

SAFETY AND EFFICACY OF BEMPEDOIC ACID AS A MONO AND COMBINED THERAPY IN STATIN HYPERLIPIDEMIC PATIENT: A SYSTEMATIC REVIEW**Asghar Badshah¹, Mubashira Asif¹, Emmama Jamil¹, Memoona Almas¹, Zumar Mehboob¹, Zimal Zainab¹, Muhammad Faisal¹, Muhammad Abubakar¹, Matti Ullah^{1*}**¹Faculty of Pharmacy, Hamdard University, Islamabad Campus, Pakistan***Corresponding Author:** mattiullah@hamdard.edu.pk**ABSTRACT**

Cardiovascular diseases (CVD) are the prominent cause of death both in the United States and worldwide. Hyperlipidemia is the primary risk factor that leads to atherosclerosis and several other vascular diseases. statin therapy has been the most prescribed therapy for hyperlipidemia for almost three decades, but the prescription comes with some adverse side effects. Bempedoic acid is a novel oral drug recently approved by the FDA for hyperlipidemia patients especially it is beneficial for those who are facing statin intolerance. The studies were collected from different databases i.e. PubMed, clinicaltrials.gov, web of Science, and Google Scholar. The selection criteria were based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline. The phase 2 trials showed reducing Low-density lipoproteins (LDL) by 27% at a dosage of 120 mg of Bempedoic acid. When Bempedoic acid and ezetimibe are administered alone, LDL-C levels are reduced by 13-23% and 13-20%, respectively. Bempedoic acid+ atorvastatin causes a reduction of LDL to 22%, but with a placebo treatment, there will be no reduction in LDL level. Bempedoic acid 120 mg plus ezetimibe 10mg LDL-C levels decreased by 43% and 48% with Bempedoic acid 180 mg plus ezetimibe 10mg. Bempedoic acid has an interesting biochemical profile and presents an interesting new option for managing the complex dyslipidemia issue. The FDA has approved Bempedoic acid and Bempedoic acid plus antihyperlipidemic agents for the treatment of people with Heterozygous Familial Hypercholesterolemia (HeFH) or established atherosclerotic cardiovascular disease (ASCVD) who need further LDL-C reduction with statin therapy that is maximally tolerable.

Keywords: Bempedoic acid, Hyperlipidemia, statin therapy, cardiovascular diseases**INTRODUCTION**

Cardiovascular disease (CVD) is the prominent cause of death both in the United States and worldwide [1]. The fat-like substance is necessary for the body to function properly but too much low-density, LDL cholesterol can lead to buildup in the blood vessels [2]. Hyperlipidemia is the primary risk factor that leads to atherosclerosis and several other vascular diseases [3]. Hyperlipidemia causes increased Low-density lipoprotein cholesterol (LDL-C) which plays a key role in the development of Heart and vascular diseases [4, 5]. However, following acute cardiovascular events, women face higher mortality rates and poorer scenarios than men. These gender-specific differences in CVD exhibition and outcomes highlight the significance of personalized approaches to prevention, diagnosis, and treatment to address the unique challenges faced by each gender [6]. While several medications exist for treatment, statin therapy has been the most prescribed therapy for hyperlipidemia for almost three decades, but the prescription comes with some adverse side effects [7]. Statins are competitive inhibitors of 3-hydroxy-3-methylglutaryl

coenzyme A (HMG-COA) reductase and reduce LDL levels, Despite the effectiveness of statins, many patients do not reach optimal LDL-C levels even after taking maximum statin tolerated dose with or without the addition of non-statin agents such as ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors [8]. PCSK9 inhibitors are present in injectable form and are very expensive due to which patient compliance decreases [9].

Several studies show that patients taking statin therapy complain about muscle pain (myalgia) and diabetes mellitus which reduce patient adherence to therapy [10, 11]. it is important to note that there exists a subset of patients who are unable to tolerate appropriate or any form of statin therapy. Consequently, these individuals necessitate an alternative pharmacological approach to achieve a satisfactory lowering of low-density lipoprotein cholesterol (LDL-C) [4, 5].

