Review

Bempedoic Acid and Statins in Lipid-Lowering Strategy: Which Came First, the Egg or the Chicken?

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Abstract: The goal in cardiovascular prevention is the reduction of morbidity and mortality through the promotion of healthy lifestyles in the general population. The management of modifiable risk factors with pharmacological and non-pharmacological interventions, based on the individual risk is the first strategy suggested by the current guidelines. Several epidemiological studies have clearly shown the direct correlation between high levels of low-density lipoprotein cholesterol (LDL-C) and incidence of cardiovascular diseases. On the other hand, numerous randomized clinical studies have reported a huge benefit in terms of major cardiovascular events achievable by the reduction of LDL-C, thus supporting the notion that "the lower is better". Among the lipid-lowering strategies, statins are the drugs of choice in cardiovascular prevention, at both primary and secondary level. To achieve the ambitious targets suggested by the current guidelines, other lipid-lowering therapies are currently available in addition to statins, such as ezetimibe the inhibitors of the PCSK9. Pharmacological research has recently led to the development of a new drug, the bempedoic acid, which further enrich the available therapies. This drug also acts on the biosynthesis of cholesterol but at upstream level than statins. From the biochemical point of view, it has the potential to be considered before the statin with consequent titration of statins to achieve the desirable LDL-C target. In the present review, the biochemical and pharmacological characteristics of bempedoic acid are discussed. An overview of the clinical data that support its use in the management of the cardiovascular patient and its allocation in the lipid-lowering scenario will be also provided.

Keywords: low-density lipoproteins; atherosclerosis; lipid-lowering strategy

1. Introduction

The relationship between low-density lipoprotein cholesterol (LDL-C) levels and cardiovascular events, such as myocardial infarction and stroke, has been confirmed by epidemiological, clinical, and Mendelian studies [1,2]. Based on this evidence, reducing LDL-C has become a key therapeutic target in the management of cardiovascular diseases (CVD) [3,4]. Over the past two decades, the concept "The lower the better" has been established indicating that higher is the LDL-C reduction, greater will be the benefits in terms of cardiovascular events [3]. The most recent guidelines from the European Society of Cardiology (ESC) on the management of dyslipidemias have further reduced the therapeutic targets of LDL-C in patients at high and very high cardiovascular risk, suggesting the ambitious value of 70 and 55 mg/dL, respectively [5]. Furthermore, in the patients with a previous acute coronary syndrome (ACS) who undergo a further event, an LDL-C levels < 40 mg/dL is suggested, identifying a class of patients defined at extreme cardiovascular risk [6]. These targets are now achievable owing to the availability of highly effective drugs such as statins, which today represent the most prescribed first-line drugs [7] in addition to a healthy lifestyle. However, in the real world, statin use is associated with

large inter-individual variability in terms of response to a fixed statin dose [8] and with the risk of intolerance especially due to reported muscle toxicity [9] which often translates into reduced therapeutic adherence [10]. In case that statin therapy is not tolerated or does not allow to achieve the recommended LDL-C values, the use of other lipid-lowering drugs is necessary [11]. Additional therapeutical options currently available include ezetimibe and the proprotein convertase subtilisin/kexin type 9 (PCSK9i) inhibitors [12]. The higher cost of this latest strategy makes its wide-ranging use difficult, thus, in several country eligible criteria have been defined [13]. For this reason, scientific research in the field of CVD and especially in the management of atherosclerotic diseases, has led to the development of new therapeutic options to lower LDL-C. Among the emerging molecules, bempedoic acid might represent an interesting emerging option [14]. It is a prodrug activated at the hepatic level, which blocks the synthesis of cholesterol upstream of the target enzyme of statins [15]. The efficacy of bempedoic acid in reducing plasma LDL-C levels has been extensively proven in preclinical and clinical studies [16]. Bempedoic acid faces the complex scenario of dyslipidemia with an intriguing pharmacological potential that could make it an interesting alternative in the management of LDL-C-related atherosclerotic diseases. In the present work, its biochemical properties and therapeutic potential mainly vs. statins will be discussed because of their sequential mechanism of action. Evidence on biochemical and pharmacological features of the molecule was homogeneous and non-conflicting thus a non-systematic approach was utilized in selecting articles. In the section focused on clinical trials, a systematic approach was utilized. All phase 2 and 3 clinical trials involving the administration of Bempedoic acid published up to March 2023 have been evaluated and briefly summarized.

2. Bempedoic Acid: Biochemical and Pharmacological Features

2.1. Cholesterol Biosynthesis: The Upstream Effect

Bempedoic acid (2,2,14,14-tetramethyl-8-hydroxy-pentadecanoic acid) belongs to a new class of drugs whose primary mechanism of action is direct, competitive inhibition of hepatic adenosine-triphosphate citrate lyase ACLY [17]. It is a cytosolic enzyme involved in the process of cholesterol synthesis that acts upstream of the enzyme 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMGCR), target of statins.

It is a prodrug that requires an activation step to exert its inhibitory effect, catalyzed by the enzyme very long chain acyl CoA synthetase-1 (ACSVL1), expressed in the liver but absent in the adipose tissue, intestine, and skeletal muscle [15,18]. Hence, bempedoic acid is activated only in the liver without muscle involvement [19]. This allows a reduction in the risk of potential adverse events affecting the muscles, such as myalgia and myopathy, which instead might occur during the statins use [20].

The ACSVL1 enzyme inserts an acyl-CoA into the prodrug [15,18], leading to the formation of the active metabolite, bempedoic acid-CoA, and its reversible conversion to ESP15228, another active metabolite, obtained by oxidation of bempedoic acid [17,21]. ESP15228 probably contributes less to the overall clinical activity than bempedoic acid [21].

The bempedoic acid-CoA complex competes for the ACLY enzyme with the citrate deriving from the mitochondrial Krebs cycle, preventing its transformation into acyl-CoA and thus blocking the chain of biochemical reactions occurring in the synthesis process of cholesterol [15]. This results in a reduction in the endogenous synthesis of cholesterol in the liver [18]. At the molecular level, the block of cholesterol synthesis activates a specific transcription factor (SREBP2) which in turn promotes the transcription of the gene for the LDL receptor (LDL-R), thus leading to an increased expression of the LDL-R [15]. Clinical data document a reduction in LDL-C levels, but also in non-high-density lipoproteins cholesterol (non HDL-C), apolipoprotein B (ApoB), and total cholesterol (TC) in patients with hypercholesterolemia or mixed dyslipidemia [16]. A schematic view of bempedoic acid function in cholesterol biosynthesis is shown in Figure 1.
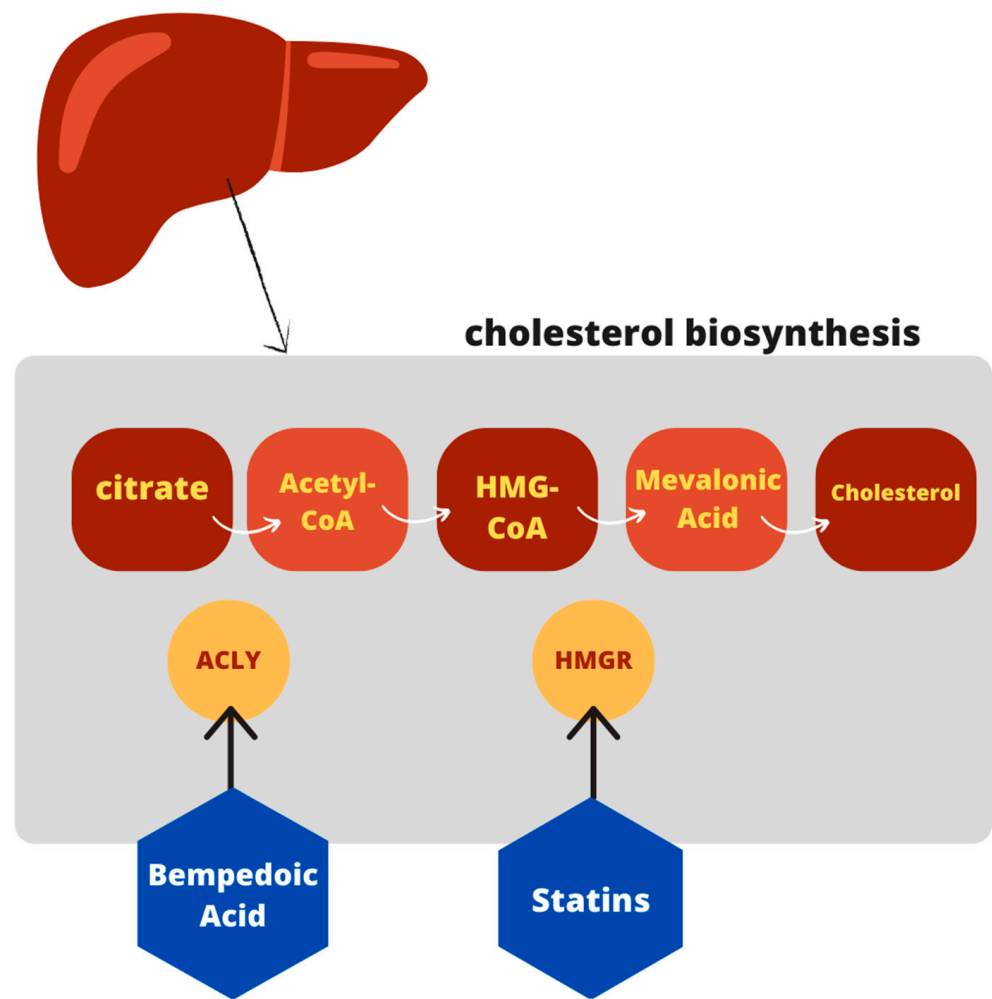
Figure 1. Schematic view of bempedoic acid function in cholesterol pathway.

