بنام خداوند جان و خرد

BEMPEDOIC ACID, DEVELOPMENT AND CLINICAL APPLICATION

M Siavash
Professor of endocrinology
Isfahan University of medical sciences
Fall 2024

Arena LIFE SCIENCE

This activity is supported by Arena life science.

Health First Always

The story, from the history

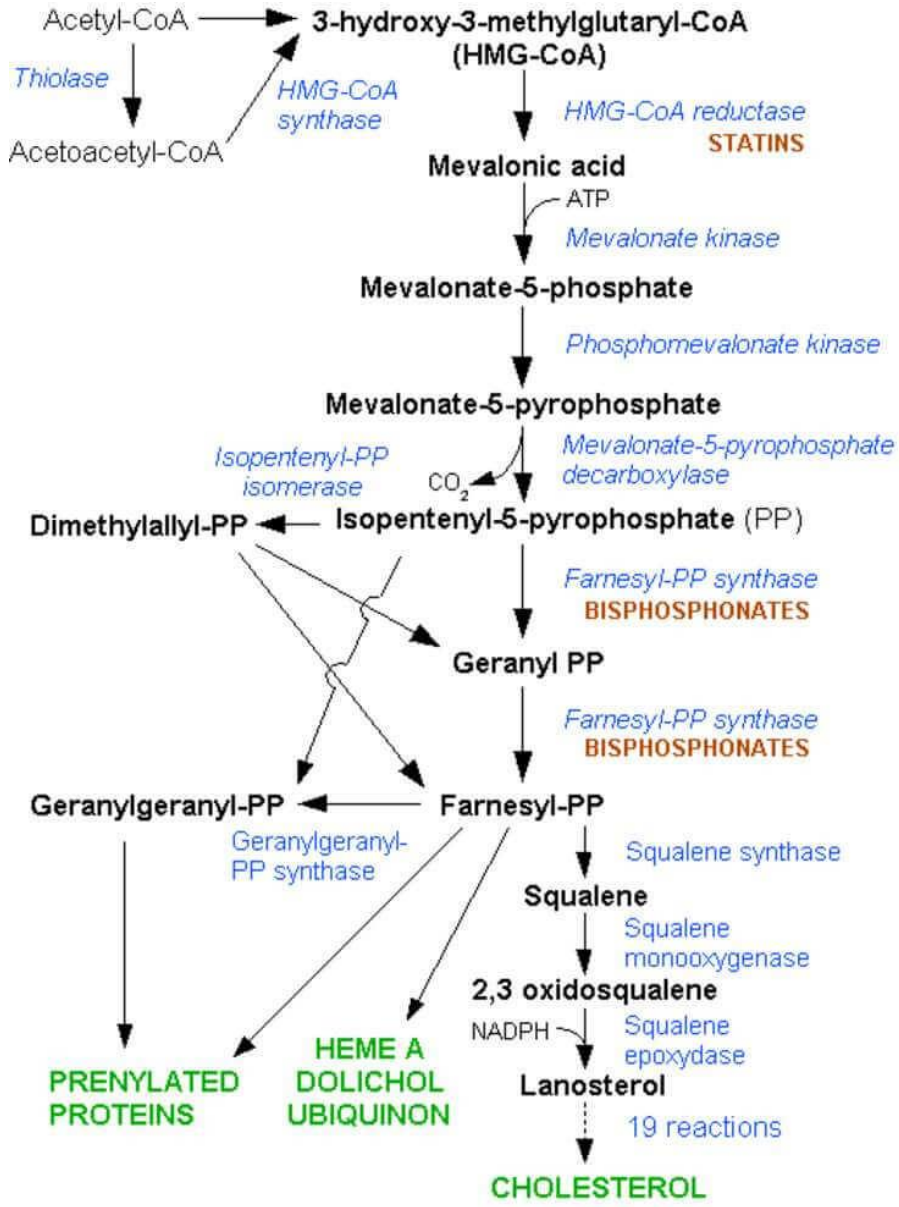
- ✓ Correlation of fat consumption and infarction/stroke was known from long times ago.
- ✓ Cholesterol was first identified in 1769 by the French chemist François Poulletier de la Salle. He discovered it in gallstones.
- ✓ In the 19th century, researchers observed that certain individuals with high cholesterol levels often had an increased incidence of cardiovascular diseases, but the understanding of this relationship was not well defined.
- ✓ The most significant step in establishing the link between cholesterol and heart disease came with the development of the lipid hypothesis in the 1950s.
- ✓ An important study was the Framingham Heart Study, which started in 1948 and helped establish risk factors for heart disease, including high levels of blood cholesterol.
- ✓ Low-density lipoprotein (LDL) was first described in 1959 by the American biochemist John Gofman.
- ✓ Research during 1970s - 1980s provided further evidence of the role of low-density lipoprotein (LDL) cholesterol in atherosclerosis.
- ✓ The first statin, mevastatin, was discovered in 1976 by Dr. Akira Endo. It was derived from the fungus Penicillium citrinum.
- ✓ The first statin approved for clinical use was lovastatin (marketed as Mevacor), which was derived from the fermentation of Aspergillus terreus.
- ✓ It received FDA approval in 1987.
- ✓ Muscular side effects, including myopathy (muscle weakness) and rhabdomyolysis (a severe form of muscle breakdown), began to be reported in clinical trials and post-marketing surveillance at Late 1980s to Early 1990s.

While the exact mechanisms behind statin-induced muscular symptoms remain unclear, several hypotheses have been proposed:

Inhibition of Coenzyme Q10 (CoQ10): Statins can lower CoQ10 levels, which is essential for mitochondrial energy production, possibly leading to muscle weakness.

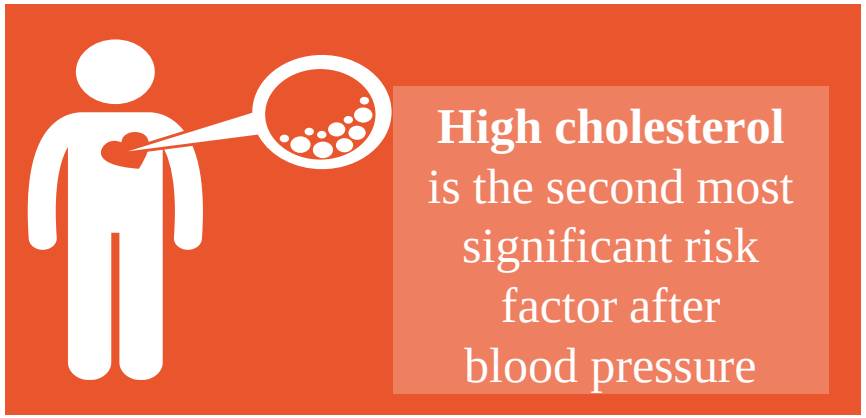
Protein Prenylation Deficiency: Statins disrupt the mevalonate pathway, reducing geranylgeranylation of proteins that play crucial roles in muscle function and viability.

Inflammatory and Immune Responses: Some patients may develop an immune-mediated necrotizing myopathy characterized by progressive weakness and high CK levels.



Clinical Approaches to Reduce Level of LDL-c

Why cholesterol management is important in CVD prevention?



