Cardiology and Angiology: An International Journal

Volume 12, Issue 4, Page 113-122, 2023; Article no.CA.101076
ISSN: 2347-520X, NLM ID: 101658392

Real World Evidence of Bempedoic Acid on Efficacy and Safety in Patients with Uncontrolled LDL-c and at High Risk of CVD

S. Manoj [a++], Jay Shah [b#], Dilip Kumar [c#], Akshaya Pradhan [d†], Amit B. Kinare [e#], Ashwani Kumar Sharma [f#], M. S. Aditya [g++], Ram Anil Raj [h#], Akhter Amin Raina [i‡], Ashish Patel [j‡], Biswajit Das [k‡], Dipak Suresh Bathe [l‡], Sameer Muchhala [m^] and Kunal Jhaveri [m##*]

[a] Kauvery Hospital, Chennai, Tamil Nadu, India.
[b] HCG Hospital, Ahmedabad, Gujarat, India.
[c] Medica Superspecialty Hospital, Kolkata, West Bengal, India.
[d] King George's Medical University, Lucknow, Uttar Pradesh, India.
[e] Samadhan Heart Centre, Jabalpur, Madhya Pradesh, India.
[f] Fortis Escort Hospital, Jaipur, Rajasthan, India.
[g] Yashoda Hospital, Secunderabad, Telangana, India.
[h] Bhagwan Mahavir Jain Hospital, Bangalore, Karnataka, India.
[i] Sub District Hospital, Seer Hamdan, Anantnag, Jammu & Kashmir, India.
[j] Jaynil Hospital, Vadodara, Gujarat, India.
[k] Murshidabad Medical College, Behrampore, West Bengal, India.
[l] Lifeline Medical, Durgapur, West Bengal, India.
[m] Zydus Lifesciences Limited, Mumbai, Maharashtra, India.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/CA/2023/v12i4350

[++] Senior Consultant Interventional Cardiologist;
[#] Consultant Interventional Cardiologist;
[†] Additional Professor
[‡] Consultant Physician;
[^] GM- Medical Affairs;
[##] DGM- Medical Affairs;
**Corresponding author: Email: Kunal.Jhaveri@zyduslife.com;*

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/101076

Original Research Article

Received: 07/04/2023
Accepted: 09/06/2023
Published: 16/06/2023

ABSTRACT

Background and Objective: Cardiovascular disease (CVD) is a significant cause of morbidity and mortality worldwide, with high-risk patients requiring effective management to reduce their risk of cardiovascular events. Bempedoic acid is a novel therapeutic agent recently approved as an add-on therapy to statins in patients with uncontrolled LDL-c. Bempedoic acid inhibits cholesterol synthesis in the liver, which ultimately reduces the risk of cardiovascular events. Therefore, the present study aims to assess the efficacy and safety of bempedoic acid in patients with uncontrolled LDL-c (Previously on moderate or high-intensity statins) with a high risk of CVD in real-world settings.
Methods: This is a multicenter, retrospective, observational study on the data of high-risk-CVD patients collected from Bempedoic Acid on Efficacy and Safety in patients (BEST) Registry. The clinical data of 140 patients who were already on statin therapy and were receiving Bempedoic acid at a dose of 180 mg, along with measurements of the level of LDL-c, HbA1c, HDL, TG, TC, PPPG, FPG, AST, ALT, serum creatinine was taken into consideration. The primary outcome includes a change in LDL-c level, and secondary outcomes involve a change in the level of HbA1c, HDL, TG, TC, PPPG, FPG, AST, ALT, and serum creatinine at week 12 and 24. Adverse events were reported at both time points.
Results: A total of 140 patients were included in the present study with a mean age of 51.8 ± 9.2 years and had primary confirmed diagnosis of dyslipidemia with uncontrolled LDL-c. The mean levels of LDL-c decreased from the mean baseline value of 142.67 ± 46.49 mg/dL, to 106.78 ±33.92 mg/d; a statistically significant reduction by 23.23% ($p < 0.01$) at week 12. Similarly, at week 24, the mean LDL-c value reduced to 90.39 ± 38.89 mg/dL. A 33.38 % decrease was observed ($p < 0.01$). Other parameters such as non-HDL, FPG, PPPG, AST and serum creatinine also showed statistically significant reduction at week 12 and week 24.
Conclusion: The present study demonstrates that bempedoic acid is an effective add-on medication in lowering LDL-c levels in high-risk CVD patients with uncontrolled LDL-c.

