Unmet Need for Further LDL-C Lowering in India despite Statin Therapy: Lipid Association of India Recommendations for the Use of Bempedoic Acid


ABSTRACT

Lipid-lowering therapy plays a crucial role in reducing adverse cardiovascular (CV) events in patients with established atherosclerotic cardiovascular disease (ASCVD) and familial hypercholesterolemia. Lifestyle interventions along with high-intensity statin therapy are the first-line management strategy followed by ezetimibe. Only about 20–30% of patients who are on maximally tolerated statins reach recommended low-density lipoprotein cholesterol (LDL-C) goals. Several factors contribute to the problem, including adherence issues, prescription of less than high-intensity statin therapy, and de-escalation of statin dosages, but in patients with very high baseline LDL-C levels, including those with familial hypercholesterolemia and those who are intolerant to statins, it is critical to expand our arsenal of LDL-C-lowering medications. Moreover, in the extreme risk group of patients with an LDL-C goal of ≤30 mg/dL according to the Lipid Association of India (LAI) risk stratification algorithm, there is a significant residual risk requiring the addition of non-statin drugs to achieve LAI recommended targets. This makes bempedoic acid a welcome addition to the existing non-statin therapies such as ezetimibe, bile acid sequestrants, and PCSK9 inhibitors. A low frequency of muscle-related side effects, minimal drug interactions, a significant reduction in high-sensitivity C-reactive protein (hsCRP), and a lower incidence of new-onset or worsening diabetes make it a useful adjunct for LDL-C lowering. However, the CV outcomes trial results are still pending. In this LAI consensus document, we discuss the pharmacology, indications, contraindications, advantages, and evidence-based recommendations for the use of bempedoic acid in clinical practice.

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INTRODUCTION

The high prevalence of ASCVD in India has ensured that it is not only the leading cause of death but also responsible for the loss of young lives. The presentation of coronary artery disease (CAD) in India is at a younger age compared to Western countries with up to 25% of myocardial infarctions (MI) occurring in patients under the age of 40 years. While the incidence of CAD has been declining in the last 1–2 decades in Western countries, deaths from CAD in India have nearly doubled. In fact more than 50% of deaths in India related to CAD occur in individuals below the age of 50 years.

The younger age of MI in South Asian individuals has been ascribed to the high prevalence of CV risk factors such as sedentary lifestyle, abdominal obesity, diabetes, increased apo B100/apo AI ratio, hypertension, and psychosocial factors. Also the prevalence of dyslipidemia is very high in India with 79% of subjects having at least one lipid abnormality.

While numerous risk factors like smoking, sedentary lifestyle, obesity, diabetes, and hypertension may predispose to the development of ASCVD, dyslipidemia is the major factor essential for the initiation of atherosclerosis. Indian patients have ASCVD at lower LDL-C levels than Western populations, necessitating lower treatment goals. Although ASCVD risk reduction with statin therapy has been demonstrated regardless of baseline LDL-C levels, patients with higher baseline LDL-C levels and those with a larger decrement in on-treatment LDL-C levels experience greater risk reduction with statin therapy.

Lipid Association of India Risk Stratification Algorithm

The LAI had advocated an LDL-C treatment target of <50 mg/dL in patients with established ASCVD in 2016 due to the increased risk at a younger age despite modest LDL-C elevation in Indian subjects. However, the coexistence of other comorbidities, the number of risk factors, and the extent of atherosclerosis all affect the likelihood of ASCVD events. Due to their very high risk, patients with multiple risk factors and comorbidities need even more rigorous LDL-C lowering and risk factor control. The LAI recommended a new risk group called “extreme risk” in order to appropriately risk stratify patients with noticeably elevated ASCVD risk. In the LAI consensus statements, the justifications for the extreme risk group are elaborated in detail.

To attenuate the risk of future CV events, these patients require intensive LDL-C lowering. Depending on the underlying risk factors and comorbidities, the extreme risk group is further classified into category A and category B (Fig. 1). In extreme risk category A, an LDL-C target of <50 mg/dL is advised, with an optional aim of ≤30 mg/dL, whereas in extreme risk category B, an LDL-C target of ≤30 mg/dL is advised.