A further effect of bempedoic acid is to block the endogenous synthesis of fatty acids: the inhibition of the ACLY enzyme prevents the formation of acetyl-CoA, a key metabolite involved not only in the synthesis of cholesterol but also in the metabolic pathway of synthesis of free fatty acids [22]. The result is a stimulus to the mitochondrial beta oxidation [23].

2.2. Alternative Biochemical Pathway beyond Cholesterol Synthesis

An additional target of bempedoic acid has also been demonstrated in experimental animals: the drug has shown the ability to activate adenosine monophosphate-activated protein kinase (AMPK) [24], which leads to a reduction in plasma cholesterol concentrations, triglycerides, and inflammatory markers. Moreover, the activation of the kinase could have positive effects on glycemia and insulin resistance [25]. However, it appears to be specific for the AMPK beta 1 isoform, which represents the isoform expressed in the murine liver; vice versa in the human liver where the prevalent form is Beta 2, toward which the drug does not show activity [26]. Thus, this hypothesis need to be corroborated by further evidence in humans. A schematic view is provided in Figure 2.
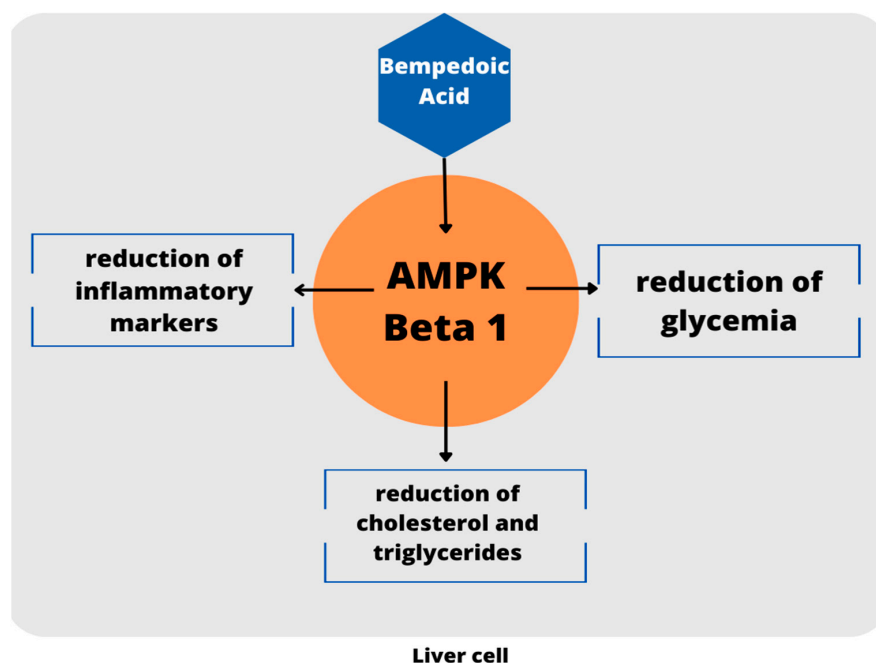
Figure 2. Schematic view of AMPK activation. To date, these evidence are limited to the mouse model.

2.3. Pharmacological Properties

Bempedoic acid is a drug that is taken orally and absorbed in the small intestine. Concomitant food intake had no effect on the oral bioavailability of the drug. The apparent volume of distribution (V/F) is approximately 18 liters, suggesting a distribution predominantly into the vascular compartment. Bempedoic acid and its active metabolite bind plasma proteins up to 99% [15].

The conversion of bempedoic acid to active drug occurs in the liver. In vitro studies suggest that bempedoic acid, its active metabolite, and glucuronidated forms are not metabolized by cytochrome P450 enzymes thus, indicating few potential interactions with drugs metabolized by cytochrome P450 itself [15]. The active form of bempedoic acid are metabolized to their inactive glucuronide conjugates by the glucuronyltransferase UGT2B7, which is predominantly expressed in the liver and gastrointestinal tract [27]. Once glucuronidated, the two inactive metabolites are mainly eliminated by the kidneys (70%) and partly by the liver (30%) [15].

Bempedoic acid and its metabolites are weak inhibitors of hepatic transporter proteins such as organic anion-transporting polypeptide 1B1 (OATP1B1) and 1B3 (OATP1B3) involved in the hepatic uptake of numerous drugs including some statins such as atorvastatin, prevastatin, fluvastatin, pitavastatin, rosuvastatin, and simvastatin [28]. For this reason, the interactions between bempedoic acid 180 mg and simvastatin 40 mg, atorvastatin 80 mg, pravastatin 80 mg, and rosuvastatin 40 mg have been analyzed in various clinical studies [29]. A study on the combination between bempedoic acid 180 mg plus atorvastatin 80 mg did not lead to a clinically significant increase in the concentration of the latter, so it is possible to administer them in combination [30].

Conversely, the use of bempedoic acid in combination with high doses of simvastatin has shown an increased risk of interactions [15]: in particular, the administration of a single dose of simvastatin 40 mg with bempedoic acid 180 mg at steady state resulted in a two-fold increase in simvastatin acid exposure [29]. It follows that the dose of simvastatin should not exceed 20 mg or 40 mg per day for patients with severe hypercholesterolemia [29].

Bempedoic acid is also a weak inhibitor of the carrier protein organic anion transporter-2 (OAT2) [28], localized at the level of the basolateral membrane of the proximal renal tubular cells and involved in the Na-independent transport of organic anions/dicarboxylates, including uric acid (UA), from peripheral blood to the cytosol of renal cells [31]. This effect

could explain the increase in serum uric acid levels following the intake of bempedoic acid. Therefore, monitoring of uric acid levels during the treatment with bempedoic acid [32] is recommended in patients diagnosed with gout [33]. The increased plasma UA levels are transient and reversible on discontinuation of the bempedoic acid treatment [34].

