Effects of bempedoic acid on markers of inflammation and Lp(a)

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Purpose of review
To study the effect of bempedoic acid on markers of inflammation and lipoprotein (a) to help determine if the drug would be useful to treat patients with elevated cardiovascular risks and residual cardiovascular risk despite optimal low-density lipoprotein cholesterol (LDL-C) levels.

Recent findings
Bempedoic acid is found to cause significant reduction in LDL-C and high-sensitivity C-reactive protein (hs-CRP) in various randomized clinical trials. Multiple meta-analyses have also found that bempedoic acid therapy leads to reduction in non–high-density lipoprotein cholesterol (non-HDL-C), total cholesterol (TC) and apolipoprotein B (ApoB) levels. However, it has minimal effect on lipoprotein (a) (Lp(a)) level.

Summary
Bempedoic acid is a new lipid-lowering agent that inhibits enzyme ATP-citrate lyase in the cholesterol biosynthesis pathway. Major risk of cardiovascular events and its associated morbidity and mortality are proportional to LDL-C and inflammatory markers levels. It was found that bempedoic acid significantly lowers LDL-C, hs-CRP and other inflammatory markers levels. This drug could potentially be used in patients with elevated cardiovascular risk, in patients with residual cardiovascular risk despite attaining LDL-C goal and in statin intolerant patients.

Keywords
bempedoic acid, high-sensitivity C-reactive protein, lipoprotein (a), low-density lipoprotein cholesterol

INTRODUCTION

Bempedoic acid is a new lipid-lowering agent that inhibits enzyme ATP-citrate lyase in the cholesterol biosynthesis pathway [1▪]. Major risk of cardiovascular events and its associated morbidity and mortality are proportional to low-density lipoprotein cholesterol (LDL-C) and inflammatory markers levels [1▪,2▪▪]. Statins are currently the mainstay drugs used to control LDL-C levels. Despite being on high intensity statin or maximally tolerated statin, patients fail to achieve recommended LDL-C goals. For such patients, alternative lipid-lowering agents like bile acid sequestrants, ezetimibe, and proprotein convertase subtilisin/kexin 9 (PCSK9) inhibitors are available [3▪▪]. Despite optimization of LDL-C levels by various lipid-lowering agents, recurrence of cardiovascular disease implies the need for addressing factors related with residual cardiovascular risk. Markers of inflammation such as high-sensitivity C-reactive protein (hs-CRP) and lipoprotein (a) (Lp(a)) are key determinants of cardiovascular risk [4▪].

Bempedoic acid was studied in Cholesterol Lowering via bempedoic Acid, an ACL-inhibiting Regimen (CLEAR) studies. Patients with atherosclerotic cardiovascular risk (ASCVD) and/or heterogeneous familial hypercholesterolemia (HeFH) or hypercholesterolemia were part of these studies [5▪▪]. It was found that bempedoic acid significantly lowers LDL-C and hs-CRP levels [1▪]. This review provides a comprehensive view of this drug's known pharmacokinetics, pharmacodynamics, clinical trials and most importantly its effect on markers of inflammation and Lp(a).

BEMPEDOIC ACID

Bempedoic acid also known as 8-hydroxy-2,2,14,14-tetramethylpentadecanedioic acid is an oral lipid-lowering agent, which is a prodrug that gets activated

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KEY POINTS

- Bempedoic acid is an oral agent with significant lipid-lowering and anti-inflammatory activity.
- Bempedoic acid can be used in patients with statin intolerance due to lower incidence of muscular side effects.
- Bempedoic acid can be used in patients with residual cardiovascular risk despite attaining LDL-C goal due to its anti-inflammatory activity.

to its active form in the liver. USA Food and Drug Administration (FDA) approved the use of this drug in February 2020 for adults with established ASCVD and/or heterozygous familial hypercholesterolemia.

Mechanism of action

Cholesterol synthesis is a multistep process that takes place in the liver with acetyl-CoA as the precursor. Acetyl-CoA is transported as citrate from mitochondria to cytoplasm of the cell. In the cytoplasm, citrate is converted to acetyl CoA by enzyme adenosine triphosphate citrate-lyase (ACL).