In this context, Bempedoic acid emerges as a novel solution. It is a pioneering, orally administered, small-molecule inhibitor of cholesterol biosynthesis [12]. Intriguingly, it operates within the same biological pathway as

statins, effectively reducing LDL-C levels [13]. Currently, Bempedoic acid therapy is being increasingly favored for patients exhibiting statin intolerance and dyslipidemia. Moreover, it has demonstrated efficacy in mitigating cardiovascular events, underscoring its therapeutic potential [14]. Bempedoic acid is a pro-drug, upon activation by liver metabolism it inhibits adenosine triphosphate-citrate lyase (ACL) in the liver as a result decreases LDL-C levels [11, 15]. A meta-analysis study (including 13 randomized control trials) reported the safety

and efficacy of Bempedoic acid to lower LDL-C. However, the combination of Bempedoic acid with other lipid-lowering drugs may prove to be better than mono-therapy [16]. Further research and public health efforts are crucial to reducing the impact of CVD and promoting better cardiovascular health for all. The objective of this systemic review is to explore the safety and efficacy of Bempedoic acid as a mono and combination therapy in statin intolerance patients with hyperlipidemia and CV events.

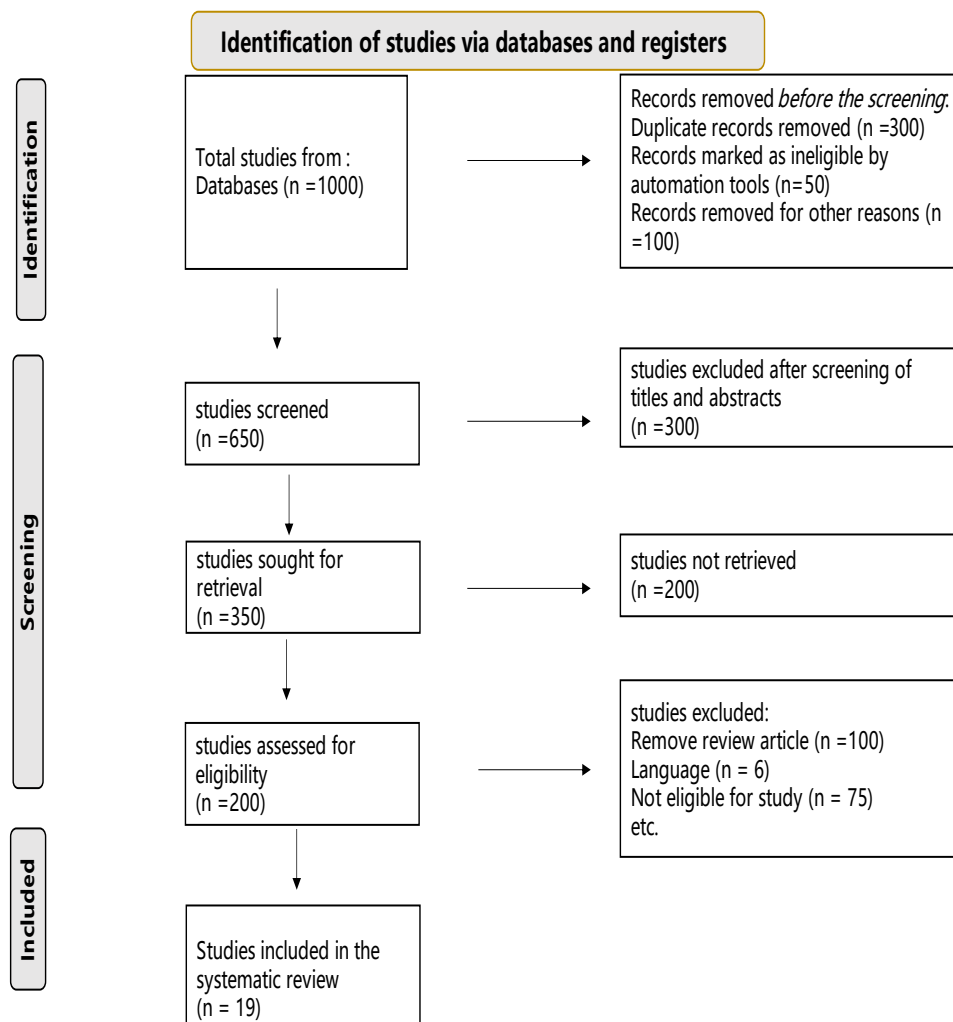


Figure1: PRISMA flow chart for searching strategy

METHODOLOGY

Search strategy

We developed a comprehensive literature search for this systematic review to identify relevant studies. The studies were collected from different databases i.e. PubMed, clinicaltrials.gov, Web of Science, and Google Scholar, and the terms used during the search were Bempedoic acid, hyperlipidemia, and statin intolerance, and the combination terms used “Bempedoic acid and dyslipidemia relation” and “Bempedoic acid therapy and statin intolerance patients” we also accomplished a manual searching by searching the reference lists from all relevant studies.