Keywords: ACL inhibitor; Bempedoic Acid (BA); Cardiovascular Diseases (CVDs); dyslipidemia; Low-Density Lipoprotein Cholesterol (LDL-c).

1. INTRODUCTION

Cardiovascular diseases (CVDs) are the most significant contributor to the public health epidemic among the various chronic or non-communicable diseases prevalent in modern society. Annually 17.9 million lives are lost to CVDs and atherosclerotic cardiovascular disease (ASCVD) [1]. Among the deaths caused by CVD, 85% are due to heart attack and stroke [1]. Other causes of CVD-related mortality include atherosclerosis of the aorta and peripheral vascular disease [2]. CVDs or ASCVDs are often preceded by dyslipidemia. The significant factors that lead to dyslipidemia are often associated with age and lifestyle choices [3,4]. However, dyslipidemia is not only associated with lifestyle choices, but can also stem from genetic disorders like Familial hypercholesterolemia.

The role of LDL-c in the pathogenesis of CVDs and ASCVDs has been evaluated extensively since the beginning of the twentieth century. Individuals with increased levels of low-density lipoprotein (LDL) cholesterol above 190 mg/dl are at six times greater risk of developing CVDs [5].

Reduction of LDL-c has been associated with lowering the risk of CVDs [6–11]. Approximately 50% reduction of circulating levels of LDL-c is linked with 29% reduction in the risk of major adverse cardiovascular events [12]. The condition is often associated with changes in other biochemical markers i.e. Total Cholesterol (TC), Triglycerides (TG), High-Density cholesterol (HDL-C), non-high density cholesterol (non-HDL-c), Fasting Plasma Glucose (FPG), Post Prandial Plasma Glucose (PPPG), glycosylated haemoglobin (HbA1c), Aspartate transaminase (AST), Alanine transaminase (ALT) and serum creatinine [12].

Administration of statins to lower elevated levels of LDL-c have become the cornerstone of modern-day therapeutic practices aimed at reducing the risk of cardiovascular events [13]. However, it has been observed that 7 to 29% of patients receiving statin therapy have reported adverse musculoskeletal effects that severely limit their ability to receive the recommended doses [14]. Other therapies include ezetimibe, and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors which have been shown to reduce LDL-c levels [13].

A cross-sectional study of 5888 European patients on lipid-lowering therapy found that only 54% achieved their 2016 LDL-c goal, and 33% achieved their 2019 goal. There are gaps between guideline recommendations and clinical practice, indicating a need for increased utilization of non-statin therapies for high-risk patients [15].

Bempedoic acid (BA) is a first-in-class, novel, non-statin, oral drug which has received the US Food and Drug Administration (FDA) approval as an adjunct to diet and maximally tolerated statin therapy for treatment of adults with heterozygous familial hypercholesterolemia or established ASCVD who have uncontrolled LDL-c level [16]. Administration of BA inhibits ATP citrate lyase, by targeting HMG-CoA reductase upstream in the cholesterol synthesis pathway, which increases the expression of LDL receptors, thus lowering LDL-c levels. [17,18] BA is the pro-drug form of its active component bempedoyl CoA, which gets converted by acyl-CoA synthetase-1 (ACSVL1), an enzyme whose expression is limited to the liver and kidney, thus restricting BA mostly to the liver [19]. BA inhibits *de novo* lipid synthesis *in vitro* and improves serum lipid profile *in vivo via* inhibition of acetyl-CoA carboxylase (ACC) and ATP-citrate lyase, leading to the attenuation of fatty acid and sterol synthesis in the liver, respectively, leading to reduced risk of CVD among patients.

To provide better understanding on the effects of BA as add-on therapy on uncontrolled LDL-c levels among patients using statin therapy, the present study was conducted to gather real-world evidence of Bempedoic acid on Efficacy and Safety in patients with uncontrolled LDL-c and a high risk of CVD—the data collected from the registry which will act as a baseline for future endeavours on the topic. To the best of our knowledge, this is the first study in the Indian population that determine the efficacy and safety of BA 180 mg as an add-on therapy in patients with uncontrolled LDL-c and at high risk of CVD in real-time clinical practice.