Treatment Options

The foundation of dyslipidemia management and CV risk reduction is a heart-healthy diet, regular physical activity, and avoiding smoking and alcohol besides control of hypertension and diabetes in afflicted individuals. In patients with established ASCVD and heterozygous familial hypercholesterolemia (HeFH) with or without ASCVD, initial LDL-C lowering should be first achieved utilizing maximally tolerated statin therapy followed by ezetimibe. If the LDL-C levels are still above goal and further reduction of ≤20% is required, the addition of bempedoic acid may be considered. PCSK9 inhibitors may be considered if >20% LDL-C lowering is required to achieve LDL-C goals as they decrease LDL-C by 50–60% and have shown CV risk reduction in large outcome trials. The benefits, costs, and side effects of aggressive lipid-lowering therapy should be discussed in detail with the patient before initiating such therapy.

There are no data regarding bempedoic acid use in subjects with homozgyous familial hypercholesterolemia.

The Rationale for Non-statin LDL-C Lowering Therapy

Residual risk: Despite patients receiving high-intensity statins, there is a sizable residual risk of ASCVD events. Over the course of 4–5 years of treatment, several randomized placebo-controlled trials of statins have shown a 25–35% reduction in the risk of adverse CV events, suggesting that the majority of patients taking a statin are not protected from ASCVD manifestations.

Reduction in ASCVD risk by further LDL-C reduction: The Improved Reduction of Outcomes: Vytoring Efficacy International Trial (IMPROVE-IT) with ezetimibe and Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) and ODYSSEY Outcomes trials with PCSK9 inhibitor monoclonal antibodies have demonstrated that non-statin therapy in combination with statins was associated with further reductions in the risk of adverse CV events with no lower LDL-C threshold at which CV benefits were not seen. The risk of recurrent ASCVD events is proportional to the LDL-C concentrations down to at least 20 mg/dL. The results of an ongoing CV outcome trial with bempedoic acid are pending, but the results of a Mendelian randomization analysis suggested that loss of function variants in APOE, the gene encoding adenosine triphosphate (ATP) citrate lyase (the target of bempedoic acid), are associated with reduced risk of ASCVD.

Statin intolerance: Although statins are mostly very well tolerated and have a low rate of side effects, statin-related muscle symptoms have been variably reported and are experienced by about 1–2% of patients. In a study of 7,924 patients with dyslipidemia on high-dose statin therapy, 832 (10.5%) patients had muscle symptoms, with most patients experiencing mild symptoms. However, 31 (4% of those with symptoms) patients reported severe muscular pain. Nevertheless, actual or perceived statin intolerance both by patients and physicians interferes with guideline-directed LDL-C lowering therapy.

Failure to achieve LDL-C goals: The importance of achieving LDL-C goals cannot be over-emphasized. However, in the real world, only 20–30% of patients are at recommended goals despite being prescribed statins. Only 29.4% of patients with stable CAD and 18.9% of patients with acute coronary syndrome (ACS) in the DYSIS II study achieved LDL-C levels <70 mg/dL at a mean daily atorvastatin dose equivalent of 25 ± 18 mg. Although the problem is multifactorial including adherence issues, prescription of less than high-intensity statin therapy, de-escalation of statin dosages, very high baseline LDL-C levels including familial hypercholesterolemia, and statin intolerance, it is imperative that we expand our armamentarium of LDL-C-lowering medications. In this regard, bempedoic acid is a welcome addition to the existing non-statin therapies that include ezetimibe, bile acid sequestrants, and PCSK9 inhibitors.

Variable response to statins: The response to statins may vary between individuals with LDL-C reductions ranging from 5 to 70%. This heterogeneity may result from a variety of mechanisms including polymorphisms in numerous genes involved in endogenous cholesterol synthesis and metabolism, such as HMGCR encoding 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase and LDLR encoding the low-density lipoprotein receptor, and genes associated with statin pharmacokinetics, such as transporter proteins [e.g., ATP-binding cassette sub-family members (e.g., ABCB1, ABC2, ABCG2), SCLO1B1, and many other genes]. In a pharmacogenetic study of 1,507 patients who were post-ACS, rs 7412 and rs 429358 polymorphisms in APOE, the
Food has no impact on the oral bioavailability of bempedoic acid. The pharmacokinetic properties are not affected by age, sex, race, or weight. After 7 days of treatment with 180 mg/day of bempedoic acid, the steady-state is reached with the area under the curve (AUC) of 289.0 µg.h/mL while the steady-state maximum drug concentration (Cmax) is 20.6 µg/mL. Bempedoic acid has a volume of distribution of 18 L which is consistent with a modest extrahepatic distribution. The drug is about 99% protein bound in plasma.