3. Preclinical Evidence: Optimal Dosage, Pleiotropic Effects and Promising Safety Profile

The first phase 2 study have tested bempedoic acid in a population of hypercholesterolemic patients aged 18 to 80 years with LDL-C values between 130 and 220 mg/dL [25]. Subjects with diabetes mellitus, hypertensive, and clinically significant CVD were excluded from the study. Restrictive inclusion criteria was used to test the efficacy and safety of three dose formulations of bempedoic acid (40, 80, and 120 mg) versus placebo for a duration of 12 weeks [25]. A total of 177 subjects were randomized in placebo (44 subjects) and treatment (133 subjects) with bempedoic acid at the above-mentioned dosages. The results of this first phase 2 experience evidenced a substantial dose-dependent efficacy of bempedoic acid, with a LDL-C reduction reaching -26.6% in the group treated with 120 mg [25]. A post-hoc analysis showed a reduction in fasting insulin in subjects treated with 40 and 80 mg of bempedoic acid who had elevated fasting insulin at baseline. A reduction in hsCRP was also detected in subjects treated with bempedoic acid reaching -26% in subjects treated with the 80 mg dosage. The safety profile was promising. Administration of bempedoic acid did not result in significant adverse effects and the side effects profile was comparable to placebo. Bempedoic acid treatment groups showed an average increase in uric acid of between 7% and 16%. There was no noticeable difference between the two arms in terms of subjects who experienced adverse events (AEs), serious adverse events (SAEs), events believed to be treatment-related, or treatment interruptions caused by adverse events. A slightly higher incidence of myalgia was noticed in the bempedoic acid treatment group [25].

Based on the results of the previous trial, a phase 2 study was conducted on diabetic hypercholesterolemic patients to test the possible AMPK activation-mediated effects on glucose metabolism regulation [35]. The monocentric, double-blind, placebo-controlled clinical trial involved 60 patients with type 2 diabetes and elevated LDL-C levels [35]. Patients discontinued previously taken lipid-lowering and diabetes therapy, then were randomized to receive bempedoic acid (80 mg daily for 2 weeks, followed by 120 mg daily for 2 weeks) or placebo for a total of 4 weeks. Results showed that bempedoic acid significantly lowered LDL-C levels by 43% compared to a 4% reduction in the placebo group at day 29 ($p < 0.0001$) [35]. In addition, a reduction in hsCRP protein was also observed (-41% vs. -11% median at day 29) with bempedoic acid compared to placebo. However, no significant changes were detected in other glycemic metabolism markers such as blood glucose and fasting insulin [35]. It should be noted that the reduction in LDL-C was more marked in this population of diabetic patients compared to the previous trial (-43% vs. -26.7%). No relevant safety concerns emerged during the trial and no patients in the treatment group reported myalgia. In addition, only a slight increase in UA levels without any reported gout attack was reported [35].

Further phase 2 experiences have focused on the better definition of the safety profile of the molecule; in particular, bempedoic acid was tested in statins-intolerant patients and in association with other lipid-lowering molecules.

In a phase 2 study, 56 statin intolerant patients were randomly assigned in a 2:1 ratio to receive bempedoic acid 60 mg daily or placebo for 8 weeks [36]. The dosage of bempedoic acid was gradually increased every two weeks, starting at 60 mg rising to 120 mg, 180 mg, and 240 mg. The lipid-lowering efficacy of the compound was confirmed, with a reduction in LDL-C of -28.7% at week 8 compared to placebo [36]. Moreover, even in this class of patients, the safety profile of bempedoic acid was confirmed and no significant difference in the occurrence of muscle-related side effects between groups was reported; none of the patients treated with bempedoic acid had to stop treatment because of these side

effects [36]. It should be emphasized that statins intolerance in this study was defined with less restrictive criteria than those defined from National Lipid Association [37]. Intolerance was defined by emergence of new symptoms such myalgia, muscle cramps, muscle pain, or muscle weakness during statin treatment with ≥1 statin, followed by improvement or resolution of symptoms within 4 weeks of discontinuation of statin therapy (no rechallenge required and 1 statin sufficient for the definition of statin intolerance) [36].

Another phase 2 trial tested bempedoic acid alone or in combination with ezetimibe, in patients with and without intolerance to statins [38]. The study showed that when used as a single agent, ezetimibe was able to lower LDL cholesterol by 21%; monotherapy with bempedoic acid at a dose of 120 mg or 180 mg resulted in a greater reduction in LDL-C levels, reaching −27% (vs. ezetimibe) and −30% (vs. ezetimibe), respectively. When bempedoic acid was combined with ezetimibe at a dose of 120 mg or 180 mg, LDL-C was reduced by 43% and 48%, respectively (both vs. ezetimibe) [38]. Among all treatment groups, muscle-related side effects were reported more frequently by patients intolerant to statins; however, bempedoic acid was well-tolerated and the frequency of muscle-related AEs was similar across all treatment groups, and no dose-related changes in laboratory parameters or clinically significant abnormalities were observed [38].

Additional study evaluated bempedoic acid administered in combination to statin therapy in hypercholesterolemic patients [39]. This study randomized 134 patients with LDL-C levels between 115 and 220 mg/dL already on stable statin therapy to receive 120 mg bempedoic acid, 180 mg bempedoic acid, or placebo for 12 weeks [39]. Stable statin therapy was defined as the continuous use of atorvastatin (at a dose of 10 or 20 mg), simvastatin (at a dose of 5, 10 or 20 mg), rosuvastatin (at a dose of 5 or 10 mg), or pravastatin (at a dose of 10, 20, or 40 mg) for a minimum of 3 months prior to pre-enrolment screening. The reduction from baseline in LDL-C at week 12 was significantly greater with bempedoic acid 120 mg (−17%) and 180 mg (−24%) compared to placebo. Similarly, according to the previous mentioned studies, the incidence of AEs, muscle-related AEs, and treatment discontinuations due to Es with bempedoic acid was comparable to those observed with placebo [39].

The safety profile of the molecule was also confirmed by further observations in which the combination of bempedoic acid (180 mg) with high-dosage atorvastatin (80 mg) was evaluated [30]. In this phase 2 study, patients were initially treated with atorvastatin 80 mg open label once daily for 4 weeks. After the stabilization phase they were randomized [30] in a 2:1 ratio to receive double-blind bempedoic acid 180 mg (*n* = 545) or placebo (*n* = 523) in addition to atorvastatin 80 mg open label for an additional 4 weeks [30]. The atorvastatin/bempedoic acid group showed a significantly greater reduction in LDL-C from baseline to day 29 compared to the atorvastatin/placebo group with a percentage change in LDL-C from baseline to day 29 of −22.2% between the bempedoic acid group and the placebo group [30]. The addition of bempedoic acid to stable high-dose atorvastatin therapy was well tolerated in the study. Only 2 patients (4%) in the atorvastatin/bempedoic acid group reported mild myalgia, while no patients in the atorvastatin/placebo group reported myalgia [30]. There were no interruptions in treatment due to myalgia. One patient in the atorvastatin/bempedoic acid group had elevated creatine phosphokinase levels on day 14. CPK values returned to normal by day 21. This event was not considered clinically significant or related to the study drug by the investigator, the patient did not report any associated clinical symptoms [30].

Safety profile was confirmed even by an additional study where the triple association of bempedoic acid at 180 mg, ezetimibe 10 mg, atorvastatin 20 mg vs. placebo was investigated [40]. The study, enrolling 43 patients in the treatment group and 20 in the placebo arm, showed a reduction in LDL-C of −63% in treatment arm compared to placebo (−3%). Most adverse events during treatment were mild to moderate in intensity [40]. None of the patients had significant increases in aminotransferase or creatine kinase levels judged to be clinically relevant.

Finally, the association of bempedoic acid with PCSK9i was also evaluated [41]. The study was conducted in three phases: a 1.5-month screening/washout period in which all lipid-lowering therapies were discontinued, followed by a 3-month period in which patients started PCSK9i background therapy, and finally a 2-month treatment period in which patients were randomized to receive bempedoic acid 180 mg or placebo once daily with continued therapy with PCSK9i in a 1:1 ratio [41]. The addition of bempedoic acid to background PCSK9i therapy resulted in a significant reduction in LDL-C levels of 30.3% ($p < 0.001$) compared to placebo [41]. The safety profile of bempedoic acid added to background PCSK9i therapy was proved to be similar to placebo. Patients who received bempedoic acid showed a slight increase in UA levels compared to those who received placebo, with the greatest increase at month 2 of treatment (+0.56 ± 0.77 mg/dL for bempedoic acid compared to −0.03 ± 0.56 mg/dL for placebo) [41]. One patient treated with bempedoic acid reported a mild case of gout with urate levels of 7.1 mg/dL at pre-treatment screening evaluation and increased to 11.4 mg/dL at the time of the event [41]. A summary of phase 2 trial2 is reported in Table 1.

