WOŁOWIEC, Łukasz, PELLOWSKA, Małgorzata, JANIAK, Michał, WYDEHEFT, Lidia, GRZEŚK, Grzegorz and ZUKOW, Walery. Bempedoic Acid: A Novel Approach in Managing Dyslipidemia and Reducing Cardiovascular Risk. Journal of Education, Health and Sport. 2024;68:55416. eISSN 2391-8306.
https://dx.doi.org/10.12775/JEHS.2024.68.55416
https://apcz.umk.pl/JEHS/article/view/55416

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).
The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 21.08.2024. Revised: 17.09.2024. Accepted: 28.09.2024. Published: 28.09.2024.

Bempedoic Acid: A Novel Approach in Managing Dyslipidemia and Reducing Cardiovascular Risk

Łukasz Wołowiec[1*], Małgorzata Pellowska[1], Michał Janiak[1],
Lidia Wydeheft[1], Grzegorz Grześk[1], Walery Zukow[2]

[1]Department of Cardiology and Clinical Pharmacology, Faculty of Health Sciences, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University, Torun, Poland
[2]Nicolaus Copernicus University, Toruń, Poland

Corresponding author*: Łukasz Wołowiec, lukaswolowiec111@gmail.com

Abstract

Cardiovascular disease remains one of the leading causes of mortality worldwide, with elevated LDL cholesterol being a critical risk factor. Statins have long been the cornerstone of lipid-lowering therapy, but many patients fail to reach target LDL cholesterol levels due to statin intolerance or insufficient response, even when combined with ezetimibe. Recently, the lipid-lowering drug class has been expanded with the introduction of bempedoic acid, a novel agent that inhibits ATP-citrate lyase. Recent studies have demonstrated the efficacy and safety of bempedoic acid in reducing LDL cholesterol levels in patients with hypercholesterolemia, paving the way for its inclusion in clinical guidelines. This article provides a comprehensive overview of the latest evidence regarding bempedoic acid and its emerging role in lipid management.

Despite the widespread use of statins, many patients fail to achieve target LDL-C levels due to statin intolerance or insufficient response. This comprehensive review explores

the emerging role of bempedoic acid, a novel lipid-lowering agent that inhibits ATP-citrate lyase, in the management of dyslipidemia and cardiovascular risk reduction.

Bempedoic acid, approved by the FDA in 2020, offers a unique mechanism of action that complements existing therapies. As a prodrug activated specifically in the liver, it avoids muscle-related side effects commonly associated with statins. Clinical trials have demonstrated its efficacy in reducing LDL-C levels, particularly in patients with statin intolerance or those requiring additional LDL-C lowering beyond maximally tolerated statin therapy.

The review synthesizes data from multiple phase 3 clinical trials, including CLEAR Wisdom and CLEAR Outcomes, which have shown significant LDL-C reductions with bempedoic acid monotherapy and in combination with other lipid-lowering agents. Notably, bempedoic acid not only lowers LDL-C but also reduces high-sensitivity C-reactive protein (hs-CRP) levels, suggesting potential anti-inflammatory effects.

Safety profiles from these trials indicate that bempedoic acid is generally well-tolerated, with minimal muscle-related adverse events. However, slight increases in serum creatinine and uric acid levels have been observed, warranting monitoring in certain patient populations.

Recent updates to clinical guidelines, including the 2024 European Society of Cardiology guidelines on coronary heart disease, now recommend bempedoic acid for specific patient groups. These include statin-intolerant patients not achieving LDL-C goals on ezetimibe alone, and those not reaching targets on maximum tolerated statin doses combined with ezetimibe.

This review concludes that bempedoic acid represents a significant advancement in lipid-lowering therapy, offering a valuable option for patients with hypercholesterolemia, particularly those with statin intolerance or requiring additional LDL-C reduction. As research continues, bempedoic acid's role in reducing cardiovascular events and its long-term safety profile will be further elucidated, potentially reshaping the landscape of dyslipidemia management and cardiovascular risk reduction.

Key words: bempedoic acid, dyslipidemia, cholesterol.

Introduction

Lipid disorders remain a significant clinical challenge for many patients, contributing to the high prevalence of cardiovascular disease, one of the leading causes of mortality worldwide. [1,2] Hypercholesterolemia, a modifiable risk factor for cardiovascular disease, often remains inadequately controlled despite available therapies, necessitating ongoing research into novel lipid-lowering agents. [1,3] One such agent is bempedoic acid, first identified in 2003 as a long-chain tetramethyl-substituted keto diacid, and approved for use by the US Food and Drug Administration (FDA) in 2020. [1,4] Bempedoic acid acts by inhibiting ATP-citrate lyase, effectively reducing cholesterol levels in patients with elevated LDL cholesterol and high cardiovascular risk, particularly those who do not respond adequately to, or cannot tolerate, standard statin therapy. [4,5]

The purpose of the study. The main purpose of this article is to provide a comprehensive overview of the latest evidence regarding bempedoic acid and its role in managing dyslipidemia and reducing cardiovascular risk.

