



International Journal of **Medicine Sciences**

ISSN Print: 2664-8881

ISSN Online: 2664-889X

Impact Factor: RJIF 8

IJMS 2023; 5(2): 01-05

www.medicinejournal.in

Received: 28-06-2023

Accepted: 09-07-2023

JP Sawhney

Chairman, Department of
Cardiology, Sir Ganga Ram
Hospital, Delhi, India

Peeyush Jain

Head, Department of
Preventive Cardiology, Fortis
Escorts, Delhi, India

Role of bempedoic acid in lipid management-An Indian perspective

JP Sawhney and Peeyush Jain

DOI: <https://doi.org/10.33545/26648881.2023.v5.i2a.36>

Abstract

In India atherosclerotic heart disease is a primary cause of mortality and morbidity. Several hypolipidemic medications target low-density lipoprotein cholesterol (LDL-C) to reduce the risk of atherosclerosis. Statins remain the gold standard for dyslipidemia management. Despite the fact that lipid-lowering medicines, particularly statins, have demonstrated significant success in lowering the risk of cardiovascular disease (CVD), many patients fail to meet the lipid targets indicated by clinical recommendations. Bempedoic acid is a novel hypolipidemic agent that inhibits the adenosine triphosphate citrate lyase enzyme in the cholesterol production pathway. Results from the Cholesterol Lowering via Bempedoic Acid [ECT1002], an ACL-Inhibiting Regimen (CLEAR) trial have demonstrated that bempedoic acid added to maximally tolerated statin therapy provided long-term safety and efficacy. Bempedoic acid is a significant addition to the therapeutic options for individuals with high LDL-C. This article explores the perspectives of Indian experts on the role of bempedoic acid in lipid management.

Keywords: Bempedoic acid, statins, low-density lipoprotein cholesterol, CLEAR trials, ATP citrate lyase inhibitor, atherosclerotic heart disease

Introduction

The prevalence of atherosclerotic cardiovascular disease (ASCVD) in India is currently at epidemic levels, with no apparent signs of decline^[1]. ASCVD is highly prevalent in India and the leading cause of mortality as well as a key reason behind the loss of young lives. In comparison to Western countries, coronary artery disease (CAD) in India manifests at a younger age. Appallingly, up to 25% of myocardial infarctions (MIs) occur in patients below 40 years of age^[2,3]. The findings of the Global Burden of Disease study reveal that India has an age-standardized cardiovascular disease (CVD) death rate of 272 per 100,000 population, which is significantly higher than the global average of 235. Indians are affected by CVD almost ten years earlier than their Western counterparts^[3]. The disease persists and shows no indications of abating in the country.

Diabetes, hypertension, smoking and obesity are the most common conventional risk factors for CAD in Indians. Apart from these conventional risk factors, physical inactivity, low fruit and vegetable intake and psychosocial stress have been reported in INTERHEART study as a cause of acute myocardial infarctions among South Asians^[4]. Experts emphasized that dyslipidemia is one of the key risk factors for developing atherosclerosis. Indian patients tend to have a lower threshold of LDL-C levels for the onset of ASCVD compared to Western populations^[5].

Although lipid-lowering treatments, especially statins, have achieved remarkable success in reducing the risk of CVD, many patients fail to meet the lipid targets recommended by clinical guidelines. Bempedoic acid offers a novel strategy for lipid-lowering therapy. With the potential to reduce LDL-C levels up to 40%, bempedoic acid could not only serve as a monotherapy but also as part of a combination lipid-lowering therapy with ezetimibe, thereby contributing to the reduction of CVD risk^[5].

Meetings were held with Indian experts to share their experiences regarding bempedoic acid and to discuss the latest advances in lipid management in India. Opinions of the experts supported by an extensive review of the literature are presented in this paper.

Corresponding Author:

Peeyush Jain

Head, Department of
Preventive Cardiology, Fortis
Escorts, Delhi, India

LDL-C: A necessary and sufficient risk factor for ASCVD

Elevated levels of LDL-C is the main contributor to ASCVD and the crucial first step in the development of atherosclerosis is the retention of LDL-C within the arterial wall. A markedly increased level of LDL-C is necessary for the development of atherosclerosis and it is a sufficient risk factor as a considerably raised level results in the development of atherosclerosis and acute MI [6]. This is evident from the results of a meta-analysis of around 200 prospective cohort studies, Mendelian randomization studies and randomized clinical trials involving more than 2 million participants, with a follow-up period of over 20 million person-years and over 150,000 ASCVD incidents; there has been a remarkably consistent log-linear association observed between the extent of LDL-C exposure of the vasculature and the risk of ASCVD, which varies based on the absolute magnitude of exposure [7].