High cholesterol is the second most significant risk factor after blood pressure

For every 1 mmol/L reduction in LDL-C there is a

23%

reduction in major vascular events

Specialists that lower LDL-C can **significantly reduce** the incidence of coronary heart disease and other major vascular events in a wide range individuals

Arena LIFE SCIENCE

The story, from the history

- ✓ The research leading to bempedoic acid began in the late 2000s, with a focus on finding a new way to lower low-density lipoprotein cholesterol (LDL-C) levels without the side effects commonly associated with statins.
- ✓ Eicosano Therapeutics was instrumental in early studies and the initial development of ACL inhibitors, including bempedoic acid.
- ✓ It laid the groundwork for further development and testing before the rights to bempedoic acid were sold to Esperion Therapeutics.
- ✓ Esperion Therapeutics: After acquiring the rights to bempedoic acid, Esperion moved forward with its clinical development.
- ✓ Under the leadership of key figures such as Timothy M. May, who served as Chief Scientific Officer, the company conducted significant research to validate the efficacy and safety of the compound.
- ✓ Dr. Robert H. Eckel : A prominent endocrinologist and cardiologist who has been involved in clinical research related to lipid management and has contributed to the understanding of bempedoic acid's role in cardiovascular health.
- ✓ Following its discovery, bempedoic acid underwent preclinical testing to evaluate its pharmacodynamics and pharmacokinetics. Animal studies assessed its ability to reduce LDL-C levels and its overall safety profile.
- ✓ Phase 1 trials focused on assessing the safety, tolerability, and pharmacokinetics of bempedoic acid in healthy subjects.
- ✓ Pivotal Phase 3 trials included studies like the CLEAR (Cholesterol Lowering via Bempedoic acid, an ACL-Inhibitor) program, which demonstrated that bempedoic acid significantly reduced LDL-C levels compared to placebo in patients with high cardiovascular risk.
- ✓ Following successful Phase 3 trials, Esperion submitted data to the FDA for approval. The application was reviewed, and in February 2020, bempedoic acid received FDA approval.

Arena LIFE SCIENCE

Bempedoic Acid: Mechanism of Action

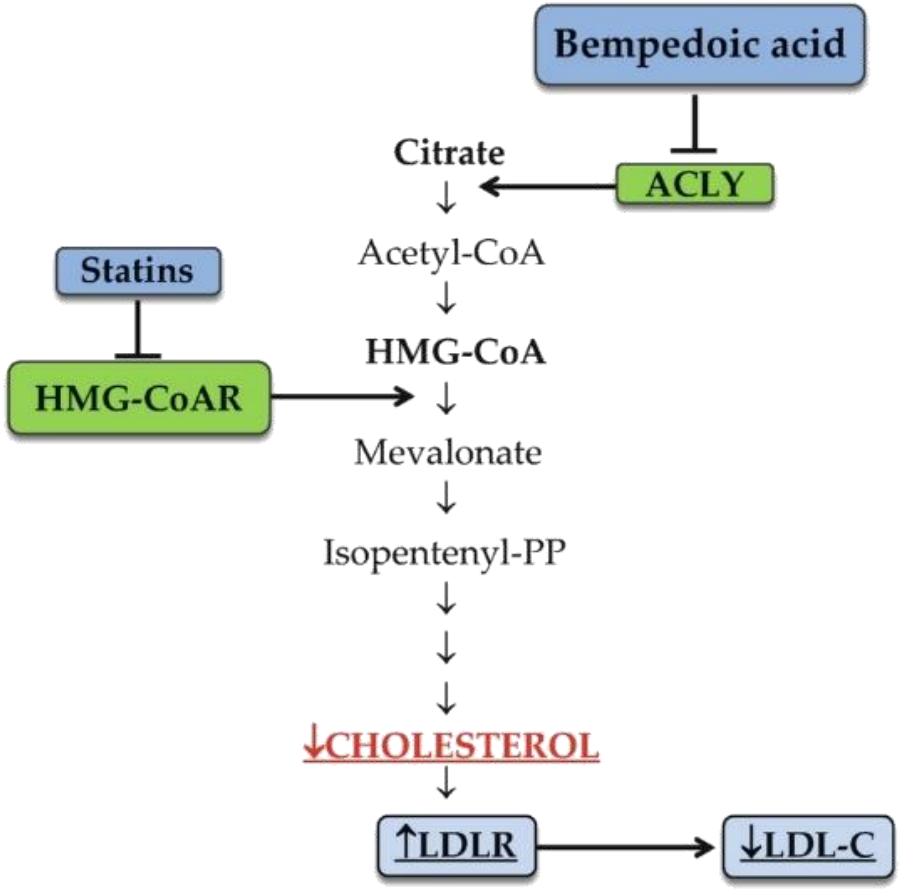
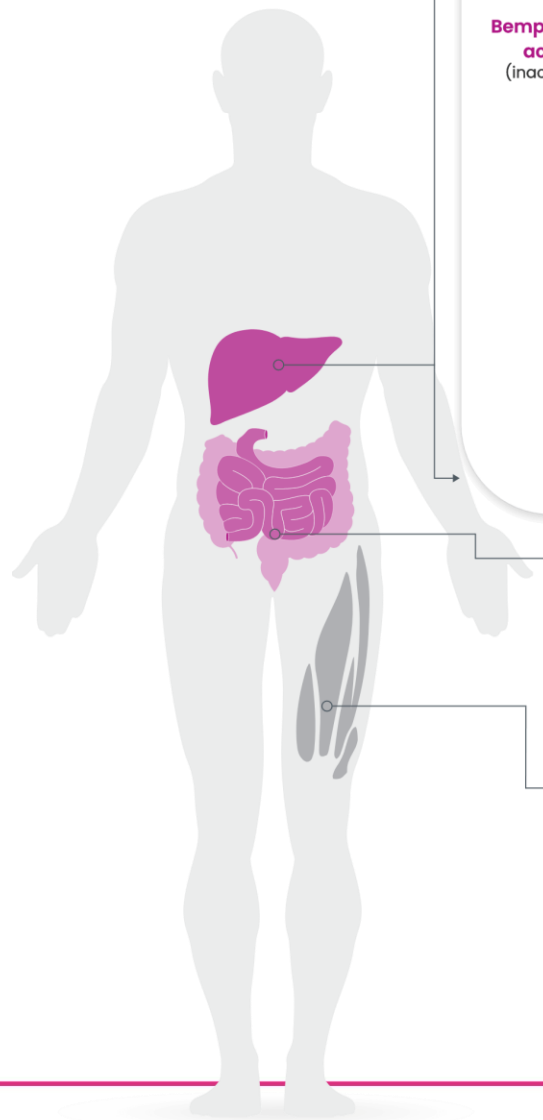
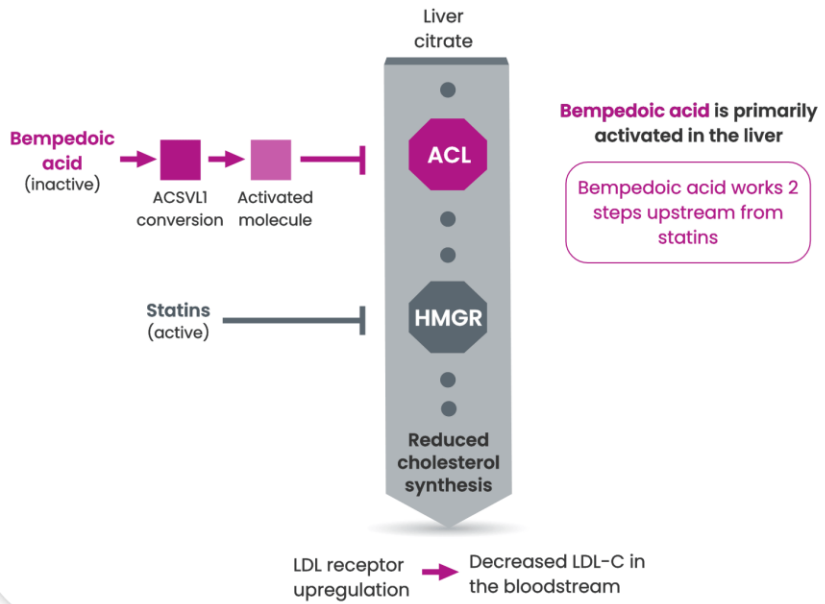