Bempedoic acid is a prodrug that gets activated to bempedoyl-CoA by liver long-chain acyl-CoA-synthetase I (ACSVL I) [6]. Bempedoyl-CoA inhibits ACL (Fig. 1). This leads to decreased cholesterol synthesis, which leads to increased LDL receptor expression with increased liver LDL uptake, ultimately leading to decrease in LDL-C levels in the body [7▪]. Enzyme ACSVL I is predominantly present in the liver and absent in skeletal muscles which leads to reduced muscular adverse effects [8▪▪].

Anti-inflammatory action of bempedoic acid is due to activation of adenosine monophosphate (AMP) activated protein kinase (AMPK) via phosphorylation. This leads to inhibition of mitogen-activated protein kinase (MAPK) pro-inflammatory pathway, which leads to decreased release of proinflammatory cytokines (Fig. 2) [8▪▪].

Pharmacokinetics

Bempedoic acid is administered orally in the daily recommended dose of 180 mg. It is absorbed in the small intestine. Absorption is unaffected by food and has a half-life of 15–24 h and reaches peak blood plasma concentrations after approximately 3.5 h. It is transported bound to protein in plasma with a distribution volume of 181 [1▪]. Undergoes conjugation with glucuronic acid primarily in the liver. Majority (70%) is eliminated by renal excretion, and other 30% is eliminated hepatically [8▪▪,9▪▪].

It was found that no renal adjustment of dosing was required for patients with mild to moderate renal impairment; however, the drug has not been sufficiently studied in patients with severe renal impairment and end-stage renal disease on dialysis [10]. Likewise, no adjustment of dosing is required in patients with mild to moderate hepatic impairment (Child Pugh class A and B); however, the drug should not be administered in patients with severe hepatic impairment (Child Pugh class C) (Table 1) [8▪▪].

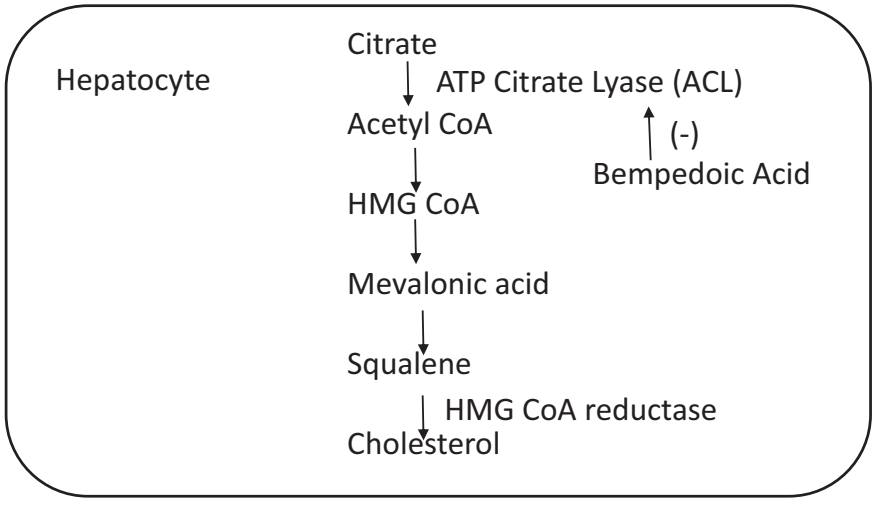

FIGURE 1. Mechanism of action of bempedoic acid. acetyl CoA, Acetyl coenzyme A; ATP citrate lyase, ATP citrate lyase; HMG CoA reductase, 3-hydroxy-3-methylglutaryl coenzyme A reductase; HMG CoA, 3-hydroxy-3-methylglutaryl coenzyme A. Adapted from [7▪].