The major metabolites of bempedoic acid are glucuronides of bempedoic acid (glucuronidation mediated by UDP-glucuronosyltransferase-2B7) and bempedoyl-CoA. With 70% of excretion occurring in urine and 30% in feces, the kidneys are the primary route of elimination. After a once-daily dose, bempedoic acid has a steady-state clearance of 11.2 mL/min. With just a small (2%) excretion of unmetabolized bempedoic acid, the acyl glucuronide conjugate is the main metabolite detected in urine. The exposure rises by 1.4 and 1.9 times in patients with mild or moderate renal impairment, respectively. Patients who have mild or moderate hepatic impairment have bempedoic acid levels that are 22% lower than normal. Patients with Child-Pugh class C hepatic cirrhosis and end-stage renal disease have bempedoic acid levels that are 22% lower than normal. Patients with a history of coronary artery disease (CAD) and a history of peripheral arterial disease (PAD) are more likely to experience adverse events with bempedoic acid. **Clinical judgment to be used if patient has atherosclerotic peripheral arterial disease instead of coronary artery disease.**

A fasting blood sugar level from 100 to 125 mg/dL. It should be confirmed by repeat testing.

**Waist circumference is to be measured at the superior border of the iliac crest just after expiration. Increased waist circumference is defined as >90 cm in men and >80 cm in women. If increased waist circumference is the only risk factor, it should again be measured after 6 months following lifestyle changes.**

**On two occasions at least 2 weeks apart. For reclassifying moderate risk group only.**

**Fig. 1: Risk stratification algorithm recommended by the LA**

<table>
<thead>
<tr>
<th>Risk factors/markers</th>
<th>Major ASCVD risk factors</th>
<th>Other high-risk features</th>
<th>Moderate risk non-conventional risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1 major ASCVD risk factor and lifetime CVD risk &lt;30%</td>
<td>1. Age ≥45 years in males and ≥55 years in females</td>
<td>1. Diabetes with 0-1 other major ASCVD risk factors and no evidence of target organ damage</td>
<td>1. Coronary calcium score 100–299 HU</td>
</tr>
<tr>
<td>2. Family history of premature ASCVD</td>
<td>2. CKD stage 3B or 4</td>
<td>2. Increased carotid IMT</td>
<td>2. Increased waist circumference*</td>
</tr>
<tr>
<td>3. Current cigarette smoking or tobacco use</td>
<td>3. Familial hypercholesterolemia (other than familial homozygous hypercholesterolemia)</td>
<td>3. Lipoprotein (a) 20–49 mg/dL</td>
<td>3. Apolipoprotein B100 mg/dL</td>
</tr>
<tr>
<td>4. High blood pressure</td>
<td>4. Extreme of a single risk factor</td>
<td>4. Impaired fasting glucose*</td>
<td>4. hsCRP ≥2 mg/L**</td>
</tr>
</tbody>
</table>

**Table 1: Updated Risk Stratification Approach Recommended by Lipid Association of India**
Unmet Need for Further LDL-C Lowering in India Despite Statin Therapy

**Mechanism of action of Bempedoic acid**

Bempedoic acid is converted into bempedoyl CoA in the hepatocyte by long-chain acyl-CoA synthetase 1, which reduces intracellular cholesterol by inhibiting ACL, one step upstream of HMG-CoA reductase enzyme, which is inhibited by statins. LDL-C receptors are therefore upregulated, resulting in a decrease in serum LDL-C levels.

