Journal of Clinical Lipidology (2025) 000, 1–9

Journal of Clinical Lipidology

Original Research

Clinical implementation of bempedoic acid in blood lipid management: Real-world data from an Italian lipid clinic

Chiara Pavanello, PhD*; Giulia Cincotto, MSc; Giuliana Germana Mombelli, MD; Sofia Castiglione, MSc; Caterina Santolamazza, MD, PhD; Laura Calabresi, PhD; Cesare Riccardo Sirtori, MD, PhD; Antonia Alberti, MD

E. Grossi Paoletti Center, Department of Pharmacological and Biomolecular Sciences, University of Milan, Milan, Italy (Cincotto, Drs Calabresi and Sirtori); Dyslipidemia Center, Niguarda Hospital, Milan, Italy (Drs Pavanello, Mombelli, Mr Castiglione, Drs Santolamazza, Sirtori, and Alberti)

KEYWORDS
Bempedoic acid;
Real-word;
Dyslipidemia;
ASCVD risk;
ESC/EAS target;
Statin-intolerance;
Familial hypercholesterolemia

BACKGROUND: Bempedoic acid (BA), an ATP citrate lyase inhibitor, is approved for low-density lipoprotein (LDL)-cholesterol reduction and is well tolerated, especially in statin-intolerant patients. Real-world evidence, particularly from Europe, remains limited.

OBJECTIVE: To assess real-world effectiveness, safety, and predictors of LDL-cholesterol target achievement with BA in Italian patients.

METHODS: We conducted a retrospective observational study of 160 patients treated with BA at a lipid clinic in Milan, Italy. Patients were followed for 12 months. LDL-cholesterol levels, laboratory parameters, clinical events, and adverse effects were collected. Effectiveness was assessed as percentage change in LDL-cholesterol from baseline. Predictors of LDL-cholesterol target achievement were identified using multivariable logistic regression.

RESULTS: BA significantly reduced LDL-cholesterol from 116.1 ± 49.3 to 78.5 ± 36.0 mg/dL (−26.1%, $P < .05$). The majority of patients (60.8%) reached European Society of Cardiology/European Atherosclerosis Society LDL-cholesterol goals (≤55 mg/dL). LDL-cholesterol reduction was greater in statin-intolerant patients (−29.0% vs −21.0%) and smaller in those with familial hypercholesterolemia (FH) (−18.0% vs −29.2%). Independent predictors of target non-achievement were FH (odds ratio [OR] 0.045, 95% CI 0.004-0.523, $P = .013$), while concomitant proprotein convertase subtilisin kexin type 9 inhibitor use predicted success (OR 31.82, 95% CI 2.57-394.17, $P = .007$). Among 69 patients not achieving LDL-cholesterol targets, 84% were on maximally tolerated lipid-lowering therapy (LLT), 67% were statin-intolerant, and 11 had FH. Safety analysis showed good tolerability; 4.0% developed hyperuricemia, and only 2 atherosclerotic cardiovascular disease events occurred during follow-up.

* Corresponding author at: Dyslipidemia Center, Niguarda Hospital, Via Balzaretti, 9, Milan 20133, Italy.
E-mail address: chiara.pavanello@unimi.it (C. Pavanello).
Submitted July 15, 2025. Accepted for publication September 23, 2025.

https://doi.org/10.1016/j.jacl.2025.09.033

Please cite this article as: Pavanello et al., Clinical implementation of bempedoic acid in blood lipid management: Real-world data from an Italian lipid clinic, Journal of Clinical Lipidology, https://doi.org/10.1016/j.jacl.2025.09.033

CONCLUSION: BA was effective and well tolerated in this high-risk cohort, including statin-intolerant and FH patients. Beyond its initial indication, BA now represents a valuable therapeutic option to optimize LDL-cholesterol lowering in patients who remain above target despite standard LLT.

Introduction

Lowering total and low-density lipoprotein (LDL)–cholesterol levels is a major goal in cardiovascular prevention. Lipid-lowering therapies (LLTs), mainly statins, can achieve this goal in a large number of patients, although with considerable variability[1] and the frequent occurrence of objective and subjective side effects, leading to reduced effectiveness or even outright refusal to continue treatment, with a percentage of intolerance reaching 42.6% in the large Goal Achievement after Utilizing an Anti-PCSK9 Antibody in Statin-Intolerant Subjects 3 (GAUSS-3) study.[2] A number of factors have been identified as potentially associated with variations in response to LLTs, in particular statins. In this context, muscular side effects[3] linked to reduced muscle mitochondrial biogenesis and altered responsiveness of mechanoreceptive and nociceptive fibers[4] appear responsible for the inadequate tolerability and variable response. Understanding these mechanisms has been of significant value in developing novel pharmacological strategies for LDL-cholesterol reduction. Among these is bempedoic acid (BA), a short-chain fatty acid[5] that acts as a prodrug, undergoing hepatic metabolism by very long-chain acyl-CoA synthetase 1 (ACSVL1) to form bempedoyl-CoA, a powerful inhibitor of cholesterol biosynthesis, upregulating hepatic LDL receptors (LDLR) and effectively reducing LDL-cholesterol levels.[6] A major advantage of BA is its liver selectivity, sparing exposure of skeletal muscle, thus not leading to myalgia.[7] BA is approved by both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA)[8] for the treatment of hypercholesterolemia, either as monotherapy or in fixed-dose combination with ezetimibe. The launch of BA in nearly all European countries preceded US authorizations and enables the acquisition of significant experience with this drug, thus providing data from daily clinical practice, in addition to those obtained in the large CLEAR OUTCOMES trial.[6] Safety data from this study have been recently published,[9] indicating a modest rise in side effects with the active drug. Gouty arthritis, tendinopathies, and cholelithiasis appear to occur at a slightly higher rate with BA compared to placebo, but data from individual countries have rarely been reported and appear desirable, given the growing daily use of this drug in many countries.

The present report investigates a series of Italian hypercholesterolemic patients followed for 1 year or longer, providing data on effectiveness and safety in a well-characterized cohort.