The selection criteria were based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline. The total studies collected (N=1000) after the duplication removal were checked for quality assessment and after evaluating the abstract and title, final studies were obtained (N=19).

Including criteria: all original research papers, review papers, and meta-analyses were included and articles were published from 2000 – 2023. Only studies done in the English language were included.

Excluding criteria: We excluded the articles published before 2000, incomplete studies and

those studies other than the English language, and articles that contain irrelevant information about Bempedoic acid.

Mechanism of action

Bempedoic acid (ETC-1002) having the chemical name 8-hydroxy-2,2,14,14-tetramethylpentadecanedioic acid is a prodrug that activated into its active metabolite, Bempedoyl CoA after first-pass metabolism in the liver to lowers cholesterol level. The liver Enzyme with very long-chain acyl-CoA synthase-1 (ACSVL1) is responsible for the activation of Bempedoic acid [17]. It locks up the enzyme ATP citrate lyase (ACLY). The ATP citrate lyase enzyme plays an important role in lipid synthesis by converting citrate to acetyl-CoA. The ATP citrate lyase (ACLY) inhibition lowers cholesterol synthesis

resulting in the upregulation of low-density lipoprotein (LDL) receptors [18]. Increased number of LDL receptors resulting in increased liver LDL uptake and decreases in serum LDL-C levels. The Bempedoic acid and Statins utilize different receptors in the liver that's why the Bempedoic acid does not interrupt the uptake of statins in the liver [5, 19]. Unlike other cholesterol-lowering agents e.g. statins Bempedoic Acid doesn't promote myotoxicity because it cannot convert into Bempedoic-CoA in skeletal muscle. The activity of Bempedoyl-CoA is limited to the liver as evidenced by the fact that it is not found in the plasma of patients treated with Bempedoic acid [20].