**Clinical Studies**

Bempedoic acid lowered LDL-C levels in 56 hypercholesterolemic individuals with statin intolerance by 28.7% greater than placebo, according to a preliminary randomized, placebo-controlled study by Thompson et al. Bempedoic acid has since been tested in four phase III trials with about 3,600 participants (Fig. 3).

Patients with hypercholesterolemia and statin intolerance were investigated in two clinical trials (CLEAR (Cholesterol Lowering through Bempedoic acid, an ACL-Inhibiting Regimen) Tranquility and CLEAR Serenity). The effects of bempedoic acid were further investigated in patients with ASCVD or high risk of ASCVD and HeFH in two larger trials, CLEAR Harmony and CLEAR Wisdom.

**CLEAR Serenity**

The bempedoic acid 180 mg or placebo once daily for 24 weeks was administered to 345 participants (2:1) with hypercholesterolemia (mean baseline LDL-C 157.6 mg/dL) and statin intolerance in the CLEAR Serenity trial. The stable baseline lipid-lowering treatment was continued. Only 8.4% of patients were on very low-dose statins, which were defined as an average daily dose of rosuvastatin (<5 mg), atorvastatin (<10 mg), simvastatin (<10 mg), lovastatin (<20 mg), pravastatin (<40 mg), fluvastatin (<40 mg), or pitavastatin (<2 mg). 34

Low-density lipoprotein cholesterol mean percent changes from baseline to week 12 served as the primary outcome measure. Between baseline and week 12, bempedoic acid significantly decreased LDL-C (placebo corrected difference: –21.4% [95% confidence interval (CI): –25.1 to –17.7%], p < 0.001).

Bempedoic acid compared to placebo significantly reduced non-high-density lipoprotein cholesterol (non-HDL-C) (–17.9%), total cholesterol (–14.8%), apo B (–15.0%), and (hsCRP) (–24.3%; p < 0.001 for all comparisons).

In the bempedoic acid group, HDL-C was significantly lower by 4.5% (p = 0.003). Also, the bempedoic acid group had a lower rate of newly developing diabetes or worsening of pre-existing diabetes than the placebo group (2.1 vs 4.5%). 34

The most frequent adverse event involving the muscles was myalgia, which was reported by 4.7% of patients...
Clear Tranquility

Bempedoic acid 180 mg or placebo once daily in addition to ezetimibe 10 mg/day for 12 weeks was given to 269 individuals (2:1) with a history of statin intolerance and LDL-C ≥100 mg/dL while on stable lipid-modifying medications. In 31% of patients, the background low dose or very low dose statins were continuing. The percent change in LDL-C from baseline to week 12 was the primary outcome. Bempedoic acid with ezetimibe resulted in a 28.5% reduction in LDL-C after adjusting for placebo (bempedoic acid –23.5%, placebo +5.0%, p < 0.001). A subgroup analysis revealed that bempedoic acid reduced LDL-C to a larger extent in patients who were not getting background statins (–34.7%) compared to those who were on statins (–20.5%), most likely because both statins and bempedoic acid act on the same pathway.

With bempedoic acid vs placebo, there were statistically significant decreases in non-HDL-C (–23.6%), total cholesterol (–18.0%), apo B (–19.3%), and hsCRP (–31.0%) with p < 0.001 for all comparisons. Bempedoic acid group lowered HDL-C considerably from baseline to week 12 compared to placebo group (–7.3 ± 1.2% and –1.4 ± 1.4%, respectively; p = 0.002). When compared to placebo, bempedoic acid had a similar incidence of side effects.35

Clear Harmony

In the CLEAR Harmony study, bempedoic acid or placebo was administered to 2,230 patients (2:1) with ASCVD, HeFH, or both who were receiving maximally tolerated statin treatment and had LDL-C values ≥70 mg/dL. At 12 weeks, the mean LDL-C levels had dropped by 19.2 mg/dL (16.5% from baseline values; p < 0.001). When comparing the overall incidence of side events, bempedoic acid group had a similar incidence compared with the placebo (78.5 vs 78.7% of patients). At week 12, the bempedoic acid group had lower levels of non-HDL-C –13.3% (95% CI –15.1 to –11.6%), total cholesterol –11.1% (95% CI –12.5 to –9.8%), apo B –11.9% (95% CI –13.6 to –10.2%), and hsCRP –21.5% (95% CI –27 to –16%), with p < 0.001 for all comparisons.36