Figure 4. Bempedoic acid mechanism of action. Adapted from Pirillo A, Norata GD, Catapano AL. LDL-Cholesterol-Lowering Therapy. 2020 Apr 30. In: von Eckardstein A, Binder CJ, editors. Prevention and Treatment of Atherosclerosis: Improving State-of-the-Art Management and Search for Novel Targets [Internet]. Cham (CH): Springer; 2022. Fig. 4, [Mechanism of action of bempedoic...]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK584301/figure/ch361.Fig4/ doi: 10.1007/164_2020_361

Bempedoic Acid 180



Bempedoic acid reduces cholesterol biosynthesis in the liver[2]



Bempedoic acid is primarily activated in the liver

Bempedoic acid works 2 steps upstream from statins

Ezetimibe reduces LDL-C by inhibiting the absorption of cholesterol by the small intestine[1]

↓

Decreased hepatic cholesterol stores

↓

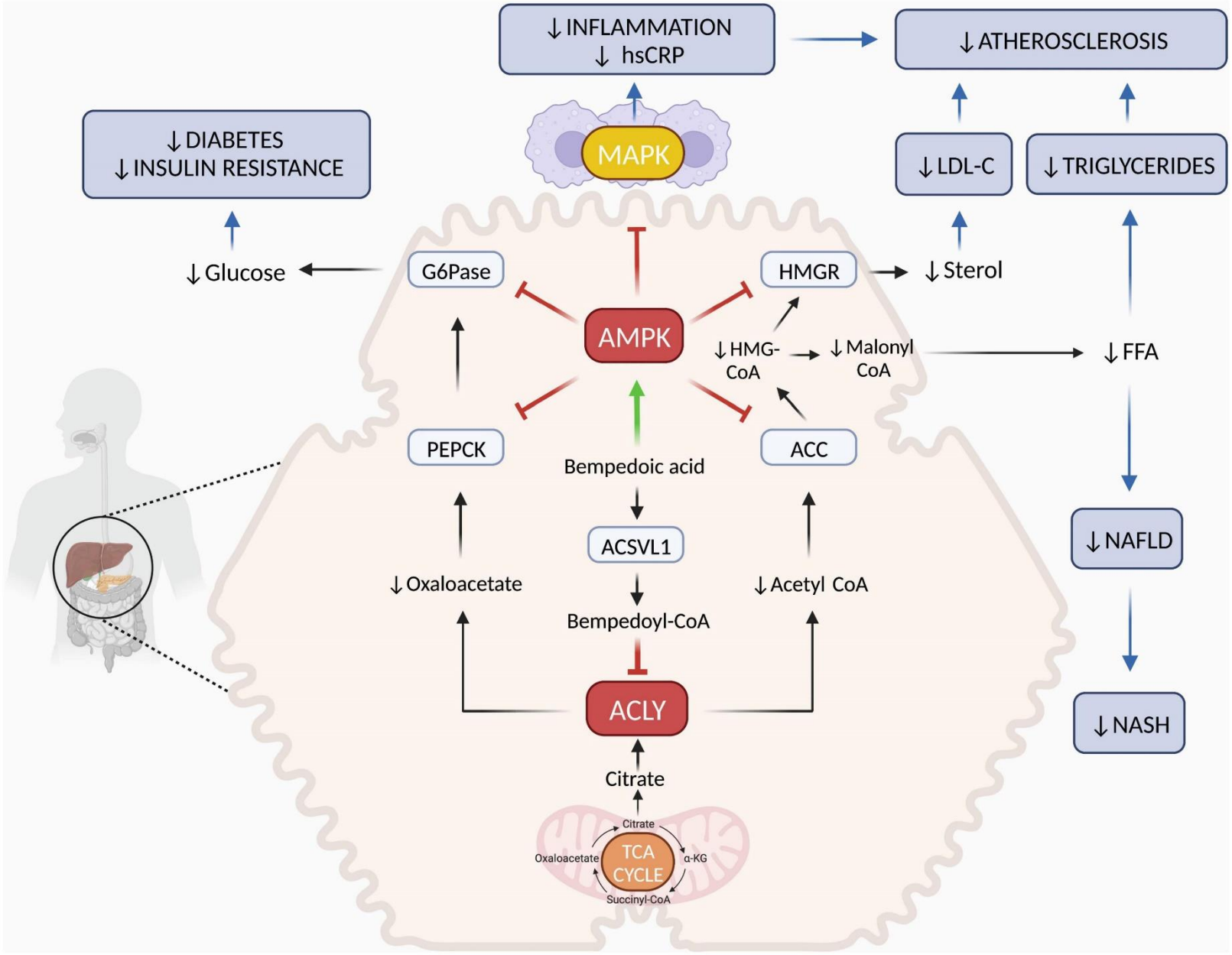
Decreased LDL-C in the bloodstream due to increase in LDL receptors

Unlike statins, bempedoic acid is not activated in skeletal muscle[2,3]

- Bempedoic acid is activated by a naturally occurring enzyme, ACSVL1, which is found in the liver—but is undetectable in skeletal muscle

Bempedoic Acid 180

Bempedoic acid is a pro-drug that is converted in the liver into the active form, bempedoyl-CoA, by the very long-chain acyl-CoA synthetase-1 (ACSVL1), an enzyme present in the hepatocyte but completely absent in skeletal muscle. The action of the active form of bempedoic acid consists in the inhibition of the enzyme ACLY. This enzyme is at the intersection between pathways of glucose and lipid metabolism, regulating gluconeogenesis and lipogenesis. Bempedoyl-CoA inhibits de novo sterol and fatty acid synthesis through the direct inhibition of ACLY.



Bempedoic Acid: Clinical Studies

- Clear Harmony
- Clear Wisdom
- Clear Outcome

CLEAR Harmony

Long-term safety, tolerability, and efficacy of bempedoic acid vs placebo in high cardiovascular risk patients with LDL-C above 1.8 mmol/L on maximally tolerated statin therapy

CLEAR Harmony: Study Design

- Aim
  - Assessing long-term overall safety and efficacy of BA in patients receiving maximally tolerated statin therapy

- Methods
  - Phase 3, double-blind, placebo-controlled, parallel-group study
  - Patients randomized 2:1 to treatment with BA 180 mg or placebo OD for 52 weeks
  - Key inclusion criteria
    - Pre-existing ASCVD and/or HeFH
    - Baseline LDL-C ≥ 1.8 mmol/L (70 mg/dL) while receiving maximally tolerated statin therapy

- Endpoints
  - Primary endpoint was safety
  - Principle efficacy endpoint: percent change from baseline to week 12 in LDL-C
  - Key secondary endpoints: percent change from baseline to week 24 in LDL-C, and week 12 in non–HDL-C, total cholesterol, apoB, and hsCRP