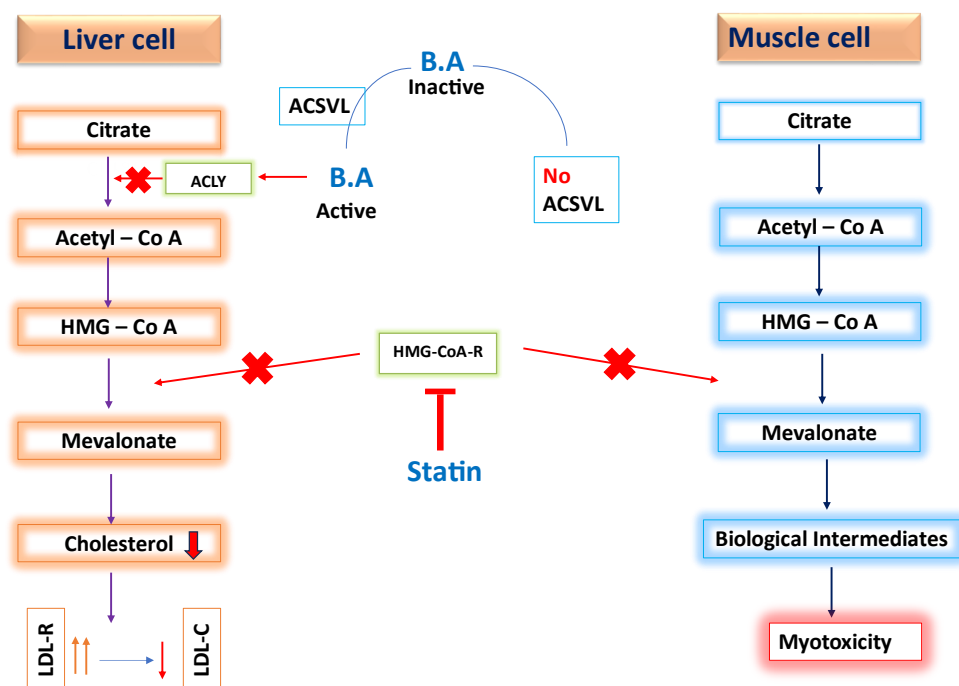


Figure 2: Mechanism of action of Bempedoic acid and Statin in liver and muscle cells. ACLY- ATP citrate lyase; ACSVL1 Acyl-CoA synthase-1, HMG-Co A- β-Hydroxy β-methylglutaryl-CoA; LDL-R - Low-density lipoprotein receptor; LDL-C – LDL Cholesterol

Initial studies have found that when ETC-1002 is used alone, it can lower LDL-C (bad cholesterol) by up to 27%. When added to existing statin therapy, it can provide an additional 24% reduction in LDL-C. When used in combination with ezetimibe, it can lead to a total reduction of up to 48% in LDL-C [21].

Approval of Bempedoic acid and current stage Phase I trial

The phase I trials overall demonstrated that Bempedoic acid was safe, with no adverse effects related to dosing [22]. The series of clinical trials, including ETC1002-001, ETC1002-002, and ETC002-004 collectively demonstrated the safety, tolerability, and pharmacokinetics of Bempedoic acid. The trials involved single and multiple-dose regimens, with participants receiving varying doses of ETC-!002 or a placebo

[23]. In the first Ia study, ETC1002-001, Bempedoic acid doses of 2.5,10,45,125, and 250mg were given to 18 healthy volunteers, and pharmacokinetic data were collected. Notably Second phase Ib study, the longer-term treatment in ETC1002-002, lasting 28 days, evaluated Bempedoic acid safety, tolerability pharmacokinetic and pharmacodynamics in mild dyslipidemia patients (n=39) and healthy volunteers (n=18) respectively. Bempedoic acid exhibited a mean reduction (36%) in LCL-C levels compared to the placebo group in healthy volunteers, and the escalating doses in ETC-1002-004 showcased the sustained safety profile of Bempedoic acid. LDL-C levels were notably reduced in the higher dose group, affirming its potential efficacy [23, 24]. Importantly, no dose-limiting side effects or serious adverse events

were observed across these trials, reinforcing the favorable safety and tolerability profile of ETC-1002 in these early-phase studies.

Table 1: Phase 1 Trial studies

Study phase	Study population (N= total/ETC-1002 treated)	Treatment Duration (weeks)	Dose range (mg)	LDL-C lowering
Phase 1a	Healthy subjects (N = 18)	Single dose	-	-
Phase 1b	Healthy subjects (N = 53/39)	2–4	20, 60, 100, 120 mg	Up to 17 %
Phase 1b	Healthy subjects (N = 24/18)	2	40, 180, 220	Up to 36 %

Phase II trial

To assess Bempedoic acid's safety and efficacy in its intended patient population, Phase II clinical trials were executed on individuals afflicted with dyslipidemia, with or without other common comorbidities, to evaluate the efficacy and safety of the medicine on its target population. It was studied both as monotherapy and in combination with other agents aimed at lowering lipid levels [25].

