSK9 inhibitors.

How might this study influence clinical practice?

It supports earlier and structured use of combination therapy, guides management of statin intolerance and residual risk, and facilitates implementation within national reimbursement pathways.

Introduction and rationale

Diabetes is a chronic metabolic condition characterised by persistently elevated blood glucose levels resulting from defects in insulin secretion, insulin action, or both. It is a major health issue that has reached alarming levels and continues to increase. In 2024, an estimated 589 million adults aged 20–79 were living with diabetes, and this number is projected to reach 853 million by 2050 [1] (Fig. 1). Two major categories of diabetes are recognised. Type 1 diabetes (T1D) results from autoimmune-mediated destruction of insulin-producing pancreatic β-cells, while type 2 diabetes (T2D), by far the most common type, is characterised by insulin resistance and a progressive decline in pancreatic ß-cell function [1, 2]. The causes underlying T2D are still not fully understood, but several contributors have been identified, including excess body weight, older age, ethnicity, and family history of diabetes [1]. The prevalence of T2D is high and continues to rise worldwide, driven by factors such as population ageing, economic development, and increasing urbanisation, which collectively heighten exposure to T2D risk factors [1]. Pre-diabetes is characterised by glucose dysregulation that may precede T2D, increasing the risk of diabetes, cardiovascular events, and mortality [3].

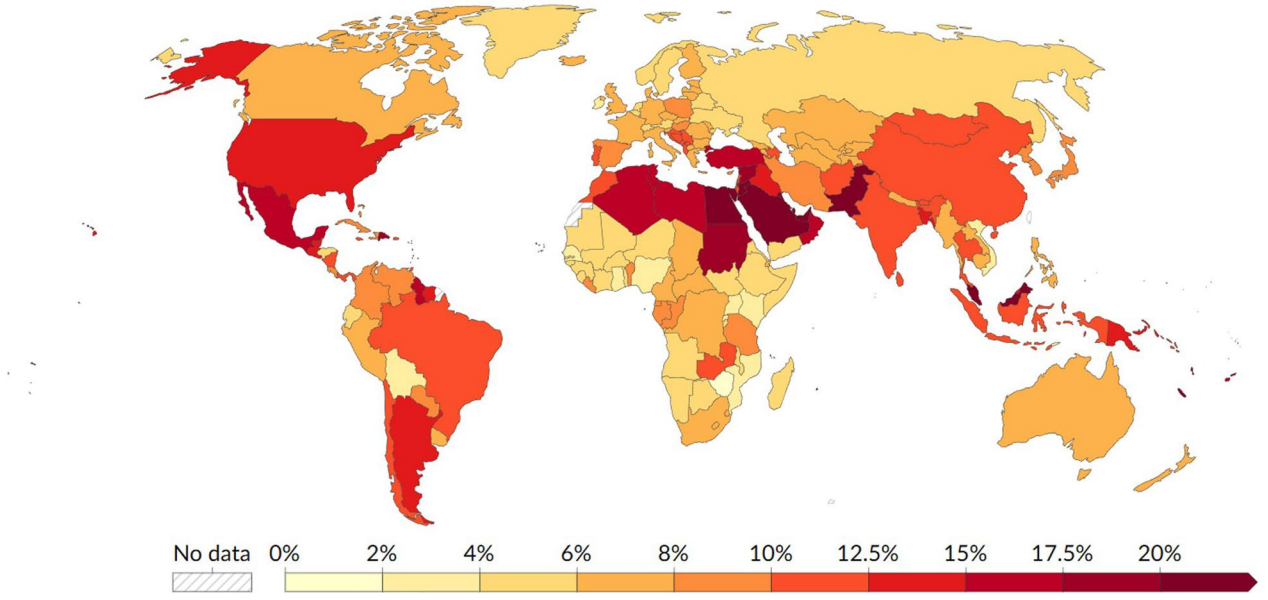


Fig. 1 Share of people with diabetes, 2024. The share of people aged 20–79 who have type I or type II diabetes. Data adapted from international diabetes federation, via World Bank. Retrieved from https://archive.ourworldindata.org/20251022-091218/grapher/diabetes-prevalence.html [online resource] (archived on October 22, 2025)

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of mortality and morbidity among individuals with diabetes [4, 5]. Diabetes confers approximately a twofold increased risk of coronary heart disease, major stroke subtypes, and deaths from other vascular causes [6]. Conditions commonly present in diabetes, such as dyslipidaemia and hypertension, are well-established risk factors for ASCVD [5]. Greater cardiovascular benefits are achieved when multiple risk factors (glycaemia, lipids, and blood pressure) are addressed simultaneously [7].

Epidemiology of dyslipidaemia in type 1 and type 2 diabetes

Dyslipidaemia is one of the most prevalent and modifiable cardiovascular risk factors in individuals with diabetes mellitus. A large proportion of patients with T2D exhibit lipid abnormalities affecting all lipoproteins, typically presenting as elevated triglycerides, reduced high-density lipoprotein cholesterol (HDL-C), and normal to slightly elevated low-density lipoprotein cholesterol (LDL-C) levels, along with increased levels of small, dense LDL (sdLDL) particles—a pattern commonly referred to as diabetic dyslipidaemia [8]. In T1D, lipid profiles may initially appear normal or even favourable in well-controlled individuals; however, poor glycaemic control and longer disease duration are strongly associated with increased triglyceride and LDL-C levels [9, 10]. The increasing global prevalence of diabetes, with projections indicating a continuous rise [1], results in a substantial and growing burden of lipid abnormalities requiring active management.

Relationship between diabetic dyslipidaemia and cardiovascular risk

Diabetic dyslipidaemia plays a central role in the pathogenesis of ASCVD. The triad of hypertriglyceridaemia, low HDL-C, and small dense LDL particles contributes to endothelial dysfunction, oxidative stress, and accelerated plaque formation [11]. Patients with diabetes, both T1D and T2D, typically have a two- to fourfold higher risk of ASCVD events than non-diabetic individuals at similar lipid levels [12], reflecting the additive impact of glycaemic dysregulation, inflammation, and insulin resistance. Although diabetic dyslipidaemia is characterised by multiple lipid abnormalities, LDL-C reduction remains the primary therapeutic target, as it is the only pharmacological approach consistently shown to reduce cardiovascular risk, including in people with diabetes. In contrast, interventions aimed at raising HDL-C or lowering triglycerides have not consistently demonstrated cardiovascular benefit in randomised clinical trials and are therefore not considered primary targets of therapy. This evidence makes LDL-C reduction crucial in this population. While the increased cardiovascular risk is well recognised in T2D, it is often underestimated in T1D, despite similar dyslipidaemic patterns. Increased levels of apolipoprotein B (apoB) and sdLDL, as well as altered composition and function of HDL, have been linked to atherogenesis in T1D [9, 13] and an increased risk of ASCVD [14–17], with atherosclerosis developing early

in life and signs of subclinical disease detectable in up to 70% of patients by age 45 [18].