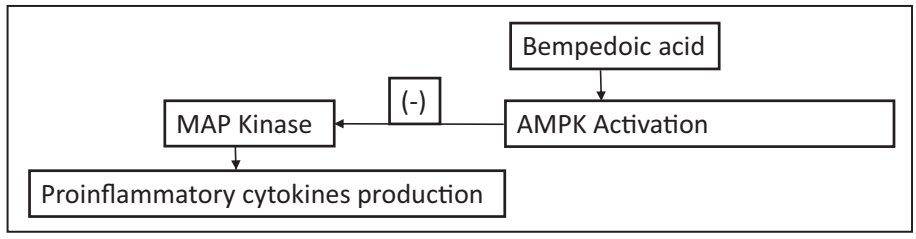

FIGURE 2. Anti-inflammatory effect of bempedoic acid. AMPK, adenosine monophosphate activated protein kinase; MAP kinase, mitogen-activated protein kinase. Adapted from [8▪▪].

Drug-drug interaction

Combination of bempedoic acid with certain statins at a specific dose have shown to cause adverse effects. Bempedoic acid when administered with simvastatin at a dose greater than 20 mg or with pravastatin at a dose greater than 40 mg were studied to have an increased risk of muscle-related adverse effects [11▪▪].

Table 1. Pharmacokinetics of bempedoic acid

Bempedoic acid	
FDA-approved indication	Adjunct to maximally tolerated statin therapy for reducing LDL-C levels in patients with ASCVD and HeFH.
Route of administration	Oral
Recommended daily dosage	180 mg
Absorption site	Small intestine
Half life	15–24 h
Time for peak plasma concentration	3.5 h
Distribution	Protein bound in plasma
Distribution volume	18 l
Metabolism	Conjugation with glucuronic acid in liver
Excretion	70% Kidney, 30% Liver
Dose adjustment	Not studied in severe renal impairment, end stage renal disease on dialysis Should not be administered in patients with severe hepatic impairment (Child Pugh class C)
Special patient population	Not recommended for pregnant patients Should be discontinued in breast feeding patients Not approved for pediatric patients
Drug-drug interaction	Should not be co-administered with simvastatin at a dose greater than 20 mg and pravastatin at a dose greater than 40 mg
Adverse effects	Hyperuricemia and gout Tendon rupture
Monitoring	Lipid panel in 8–12 weeks

ASCVD, Atherosclerotic cardiovascular risk; HeFH, Heterogeneous familial hypercholesterolemia.
Adapted from [1▪,8▪▪,9▪▪,10].

Special patient population

In pregnant women, bempedoic acid is not recommended due to lack of data on its potential risk of miscarriage, birth defects or adverse effects on the fetus. It is recommended that the drug be discontinued in breast feeding women due to potential for adverse effect on infants. This drug has not been approved for pediatric patients [1▪,9▪▪].

Adverse effects

Bempedoic acid is known to cause minimal side effects such as upper respiratory infection, bronchitis, muscle cramps and pain, nausea, abdominal pain and headaches [12▪]. However, clinical trials have indicated that bempedoic acid has lower incidence of muscle weakness, myalgia and muscle spasms compared to statins. This could be explained by absence of enzyme ACSVL I (which is required for conversion of prodrug of bempedoic acid to its active form) in skeletal muscles leading to reduced muscular adverse effects [9▪▪].

Studies have shown that bempedoic acid use has been associated with mild, asymptomatic and self-limited rise in serum aminotransferase levels. Rare instances of clinically apparent acute liver injury have also been reported [12▪].

Major side effects include hyperuricemia, gout and tendon rupture. Elevated serum uric acid levels seen in bempedoic acid users is due to glucuronide metabolite of bempedoic acid competing with uric acid for the renal organic anion transporter 2 (OAT2). Tendon rupture was seen in 0.5% of patients [8▪▪,9▪▪].

MARKERS OF INFLAMMATION AND LIPOPROTEIN (a)

High-sensitivity C-reactive protein (hsCRP) is an acute phase reactant, which is produced in the liver

in response to acute systemic inflammation. hsCRP level is a known independent predictor of ASCVD risk and subsequent morbidity and mortality. Studies have shown that hsCRP levels less than 2 mg/l provide significant ASCVD risk reduction [7▪]. Lipoprotein (a) is a modified form of LDL-C and is known to possess atherogenic potential by promoting a local inflammatory response and foam cell formation. Lp(a) levels especially at higher levels are known to increase ASCVD risk. 2018 AHA/ACC guidelines on management of blood cholesterol consider inflammatory markers as risk modulators [13].