Monotherapy of Bempedoic Acid:

A group of people (out of 177 patients 133 of them receive B.A) with dyslipidemia, having LDL-C levels of 135–230 mg/dL and triglyceride levels more than 155 mg/dL were treated with Bempedoic acid 40, 80, and 120 mg alone or placebo for 12 weeks and results show that the level of low-density lipoprotein is reduced daily is about 18%, 25%, and 27% as compared to the placebo treatment that reduces LDL to only about 2% [26].

In a study conducted on type Diabetes type 2 patients Bempedoic acid treatment reduces LDL to about 43% with a dose of 80 mg for 2 weeks and 120 mg for the next 2 weeks while placebo treatment reduces LDL to only 4% [27].

Patients with both hypertension and dyslipidemia have also been studied with Bempedoic acid monotherapy. Before the commencement of the trial, all willing participants underwent a washout period during which they were removed from their blood pressure and cholesterol-lowering drugs. Following six weeks of Bempedoic acid administration, there was a statistically significant decrease in LDL-C (21% against 3%), as compared to the placebo. Moreover, individuals receiving this therapy had decreased levels of hs-CRP, a sign of inflammation [28].

Discontinuation of statin therapy has been linked to CVS outcomes that can be worse significantly, and statins themselves can lead to muscle complaints ranging from mild myalgia to rare but potentially life-threatening rhabdomyolysis.

According to a recent extensive survey, statin-associated muscle pain is experienced by 29% of statin users and leads to discontinuation of therapy in 15% of individuals [29]. The phase 2 trial study by Thompson et al examined the effectiveness and safety profile of treatment with ETC-1002 for 8 weeks in patients who were intolerant to statins and had a history of high cholesterol. Eligible patients were randomly assigned to receive either oral B. A or a placebo. Overall, it was found that ETC-1002 significantly decreased LDL-C levels by 28.7% more than the placebo in hypercholesterolemic patients who had a history of muscle problems with statins. Reductions in non-HDL-C, total cholesterol, apo B, and hs-CRP were also seen as compared to the placebo. ETC-1002 dosage was gradually increased from 60 mg to 240 mg daily for 8 weeks, highest dose was administered only for 2 weeks. In both the Bempedoic acid and placebo groups musculoskeletal and connective tissue disorders were reported as the most commonly experienced adverse drug events with statin therapy [20, 30].

Combination Therapy with statin agents

Bempedoic acid is used in combination with atorvastatin 10 mg daily. In comparison, the dose of Bempedoic acid is 60mg (2 weeks daily), 120 mg (2 weeks daily), 180 mg (2 weeks daily), and 240 mg (2 weeks daily) for a total of 8 weeks. The result shows that the Bempedoic acid+ atorvastatin causes a reduction of LDL to 22%, but with a placebo treatment, there will be no reduction in LDL level [31]. A study conducted on 134 patients having an LDL range of 115-220 mg/dl were using different statin family drugs to lower lipid levels along with Bempedoic acid 120-180 mg for about 12 weeks. Combining Bempedoic acid and statin causes a 17% reduction of LDL for taking 120 mg of Bempedoic acid and a 24% reduction for taking 180 mg of Bempedoic acid. the placebo treatment causes only a 4% reduction of LDL. Additionally,

ETC-1002 resulted in percentage reductions in apolipoprotein B, none HDL-C, total cholesterol, and LDL particle number as well. Rates of adverse events, including muscle-related AEs of Bempedoic acid were similar to placebo. These results suggest that Bempedoic acid could be a beneficial addition to current treatments for hypercholesterolemia, providing significant percentage reductions in LDL-C levels while being well-tolerated by patients [32].

Combination Therapy with Ezetimibe

Bempedoic acid combination therapy is known for its capability to inhibit ATP citrate lyase can significantly lower LDL cholesterol levels. On the other hand, ezetimibe which impedes with retention of cholesterol in the small intestine can also remarkably reduce LDL cholesterol levels. Both ezetimibe and Bempedoic acid when manipulated as a combination therapy can react synergistically to interfere with cholesterol metabolism and reduce LDL cholesterol levels [33].