Statins for ASCVD Risk Reduction

All experts unanimously asserted that at present, statins are the mainstay of therapy, unless not tolerated by patients. A plethora of literature suggests that statins can reduce the risk of CAD by >50% and they are the first line of therapy for individuals with a high risk of ASCVD irrespective of their LDL-C levels [6]. According to one of the most significant meta-analyses of statins in secondary prevention, the Cholesterol Treatment Trialists Collaboration found that reducing LDL-C levels by 1 mmol/L (or 39 mg/dL) resulted in a 12% decrease in all-cause mortality, a 23% decrease in coronary death or myocardial infarction, a 24% decrease in coronary revascularization and a 17% decrease in nonfatal stroke [8]. However, with the growing recognition that "normal" is not synonymous with optimal, the standard for what constitutes a normal LDL-C level has been lowered. It is now widely accepted that "lower is better" across the entire spectrum of LDL-C levels, at least until it reaches 40 mg/dL [6]. For patients at very high risk, the 2019 European guidelines have reduced the target LDL-C level to below 55 mg/dL [9]. Experts suggested that LDL-C lowering is important in all cases up to below 100 mg/dL; however, for high-risk group patients, such as patients with diabetes and hypertension, it should be below 70 mg/dL. The safety and effectiveness of statins in reducing the risk of cardiovascular disease (CVD) has been demonstrated to be exceptional [10].

Unmet Needs in LDL-C Lowering

Although statins have been recommended as first-line therapy for lipid-lowering, there is a need for additional lipid-lowering agents either as monotherapy or more effectively in combination with other drugs.

Statin metabolism, adverse effects and varied response

Studies have revealed that compared to Western populations, Asians respond more strongly to statins, with racial/ethnic disparities in the pharmacokinetics of lipid-lowering medications. As a result of a slower statin metabolism and genetic variability, Asians need lower statin dosages to achieve the same level of lipid-lowering as their Western counterparts. A larger risk of statin-related side effects such as myalgia, neuropathy, increased blood glucose, and cognitive changes is however also raised by this heightened reaction. There has been little definitive research on the safety of statins among Asians, particularly Indians. More data on

efficacy and safety in various sub-groups are required to include in recommendations tailored to India [11].

Individuals' responses to statins may differ due to various factors including variations in genes involved in cholesterol metabolism and statin pharmacokinetics, such as transporter proteins. A pharmacogenetic study found significant associations between certain gene polymorphisms and heterogeneity in LDL-C lowering with atorvastatin and pravastatin. Gut microbiota may also affect variability in response to certain statins [5].

Residual risk

Even if patients are given high-intensity statins, there is still a sizable risk of ASCVD events. Placebo-controlled studies conducted over 4-5 years showed a 25%–35% decrease in adverse cardiovascular events, indicating that most patients still have a high risk of ASCVD [12].

Failure to achieve LDL-C goals

The significance of meeting LDL-C targets in patients with CVD was discussed by the experts in the meeting. Even when statins are administered, only ~20%–30% of individuals succeed in meeting desired LDL-C targets [5] because of multiple reasons, including poor adherence, low-intensity statin therapy, lowering statin dosages, elevated baseline LDL-C values and statin intolerance. Therefore, it is critical to increase the selection of LDL-C-lowering drugs. Bempedoic acid is a newly developed medication that is a welcome addition to the existing non-statin therapies, such as ezetimibe, bile acid sequestrants, and Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors [13].

Non-Statin LDL-C Lowering Therapy**Bempedoic acid: First-in-class inhibitor of adenosine triphosphate-citrate lyase**

Bempedoic acid is a tiny molecule with a half-life of 15–24 hours that is readily absorbed in the small intestine. It can be administered as a single oral dose of 180 mg as a prodrug. Food does not alter the oral bioavailability of bempedoic acid nor do age, sex, race or weight impact its pharmacokinetic properties. It quickly absorbs in the small intestine and stays in the body for 15-24 hours. Adenosine triphosphate-citrate lyase (ACL), a component of the cholesterol production pathway upstream of the enzyme hydroxy-methylglutaryl coenzyme A reductase (HMGCR), is inhibited by bempedoic acid [14].