Table 1. Efficacy of bempedoic acid in phase 2 trials.

Study	Therapy	N° of Patients	LDL-C Reduction	hs-CRP Reduction
Ballantyne et al., 2013 [25]	BA 40 vs. placebo BA 80 vs. placebo BA120 mg vs. placebo	177	*BA group* −17.9% −25% −26.6 −2.1% (Placebo)	*BA group* −21% −26% −20% −2% (Placebo)
Gutierrez et al., 2014 [35]	Bempedoic acid 80 mg for 2 weeks increased to 120 mg after week 2 vs. placebo for 4 weeks	60	*BA group* −42% −4% (Placebo)	*BA group* −41% +11% (Placebo)
Thompson et al., 2015 [36]	Bempedoic acid 60 mg increased to 240 mg at 2 weeks intervals vs. placebo	56	*BA group* −32% 3.3% (Placebo)	*BA group* −42% 0% (Placebo)
Thompson et al., 2016 [38]	BA 120 mg alone; BA 180 mg alone; BA 120mg + Ezetimibe 10 mg; BA 180 mg + Ezetimibe 10 mg Ezetimibe 10 mg alone	348	*BA group* −27% −30% *BA + EZE group* −43% −48% −21%	*BA group* −30% −40% *BA + EZE group* −38% −25% −10.5%
Ballantyne et al., 2016 [39]	Stable background statin therapy + BA 120 mg vs. placebo Stable background statin therapy + BA 120 mg vs. placebo	134	*BA group* −17% −24% −4% (Placebo)	*BA group* −21% −29% −0% (Placebo)
Lalwani et al., 2019 [30]	Atorvastatin 80 mg + Bempedoic acid 180 mg vs. placebo	68	*BA group* −13% +9.2% (Placebo)	*BA group* −34% +0.735% (Placebo)
Rubino, MacDougall, Sterling, Hanselman, et al., 2021 [40]	Bempedoic acid 180 mg + Atorvastatin 20 mg + Ezetimibe 10 mg vs. placebo	63	*BA group* −63.6% −3.1% (Placebo)	*BA group* −47.7% −2.7% (Placebo)
Rubino, MacDougall, Sterling, Kelly, et al., 2021 [41]	Evolocumab 430 mg + Bempedoic acid 180 mg vs. placebo	59	−27.5% (BA) −3.1% (Placebo)	−34% (BA) −1.6% (Placebo)

BA: bempedoic acid; EZE: ezetimibe.

4. The CLEAR Program: Exploring the Role in Clinical Practice

4.1. Bempedoic Acid in Statin Intolerant Patients: The CLEAR Tranquility and CLEAR Serenity Trials

Two large phase 3 trials have evaluated the safety and efficacy of bempedoic acid in statin intolerant patients.

The CLEAR Serenity study evaluated the safety of bempedoic acid in a population of hypercholesterolemic patients with intolerance to at least two statins, one of which was at the lowest available dosage [42]. Patients with LDL-C levels ≥ 130 mg/dL in primary prevention or ≥100 mg/dL in secondary prevention or heterozygous familial hypercholesterolemia were enrolled. Patients' baseline background cholesterol-lowering therapy was maintained during the trial. The background therapy consisted of low-dose statin (tolerated dose) or other lipid-lowering drugs such as selective cholesterol absorption inhibitors, bile acid sequestrants, fibrates, PCSK9i or niacin, alone or in combination [42]. A total of 365 patients were randomized 2:1 vs. placebo to receive bempedoic acid 180 mg once daily for 12 weeks in addition to stable lipid-lowering therapy. LDL-C reduction at week 12 was significant in the bempedoic acid group compared to placebo, with a placebo-adjusted difference of −21.4% [42]. In addition, significant reductions in non-HDL-C (17.9%), TC (14.8%), ApoB (15.0%), and hsCRP (24.3%) were observed in the bempedoic acid group compared to placebo ($p < 0.001$ for all comparisons) [42]. Treatment with bempedoic acid was safe and well tolerated. Muscle-related AEs were not significant. Myalgia was the most frequent adverse event, occurring in 4.7% and 7.2% of patients treated with bempedoic acid and placebo, respectively [42]. Among those who experienced myalgia, 3.4% of patients treated with bempedoic acid and 6.3% of patients treated with placebo discontinued the study drug. During the study period, mean UA levels in the bempedoic acid group increased from 0.68 to 0.86 mg/dL from baseline, while in the placebo group, they decreased by −0.12 mg/dL. In the study, a few proportion of patients in the bempedoic acid arm experienced an episode of gout (1.7% of patients vs. 0.9% of patients in the placebo group) [42].

The CLEAR Tranquility trial have Investigated the safety and efficacy of bempedoic acid 180 mg once daily in addition to ezetimibe 10 mg daily in addition to stable lipid-lowering therapy in patients with a history of intolerance to at least one statin and with LDL-C levels equal to or greater than 100 mg/dL, requiring further reduction of LDL-C levels [43]. Stable lipid-lowering therapy was defined as low-dose or very low-dose statin and non-statin agents such as fibrates, nicotinic acid, bile acid sequestrant, fish oil, eicosapentaenoic acid ethyl ester, omega-3 fatty acids, salmon oil, and sitosterols. The study included 269 patients, with 181 in the bempedoic acid treatment arm and 88 in the placebo arm. After a 4-week run-in period with ezetimibe 10 mg/day, patients were randomized 2:1 to receive bempedoic acid 180 mg or placebo once daily in addition to ezetimibe 10 mg/day for 12 weeks. Results showed that bempedoic acid added to basic lipid-modifying therapy with ezetimibe led to a significant −28.5% reduction in LDL-C compared to placebo [43]. In addition, a significant reduction in non-HDL-C (23.6%), TC (18.0%), ApoB (19.3%), and hsCRP (31.0%), was also observed with bempedoic acid compared to placebo. Bempedoic acid was well tolerated, with similar rates of treatment-related AEs, muscle-related AEs, and treatment discontinuations observed in the bempedoic acid or placebo groups. During the first 4 weeks of bempedoic acid treatment, there was a slight increase in mean UA concentration in the treatment group (from 5.8 ± 1.4 mg/dL at baseline to 6.4 ± 1.5 mg/dL at week 4), which remained stable throughout the study (6.3 ± 1.5 mg/dL at week 12). No new episodes of gout or worsening gout were reported during the study [43].

4.2. Patients on Maximal Lipid-Lowering Therapy: The CLEAR Harmony, CLEAR Wisdom, and FDC Trials

The CLEAR Harmony trial involved 2230 patients with 1488 enrolled in the bempedoic acid treatment arm [44]. The study population consisted of hypercholesterolemic patients with atherosclerotic cardiovascular disease or heterozygous familial hypercholesterolemia

on maximal lipid-lowering therapy with statins in combination or not with other lipid-lowering drugs. PCSK9i was permitted after week 24 of the trial only if LDL-C levels remained above 170 mg/dL. Treatment with bempedoic acid for 12 weeks resulted in a significant reduction in mean LDL cholesterol levels of −19.2 mg/dL, equivalent to a −16.5% change from baseline. The difference from baseline between bempedoic acid and placebo was −18.1 percentage points [44]. During the study period, there was no significant difference in the incidence of AEs and SAEs between the bempedoic acid group (78.5% and 14.5%, respectively) and the placebo group (78.7% and 14.0%, respectively). However, there was a higher incidence of AEs leading to discontinuation of treatment in the bempedoic acid group compared to the placebo group (10.9% vs. 7.1%). In addition, the incidence of gout was higher in the bempedoic acid group than in the placebo group (1.2% vs. 0.3%) [44]. The treatment arm showed a significant increase in uric acid levels from baseline, with a change of +0.73 mg/dL ± 1.11, compared to the placebo arm with a change of −0.06 mg/dL ± 0.87.