In a study conducted by Thompson, 2016, Bempedoic acid either alone or in combination with ezetimibe resulted in significant reductions in LDL cholesterol levels compared to ezetimibe monotherapy. Specifically, 27% LDL-C was reduced with the alone Bempedoic acid 120 mg dose and 30% with the 180 mg dose. The combination of Bempedoic acid with ezetimibe led to even greater reductions, with Bempedoic acid 120 mg plus ezetimibe 10mg LDL-C levels decreasing by 43% and 48% with Bempedoic acid 180 mg plus ezetimibe 10mg. These reductions in LDL-C were achieved within 2 weeks of treatment and maintained throughout the study. Additionally, this combination also revealed reductions in secondary endpoint non-high-density lipoprotein cholesterol, total cholesterol, apolipoprotein B, LDL particle number, and high-sensitivity C-reactive protein compared to ezetimibe alone [34].

Table 2: Summary of trial II studies of Bempedoic acid

Study	Population type	n	Study duration and therapy	Dose	LDL-C reduction (%)
Ballantyne et al., 2013 [26]	Dyslipidemia	177	12 weeks B.A vs placebo	40mg 80mg 120mg	-18 % -25% -27% (-2% placebo)
Gutierrez et al., 2014 [27]	Dyslipidemia + type II diabetes	60	4 weeks B.A vs placebo	80mg,120mg	-43 % (-4% placebo)
Medpace, Inc. [28]	Dyslipidemia + Hypertension	143	6 weeks B.A vs placebo	180mg	-21% (-3% placebo)
Thompson, P. D. et al. [30]	Dyslipidemia + statin intolerance	56	8 weeks B.A vs placebo	60 mg 120mg 180mg 240mg	-32% (-3% placebo)
Paul D. Thompson 2016 [34]	Hypercholesteremia + statin tolerance (n=172) and statin intolerance (n=177)	349	12 weeks B.A vs ezetimibe	Bempedoic acid 120mg and 180 mg ezetimibe 10mg Bempedoic acid 120mg + ezetimibe 10mg Bempedoic acid 180mg + ezetimibe 10mg	-27% and -30% -21% -43% -48%
Lalwani et al. 2019 [31]	Hypercholesterolemia	68	4 weeks Statin agents + Bempedoic acid	Atorvastatin 80 mg + Bempedoic acid 180 mg vs. placebo	-22%

			180 mg vs. placebo		
Rubino, MacDougal I, Sterling, Kelly, et al [35].	Hypercholesterolemia	59	2 months PCSK9 inhibitors + Bempedoic acid 180 mg vs. placebo	Evolocumab 430 mg + Bempedoic acid 180 mg vs. placebo	-27% (-3.1% placebo)
Rubino, MacDougal I, Sterling, Hanselman, et al [36].	Hypercholesterolemia	63	6 weeks statin agent + Ezetimibe 10 mg vs. placebo	Atorvastatin 20 mg + Ezetimibe 10 mg vs. placebo	-60% (-3% placebo)
Ballantyne et al. [32]	Hypercholesterolemia	134	Statin + Bempedoic acid therapy	Stable background statin therapy + BA 120 mg vs. placebo Stable background statin therapy + BA 180 mg vs. placebo	-17% -24% (-4% placebo)

Combination therapy of Bempedoic acid with PCSK9 Inhibitors

The study (59 patients) assessed the safety and efficacy of incorporating Bempedoic acid into proprotein convertase subtilisin/kexin type 9 inhibitor (PCSK9i) therapy among individuals with hypercholesterolemia. finding demonstrated that Bempedoic acid significantly decreased 30.3% LDL-C levels compared to placebo in patients undergoing PCSK9 inhibitors treatment. Furthermore, Bempedoic acid can decrease levels of apolipoprotein B, non-HDL cholesterol, total cholesterol, and high-sensitivity C-reactive protein. The study results reveal that Bempedoic acid and PCSK9 inhibitors combined therapy may provide effective approaches for additional reduction of LDL-C levels. In general, the study results show the potential importance of exploring combination therapies for hypercholesterolemia, especially in patients who are unable to achieve LDL-C goals with statin therapy alone [35].

