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## Efficacy and Safety of Bempedoic Acid as a Treatment Option for Hyperlipidemia: A Systematic Review

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# Efficacy and Safety of Bempedoic Acid as a Treatment Option for Hyperlipidemia: A Systematic Review

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## Abstract

### Introduction:

Bempedoic acid (BA) is an inhibitor of ATP-citrate lyase (ACL) and is used in the treatment of hyperlipidemia by inhibiting cholesterol synthesis. Randomized clinical trials (RCTs) have shown the efficacy of BA in lowering LDL-C levels and it is currently approved as a treatment option for patients with hyperlipidemia to achieve target LDL-C levels. We conducted a systematic review to further elucidate the efficacy and safety profile of BA in patients with hyperlipidemia.

### Methods:

We searched the electronic database Medline, Embase, and Cochrane Library for RCTs between 2013 and 2023. We used keywords ("Bempedoic Acid") AND ("Hypercholesterolemia") AND ("Lipid Lowering") AND ("Randomized Controlled Trials") AND ("Humans"). Pairs of reviewers also manually searched for RCTs to identify studies comparing the efficacy and safety profile of BA either alone or in combination with other lipid-lowering therapies.

### Results:

We identified 11 RCTs in our systematic review, and it showed that the addition of BA either alone or in addition to other lipid-lowering therapies (statins and ezetimibe) resulted in the lowering of LDL-C levels. In addition, BA also led to a reduction in total cholesterol (TC), non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (ApoB), and high sensitivity C reactive protein (hs-CRP) levels. For the safety profile of BA, results from the studies show that there is no difference in the incidence of adverse events between the two treatment arms. However, a few studies found that the use of BA was associated with a higher incidence of gout as compared to standard lipid-lowering therapies.

### Conclusion:

The use of BA in patients with hyperlipidemia leads to a decrease in the level of LDL-C both alone and in addition to other lipid-lowering therapies like statins and ezetimibe. The addition of BA also led to a reduction in TC, non-HDL-C, ApoB, and hs-CRP levels which resulted in reduction in cardiovascular events. The safety data shows that BA is largely safe to use and the adverse events were similar in both groups, however, the rate of gout was higher in patients receiving BA. Larger clinical trials with longer follow-up duration are needed to adequately assess its effect on cardiovascular mortality and the safety profile of BA.

## Keywords

Bempedoic Acid, Cardiovascular Mortality, Hypercholesterolemia, Lipid Lowering, Randomized Controlled Trials

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### **Conflict of Interest Statement**

There is no conflict of interest

## META-ANALYSIS/SYSTEMATIC REVIEW

# Efficacy and Safety of Bempedoic Acid as a Treatment Option for Hyperlipidemia: A Systematic Review

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## Abstract

**Introduction:** Bempedoic acid (BA) is an inhibitor of ATP-citrate lyase (ACL) and is used in the treatment of hyperlipidemia by inhibiting cholesterol synthesis. Randomized clinical trials (RCTs) have shown the efficacy of BA in lowering LDL-C levels and it is currently approved as a treatment option for patients with hyperlipidemia to achieve target LDL-C levels. We conducted a systematic review to further elucidate the efficacy and safety profile of BA in patients with hyperlipidemia.

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**Results:** We identified 11 RCTs in our systematic review, and it showed that the addition of BA either alone or in addition to other lipid-lowering therapies (statins and ezetimibe) resulted in the lowering of LDL-C levels. In addition, BA also led to a reduction in total cholesterol (TC), non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (ApoB), and high sensitivity C reactive protein (hs-CRP) levels. For the safety profile of BA, results from the studies show that there is no difference in the incidence of adverse events between the two treatment arms. However, a few studies found that the use of BA was associated with a higher incidence of gout as compared to standard lipid-lowering therapies.

**Conclusion:** The use of BA in patients with hyperlipidemia leads to a decrease in the level of LDL-C both alone and in addition to other lipid-lowering therapies like statins and ezetimibe. The addition of BA also led to a reduction in TC, non-HDL-C, ApoB, and hs-CRP levels which resulted in reduction in cardiovascular events. The safety data shows that BA is largely safe to use and the adverse events were similar in both groups, however, the rate of gout was higher in patients receiving BA. Larger clinical trials with longer follow-up duration are needed to adequately assess its effect on cardiovascular mortality and the safety profile of BA.