Methods

Study design

This report provides data from a retrospective cohort including patients ≥18 years who were prescribed BA as part of regular standard of care for atherosclerotic cardiovascular disease (ASCVD) reduction at the Dyslipidemia Center of the Niguarda Hospital, Milan, Italy. Diagnosis of familial hypercholesterolemia (FH) was made by clinical criteria employing the Dutch Lipid Clinic Network (DLCN) scoring systems for likelihood of FH with or without genetic confirmation.[10] They were prescribed BA between April 2023 and October 2024. All patients fulfilled the Italian reimbursement criteria for BA treatment being: (1) LDL-cholesterol target not reached despite maximum tolerated LLT; (2) LDL-cholesterol target not reached in the presence of a contraindication or intolerance to first- and second-line statin therapy, in particular when an additional reduction of approximately 20% in LDL-cholesterol is sufficient to achieve the target; (3) statin intolerance, defined according to the National Lipid Association (NLA) criteria, as the inability to tolerate at least 2 different statins, 1 of which at the lowest approved dose, due to adverse effects—typically muscle-related symptoms—either objectively confirmed or subjectively reported, that resolve or significantly improve upon statin discontinuation or dose reduction.[11] Patients with confirmed intolerance were eligible for BA prescription under Italian reimbursement criteria. High-intensity statins were defined as rosuvastatin ≥20 mg or atorvastatin ≥40 mg. Moderate-intensity statins included rosuvastatin 5 to 20 mg, atorvastatin 10 to 40 mg, simvastatin 20 to 40 mg, pravastatin 40 to 80 mg, fluvastatin ≥80 mg, and lovastatin 40 mg. Low-intensity statins were defined as rosuvastatin ≤2.5 mg, simvastatin 10 mg, pitavastatin 1 mg, or lovastatin 20 mg.[12] LDL-cholesterol target levels were defined according to the 2019 European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) Guidelines on dyslipidemias, ie, <1.4 mmol/L (<55 mg/dL) for very high-risk patients, <1.8 mmol/L (<70 mg/dL) for high-risk patients, and <2.6 mmol/L (<100 mg/dL) for moderate-risk patients.[13] Patients were managed according to clinical standards of care for ASCVD risk reduction, with follow-up visits and laboratory assessments tailored to each patient's needs. In general, lipid assessments were conducted at 4 time points following the initiation of BA: between 3 and 6 months, at 9 months, and at 12 months. Data were collected through a review of electronic medical records and patient

Please cite this article as: Pavanello et al., Clinical implementation of bempedoic acid in blood lipid management: Real-world data from an Italian lipid clinic, Journal of Clinical Lipidology, https://doi.org/10.1016/j.jacl.2025.09.033

visits. At all visits, a complete clinical evaluation was performed, and laboratory tests were conducted, including lipid profile (total cholesterol, high-density lipoprotein [HDL]-cholesterol, triglycerides), glucose, uric acid and liver function tests (alanine aminotransferase [ALT]), aspartate aminotransferase [AST], and gamma-glutamyltransferase [GGT]). The LDL-cholesterol was calculated using the Friedewald equation: LDL-cholesterol = total cholesterol − HDL-cholesterol − (triglycerides/5). Lipoprotein(a) levels[14] were assessed in all patients; repeat testing was performed after 12 months of treatment. Additionally, clinical information such as new ASCVD events, significant side effects, and concomitant use of LLTs were documented at each visit. All participating patients gave informed consent to use their clinical information for research. The study was notified to the Ethics Committee of the ASST Grande Ospedale Metropolitano Niguarda and conducted according to the 1975 Declaration of Helsinki (approval 612-11102022).

Statistical analysis

Statistical analyses were conducted using SPSS version 29.0 (IBM Corp) and GraphPad Prism version 10.4 (GraphPad Software). Continuous variables are expressed as mean ± SD, and categorical variables as counts and percentages, unless differently stated. Changes in lipid and safety parameters over time were analyzed using a mixed-effects model for repeated measures, accounting for within-subject variability. post hoc comparisons to baseline were performed where applicable. For LDL-cholesterol, both absolute and percentage changes from baseline were reported. Subgroup analyses of LDL-cholesterol percentage reduction at last follow-up were performed using independent-sample t-tests or Mann–Whitney U tests, depending on data distribution, and one-way analysis of variance for comparisons across more than 2 groups (eg, statin intensity categories). To identify independent predictors of LDL-cholesterol target achievement, a multivariable logistic regression analysis was performed. The dependent variable was the achievement of the LDL-cholesterol goal at the last available follow-up. Covariates included in the model were selected based on clinical relevance and prior evidence of association with LDL-cholesterol reduction response. Regression was initially performed including all clinically relevant covariates. A reduced model was then generated using stepwise backward elimination based on likelihood ratio, retaining variables with $P < .10$ or strong clinical plausibility. These included: age, sex, body mass index (BMI), FH, statin intensity (categorized as low, moderate, or high), concomitant use of proprotein convertase subtilisin kexin type 9 (PCSK9)-targeting therapies, and baseline LDL-cholesterol levels.

The results are presented as odds ratios (OR) with 95% CI. Multicollinearity was assessed using variance inflation factors (VIF), and variables with excessive collinearity were considered for exclusion or adjustment. All statistical tests were two-sided, and P values $<.05$ were considered statistically significant.