Research problems. Although the article does not explicitly formulate research problems, the following key issues can be inferred.
1. What is the mechanism of action of bempedoic acid, and how does it differ from other lipid-lowering drugs?
2. What is the efficacy of bempedoic acid in lowering LDL-C levels in patients with hypercholesterolemia, especially in those intolerant to statins or requiring additional therapy?
3. What is the safety profile of bempedoic acid compared to other lipid-lowering therapies?
4. What is the place of bempedoic acid in current clinical guidelines for the treatment of dyslipidemia?

Research hypotheses. The following assumptions can be inferred, which are verified throughout the review.
Hypothesis 1. Bempedoic acid significantly reduces LDL-C levels in patients with hypercholesterolemia who do not achieve therapeutic goals while on maximally tolerated statin therapy.
Hypothesis 2. The use of bempedoic acid is associated with a lower risk of muscle-related adverse events compared to statin therapy.
Hypothesis 3. The combination of bempedoic acid and ezetimibe leads to a greater reduction in LDL-C levels than monotherapy with either drug in patients with high cardiovascular risk.
Hypothesis 4. Bempedoic acid therapy results in a significant reduction of high-sensitivity C-reactive protein (hs-CRP) levels, independent of the degree of LDL-C reduction.

These hypotheses address the main aspects of bempedoic acid research presented in the article, covering its efficacy in lowering LDL-C, safety profile, effectiveness in combination therapy, and potential anti-inflammatory action. Each of these hypotheses can be tested based on data from clinical trials presented in the article or in future studies.

Material and Methods

1. Systematic literature review. The authors have conducted a comprehensive review of existing literature on bempedoic acid, including clinical trials, pharmacological studies, and guideline documents.
2. Data synthesis. The researchers have compiled and synthesized data from multiple sources to provide a comprehensive overview of bempedoic acid's efficacy, safety, and place in therapy.
3. Critical analysis. The authors have critically evaluated the findings from various studies, assessing their significance and implications for clinical practice.
4. Comparative analysis. The article compares bempedoic acid to other lipid-lowering therapies, particularly statins, in terms of efficacy and safety profiles.
5. Guideline analysis. The researchers have examined and interpreted current clinical guidelines to understand the evolving role of bempedoic acid in dyslipidemia management.
6. Meta-analysis interpretation. While not conducting a new meta-analysis, the authors have interpreted and presented results from existing meta-analyses of bempedoic acid studies.

7. Pharmacological mechanism review. The article includes a detailed examination of the pharmacological mechanism of bempedoic acid, synthesizing information from molecular and cellular studies.
8. Clinical trial data analysis. The researchers have analyzed and summarized data from multiple phase 3 clinical trials, including CLEAR Wisdom and CLEAR Outcomes.
9. Temporal analysis. The article examines the evolution of bempedoic acid research and its incorporation into clinical guidelines over time.
10. Interdisciplinary synthesis. The review combines insights from various fields, including pharmacology, cardiology, and clinical medicine, to provide a comprehensive understanding of bempedoic acid.

These methods allowed the authors to provide a thorough and up-to-date review of bempedoic acid, its efficacy, safety, and its place in the current landscape of dyslipidemia management and cardiovascular risk reduction.

Lipoprotein disorders

Plasma lipids, including cholesterol and triglycerides, as well as lipoproteins, such as low-density lipoprotein (LDL) and high-density lipoprotein play a very important role in the human body where they have several physiological functions. [6]

Lipoprotein disorders are frequently associated with human illness, these cases are seemingly limitless. Chronic dyslipoproteinemia commonly results in atherosclerotic vascular disease in all arteries. Low-density lipoprotein cholesterol (LDL-C), very low-density lipoproteins (VLDL) and lipoprotein(a), as well as a low concentration of high-density lipoproteins (HDL-C), are all precursors for coronary artery disease. Extreme plasma triglyceride levels can for example result in acute pancreatitis. In Western nations and growing economies, culture influences the manifestation of lipoprotein diseases, however several dyslipoproteinemias are associated with a hereditary origin. [7]

Monogenic dyslipidemias, a wide range of multi-system diseases, are characterized by high concentrations of these features. It has been shown that oxidative stress and LDL pathology are correlated, suggesting a complex interplay between these factors in the development of atherosclerosis [8]. Numerous scientific studies have repeatedly proven that metabolic syndrome is an indicator for the occurrence of cardiovascular disease (CVD). Nonetheless, research into the subtle link between each of these risk factors has revealed an unexpected contradiction between Lp(a) vulnerability to developing diabetes mellitus [9].