The bempedoic acid group had a lower incidence of newly developing or worsening diabetes mellitus than the placebo group: 3.3 vs 5.4%, p = 0.02. Even though the p-value was not provided, there was a 5.8% decrease in HDL-C in the bempedoic acid group when compared to the placebo group. When compared to placebo, bempedoic acid increased the likelihood of developing gout (18 patients [1.2%] vs two patients [0.3%]). Over the course of the first year of bempedoic acid treatment, the mean hemoglobin levels dropped by approximately 4.1%. Through week 52, bempedoic acid had sustained efficacy.36,37

Patients who continued bempedoic acid treatment in the 78-week, open-label extension (OLE) study (for a total of 130 weeks) that was conducted after the CLEAR Harmony study, along with patients who had previously received placebo and were initiated on bempedoic acid treatment (for a total of 78 weeks) were studied for drug’s efficacy and safety.38 At 78 weeks, the mean LDL-C reduced by 14.2–15%, the total cholesterol by 10%, the non-HDL-C by 11%, the apo B by 7%, and the hsCRP by 17%.38 Myalgia (0.6%) and muscle spasms (0.5%) were the most frequent side effects that caused patients to stop receiving bempedoic acid, but their frequency did not rise over the course of the lengthier follow-up period. Tendon ruptures occurred at a rate of 0.3%, whereas new-onset or worsened diabetes occurred in 5.5% of cases. The safety profile of bempedoic acid was comparable in the OLE and CLEAR Harmony investigations.38 Overall bempedoic acid was well tolerated and the LDL-C lowering efficacy was maintained during the 2.5 years of follow-up.

Clear Wisdom

In the CLEAR Wisdom study, 779 patients (2:1) with ASCVD, HeFH, or both were randomized to receive bempedoic acid or placebo for 52 weeks while receiving maximally-tolerated statin...
Treatment. The average LDL-C level at baseline was 120.4 ± 37.9 mg/dL. At 12 weeks, the addition of bempedoic acid 180 mg per day significantly reduced LDL-C levels when compared to placebo (−15.1 vs 2.4%, p < 0.01). Bempedoic acid also significantly reduced levels of apo B (−9.3 vs 3.7%), non-HDL-C (−10.8 vs 2.3%), total cholesterol (−9.9 vs 1.3%), and hsCRP (−18.7 vs −9.4%) when compared to placebo. Intriguingly, the bempedoic acid group showed a decrease in HDL-C levels by 6.1%, p < 0.001. Common adverse events included nasopharyngitis (5.2% vs 5.1%), urinary tract infection (5.0 vs 1.9%), and hyperuricemia (4.2 vs 1.9%) with bempedoic acid vs placebo, respectively.37,39

In a pooled analysis of 3,623 patients included in four randomized trials, the mean baseline LDL-C levels in patients with ASCVD or HeFH or both and 144.4 mg/dL in patients with statin intolerance. LDL-C levels decreased –16.0% with bempedoic acid vs 1.8% with placebo (p < 0.001) at week 12 in patients with ASCVD or HeFH or both, while the changes in LDL-C levels at week 12 in patients with statin intolerance were –23.0% in the bempedoic acid group vs 1.5% in the placebo group (p < 0.001). The decrease in LDL-C levels with bempedoic acid was sustained at week 52. Increased blood uric acid levels (2.1 vs 0.5%), gout (1.4 vs 0.4%), decreased glomerular filtration rate (0.7 vs 0.1%), and higher levels of hepatic enzymes (2.8 vs 1.3%) were among the side effects that occurred more frequently with bempedoic acid than with placebo.40

Bempedoic acid has a reasonable LDL-C lowering efficacy and safety profile, but its effects on clinical endpoints are still unknown. The ongoing randomized, double-blind, placebo-controlled CLEAR Outcomes study is evaluating the effects of bempedoic acid on CV outcomes in patients with high ASCVD risk and documented statin intolerance with an LDL-C ≥100 mg/dL on maximally tolerable lipid-lowering therapy to see if bempedoic acid 180 mg per day reduces the incidence of adverse CV events. The trial’s enrollment is complete, and results are anticipated in 2023.41 Additional knowledge about the potential negative effects of minor HDL-C decrease on ASCVD risk may be learned from this investigation.