Bempedoic Acid: Clinical Studies

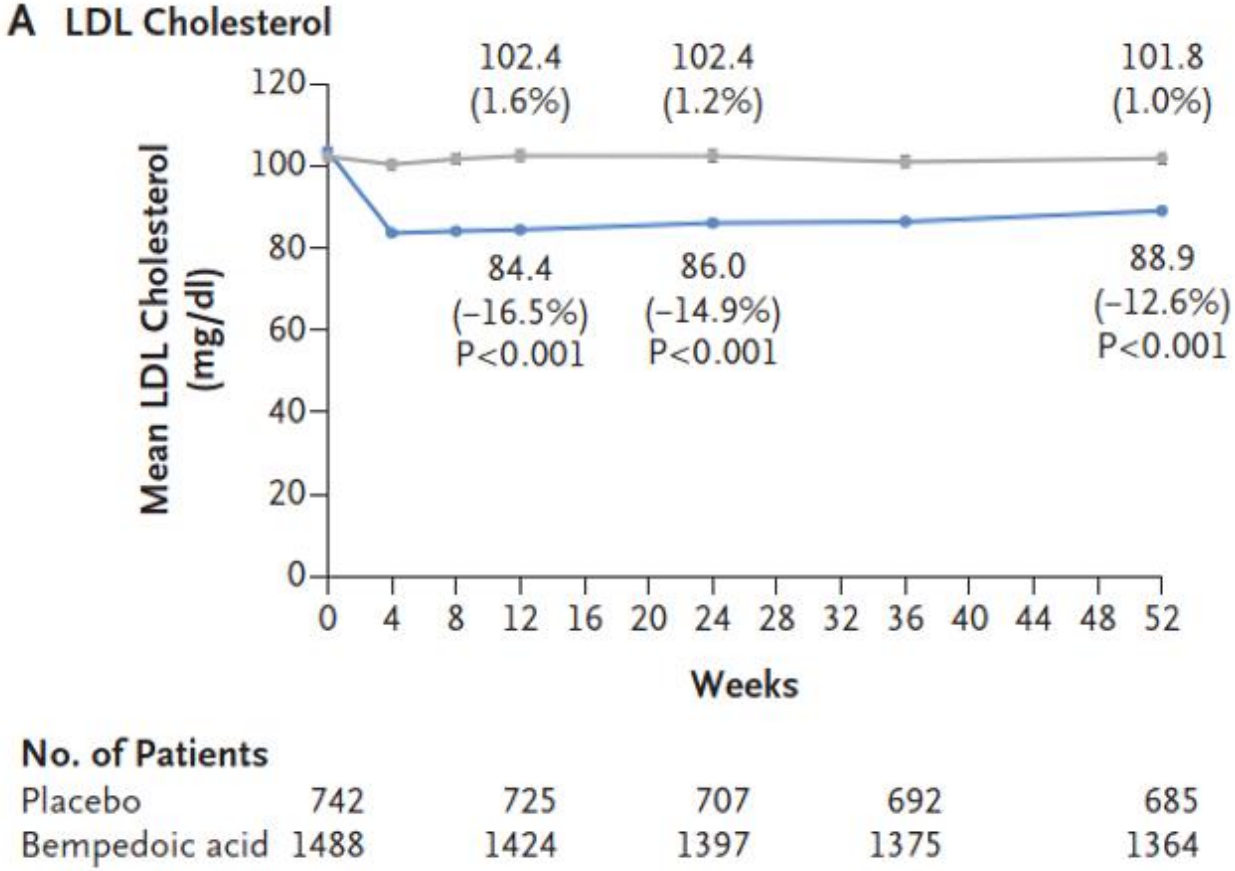
Parameter	CLEAR HARMONY
Study Design	Double-blind, randomized, placebo-controlled
Population	Patients with atherosclerotic cardiovascular disease, heterozygous familial hypercholesterolemia, or both. Patients had to have an LDL cholesterol level of at least 70 mg per deciliter while they were receiving maximally tolerated statin therapy with or without additional lipid-lowering therapy
No. of Participants	**2230 patients** (1488 bempedoic acid; 742 placebo)
Primary Outcome	Overall safety
Secondary Outcome	Percentage change in the LDL cholesterol level at week 12 of 52 weeks; the percentage changes in the levels of non–high-density lipoprotein (non-HDL) cholesterol, total cholesterol, apolipoprotein B, and high-sensitivity C-reactive protein from baseline to week 12

CLEAR Harmony: Safety (Primary Endpoint)

Variable*	Patients, %		*P* value†
	Placebo (n=742)	Bempedoic Acid (n=1487)	
Any AE	78.7	78.5	NS
Serious AE	14.0	14.5	NS

*Includes adverse events (AEs) occurring from the first dose through 30 days after the last dose of study drug.
†*P* values are nominal without adjustment for multiplicity and are provided for descriptive purposes only. $P \geq 0.05$ labelled as not significant (NS).

CLEAR Harmony: Efficacy

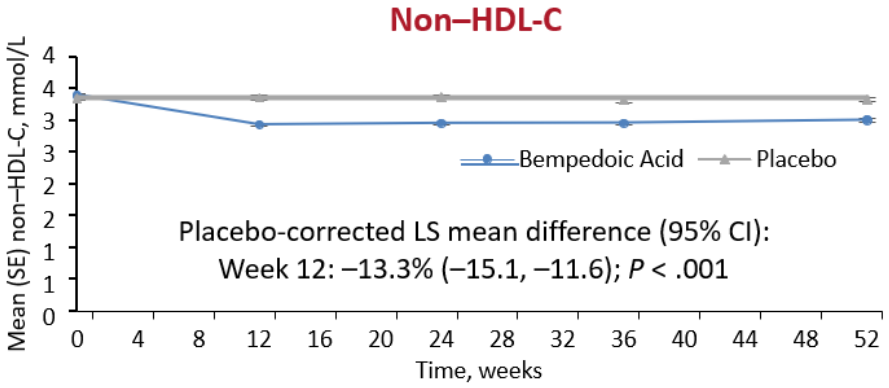


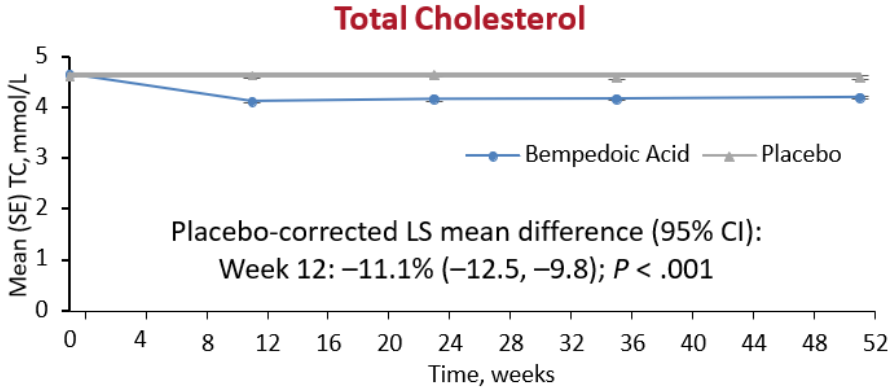
18.1%

Figure 5. Effects of bempedoic acid on lipoproteins. Adapted from Ray, K. K., Bays, H. E., Catapano, A. L., Lalwani, N. D., Bloedon, L. T., Sterling, L. R., ... & Ballantyne, C. M. (2019). Safety and efficacy of bempedoic acid to reduce LDL cholesterol. New England Journal of Medicine, 380(11), 1022-1032.