**Keyword:** Bempedoic acid, Cardiovascular mortality, Hypercholesterolemia, Lipid lowering, Randomized controlled trials

## 1. Introduction

One of the leading causes of mortality in the United States is cardiovascular disease which accounts for 1 in every 3 deaths.<sup>1</sup> In addition to

affecting the functioning of the heart by the development of atherosclerosis, hypercholesterolemia also directly affects the systolic function and electrophysiological functioning of the heart due to systemic oxidative stress, proinflammatory state, and

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mitochondrial dysfunction.<sup>2</sup> In many populations, elevated LDL-C levels are associated with an increased risk of cardiovascular disease (CVD) development and death.<sup>3</sup> Many studies have explored the association between elevated LDL-C levels and mortality with elevated LDL-C levels serving as a marker for increased cardiovascular mortality. Ravnskov et al<sup>4</sup> concluded that LDL-C level has an inverse relationship with all-cause mortality which makes LDL-C levels a primary target to reduce cardiovascular mortality. Therefore, preventive strategies play a big role in managing the cardiovascular disease burden in the population. One of the main strategies includes lipid-lowering therapies which specifically target the LDL-C to reduce cardiovascular events, and thus statins play an important role in both primary and secondary risk prevention.<sup>5,6</sup> Statins form an important part of reducing cardiovascular mortality but statin intolerance is reported in about 6%–29% of the population and the major symptom reported is muscle-related side effects like muscle cramps.<sup>7</sup> In addition, some patients fail to reach their LDL-C goal even while taking statins especially people with heterozygous familial hypercholesterolemia. Hence for these patients, 2018 multi-society guidelines support the use of non-statin agents to help reduce LDL-C levels and lower cardiovascular mortality.<sup>8</sup>

BA is an inhibitor of ATP-citrate lyase (ACL) and is used in the treatment of hyperlipidemia by inhibiting cholesterol synthesis. ACL is a key enzyme that works in the upstream pathway of 3 hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) inhibition of cholesterol synthesis and it indicates that ACL inhibition might have a similar effect on LDL-C reduction and cardiovascular mortality as (HMGCR) inhibition.<sup>9</sup> RCTs have shown the efficacy of BA in lowering LDL-C levels and in 2020, the Food and Drug Administration (FDA) approved the use of BA for lowering LDL-C levels in patients who require additional reduction of LDL-C or are intolerant to statins.<sup>10</sup>

The prevalence of hypercholesterolemia increased by 17.6% between 1999–2002 and 2013–2016,<sup>11</sup> signifying the increasing disease burden and therefore requiring alternative treatments, especially in populations who fail to reach their LDL-C goal on statins. Since the mechanism of action of BA is similar to statins, it can be used to lower LDL-C levels in patients who are intolerant to statins. Therefore, it is important to elucidate the clinical efficacy of BA and to see its effect on cardiovascular mortality. We performed a systematic review to

assess the potential efficacy and safety of BA in the prevention of cardiovascular events and its effect on the reduction of LDL-C levels.

## 2. Methods

### 2.1. Eligibility criteria

The following inclusion criteria were set for our study. (1) Population: Patients with hypercholesterolemia (age >18 years) who received BA alone or with another lipid-lowering agent. (2) Intervention: BA. (3) Comparison Intervention: Placebo or in addition to a second lipid-lowering agent. (4) Outcomes: Mean reduction in LDL-C. (5) Study Design: Randomized controlled trials (RCTs). (6) Period: Between 2013 and 2023. (7) Language: Only English language.

The following data was extracted from the eligible articles: author name, year of publication, number of patients, mean age, follow-up period, male %, white race %, baseline LDL-C, treatment arms, 95% confidence interval of reduction in LDL-C, and p-value of the study.

### 2.2. Data source and search strategy

We searched the electronic databases Medline, Embase, and Cochrane Library for RCTs between 2013 and 2023. Two major methods were used to search the literature. First, we used keywords (“Bempedoic Acid”) AND (“Hypercholesterolemia”) AND (“Lipid Lowering”) AND (Randomized Controlled Trials”) AND (“Humans”); Second, we also manually searched for articles by checking the reference lists of eligible studies.