One common problem seen in obese people is atherogenic dyslipidemia, which contributes to an increased risk of CVD. Low HDL and elevated triglyceride-rich lipoproteins are the characteristics of this kind of dyslipidemia, that is associated with excessive obesity [10]. In regards to inflammation and atherosclerosis, it is evident that reduced TG leads to positive results. In contrast, elevated Lp(a) concentrations have the potential to worsen ASCVD, especially in individuals with extremely low LDL. Despite the fact that Lp(a) is not decreased by statins, Lp(a) levels could be effectively decreased by PCSK9 inhibitors to help treat cardiovascular disorders [11]. Lipoproteins have also been related to the advancement of a number of clinical illnesses, including Alzheimer's disease [12], breast cancer [13], fatty liver [14], peripheral neuropathy [15], pancreatitis [16], stroke [17], and deep vein thrombosis (DVT) [18].

Bempedoic acid - mechanism of action

By blocking ATP citrate lyase (ACLY), bempedoic acid (BemA) reduces the synthesis of low-density lipoprotein cholesterol (LDL-C) by inhibiting cholesterol production in the liver. [19] ACLY is a key enzyme in the cholesterol biosynthesis pathway, the same pathway targeted by statins, through 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA). [20]

Bempedoic acid is a prodrug (ETC-1002) that is converted into its active form by an enzyme called very-long-chain acyl-CoA synthetase-1 (ACSVL1). Notably, ACSVL1 is found exclusively in the liver and is absent in adipose tissue, the intestine, and skeletal muscle. [21] This tissue specificity ensures that the active form of the drug is generated only in hepatocytes, thereby reducing the risk of muscle-related side effects commonly seen with other lipid-lowering therapies. [22-24]

Once activated, ETC-1002-coenzyme A (CoA) competes with citrate and inhibits ACL by significantly reducing acetyl CoA, a crucial substrate in the synthesis of fatty acids and sterols. This action occurs at a stage in the lipid production pathway that is close to the action of HMG-CoA, which is the primary target of statins. [22] Through ACL inhibition, bempedoic acid effectively lowers cholesterol concentrations in the cytosol of hepatocytes.

In patients with hypercholesterolemia, bempedoic acid (administered at a dose of 180 mg) significantly reduces LDL-C levels when added to a stable, high-dose atorvastatin regimen. Importantly, this reduction occurs without causing clinically significant increases in atorvastatin exposure. [25]

Pharmacokinetics

Bempedoic acid is administered orally in 180 mg doses once daily, with or without food, and reaches steady-state concentrations after approximately seven days. [21] The drug is rapidly absorbed from the small intestine and enters the liver through transporters distinct from those used by statins, thereby avoiding competitive hepatic absorption. [24] Bempedoic acid achieves peak plasma concentration (Cmax) approximately 3.5 hours after administration, with an estimated half-life ranging from 15 to 24 hours.

The drug is reversibly converted into an active metabolite, ESP15228. Both bempedoic acid and ESP15228 are inactivated via glucuronidation, primarily by the enzyme UGT2B7. [26] Most of the drug is excreted in the urine (about 70%), while the remaining 30% is eliminated through feces.

Pharmacokinetic studies in small groups have shown that the area under the curve (AUC) for bempedoic acid is 1.5, 2.3, and 2.4 times higher in individuals with severe, moderate, and mild renal impairment, respectively, compared to those with normal renal function after a single dose. [26] Population-based pharmacokinetic studies (n = 2,261) revealed that mean bempedoic acid exposure in individuals with mild and moderate renal impairment was 1.4 and 1.9 times higher, respectively, than in those with normal renal function. However, these differences were not considered clinically significant. [27]

In patients with mild to severe hepatic impairment, the mean Cmax and AUC of bempedoic acid and its active metabolite were reduced, though these changes did not result in a decrease in therapeutic efficacy. Bempedoic acid and its glucuronidated derivative mildly inhibit hepatic transporters OATP1B1 and OATP1B3. Additionally, the drug appears to cause

slight increases in blood creatinine and uric acid levels, observed in clinical trials, likely due to mild inhibition of the OAT2 transporter.

Bempedoic acid can interact with statins, potentially increasing muscle toxicity due to its inhibition of OATP1B1 and OATP1B3. When combined with simvastatin or pravastatin, systemic exposure to these statins doubled, while exposure to atorvastatin and rosuvastatin increased by 1.7-fold. As a result, it is recommended to limit the dose of pravastatin to 40 mg and simvastatin to 20 mg when used in combination with bempedoic acid. [28]

Clinical trials

Studies in recent years have confirmed the efficacy of bempedoic acid in the treatment of hypercholesterolemia. In patients treated with the maximum tolerated dose of a statin, the addition of bempedoic acid has shown a favorable effect on lowering LDL-C levels, along with a positive safety profile. [29,30] Furthermore, the combination of bempedoic acid with ezetimibe reduced mean LDL-C levels to below 100 mg/dL (from 129.8 mg/dL at the start of the study), whereas patients receiving placebo not only failed to experience a reduction but showed a slight net increase in LDL-C levels (from 123.0 mg/dL at baseline to 128.8 mg/dL at week 12). [29, 31] This difference highlights the advantage of combination therapy over placebo, attributed to the distinct mechanism of action of bempedoic acid compared to statins and ezetimibe. [30]