Another large study designed to investigate the efficacy and safety of bempedoic acid in patients on maximal lipid-lowering therapy is the CLEAR Wisdom trial [45]. In this study, a population of 779 patients was randomized 2:1 to bempedoic acid vs. placebo. Patients were at high cardiovascular risk because of heterozygous familial hypercholesterolemia or ASCVD. Simvastatin at a dose of ≥40 mg, mipomersen, lomitapide, lipoprotein apheresis, gemfibrozil, and cholestin were not permitted as basal lipid-lowering therapy. At week 12, bempedoic acid arm showed a significant reduction in LDL-C levels compared to placebo (−15.1% vs. 2.4%, respectively). In addition, significant decreases were observed in non-HDL-C (−10.8% vs. 2.3%), TC (−9.9% vs. 1.3%), ApoB (−9.3% vs. 3.7%), and hsCRP (−18.7% vs. −9.4%) [45]. Of the patients in the bempedoic acid arm, 2.1% experienced gout and 2.7% had an increase in blood UA level, compared with 0.8% and 0.4% of patients in the placebo group respectively. Of the 11 patients who reported gout in the bempedoic acid group, 5 had a history of previous gout attacks and 3 had a history of hyperuricemia before participating in the study. In addition, 10 of the 11 patients who experienced gout in the bempedoic acid group had higher-than-normal UA levels already at baseline [45].

In the fix-dose combination (FDC) trial, a total of 301 patients at high cardiovascular risk, with atherosclerotic cardiovascular disease, heterozygous familial hypercholesterolemia, or multiple cardiovascular risk factors were randomly assigned (in a 2:2:2:1 ratio) to receive treatment with one of the following four options for 12 weeks: a FDC of ezetimibe 10 mg and bempedoic acid 180 mg, Bempedoic acid 180 mg, ezetimibe 10 mg or placebo added to stable therapy with statins [46]. At week 12, the FDC demonstrated a significant reduction in LDL-C among patients included in the analysis (−36.2%) compared to placebo (1.8%), ezetimibe alone (−23.2%) or bempedoic acid alone (−17.2%). The FDC demonstrated similar reductions in LDL-C levels in all subgroups, regardless the high-intensity or non-high-intensity statin therapy [46]. The combined treatment of bempedoic acid + ezetimibe showed a significant reduction in hsCRP levels (−35.1%) compared to a +21.6% increase in the placebo group. Ezetimibe group showed a reduction of only 8.2% but still significant in hsCRP levels. The FDC had a generally similar safety profile compared to bempedoic acid, ezetimibe, or placebo in this study. The bempedoic acid + ezetimibe and bempedoic acid treatment groups showed a slight increase in mean uric acid levels (11.8% and 16.1%, respectively), but gout was reported.

4.3. First Evidence on Cardiovascular Events: The CLEAR Outcomes Trial

The efficacy of bempedoic acid on major cardiovascular endpoints beyond LDL-C reduction was investigated in the CLEAR Outcomes trial [47]. A double-blind, randomized, placebo-controlled trial was conducted, involving statin-intolerant patients with cardiovascular disease or that were at high risk for it. Patients were randomized to receive either 180 mg daily of oral bempedoic acid or placebo in addition to other lipid-lowering therapies as monotherapy or in combination (ezetimibe, niacin, bile acid resins, fibrates, PCSK9i or very low statin dose without unacceptable adverse effects). Up to 13,970 pa-

tients were randomized, with 6992 in the bempedoic acid group and 6978 in the placebo group. The primary endpoint was a composite of the four following entities: major adverse cardiovascular events including death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization. The median follow-up duration was 40.6 months, and the baseline mean LDL cholesterol level was 139.0 mg/dL in both groups. Bempedoic acid resulted in a 21.1 percentage point reduction in LDL cholesterol levels compared to placebo after 6 months. The use of bempedoic acid resulted in a significantly lower incidence of a primary end-point event (11.7% vs. 13.3% patients, *p* = 0.004). In addition, the incidence of a composite of death from cardiovascular causes, nonfatal stroke, or nonfatal myocardial infarction were also significantly lower with bempedoic acid (8.2% vs. 9.5%; *p* = 0.006), as were the incidence of fatal or nonfatal myocardial infarction (3.7% vs. 4.8%; *p* = 0.002), and coronary revascularization (6.2% vs. 7.6%; *p* = 0.001). However, bempedoic acid did not have a significant effect on fatal or nonfatal stroke, death from cardiovascular causes, or death from any cause. There were no significant differences in the overall incidences of adverse events, serious adverse events, and adverse events leading to discontinuation of the trial regimen between the bempedoic acid and placebo groups. However, the incidence of gout and cholelithiasis was higher in the bempedoic acid group than in the placebo group (3.1% vs. 2.1% and 2.2% vs. 1.2%, respectively). Bempedoic acid group experienced small increases in serum creatinine (mean change from baseline after 6 months: +0.05 ± 0.2 mg/dL), uric acid (mean change from baseline after 6 months: +0.76 ± 1.2 mg/dL), and hepatic enzyme levels. It is worth mentioning that in contrast to statins, bempedoic acid did not result in an elevation of glycated hemoglobin levels or a higher occurrence of new-onset diabetes, as demonstrated in comparison with the placebo group. A summary of phase 3 trials is reported in Table 2.

Table 2. Efficacy of bempedoic acid in phase 3 trials.

Study	Therapy	N° of Patients	LDL-C Reduction	hs-CRP Reduction
Ballantyne et al., 2018 CLEAR Tranquility [43]	Bempedoic acid 180 mg + Ezetimibe 10 mg vs. Placebo + Ezetimibe 10 mg in addition to lipid-lowering therapy including low-dose or very low-dose statin.	269	−23.5% vs. + 5%	−32% vs. +2.1%
Laufs et al., 2019 CLEAR Serenity [42]	Bempedoic acid 180 mg vs. Placebo in addition to stable lipid-lowering therapy including low-dose or very low-dose statin.	345	−23.6% vs. −1.3%	−25.4% vs. +2.7%
Ray et al., 2019 CLEAR Harmony [44]	Bempedoic acid 180 mg vs. Placebo in addition to maximally tolerated statin therapy with or without additional lipid-lowering therapy	2230	−16.5% vs. +1.6%	−22.4% vs. +2.6%
Goldberg et al., 2019 CLEAR Wisdom [45]	Bempedoic acid 180 mg vs. Placebo in addition to tolerated statin therapy with or without additional lipid-lowering therapy	779	−15.1% vs. 2.4%	−18.7% vs. −9.4%
Ballantyne et al., 2020 [46]	BA 180 mg + EZE 10 mg	301	−36.2%	−35.1%
	BA 180 mg		−17.2%	−31.9%
	EZE 10 mg		−23.2%	−8.2%
	Placebo (in addition to maximally tolerated statin therapy)		+1.8%	+21.6%
Nissen et al., 2023 CLEAR Outcomes [47]	BA 180 mg Placebo in addition to stable lipid-lowering therapy including very low-dose statin.	13,970	−21.7% −0.6% (at 6th month)	−22.2% +2.4% (at 6th month)

BA: bempedoic acid; EZE: ezetimibe.

5. Discussion

Although in the first phase 2 trial bempedoic acid [25] that was used as a monotherapy at a dosage of 120 m, proved to be effective in reducing LDL cholesterol by 27%, in other phase 2 and phase 3 studies the molecule was evaluated mainly as an add-on therapy with statins and/or other lipid-lowering drugs, resulting in an additional reduction of at least 20% of LDL-C at a dosage of 180 mg. Consequently, the molecule, approved in the market starting from 2020 in the USA and in some EU states from January 2023, is currently indicated as an add-on therapy to lipid-lowering drugs already on the market, in primary or secondary prevention, in patients with familial or non-familial hypercholesterolemia, who do not reach the LDL-C target with standard combination therapies [48]. To date, bempedoic acid may be considered as the first-line therapy exclusively in patients with statin intolerance. Despite this indication, the biochemistry of the molecule, such as its upstream inhibition, non-statins competition in the cholesterol synthesis chain, its hepato-selectivity, and its favorable safety profile, encourages the use of bempedoic acid as a potential first-line therapy in hypercholesterolemic patients in primary or secondary prevention, giving the opportunity to titrate statins according the LDL-C target values to be achieved. However, prespecified clinical trials are needed to corroborate this hypothesis.