Based on this evidence, current international guidelines classify diabetes as a high or very high cardiovascular risk condition, recommending intensive lipid-lowering therapy from the outset of treatment [19–21].

Evidence from clinical trials and gaps in lipid management in people with diabetes

In clinical practice guidelines, diabetes is considered a statin-indicated condition [4, 5, 20]. Reducing LDL-C by 1 mmol/L with statin therapy lowers overall mortality by 9% and cardiovascular mortality by 13% in patients with diabetes [22], reinforcing the crucial role of statin therapy in reducing LDL-C and cardiovascular risk in people with diabetes. Although statin therapy has been associated with a modest increase in glycaemia and a small increased risk of new-onset diabetes, recent individual participant data meta-analyses from the Cholesterol Treatment Trialists' (CTT) Collaboration confirm that these effects are limited in magnitude and are outweighed by the substantial reduction in major cardiovascular events [23]. Therefore, statins remain the first-line lipid-lowering therapy for people with diabetes and should be used whenever not contraindicated or not tolerated. Despite the clear benefit of statins, residual cardiovascular risk remains substantial among people with diabetes on maximally tolerated statin therapy [24]. People with diabetes often present with complex lipid profiles, including elevated triglycerides, low HDL-C, and high apoB levels [25], which cannot be optimally addressed by statins alone [26]. In addition, most patients with diabetes fall into high or very high cardiovascular risk categories, for whom recommended LDL-C goals can be difficult to achieve with monotherapy and require upfront combination therapy.

Several trials have shown that patients with diabetes mellitus derive significantly greater cardiovascular benefits from the addition of lipid-lowering agents compared to statin monotherapy, including ezetimibe [27], proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) [28, 29], and bempedoic acid [30]. A recent post hoc analysis of data from patients with T1D in the FOURIER trial showed that evolocumab on top of high- or moderate-intensity statins, with or without ezetimibe, provides LDL-C reductions similar to those observed in T2D patients and a trend towards reduced cardiovascular risk [31]. However, these findings are based on a small subgroup analysis and should be interpreted with caution. Dedicated randomised clinical trials in T1D are lacking, and the impact of lipid-lowering therapies on cardiovascular outcomes in this population remains insufficiently characterised.

Despite this evidence, real-world data reveal treatment gaps in lipid management for diabetes that can be attributed to underuse of combination therapy, therapeutic inertia, and low adherence rates to statins due to perceived or actual intolerance [32, 33]. The costs and accessibility of PCSK9i further widen the gap between evidence and practice. The management of dyslipidaemia in patients with T1D, as well as in younger adults with T2D, remains particularly underrepresented in current guidance. Taken together, these gaps underscore the need for therapies that are both effective and safe, ideally combining complementary mechanisms of action and suitable for implementation across diverse healthcare settings.

Rationale for an expert opinion and the need for tailored national guidance

Given the specific pathophysiology of diabetic dyslipidaemia, the high residual risk in people with diabetes despite optimal statin therapy, and the treatment gaps observed in clinical practice, an expert opinion led by diabetologists is warranted. This expert opinion summarises current evidence on lipid management in diabetes, highlights residual risk and unmet therapeutic needs, and defines the role of bempedoic acid within an integrated, comprehensive lipid-lowering strategy. By integrating contemporary clinical trial evidence with the evolution of international guidelines, it also provides practical recommendations to support clinicians in optimising lipid management for patients with diabetes across diverse clinical settings.

Scientific evidence on the effect of bempedoic acid in people with diabetes

Mechanism of action and pharmacology

Bempedoic acid is a first-in-class, orally administered inhibitor of ATP-citrate lyase (ACL), an enzyme upstream of HMG-CoA reductase in the cholesterol biosynthesis pathway [34]. By inhibiting ACL in hepatocytes, bempedoic acid reduces the conversion of citrate to acetyl-CoA and inhibits cholesterol synthesis, thereby upregulating hepatic LDL receptor (LDLR) expression. A notable characteristic of bempedoic acid is its liver-selective activation: as a prodrug, it requires conversion to its active form (bempedoyl-CoA) by the enzyme very-long-chain acyl-CoA synthetase-1 (ACSVL1), which is present in the liver but absent in skeletal muscle [35]. This tissue selectivity accounts for its favourable safety profile on muscles, reducing the risk of myalgia or creatine kinase elevations commonly associated with statin use [36].

Bempedoic acid has a half-life of approximately 21 hours [37], allowing once-daily dosing at 180 mg, with minimal drug-drug interactions. It is primarily glucuronidated and excreted renally, with no dose adjustment

required for mild to moderate renal impairment. These pharmacological characteristics make it particularly suitable for people with diabetes and statin intolerance, or those taking multiple medications.

Several studies have suggested that bempedoic acid exerts effects beyond ACL inhibition. Bempedoic acid has been shown to activate AMP-activated protein kinase (AMPK) [34], which regulates several substrates involved in inflammatory signalling and lipid metabolism, and is also involved in carbohydrate metabolism [38]. More recently, bempedoic acid was shown to inhibit fatty acid synthesis and promote fatty acid oxidation in mice, resulting in inhibition of diet-induced hepatic steatosis, an effect independent of ACL[39]. Bempedoic acid directly binds to and activates peroxisome proliferator-activated receptor alpha (PPARα) and its transcriptional networks, leading to increased transcription of PPARα target genes and induction of fatty acid catabolism [40]. Although preliminary, these findings, together with the observation that bempedoic acid reduces MASLD and fibrosis in mice, suggest it as a potential strategy for metabolic dysfunction-associated steatotic liver disease (MASLD), a condition that affects approximately 70% of people with T2D [41] and approximately 22% of people with T1D [42].

Lipid-lowering efficacy of bempedoic acid in people without and with diabetes

Across pivotal phase 2 and phase 3 studies (Table 1), including trials from the CLEAR Programme, bempedoic acid has shown consistent LDL-C reductions of 21.4–28.5% as monotherapy in statin-intolerant patients, and approximately 17–18% in patients on maximally tolerated lipid-lowering therapy [38].

Subgroup analyses have confirmed similar efficacy in patients with and without diabetes, indicating that glycaemic status does not attenuate its lipid-lowering response [30]. Importantly, bempedoic acid also lowers apoB and non-HDL-C, while its effect on triglycerides is inconsistent [30, 43].