Clinical trials with bemepoic acid

Multiple randomized, double-blind, placebo-controlled, parallel-group, multicenter, phase 3 studies were conducted from 2016 to 2018 (Table 2) [6].

CLEAR Harmony

A study of bempedoic acid in patients with ASCVD and/or HeFH with LDL-C greater than or equal to 70 mg/dl despite maximally tolerated statin therapy. Total 2230 patients were part of the study, 1488 of them received bempedoic acid and the other 742 received placebo over 52 weeks. Incidence of treatment-related adverse effects was the primary objective studied. Bempedoic acid group was noted to have a higher incidence of gout (1.2%) as compared to placebo (0.3%). Bempedoic acid group was also found to have reduced LDL-C levels by 18.1% [95% confidence interval (95% CI) −20.0 to −16.1, $P < 0.001$] at week 12, 16.1% at week 24 and 13.6% at week 52. Levels of hsCRP showed a similar trend with a 25% reduction in week 12, 19.1% in week 24, 16.2% in week 52 [1▪,7▪,8▪▪].

CLEAR Wisdom

A study of bempedoic acid in patients with ASCVD and/or HeFHwith LDL-C greater than or equal to 70 mg/dl despite maximally tolerated statin therapy. Total 779 patients were part of the study, 522 of them received bempedoic acid and the other 257 received placebo over 12 weeks. Reduction in LDL-C levels was the primary objective studied. Percentage reduction in LDL-C levels at week 12 was found to be 17.5% (95% CI: −21.0 to −13.9, $P < 0.001$) and reduction in hsCRP levels at week 12 was 9.3% [6,7▪].

CLEAR Serenity

A study of bempedoic acid in patients with hypercholesterolemia intolerant to statins and inadequately controlled LDL-C levels. Patients who were intolerant to at least two statins and one of them at the lowest available dose were part of the study. Total 345 patients were part of the study, 234 of them received bempedoic acid and the other 111 received placebo over 24 weeks. Reduction in LDL-C levels was the primary objective studied. Percentage reduction in LDL-C levels at week 12 was found to be 22.3% (95% CI: −25.1 to −17.7, $P < 0.001$) and reduction in hsCRP levels at week 12 was 28.1% [6,7▪,8▪▪].

CLEAR Tranquility

A study of bempedoic acid in patients with hypercholesterolemia intolerant to statins and with LDL-C greater than or equal to 100 mg/dl on ezetimibe

Table 2. Clinical trials on bempedoic acid

	CLEAR Harmony	CLEAR Wisdom	CLEAR Serenity	CLEAR Tranquility
Total participants (*N*)	2230	779	345	269
Participant distribution (Bempedoic acid/placebo)	1488/742	522/257	234/111	181/88
Lipid-lowering therapy	Maximally tolerated statin therapy	Maximally tolerated statin therapy	Statin intolerance on no or low statin therapy	Statin intolerance on no or low statin therapy
Primary objective	Incidence of treatment related adverse effects	% change in LDL-C after 12 weeks of therapy	% change in LDL-C after 12 weeks of therapy	% change in LDL-C after 12 weeks of therapy
Duration	52 weeks	12 weeks	24 weeks	12 weeks
LDL-C change at 12 weeks (%) (Bempedoic acid/placebo)	−16.5/+1.6	−15.1/+2.4	−23.6/−1.3	−23.5/+5.0
hsCRP change at 12 weeks (%) (Bempedoic acid/placebo)	−22.4/+2.6	−18.7/−9.4	−25.4/+2.7	−32.5/+2.1

hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol.
Adapted from [7▪,8▪▪].

therapy. Patients who were intolerant to at least two statins and one of them at the lowest available dose were part of the study. Total 269 patients were part of the study, 181 of them received bempedoic acid and the other 88 received placebo over 24 weeks. Reduction in LDL-C levels was the primary objective studied. Percentage reduction in LDL-C levels at week 12 was found to be 28.5% (95% CI: −34.4.0 to −22.5, $P < 0.001$) and reduction in hsCRP levels at week 12 was 33%. Significant reduction was also noted in non-HDL-C (23.6%), total cholesterol (TC, 18.0%), ApoB (19.3%) levels [1▪,6,7▪,8▪▪,14▪].