CLEAR Harmony: Efficacy

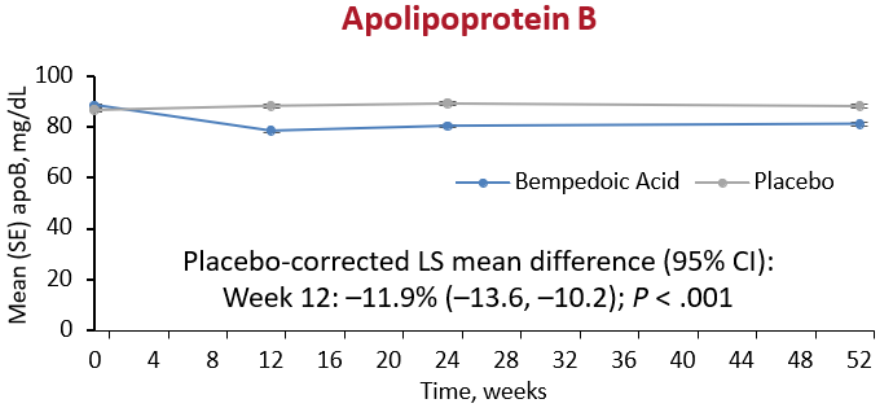
13.4%

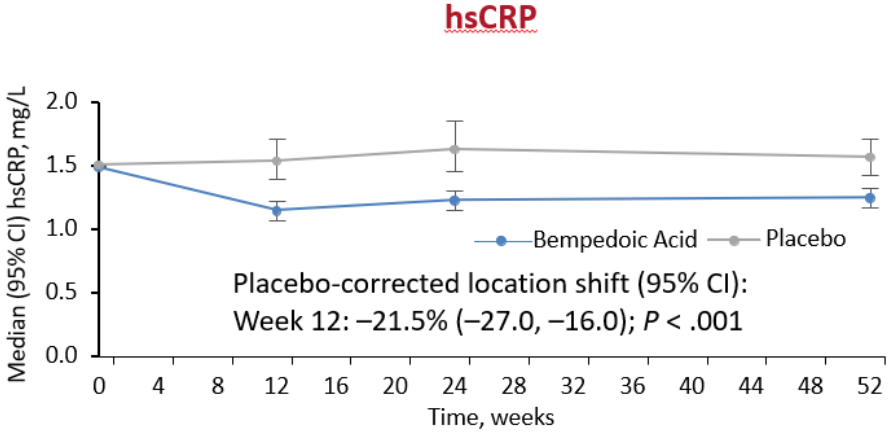




11.1%

11.9%





21.5%

Figure 6. Effects of bempedoic acid on lipoproteins. Adapted from Ray, K. K., Bays, H. E., Catapano, A. L., Lalwani, N. D., Bloedon, L. T., Sterling, L. R., ... & Ballantyne, C. M. (2019). Safety and efficacy of bempedoic acid to reduce LDL cholesterol. New England Journal of Medicine, 380(11), 1022-1032.

Clear Harmony: Conclusion

- **CLEAR Harmony** provides the largest evidence to date that **bempedoic acid** is **safe** as an adjunct to a guideline-based statin regimen.
  - Adverse event profile of BA was generally similar to that of placebo
  - Background statin intensity did not influence the safety profile of bempedoic acid

- **Bempedoic acid**
  - Significant reductions in LDL-C were observed through to week 52
  - BA also significantly lowered non–HDL-C, total cholesterol, apoB, and hsCRP

- **Bempedoic acid** provided an additional therapeutic option to safely lower LDL-C in high ASCVD risk patients treated with statins.

CLEAR Wisdom

Assessing the efficacy of bempedoic acid vs placebo in patients at high cardiovascular risk receiving maximally tolerated lipid-lowering therapy

Parameter	CLEAR WISDOM
Study Design	Double-blind, randomized, placebo-controlled
Population	Patients with atherosclerotic cardiovascular disease, heterozygous familial hypercholesterolemia, or both. Patients had to have an LDL cholesterol level of at least 70 mg per deciliter while they were receiving maximally tolerated statin therapy with or without additional lipid-lowering therapy
No. of Participants	779 patients (522 bempedoic acid; 257 placebo)
Primary Outcome	Percent change from baseline in LDL-C level at week 12
Secondary Outcome	Changes in levels of lipids, lipoproteins, and biomarkers

CLEAR Wisdom: Study Design

Aim

Assessing the efficacy of bempedoic acid vs placebo in patients at high cardiovascular risk receiving maximally tolerated lipid-lowering therapy

Methods

- Phase 3, randomized, double-blind, placebo-controlled clinical trial
- Patients were randomized 2:1 to treatment with bempedoic acid (180 mg) (n = 522) or placebo (n = 257) once daily for 52 weeks.

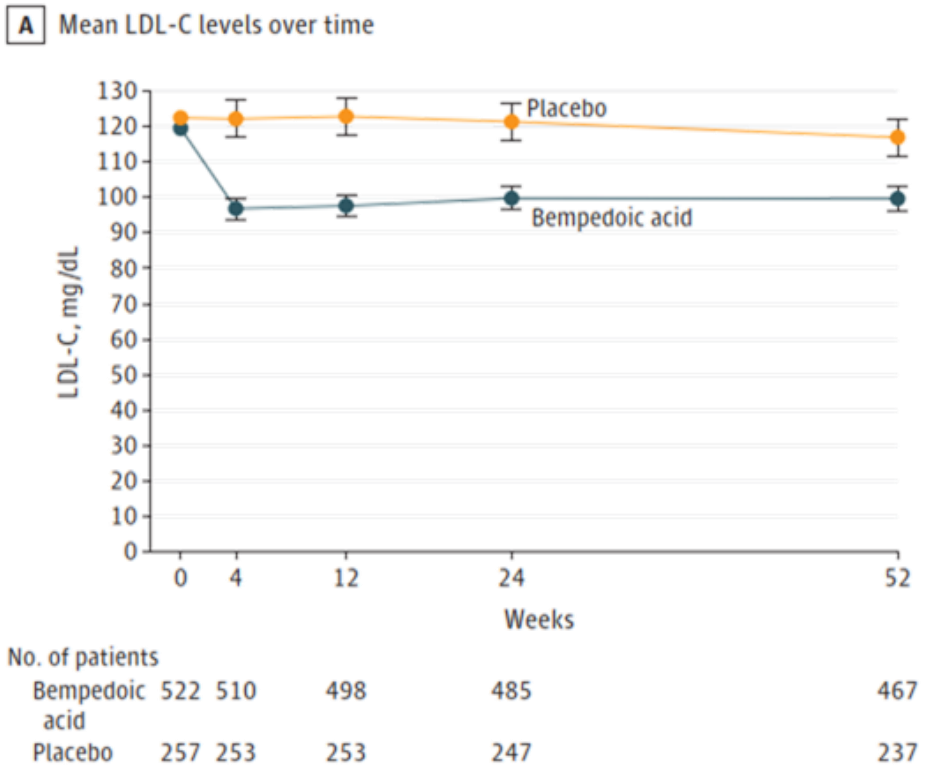
- Key inclusion criteria
  - Pre-existing ASCVD and/or HeFH
  - Baseline LDL-C ≥ 1.8 mmol/L (70 mg/dL) while receiving maximally tolerated statin therapy

Endpoints

- The primary end point was percent change from baseline in LDL-C level at week 12
- Secondary measures included changes in levels of lipids, lipoproteins, and biomarkers

CLEAR Wisdom: Results

17.5%



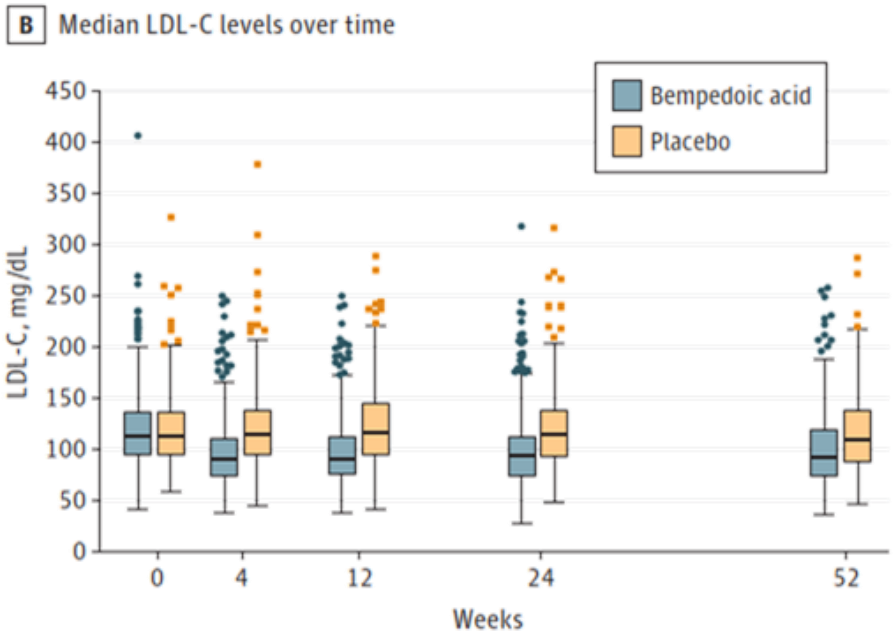


Figure 7. Effect of bempedoic acid on mean LDL-c level over time. Adapted from Goldberg, A. C., Leiter, L. A., Stroes, E. S., Baum, S. J., Hanselman, J. C., Bloedon, L. T., ... & Duell, P. B. (2019). Effect of bempedoic acid vs placebo added to maximally tolerated statins on low-density lipoprotein cholesterol in patients at high risk for cardiovascular disease: the CLEAR wisdom randomized clinical trial. Jama, 322(18), 1780-1788.