Moreover, the specificity for the liver of bempedoic acid greatly reduces, indeed, muscle-related adverse events typical of statins. In the trials available to date, bempedoic acid showed good tolerability. The overall incidence of AEs was comparable between the bempedoic acid and placebo groups. In addition, there was no statistically significant difference in the occurrence of SAEs or, in particular, muscle-related adverse events [49]. Although the cardiovascular benefits of statins exceed the risk of muscle-related symptoms and the other side effects [9,50–52], in a novel pharmacological scenario where new powerful drugs become available, alternative lipid-lowering strategies should be considered. Despite the risk of statin-induced rhabdomyolysis is generally low, it may increase in presence of certain triggers factors such as the use of CYP3A4 inhibitors or intense physical activity [53]. For this reason, if the safety and efficacy profile of bempedoic acid is confirmed from real world data, this molecule could replace statins as first-line lipid-lowering therapy, also considering its pleiotropic effects such as the lowering of hsCRP and the favorable impact on glucose metabolism that could lead to an additional reduction of cardiovascular events independent of the reduction of LDL-C.

In fact, although the mechanisms are not yet fully defined, the inhibition of ATP citrate lyase seems to induce a reduction in hepatic gluconeogenesis leading to better glycemic control. Clinical data seem to confirm this hypothesis. In the CLEAR Wisdom trial, new-onset diabetes or worsening of pre-existing diabetes occurred in 7% of patients in both placebo-treated and bempedoic acid-treated patients [45]. Among the patients diagnosed with diabetes at baseline, a reduction in glycated hemoglobin of −0.08% was observed at 3 months compared to an increase of +0.13% in the placebo group, thus confirming a favorable effect on diabetes or at least a stability of glycemic control in patients treated with bempedoic acid. Conversely, in the CLEAR Harmony trial, new-onset diabetes or worsening of pre-existing diabetes occurred in 3.3% of patients treated with bempedoic acid and in 5.4% of patients treated with placebo [44]. Data on statins, on the other hand, indicate a potential diabetogenic effect of this class of drugs with an increased incidence of new-onset diabetes or worsening of pre-existing diabetes in patients treated with high-intensity statins [54,55].

Despite the increase in serum UA levels in bempedoic acid-treated patients with an overall estimated mean increase of 0.74 mg/dL, in all available trials the incidence of gout was generally low with higher risk in patients with baseline value already increased [16,32,33]. We should take into account that in our clinical practice, several widely used drugs (i.e., Thiazides) exhibit similar side effects, such as hyperuricemia and gout. In a large study about the relationship between thiazides and hyperuricemia, it was noted that 50.3% of 748 men and 23.3% of 554 women treated with thiazides, 4 months after starting treatment, had uric acid levels of >8 mg/dL [56]. Only 8.6% and 2.7% of men and women respectively

had uric acid levels >8 mg/dL at baseline. Dividing subjects into quartiles based on uric acid levels at baseline, the increase in uric acid levels at 4 months after treatment initiation was 1.42 ± 1.02 in the first quartile and 0.96 ± 1.24 in the fourth quartile. Only 15 of the total 3693 patients reported an episode of gout during the trial. In this study, discontinuation of therapy due to clinical manifestation of gout or hyperuricemia occurred in 18 and 34 patients, respectively [56]. Bempedoic acid appears to have a similar, if not more favorable, safety profile than thiazide diuretics regarding hyperuricemia.

6. Conclusions and Future Perspectives

In the scenario of lipid-lowering strategy, the future is full of opportunities, thanks to the ongoing research. We are now able to achieve very low target that was a dream few years ago. Unfortunately, some of these strategies remain expensive, such as the use of pro-protein convertase subtilisin/kexin type 9 inhibitors, thus new agents with more affordable cost/effectiveness ratio are welcome. Bempedoic acid is an interesting new opportunity to manage the complex scenario of dyslipidemia with an intriguing biochemical profile. The fix-dose combination with ezetimibe with the opportunity to modulate statin dose according to goal to achieve might be the starting therapy for the majority of hypercholesterolemic patients. The side-effects reported in the clinical trials may be easily managed. In conclusion, in light of the existing body of evidence, bempedoic acid might have a broad utilization, even as first line therapy for LDL-C-related atherosclerotic diseases when the gap to the goal is high. Its biochemical features encourage a possible use anticipating the statin treatment. However, at the time of writing the present manuscript, no clinical data were available to support this hypothesis. Future studies are welcome to expand the use of this new molecule in the complex scenario of hypercolesterolemic disorders.

References

1. Silverman, M.G.; Ference, B.A.; Im, K.; Wiviott, S.D.; Giugliano, R.P.; Grundy, S.M.; Braunwald, E.; Sabatine, M.S. Association Between Lowering LDL-C and Cardiovascular Risk Reduction among Different Therapeutic Interventions: A Systematic Review and Meta-analysis. *JAMA* **2016**, *316*, 1289–1297. [CrossRef]
2. Abdullah, S.M.; Defina, L.F.; Leonard, D.; Barlow, C.E.; Radford, N.B.; Willis, B.L.; Rohatgi, A.; McGuire, D.K.; de Lemos, J.A.; Grundy, S.M.; et al. Long-Term Association of Low-Density Lipoprotein Cholesterol with Cardiovascular Mortality in Individuals at Low 10-Year Risk of Atherosclerotic Cardiovascular Disease. *Circulation* **2018**, *138*, 2315–2325. [CrossRef]
3. Cannon, C.P. Low-Density Lipoprotein Cholesterol: Lower Is Totally Better. *J. Am. Coll. Cardiol.* **2020**, *75*, 2119–2121. [CrossRef] [PubMed]
4. Packard, C.; Chapman, M.J.; Sibartie, M.; Laufs, U.; Masana, L. Intensive low-density lipoprotein cholesterol lowering in cardiovascular disease prevention: Opportunities and challenges. *Heart* **2021**, *107*, 1369–1375. [CrossRef]
5. Mach, F.; Baigent, C.; Catapano, A.L.; Koskinas, K.C.; Casula, M.; Badimon, L.; Chapman, M.J.; De Backer, G.G.; Delgado, V.; Ference, B.A.; et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk. *Eur. Heart J.* **2020**, *41*, 111–188. [CrossRef]
6. Dyrbus, K.; Gasior, M.; Penson, P.E.; Banach, M. Extreme cardiovascular risk-do we need a new risk category? *Eur. Heart J.* **2022**, *43*, 1784–1786. [CrossRef]
7. Collins, R.; Reith, C.; Emberson, J.; Armitage, J.; Baigent, C.; Blackwell, L.; Blumenthal, R.; Danesh, J.; Smith, G.D.; DeMets, D.; et al. Interpretation of the evidence for the efficacy and safety of statin therapy. *Lancet* **2016**, *388*, 2532–2561. [CrossRef] [PubMed]

8. Iwaki, Y.; Lee, W.; Sugiyama, Y. Comparative and quantitative assessment on statin efficacy and safety: Insights into inter-statin and inter-individual variability via dose- and exposure-response relationships. *Expert Opin. Drug Metab. Toxicol.* **2019**, *15*, 897–911. [CrossRef]

9. Ward, N.C.; Watts, G.F.; Eckel, R.H. Statin Toxicity. *Circ. Res.* **2019**, *124*, 328–350. [CrossRef] [PubMed]

10. Birtcher, K. When compliance is an issue-how to enhance statin adherence and address adverse effects. *Curr. Atheroscler. Rep.* **2015**, *17*, 471. [CrossRef]