Phase III trails

In the fix-dose combination (FDC) trial, a total of 301 patients at high cardiovascular risk, were randomly allocated (in a 2:2:2:1 ratio) to undergo treatment with one of the four options for 12 weeks: an FDC comprising ezetimibe 10 mg and Bempedoic acid 180 mg, Bempedoic acid 180 mg alone, ezetimibe 10 mg alone, or placebo added to the stable regimen of statins. By the end of the 12th week, the FDC displayed a significant reduction in LDL-C among patients involved in the investigation BA 180 mg + EZE 10 mg

(-36.2%) compared to placebo (1.8%), ezetimibe alone (-23.2%) or Bempedoic acid alone (-17.2%) [37].

The safety of Bempedoic acid was evaluated in the CLEAR Serenity study, in individuals with high cholesterol who were intolerant to at least two statins, one of which was at the lowest possible dosage. Individuals with ≥ 130 mg/dL of LDL-C were limited to those with heterozygous familial hypercholesterolemia or ≥ 100 mg/dL in secondary or primary prevention. Throughout the trial, the patients' initial cholesterol-lowering medication was continued. The background therapy included low-dose (tolerated dose) statins or other lipid-lowering medications, either alone or in combination, such as fibrates, PCSK9i, niacin, bile acid sequestrants, selective cholesterol absorption inhibitors, or fibrates. 365 individuals received Bempedoic acid 180 mg once daily for 12 weeks in addition to stable lipid-lowering treatment in a 2:1 randomization compared to a placebo. At week 12, the Bempedoic acid group showed a significant reduction -21.4% in LDL-C levels compared to the placebo group [38].

The CLEAR Tranquility trial examined the safety and effectiveness of treating patients who had previously developed a statin intolerance and whose LDL-C levels were equal to or higher than 100 mg/dL, necessitating additional LDL-C reduction. Bempedoic acid 180 mg in addition to ezetimibe 10 mg daily. There were 269 participants in the trial; 181 were in the Bempedoic acid therapy group and 88 were in the

placebo group. 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. Adding Bempedoic acid to ezetimibe-based basic lipid-modifying therapy resulted in a significant reduction -28.5% in LDL-C levels compared to placebo [39].

Out Of the 2230 patients participating in the CLEAR Harmony study, 1488 were assigned to the Bempedoic acid therapy arm. Patients with hypercholesterolemia who had either heterozygous familial hypercholesterolemia or atherosclerotic cardiovascular disease made up the study population on the highest level of lipid-lowering treatment using statins alone or in conjunction with other lipid-lowering medications. After week 24 of the experiment, PCSK9i was only approved if LDL-C levels stayed over 170 mg/dL. After receiving

Bempedoic acid treatment for 12 weeks, mean LDL cholesterol levels significantly decreased to -19.2 mg/dL, or -16.5%, below baseline [40].

The CLEAR Wisdom study is for individuals receiving maximal lipid-lowering medication A more extensive investigation aimed at examining the effectiveness and safety of Bempedoic acid. In this investigation, a 2:1 randomization paired 779 patients against a placebo or Bempedoic acid. Individuals were believed to have heterozygous familial hypercholesterolemia, putting them at elevated cardiovascular risk, or ASCVD. Lipoprotein apheresis, Lomitapide, Mipomersen, and Simvastatin at a dose of at least 40 mg Cholestain and Gemfibrozil were not approved as initial lipid-lowering treatments. By week twelve Compared to the placebo, the Bempedoic acid arm demonstrated a significant decrease in LDL-C values. (-15.1% vs. 2.4%, in that order) [41].