Adverse Events
Nasopharyngitis, urinary tract infection, arthralgia, muscle spasms, pain in the extremity, myalgia, and muscle weakness were common side effects reported in the phase III bempedoic acid clinical trials and occurred equally frequently in the bempedoic acid and placebo groups. Muscle-related side effects were noted in patients on concomitant statin therapy while muscle-related symptoms like myalgia were not increased with bempedoic acid relative to placebo.29,42 The real-world use of bempedoic acid was reported in a retrospective study of 64 patients who initiated the therapy, the majority of whom had an intolerance to statins and other medications. There was marked inter-individual heterogeneity in LDL-C lowering (>5 to −80%). Treatment-emergent adverse effects were observed in 50% of patients resulting in discontinuation of the treatment in about one-third of patients of the total cohort. Musculoskeletal events, including myalgia, muscle cramps, and arthralgias accounted for 62.5% of the adverse events.43 The high rates of adverse events in this cohort are inconsistent with results from randomized placebo-controlled clinical trials, which probably reflects high baseline rates of medication intolerance in this cohort.

Bempedoic acid reversibly increases uric acid levels with a mean increase in uric acid levels [mean change at week 12, 0.82 mg/dL (bempedoic acid) vs –0.02 mg/dL (placebo)] occurring within the first 4 weeks of treatment and levels were stable over time. Therefore, it can precipitate gout or increase the risk of gout in patients who do not have an established diagnosis of gout, but the incidence of gout during treatment with bempedoic acid was low. Clinically warranted testing for uric acid levels is recommended in patients who experience symptoms.42

In the CLEAR Harmony and CLEAR Wisdom studies among those on moderate to high doses of statin, 10 (0.5%) patients out of a total of 2,009 patients treated with bempedoic acid reported tendon rupture or damage; in contrast, no patients receiving placebo (n = 999) did so.26,44 There were several other risk factors present in subjects experiencing this side effect, including fluoroquinolone use, systemic corticosteroids, diabetes, gout, rheumatoid arthritis, statin use, renal failure, age >60 years, male gender, and history of tendon disorders. Therefore, patients should be advised to seek medical attention if any arm, shoulder, back, or ankle discomfort or swelling occurs even though the medication is unlikely to be mechanistically linked to tendon rupture or injury. If a tendon rupture occurs and a different explanation cannot be found or cannot be managed, bempedoic acid should be stopped.

Treatment with bempedoic acid has been linked to a mild, reversible drop in hemoglobin levels, with a small proportion of patients experiencing related clinical symptoms. The median change in hemoglobin level at week 12 was −0.3 gm/dL (bempedoic acid) vs 0.1 gm/dL (placebo).42 Patients who have lower hemoglobin levels at baseline may require periodic monitoring on an individualized basis.

The bempedoic acid group had a lower glomerular filtration rate (0.8 vs 1.4%) than the placebo group in the pooled analysis of four randomized trials.42 In the CLEAR Harmony and CLEAR Wisdom trials, 1.3% of men in bempedoic acid group had new-onset benign prostatic hyperplasia or prostatomegaly compared with 0.1% of men in the placebo group.29

Risk of New-onset or Worsening Diabetes
Patients receiving bempedoic acid compared to treatment had considerably lower rates of new-onset or worsening diabetes (4.0 vs 5.6%; nominal p < 0.05) in the pooled data analysis of 3,623 patients from the aforementioned four randomized trials.40 In another meta-analysis comprising 4,311 patients, bempedoic acid was associated with a lower risk of new/worsening diabetes (RR 0.68; 95% CI 0.51–0.91; p = 0.01, I² = 0) compared with placebo.44 A patient-level pooled analysis of four phase III trials in 3,621 patients on maximally tolerated statins who were randomized (2:1) to oral bempedoic acid 180 mg or placebo once daily evaluated changes in glycemia based on baseline glycemic status over a median follow-up of 1 year. The annual rate of new-onset diabetes for bempedoic acid vs placebo in patients with normoglycemia at baseline (n = 618) was 0.3 vs 0.8%, and for prediabetes at baseline (n = 1688) was 4.7 vs 5.9%. In patients with diabetes and prediabetes, bempedoic acid significantly (p < 0.0001) reduced HbA1c by −0.12 and −0.06%, respectively. The safety of bempedoic acid was similar across glycemic strata and comparable with placebo.45