11. Abdul-Rahman, T.; Bukhari, S.M.A.; Herrera, E.C.; Awuah, W.A.; Lawrence, J.; de Andrade, H.; Patel, N.; Shah, R.; Shaikh, R.; Capriles, C.A.A.; et al. Lipid Lowering Therapy: An Era Beyond Statins. *Curr. Probl. Cardiol.* **2022**, *47*, 101342. [CrossRef] [PubMed]

12. Ciccarelli, G.; D'Elia, S.; De Paulis, M.; Golino, P.; Cimmino, G. Lipid Target in Very High-Risk Cardiovascular Patients: Lesson from PCSK9 Monoclonal Antibodies. *Diseases* **2018**, *6*, 22. [CrossRef] [PubMed]

13. Azari, S.; Rezapour, A.; Omidi, N.; Alipour, V.; Behzadifar, M.; Safari, H.; Tajdini, M.; Bragazzi, N.L. Cost-effectiveness analysis of PCSK9 inhibitors in cardiovascular diseases: A systematic review. *Heart Fail. Rev.* **2020**, *25*, 1077–1088. [CrossRef]

14. Smith, W.; Cheng-Lai, A.; Nawarskas, J. Bempedoic Acid: A New Avenue for the Treatment of Dyslipidemia. *Cardiol. Rev.* **2021**, *29*, 274–280. [CrossRef]

15. Masana Marin, L.; Plana Gil, N. Bempedoic acid. Mechanism of action and pharmacokinetic and pharmacodynamic properties. *Clin. Investig. Arterioscler.* **2021**, *33*, 53–57. [CrossRef]

16. Di Minno, A.; Lupoli, R.; Calcaterra, I.; Poggio, P.; Forte, F.; Spadarella, G.; Ambrosino, P.; Iannuzzo, G.; Di Minno, M.N.D. Efficacy and Safety of Bempedoic Acid in Patients with Hypercholesterolemia: Systematic Review and Meta-Analysis of Randomized Controlled Trials. *J. Am. Heart Assoc.* **2020**, *9*, e016262. [CrossRef]

17. Ruscica, M.; Banach, M.; Sahebkar, A.; Corsini, A.; Sirtori, C.R. ETC-1002 (Bempedoic acid) for the management of hyperlipidemia: From preclinical studies to phase 3 trials. *Expert Opin. Pharmacother.* **2019**, *20*, 791–803. [CrossRef]

18. Pinkosky, S.L.; Newton, R.S.; Day, E.A.; Ford, R.J.; Lhotak, S.; Austin, R.C.; Birch, C.M.; Smith, B.K.; Filippov, S.; Groot, P.H.E.; et al. Liver-specific ATP-citrate lyase inhibition by bempedoic acid decreases LDL-C and attenuates atherosclerosis. *Nat. Commun.* **2016**, *7*, 13457. [CrossRef]

19. Watkins, P.A. Very-long-chain acyl-CoA synthetases. *J. Biol. Chem.* **2008**, *283*, 1773–1777. [CrossRef]

20. Ruscica, M.; Sirtori, C.R.; Carugo, S.; Banach, M.; Corsini, A. Bempedoic Acid: For Whom and When. *Curr. Atheroscler. Rep.* **2022**, *24*, 791–801. [CrossRef]

21. Feng, X.; Zhang, L.; Xu, S.; Shen, A.Z. ATP-citrate lyase (ACLY) in lipid metabolism and atherosclerosis: An updated review. *Prog. Lipid Res.* **2020**, *77*, 101006. [CrossRef]

22. Oniciu, D.C.; Myers, J.L. Bempedoic Acid and the Fraudulent Fatty Acid Family: The Gold Rush to Cardiovascular Therapies in the New Millennium. *Org. Process Res. Dev.* **2021**, *25*, 365–372. [CrossRef]

23. Velazquez, A.M.; Bentanachs, R.; Sala-Vila, A.; Lazaro, I.; Rodriguez-Morato, J.; Sanchez, R.M.; Laguna, J.C.; Roglans, N.; Alegret, M. KHK, PNPLA3 and PPAR as Novel Targets for the Anti-Steatotic Action of Bempedoic Acid. *Biomedicines* **2022**, *10*, 1517. [CrossRef]

24. Paton, D.M. Bempedoic acid. ATP-citrate lyase inhibitor, AMPK activator, Treatment of hypercholesterolemia. *Drugs Future* **2017**, *42*, 201. [CrossRef]

25. Ballantyne, C.M.; Davidson, M.H.; Macdougall, D.E.; Bays, H.E.; Dicarlo, L.A.; Rosenberg, N.L.; Margulies, J.; Newton, R.S. Efficacy and safety of a novel dual modulator of adenosine triphosphate-citrate lyase and adenosine monophosphate-activated protein kinase in patients with hypercholesterolemia: Results of a multicenter, randomized, double-blind, placebo-controlled, parallel-group trial. *J. Am. Coll. Cardiol.* **2013**, *62*, 1154–1162. [CrossRef]

26. Pinkosky, S.L.; Filippov, S.; Srivastava, R.A.; Hanselman, J.C.; Bradshaw, C.D.; Hurley, T.R.; Cramer, C.T.; Spahr, M.A.; Brant, A.F.; Houghton, J.L.; et al. AMP-activated protein kinase and ATP-citrate lyase are two distinct molecular targets for ETC-1002, a novel small molecule regulator of lipid and carbohydrate metabolism. *J. Lipid Res.* **2013**, *54*, 134–151. [CrossRef]

27. Mackenzie, P.I.; Miners, J.O.; McKinnon, R.A. Polymorphisms in UDP glucuronosyltransferase genes: Functional consequences and clinical relevance. *Clin. Chem. Lab. Med.* **2000**, *38*, 889–892. [CrossRef]

28. Biolo, G.; Vinci, P.; Mangogna, A.; Landolfo, M.; Schincariol, P.; Fiotti, N.; Mearelli, F.; Di Girolamo, F.G. Mechanism of action and therapeutic use of bempedoic acid in atherosclerosis and metabolic syndrome. *Front. Cardiovasc. Med.* **2022**, *9*. [CrossRef]

29. Jadhav, S.B.; Crass, R.L.; Chapel, S.; Kerschnitzki, M.; Sasiela, W.J.; Emery, M.G.; Amore, B.M.; Barrett, P.H.R.; Watts, G.F.; Catapano, A.L. Pharmacodynamic effect of bempedoic acid and statin combinations: Predictions from a dose-response model. *Eur. Heart J. Cardiovasc. Pharmacother.* **2022**, *8*, 578–586. [CrossRef]

30. Lalwani, N.D.; Hanselman, J.C.; MacDougall, D.E.; Sterling, L.R.; Cramer, C.T. Complementary low-density lipoprotein-cholesterol lowering and pharmacokinetics of adding bempedoic acid (ETC-1002) to high-dose atorvastatin background therapy in hypercholesterolemic patients: A randomized placebo-controlled trial. *J. Clin. Lipidol.* **2019**, *13*, 568–579. [CrossRef]

31. Sato, M.; Mamada, H.; Anzai, N.; Shirasaka, Y.; Nakanishi, T.; Tamai, I. Renal secretion of uric acid by organic anion transporter 2 (OAT2/SLC22A7) in human. *Biol. Pharm. Bull.* **2010**, *33*, 498–503. [CrossRef]

32. Ray, K.K.; Bakris, G.L.; Banach, M.; Catapano, A.; Duell, P.B.; Mancini, G.B.J.; Bloedon, L.; Feng, A.; Gotto Jr, A.M. Effect of bempedoic acid on uric acid and gout in 3621 patients with hypercholesterolemia: Pooled analyses from phase 3 trials. *Eur. Heart J.* **2020**, *41*, ehaa946-3001. [CrossRef]

33. Cicero, A.F.G.; Pontremoli, R.; Fogacci, F.; Viazzi, F.; Borghi, C. Effect of Bempedoic Acid on Serum Uric Acid and Related Outcomes: A Systematic Review and Meta-analysis of the available Phase 2 and Phase 3 Clinical Studies. *Drug Saf.* **2020**, *43*, 727–736. [CrossRef]