Table 3: Summary of Phase III trial studies of Bempedoic acid

Study	No of patients	Therapy	LDL-C reduction
Ballantyne et al., 2020 [37]	301	BA 180 mg + EZE 10 mg	-36.2%
		BA 180 mg	-17.2%
		EZE 10 mg	-23.2%
		Placebo	+1.8%
Laufs et al., 2019 CLEAR Serenity [42]	345	Bempedoic acid 180 mg vs. Placebo In addition to low-dose statin agents	-23.6% Vs -1.3%
Ballantyne et al., 2018 CLEAR Tranquility [39]	269	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.	-28.5% Vs +5%
Nissen et al., 2023 CLEAR Outcomes [38]	13970	BA 180 mg vs	-21.7%
		Placebo in addition to very low-dose statin.	-0.6%
Goldberg et al., 2019 CLEAR Wisdom [41]	779	Bempedoic acid 180 mg vs. Placebo	-15.1% Vs 2.4%
Ray et al., 2019 CLEAR Harmony [40]	2230	Bempedoic acid 180 mg vs. Placebo	-16.5% Vs +1.6%

DISCUSSION

Bempedoic acid is a novel oral drug recently approved by the FDA for hyperlipidemia patients especially it is beneficial for those who are facing statin intolerance [43]. As a prodrug, Bempedoic acid is activated by the liver to produce

Bempedoyl CoA, the active form that prevents the liver's adenosine triphosphate-citrate lyase (ACL) from functioning. Because of the disruption of cholesterol production caused by this inhibition, LDL receptors are upregulated, which lowers LDL-C levels [2]. The mechanism

of action of Bempedoic acid is remarkably different from that of statins, which are always associated with side effects and provide an effective alternative for those who cannot tolerate statin therapy [17].

The fixed-dose combination of Bempedoic acid with ezetimibe for individuals with proven to maximally tolerated statins needing further LDL-C dropping will impact future lipid management. One of the major problems with statin agents is they lead to myalgia when used for long terms. Whoever, this novel discovery can overcome this problem with efficient therapeutic effects. Adherence to statin therapy is a known challenge, particularly among patients taking low-intensity treatment. A study reported therapy in patients on high-intensity treatment with CVD adherence levels of 84% after 1 year compared with patients on low-intensity therapy with only 57% adherence. Following 6 years of treatment, these rates in both high- and low-intensity cohort groups fell to 72% and 48%, respectively [44]. These results are supported by a recent study that observed patients for statin adherence. Overall, almost 53% of patients adhered to statin therapy [45]. Patients receiving high-intensity therapy were found to be more adherent (63.7%) and less likely to terminate treatment than those receiving moderate- or low-intensity therapy. Adherence and discontinuation were also correlated with intensity levels [45].

However, the results of one of the phase 2 trials showed reducing LDL cholesterol by 27% at a dosage of 120 mg of Bempedoic acid [26]. When Bempedoic acid and ezetimibe are administered alone, LDL-C levels are reduced by 13-23% and 13-20%, respectively [36].

Clinical trials have indicated that combination therapy (Bempedoic acid + ezetimibe) reduces LDL-C levels by 36% [37]. Bempedoic acid added with PCSK9 inhibitors a significant reduction in LDL-C was observed. In clinical trials, have been demonstrated that PCSK9 inhibitors in monotherapy and combination with statin therapy significantly lower LDL-C levels by 40–72% [35]. Some study results show that in addition to its LDL-C-lowering activity Bempedoic acid has also the ability to improve glucose homeostasis [46], anti-atherosclerotic effects [47], inflammation, and blood pressure [48].

CONCLUSION

the safety and efficacy of Bempedoic acid as both mono and combination therapy for hyperlipidemic patients provide compelling evidence for its role in managing dyslipidemia, especially for those intolerant to statins. Its ability to significantly reduce LDL-C levels as

monotherapy and with other agents makes it a valuable addition to current lipid-lowering strategies. Moreover, combination therapies of Bempedoic acid with statins or PCSK9 inhibitors further enhanced its lipid-lowering efficacy. This comprehensive evaluation supports Bempedoic acid as a versatile and effective treatment option for hyperlipidemia, particularly for individuals who are statin-intolerant or require enhanced lipid management.

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