It is hypothesized that bempedoic acid may improve insulin sensitivity and reduce diabetes risk by modulating AMP-activated protein kinase activity,46 but further studies are required to verify the impact on diabetes risk and elucidate possible mechanisms.

Regulatory Approval
The bempedoic acid and fixed-dose combination of bempedoic acid/ezetimibe were recommended for approval by the European Medicines Agency on 30th January.
Unmet Need for Further LDL-C Lowering in India Despite Statin Therapy

 algorithm. High-intensity statin therapy (atorvastatin 40–80 mg or rosuvastatin at 20–40 mg once daily) is the mainstay of treatment followed by ezetimibe 10 mg once daily.
• If LDL-C goals are not achieved despite maximally tolerated statin therapy and ezetimibe, bempedoic acid may be added as one of the non-statin drugs in patients with established ASCVD and HeFH (Fig. 4).
• In patients with true statin intolerance or contraindications, ezetimibe 10 mg once a day in combination with bempedoic acid 180 mg once a day is recommended.
• Bempedoic acid may be initiated in patients presenting with ACS who are not at LDL-C goal despite statins and ezetimibe as per the LAI risk stratification algorithm for LDL-C management in ACS⁴⁸ (Fig. 5).
• The possibility of decreased rates of new-onset diabetes with bempedoic acid makes it a reasonable consideration in patients with metabolic syndrome who require additional LDL-C reduction after statin therapy. Whether it can be initiated as initial lipid-lowering therapy in such patients has not been studied.
• Because of minimal drug–drug interactions, bempedoic acid may be useful in treating dyslipidemia in human immunodeficiency virus patients and other medical conditions where statin treatment may lead to drug interactions. Further studies are needed to verify the safety and efficacy of this approach.
• PCSK9 inhibitors may be reserved, if cost is a consideration, after maximally tolerated statin and ezetimibe. In such cases, bempedoic acid may be added to see if the target LDL-C is achieved on such triple therapy.
• Bempedoic acid should not be prescribed in patients with severe renal or hepatic dysfunction, or in pregnant or breastfeeding females.
• Consider avoiding the use of bempedoic acid in patients with a history of tendon rupture.
• Patients with a history of gout may have recurrent attacks during treatment with bempedoic acid if their uric acid concentration is not controlled. In these patients, bempedoic acid should be initiated (preferably with uricosuric drugs) only if the benefits outweigh the risks and only after a detailed discussion with the patient. Regular monitoring of uric acid levels is warranted.
• Consider avoiding bempedoic acid in patients with hyperuricemia >6–7 mg/dL. Uricosuric drugs may be added to the treatment.

Lipid Association of India
Recommendations for Use of Bempedoic Acid in Secondary Prevention