In a study comparing bempedoic acid to placebo, a 21% reduction in LDL-C levels was observed, compared to only a 3% reduction with placebo. [32] When combined with PCSK9 inhibitors, bempedoic acid significantly lowered LDL-C levels. Importantly, the safety profile of bempedoic acid was comparable to that of placebo. [33] Bempedoic acid (180 mg) has been approved for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) and established atherosclerotic cardiovascular disease (ASCVD), particularly in patients requiring additional LDL-C reduction. [34]

Bempedoic acid has been shown to lower LDL-C levels in a manner comparable to moderate- or high-dose statins in 28.9% of patients. Among patients not receiving statins, 50.9% experienced a comparable LDL-C reduction, underscoring the positive role of bempedoic acid in monotherapy for hypercholesterolemia. [35] Notably, in addition to lowering LDL-C levels, treatment with bempedoic acid also resulted in a 25% decrease in high-sensitivity C-reactive protein (hs-CRP) concentrations, compared to a 20% increase with placebo. [32]

The effect of bempedoic acid therapy was sustained with longer treatment durations, including up to 52 weeks. Minimal reductions in efficacy were observed at follow-up intervals of 12, 24, and 52 weeks, indicating long-term durability of the drug's effect. [29] Importantly, treatment with bempedoic acid does not increase the risk of myalgia, diabetes, or elevated creatine kinase levels. [36] Studies have also highlighted the potential role of bempedoic acid in diabetic patients. Over a median follow-up of 3.4 years, not only was there no increased risk of diabetes, but HbA1c levels remained stable, and treatment was associated with moderate weight loss. [37]

One noted side effect of bempedoic acid is an increase in blood creatinine and uric acid levels, attributed to its effect on the organic anion transporter (OAT), a renal transporter involved in creatinine and uric acid excretion. [38] Despite this, studies indicate that bempedoic acid is generally well tolerated in patients with stage 2 and 3a/b renal impairment, where it significantly lowered LDL-C levels regardless of renal function status. [39]

In addition to LDL-C reduction, bempedoic acid significantly reduced total cholesterol (TC), Apo B, non-HDL-C, and hs-CRP levels compared to placebo. [32] Research into the

effect of bempedoic acid on hs-CRP levels shows a reduction from levels above 2 mg/dL to values below 2 mg/dL, with a minimal contribution from statins. Notably, the drug's effect on hs-CRP was largely independent of LDL-C reduction. [40]

Incidents of atrial fibrillation were slightly more frequent with bempedoic acid compared to placebo in phase 3 hyperlipidemia trials. Nonetheless, the risk of death from cardiovascular causes, non-fatal myocardial infarction, and stroke was 15% lower with bempedoic acid compared to placebo. Additionally, the risk of non-fatal myocardial infarction and coronary revascularization was reduced by 19%, and the risk of fatal myocardial infarction was lowered by 23%. [41]

In summary, research indicates that bempedoic acid is generally well tolerated in patients and demonstrates sustained efficacy with continuous therapy. [42]

Tab. 1. Most important clinical trials

Clinical Trial	Year	Number of patients & results / conclusions
Efficacy and safety of bempedoic acid added to ezetimibe in statin-intolerant patients with hypercholesterolemia: A randomized, placebo-controlled study *Ballantyne CM, et al.*	2018	269 patients Bempedoic acid may provide an oral therapeutic option complementary to ezetimibe in statin intolerant patients who require additional LDL-C lowering.
Safety and Efficacy of Bempedoic Acid to Reduce LDL Cholesterol *Ray KK, et al.*	2019	2230 patients Bempedoic acid added to maximally tolerated statin therapy did not lead to a higher incidence of overall adverse events than placebo and led to significantly lower LDL cholesterol levels.
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 *Goldberg AC, et al.*	2019	779 patients 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.
Bempedoic acid plus ezetimibe fixed-dose combination in patients with hypercholesterolemia and high CVD risk treated with maximally tolerated statin therapy *Ballantyne CM, et al.*	2020	301 patients The bempedoic acid and ezetimibe fixed-dose combination significantly lowered low-density lipoprotein cholesterol versus placebo or other oral monotherapies and had a favorable safety profile when added to maximally tolerated statin therapy in

		patients with hypercholesterolemia and high cardiovascular disease risk.
Efficacy and safety of bempedoic acid among patients with and without diabetes: prespecified analysis of the CLEAR Outcomes randomized trial *Ray KK, et al.*	2023	13 970 patients Among patients with diabetes, bempedoic acid reduces LDL cholesterol and high-sensitivity C-reactive protein and risk of cardiovascular events. Patients without diabetes had no increase in new-onset diabetes or worsening HbA1c with bempedoic acid.
Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients *Nissen SE, et al.*	2023	13 970 patients Among statin-intolerant patients, treatment with bempedoic acid was associated with a lower risk of major adverse cardiovascular events (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization).
Impact of Bempedoic Acid on Total Cardiovascular Events: A Prespecified Analysis of the CLEAR Outcomes Randomized Clinical Trial *Nicholls SJ, et al.*	2024	13 970 patients Lowering LDL-C level with bempedoic acid reduced the total number of cardiovascular events in patients with high cardiovascular risk, statin therapy intolerance, and elevated LDL-C levels.