### 2.3. Study selection

Two authors (MK and SRS) independently reviewed the eligibility of the articles found in the electronic search by their title and abstract. For potentially relevant articles, the full text was also screened to ensure eligibility according to our set criteria. After searching the 3 databases, a total of 185 studies were identified. Of these, 54 were retained after the removal of 131 duplicates. Based on the title and abstract, 32 studies were removed and 22 were selected for full text analysis. The 22 full texts were evaluated and a further 11 studies were excluded as they didn't meet our eligibility criteria. In addition, we validated the quality of each RCT using the Cochrane RCT tool. The details of the search algorithm are included in Fig. 1.

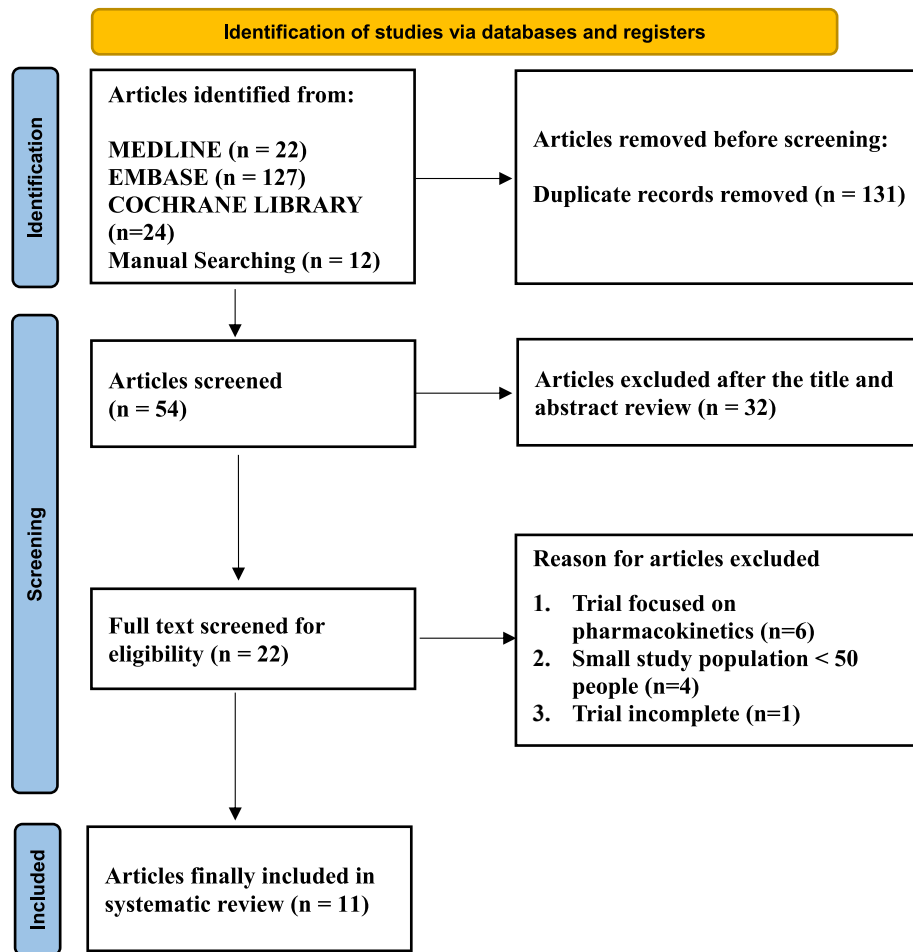


Fig. 1. Flow diagram of study screening.

Table 1 describes the important characteristics of the studies included in our article.

#### 2.4. Bias risk assessment

The Cochrane risk of bias assessment tool was used to analyze the risk of bias in the studies included in our systematic review. Three investigators (OSK, MHJ, and AA) independently analyzed the allocation sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, completeness of outcome data, and selective outcome reporting of individual trials. The Bias risk assessment is given in Fig. 2.

### 3. Results

Nissen et al<sup>12</sup> conducted a study and found that the use of BA in statin-intolerant patients led to a decrease in Major Adverse Cardiovascular events

(MACE) outcomes, which is a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization. The study also showed that the use of BA led to a statistically significant decrease in the level of LDL-C as compared to placebo. However, the safety data of the study concluded that the use of BA led to an increase in the incidence of gout (3.1%) and cholelithiasis (2.2%) as compared to placebo (2.1%). Similarly, Ray et al<sup>14</sup> and Goldberg et al<sup>15</sup> compared the efficacy and safety of BA versus placebo in the background of maximally tolerated statin therapy, and found that the use of BA leads to a substantial decrease in the LDL-C levels (p-value 0.0001). The safety data from Ray et al<sup>11</sup> showed that the incidence of adverse events did not differ substantially between the two groups during the intervention period, but the incidence of adverse events leading to discontinuation of the regimen was higher in the BA group than in the placebo