Results

Baseline information

The cohort consisted of 160 patients (mean age 66.0 ± 11.4; 51.3% males) who were prescribed BA during the study interval. Baseline characteristics of the study population are summarized in Table 1. The mean BMI was 26.0 ± 4.0 kg/m². A high prevalence of ASCVD risk factors was observed, with 65.6% of patients affected by hypertension, 10.6% by diabetes mellitus, and 15.0% meeting criteria for obesity (BMI ≥ 30 kg/m²). FH was diagnosed in 24.0% of patients, including 3 cases (7.9%) of homozygous FH. A substantial proportion of the cohort (61.3%) was statin-intolerant, with 84 patients (52.5%) classified as very-high ASCVD risk and 76 (47.5%) as high risk according to ESC/EAS Guidelines.[13]

At baseline, mean LDL-cholesterol levels were 116.1 ± 49.3 mg/dL, while non-HDL-cholesterol and triglycerides were 140.2 ± 53.9 mg/dL and 126.4 ± 70.0 mg/dL, respectively. HDL-cholesterol averaged 54.4 ± 14.8 mg/dL. Lipoprotein(a) levels were elevated, with a mean of 55.5 ± 62.5 mg/dL. Regarding LLTs, 53.1% of patients were on statins (of whom 62.4% received high-intensity therapy), 74.4% were on ezetimibe, and 23.8% were on PCSK9-targeting therapies (including $n = 16$ evolocumab 140 mg, $n = 19$ alirocumab 75/100 mg, and $n = 3$ inclisiran 284 mg). These data reflect a cohort with high residual ASCVD risk and significant baseline lipid abnormalities despite ongoing treatments, highlighting the need for further LDL-cholesterol reduction strategies such as BA.

Effectiveness of BA

One hundred twenty-six patients had at least 1 follow-up lipid determination. Treatment with BA was associated with a progressive and sustained improvement in the lipid profile over time (Table 2, panel A). Mean LDL-cholesterol levels went down significantly, ie, from 116.1 ± 49.3 mg/dL at baseline to 78.5 ± 36.0 mg/dL at the last available follow-up ($n = 126$), corresponding to a median relative reduction of −26.1% (95% CI 46.1, −9.68, $P < .01$). The absolute LDL-cholesterol reduction at last follow-up was −32.3 ± 37.1 mg/dL. Reductions in total and non-HDL-cholesterol were also observed: non-HDL-cholesterol decreased from 140.2 ± 53.9 to 102.3 ± 38.5 mg/dL ($P < .01$), corresponding to ∼ 27%. Mean triglyceride levels remained unchanged, while HDL-cholesterol showed a modest but significant reduction at month 6 (−7.7%, $P < .05$), followed by stabilization thereafter. In Figure 1 a wide interindividual variability in LDL-cholesterol response to BA, reflecting not only individual biological differences, is clearly evident, possibly also dependent upon changes in concomitant LLTs over time. While the majority of patients experienced a reduction in LDL-cholesterol, a subset showed minimal or no response, suggesting heterogeneous individual efficacy, possibly influenced by baseline characteristics, concomitant therapies, or genetic factors (Fig. 1). Subgroup

Please cite this article as: Pavanello et al., Clinical implementation of bempedoic acid in blood lipid management: Real-world data from an Italian lipid clinic, Journal of Clinical Lipidology, https://doi.org/10.1016/j.jacl.2025.09.033

Table 1. General characteristics of patients.

Variable	
N	160
Age (y)	66.0 ± 11.4
Sex (male/female)	82/78
BMI (kg/m²)	26.0 ± 4.0
Systolic blood pressure (mm Hg)	126.8 ± 17.4
Diastolic blood pressure (mm Hg)	73.5 ± 8.8
Heart rate (bpm)	70.0 ± 11.8
Postmenopausal women (n, %)	76 (97.4)
Active smokers (n, %)	12 (7.5)
Hypertension (n, %)	105 (65.6)
Diabetes (n, %)	17 (10.6)
Obesity (n, %)	24 (15.0)
Family history of ASCVD (n, %)	92 (57.5)
Family history of hypercholesterolemia (n, %)	108 (67.5)
Familial hypercholesterolemia (n, %)	39 (24.0)
Homozygous FH (n, %)	3 (7.9)
Statin intolerance (n, %)	98 (61.3)
ESC/EAS risk class (n, %)	
High risk	76 (47.5)
Very-high risk	84 (52.5)
Naïve lipid profile	
Total cholesterol (mg/dL)	302.1 ± 79.1
Non-HDL-cholesterol (mg/dL)	249.7 ± 81.8
Triglycerides (mg/dL)	177.9 ± 164.1
HDL-cholesterol (mg/dL)	52.8 ± 18.2
LDL-cholesterol (mg/dL)	207.3 ± 84.6
Lipid profile at baseline	
Total cholesterol (mg/dL)	195.3 ± 56.5
Non-HDL-cholesterol (mg/dL)	140.2 ± 53.9
Triglycerides (mg/dL)	126.4 ± 70.0
HDL-cholesterol (mg/dL)	54.4 ± 14.8
LDL-cholesterol (mg/dL)	116.1 ± 49.3
Lipoprotein(a) (mg/dL)	55.5 ± 62.5
Lipid-lowering treatments (n, %)	
Statins	85 (53.1)
High-intensity	53 (62.4)
Moderate-intensity	24 (28.2)
Low-intensity	8 (9.4)
Ezetimibe	119 (74.4)
PCSK9-targeting therapies	38 (23.8)
Fibrates	10 (6.3)
Others*	11 (6.9)

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; ESC/EAS, European Society of Cardiology/European Atherosclerosis Society; FH, familial hypercholesterolemia; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PCSK9, proprotein convertase subtilisin kexin type 9.

Values are expressed as mean ± SD or number (percentage).