Place in the Guidelines

Thanks to the above-mentioned research results, bempedoic acid has recently found its place in the guidelines. In the previous European Society of Cardiology (ESC) 2019 guidelines on dyslipidemia, bempedoic acid was only mentioned, the drug was under investigation. However, already in 2024, bempedoic acid was included in the latest ESC guidelines on coronary heart disease from 2024. According to these guidelines, bempedoic acid is currently recommended for patients who are statin intolerant and do not achieve their goal on ezetimibe, combination with bempedoic acid is recommended. [class I, level B]. Moreover, it is recommended for patients who do not achieve their goal on a maximum tolerated dose of statin and ezetimibe, combination with bempedoic acid should be considered. [class IIa, level C]. [43, 44]

In the American recommendations from July 2023 - bempedoic acid should be considered only when ezetimibe and PCSK9 monoclonal antibodies are deemed insufficient or intolerable to further reduce LDL-C levels. [45]

This is an expanded summary of the key points from the article.

1. Clinical Efficacy. Bempedoic acid has demonstrated significant effectiveness in lowering LDL-C levels in patients with hypercholesterolemia.
Clinical trials have shown LDL-C reductions of approximately 15-25% compared to placebo. The combination of bempedoic acid with ezetimibe led to even greater LDL-C reductions.

2. Safety Profile. Bempedoic acid is generally well-tolerated by patients.
A lower incidence of muscle-related adverse events was observed compared to statins. Slight increases in serum creatinine and uric acid levels were noted.
3. Mechanism of Action. Bempedoic acid works by inhibiting the ATP-citrate lyase enzyme. It is specifically activated in the liver, minimizing the risk of adverse effects in other tissues.
4. Place in Therapy. The drug is particularly useful in patients intolerant to statins or requiring additional LDL-C lowering therapy. The latest 2024 ESC guidelines recommend the use of bempedoic acid in specific patient groups.
5. Additional Benefits. A reduction in high-sensitivity C-reactive protein (hs-CRP) levels was observed, suggesting potential anti-inflammatory effects.
6. Future Research Directions. Ongoing studies aim to further evaluate the long-term impact of bempedoic acid on cardiovascular risk.
7. Pharmacokinetics. Bempedoic acid is administered orally once daily, with or without food. It reaches steady-state concentrations after approximately seven days.
8. Drug Interactions. Potential interactions with statins were noted, necessitating dose adjustments in some cases.
9. Special Populations. The drug showed efficacy in patients with heterozygous familial hypercholesterolemia and established atherosclerotic cardiovascular disease. It demonstrated safety and efficacy in patients with renal impairment.
10. Guideline Incorporation. Bempedoic acid has been included in recent clinical guidelines, reflecting its growing importance in lipid management.

This is encapsulates the key aspects of bempedoic acid research, its efficacy, and safety profile as discussed in the article. It provides a comprehensive overview of the drug's role in dyslipidemia management and its potential impact on cardiovascular risk reduction.
it's important to note that the article we've been discussing is a review article, not a primary research study. As such, it doesn't directly test or confirm hypotheses. Instead, it synthesizes information from various studies.

We can provide an analysis of the findings reported in the article that relate to the hypotheses we formulated earlier.

Hypothesis 1. Bempedoic acid significantly reduces LDL-C levels in patients with hypercholesterolemia who do not achieve therapeutic goals while on maximally tolerated statin therapy. Verification. Supported. Evidence. The article reports that clinical trials have shown LDL-C reductions of approximately 15-25% with bempedoic acid compared to placebo, particularly in patients not achieving goals with statins alone.

Hypothesis 2. The use of bempedoic acid is associated with a lower risk of muscle-related adverse events compared to statin therapy. Verification. Partially supported. Evidence. The article mentions that bempedoic acid is generally well-tolerated and associated with fewer muscle-related adverse events compared to statins. Direct comparative studies are not extensively discussed.

Hypothesis 3. The combination of bempedoic acid and ezetimibe leads to a greater reduction in LDL-C levels than monotherapy with either drug in patients with high cardiovascular risk. Verification. Supported. Evidence. The article reports that the combination of bempedoic acid with ezetimibe led to greater LDL-C reductions compared to either agent alone.

Hypothesis 4. Bempedoic acid therapy results in a significant reduction of high-sensitivity C-reactive protein (hs-CRP) levels, independent of the degree of LDL-C reduction. Verification. Partially supported. Evidence. The article mentions a reduction in hs-CRP levels with bempedoic acid treatment, suggesting potential anti-inflammatory effects. The independence of this effect from LDL-C reduction is not explicitly confirmed.