Clear Wisdom : Conclusion

Among patients at high risk for cardiovascular disease receiving maximally tolerated statins, the addition of bempedoic acid compared with placebo resulted in **a significant lowering of LDL-C** level over 12 weeks

CLEAR Outcome

Assessing the efficacy of bempedoic acid vs placebo in patients at high cardiovascular risk who were unable or unwilling to take statins owing to unacceptable adverse Effects ("statin-intolerant" patients).

Bempedoic Acid: Clinical Studies

Parameter	CLEAR OUTCOME
Study Design	Double-blind, randomized, placebo-controlled
Population	Patients who were unable or unwilling to take statins owing to unacceptable adverse effects ("statin-intolerant" patients) and had, or were at high risk for, cardiovascular disease
No. of Participants	**13970 patients** (6992 bempedoic acid, 6978 placebo)
Primary Outcome	Four-component composite of major adverse cardiovascular events, defined as death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization
Secondary Outcome	Three-component composite of death from cardiovascular causes, nonfatal stroke, or nonfatal myocardial infarction; fatal or nonfatal myocardial infarction; coronary revascularization; fatal or nonfatal stroke; death from cardiovascular causes; and death from any cause

CLEAR Outcome: Results

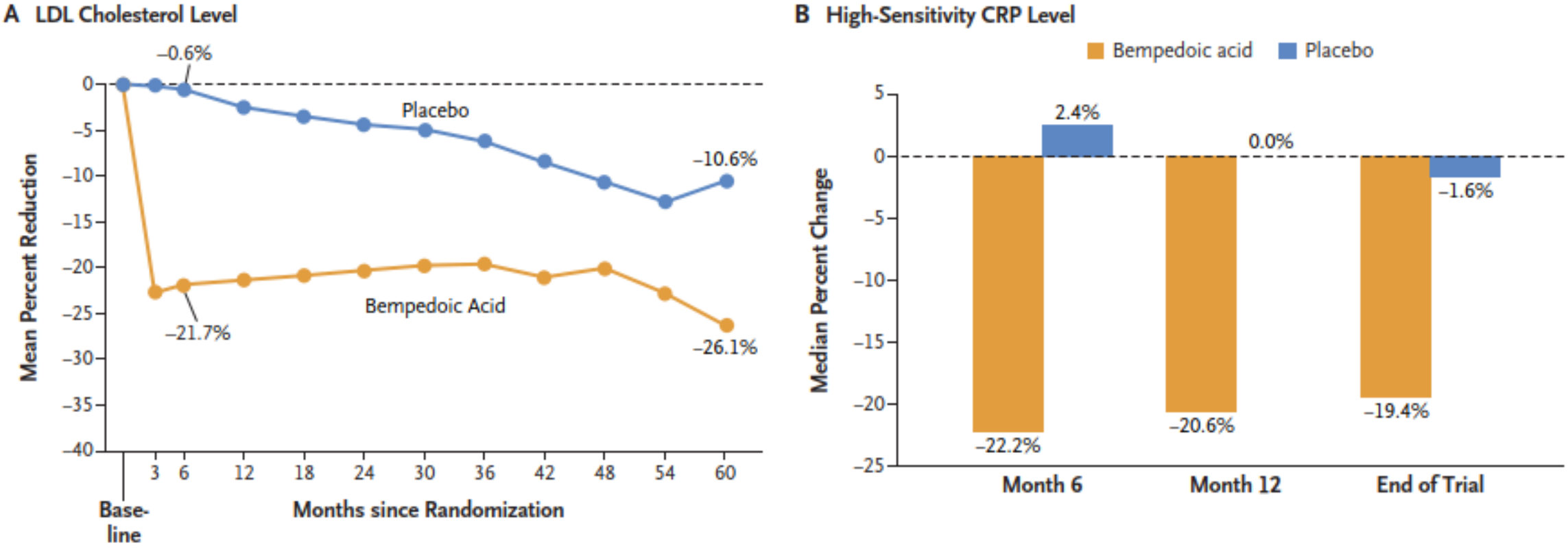
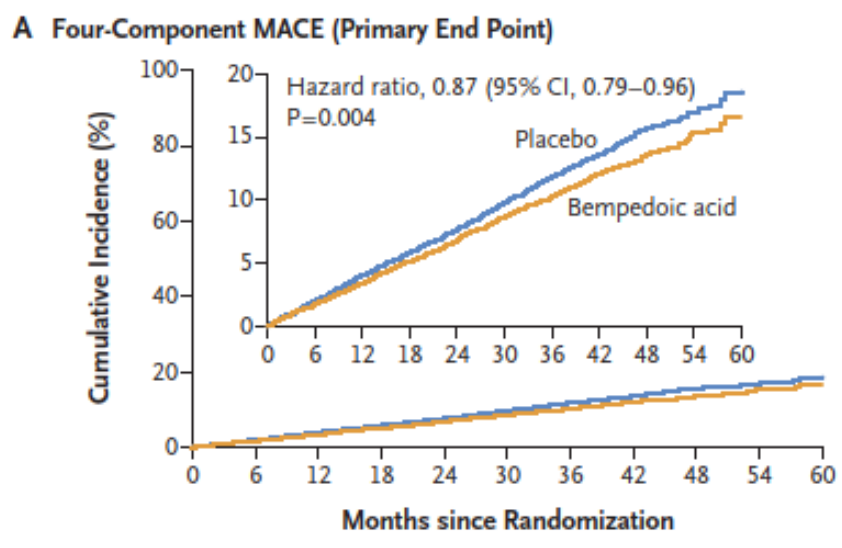


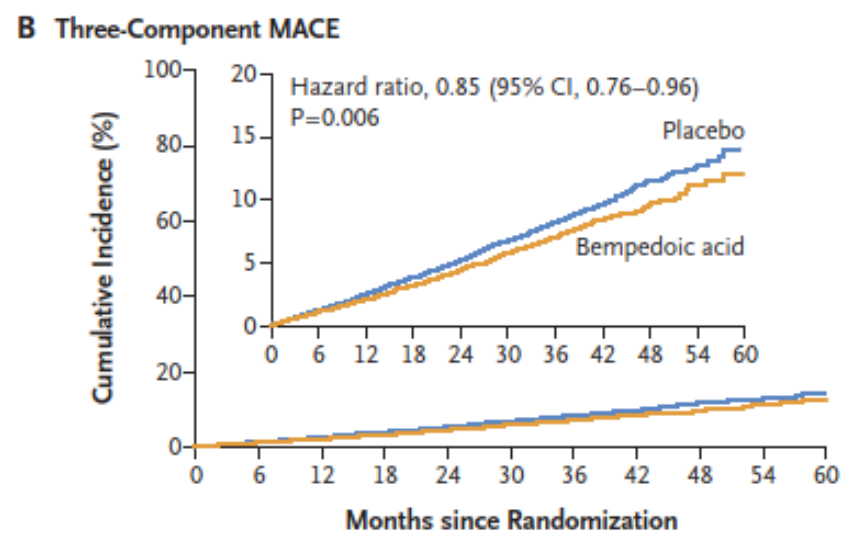
Figure 8. Effect of bempedoic acid on LDL-c level, CRP level, four-component, and 3-component MACE. Adapted from Nissen SE, Lincoff AM, Brennan D, et al. Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients. *N Engl J Med*. 2023;388(15):1353-1364. doi:10.1056/NEJMoa2215024

CLEAR Outcome: Results

RRR
13%
after 40.6 months of follow-up



Four-component composite of major adverse cardiovascular events, defined as death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization



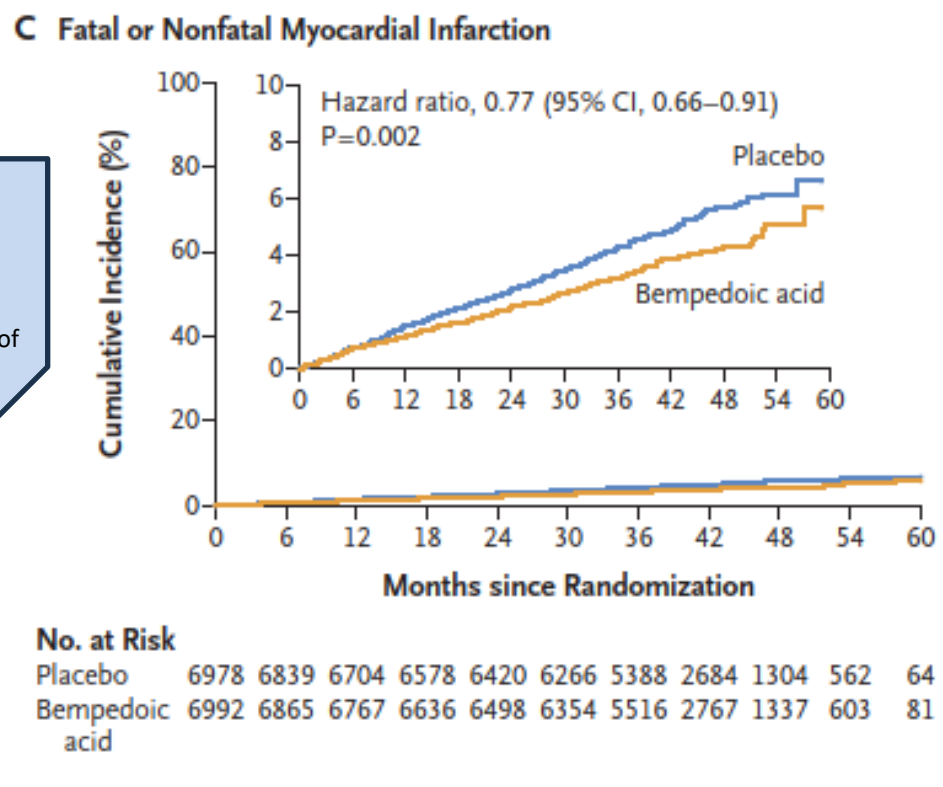
Three-component composite of death from cardiovascular causes, nonfatal stroke, or nonfatal myocardial infarction

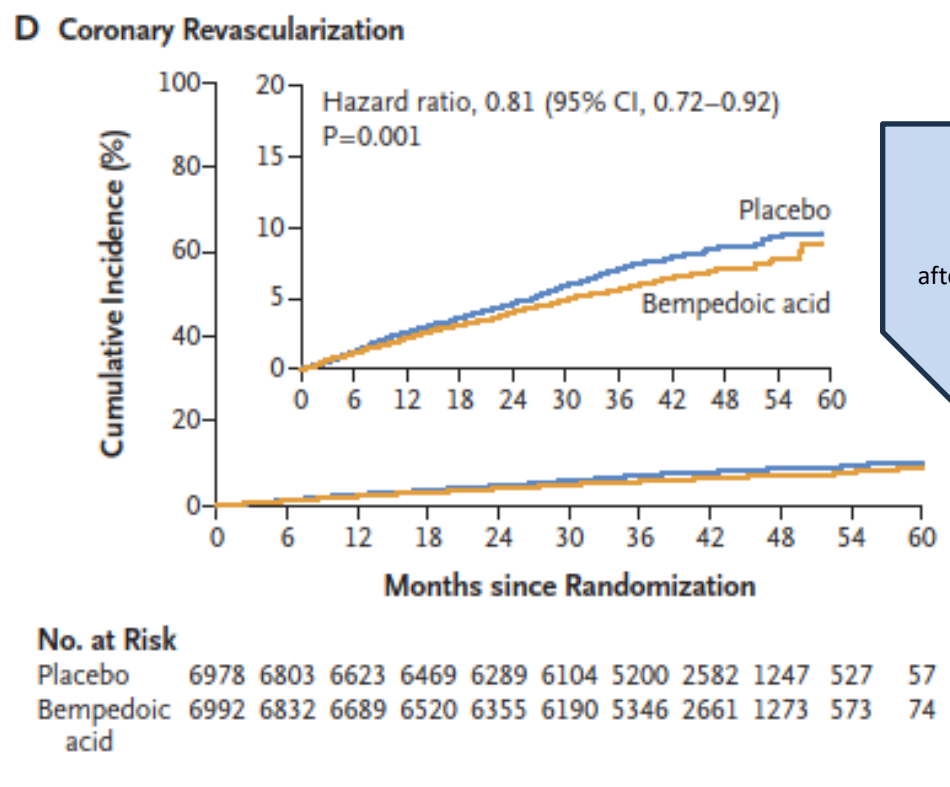
RRR
15%
after 40.6 months of follow-up

Figure 9. Effect of bempedoic acid on LDL-c level, CRP level, four-component, and 3-component MACE. Adapted from Nissen SE, Lincoff AM, Brennan D, et al. Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients. *N Engl J Med*. 2023;388(15):1353-1364. doi:10.1056/NEJMoa2215024

CLEAR Outcome: Results

RRR
23%
after 40.6 months of follow-up

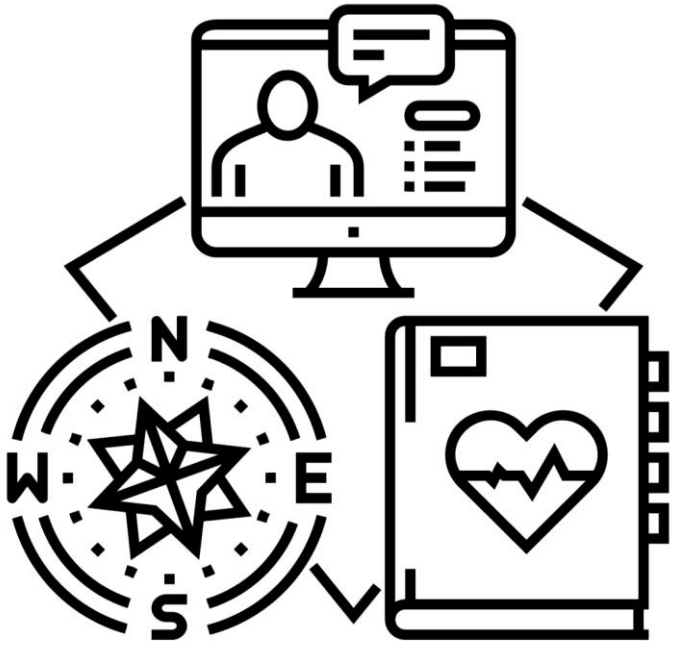




RRR
19%
after 40.6 months of follow-up

Figure 10. Effect of bempedoic acid on LDL-c level, CRP level, four-component, and 3-component MACE. Adapted from Nissen SE, Lincoff AM, Brennan D, et al. Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients. *N Engl J Med*. 2023;388(15):1353-1364. doi:10.1056/NEJMoa2215024

Bempedoic Acid: Guidelines



Bempedoic acid is the **only non-statin FDA-approved agent** to lower LDL-C and reduce the risk of MI and coronary revascularization in primary and secondary prevention settings.

Arena LIFE SCIENCE

Bempedoic Acid: Guidelines

2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Chronic Coronary Disease Guideline

Recommendations for Lipid Management
Referenced studies that support the recommendations are summarized in the Online Data Supplement.

COR	LOE	RECOMMENDATIONS
2b	B-R	11. In patients with CCD on maximally tolerated statin therapy who have an LDL-C level ≥70 mg/dL (≥1.8 mmol/L), and in whom ezetimibe and PCSK9 monoclonal antibody are deemed insufficient or not tolerated, it may be reasonable to add bempedoic acid[33,34] or inclisiran[35] (in place of PCSK9 monoclonal antibody) to further reduce LDL-C levels.