34. Ballantyne, C.M.; Bays, H.; Catapano, A.L.; Goldberg, A.; Ray, K.K.; Saseen, J.J. Role of Bempedoic Acid in Clinical Practice. *Cardiovasc. Drugs Ther.* **2021**, *35*, 853–864. [CrossRef]

35. Gutierrez, M.J.; Rosenberg, N.L.; Macdougall, D.E.; Hanselman, J.C.; Margulies, J.R.; Strange, P.; Milad, M.A.; McBride, S.J.; Newton, R.S. Efficacy and safety of ETC-1002, a novel investigational low-density lipoprotein-cholesterol-lowering therapy for the treatment of patients with hypercholesterolemia and type 2 diabetes mellitus. *Arterioscler. Thromb. Vasc. Biol.* **2014**, *34*, 676–683. [CrossRef]

36. Thompson, P.D.; Rubino, J.; Janik, M.J.; MacDougall, D.E.; McBride, S.J.; Margulies, J.R.; Newton, R.S. Use of ETC-1002 to treat hypercholesterolemia in patients with statin intolerance. *J. Clin. Lipidol.* **2015**, *9*, 295–304. [CrossRef]

37. Cheeley, M.K.; Saseen, J.J.; Agarwala, A.; Ravilla, S.; Ciffone, N.; Jacobson, T.A.; Dixon, D.L.; Maki, K.C. NLA scientific statement on statin intolerance: A new definition and key considerations for ASCVD risk reduction in the statin intolerant patient. *J. Clin. Lipidol.* **2022**, *16*, 361–375. [CrossRef]

38. Thompson, P.D.; MacDougall, D.E.; Newton, R.S.; Margulies, J.R.; Hanselman, J.C.; Orloff, D.G.; McKenney, J.M.; Ballantyne, C.M. Treatment with ETC-1002 alone and in combination with ezetimibe lowers LDL cholesterol in hypercholesterolemic patients with or without statin intolerance. *J. Clin. Lipidol.* **2016**, *10*, 556–567. [CrossRef]

39. Ballantyne, C.M.; McKenney, J.M.; MacDougall, D.E.; Margulies, J.R.; Robinson, P.L.; Hanselman, J.C.; Lalwani, N.D. Effect of ETC-1002 on Serum Low-Density Lipoprotein Cholesterol in Hypercholesterolemic Patients Receiving Statin Therapy. *Am. J. Cardiol.* **2016**, *117*, 1928–1933. [CrossRef]

40. Rubino, J.; MacDougall, D.E.; Sterling, L.R.; Hanselman, J.C.; Nicholls, S.J. Combination of bempedoic acid, ezetimibe, and atorvastatin in patients with hypercholesterolemia: A randomized clinical trial. *Atherosclerosis* **2021**, *320*, 122–128. [CrossRef]

41. Rubino, J.; MacDougall, D.E.; Sterling, L.R.; Kelly, S.E.; McKenney, J.M.; Lalwani, N.D. Lipid lowering with bempedoic acid added to a proprotein convertase subtilisin/kexin type 9 inhibitor therapy: A randomized, controlled trial. *J. Clin. Lipidol.* **2021**, *15*, 593–601. [CrossRef]

42. Laufs, U.; Banach, M.; Mancini, G.B.J.; Gaudet, D.; Bloedon, L.T.; Sterling, L.R.; Kelly, S.; Stroes, E.S.G. Efficacy and Safety of Bempedoic Acid in Patients with Hypercholesterolemia and Statin Intolerance. *J. Am. Heart Assoc.* **2019**, *8*, e011662. [CrossRef]

43. Ballantyne, C.M.; Banach, M.; Mancini, G.B.J.; Lepor, N.E.; Hanselman, J.C.; Zhao, X.; Leiter, L.A. 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. [CrossRef] [PubMed]

44. Ray, K.K.; Bays, H.E.; Catapano, A.L.; Lalwani, N.D.; Bloedon, L.T.; Sterling, L.R.; Robinson, P.L.; Ballantyne, C.M.; Trial, C.H. Safety and Efficacy of Bempedoic Acid to Reduce LDL Cholesterol. *N. Engl. J. Med.* **2019**, *380*, 1022–1032. [CrossRef] [PubMed]

45. Goldberg, A.C.; Leiter, L.A.; Stroes, E.S.G.; Baum, S.J.; Hanselman, J.C.; Bloedon, L.T.; Lalwani, N.D.; Patel, P.M.; Zhao, X.; Duell, P.B. 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*, 1780–1788. [CrossRef] [PubMed]

46. Ballantyne, C.M.; Laufs, U.; Ray, K.K.; Leiter, L.A.; Bays, H.E.; Goldberg, A.C.; Stroes, E.S.; MacDougall, D.; Zhao, X.; Catapano, A.L. 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.* **2020**, *27*, 593–603. [CrossRef]

47. Nissen, S.E.; Lincoff, A.M.; Brennan, D.; Ray, K.K.; Mason, D.; Kastelein, J.J.P.; Thompson, P.D.; Libby, P.; Cho, L.; Plutzky, J.; et al. Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients. *N. Engl. J. Med.* **2023**. [CrossRef]

48. Atar, D.; Jukema, J.W.; Molemans, B.; Taub, P.R.; Goto, S.; Mach, F.; CerezoOlmos, C.; Underberg, J.; Keech, A.; Tokgozoglu, L.; et al. New cardiovascular prevention guidelines: How to optimally manage dyslipidaemia and cardiovascular risk in 2021 in patients needing secondary prevention? *Atherosclerosis* **2021**, *319*, 51–61. [CrossRef]

49. Dai, L.; Zuo, Y.; You, Q.; Zeng, H.; Cao, S. Efficacy and safety of bempedoic acid in patients with hypercholesterolemia: A systematic review and meta-analysis of randomized controlled trials. *Eur. J. Prev. Cardiol.* **2021**, *28*, 825–833. [CrossRef]

50. Yu, D.; Liao, J.K. Emerging views of statin pleiotropy and cholesterol lowering. *Cardiovasc. Res.* **2021**, *118*, 413–423. [CrossRef]

51. Proute, M.C.; Kothur, N.; Georgiou, P.; Serhiyenia, T.; Shi, W.; Kerolos, M.E.; Pradeep, R.; Akram, A.; Khan, S. The Effect of Statin Therapy on Inflammatory Biomarkers: A Systematic Review. *Cureus* **2021**, *13*, e18273. [CrossRef] [PubMed]

52. Li, M.; Wang, X.; Li, X.; Chen, H.; Hu, Y.; Zhang, X.; Tang, X.; Miao, Y.; Tian, G.; Shang, H. Statins for the Primary Prevention of Coronary Heart Disease. *BioMed Res. Int.* **2019**, *2019*, 4870350. [CrossRef] [PubMed]

53. Safitri, N.; Alaina, M.F.; Pitaloka, D.A.E.; Abdulah, R. A Narrative Review of Statin-Induced Rhabdomyolysis: Molecular Mechanism, Risk Factors, and Management. *Drug Healthc. Patient Saf.* **2021**, *13*, 211–219. [CrossRef]

54. Kohli, P.; Waters, D.D.; Nemr, R.; Arsenault, B.J.; Messig, M.; DeMicco, D.A.; Laskey, R.; Kastelein, J.J.P. Risk of new-onset diabetes and cardiovascular risk reduction from high-dose statin therapy in pre-diabetics and non-pre-diabetics: An analysis from TNT and IDEAL. *J. Am. Coll. Cardiol.* **2015**, *65*, 402–404. [CrossRef]

55. Ridker, P.M.; Pradhan, A.; MacFadyen, J.G.; Libby, P.; Glynn, R.J. Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: An analysis from the JUPITER trial. *Lancet* **2012**, *380*, 565–571. [CrossRef] [PubMed]

56. Langford, H.G.; Blaufox, M.D.; Borhani, N.O.; Curb, J.D.; Molteni, A.; Schneider, K.A.; Pressel, S. Is thiazide-produced uric acid elevation harmful? Analysis of data from the Hypertension Detection and Follow-up Program. *Arch. Intern. Med.* **1987**, *147*, 645–649. [CrossRef]