Bempedoic acid can be combined with statins to further lower LDL-C levels [38], as well as with ezetimibe [44, 45], which offers a complementary mechanism of action. This enables combination therapy for patients unable to achieve LDL-C goals with statins alone or for those intolerant to statins. Given the persistently high residual risk in diabetic dyslipidaemia and frequent statin

Table 1 Summary of major characteristics and results of the phase 3 randomised controlled trials investigating bempedoic acid

Study	Follow-up	% patients with diabetes	Treatment arms (N patients)	Background therapy		Baseline LDL-C (mg/dL ± SD)	% LDL-C reduction (placebo-corrected)	Clinical outcomes
CLEAR Harmony	52 weeks	28.6% BA 28.6% pla	BA (N = 1,488) Placebo (N = 742)	Maximally tolerated statin background therapy	Statin 99.8–100% Ezetimibe 7.8–7.5% Fibrate 3.6–3.5% None 0.1–0%	103.6 ± 29.1 BA 102.3 ± 30.0 pla	*Week 12:* – 18.1% (95% CI, – 20.0% to – 16.1%)	/
CLEAR Wisdom	52 weeks	29.7% BA 31.5% pla	BA (N = 522) Placebo (N = 257)		Statin monotherapy 79.7–76.3% Statin + other LLT 10.3–12.5% Nonstatin(s) alone 4.2–5.8% None 5.7–5.4%	119.4 ± 37.7 BA 122.4 ± 38.3 pla	*Week 12:* – 17.4% (95% CI, – 21.0% to – 13.9%)	/
CLEAR Serenity	24 weeks	26.9% BA 23.4% pla	BA (N = 234) Placebo (N = 111)	Low, very low, or no statin background therapy	Very-low-dose statin 9.9–7.7% Nonstatin 29.7–35.5% None 60.4–56.8%	158.5 ± 40.4 BA 155.6 ± 38.8 pla	*Week 12:* – 21.4% (95% CI, – 25.1% to – 17.7%)	/
CLEAR Tranquility	12 weeks	19.3% BA 19.3% pla	BA (N = 181) Placebo (N = 88)		Statin 28.4–32.6% Fibrate 3.4–3.9% Nicotinic acid 4.6–1.7% Bile acid sequestrant 1.1–0.6% Other 9.2–10.5%	129.8 ± 30.9 BA 123.0 ± 27.2 pla	*Week 12:* – 28.5% (95% CI: – 34.4% to – 22.5%)	/
CLEAR Outcomes	40.6 months	*Diabetes* 45.0% BA 46.3% pla *Pre-diabetes* 41.6% BA 41.3% pla	BA (N = 6,992) Placebo (N = 6,978)		Statin 22.9–22.5% Ezetimibe 11.5–11.6% Bile acid sequestrant 0.5–07% Fibrates 5.3–5.6% PCSK9i 0.5–0.7% Niacin derivatives 0.5–0.7%	139.0 ± 34.9 BA 139.0 ± 35.2 pla	*Month 6:* – 21.1% (95% CI, – 21.9% to – 20.3%)	*MACE-4:* HR 0.87 (95% CI, 0.79–0.96; *P* = 0.004) *MACE-3:* HR 0.85 (95% CI, 0.76–0.96; *P* = 0.004)

BA, bempedoic acid; CI, confidence interval; HR, hazard ratio; LLT, lipid-lowering therapy; MACE, major adverse cardiovascular events; pla, placebo

intolerance, this agent provides a practical and evidence-based oral bridge between statins/ezetimibe and injectable lipid-lowering therapies.

Notably, treatment with bempedoic acid significantly reduced LDL-C levels in patients with metabolic syndrome, a condition associated with increased risk of ASCVD and new-onset diabetes. The placebo-corrected mean percent reduction in LDL-C was slightly greater in patients with metabolic syndrome than in those without in a pooled analysis of four phase 3 clinical trials, with a comparable safety profile [46].

Cardiovascular outcomes: insights from the CLEAR Outcomes study and sub-analyses

The evidence discussed is largely derived from major randomised clinical trials, particularly the CLEAR Outcomes study, which included a substantial proportion of individuals with diabetes or pre-diabetes, enabling subgroup analyses according to glycaemic status [30, 47]. The CLEAR Outcomes trial [47] was a landmark study that enrolled 13,970 patients defined as statin-intolerant, including those unable or unwilling to take statins due to unacceptable adverse effects, who had or were at high risk of cardiovascular disease. These patients were randomised to receive bempedoic acid 180 mg daily or placebo, with a median follow-up of 40.6 months. Nearly 48% of the enrolled patients had diabetes.

Overall, bempedoic acid achieved a 20.3% reduction in LDL-C (placebo-corrected) at 6 months and a 13% relative reduction in major adverse cardiovascular events (MACE), which translated to an absolute risk reduction of 1.6% and a number needed to treat to prevent one event of 63. The observed reduction was driven primarily by decreases in myocardial infarction and coronary revascularisation [47].

A prespecified analysis of the efficacy and safety of bempedoic acid by baseline glycaemic status in the CLEAR Outcomes trial showed that, over a median follow-up of 3.4 years, patients with diabetes had relative risk reductions in MACE comparable to those of normoglycaemic patients or those with pre-diabetes (Fig. 2). However, due to the higher baseline risk of cardiovascular events in people with diabetes, greater absolute risk reductions were observed in the diabetes population (2.4% vs 1.9% for MACE-4 and 2.1% vs 0.3% for MACE-3) [30]. Notably, bempedoic acid did not worsen glycaemic control, and the incidence of new-onset diabetes among people without diabetes was lower compared with placebo. This study provided evidence that, in patients with diabetes, bempedoic acid confers substantial cardiovascular benefit, making it the first oral non-statin cholesterol synthesis inhibitor to demonstrate cardiovascular outcome benefits, thereby complementing the established effects of ezetimibe and PCSK9i. In diabetic