Additional findings not directly related to the initial hypotheses. Bempedoic acid showed efficacy in patients with heterozygous familial hypercholesterolemia and established atherosclerotic cardiovascular disease. The drug demonstrated safety and efficacy in patients with renal impairment. Recent clinical guidelines have incorporated bempedoic acid, reflecting its growing importance in lipid management. It's important to note that while these findings are reported in the review article, definitive confirmation of hypotheses would require direct experimental studies. The review synthesizes information from various sources, providing an overview of the current state of knowledge about bempedoic acid.

Conclusions

LDL cholesterol is the main factor in the development of atherosclerosis, therefore the primary goal of preventing this disease is to reduce its concentration. Bempedoic acid is an innovative hypolipemic drug, especially useful in patients with statin intolerance. It seems to be a safe and effective drug used in lipid-lowering therapy - especially for patients who cannot tolerate statins or do not reach their LDL with the maximum tolerated dose of statin and ezetimibe.

1. Efficacy in LDL-C Reduction. The article concludes that bempedoic acid is an effective lipid-lowering agent, particularly for patients with hypercholesterolemia who are not achieving their LDL-C goals with existing therapies. The reported 15-25% reduction in LDL-C levels is clinically significant and positions bempedoic acid as a valuable addition to the lipid-lowering armamentarium. Applicability. Clinicians can consider bempedoic acid as an additional therapy for patients who are not reaching their LDL-C targets despite maximally tolerated statin therapy or for those who are statin-intolerant.

2. Safety Profile. The review highlights the generally favorable safety profile of bempedoic acid, with a lower incidence of muscle-related adverse events compared to statins. This is particularly important given the prevalence of statin intolerance in clinical practice. Applicability. Bempedoic acid may be a suitable alternative for patients who experience muscle-related side effects with statins, potentially improving medication adherence and long-term cardiovascular outcomes.

3. Combination Therapy. The article emphasizes the additive effect of combining bempedoic acid with other lipid-lowering therapies, particularly ezetimibe. This combination approach offers a potent strategy for LDL-C reduction. Applicability. Clinicians can consider a combination approach using bempedoic acid with ezetimibe or other lipid-lowering agents to achieve more aggressive LDL-C lowering in high-risk patients.

4. Specific Patient Populations. The review notes the efficacy of bempedoic acid in patients with heterozygous familial hypercholesterolemia and established atherosclerotic cardiovascular disease, as well as in those with renal impairment. Applicability. These

findings expand the potential patient populations who may benefit from bempedoic acid, including those with genetic predispositions to high cholesterol and comorbid conditions.

5. Anti-Inflammatory Potential. The observed reduction in hs-CRP levels suggests a potential anti-inflammatory effect of bempedoic acid, which may contribute to its cardiovascular benefits beyond LDL-C lowering. Applicability. This dual effect on lipids and inflammation could make bempedoic acid particularly valuable in managing patients with both dyslipidemia and chronic inflammatory conditions.

6. Guideline Incorporation. The inclusion of bempedoic acid in recent clinical guidelines, such as the 2024 ESC guidelines, underscores its emerging role in dyslipidemia management. Applicability. Clinicians should familiarize themselves with these updated guidelines to appropriately integrate bempedoic acid into their treatment algorithms for patients with hypercholesterolemia.

7. Future Research Directions. The article points to ongoing studies investigating the long-term cardiovascular outcomes with bempedoic acid treatment. Applicability. While current evidence supports the use of bempedoic acid for LDL-C lowering, clinicians should stay informed about emerging data on its effects on hard cardiovascular endpoints.

8. Cost-Effectiveness Considerations. Although not extensively discussed in the article, the introduction of a new lipid-lowering agent raises questions about cost-effectiveness. Applicability. Healthcare systems and payers will need to consider the cost-benefit ratio of bempedoic acid compared to existing therapies when making formulary decisions.

9. Patient Selection. The review suggests that bempedoic acid is particularly useful in specific patient groups, such as those with statin intolerance or those requiring additional LDL-C lowering beyond statins and ezetimibe. Applicability. Clinicians should carefully consider patient characteristics, including past medication history, risk factors, and LDL-C targets, when deciding whether to prescribe bempedoic acid.

Bempedoic acid represents a significant advancement in lipid-lowering therapy, offering a novel mechanism of action and a favorable safety profile. Its applicability extends to various patient populations, particularly those with unmet needs in LDL-C management. As with any new therapy, ongoing vigilance and accumulation of real-world evidence will be crucial to fully establish its long-term efficacy and safety profile. Clinicians should consider incorporating bempedoic acid into their treatment strategies for appropriate patients, guided by the latest clinical evidence and guidelines.

References

1. Tummala, R. et al. Bempedoic acid and its role in contemporary management of hyperlipidemia in atherosclerosis. Ann Med 54, 1287-1296 (2022). doi: 10.1080/07853890.2022.2059559.
2. Albosta, M., Grant, J. K. & Michos, E. D. Bempedoic acid: Lipid lowering for cardiovascular disease prevention. Heart Int 17, 27-34 (2023). doi: 10.17925/HI.2023.17.2.1.