Bempedoic acid increases LDL receptor levels, just like statins, which lowers plasma LDL-C levels. Bempedoic acid also reduces plasma glucose by gluconeogenesis inhibition and suppression of hepatic glucose production. Because bempedoic acid is converted to its active form, bempedoyl-CoA, by the hepatocyte-specific enzyme very-long-chain acyl-CoA synthetase-1 (ACSVL1), which is not expressed in adipose tissue, the gut or skeletal muscle, it has fewer detrimental effects on the muscles than statin therapy [15].

Because bempedoic acid does not influence cytochrome P450 enzymes, drug-drug interactions are decreased. However, *in vitro* research indicates that bempedoic acid inhibits the organic anion transporter OAT2, which could result in very modest increase in serum uric acid and creatinine. Simvastatin and pravastatin should be used with bempedoic acid with caution because of possible drug-drug interactions [15].

Clinical Evidence

Two clinical trials, CLEAR tranquilly and CLEAR Serenity (Cholesterol Lowering by Bempedoic acid, an ACL-Inhibiting Regimen), examined patients with hypercholesterolemia and statin intolerance. In two larger trials, CLEAR Harmony and CLEAR Wisdom, the effects of bempedoic acid were further studied in patients with ASCVD or high risk of ASCVD and heterozygous familial hypercholesterolemia (HeFH).

CLEAR Serenity

In the CLEAR Serenity study, 345 patients with hypercholesterolemia (mean baseline LDL-C 157.6 mg/dL) and statin intolerance were randomized in a ratio of 2:1 to receive either 180 mg of bempedoic acid or placebo once daily for 24 weeks. Besides, stable baseline lipid-lowering treatment was continued. Only 8.4% of patients were on very low-dose statins, with average daily doses of rosuvastatin (<5 mg), atorvastatin (<10 mg), simvastatin (<10 mg), lovastatin (<20 mg), pravastatin (<40 mg), fluvastatin (<40 mg), or pitavastatin (<2 mg)^[16].

The primary outcome measure was the mean percent change in LDL-C from baseline to week 12. Bempedoic acid significantly reduced LDL-C between baseline and week 12 (placebo-corrected difference: -21.4% [95% confidence interval (CI): -25.1% to -17.7%]; $p < 0.001$). Bempedoic acid significantly decreased non-high-density lipoprotein cholesterol (non-HDL-C; -17.9%), total cholesterol (-14.8%), apolipoprotein B (-15.0%), and high-sensitivity C-reactive protein (hs-CRP; -24.3%) when compared to placebo ($p < 0.001$ for all comparisons)^[16].

HDL-C was 4.5% lower in the bempedoic acid group, which was statistically significant ($p = 0.003$). Additionally, compared to the placebo group, the bempedoic acid group showed a reduced rate of new cases of diabetes or a worsening of pre-existing cases of diabetes (2.1% vs. 4.5%). Myalgia was the most common side effect involving the muscles, reported by 4.7% of individuals receiving bempedoic acid versus 7.2% of patients getting a placebo^[16].

CLEAR Tranquility

In this study, 269 people with a history of statin intolerance and LDL-C ≥ 100 mg/dL when on stable lipid-modifying drugs were given bempedoic acid 180 mg or placebo (2:1) once daily in addition to ezetimibe 10 mg/day for 12 weeks. Background low-dose or very low-dose statins were continued in 31% of individuals ($p = 0.002$). Bempedoic acid exhibited a similar rate of side events when compared with placebo. The primary outcome was a % change in LDL-C from baseline to week 12. After correcting for the placebo, bempedoic acid with ezetimibe resulted in a 28.5% reduction in LDL-C (bempedoic acid, -23.5%; placebo, +5.0%; $p < 0.001$)^[17].

A subgroup study found that bempedoic acid lowered LDL-C by a greater amount in patients who did not receive background statins (-34.7%) than in those who did (-20.5%), most likely because statins and bempedoic acid both work on the same pathway^[17].