*Other treatments include: red yeast rice extract, berberine, phytosterols.

analysis (Fig. 2) revealed, in fact, that the LDL-cholesterol lowering effect of BA was generally consistent across most clinical subgroups, with no statistically significant interactions observed for age, sex, presence of hypertension, diabetes, ASCVD, obesity, or smoking status. A few notable findings emerged, however. First, patients with FH showed a significantly attenuated LDL-cholesterol reduction compared to those without FH (−18.0% vs −29.2%, $P = .038$), suggesting a potentially lower response in this population, consistent with the mechanism of action of BA, requiring functional LDLR for maximal effect[15] and possibly less effective in individuals with genetically impaired LDLR activity. Second, patients not on statins experienced a significantly larger LDL-cholesterol reduction compared to those on statin therapy (−32.7% vs −20.6%, $P = .015$). This may reflect overlapping mechanisms of action, as both BA and statins inhibit enzymes in the same cholesterol biosynthetic pathway. When used in combination, the incremental effect of BA may be diminished due to downstream inhibition already achieved by statins. A numerically greater LDL-cholesterol reduction was also observed in patients with statin intolerance (−29.0% vs −21.0%), though this difference did not reach statistical significance ($P = .117$). This effect may be partially explained by the lower background use of statins in this group, which could amplify the relative impact of BA as a stand-alone or add-on therapy. Importantly, the proportion of patients achieving LDL-cholesterol targets increased over time. At the last follow-up, 23.5% of patients reached an LDL-cholesterol ≤70 mg/dL and 60.8% achieved the more stringent goal of ≤55 mg/dL, consistent with ESC/EAS recommendations for high- and very high-risk patients (Table 2, panel A). In multivariable logistic regression, FH was significantly associated with a lower likelihood of achieving LDL-cholesterol targets (OR 0.045, 95% CI 0.004-0.523, $P = .013$), while the use of PCSK9-targeting therapies was strongly associated with target achievement (OR 31.82, 95% CI 2.57-394.17, $P = .007$). High-intensity statin therapy showed a trend toward improved target attainment (OR 17.13, 95% CI 0.77-382.30, $P = .073$), although the association did not reach statistical significance (Table 3). Among the 69 patients who did not achieve their LDL-cholesterol target at last follow-up, 58 (84.1%) were already receiving the maximum tolerated combination of LLTs available according to current clinical practice. Forty-six (66.7%) were statin-intolerant, and among them, 11 patients had a diagnosis of FH. In these 11 FH patients, BA was initiated before the escalation to PCSK9-targeting therapies, serving as an intermediate step in the therapeutic pathway.

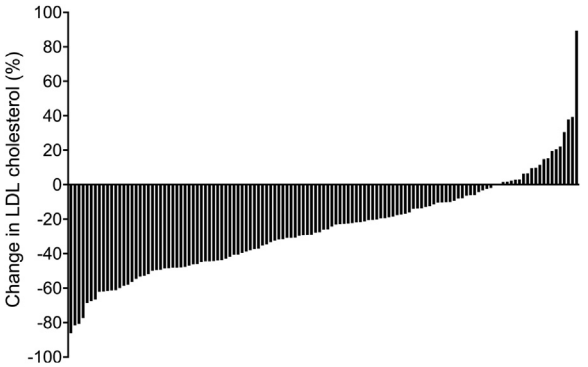

Figure 1. LDL-cholesterol change of individual patients at last follow-up ($n = 126$). Abbreviation: LDL, low-density lipoprotein.

Table 2. Effectiveness and safety of BA.

	Baseline ($n = 160$)	M3 ($n = 93$)	M6 ($n = 66$)	M9 ($n = 44$)	M12 ($n = 55$)	Last FU ($n = 126$)
(A) Effectiveness of BA						
Total cholesterol (mg/dL)	195.3 ± 56.5	155.0 ± 49.4	152.1 ± 44.4	147.3 ± 42.8	149.5 ± 38.0	154.0 ± 42.8
Non-HDL-cholesterol (mg/dL)	140.2 ± 53.9*	104.6 ± 45.5*	101.9 ± 39.3*	99.2 ± 38.3*	98.1 ± 35.8*	102.3 ± 38.5*
HDL-cholesterol (mg/dL)	54.4 ± 14.8	50.5 ± 14.8	50.2 ± 16.9*	48.1 ± 17.7	50.7 ± 15.6	51.7 ± 15.8
Triglycerides (mg/dL)	126.4 ± 70.0	126.9 ±78.9	121.0 ± 93.8	124.4 ± 69.2	133.1 ± 146.8	128.4 ± 111.7
Lipoprotein(a) (mg/dL)†	63.1 ± 73.8	-	-	-	-	58.2 ± 68.4
LDL-cholesterol (mg/dL)	116.1 ± 49.3	78.7 ± 43.0*	76.0 ± 38.5*	76.6 ± 35.1*	75.2 ± 30.1*	78.5 ± 36.0*
Change in LDL-cholesterol (%)	-	−22.9 (−40.2, −9.0)	−28.0 (−51.7, −1.4)	−25.5 (−44.0, −0.5)	−26.4 (−46.1; −6.1)	−26.1 (−46.1; −9.68)
LDL-cholesterol absolute change	-	−27.9 ± 36.8	−32.2 ± 41.0	−29.4 ± 34.9	−32.7 ± 42.1	−32.3 ± 37.1
LDL-cholesterol by treatment goal (n, %)						
≤70 mg/dL	-	7 (23.3)	6 (30.0)	1 (7.7)	3 (14.3)	12 (23.5)
≤55 mg/dL	-	25 (39.7)	18 (40.9)	15 (48.4)	16 (45.7)	45 (60.8)
Distance to target (mg/dL)	56.7 ± 43.8	36.2 ± 36.7	33.3 ± 30.8	30.8 ± 27.0	25.8 ± 20.9	38.4 ± 27.4
(B) Safety of BA						
Uric acid (mg/dL)	5.08 ± 1.40	5.68 ± 1.54	5.98 ± 1.35*	5.69 ± 1.43*	5.55 ± 1.54	5.80 ± 1.49*
Increase in uric acid (n, %)	-	3 (3.2)	0 (0)	1 (2.3)	1 (1.8)	5 (4.0)
Fasting blood glucose (mg/dL)	98.2 ± 15.3	98.4 ± 14.5	101.0 ± 17.4	95.1 ± 12.6	102.0 ± 18.6	100.0 ± 16.3
Transaminases elevation (n, %)	-	0 (0)	1 (1.5)	0 (0)	0 (0)	0 (0)
Myalgia (n, %)	-	3 (3.2)	1 (1.5)	0 (0)	1 (1.8)	5 (4.0)
Gastrointestinal disorders (n, %)						
Nausea	-	1 (1.1)	0 (0)	0 (0)	0 (0)	0 (0)
Vomiting	-	1 (1.1)	1 (1.5)	0 (0)	0 (0)	0 (0)
Diarrhea	-	0 (0)	1 (1.5)	0 (0)	0 (0)	0 (0)
Abdominal pain	-	1 (1.1)	0 (0)	0 (0)	0 (0)	1 (.8)
Other (n, %)	-	0 (0)	0 (0)	0 (0)	1 (1.8)	1 (.8)
Treatment discontinuation (n, %)	-	4 (4.3)	5 (7.6)	2 (4.5)	1 (1.8)	12 (9.5)

Abbreviations: BA, bempedoic acid; FU, follow-up; HDL, high-density lipoprotein; LDL, low-density lipoprotein; M, month.