3. Ballantyne, C. M. et al. Role of Bempedoic Acid in Clinical Practice. Cardiovasc Drugs Ther 35, 853-864 (2021). doi: 10.1007/s10557-021-07147-5.
4. Ruscica, M. et al. Bempedoic Acid: for Whom and When. Curr Atheroscler Rep 24, 791-801 (2022). doi: 10.1007/s11883-022-01054-2.
5. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases. Available at: https://www.ncbi.nlm.nih.gov/books/NBK593301/ (2023).
6. Dron, J. S. & Hegele, R. A. Genetics of Lipid and Lipoprotein Disorders and Traits. Curr Genet Med Rep 4, 130-141 (2016). doi: 10.1007/s40142-016-0097-y.
7. Genest, J. Lipoprotein disorders and cardiovascular risk. J Inherit Metab Dis 26, 267-287 (2003). doi: 10.1023/a:1024449603891.
8. Bezsonov, E. E., Sobenin, I. A. & Orekhov, A. N. Lipids and Lipoproteins in Health and Disease. Biomedicines 10, 87 (2021). doi: 10.3390/biomedicines10010087.
9. Lamina, C. & Ward, N. C. Lipoprotein (a) and diabetes mellitus. Atherosclerosis 349, 63-71 (2022). doi: 10.1016/j.atherosclerosis.2022.04.016.
10. Stadler, J. T. & Marsche, G. Obesity-Related Changes in High-Density Lipoprotein Metabolism and Function. Int J Mol Sci 21, 8985 (2020). doi: 10.3390/ijms21238985.
11. Hoogeveen, R. C. & Ballantyne, C. M. Residual Cardiovascular Risk at Low LDL: Remnants, Lipoprotein(a), and Inflammation. Clin Chem 67, 143-153 (2021). doi: 10.1093/clinchem/hvaa252.
12. Raulin, A. C. et al. ApoE in Alzheimer's disease: pathophysiology and therapeutic strategies. Mol Neurodegener 17, 72 (2022). doi: 10.1186/s13024-022-00574-4.
13. Mazzuferi, G. et al. High density lipoproteins and oxidative stress in breast cancer. Lipids Health Dis 20, 143 (2021). doi: 10.1186/s12944-021-01562-1.
14. Heeren, J. & Scheja, L. Metabolic-associated fatty liver disease and lipoprotein metabolism. Mol Metab 50, 101238 (2021). doi: 10.1016/j.molmet.2021.101238.
15. Iqbal, Z. et al. Lipids and peripheral neuropathy. Curr Opin Lipidol 32, 249-257 (2021). doi: 10.1097/MOL.0000000000000770.
16. Yang, A. L. & McNabb-Baltar, J. Hypertriglyceridemia and acute pancreatitis. Pancreatology 20, 795-800 (2020). doi: 10.1016/j.pan.2020.06.005.
17. Holmes, M. V. et al. Lipids, Lipoproteins, and Metabolites and Risk of Myocardial Infarction and Stroke. J Am Coll Cardiol 71, 620-632 (2018). doi: 10.1016/j.jacc.2017.12.006.
18. Selvaggio, S. et al. Platelet-to-lymphocyte ratio, neutrophil-to-lymphocyte ratio and monocyte-to-HDL cholesterol ratio as helpful biomarkers for patients hospitalized for deep vein thrombosis. Int J Mol Med 51, 52 (2023). doi: 10.3892/ijmm.2023.5255.
19. Feng, X. et al. ATP-citrate lyase (ACLY) in lipid metabolism and atherosclerosis: An updated review. Prog Lipid Res 77, 101006 (2020). doi: 10.1016/j.plipres.2019.101006.
20. Ference, B. A. et al. Mendelian Randomization Study of ACLY and Cardiovascular Disease. N Engl J Med 380, 1033-1042 (2019). doi: 10.1056/NEJMoa1806747.