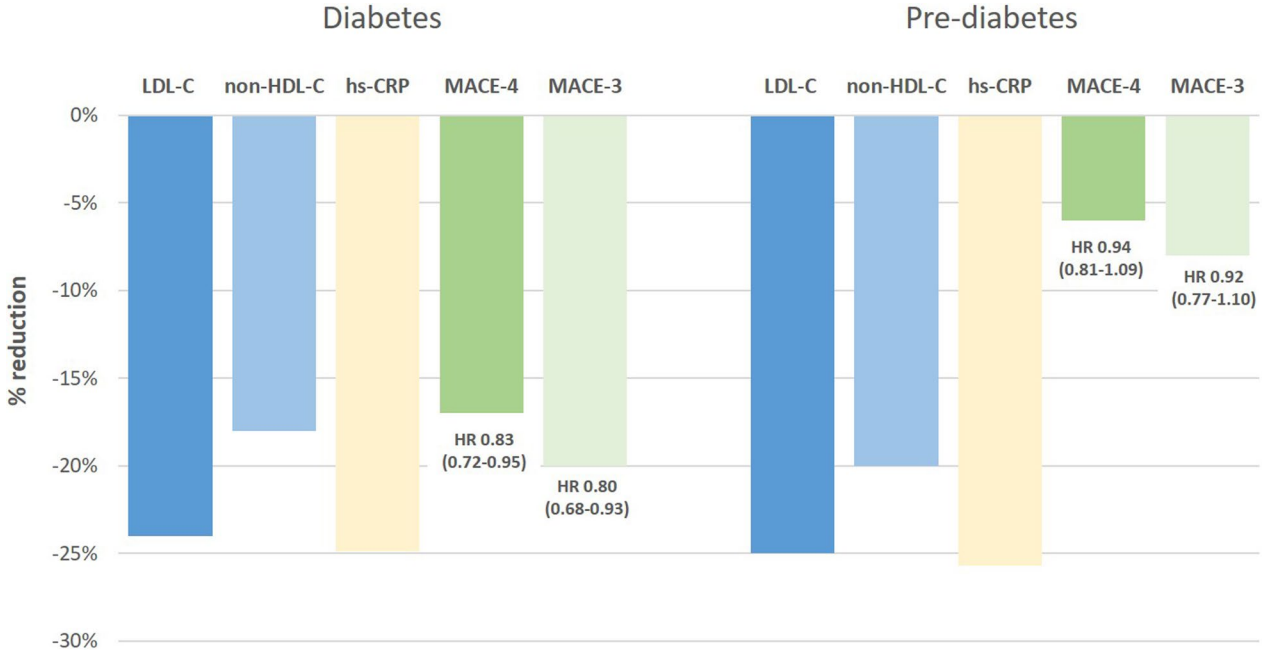


Fig. 2 Percent change in lipid and inflammatory biomarkers and associated cardiovascular outcomes. Bars show percent changes from baseline in LDL-C, non-HDL-C, and hs-CRP, along with effects on major adverse cardiovascular events defined using 4-point (MACE-4) and 3-point (MACE-3) composites in people with diabetes (left panel) or pre-diabetes (right panel). Data retrieved from Ray KK et al., *Efficacy and safety of bempedoic acid among patients with and without diabetes: prespecified analysis of the CLEAR Outcomes randomised trial,* Lancet Diabetes Endocrinol 2024; 12: 19–28. https://doi.org/10.1016/S2213-8587(23)00316-9 hs-CRP, high-sensitivity C-reactive protein; HR, hazard ratio; LDL—C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events non-HDL—C, non-high-density lipoprotein cholesterol;

dyslipidaemia, where residual risk persists despite intensive statin therapy, bempedoic acid may represent a valuable option, particularly for patients with statin intolerance, polypharmacy, or limited access to injectable agents.

Safety and tolerability, focusing on diabetic populations

Results from clinical trials indicate that the most common adverse events associated with bempedoic acid are mild. Rates of muscle-related adverse events, myalgia, and neurocognitive disorders are comparable to placebo [48]. A post hoc patient-level pooled analysis of four phase 3 randomised clinical trials from the CLEAR programme showed that bempedoic acid significantly lowered LDL-C across glycaemic strata and did not worsen glycaemic variables or increase the incidence of new-onset diabetes compared with placebo over a median follow-up of one year [49]. Among participants in the CLEAR Outcomes trial who were free from diabetes at baseline, treatment with bempedoic acid over an average follow-up of 3.4 years did not result in an increase in HbA1c or glucose concentrations, nor in the incidence of new-onset diabetes [30, 50].

Bempedoic acid therapy has been associated with stable and reversible elevations in uric acid levels, as well as an increased risk of gout [48]. Across randomised clinical trials and meta-analyses, treatment with bempedoic acid has been associated with a mean increase in serum uric acid of approximately 0.6–0.9 mg/dL [51, 52]. In the CLEAR Outcomes trial, hyperuricaemia occurred more frequently in the bempedoic acid group than in the placebo group (10.9% vs 5.6%), as did gout (3.1% vs 2.1%), with an increase in uric acid level of 0.76 mg/dL after six months of therapy in the overall population [47]. In the diabetic subgroup, hyperuricaemia was reported in 12.4% of patients treated with bempedoic acid and 6.4% of patients who received placebo [30]. These effects are likely mediated by inhibition of renal uric acid transporters, leading to reduced uric acid excretion. However, clinical trials enrol selected populations and may underestimate the incidence of uric acid-related adverse events in real-world practice, particularly among patients with pre-existing hyperuricaemia, gout, or renal impairment. Patients with elevated serum uric acid levels at baseline, or a history of gout or gouty arthritis, are at higher risk of developing gout [50]. Assessing serum uric acid levels or history of gout at baseline, and concomitant use of urate-lowering drugs, may help to minimise the risk of new-onset gout or gout flares in patients treated with bempedoic acid [52]. The risk of gout may be further reduced by pre-treatment with uric acid-lowering medication when clinically indicated or initiation after an episode of gout [53, 54]. Of note, a post hoc analysis of the CLEAR Outcomes trial demonstrated similar cardiovascular benefit of bempedoic acid in patients with or without prior gout, and gout incidence was lower in patients using uric acid-lowering medication during the trial [54].

Bempedoic acid is associated with slightly higher rates of liver enzyme and creatinine elevations compared with placebo, but these abnormalities are infrequent, mild, and not clinically significant (e.g., creatinine increases of ~ 0.05 mg/dL fall within normal variability) [47]. Similar mild liver enzyme elevations are also seen with other lipid-lowering agents. When stratified by presence or absence of diabetes, elevations in liver enzymes were higher in people with diabetes treated with bempedoic acid than with placebo [30]. Importantly, these laboratory changes do not outweigh the proven cardiovascular benefits of therapy, and overall safety remains favourable.

It should be noted that patients with documented intolerance to ezetimibe were not specifically represented in the CLEAR programme, therefore extrapolation of safety results to this subgroup should be made with caution, as real-world data may reveal different tolerability patterns. However, published evidence shows that, although intolerance to ezetimibe can occur (for example mild muscle symptoms, gastrointestinal effects, or rare liver abnormalities), it is uncommon, usually not severe, and not regarded as a major clinical limitation compared with other agents such as statins [55].

Overall, the safety profile supports the use of bempedoic acid in both primary and secondary prevention settings among people with diabetes.