2. METHODS

2.1 Study Design and Participants

This is a multicenter, retrospective, observational study conducted on the data of dyslipidemia patients with high risk-CVD, collected from BEST Registry from July 2022 to February 2023. The clinical data of 140 dyslipidemia patients with high risk-CVD with age between 18-80 years, who were already on statin therapy and were receiving Bempedoic acid as an add-on therapy at a dosage of 180 mg, with comorbidities such as diabetes and hypertension, and uncontrolled LDL-c level as per the ESC Cholesterol Guidelines 2019 [20]. Patients having total fasting triglyceride level ≥500mg/dL, BMI as ≥50 kg/m^2, and severe renal impairment were excluded from the study.

2.1.1 Outcome

The primary outcome include change in LDL-c level and the secondary outcomes involve change in other biochemical markers i.e., TC, TG, HDL-c, non HDL-c, FPG, PPPG, HbA1c, AST, ALT and serum creatinine at week 12 and 24.

2.1.2 Safety

Adverse events (AEs) were graded by National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 and have been reported during the study.

2.2 Statistical Analysis

The data collected were pooled in a Microsoft Excel spreadsheet and then transferred for statistical calculations to the SPSS (version 25) software. The primary and secondary endpoints

were reported with two-sided 95% CIs; calculated using paired t-test. A p-value of <0.05 is considered statistically significant.

3. RESULTS

A total of 140 patients were included in the present study with a mean age of 51.8 ± 9.2 years, primary confirmed diagnosis (100%) and comorbidities such as diabetes mellitus (25%) and hypertension (24.29%). The baseline demographics have been listed in Table 1.

All patients were using statins prior to BA therapy, among which 42.80% (60 of 140) were being treated with Atorvastatin (mean 40 mg), and 57.20% (80 of 140) were receiving Rosuvastatin (mean 20 mg) (Table 2).

Table 1. Baseline demographic and clinical characteristics of the study population

Total number of patients	**140**	
Mean age (years)	51.8 ±9.2*	
Mean BMI (kg/m^2)	28.61 ±3.25*	
Primary diagnosis	**n**	**%**
Dyslipidemia with uncontrolled LDL-c	140	100
Co-morbid conditions		
Diabetes Mellitus	35	25
Hypertension	34	24.29
Fatty Liver / NASH	9	6.43
Chronic Kidney Disease	1	0.71
Prior history of ASCVD (MI, CAD, PAD, Stroke)	7	5
Hypothyroidism	7	5
Gout	1	0.71
Smoker	2	1.43
Heart failure	0	0
None	3	2.14
Others	41	29.29

*[Note: LDL-c, Low Density Lipoprotein cholesterol; ASCVD, atherosclerotic cardiovascular disease; NASH, Non-Alcoholic Steatohepatitis; MI, Myocardial Infarction; CAD, Coronary artery disease; PAD, Peripheral artery disease. * data in Mean ± standard deviation (SD)]*

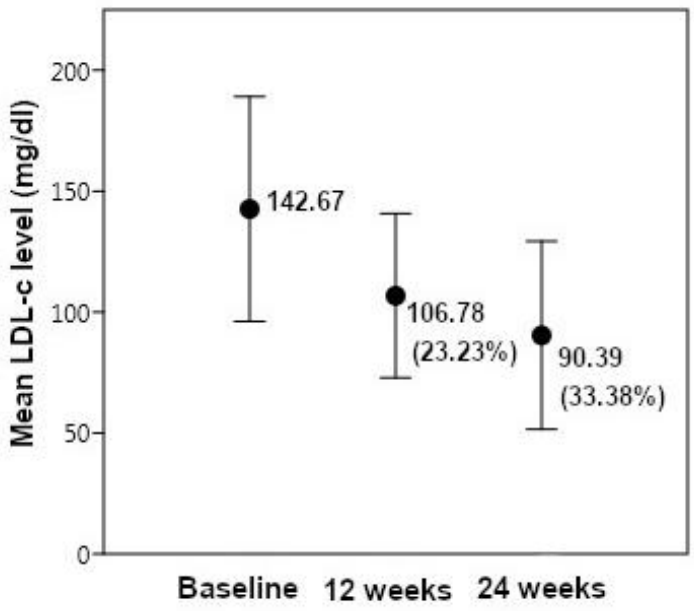

Fig. 1. Change in mean LDL-c level from baseline, at 12 weeks and at 24 weeks

Table 2. Ongoing medications prior to initiation of Bempedoic acid (BA) treatment