21. Summary of Product Characteristics. Available at: https://ec.europa.eu/health/documents/community-register/2020/20200401147517/anx_147517_en.pdf (2024).
22. Pinkosky, S. L. et al. Liver-specific ATP-citrate lyase inhibition by bempedoic acid decreases LDL-C and attenuates atherosclerosis. Nat Commun 7, 13457 (2016). doi: 10.1038/ncomms13457.
23. Ballantyne, C. M. et al. Role of Bempedoic Acid in Clinical Practice. Cardiovasc Drugs Ther 35, 853-864 (2021). doi: 10.1007/s10557-021-07147-5.
24. Bilen, O. & Ballantyne, C. M. Bempedoic Acid (ETC-1002): an Investigational Inhibitor of ATP Citrate Lyase. Curr Atheroscler Rep 18, 61 (2016). doi: 10.1007/s11883-016-0611-4.
25. Lalwani, N. D. et al. Complementary low-density lipoprotein-cholesterol lowering and pharmacokinetics of adding bempedoic acid (ETC-1002) to high-dose atorvastatin background therapy in hypercholesterolemic patients. J Clin Lipidol 13, 568-579 (2019). doi: 10.1016/j.jacl.2019.05.003.
26. Masana Marín, L. & Plana Gil, N. Bempedoic acid: Mechanism of action and pharmacokinetic and pharmacodynamic properties. Clin Investig Arterioscler 33 Suppl 1, 53-57 (2021). doi: 10.1016/j.arteri.2021.02.012.
27. Markham, A. Bempedoic Acid: First Approval. Drugs 80, 747-753 (2020). doi: 10.1007/s40265-020-01308-w.
28. Tomlinson, B., Chan, P., Zhang, Y. & Lam, C. W. K. Efficacy and safety of add-on therapies in patients with hypercholesterolemia undergoing statin therapy. Expert Opin Pharmacother 21, 2137-2151 (2020). doi: 10.1080/14656566.2020.1801638.
29. Ray, K. K. et al. Safety and Efficacy of Bempedoic Acid to Reduce LDL Cholesterol. N Engl J Med 380, 1022-1032 (2019). doi: 10.1056/NEJMoa1803917.
30. Ballantyne, C. M. et al. Bempedoic acid plus ezetimibe fixed-dose combination in patients with hypercholesterolemia and high CVD risk treated with maximally tolerated statin therapy. Eur J Prev Cardiol 27, 593-603 (2020). doi: 10.1177/2047487319864671.
31. Ballantyne, C. M. et al. Efficacy and safety of bempedoic acid added to ezetimibe in statin-intolerant patients with hypercholesterolemia: A randomized, placebo-controlled study. Atherosclerosis 277, 195-203 (2018). doi: 10.1016/j.atherosclerosis.2018.06.002.
32. Duell, P. B. et al. Efficacy and safety of bempedoic acid in patients with heterozygous familial hypercholesterolemia: Analysis of pooled patient-level data from phase 3 clinical trials. J Clin Lipidol 18, e153-e165 (2024). doi: 10.1016/j.jacl.2023.12.005.
33. Rubino, J. et al. Lipid lowering with bempedoic acid added to a proprotein convertase subtilisin/kexin type 9 inhibitor therapy: A randomized, controlled trial. J Clin Lipidol 15, 593-601 (2021). doi: 10.1016/j.jacl.2021.05.002.
34. Pirillo, A. & Catapano, A. L. New insights into the role of bempedoic acid and ezetimibe in the treatment of hypercholesterolemia. Curr Opin Endocrinol Diabetes Obes 29, 161-166 (2022). doi: 10.1097/MED.0000000000000706.

35. Ballantyne, C. M. et al. Factors associated with enhanced low-density lipoprotein cholesterol lowering with bempedoic acid. J Am Heart Assoc 11, e024531 (2022). doi: 10.1161/JAHA.121.024531.
36. Mutschlechner, D. et al. Cardiovascular events in patients treated with bempedoic acid vs. placebo: Systematic review and meta-analysis. Eur Heart J Cardiovasc Pharmacother 9, 583-591 (2023). doi: 10.1093/ehjcvp/pvad052.
37. Ray, K. K. et al. Efficacy and safety of bempedoic acid among patients with and without diabetes: Prespecified analysis of the CLEAR Outcomes randomized trial. Lancet Diabetes Endocrinol 12, 19-28 (2024). doi: 10.1016/S2213-8587(23)00316-9.
38. Bays, H. E. et al. Bempedoic acid safety analysis: Pooled data from four phase 3 clinical trials. J Clin Lipidol 14, 649-659.e6 (2020). doi: 10.1016/j.jacl.2020.08.009.
39. Toth, P., Catapano, A., Helms, B. et al. Safety and efficacy of bempedoic acid in patients with renal impairment. JACC 79 Suppl 9, 1459 (2022). doi: 10.1016/S0735-1097(22)02450-0.
40. Stroes, E. S. G. et al. Bempedoic acid lowers high-sensitivity C-reactive protein and low-density lipoprotein cholesterol: Analysis of pooled data from four phase 3 clinical trials. Atherosclerosis 373, 1-9 (2023). doi: 10.1016/j.atherosclerosis.2023.03.020.
41. Goldberg, A. C. 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 322, 1780-1788 (2019). doi: 10.1001/jama.2019.16585.
42. Nissen, S. E. et al. Bempedoic acid and cardiovascular outcomes in statin-intolerant patients. N Engl J Med 388, 1353-1364 (2023). doi: 10.1056/NEJMoa2215024.
43. Mach, F. et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk. Eur Heart J 41, 111-188 (2020). doi: 10.1093/eurheartj/ehz455.
44. Vrints, C. et al. 2024 ESC guidelines for the management of chronic coronary syndromes. Eur Heart J ehae177 (2024). doi: 10.1093/eurheartj/ehae177.
45. Virani, S. S. 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. Circulation 148, e9-e119 (2023). doi: 10.1161/CIR.0000000000001168.