Effects of bempedoic acid beyond LDL-C reduction

Beyond lowering LDL-C levels, bempedoic acid has been shown to significantly reduce other atherogenic lipid components, such as non-HDL-C and apoB, the latter of which better represents total atherogenic particles than LDL-C [47, 56] (Fig. 2). In addition, bempedoic acid appears to exert pleiotropic anti-inflammatory effects that may further contribute to cardiovascular risk reduction. Substantial evidence supports a role for chronic, low-grade inflammation in the initiation and progression of ASCVD, with high-sensitivity C-reactive protein (hs-CRP) serving as a well-established biomarker of this process, and seminal randomised controlled trials have demonstrated that targeting inflammation reduces cardiovascular risk independently of lipid lowering [57]. Across multiple trials, treatment with bempedoic acid has been associated with significant reductions in hs-CRP [56] (Fig. 2). In patients with baseline hs-CRP levels ≥ 2 mg/L, bempedoic acid reduced hs-CRP by approximately 18% in those using maximally tolerated statin therapy and by approximately 27% in those with a history of statin intolerance who were using low-intensity or no statin from baseline to week 12, independent

of LDL-C changes [43, 58]. Among participants in the CLEAR Outcomes trial, baseline hs-CRP predicted the risk of future cardiovascular events and death more strongly than baseline LDL-C levels. In these patients, bempedoic acid reduced median hs-CRP by 21.6% and mean LDL-C by 21.1% after six months of therapy [59]. This anti-inflammatory profile aligns with the known role of ACL inhibition in attenuating hepatic and systemic inflammation via downregulation of acetyl-CoA-dependent cytokine pathways [60, 61].

In people with diabetes, who often exhibit chronic low-grade inflammation that triggers an immune response damaging tissues, including blood vessels, nerves, and the heart, targeting inflammation is crucial to prevent cardiac complications and other health issues. The hs-CRP reduction observed with bempedoic acid may provide an additional layer of vascular protection, similar to that observed with statins and IL-1β blockade in the CANTOS study [62].

Taken together, the available evidence positions bempedoic acid as an effective, well-tolerated, and mechanistically complementary component of the lipid-lowering armamentarium. Its oral administration, liver-specific activation, and lack of adverse effects on glycaemic control make it particularly well suited for patients with diabetes who are statin intolerant or have persistently elevated LDL-C levels.

As cardiovascular outcome data emerge and real-world experience increases, integrating bempedoic acid into diabetes-specific lipid management algorithms, either as an add-on to statins or as part of combination oral therapy with ezetimibe, represents a rational, evidence-based step towards addressing residual risk gaps in this high-risk population.

Clinical evidence supporting oral triple therapy

Growing clinical and real-world evidence supports the efficacy of oral triple therapy (statin, ezetimibe, and bempedoic acid) in patients whose LDL-C levels remain above goal despite dual therapy. This approach combines complementary mechanisms to achieve substantial and rapid LDL-C reductions while maintaining an oral regimen. In a randomised trial of atorvastatin, ezetimibe, and bempedoic acid [63], LDL-C was reduced by approximately 64% with atorvastatin 20 mg; at week 6, about 95% of patients achieved an LDL-C reduction of ≥ 50%, 90% reached LDL-C < 70 mg/dL, and 58.5% achieved LDL-C < 55 mg/dL. Model-based analyses of over 3,900 patients confirm greater LDL-C reduction with triple therapy compared to mono- or dual therapy, with reductions of approximately 69%, 65%, and 60% when combined with high-, moderate-, and low-intensity statins, respectively [64]. The LAI-REACT study demonstrated that early triple therapy after acute coronary syndrome reduced LDL-C by 57.7% after one week, with sustained reductions of 60–62% at 4–6 weeks; over 90% of patients achieved LDL-C < 70 mg/dL within 2 weeks, and 70–80% reached LDL-C < 55 mg/dL within the first weeks of treatment [65]. Of note, the recent ES-BempedACS trial did not show superiority of triple lipid-lowering therapy (high-dose, high-intensity statin + ezetimibe + bempedoic acid) over dual therapy (high-dose, high-intensity statin + ezetimibe) after acute coronary syndrome [66]. However, the strength of these results is limited by the small patient population, short follow-up, and, most importantly, the lack of accurate monitoring of medication adherence, thus requiring further investigation.

Real-world data support the feasibility of oral triple therapy, suggesting that bempedoic acid may delay the need for PCSK9 inhibitors and reduce costs [67]. Prospective evidence also shows that adding bempedoic acid to statin-ezetimibe lowers LDL-C more than increasing the statin dose (– 22.9% vs – 7.5%) and improves goal attainment (63% vs 37%) [68]. Overall, oral triple therapy is an effective and pragmatic strategy to achieve substantial LDL-C reduction and improve goal attainment in clinical practice before considering injectable therapies, especially when access is limited. Ongoing studies (TRICONOS: NCT06686615; PERSUADE: NCT07440381) will further define the role of bempedoic acid as part of oral triple therapy across different patient populations and clinical settings. The development of fixed-dose combinations including bempedoic acid, ezetimibe, and a statin, may further enhance implementation and adherence in clinical practice [63].

Therapeutic positioning of bempedoic acid in people with diabetes

Bempedoic acid is a valuable addition to lipid-lowering therapy for patients with diabetes and should be considered across the spectrum of dysglycaemia, including patients with type 1 diabetes with coexisting risk factors, type 2 diabetes, and pre-diabetes, who often present with an atherogenic lipid profile and increased long-term cardiovascular risk [69]. Notably, although evidence is more limited compared with T2D, patients with T1D and additional cardiovascular risk factors should be included within the same intensive lipid-lowering framework.

Assessment of cardiovascular risk is essential for determining the appropriate therapeutic approach. The SCORE2-Diabetes algorithm provides an individualised estimate of 10-year cardiovascular risk in people with diabetes in Europe by integrating information on conventional cardiovascular risk factors (age, smoking status, systolic blood pressure, total cholesterol, and HDL-C) with diabetes-specific information (age at diabetes diagnosis, HbA1c, and eGFR) [70]. In this context, it can complement ESC/EAS risk categories by refining

risk stratification within broadly defined groups (such as high or very high risk), thereby supporting more personalised treatment decisions. Its use may help identify patients who could benefit from earlier or more intensive lipid-lowering strategies, particularly when larger LDL-C reduction is required to achieve the recommended goal. Based on these criteria, individuals with T2D are categorised into different cardiovascular risk groups (Fig. 3). Individual characteristics such as glycaemic control, duration of diabetes, presence of target-organ damage, albuminuria, coexisting metabolic dysfunction, hepatic steatosis, or family history of premature ASCVD must all be integrated into a comprehensive risk assessment.

In this context, bempedoic acid may be considered for people with diabetes in the following situations:

1. *Inadequate LDL-C control despite maximally tolerated statin plus ezetimibe therapy*. Most patients with T2D are classified as having high or very high cardiovascular risk and, according to guidelines, require achievement of very low LDL-C levels (< 75 mg/dL and < 55 mg/dL, respectively, and an LDL-C reduction of at least 50%) [4, 20], which may be difficult to achieve with monotherapy. Combination therapy is often necessary. For most of these patients, monotherapy is inappropriate, and upfront combination therapy with high-intensity statin and ezetimibe should be the preferred approach [4, 20, 26]. The addition of bempedoic acid may generally be considered as a second step when LDL-C goals are not reached with the combination of high-intensity statin and ezetimibe [26].
2. *Statin intolerance (partial or complete)*. Several clinical criteria have been proposed to define partial and complete statin intolerance, including the type and dose of statins tested and the reproducibility of adverse effects upon rechallenge [71, 72]. Diabetes is associated with increased prevalence of statin intolerance [73], so there is a need to provide an alternative therapeutic approach for patients who exhibit actual or perceived statin intolerance. Bempedoic acid has been shown to be effective in reducing the risk of MACE in people with diabetes intolerant to statins [30].