Medication	Number of participants	%
Antihyperlipidemic - Statin	**140**	**100**
Atorvastatin (Dosage mean - 40 mg)	60	42.80
Rosuvastatin (Dosage mean - 20 mg)	80	57.20
Ezetimibe	9	6.43
Fenofibrate	9	6.43
Antidiabetic medications		
Metformin	33	23.57
Glimepiride	18	12.86
Dapagliflozin	15	10.71
Sitagliptin	13	9.29
Vildagliptin	7	5
Voglibose	2	1.43
Antihypertensive medications		
Amlodipine	14	10
Telmisartan	33	23.57
Losartan	3	2.14
Metoprolol	13	9.29
Olmesartan	3	2.14
Bisoprolol	3	2.14
Anti-anginal drug	14	10
Antiplatelet medications		
Ticagrelor	18	12.86
Clopidogrel	6	4.29
Aspirin	32	22.86
Other medications		
Pantoprazole	12	8.57
Rabeprazole	19	13.57
Salmeterol	3	2.14
Torsemide	4	2.86
Thyroxine	5	3.57
Ursodeoxycholic acid	7	5
Vitamin E	2	1.43

3.1 Efficacy

The mean level of LDL-c decreased from the mean baseline value of 142.67 ± 46.49 mg/dL, to 106.78 ±33.92 mg/dL; a statistically significant reduction by 23.23% ($p < 0.01$) at week 12 and 90.39 ± 38.89 mg/dL, 33.38 % decrease at week 24 ($p < 0.01$) was observed (Fig. 1). At week 12, mean levels of TG and TC also significantly decreased by 7.64% and 14.02%, respectively ($p < 0.01$). Statistically significant reduction in the mean level of circulating concentrations was observed in the case of non-HDL (19.59%), FPG (5.9%), PPPG (3.05%), AST (10.78%) and serum creatinine (5.78%). However, an increase was observed in the case of HbA1c and ALT by 8.63% and 11.68%, respectively. On the other hand, mean levels of HDL displayed a mild increase during this period, from the mean value of 40.24 ±8.04 mg/dL to 42.82 ±14.37 mg/dL (Table 3).

At the 24-week follow-up, decreasing trend from 12 weeks follow-up was sustained in the case of TG (19.67%), TC (16.21%), non-HDL (29.53%), FPG (4.8%), AST (20.69%) and serum creatinine (1.57%). An increasing trend was present in the case of HDL (10.15%) and HbA1c (4.22%) and a decrease of 16.28% was observed at the ALT level (Table 4).

Table 3. Values of clinical parameters observed at 12 weeks, along with changes observed as compared to baseline values and corresponding p-values testing for statistical significance

Lab Parameters	Baseline value		12 weeks		% change	*p*-value (12 weeks results compared with Baseline)
	Mean	± Std. Dev.	Mean	± Std. Dev.		
LDL-c (mg/dL)	142.67	46.49	106.78	33.92	-23.23	<0.01
TG (mg/dL)	251.1	116.09	210.86	86.47	-7.64	<0.01
TC (mg/dL)	227.91	55.88	192.29	43.85	-14.02	<0.01
HDL(mg/dL)	40.24	8.04	42.82	14.37	+7	0.021
Non-HDL (mg/dL)	182.06	25.31	144.07	22.61	-19.59	<0.01
FPG (mg/dL)	121.8	31.41	117.39	22.74	- 5.9	<0.01
PPPG (mg/dL)	170.61	54.56	164.18	44.55	- 3.05	<0.01
HbA1c (%)	6.44	0.27	6.97	1.31	+8.63	<0.01
AST (U/L)	43.59	13.51	37.92	9.95	-10.78	<0.01
ALT (U/L)	34.74	5.43	37.77	10.13	+11.68	0.001
S. creatinine (mg/dL)	0.98	0.24	0.92	0.25	-5.78	<0.01

[Note: Total Cholesterol (TC), Triglycerides (TG), High Density Lipoprotein cholesterol (HDL-c), Non-HDL cholesterol (non-HDL-C), Fasting Plasma Glucose (FPG), Post Prandial Plasma Glucose (PPPG), glycosylated hemoglobin (HbA1c), Aspartate transaminase (AST), Alanine transaminase (ALT)]