There were statistically significant decreases in non-HDL-C (-23.6%), total cholesterol (-18.0%), apo B (-19.3%), and hs-CRP (-31.0%) with bempedoic acid versus placebo ($p < 0.001$ for all comparisons). Bempedoic acid significantly reduced HDL-C from baseline to week 12 versus placebo

(-7.3% vs -1.4%; $p = 0.002$). Bempedoic acid exhibited a similar rate of side events when compared with placebo^[17].

CLEAR Harmony

Bempedoic acid or placebo was given to 2,230 patients (2:1) with ASCVD, HeFH, or both who were undergoing maximally tolerated statin medication and had LDL-C values ≥ 70 mg/dL in the CLEAR Harmony trial. At 12 weeks, mean LDL-C levels had decreased by 19.2 mg/dL (16.5% from baseline; $p < 0.001$)^[18].

When evaluating the total incidence of side effects, the bempedoic acid group and the placebo group exhibited a similar incidence (78.5% vs 78.7%). Proportion of patients with elevated 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 hs-CRP (-21.5% [95% CI: -27.0% to -16.0%]) levels were lower in the bempedoic acid group at week 12 ($p < 0.001$ for all comparisons). Proportion of patients with newly diagnosed diabetes mellitus or those with worsening diabetes mellitus was significantly lower in the bempedoic acid group than in the placebo group (3.3% vs 5.4%; $p = 0.02$). The bempedoic acid group had a 5.8% decrease in HDL-C when compared with the placebo group. Bempedoic acid increased the likelihood of developing gout as compared to placebo [18 patients (1.2%) vs two patients (0.3%)]. The average haemoglobin level decreased by 4.1% over the first year of bempedoic acid treatment. Bempedoic acid maintained its potency through week 52^[18].

CLEAR Wisdom

In the CLEAR Wisdom study, 779 patients with ASCVD, HeFH, or both were randomized 2:1 to receive bempedoic acid or placebo for 52 weeks while receiving maximally tolerated statin therapy. At baseline, the average LDL-C level was 120.4 ± 37.9 mg/dL. The addition of 180 mg per day of bempedoic acid significantly lowered LDL-C levels when compared with placebo after 12 weeks of treatment (-15.1% vs 2.4%; $p < 0.01$)^[19].

When compared with placebo, bempedoic acid significantly lowered 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 hs-CRP (-18.7% vs -9.4%). Surprisingly, the bempedoic acid group had a 6.1% drop in HDL-C levels ($p < 0.001$). Nasopharyngitis (5.2% vs 5.1%), urinary tract infection (5.0% vs 1.9%), and hyperuricemia (4.2% vs 1.9%) were the most common side events with bempedoic acid vs placebo, respectively^[19].

Place in the therapy of bempedoic acid: Experts' recommendations

The experts opined that the first line of treatment for dyslipidemia remains statins. Bempedoic acid could be a choice of treatment for patients who have not achieved the necessary LDL-C reductions with >4 weeks of high-intensity statin therapy. In addition, in patients who are statin-intolerant or in whom statins are contraindicated and in patients with established ASCVD and HeFH, bempedoic acid may be introduced as one of the non-statin medications if LDL-C targets are not met despite maximally tolerated statin therapy and ezetimibe.

Current European guidelines advocate a phased approach to dyslipidemia therapy for people at high/very high cardiovascular risk. This strategy begins with the highest

tolerable dose of a high-intensity statin, followed by ezetimibe if the targets are not accomplished after four weeks. If the second 4-week dual therapy with statins and ezetimibe fails to reach the desired LDL-C target level, a PCSK9 inhibitor should be added. In theory, because triple therapy (statin/ezetimibe/PCSK9 inhibitor) can reduce baseline LDL-C levels by 85%, this step-by-step strategy should ensure that all patients attain their treatment targets. Aside from practical issues like cost and administration route, there are at least two major impediments to this strategy [20].