Proposed treatment algorithms

The proposed algorithms are intended as flexible, practice-oriented tools to support clinical decision-making, to be adapted to individual patient characteristics and local reimbursement policies.

People with diabetes at moderate cardiovascular risk

For these patients, lipid-lowering therapy starts with lifestyle modification and statins in statin-tolerant individuals, aiming for an LDL-C level below 100 mg/dL (< 2.6 mmol/L) (Fig. 4A). Treatment may be intensified by optimising the statin dose and adding ezetimibe. For patients who are statin intolerant or can tolerate only low doses, bempedoic acid represents an effective alternative or adjunct, enabling further LDL-C reduction without statin-associated muscle adverse effects. In this risk category, LDL-C targets are generally achievable with oral therapies.

People with diabetes at high cardiovascular risk

For these patients, with an LDL-C goal of < 70 mg/dL (< 1.8 mmol/L) and a ≥ 50% reduction from baseline, the distinction between statin tolerance and intolerance becomes more clinically significant (Fig. 4B). Lifestyle measures are universally recommended but must be complemented by prompt pharmacological treatment. A key aspect of this algorithm is the early use of combination therapy, recognising that monotherapy is often insufficient to achieve the recommended goal. This approach maximises LDL-C reduction and minimises delays in reaching the therapeutic goal.

Cardiovascular risk categories	Criteria
Very high risk	✓ Clinically established ASCVD or ✓ Severe target-organ damage ✓ or 10-year CVD risk ≥20% using SCORE2-Diabetes
High risk	• 10-year CVD risk 10 to <20% using SCORE2-Diabetes
Moderate risk	• 10-year CVD risk 5 to <10% using SCORE2-Diabetes
Low risk	• 10-year CVD risk <5% using SCORE2-Diabetes

Fig. 3 Cardiovascular risk categories in people with diabetes. Individuals with T2DM can be categorised into different cardiovascular risk groups based on specific criteria. ASCVD, atherosclerotic cardiovascular disease; CVD, cardiovascular disease; SCORE2-Diabetes, type 2 diabetes-specific 10-year CVD risk score; for the definition of severe target-organ damage, see Marx N et al., *2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes*, Eur Heart J 44(39):4043–4140. https://doi.org/10.1093/eurheartj/ehad192

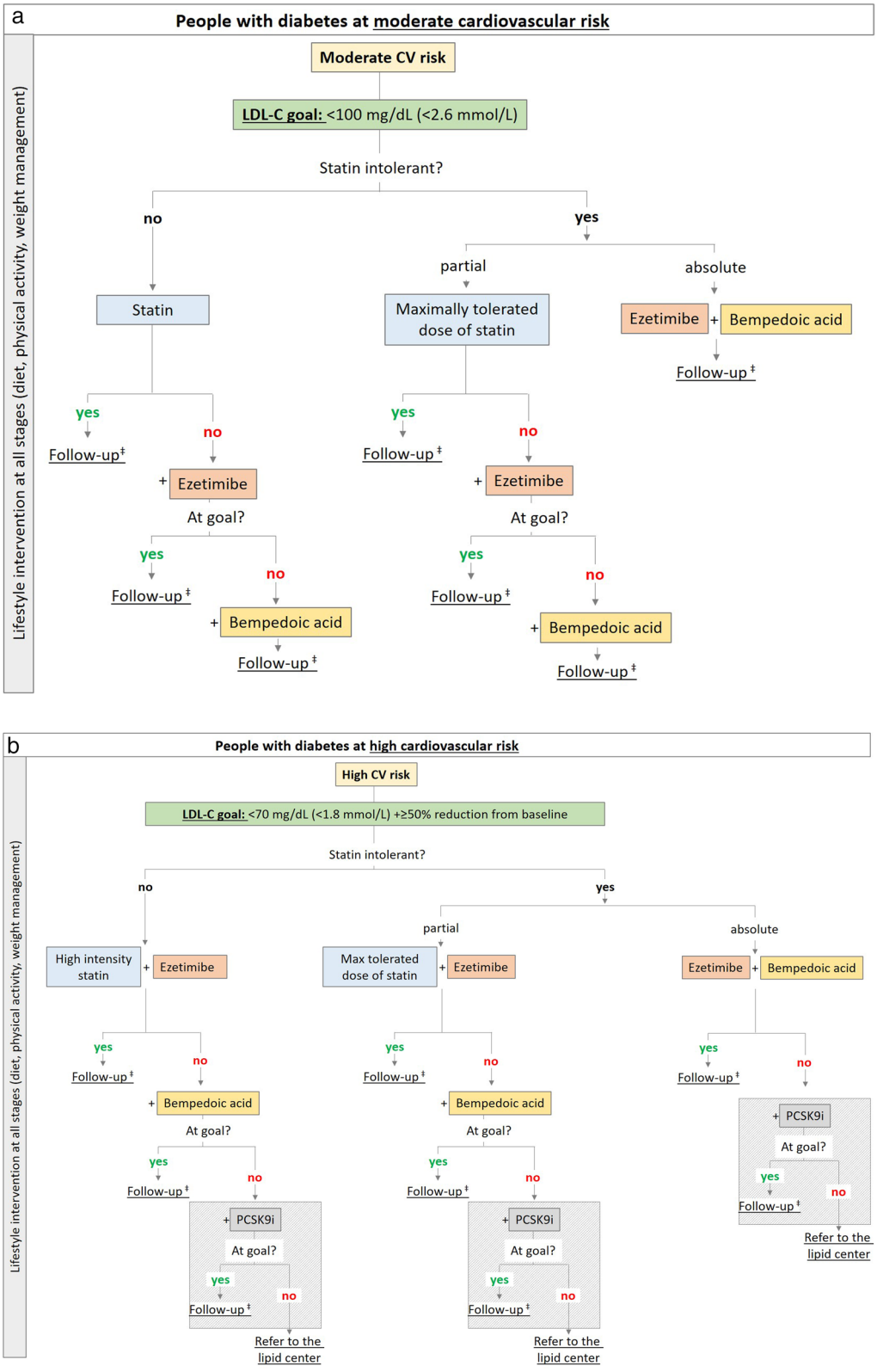


Fig. 4 (See legend on next page.)