Table 4. Values of clinical parameters observed at 24 weeks, along with changes observed as compared to baseline values and corresponding *p*-values testing for statistical significance

Lab Parameters	Baseline value		24 weeks		% change	*p*-value (24 weeks results compared with Baseline)
	Mean	± Std. Dev.	Mean	± Std. Dev.		
LDLc (mg/dL)	142.67	46.49	90.39	38.89	-33.38	<0.01
TG (mg/dL)	251.1	116.09	176.13	49	-19.67	<0.01
TC (mg/dL)	227.91	55.88	185.88	42.1	-16.21	<0.01
HDL (mg/dL)	40.24	8.04	43.66	6.15	+10.15	<0.01
Non-HDL (mg/dL)	182.06	25.31	125.8	16.83	-29.53	<0.01
FPG (mg/dL)	121.8	31.41	114.24	19.53	-7.96	<0.01
PPPG (mg/dL)	170.61	54.56	157.87	34.29	-4.8	<0.01
HbA1c (%)	6.44	0.27	6.7	0.68	+4.22	<0.01
AST (U/L)	43.59	13.51	28.49	3.65	-20.69	<0.01
ALT (U/L)	34.74	5.43	28.53	4.05	-16.28	<0.01
S. creatinine (mg/dL)	0.98	0.24	0.96	0.26	-1.57	0.067

[Note: Total Cholesterol (TC), Triglycerides (TG), High-Density Lipoprotein cholesterol (HDL-c), Non-HDL cholesterol (non-HDL-c), Fasting Plasma Glucose (FPG), Post Prandial Plasma Glucose (PPPG), glycosylated hemoglobin (HbA1c), Aspartate transaminase (AST), Alanine transaminase (ALT)]

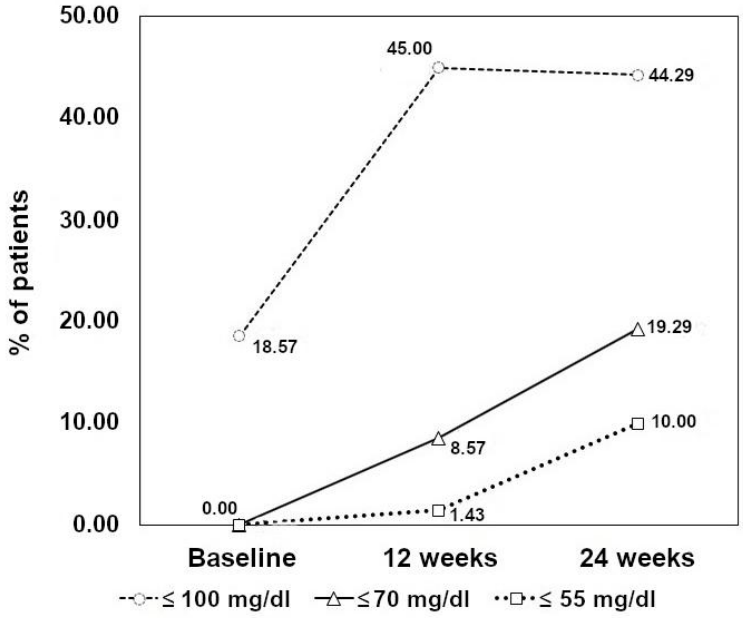

Fig. 2. Percentage composition of patients (%) who achieved LDL-c values of ≤ 100 mg/dl, ≤ 70 mg/dL, and ≤ 55 mg/dL over the study duration

Lowering of LDL-c values across the patients was observed during the study duration. Fig. 2 presents the percentage of participants at each time point, with LDL-c concentrations below 100 mg/dL, 70 mg/dL and 55 mg/dL. The percentage of patients in each level of concentration increased over the time period. The percentage of patients having LDL-c values less than 55 mg/dL increased from the start of the study to 1.43% at 12 weeks and then to 10.0% at 24 weeks. The percentage of patients having less than 70 mg/dL also increased from the baseline to 8.57% and 19.29% at 12 weeks and 24 weeks respectively.

3.2 Safety

No adverse events were observed during the study.