Table 1. Characteristics of studies included in the systematic review

Study	No of Patients	Mean Age	Follow up Period	Male %	White %	Baseline LDL-C (mean $\pm$ SD) (mg/dl)	Treatment Arms	Reduction in LDL-C with addition of BA 95% CI	P-Value
Nissen, S.E. 2023 <sup>12</sup>	13,970	65.5 $\pm$ 9.0	174 weeks	51.7	90.2	139.0 $\pm$ 35.1	BA vs Placebo	-20.3 (-21.1 to -19.5)	NR
Laufs, U. 2019 <sup>13</sup>	345	65.2 $\pm$ 9.5	24 weeks	43.8	89.0	157.6 $\pm$ 39.9	BA vs Placebo	-18.9 (-23.0 to -14.9)	<0.001
Ray, K.K. 2019 <sup>14</sup>	2230	66.1	52 weeks	73	95.9	103.2 $\pm$ 29.4	BA + statin vs. placebo + statin	-18.1 (-20.0 to -16.1)	<0.001
Goldberg, A.C. 2019 <sup>15</sup>	779	64.3	52 weeks	63.7	94.4	120.4 $\pm$ 37.9	BA + statin vs. placebo + statin	-17.4 (-21 to -13.9)	<0.001
Lalwani, N.D. 2019 <sup>16</sup>	68	58	4 weeks	51.5	72.1	76.4 $\pm$ 22.8	BA + Atorva vs. placebo + Atorva	-22.2 (-36.4 to -8.0)	NR
Ballantyne, C.M. 2018 <sup>17</sup>	269	63.8	12 weeks	38.7	89.2	127.6	BA + EZE vs. placebo + EZE	-28.5 (-34.4 to -22.5)	<0.001
Thompson, P.D. 2016 <sup>18</sup>	349	60	12 weeks	70	51.6	164.5 $\pm$ 25	BA + EZE vs. placebo + EZE	-26.5 (-32.1 to -20.9)	<0.0001
Ballantyne, C.M. 2016 <sup>19</sup>	134	57	12 weeks	41	82.8	135.4 $\pm$ 24	BA + statin vs. placebo + statin	-16.7 (-26.7 to -6.7)	<0.0001
Thompson, P.D. 2015 <sup>20</sup>	56	62 $\pm$ 6	8 weeks	50	96.4	179 $\pm$ 35.7	BA vs placebo	-28.7(-35.4 to -22.1)	<0.0001
Gutierrez, M. J. 2014 <sup>21</sup>	60	55.7	4 weeks	61.7	95	126.8 $\pm$ 27.8	BA vs placebo	-39 (-46.2 to -31.7)	<0.0001
Ballantyne, C.M. 2013 <sup>22</sup>	177	57	12 weeks	55.4	85.9	166.3 $\pm$ 24	BA vs placebo	-21.1 (-26 to -16.2)	<0.0001

Note: BA: Bempedoic Acid, EZE: Ezetimibe, NR: Not Reported, CI: Confidence Interval.

group (10.9% vs 7.1%) as well as the incidence of gout (1.2% vs 0.3%).

Laufs et al<sup>13</sup> compared the efficacy and safety profile of BA versus placebo and found that BA resulted in a statistically significant reduction in LDL-C level as compared to placebo (p-value <0.001). BA also resulted in a significant reduction in non-high-density lipoprotein cholesterol (Non-HDL-C) (-17.9%), total cholesterol (TC) (-14.8%), apolipoprotein B (Apo B) (-15.0%), and high-sensitivity C-reactive protein (hs-CRP) (-24.3%). The safety data from the study showed that BA was safe and well tolerated. Similarly, Lalwani et al<sup>16</sup> compared the effect of BA in the reduction of LDL-C as compared to placebo in the background of atorvastatin, and showed that there was a significant reduction in LDL-C levels with the use of BA. There was also a significant reduction in TC (-10%), non-HDL-C (-13%), apo B (-15%), and hs-CRP (-44%).<sup>15</sup>