The first is the significant proportion of statin-intolerant patients, particularly those who develop muscle-related symptoms, which can result in a high dropout rate (up to 75%) within two years of initiating statin medication. The second explanation is when a patient fails to achieve the required lipid-lowering objective while receiving numerous lipid-lowering medications, such as triple therapy with statin/ezetimibe/PCSK9 inhibitor. This is especially true for those who are at extremely high risk (LDL-C < 55 mg/dL) or extreme risk (LDL-C < 40mg/dL) [14]. In all these circumstances, bempedoic acid may be used as a replacement (statin intolerance) or as an add-on medication to improve treatment outcomes [14]. In a recently published randomized trial, in patients with hypercholesterolemia, the combination of bempedoic acid, ezetimibe and atorvastatin demonstrated a significant reduction in LDL-C by 60.5% compared to placebo. This treatment approach enabled over 90% of the study participants to achieve the recommended LDL-C goal of <70 mg/dL. Most of the treatment-emergent adverse events were of mild to moderate severity and there were no instances of clinically significant increases in aminotransferase or creatine kinase levels among the patients [21].

Experts mentioned that Based on the data from the CLEAR Tranquility study, the use of bempedoic acid in combination with ezetimibe offers a valuable approach for treating hypercholesterolemia, particularly in patients who are intolerant to statins.

Experts also stated that bempedoic acid is beneficial in pre-diabetic and diabetic individuals because it does not influence glucose levels. Experts consider this a clinical advantage for bempedoic acid because many dyslipidemic patients are diabetic and many diabetic individuals are dyslipidemic.

Furthermore, many diabetic individuals have low vitamin D levels, which can lead to myalgia from statins or statin intolerance, especially at high doses. In such circumstances, a low-dose statin combined with BA treatment may be more beneficial.

Conclusion

Bempedoic acid is an important addition to the treatment arsenal for individuals with high/very high/extreme ASCVD risk and persistent LDL-C increases despite the administration of maximally tolerated statins and ezetimibe. It is generally well accepted with few side effects and regular blood monitoring can help to reduce the chances of adverse events. Along with statins, ezetimibe and PCSK9 inhibitors, bempedoic acid is one of the four pillars of current lipid-lowering medications. Individual tailoring of medications aimed not just at LDL-C control but also at non-LDL-C levels will be possible in the future, thanks to personalized medicine [14].

Bempedoic acid is a well-tolerated medication with few side effects and the risk of adverse events can be reduced with regular blood monitoring. Because it is not metabolized in the muscle, it may lower the likelihood of muscle-related side effects. It could be utilized as an additional therapeutic option

for people who have high LDL-C levels despite taking the highest doses of statins and ezetimibe. Bempedoic acid is a valuable complement to the therapeutic choices for people with elevated LDL-C.

Author Contributions

Both authors made significant contributions to the advisory board meetings' inception, documented the conversations, and substantively evaluated and approved the final version for submission.

Source of Funding

The expert panel discussion was organized in collaboration with Abbott Healthcare Pvt. Ltd. This article is based on the expert groups' discussion viewpoints. The views expressed and discussed in the meetings, as well as those presented in this paper, are the authors' independent views, not those of Abbott Healthcare Pvt. Ltd.

Conflict of Interest

For their involvement in the focused group discussion, both authors received speakers' honoraria from Abbott. In addition, J. P. Sawhney is a member of the Cardiological Society of India, the European Society of Heart Failure, the European Society of Preventive Cardiology, and European Atherosclerosis Society. Peeyush Jain received research grant from Sun Pharmaceuticals

Acknowledgement

The author thanks Indyte medical communication (C2C) for medical writing support and editorial assistance.

References

1. Duell PB, Mehta V, Nair D, Puri S, Nanda R, Puri R. The epidemic of atherosclerotic cardiovascular disease in India- Editorial. *J Clin Lipidol.* 2020;14:170-2.
2. Mehta V, Iyengar SS, Yusuf J, Mukhopadhyay S, Sattur GB, Puri R. Fighting the atherosclerotic cardiovascular disease epidemic: Declaring war on lipids by Lipid Association of India. *J Assoc Physicians India.* 2020;68(11[Special]):6-7.
3. Ardeshta DR, Bob-Manuel T, Nanda A, Sharma A, Skelton WP 4th, *et al.* Asian-Indians: A review of coronary artery disease in this understudied cohort in the United States. *Ann Transl Med.* 2018;6(1):12.
4. Sreenivas Kumar A, Sinha N. Cardiovascular disease in India: A 360-degree overview. *Med J Armed Forces India.* 2020;76(1):1-3.
5. Mehta V, Puri R, Duell PB, Iyengar SS, Wong ND, Yusuf J, *et al.* Unmet Need for Further LDL-C Lowering in India Despite Statin Therapy: Lipid Association of India Recommendations for the Use of Bempedoic Acid. *J Assoc Physicians India.* 2022;70(9):11-12.
6. Enas EA, Varkey B, Gupta R. Expanding statin use for prevention of ASCVD in Indians: Reasoned and simplified proposals. *Indian Heart J.* 2020;72(2):65-69.
7. Ference BA, Ginsberg HN, Graham I, Ray KK, Packard CJ, Bruckert E, *et al.* Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur Heart J.* 2017;38(32):2459-2472.
8. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, *et al.* Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data