4. DISCUSSION

The European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) released their revised guideline for primary prevention using statins in 2019. The revised goal for LDL-c levels for very high-risk ASCVD has been set at ≤ 55 mg/dL. An updated Systematic Coronary Risk Evaluation (SCORE) system was also introduced. In this new system, the LDL-c criteria for initiating risk-based statin treatment has also been lowered. For a SCORE risk of 5 – 10% the level of LDL-c has been reduced to 100 mg/dL, and for ≥10% it's been lowered to 70 mg/dL. These changes have emphasized the role of statin therapy as an effective treatment pathway in subjects with relatively low-cholesterol level [20]. In the present study, a gradual decrease by 23.23% and 33.38% was observed in the levels of LDL-c, with a concomitant increase in the percentage of patients with lowered LDL-c values (Fig. 1). This lowering of LDL-c along with the lowering of other markers of dyslipidemia like HDL, TC, TG substantiates the efficacy of Bempedoic acid treatment [21].

Four phase III clinical trials have reported the efficacy of BA in patients with dyslipidemia. These studies are known as the Cholesterol Lowering *via* ETC-1002, an ACL (ATP-citrate lyase)-Inhibiting Regimen (CLEAR) trials [22]. The CLEAR Harmony and CLEAR Wisdom have demonstrated the safety and efficacy of BA with respect to lowering of LDL-c in patients with hypercholesterolemia as an add-on or alternative to currently existing lipid-lowering therapies. In the CLEAR Wisdom trial, the addition of BA significantly lowered LDL-c levels over 12 weeks when compared to placebo (–17.4%, placebo corrected difference; p<0.001) in patients receiving maximally tolerated statins. Similarly, in

the CLEAR Harmony trial, the addition of BA to maximally tolerated statin therapy resulted in significantly lower LDL-c levels from baseline (-18.1%, placebo corrected difference $p<0.001$) without an increased incidence of overall adverse events compared to placebo at 12 weeks. These findings collectively suggest that BA holds promise as an adjunct therapy for further reducing LDL-c levels in high-risk patients while maintaining a favorable safety profile. [23,24] In the present study, a similar reduction (23.23%) of LDL-c values was observed at 12 weeks, and a greater reduction (33.38%) was present at the 24-week follow-up. Non-HDL cholesterol values were also reduced by 19.59% and 29.53% at respective points of observation. Comparable values were also observed in the case of TC. However, HDL-c levels displayed an increase, as compared to previous studies.

The literature survey further suggested that by combining the results of the CLEAR Serenity and CLEAR Tranquility trials, it is evident that BA also offers a promising solution for patients who are unable to tolerate statins. In both studies, BA demonstrated significant reductions in LDL-c (-21.4% and -23.5%, respectively), as well as improvements in non-HDL cholesterol, total cholesterol, apolipoprotein B, and high-sensitivity C-reactive protein ($p < 0.001$ for all). Importantly, BA was well tolerated, with similar rates of adverse events compared to placebo. These findings highlight the potential of BA as an effective and safe alternative for lipid-lowering therapy in statin-intolerant patients [21,25]. Recently the results of CLEAR Outcomes demonstrated lower risk of major adverse cardiovascular events (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization) among statin-intolerant patients treated with BA [BA (11.7%) vs. placebo (13.3%); $p=0.004$] [26].

In a fixed dose study with a combination of BA and Ezetimibe, among patients who were already receiving maximally tolerated statin therapy for hypercholesterolemia with a high risk of CVD, statistically significant reduction of LDL-c values was observed (38%, $p < 0.001$), as compared to placebo groups. [25,27]. In the present study, reduction in LDL-c values over 12 weeks of observation was also low (23.23%) when compared to previously reported value of BA administration in combination with ezetimibe [27].

The patients receiving BA treatment in the current study have already been diagnosed with other complications, with diabetes and hypertension being the two most common comorbidities present. BA has been associated with lower incidence of emergence of diabetes mellitus among patients, along with a significant reduction of HbA1c over a period of 1 year [28]. Unlike In the present study HbA1c values did not display any decrease but eventually increased by 4.22% over 24 weeks, while FBS and PPBS at week 12 and 24 shows lower than at start of the study**,** which need further follow up to understand the effect of BA on glycemic parameters. This study demonstrated a remarkable absence of adverse events, highlighting the safety profile of the intervention. The findings suggest that the treatment is well-tolerated and devoid of any significant untoward effects. This favorable outcome further supports the feasibility and potential benefits of the intervention in clinical practice.