CLEAR Harmony open-label extension

A study of bempedoic acid in patients with ASCVD and/or HeFH with LDL-C greater than or equal to 70 mg/dl despite maximally tolerated statin therapy. This is an extension study of the CLEAR Harmony study, done to determine the long-term safety and efficacy of bempedoic acid. Total 1462 patients were part of the study. Of these, 970 were part of the parent study and had already received bempedoic acid for 52 weeks. These patients received bempedoic acid for additional 78 weeks, making the total duration of therapy as 130 weeks. Other 492 patients received placebo in the parent study. These patients received bempedoic acid for a total of 78 weeks. Primary objective of the study was to determine the safety of the drug by assessing the incidence of treatment-emergent adverse events (TEAEs), serious TEAEs, TEAEs leading to drug discontinuation and TEAES with fatal outcome. Groups that received bempedoic acid for 130 versus 78 weeks had similar incidents of TEAEs (78.1%, 78.3%), serious TEAEs (20.8%, 19.7%), TEAEs leading to drug discontinuation (7.1%, 9.1%) and TEAES with fatal outcome (1%, 0.6%). The decrease in LDL-C levels remained stable during long-term use. It was also found that bempedoic acid reduced non–high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (Apo B), TC and hsCRP levels irrespective of treatment duration. At week 78, the mean % change from parent study baseline was −11% for non–HDL-C, −7% for Apo B, −10% for TC; the median % change from parent study baseline was −17% for hsCRP [15▪▪].

CLEAR Outcome

A study of bempedoic acid in patients with ASCVD or at high risk of developing ASCVD with intolerant to statins and with LDL-C greater than or equal to 100 mg/dl [16]. Total 13 970 patients were part of the study, 6992 of them received bempedoic acid and the other 6978 received placebo over a mean duration of 40.6 months. Occurrence of major cardiovascular events (MACE), which include death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke and coronary revascularization were the primary outcome studied. MACE were found to be lower on patients taking bempedoic acid (11.7%) as compared to placebo (13.3%) (hazard ratio 0.87; 95% CI: 0.79–0.96, $P < 0.004$) [17▪▪].

Other studies

Secondary analysis on CLEAR Harmony trail was done to determine the effect of bempedoic acid on hsCRP, interleukin-6 (IL-6), fibrinogen and Lp (a) in patients with residual inflammatory risk. It was found that at week 12, bempedoic acid use leads to 3.7% reduction in IL-6, 2.1% increase in fibrinogen and 2.4% increase in Lp(a) levels. To conclude, bempedoic acid reduces hsCRP levels with minimal effect on fibrinogen, IL-6 or Lp(a) levels [5▪▪].

A randomized, double-blind, active comparator-controlled, parallel-group study was conducted on patients with LDL-C greater than or equal to 130 mg/dl. Patients with and without statin intolerance were part of the study. Individuals were randomized to receive 12-week treatment with bempedoic acid 120 mg alone, bempedoic acid 180 mg alone, ezetimibe alone, bempedoic acid 120 mg plus ezetimibe or bempedoic acid 180 mg plus ezetimibe. It was found that bempedoic acid alone or in combination with ezetimibe reduces non-HDL-C, TC, Apo B, LDL particle number and hsCRP compared with ezetimibe alone. A dose-dependent effect of bempedoic acid in reduction of hsCRP levels (30.1% for 120 mg versus 40.2% for 180 mg) was also found [2▪▪].

A double-blind clinical trial was conducted on patients with ASCVD, HeFH or multiple cardiovascular disease risk factors. Patients were randomly assigned into four groups in 2 : 2:2 : 1 ratio to receive bempedoic acid plus ezetimibe combination, bempedoic acid, ezetimibe or placebo for total of 12 weeks. Significant reduction in LDL-C was noted in bempedoic acid plus ezetimibe combination (36.2%) in comparison to bempedoic acid (17.2%), ezetimibe (23.2%) and placebo. The bempedoic acid plus ezetimibe combination was also found to lower hs-CRP (35.1%) and other lipid levels, including non-HDL-C, TC and Apo B [7▪].