Values are expressed as mean ± standard deviation or number (percentage). Change in LDL-cholesterol is expressed as median and 95% confidence interval. Data were analyzed using a mixed-effects model.

Values are expressed as mean ± standard deviation or median (25th and 75th percentile) or number (percentage). Data were analyzed using a mixed-effects model.

*$P < .05$ vs baseline.

†$n = 55$.

Please cite this article as: Pavanello et al., Clinical implementation of bempedoic acid in blood lipid management: Real-world data from an Italian lipid clinic, Journal of Clinical Lipidology, https://doi.org/10.1016/j.jacl.2025.09.033

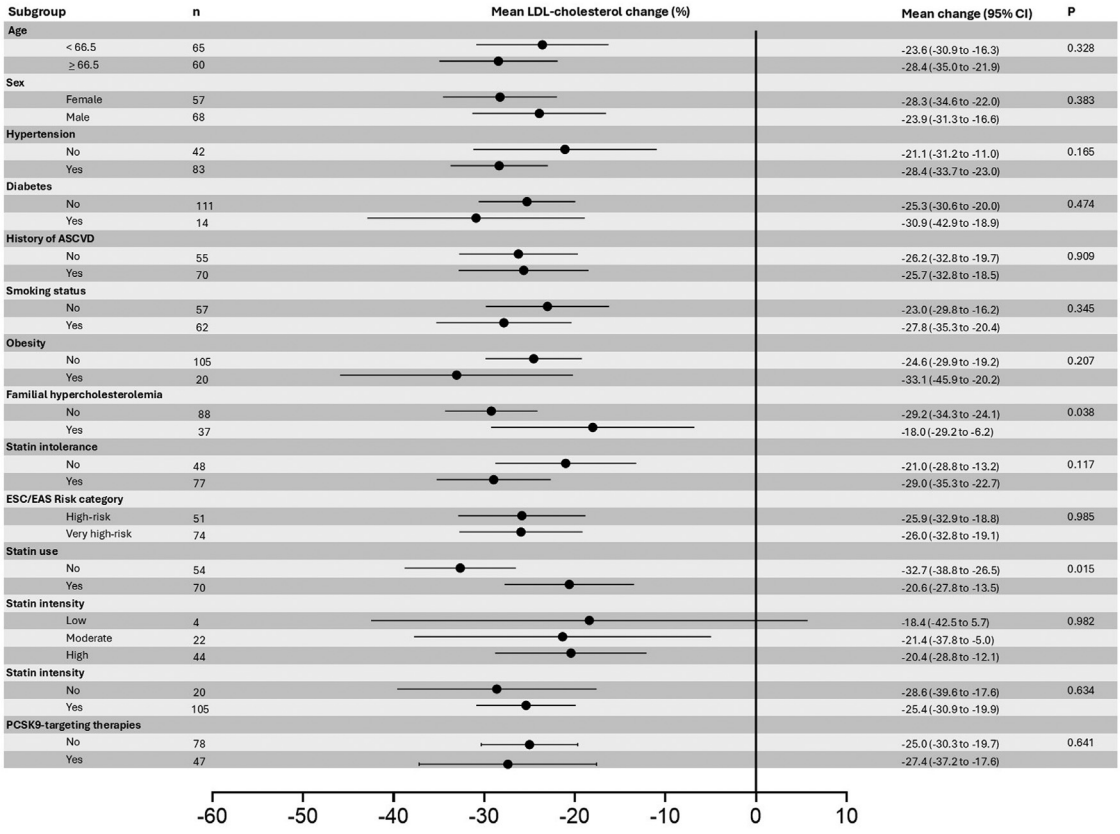

Figure 2. Subgroup analysis of BA efficacy at last follow-up—values are expressed as mean (95% CI). Groups were compared by independent-sample t-tests or Mann–Whitney U tests, depending on data distribution, and one-way analysis of variance for comparisons across more than 2 groups. Abbreviations: ASCVD, atherosclerotic cardiovascular disease; BA, bempedoic acid; ESC/EAS, European Society of Cardiology/European Atherosclerosis Society; LDL, low-density lipoprotein; PCSK9, proprotein convertase subtilisin kexin type 9.

Table 3. Predictors of LDL-cholesterol target achievement at follow-up.

Variable	OR (Exp[B])	95% CI	*P*
Age (per year)	1.045	0.991-1.103	.106
Male sex	1.586	0.497-5.063	.436
BMI	1.005	0.861-1.172	.953
Familial hypercholesterolemia	0.045	0.004-0.523	.013
Statin intensity-moderate	9.764	0.443-215.093	.149
Statin intensity-high	17.125	0.767-382.298	.073
PCSK9-targeting therapies use	31.817	2.568-394.167	.007
Baseline LDL-cholesterol	1.008	0.990-1.027	.377

Abbreviations: BMI, body mass index; LDL, low-density lipoprotein; OR, odds ratio; PCSK9, proprotein convertase subtilisin kexin type 9.

Multivariable logistic regression model evaluating independent predictors of LDL-cholesterol target achievement at last available follow-up, according to European Society of Cardiology/European Atherosclerosis Society 2019 goals (<55 mg/dL for very high-risk, <70 mg/dL for high-risk patients). Results are expressed as OR with 95% CI. Statin intensity at follow-up was categorized as moderate or high, with low intensity as reference. *P* values <.05 were considered statistically significant.