5. CONCLUSION

The present study further establishes the efficacy of BA as an add-on therapy in lowering LDL-c and other markers among patients who have been diagnosed with dyslipidemia or have other co-morbid conditions. A significant reduction of LDL-c values was observed along with decrease of TG, TC, non-HDL, FPG, PPPG, AST and serum creatinine values across the observation period of 12 weeks and 24 weeks. Similar magnitude of LDL-c reduction has been reported by previous studies globally. In the case of certain markers, where the observed value did not match with previous reports, can be considered to stem from the lower time frame considered for the present investigation. However, these observations highlighted the importance of long-term clinical observations on BA efficacy. The BEST registry is aimed to fulfill this need precisely. Further investigations on BA efficacy and safety in patients with a high risk of CVD is thus warranted.

CONSENT

As per international standard or university standard, patient (s) written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

In view of the retrospective nature of the study, all procedures being performed as a part of the routine care. Therefore, the ethical approval was not applied to any Ethics Committee.

ACKNOWLEDGEMENT

All authors have declared that they have no financial support to disclose.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Cardiovascular diseases (CVDs) by World Health Organization (WHO). Available: https://www.who.int/health-topics/cardiovascular-diseases. Accessed on April 30, 2023.
2. Mendis S, Puska P, Norrving B, Organization WH, Federation WH, Organization WS. Global atlas on cardiovascular disease prevention and control / edited by: Shanthi Mendis ... [et al.]. World Health Organization; 2011. Published by the World Health Organization in collaboration with the World Heart Federation and the World Stroke Organization.
3. Pol T, Held C, Westerbergh J, Lindbäck J, Alexander JH, Alings M, et al. Dyslipidemia and Risk of Cardiovascular Events in Patients With Atrial Fibrillation Treated With Oral Anticoagulation Therapy: Insights From the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) Trial. J Am Heart Assoc. 2018 Feb 6;7(3):e007444.
4. Carroll MD, Fryar CD, Kit BK. Total and High-density Lipoprotein Cholesterol in Adults: United States, 2011-2014. NCHS Data Brief. 2015 Dec;(226):1–8.
5. Sadananda SN, Foo JN, Toh MT, Cermakova L, Trigueros-Motos L, Chan T, et al. Targeted next-generation sequencing to diagnose disorders of HDL cholesterol. J Lipid Res. 2015 Oct;56(10):1993–2001.
6. Schwartz GG, Olsson AG, Abt M, Ballantyne CM, Barter PJ, Brumm J, et al. Effects of Dalcetrapib in Patients with a Recent Acute Coronary Syndrome. N Engl J Med. 2012 Nov 29;367(22):2089–99.
7. Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, et al. Intensive versus Moderate Lipid Lowering with Statins after Acute Coronary Syndromes. N Engl J Med. 2004 Apr 8;350(15):1495–504.
8. Evolocumab in Patients with Cardiovascular Disease. N Engl J Med. 2017 Aug 24;377(8):785–8.
9. Amarenco P, Kim JS, Labreuche J, Charles H, Abtan J, Béjot Y, et al. A Comparison of Two LDL Cholesterol Targets after Ischemic Stroke. N Engl J Med. 2020 Jan 2;382(1):9–19.
10. Ouchi Y, Sasaki J, Arai H, Yokote K, Harada K, Katayama Y, et al. Ezetimibe Lipid-Lowering Trial on Prevention of Atherosclerotic Cardiovascular Disease in 75 or Older (EWTOPIA 75): A Randomized, Controlled Trial. Circulation. 2019 Sep 17;140(12):992–1003.
11. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 139(25)e1082–e1143. Available:https://www.ahajournals.org/doi/10.1161/CIR.0000000000000625
12. Ray KK, Ginsberg HN, Davidson MH, Pordy R, Bessac L, Minini P, et al. Reductions in Atherogenic Lipids and Major Cardiovascular Events: A Pooled Analysis of 10 ODYSSEY Trials Comparing Alirocumab With Control. Circulation. 2016 Dec 13;134(24):1931–43.
13. Wang Q, Liang C. Role of Lipid-Lowering Therapy in Low-Density Lipoprotein Cholesterol Goal Attainment: Focus on Patients With Acute Coronary Syndrome. J Cardiovasc Pharmacol. 2020 Dec;76(6):658–70.
14. Bytyçi I, Penson PE, Mikhailidis DP, Wong ND, Hernandez AV, Sahebkar A, et al. Prevalence of statin intolerance: a meta-analysis. Eur Heart J. 2022 Sep 7;43(34):3213–23.
15. Ray KK, Molemans B, Schoonen WM, Giovas P, Bray S, Kiru G, et al. EU-Wi *d* e Cross-Section *a* l Obser *v* at *i* o *n* al Study of Lipid-Modifying Therapy Use in Se *c* ondary and Pr *i* mary Care: the DA VINCI study. Eur J Prev Cardiol. 2021 Sep 20;28(11):1279–89.
16. Nexletol (Bempedoic Acid) Prescribing Information. Available:https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/211616s000lbl.pdf.