Ballantyne et al<sup>17,19,22</sup> conducted studies to assess the efficacy of BA versus placebo in 2013, BA versus placebo in the background of statins in 2016, and BA versus placebo in the background of ezetimibe in 2018. The primary endpoint in all three of these studies was to assess the reduction in LDL-C with the addition of BA. The results of the study showed that the addition of BA led to a statistically significant reduction in LDL-C levels (p-value <0.0001), and the safety data showed that there was no clinically meaningful difference in the rates of adverse events between the two groups.<sup>17,19,22</sup> Similarly, Thompson et al<sup>18,20</sup> performed studies to compare the effect of BA on lowering LDL-C levels by comparing BA versus placebo in 2015 and comparing BA versus placebo in the background of ezetimibe in 2016. The results of his study showed that the use of BA led to a reduction in LDL-C levels (p-value <0.0001), and there was no significant difference in the rate of adverse events between the two groups.<sup>18,20</sup> As a result, BA was found to be safe with no discontinuation in the treatment arm.<sup>18,20</sup>

Gutierrez et al<sup>21</sup> conducted a study to compare the effects of BA versus placebo in lowering LDL-C levels in the diabetic population and found a statistically significant reduction in LDL-C between the two treatment arms. Non-HDL-C, TC, and hs-CRP were also significantly lowered by BA compared to placebo (P < 0.0001).<sup>21</sup> There were no clinically meaningful safety findings observed during the study.<sup>21</sup>

Fig. 3 shows a graphical representation of the reduction in LDL-C across all the studies.

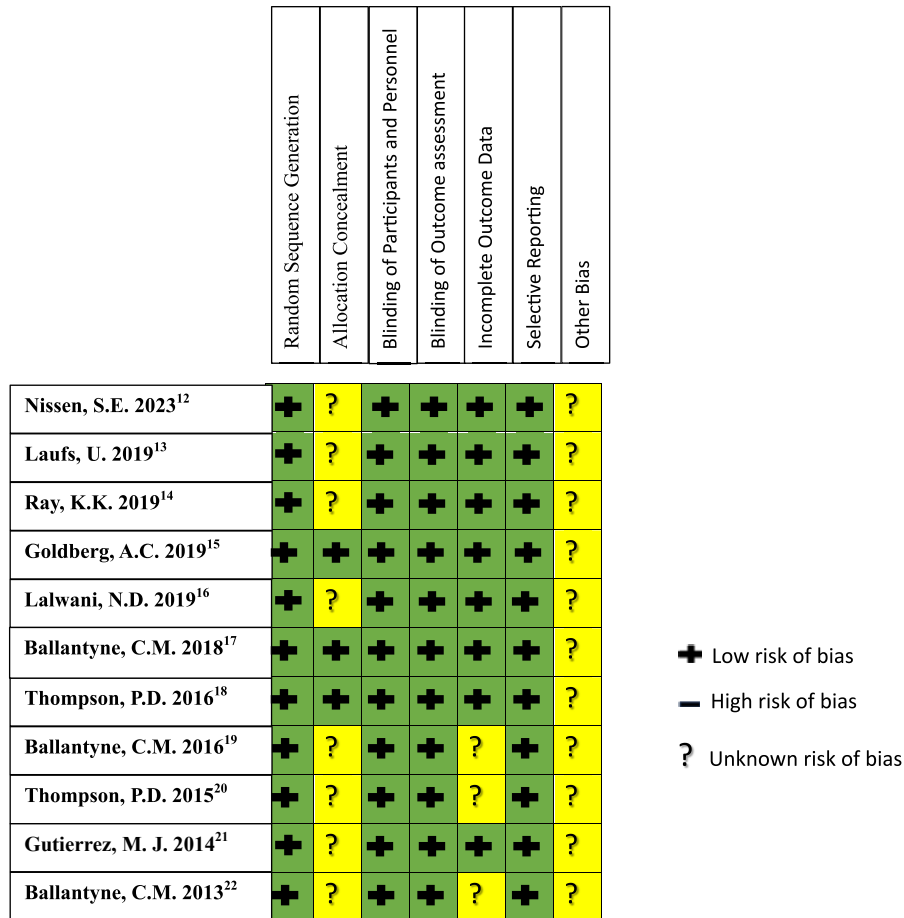


Fig. 2. Bias Risk Assessment Summary.