A meta-analysis of seven randomized clinical trials was performed to assess the percentage change in LDL-C and hsCRP levels in patients on bempedoic acid versus placebo. Bempedoic acid therapy was shown to have significant reduction in LDL-C (20.3%), Apo B (14.3%), non-HDL-C (15.5%) and hsCRP (23.4%) levels [16].

Anti-inflammatory properties of bempedoic acid were studied in primary human monocyte-derived macrophages (MDMs). It was found that bempedoic acid strongly suppressed the release of

TNF-α, IL-1β, IL-6 and IL-8 by stimulated MDMs in concentration-dependent manner with inhibitory effects ranging from 15 to 77% ($P < 0.05$) [18].

In a study, differential effects of statins and bempedoic acid on macrophage activation was explored. Treatment of primary murine macrophages with statins impaired phagocytotic activity and, concurrently, enhanced pro-inflammatory responses, characterized by an induction of TNF, interleukin (IL) 1β and IL6. Whereas bempedoic acid was found to have negligible impact on macrophage responses [19].

CONCLUSION

Bempedoic acid, also known as 8-hydroxy-2,2,14,14-tetramethylpentadecanedioic acid, is an oral lipid lowering agent that inhibits enzyme ATP-citrate lyase in the cholesterol biosynthesis pathway. Anti-inflammatory action of bempedoic acid is due to activation of AMPK, which inhibits MAPK pro-inflammatory pathway. It is found to cause significant reduction in LDL-C and hs-CRP in various randomized clinical trials. Multiple meta-analyses have also found that bempedoic acid therapy leads to reduction in non-HDL-C, TC and ApoB levels. However, it was found to have minimal effect on Lp(a) level. Higher incidence of gout was also noted. This drug could potentially be used in patients with elevated cardiovascular risk, in patients with residual cardiovascular risk despite attaining LDL-C goal and in statin-intolerant patients.

Acknowledgements

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None.

Conflicts of interest

None.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Ruscica M, Sirtori CR, Carugo S, *et al.* Bempedoic acid: for whom and when. ■ Curr Atheroscler Rep 2022; 24:791–801.

This article highlights the clinical situations in which bempedoic acid can be used. This knowledge may help in proper management of hyperlipidemia.

2. Maierean S, Webb R, Banach M, Mazidi M. The role of inflammation and the ■■ possibilities of inflammation reduction to prevent cardiovascular events. Eur Heart J Open 2022; 2:oeac039.

This review discusses the role of inflammation and the possibilities of inflammation reduction to prevent major cardiovascular events. Bempedoic acid usage leading to significant reduction in circulating hs-CRP levels has been discussed. This may help guide clinicians towards prescribing bempedoic acid to reduce cardiovascular events.

3. Abdul-Rahman T, Bukhari SM, Herrera EC, *et al.* Lipid lowering therapy: an era ■■ beyond statins. Curr Probl Cardiol 2022; 47:101342.

This article discusses the pharmacology of various nonstatin lipid-lowering agents. Mechanism of action of each of these agents were discussed in detail.

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This review discusses the key determinants of residual cardiovascular risk and various available therapies to manage the same. These findings may help in further management of cardiovascular disease events after optimization of LDL-C levels.

5. Ridker PM, Lei L, Ray KK, *et al.* Effects of bempedoic acid on CRP, IL-6, fibrinogen ■■ and lipoprotein (a) in patients with residual inflammatory risk: a secondary analysis of the CLEAR harmony trial. J Clin Lipidol 2023; 17:297–302.

This study established that bempedonic acid appears to significantly lower LDL-C and hsCRP. This finding may have significance in treating patients with ASCVD on maximally tolerated statin therapy.

6. Ruscica M, Sirtori CR, Ferri N, Corsini A. New players in the treatment of hypercholesterolaemia: focus on bempedoic acid and inclisiran. Eur Heart J Suppl 2021; 23(Suppl E):E59–E62.

7. Tummala R, Gupta M, Devanabanda AR, *et al.* Bempedoic acid and its role in ■ contemporary management of hyperlipidemia in atherosclerosis. Ann Med 2022; 54:1287–1296.