Safety of BA

BA was generally well tolerated throughout the follow-up period (Table 2, panel B). A modest but statistically significant increase in serum uric acid was observed as early as month 6 (5.98 ± 1.35 mg/dL) and month 9 (5.69 ± 1.43 mg/dL), compared to baseline values (5.08 ± 1.40 mg/dL, $P < .05$). This trend persisted at the last follow-up (5.80 ± 1.49 mg/dL). Clinically relevant hyperuricemia occurred in 5 patients (4.0%), in whom allopurinol therapy was initiated, allowing for effective management of the condition without treatment discontinuation. Fasting glucose remained stable over time, with no relevant changes compared to baseline. Regarding adverse events, muscle-related symptoms were reported in 5 patients (4.0%), while gastrointestinal side effects were infrequent and mild, including isolated cases of nausea, vomiting, diarrhea, and abdominal pain (all <2%).

Transient and asymptomatic transaminase elevations—defined as 3 times the upper limit of normal increase—was observed in only 1 case (1.5%) during follow-up, and no hepatotoxicity was documented. Treatment discontinuation occurred in 12 patients (9.5%) overall, with no clear clustering of adverse events driving withdrawal. During follow-up, 2 new ASCVD events were recorded: 1 case of minor ischemic stroke due to occlusion of the right posterior cerebral artery, and 1 case of chronic coronary syndrome in a patient with a history of myocardial infarction. Both events occurred in patients at high-risk.

Discussion

This relatively large study on BA, conducted in a European country where the prescription of this drug is widespread, confirms its excellent tolerability and clinical effectiveness. The present series of patients confirmed the excellent LDL-cholesterol lowering activity of BA, that, when given in combination with ezetimibe, leads to falls in the range of those occurring with high intensity statins.[16] In the forecast of future development of a triple drug, BA, ezetimibe, and statin,[17] the excellent tolerability of BA will provide a safe and very effective treatment (>60% LDL-cholesterol reduction) to a large number of patients not wishing to undergo repeated injections. Three months after the first administration, BA led to a median LDL-cholesterol reduction of 22.9%, consistent with a meta-analysis reporting a mean reduction of 22.4%.[18] This lipid-lowering effect was sustained throughout follow-up. The magnitude of LDL-cholesterol reduction varied among patient subgroups: –26% in patients with diabetes,[19] −21.1% in statin-intolerant individuals,[6] and −15.1% in patients with FH.[16] In our cohort, patients with FH experienced an LDL-cholesterol reduction of −18%, which is consistent with findings from CLEAR Wisdom. However, unlike what was observed in randomized clinical trials, the reduction in LDL-cholesterol among FH patients in our study was lower than that seen in non-FH individuals. Additionally, we observed a greater LDL-cholesterol reduction in patients treated with BA as monotherapy compared to those on combination therapy with statins (−30.7% vs −23.6%). Among patients on statins, LDL-cholesterol reduction was more pronounced in those receiving moderate-intensity statins compared to high-intensity regimens (−75.4% vs −53.2%). These findings from our cohort underscore the heterogeneity of response to BA in clinical practice, raising the question of how these results compare with those observed in broader, real-world populations.

Only a few studies have evaluated the effectiveness of BA in real-world clinical settings. A retrospective study conducted at the Preventive Cardiology Center of Oregon Health & Science University (OHSU)[20] reported a greater LDL-cholesterol reduction (−36.7%), which occurred primarily within the first 3 months of treatment. This was followed by a gradual decrease in the effect over time, with LDL-cholesterol reductions aligning more closely with those observed in our cohort (−31% and −20.3% at 6 and 12 months, respectively). This study also highlighted interindividual variability in treatment response, identifying both hyper-responders and hypo-responders. Similarly, the OHSU study found that hypo-responders were predominantly patients taking higher doses of high-intensity statins and other nonstatin therapies, confirming observations from phase 3 clinical trial data. However, it was noted that the subgroups analyzed were too small to allow for robust statistical analysis.[21] Similar findings were reported in 2 other real-world studies conducted in the United Kingdom and Belgium, which documented mean LDL-cholesterol reductions of −32.3% and −27%, respectively.[22] Another real-world Italian study, conducted in a Southern region of the country and involving a non-FH cohort with a shorter follow-up, reported a greater LDL-cholesterol reduction (approximately −36%) and a comparable proportion of patients achieving the <55 mg/dL target, despite differences in baseline characteristics and treatment context.[23] Moreover, that study highlighted excellent adherence (99%) and persistence (90%) to BA, with infrequent and reversible adverse events. Importantly, an exploratory pharmacoeconomic analysis suggested cost savings associated with BA use in patients not achieving LDL-cholesterol goals on background therapy.[23]

Notably, the occurrence of major side effects listed in the Summary of Product Characteristics (SmPC)—namely hyperuricemia leading to gout and tendon rupture—was minimal and manageable in our cohort. Liver and hematological safety also appeared satisfactory. No significant differences in lipid-lowering response were observed between sexes, supporting the evidence that the cardiovascular benefits of BA are independent of sex.[24]

Beyond its clinical performance, a deeper look into the chemical nature and pharmacological class of BA provides further insight into its mechanisms and potential pleiotropic effects.