- from 90,056 participants in 14 randomised trials of statins. *Lancet*. 2005;366(9493):1267-78.
9. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, *et al.*, ESC Scientific Document Group. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J*. 2020; 41(1):111-188.
 10. Collins R, Reith C, Emberson J, Armitage J, Baigent C, Blackwell L, *et al.* Interpretation of the evidence for the efficacy and safety of statin therapy. *Lancet*. 2016;388(10059):2532-2561.
 11. Misra S, Lyngdoh T, Mulchandani R. Guidelines for dyslipidemia management in India: A review of the current scenario and gaps in research. *Indian Heart J*. 2022;74(5):341-350.
 12. Libby P. The forgotten majority: unfinished business in cardiovascular risk reduction. *J Am Coll Cardiol*. 2005;46(7):1225-8.
 13. Stroes ES, Thompson PD, Corsini A, Vladutiu GD, Raal FJ, *et al.* European Atherosclerosis Society Consensus Panel. Statin-associated muscle symptoms: impact on statin therapy-European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management. *Eur Heart J*. 2015;36(17):1012-22.
 14. Bilato C, Sesti G, Averna M. Bempedoic Acid: A New Tool for LDL-Cholesterol Control in Patients with Coronary Artery Disease. *Rev. Cardiovasc. Med*. 2022;23(5):156.
 15. Ballantyne CM, Bays H, Catapano AL, Goldberg A, Ray KK, Saseen JJ. Role of Bempedoic Acid in Clinical Practice. *Cardiovascular Drugs and Therapy*. 2021;35:853-864.
 16. Laufs U, Banach M, Mancini GBJ, Gaudet D, Bloedon LT, Sterling LR, *et al.* Efficacy and Safety of Bempedoic Acid in Patients With Hypercholesterolemia and Statin Intolerance. *J Am Heart Assoc*. 2019;8(7):e011662.
 17. Ballantyne CM, Banach M, Mancini GBJ, Lepor NE, Hanselman JC, Zhao X, *et al.* Efficacy and safety of bempedoic acid added to ezetimibe in statin-intolerant patients with hypercholesterolemia: A randomized, placebo-controlled study. *Atherosclerosis*. 2018;277:195-203.
 18. Ray KK, Bays HE, Catapano AL, Lalwani ND, Bloedon LT, Sterling LR, *et al.* CLEAR Harmony Trial. Safety and Efficacy of Bempedoic Acid to Reduce LDL Cholesterol. *N Engl J Med*. 2019;380(11):1022-1032
 19. Goldberg AC, Leiter LA, Stroes ESG, Baum SJ, Hanselman JC, Bloedon LT, *et al.* Effect of Bempedoic Acid vs Placebo Added to Maximally Tolerated Statins on Low-Density Lipoprotein Cholesterol in Patients at High Risk for Cardiovascular Disease: The CLEAR Wisdom Randomized Clinical Trial. *JAMA*. 2019;322(18):1780-1788.
 20. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, *et al.*, 2019 ESC/EAS Guidelines for the management of dyslipidemias: lipid modification to reduce cardiovascular risk. *European Heart Journal*. 2020;41:111-188.
 21. Rubino J, MacDougall DE, Sterling LR, Hanselman JC, Nicholls SJ. Combination of bempedoic acid, ezetimibe and atorvastatin in patients with hypercholesterolemia: A randomized clinical trial. *Atherosclerosis*. 2021;320:122-128.