This article provided a comprehensive review of the mechanism of action, preclinical and clinical trials on bempedoic acid. Bempedoic acid being a favorable alternative to other nonstatin lipid-lowering agents was discussed.

8. Biolo G, Vinci P, Mangogna A, *et al.* Mechanism of action and therapeutic use ■■ of bempedoic acid in atherosclerosis and metabolic syndrome. Front Cardiovasc Med 2022; 9:1028355.

This review explains in detail regarding the biochemistry involved and mechanism of action of bempedoic acid. Various clinical applications of the drug are discussed as well. This review helps in deeper understanding of the pharmacokinetics of the drug.

9. Chandramahanti S, Farzam K. Bempedoic acid [Internet]. PubMed. Treasure ■■ Island (FL): StatPearls Publishing; 2024 [cited 2 February 2024]. https://pubmed.ncbi.nlm.nih.gov/37603623/

This chapter in the book discusses the indications, mechanism of action and pharmacokinetics of bempedoic acid. It also discusses specific dosing in various patient populations. These findings may be helpful in guiding physicians in prescribing this drug.

10. Amore BM, Sasiela WJ, Ries DK, *et al.* Pharmacokinetics of bempedoic acid in patients with renal impairment. Clin Transl Sci 2022; 15:789–798.

11. Jadhav SB, Crass RL, Chapel S, *et al.* Pharmacodynamic effect of bempedoic ■■ acid and statin combinations: predictions from a dose–response model. Eur Heart J Cardiovasc Pharmacother 2022; 8:578–586.

This study discusses the pharmacodynamic effect of combining bempedoic acid and statins. It highlights that combination of bempedoic acid with lower dose statins can provide therapeutic options for patients who cannot tolerate high-intensity statins or achieve LDL-C thresholds with maximally tolerated statin therapy alone.

12. Bempedoic acid. LiverTox: clinical and research information on drug-induced ■ liver injury [Internet]. Bethesda, MD: National Institute of Diabetes and Digestive and Kidney Diseases; 2023.

This chapter in the book discusses various adverse effects of bempedoic acid, with special emphasis on hepatotoxicity. These findings help in dose adjustment of the drug in patients with hepatic impairment.

13. Grundy SM, Stone NJ, Bailey AL, *et al.* 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2019; 139:e1082–e1143.

14. Kim KA, Park HJ. New therapeutic approaches to the treatment of dyslipi- ■ demia 2: LDL-C and Lp (a). J Lipid Atheroscler 2023; 12:37.

This article discusses the recent progress made in approaches to treat dyslipidemia. It also discusses various drugs that target lipoprotein (a) and their role in prevention of atherosclerosis. These findings may help guide further treatment of dyslipidemia.

15. Ballantyne CM, Banach M, Bays HE, *et al.* Long-term safety and efficacy of ■■ bempedoic acid in patients with atherosclerotic cardiovascular disease and/or heterozygous familial hypercholesterolemia (from the CLEAR Harmony Open-Label Extension Study). Am J Cardiol 2022; 174:1–11.

This study highlights the long-term safety of using bempedoic acid. It discusses the various adverse reactions seen with bempedoic acid use. This study may help clinicians in knowing the side effects associated with long-term use of this drug and help guide the judgement on when the drug should be discontinued if needed.

16. Masson W, Lobo M, Lavalle-Cobo A, Molinero G. Effect of bempedoic acid on atherogenic lipids and inflammation: a meta-analysis. Clín Investig Arterioscler 2021; 33:117–126.

17. Nissen SE, Lincoff AM, Brennan D, *et al.* Bempedoic acid and cardiovascular ■■ outcomes in statin-intolerant patients. N Engl J Med 2023; 388:1353–1364.

This clinical trial was done to assess the long-term effect of bempedoic acid on major cardiovascular events in patients with statin intolerance. Death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke and coronary revascularization were the events assessed. This study may help clinicians in treating hyperlipidemia in statin intolerant patients.

18. Filippov S, Pinkosky SL, Lister RJ, *et al.* ETC-1002 regulates immune response, leukocyte homing, and adipose tissue inflammation via LKB1-dependent activation of macrophage AMPK. J Lipid Res 2013; 54:2095–2108.

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