BA represents the most recent development in the chemical class of so-called "fraudulent fatty acids."[25] This class, which includes fibrates, omega-3 fatty acids, certain herbicides, and other agents, is generally associated with peroxisome proliferation and liver enlargement, and, in some cases, has been linked to hepatic tumor formation.[8] Interestingly, although BA shares some chemical features with classical peroxisome proliferators (eg, long hydrocarbon chain diols or diacids with central ether or ketone moieties),[26] its effect on liver weight is modest. Even more unexpectedly, BA has been shown to induce regression of hepatic steatosis independently of its ATP citrate lyase (ACLY)-inhibitory activity.[27,28]

The unique mechanism of action of the agent, ie, inhibition of ACLY, with a potential additional activation of AMP-activated protein kinase (AMPK),[29] has highlighted other possible beneficial effects. Although AMPK activation is a major mechanism of action of other metabolic agents, such as metformin (Glucophage),[30] ACLY inhibition may exert distinct and complementary actions. One of the most promising among these is the potential of ACLY inhibitors to overcome resistance to immune checkpoint inhibitors in cancer treatment, by upregulating PD-L1 expression through polyunsaturated fatty acid peroxidation and cGAS–STING pathway activation of innate immunity.[31] The potential of the drug to suppress diet-induced liver steatosis[32] has also indicated some novel aspects of the BA mechanism. It appears, in fact, that the antisteatotic effect is independent of ACLY. ACLY deficiency, in fact, paradoxically leads to raised liver fat in animals on an appropriate diet.[33] By a similar mechanism, ie, by acting on *de novo* lipogenesis, ACLY could promote cardiac fibrosis in pathological conditions. Gene silencing of ACLY reduced fibrosis, a major form of left ventricular

Please cite this article as: Pavanello et al., Clinical implementation of bempedoic acid in blood lipid management: Real-world data from an Italian lipid clinic, Journal of Clinical Lipidology, https://doi.org/10.1016/j.jacl.2025.09.033

remodeling in heart failure, thus providing a new therapeutic target for this severe clinical condition.[34] A further unexpected beneficial activity of BA is in the management of polycystic renal disease,[35] a condition where the agent could positively interact with tolvaptan, the only drug available for this condition. Apparently, a fixed dose combination of the 2 could soon become available.

While these mechanistic insights expand our understanding of BA's potential, its practical value ultimately depends on how it is integrated into real-world lipid-lowering strategies. It is important to highlight that the initial indication for BA was limited to patients with statin intolerance. However, clinical practice—as well as our own findings—suggests a broader role for this agent. In particular, BA now represents a valuable therapeutic option also for patients who are not fully at LDL-cholesterol target, even in the absence of complete statin intolerance, when the residual gap to goal is modest (∼20%-25%). This approach is especially useful in high- or very high-risk patients already receiving oral combination therapy (statin + ezetimibe) but still not at target, where the addition of BA may help avoid—or at least delay—the need for injectable therapies.

Nonetheless, the current regulatory limitation imposed by Italian reimbursement criteria, which restricts prescription to patients who fail to reach their LDL-cholesterol goal despite maximally tolerated therapy, represents a barrier to the earlier and more strategic use of BA. The adoption of more flexible criteria—based on the actual "gap to goal" rather than absolute intolerance or therapeutic failure—could broaden access to this medication, allowing it to become an integral component of a dynamic and stepwise lipid-lowering algorithm, in line with ESC/EAS recommendations.

Limitations

This study has several limitations: (i) its retrospective and single-center design may limit the applicability of the results to other settings; (ii) although the cohort was relatively large, the number of patients in certain subgroups (eg, FH or PCSK9 inhibitor users) was limited, potentially affecting the power of subgroup analyses. Third, adherence to BA and concomitant therapies was assessed through patient self-report during clinical visits, without objective measures such as pharmacy refill data or electronic monitoring, which may have introduced reporting bias and overestimated true adherence. Additionally, variability in follow-up duration and background LLT may have influenced the magnitude of LDL-cholesterol reduction observed.

CRediT authorship contribution statement

Chiara Pavanello: Writing – review & editing, Writing – original draft, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Giulia Cincotto:** Writing – review & editing, Data curation. **Giuliana Germana Mombelli:** Writing – review & editing, Investigation. **Sofia Castiglione:** Writing – review & editing, Investigation, Data curation. **Caterina Santolamazza:** Writing – review & editing, Investigation. **Laura Calabresi:** Writing – review & editing, Supervision, Funding acquisition. **Cesare Riccardo Sirtori:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Conceptualization. **Antonia Alberti:** Writing – review & editing, Supervision, Resources, Investigation.

Ethical approval

The study was notified to the Ethics Committee of the ASST Grande Ospedale Metropolitano Niguarda and conducted according to the 1975 Declaration of Helsinki (approval 612-11102022).

Declaration of generative AI and AI-assisted technologies in the writing process

Artificial intelligence tools (specifically, OpenAI) were used to improve the English language of this manuscript. The authors reviewed and approved all AI-assisted edits to ensure accuracy and appropriateness.

Funding

This work was supported by a funding by Fondazione Carlo Sirtori to CP. LC received funding by Pfizer Independent Grants (GA 70215089) and the Italian Ministry of Research and University (PRIN 2022JFCXH7).

Declaration of competing interest

CP, GC, SC, CS, LC, CRS declare that they have no conflict of interest with respect to this study.

GGM and AA have served as investigators in trials supported by Daiichi Sankyo.

References

1. Boekholdt SM, Hovingh GK, Mora S, et al. Very low levels of atherogenic lipoproteins and the risk for cardiovascular events: a meta-analysis of statin trials. *J Am Coll Cardiol*. 2014;64:485–494.
2. Nissen SE, Stroes E, Dent-Acosta RE, et al. Efficacy and tolerability of Evolocumab versus Ezetimibe in patients with muscle-related statin intolerance: the GAUSS-3 randomized clinical trial. *JAMA*. 2016;315:1580–1590.
3. Parker BA, Capizzi JA, Grimaldi AS, et al. Effect of statins on skeletal muscle function. *Circulation*. 2013;127:96–103.
4. Macchi C, Bonalume V, Greco MF, et al. Impact of atorvastatin on skeletal muscle mitochondrial activity, locomotion and axonal excitability-evidence from ApoE(-/-) mice. *Int J Mol Sci*. 2022;23:5415– 5431.
5. Cramer CT, Goetz B, Hopson KL, et al. Effects of a novel dual lipid synthesis inhibitor and its potential utility in treating dyslipidemia and metabolic syndrome. *J Lipid Res*. 2004;45:1289–1301.