Virani SS, Newby LK, Arnold SV, et al. 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the Management of Patients With Chronic Coronary Disease: A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines [published correction appears in Circulation. 2023 Sep 26;148(13):e148] [published correction appears in Circulation. 2023 Dec 5;148(23):e186]. *Circulation*. 2023;148(9):e9-e119. doi:10.1161/CIR.0000000000001168

Bempedoic Acid: Guidelines

American Diabetes Association®

10. Cardiovascular Disease and Risk Management: *Standards of Care in Diabetes—2024*

Diabetes Care 2024;47(Suppl. 1):S179–S218 | https://doi.org/10.2337/dc24-S010

→ Primary Prevention

In people with diabetes intolerant to statin therapy, treatment with **bempedoic acid** is recommended to reduce cardiovascular event rates as an alternative cholesterol-lowering plan.

→ Secondary Prevention

For people with diabetes and ASCVD intolerant to statin therapy, PCSK9 inhibitor therapy with monoclonal antibody treatment, **bempedoic acid** therapy, and or PCSK9 inhibitor therapy with inclisiran siRNA should be considered as an alternative cholesterol-lowering therapy.

Arena LIFE SCIENCE

Bempedoic Acid: Indications

- ✓ **Established ASCVD or a high risk for ASCVD** who unable to take statin to **reduce the risk of myocardial infarction and coronary revascularization.**

- ✓ Primary hyperlipidemia as an **adjunct to diet and statin therapy** in adult with **heterozygous familial hypercholesterolemia (HeFH)** who require additional lowering of LDL cholesterol

- ✓ Primary hypercholesterolemia (heterozygous familial and non-familial) or mixed dyslipidemia, **alone or in combination with other lipid-lowering therapies** as an adjunct to diet in patients who are **statin-intolerant, or for whom a statin is contraindicated** (EMA approved)

Bempedoic Acid: Pharmacokinetics

Metabolism: hepatic	**Elimination half-life:** 22 hours
Plasma distribution volume: 18 L	**T_{max}:** 3.5 hours
Plasma protein binding: 99.3%	**Excretion:** Urine (70%); Feces (30%)

Bempedoic Acid: Contraindications

No absolute contraindications has been found yet

Bempedoic Acid: Drug Interactions

X	Bempedoic Acid (OATP1B1/1B3 (SLCO1B1/1B3) Inhibitors) Asunaprevir
X	Bempedoic Acid (OATP1B1/1B3 (SLCO1B1/1B3) Inhibitors) Elagolix
X	Bempedoic Acid (OATP1B1/1B3 (SLCO1B1/1B3) Inhibitors) Elagolix, Estradiol, and Norethindrone
X	Bempedoic Acid (OATP1B1/1B3 (SLCO1B1/1B3) Inhibitors) Elbasvir and Grazoprevir
X	Bempedoic Acid (OATP1B1/1B3 (SLCO1B1/1B3) Inhibitors) Resmetirom
X	Bempedoic Acid (OATP1B1/1B3 (SLCO1B1/1B3) Inhibitors) Revefenacin
X	Bempedoic Acid (OATP1B1/1B3 (SLCO1B1/1B3) Inhibitors) Taurursodiol
X	Bempedoic Acid (OATP1B1/1B3 (SLCO1B1/1B3) Inhibitors) Voxilaprevir
X	Bempedoic Acid (OATP1B1/1B3 (SLCO1B1/1B3) Inhibitors) Zavegepant

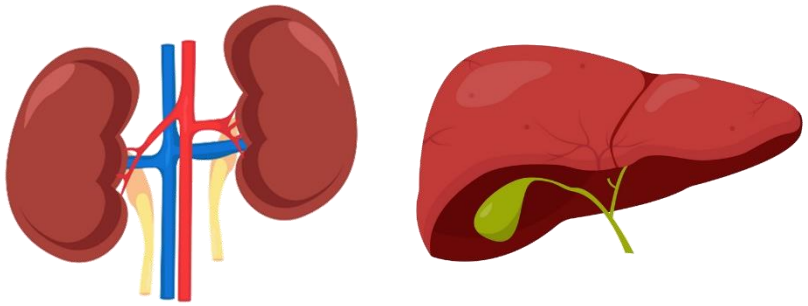
D	Bempedoic Acid (OATP1B1/1B3 (SLCO1B1/1B3) Inhibitors) Atogepant
D	Bempedoic Acid (OATP1B1/1B3 (SLCO1B1/1B3) Inhibitors) Brincidofovir
D	Bempedoic Acid (OATP1B1/1B3 (SLCO1B1/1B3) Inhibitors) Eluxadoline
D	Bempedoic Acid Pravastatin
D	Bempedoic Acid Simvastatin

Arena LIFE SCIENCE

Lexicomp®

Bempedoic Acid: Dosing

180 mg, once a day, without regard to meal



Mild to moderate impairment: 180 mg, once a day, without regard to meal

Severe impairment: lack of sufficient evidence

Bempedoic Acid: Pregnancy

Based on the mechanism of action, in-utero exposure to bempedoic acid may cause fetal harm.

In general, bempedoic acid **should be discontinued** when pregnancy is recognized unless the benefits of therapy outweigh the potential risks to the fetus.

Bempedoic Acid: Lactation

Summary of Use during Lactation

No relevant published information exists on the use of bempedoic acid during breastfeeding. Bempedoic acid and its metabolites are 99% plasma protein bound, so amounts in milk are likely very low. However, because of a concern with disruption of infant lipid metabolism, bempedoic acid is best avoided during breastfeeding. An alternate drug is preferred, especially while nursing a newborn or preterm infant.

Bempedoic Acid: safety, adverse effects, precautions

Bempedoic acid is contraindicated in patients with a prior hypersensitivity to bempedoic acid or any of the excipients. Serious hypersensitivity reactions including anaphylaxis, angioedema, rash, and urticaria have been reported.

Hyperuricemia: Bempedoic acid, may increase blood uric acid levels, which may lead to gout. Hyperuricemia may occur early in treatment and persist throughout treatment, returning to baseline following discontinuation of treatment. Assess uric acid levels periodically as clinically indicated. Monitor for signs and symptoms of hyperuricemia, and initiate treatment with urate-lowering drugs as appropriate.

Tendon Rupture : Bempedoic acid, is associated with an increased risk of tendon rupture or injury. Tendon rupture may occur more frequently in patients over 60 years of age, in those taking corticosteroid or fluoroquinolone drugs, in patients with renal failure, and in patients with previous tendon disorders. Discontinue bempedoic acid at the first sign of tendon rupture. Consider alternative therapy in patients who have a history of tendon disorders or tendon rupture.

Bempedoic Acid: safety, adverse effects, precautions

The most common adverse reactions in the primary hyperlipidemia trials of bempedoic acid, in ≥2% of patients and greater than placebo were upper respiratory tract infection, muscle spasms, hyperuricemia, back pain, abdominal pain or discomfort, bronchitis, pain in extremity, anemia, and elevated liver enzymes.

The most common adverse reactions in the cardiovascular outcomes trial for bempedoic acid, at an incidence of ≥2% and 0.5% greater than placebo were hyperuricemia, renal impairment, anemia, elevated liver enzymes, muscle spasms, gout, and cholelithiasis.

Concomitant use of bempedoic acid with greater than 20 mg of simvastatin or 40 mg of pravastatin should be avoided due to the potential for increased risk of simvastatin- or pravastatin-related myopathy.

Discontinue bempedoic acid when pregnancy is recognized unless the benefits of therapy outweigh the potential risks to the fetus. Because of the potential for serious adverse reactions in a breast-fed infant, breastfeeding is not recommended during treatment with bempedoic acid.

Thank you and hope for a good rain

Arena LIFE SCIENCE