• The LAI recommends that LDL-C goals must be achieved in all patients according to the LAI risk stratification algorithm. High-intensity statin therapy (atorvastatin 40–80 mg or rosuvastatin at 20–40 mg once daily) is the mainstay of treatment followed by ezetimibe 10 mg once daily.
• If LDL-C goals are not achieved despite maximally tolerated statin therapy and ezetimibe, bempedoic acid may be added as one of the non-statin drugs in patients with established ASCVD and HeFH (Fig. 4).
• In patients with true statin intolerance or contraindications, ezetimibe 10 mg once a day in combination with bempedoic acid 180 mg once a day is recommended.
• Bempedoic acid may be initiated in patients presenting with ACS who are not at LDL-C goal despite statins and ezetimibe as per the LAI risk stratification algorithm for LDL-C management in ACS⁴⁸ (Fig. 5).
• The possibility of decreased rates of new-onset diabetes with bempedoic acid makes it a reasonable consideration in patients with metabolic syndrome who require additional LDL-C reduction after statin therapy. Whether it can be initiated as initial lipid-lowering therapy in such patients has not been studied.
• Because of minimal drug–drug interactions, bempedoic acid may be useful in treating dyslipidemia in human immunodeficiency virus patients and other medical conditions where statin treatment may lead to drug interactions. Further studies are needed to verify the safety and efficacy of this approach.
• PCSK9 inhibitors may be reserved, if cost is a consideration, after maximally tolerated statin and ezetimibe. In such cases, bempedoic acid may be added to see if the target LDL-C is achieved on such triple therapy.
• Bempedoic acid should not be prescribed in patients with severe renal or hepatic dysfunction, or in pregnant or breastfeeding females.
• Consider avoiding the use of bempedoic acid in patients with a history of tendon rupture.
• Patients with a history of gout may have recurrent attacks during treatment with bempedoic acid if their uric acid concentration is not controlled. In these patients, bempedoic acid should be initiated (preferably with uricosuric drugs) only if the benefits outweigh the risks and only after a detailed discussion with the patient. Regular monitoring of uric acid levels is warranted.
• Consider avoiding bempedoic acid in patients with hyperuricemia >6–7 mg/dL. Uricosuric drugs may be added to the treatment.

Fig. 4: Risk stratification, LDL-C targets, and management algorithm in stable ASCVD and HeFH patients²⁻¹¹
Unmet Need for Further LDL-C Lowering in India Despite Statin Therapy

LAI 2022 Lipid Management Algorithm in Acute Coronary Syndrome

- Statin-naive patients (Group 1)
- Patients on low or moderate-intensity statins (Group 2)
- Patients on high-intensity statins (HIS) (Group 3)
- Patients with established statin intolerance (Group 4)

On admission
1. Send blood sample for extended lipid profile including Lp(a) at emergency triage
2. Stratify ASCVD risk according to LAI risk algorithm and define LDL-C target

On receiving lipid profile report in hospital, continue HIS + Ezetimibe (EZ)

On admission
Start/Continue HIS + Ezetimibe (EZ)
Start/Continue EZ

Fig. 5: 2022 lipid management algorithm in ACS

- In patients without a history of hyperuricemia, uric acid levels should be monitored as and when clinically indicated.
- Patients on moderate to high doses of simvastatin (>20 mg) or pravastatin (>40 mg) should be switched to another statin before starting bempedoic acid because of possible drug interactions.
- Physician judgment is essential regarding indications, contraindications, and appropriateness of initiation of bempedoic acid in an individual patient. The patient needs to be involved in shared decision-making.

Conclusions
Lipid-lowering therapy is key to improving CV outcomes in patients with established ASCVD and HeFH. Lifestyle interventions in combination with high-intensity statin therapy are the first-line management strategy followed by ezetimibe. However, there are several instances in which additional non-statin therapy may be required. This includes patients who are unable to achieve recommended LDL-C goals according to the LAI risk stratification algorithm despite being on high-intensity statins with ezetimibe and patients with statin intolerance. In such patients, there are a few options available such as bile acid sequestrants and PCSK9 inhibitors. These are associated with some disadvantages that include the high cost of PCSK9 inhibitors, but both have been shown to reduce the risk of CV events.

Bempedoic acid is a new addition to our lipid-lowering armamentarium that can facilitate further LDL-C lowering as shown in numerous clinical studies either as monotherapy or in combination with ezetimibe, with or without statins in subjects with hypercholesterolemia. This LAI consensus document describes the pharmacology, indications, contraindications, advantages, and evidence-based recommendations for use of bempedoic acid in clinical practice. The low incidence of muscle-related side effects, minimal drug interactions, a significant reduction in hsCRP, and the possibility of beneficial effects on glycemic control make it a useful adjunct for LDL-C lowering. The results of the ongoing CV outcomes trial will better define its place in the management algorithm for ASCVD prevention, but in the meantime, it is a useful agent for adjunctive LDL-C lowering.
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REFERENCES


18. Recommendations of the SEC (Cardiovascular & Renal) made its 100th meeting held on 06.04.2022 at CDSCO (HQ), New Delhi. Recommendations Cardio 06.04.22. pdf (cdsco.gov.in).