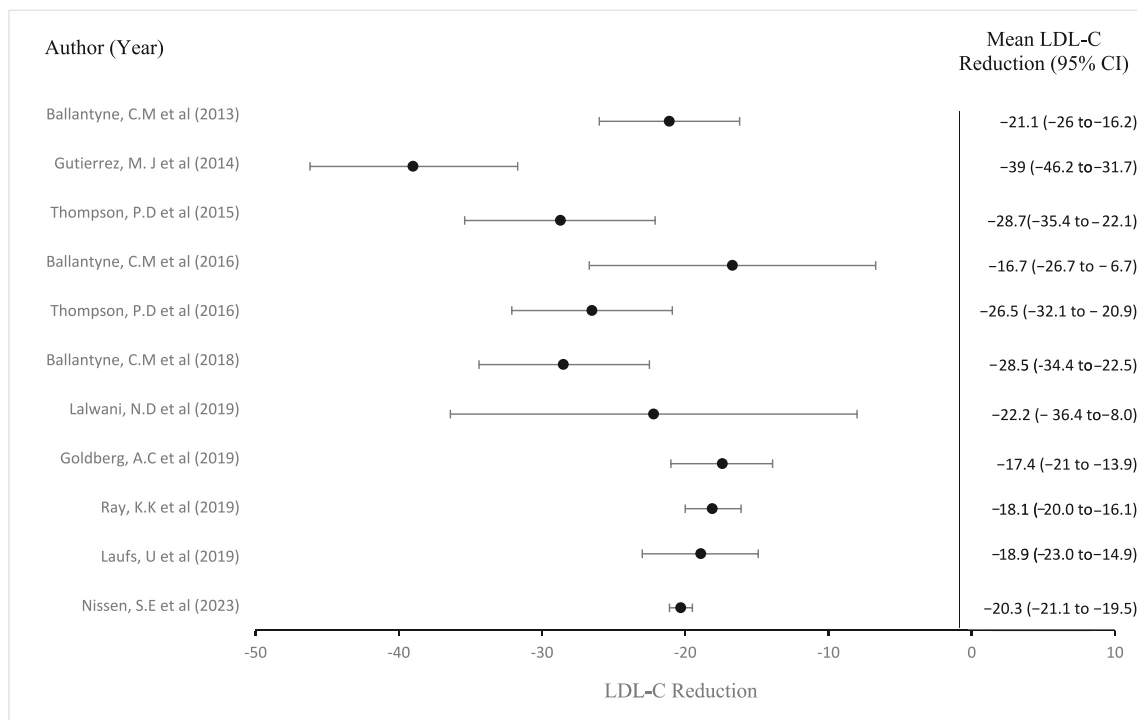


Fig. 3. Forest Plot.



#### 4. Discussion

Our systematic review included the findings of 11 RCTs and it showed that the addition of BA either alone or in addition to other lipid-lowering therapies (statins and ezetimibe) resulted in the lowering of LDL-C levels. Our findings were consistent with prior systematic reviews and meta-analysis.<sup>23–25</sup> In addition, BA also led to a reduction in TC, non-HDL-C, ApoB, and hs-CRP levels. High levels of hs-CRP play a role in the development of cardiovascular events, so the fact that BA reduces hs-CRP indicates that it will reduce cardiovascular events in ways in addition to its effect on LDL-C levels. Five RCTs, Nissen SE et al,<sup>12</sup> Laufs U et al,<sup>13</sup> Thompson PD et al,<sup>18,20</sup> and Ballantyne CM et al<sup>17</sup> included patients with statin intolerance in their trials and found that the addition of BA reduced LDL-C levels in that population subset which then ultimately leads to lower cardiovascular events. From a clinical standpoint, this information has great significance since the population with statin intolerance has a lower likelihood of achieving goal LDL-C levels as compared to statin tolerant population, and this high LDL-C level then manifests as a higher incidence of cardiovascular events.

Furthermore, based on the results shown in Ray KK et al,<sup>14</sup> BA can also be a very useful option in high-risk patients with heterozygous familial hypercholesterolemia. Data from the Voyager study shows that only 22% of patients with heterozygous familial hypercholesterolemia receiving optimal lipid-lowering therapy were able to achieve the therapeutic goal of LDL-C < 100 mg/dL.<sup>26</sup> Since patients with heterozygous familial hypercholesterolemia may fail to achieve adequate reduction in LDL-C level despite being on optimal lipid-lowering therapy due to their high baseline LDL-C level, the addition of BA for such patients will serve as an important strategy to achieve the therapeutic goal LDL-C. BA has great clinical implications as it forms an important treatment option for statin-intolerant populations and patients with heterozygous familial hypercholesterolemia.<sup>27</sup>