6. Nissen SE, Lincoff AM, Brennan D, et al. Bempedoic acid and cardiovascular outcomes in statin-intolerant patients. *N Engl J Med*. 2023;388:1353–1364.
7. Pinkosky SL, Newton RS, Day EA, et al. Liver-specific ATP-citrate lyase inhibition by bempedoic acid decreases LDL-C and attenuates atherosclerosis. *Nat Commun*. 2016;7:13457.
8. Reddy JK, Goel SK, Nemali MR, et al. Transcription regulation of peroxisomal fatty acyl-CoA oxidase and enoyl-CoA hydratase/3-hydroxyacyl-CoA dehydrogenase in rat liver by peroxisome proliferators. *Proc Natl Acad Sci U S A*. 1986;83:1747–1751.
9. Bays HE, Bloedon LT, Lin G, et al. Safety of bempedoic acid in patients at high cardiovascular risk and with statin intolerance. *J Clin Lipidol*. 2024;18:e59–e69.
10. Averna M, Cefalu AB, Casula M, et al. Familial hypercholesterolemia: The Italian Atherosclerosis Society Network (LIPIGEN). *Atheroscler Suppl*. 2017;29:11–16.
11. Cheeley MK, Saseen JJ, Agarwala A, et al. 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.
12. Stone NJ. Statins in secondary prevention: intensity matters. *J Am Coll Cardiol*. 2017;69:2707–2709.
13. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J*. 2020;41:111–188.
14. Kronenberg F, Bedlington N, Ademi Z, et al. The Brussels International Declaration on Lipoprotein(a) Testing and Management. *Atherosclerosis*. 2025;406:119218.
15. Pinkosky SL, Filippov S, Srivastava RA, 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.
16. Goldberg AC, Leiter LA, Stroes ESG, et al. Effect of Bempedoic acid versus 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.
17. Rubino J, MacDougall DE, Sterling LR, Hanselman JC, Nicholls SJ. Combination of bempedoic acid, ezetimibe, and atorvastatin in patients with hypercholesterolemia: a randomized clinical trial. *Atherosclerosis*. 2021;320:122–128.
18. De Filippo O, D'Ascenzo F, Iannaccone M, et al. Safety and efficacy of bempedoic acid: a systematic review and meta-analysis of randomised controlled trials. *Cardiovasc Diabetol*. 2023;22:324.
19. Ray KK, Bays HE, Catapano AL, et al. Safety and efficacy of bempedoic acid to reduce LDL cholesterol. *N Engl J Med*. 2019;380:1022–1032.
20. Warden BA, Guyton JR, Kovacs AC, et al. Assessment and management of statin-associated muscle symptoms (SAMS): a clinical perspective from the National Lipid Association. *J Clin Lipidol*. 2023;17:19–39.
21. Warden BA, Cardiology BA, Purnell JQ, Duell PB, Fazio S. Real–world utilization of bempedoic acid in an academic preventive cardiology practice. *J Clin Lipidol*. 2022;16:94–103.
22. McCarron EP, Hamilton P, Roberts BV. Real world efficacy of bempedoic acid in statin-intolerant patients with high cardiovascular risk. *Atherosclerosis*. 2022;355:220.
23. Russo V, Ratti G, Parrella A, et al. Clinical utilization and performance of bempedoic acid in an Italian real-world setting: insight from Campania region. *J Clin Med*. 2025;14.
24. Cho L, Plutzky J, Brennan D, et al. Impact of bempedoic acid on cardiovascular outcomes by sex. *Circulation*. 2024;149:1775–1777.
25. Sirtori CR, Galli C, Franceschini G. Fraudulent (and non fraudulent) fatty acids for human health. *Eur J Clin Invest*. 1993;23:686–689.
26. Oniciu DC, Pop E, Dasseux JL, et al. Long hydrocarbon chain diols and diacids with central ether or ketone moieties that favorably alter lipid disorders. *Pharmazie*. 2006;61:157–165.
27. Butera E, Termite F, Esposto G, et al. Exploring the role of bempedoic acid in metabolic dysfunction associated steatotic liver disease: actual evidence and future perspectives. *Int J Mol Sci*. 2024:25.
28. Liu JY, Kuna RS, Pinheiro LV, et al. Bempedoic acid suppresses diet-induced hepatic steatosis independently of ATP-citrate lyase. *Cell Metab*. 2025;37:239–254.e237.
29. Samsoondar JP, Burke AC, Sutherland BG, et al. Prevention of diet-induced metabolic dysregulation, inflammation, and atherosclerosis in Ldlr(-/-) mice by treatment with the ATP-citrate lyase inhibitor bempedoic acid. *Arterioscler Thromb Vasc Biol*. 2017;37:647–656.
30. Sirtori CR, Castiglione S, Pavanello C. Metformin: From diabetes to cancer to prolongation of life. *Pharmacol Res*. 2024;208:107367.
31. Xiang W, Lv H, Xing F, et al. Inhibition of ACLY overcomes cancer immunotherapy resistance via polyunsaturated fatty acids peroxidation and cGAS-STING activation. *Sci Adv*. 2023;9:eadi2465.
32. Kim CW, Addy C, Kusunoki J, et al. Acetyl CoA carboxylase inhibition reduces hepatic steatosis but elevates plasma triglycerides in mice and humans: a bedside to bench investigation. *Cell Metab*. 2017;26:394–406.e396.
33. Wang Q, Li S, Jiang L, et al. Deficiency in hepatic ATP-citrate lyase affects VLDL-triglyceride mobilization and liver fatty acid composition in mice. *J Lipid Res*. 2010;51:2516–2526.
34. Kuwahara N, Nagao M, Shinohara M, et al. ACLY promotes cardiac fibrosis via the regulation of DNL and histone acetylation. *Hypertension*. 2025;82:1116–1128.
35. Hallows KR, Li H, Saitta B, et al. Beneficial effects of bempedoic acid treatment in polycystic kidney disease cells and mice. *Front Mol Biosci*. 2022;9:1001941.

Please cite this article as: Pavanello et al., Clinical implementation of bempedoic acid in blood lipid management: Real-world data from an Italian lipid clinic, Journal of Clinical Lipidology, https://doi.org/10.1016/j.jacl.2025.09.033