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Fig. 4 Treatment algorithms based on cardiovascular risk. Algorithms for LDL-C-lowering therapy in people with diabetes at moderate (**A**), high (**B**), and very high or extreme cardiovascular risk (**C**), estimated by the SCORE2-Diabetes algorithm [70]. Lifestyle advice is recommended for all and at all stages of management. Treatment selection is guided by LDL-C goals, statin tolerance (none, partial, or absolute intolerance), and on-treatment goal attainment, with stepwise addition of ezetimibe, bempedoic acid, and/or PCSK9i, each step followed by follow-up. PCSK9-targeted therapy may be considered depending on local restrictions. The proposed algorithms are intended as flexible, practice-oriented tools to support clinical decision-making, to be adapted to individual patient characteristics and local reimbursement policies. *Triple-combination therapy may be considered in special situations; [§]addition of bempedoic acid if patients did not receive upfront triple therapy. [‡] *Annual follow-up or more frequent, if required.* CV, cardiovascular; LDL—C, LDL cholesterol; PCSK9i, proprotein convertase subtilisin/kexin type 9 inibitor

In statin-tolerant patients, therapy is initiated with a high-intensity statin plus ezetimibe, followed by LDL-C reassessment at follow-up. Patients who achieve recommended levels continue the established regimen, while those not at goal despite optimised statin plus ezetimibe therapy receive add-on bempedoic acid, allowing further LDL-C reduction while maintaining an oral treatment strategy and delaying escalation to injectable therapies.

In statin-intolerant patients, management is tailored according to the degree of intolerance. Those with partial intolerance receive the maximally tolerated statin dose combined with ezetimibe, with bempedoic acid added if the LDL-C goal is not achieved. In cases of complete statin intolerance, initial therapy consists of ezetimibe plus bempedoic acid, initiated upfront to achieve clinically meaningful LDL-C reductions in the absence of statins.

Across all pathways, PCSK9i should be reserved for individuals who, despite optimised oral therapy, are unable to reach their LDL-C goal, including those with conditions such as familial hypercholesterolaemia or persistent severe dyslipidaemia. Their use is conditional rather than routine.

Overall, this algorithm supports a stepwise yet proactive approach, prioritising early combination oral therapy and positioning bempedoic acid as a key intermediary option between statins and PCSK9i. By integrating statin tolerance, treatment intensity, and reimbursement considerations, it offers a practical and sustainable framework for achieving LDL-C targets in patients with diabetes at high cardiovascular risk.

People with diabetes at very high or extreme cardiovascular risk

In patients with diabetes at very high or extreme cardiovascular risk, the recommended LDL-C goals are < 55 mg/dL (< 1.4 mmol/L) with a ≥ 50% reduction from baseline, and < 40 mg/dL (< 1.0 mmol/L), respectively (Fig. 4C). Given the difficulty of achieving these goals with monotherapy, the algorithm prioritises early combination therapy within a structured, stepwise escalation framework.

For statin-tolerant patients, first-line therapy is a high-intensity statin plus ezetimibe. In selected high-risk scenarios, such as markedly elevated baseline LDL-C or extreme cardiovascular risk, early initiation of triple oral therapy including bempedoic acid may be considered to achieve rapid and substantial LDL-C reductions. LDL-C is reassessed at follow-up, with escalation to PCSK9i reserved for patients who remain above target despite optimised oral therapy. For statin-intolerant patients, treatment is tailored according to the severity of intolerance. Those with partial intolerance receive the maximally tolerated statin dose plus ezetimibe, with early addition of bempedoic acid if needed. In cases of complete statin intolerance, ezetimibe and bempedoic acid are initiated upfront. Treatment response guides further intensification. PCSK9i are reserved for patients with persistent residual hypercholesterolaemia despite maximised oral therapy and who meet specific clinical and reimbursement criteria. Lifestyle interventions must remain a continuous component at all stages of management.

Overall, the algorithm supports early, intensive, and sustained LDL-C lowering, positioning bempedoic acid as a key oral intermediary between statins and injectable therapies.

Practical considerations for Italian diabetes clinics

Several practical factors must be considered when integrating bempedoic acid into daily clinical practice in diabetes clinics. These include regulatory requirements, adaptations to clinical workflows, patient engagement strategies, and monitoring procedures essential for safe and effective use.

1) The implementation of bempedoic acid in routine practice must take into account the Italian regulatory framework. In 2023, AIFA (*Agenzia Italiana del Farmaco*) approved reimbursement for bempedoic acid and the fixed-dose combination of bempedoic acid and ezetimibe for adult patients whose LDL-C levels remain elevated despite therapy with statins and other lipid-lowering agents [74, 75]. According to AIFA Nota 13, reimbursement is granted when LDL-C levels exceed the target defined by the patient's cardiovascular risk profile (e.g. 100 mg/dL in high-risk patients and 70 mg/dL in very high-risk patients), within a margin not exceeding 20% above the target, despite first- and second-line lipid-lowering therapies. Clinicians should be familiar with

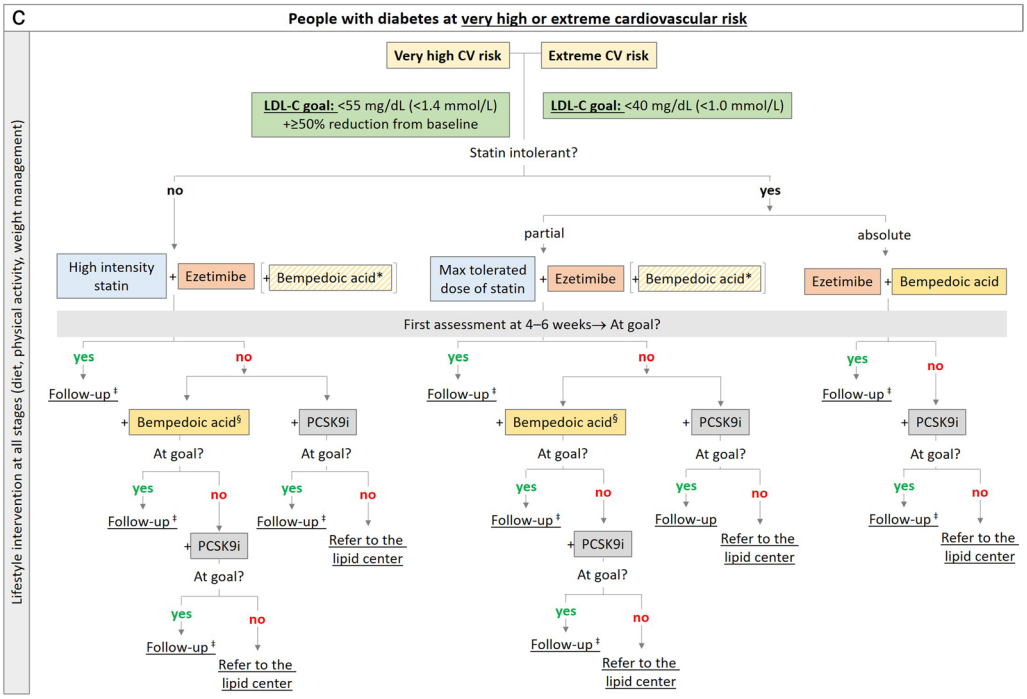

Fig. 4 (continued)

national prescribing rules to ensure appropriate and timely access for eligible patients.