In terms of the safety profile of BA, results from the studies show that there is no difference in the incidence of adverse events between the two treatment arms. This shows that the addition of BA is well tolerated by the patients. This fact is of particular importance for patients with high risk for cardiovascular events and statin intolerance as these patients usually require high doses of statins or other lipid-lowering therapies to achieve the target LDL-C level. So, BA can be used as a viable option for these patients. However, Nissen et al<sup>12</sup> and Ray

et al<sup>14</sup> found that the use of BA was associated with a higher incidence of gout as compared to standard lipid-lowering therapies. This effect is most likely secondary to competition between uric acid and the glucuronide metabolite of BA for the same renal transporter.<sup>14</sup> Larger studies are required to adequately assess the safety profile of BA as it is very important for clinical practice to thoroughly assess whether the addition of BA to statins and other lipid-lowering therapies is a safe option for high-risk patients.

These findings have great clinical implications concerning decreasing the cardiovascular mortality of the population. Elevated LDL-C levels are a major risk factor for the development of atherosclerosis and cardiovascular disease. Lowering LDL-C levels has been shown to decrease the risk of cardiovascular events which can lead to reduced cardiovascular mortality.<sup>3</sup> Lower LDL-C levels can slow or even reverse the progression of atherosclerosis, which is the underlying cause of coronary artery disease, and thus reduce overall cardiovascular mortality. Reducing cardiovascular mortality by lowering LDL-C levels can lead to significant cost savings in terms of healthcare expenditures by decreasing the need for hospitalizations, surgeries, and long-term care for cardiovascular diseases.<sup>28</sup> Hence lowering the LDL-C levels in patients has great benefits in terms of cardiovascular mortality, especially in patients with statin intolerance or heterozygous familial hypercholesterolemia in which additional lipid-lowering therapies like BA are indicated to achieve target LDL-C levels.

Some limitations of our study are as follows. First, most of the studies focused on determining the efficacy of BA in lowering LDL-C levels but the data regarding its effect on cardiovascular outcomes is lacking. Second, most of the studies had a follow-up duration of less than 1 year which makes it difficult to assess the long-term outcomes and safety data of BA. There is no data regarding safety of BA in patients with severe renal impairment or those requiring hemodialysis. Similarly, no safety data is available in pregnancy and lactation. Third, the studies included in our systematic review had different inclusion and exclusion criteria which leads to heterogeneity among studies.

Upon analysis of the included RCTs in our systematic review, we have identified a few potential areas for future research. The use of BA in combination with PCSK9 inhibitors may be explored to determine the potential benefits of these combinations. Long-term studies are essential to evaluate the sustained cholesterol-lowering effects of BA and to monitor any potential side effects or adverse events

over extended periods since the included RCTs mostly had follow-up periods of less than one year. Further research on the safety and tolerability of BA especially when used in combination with other medications, is crucial to understanding its overall risk–benefit profile. It is important to investigate the responsiveness of specific patient subgroups to BA treatment to see whether certain genetic or metabolic factors influence its effectiveness. Studies on the cost-effectiveness of BA compared to other cholesterol-lowering therapies will help guide healthcare decisions regarding the selection of appropriate therapeutic options.

## 5. Conclusion

The use of BA in patients with hypercholesterolemia leads to a decrease in the level of LDL-C both alone and in addition to other lipid-lowering therapies like statins and ezetimibe. Reduction in LDL-C levels results in a decrease in cardiovascular mortality. The addition of BA also led to a reduction in TC, non-HDL-C, ApoB, and hs-CRP levels which resulted in a reduction in cardiovascular events. The safety data shows that the rate of adverse events was similar between the two groups, however, the rate of gout was higher in patients receiving BA. Larger clinical trials with longer follow-up duration are needed to adequately assess the safety profile of BA and to determine its effect on cardiovascular mortality through the reduction of MACE. A few areas of future research are to determine the lipid-lowering effect of the combination of BA with advanced therapies like PCSK9 inhibitors, to assess the responsiveness of specific patient subgroups to BA treatment to see whether certain genetic or metabolic factors influence its effectiveness, and to analyze the safety and tolerability of BA especially when used in combination with other medications. BA is a novel treatment option for hypercholesterolemia and will benefit from longer clinical trials to adequately assess its efficacy and safety in patients.

## Conflicts of interest

There are no conflicts of interest.

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