17. Niman S, Rana K, Reid J, Sheikh-Ali M, Lewis T, Choksi RR, et al. A Review of the Efficacy and Tolerability of Bempedoic Acid in the Treatment of Hypercholesterolemia. Am J Cardiovasc Drugs. 2020 Dec;20(6): 535–48.
18. Pinkosky SL, Filippov S, Srivastava RAK, Hanselman JC, Bradshaw CD, Hurley TR, 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 Jan;54(1): 134–51.
19. Ballantyne CM, Bays H, Catapano AL, Goldberg A, Ray KK, Saseen JJ. Role of Bempedoic Acid in Clinical Practice. Cardiovasc Drugs Ther. 2021 Aug;35(4): 853–64.
20. Mortensen MB, Nordestgaard BG. 2019 vs. 2016 ESC/EAS statin guidelines for primary prevention of atherosclerotic cardiovascular disease. Eur Heart J. 2020 Aug 14;41(31): 3005–15.
21. Laufs U, Banach M, Mancini GBJ, Gaudet D, Bloedon LT, Sterling LR, et al. Efficacy and Safety of Bempedoic Acid in Patients With Hypercholesterolemia and Statin Intolerance. J Am Heart Assoc. 2019 Apr 2;8(7):e011662.
22. Agarwala A, Quispe R, Goldberg AC, Michos ED. Bempedoic Acid for Heterozygous Familial Hypercholes-terolemia: From Bench to Bedside. Drug Des Devel Ther. 2021;15:1955–63.
23. Goldberg AC, Leiter LA, Stroes ESG, Baum SJ, Hanselman JC, Bloedon LT, et al. Effect of Bempedoic Acid vs Placebo Added to Maximally Tolerated Statins on Low-Density Lipoprotein Cholesterol in Patients at High Risk for Cardiovascular Disease: The CLEAR Wisdom Randomized Clinical Trial. JAMA. 2019 Nov 12;322(18):1780–8.
24. Ballantyne CM, Banach M, Bays HE, Catapano AL, Laufs U, Stroes ESG, et al. Long-Term Safety and Efficacy of Bempedoic Acid in Patients With Atherosclerotic Cardiovascular Disease and/or Heterozygous Familial Hypercholesterolemia (from the CLEAR Harmony Open-Label Extension Study). Am J Cardiol. 2022 Jul 1;174:1–11.
25. Ballantyne CM, Banach M, Mancini GBJ, Lepor NE, Hanselman JC, Zhao X, et al. Efficacy and safety of bempedoic acid added to ezetimibe in statin-intolerant patients with hypercholesterolemia: A randomized, placebo-controlled study. Atherosclerosis. 2018 Oct;277:195–203.
26. Nissen SE, Lincoff AM, Brennan D, Ray KK, Mason D, Kastelein JJP, et al. Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients. N Engl J Med. 2023 Apr 13;388(15):1353–64.
27. Ballantyne CM, Laufs U, Ray KK, Leiter LA, Bays HE, Goldberg AC, et al. Bempedoic acid plus ezetimibe fixed-dose combination in patients with hypercholesterolemia and high CVD risk treated with maximally tolerated statin therapy. Eur J Prev Cardiol. 2020 Apr;27(6):593–603.
28. Leiter LA, Banach M, Catapano AL, Duell PB, Gotto AM, Laufs U, et al. Bempedoic acid in patients with type 2 diabetes mellitus, prediabetes, and normoglycaemia: A post hoc analysis of efficacy and glycaemic control using pooled data from phase 3 clinical trials. Diabetes Obes Metab. 2022 May;24(5): 868–80.

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/101076