2) Adapting ESC/EAS guidelines to the realities of Italian diabetology is also essential. Many people with diabetes in Italy receive care primarily through diabetes clinics, where the integration of lipid-lowering algorithms, shared electronic records, and structured follow-up protocols can optimise LDL-C management.
3) Patient education is another key aspect. Explaining the rationale for combination therapy, the importance of LDL-C goals, and the mechanism of action of bempedoic acid can foster a more collaborative approach, with the patient actively participating in their treatment plan. This aligns with the principles of patient-centred care and leads to improved adherence and persistence, both of which are critical to achieving and maintaining therapeutic goals in chronic diseases.
4) Clinicians should implement processes for monitoring treatment response, including periodic lipid profiling, evaluation of adherence, and assessment of potential side effects such as changes in uric acid or liver enzymes.
5) Prescribing conditions for lipid-lowering therapies should also be considered, as they may affect treatment access and implementation in routine clinical practice. In Italy, these therapies are regulated by specific therapeutic plans and reimbursement criteria, which may vary across drug classes and require adherence to defined eligibility conditions. Certain treatments, such as PCSK9 inhibitors and inclisiran, can only be prescribed by specialists working in authorised prescribing centres identified at the regional level and require a dedicated AIFA web-based therapeutic plan, which may limit their accessibility in routine clinical practice. In contrast, bempedoic acid can be prescribed by all specialists involved in the management of dyslipidaemia, including general practitioners, and does not require a centralised prescribing system, potentially facilitating its integration into routine care. However, in a few regions, it is still dispensed through direct hospital distribution channels, which may pose practical challenges for accessibility. These organisational and regulatory aspects may contribute to variability in treatment access and should be considered when translating guideline-based recommendations into real-world clinical practice.

Final recommendations

Based on current evidence, this expert opinion aims to support harmonised, evidence-based lipid management across different clinical settings and provide key recommendations on the use of bempedoic acid for managing dyslipidaemia in people with diabetes. Individuals with diabetes—whether type 1, type 2, or pre-diabetes—are at substantially increased risk of ASCVD, making early, intensive, and sustained LDL-C lowering a cornerstone of cardiovascular prevention. Accordingly, international

guidelines consistently recommend aggressive lipid-lowering strategies for patients with diabetes, particularly those at high or very high ASCVD risk [5, 20, 21].

First, the panel recommends considering bempedoic acid in patients who do not to achieve LDL-C goals despite maximally tolerated high-intensity statin therapy combined with ezetimibe. Clinical trials have demonstrated that bempedoic acid provides an additional 18–25% LDL-C reduction when added to background lipid-lowering therapy, with a favourable safety profile [76, 77]. Importantly, the CLEAR Outcomes trial showed a significant reduction in major cardiovascular events in statin-intolerant patients, including a large proportion with diabetes [47].

Second, the panel supports the use of bempedoic acid in patients with partial or complete statin intolerance, particularly those unable to tolerate adequate statin doses because of muscle symptoms. As bempedoic acid is activated only in the liver and not in skeletal muscle, it is associated with a low risk of muscle adverse effects [35], a clinically relevant advantage in people with diabetes, who commonly report statin-associated muscle symptoms [78].

Third, the panel endorses the use of bempedoic acid as part of early or upfront combination therapy in people with diabetes at high or very high cardiovascular risk. This approach aligns with emerging strategies aimed at achieving rapid LDL-C reduction to reduce cumulative exposure to atherogenic lipoproteins and lower lifetime cardiovascular risk [79, 80].

Finally, the panel emphasises the need for national guidelines specifically addressing lipid management in people with diabetes and incorporating newer lipid-lowering agents such as bempedoic acid. Implementation should be supported through regional and local diagnostic-therapeutic pathways and multidisciplinary collaboration among diabetologists, cardiologists, lipidologists, and nephrologists. In this context, the development of Italy-specific recommendations reflecting evolving evidence is strongly encouraged.

Future perspectives and unmet needs

Despite significant advances in the evidence supporting bempedoic acid, important knowledge gaps remain. The CLEAR Outcomes trial has reinforced its cardiovascular benefit in statin-intolerant patients [47], but further research is needed to define long-term efficacy and safety, particularly through extended follow-up and analyses of specific clinical subgroups, including patients with diabetes.

The panel also anticipates significant changes in international lipid-management guidelines as combination therapy becomes increasingly adopted as a first-line strategy for high-risk patients. Timely national adaptation of evolving ESC/EAS and ADA recommendations [5, 21] will be essential to ensure that clinical practice reflects the most up-to-date evidence and guarantees equitable access to effective lipid-lowering therapies.

Overall, addressing current evidence gaps and developing nationally tailored guidelines could substantially improve dyslipidaemia management in people with diabetes, contributing to a meaningful reduction in cardiovascular morbidity and mortality in this rapidly expanding population.

Abbreviations

ACL	ATP-citrate lyase
ACSVL1	Very-long-chain acyl-CoA synthetase-1
ADA	American diabetes association
AIFA	Agenzia Italiana del Farmaco
ApoB	Apolipoprotein B
ASCVD	Atherosclerotic cardiovascular disease
BA	Bempedoic acid
CK	Creatine kinase
CV	Cardiovascular
CVD	Cardiovascular disease
ESC	European society of cardiology
EAS	European atherosclerosis society
HbA1c	Glycated haemoglobin
HDL-C	High-density lipoprotein cholesterol
hs-CRP	High-sensitivity C-reactive protein
LDL-C	Low-density lipoprotein cholesterol
LDLR	Low-density lipoprotein receptor
MACE	Major adverse cardiovascular events
non-HDL-C	Non-high-density lipoprotein cholesterol
PCSK9	Proprotein convertase subtilisin/kexin type 9
PCSK9i	Proprotein convertase subtilisin/kexin type 9 inhibitors
RCT	Randomised controlled trial
sdLDL	Small dense low-density lipoprotein
SCORE2-Diabetes	Systematic coronary risk evaluation 2–diabetes
T1D	Type 1 diabetes
T2D	Type 2 diabetes

Author contributions

All authors contributed to the interpretation of the available evidence. AP drafted the manuscript; MF, RC, and AA critically revised the manuscript. All authors read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Competing interests

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