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Pleiotropic effects of bempedoic acid on endothelial function and arterial stiffness: a preliminary study

Angelica Cersosimo*, Riccardo Rovelli*, Andrea Drera, Elio Gorga, Elisa Brangi, Marco Metra and Enrico Vizzardi

Background Bempedoic acid is a novel lipid-lowering agent that reduces circulating low- density lipoprotein cholesterol (LDL) levels by inhibiting ATP citrate lyase, a key enzyme upstream of HMG-CoA reductase. While other lipid-lowering therapies such as statins and PCSK9 inhibitors have demonstrated pleiotropic vascular benefits, including improvements in endothelial function and aortic stiffness, these effects have not been thoroughly evaluated for bempedoic acid in clinical settings.

Methods This observational, longitudinal, single-center study enrolled statin-intolerant patients eligible for bempedoic acid therapy based on predefined clinical criteria.

The enrollment period spanned April 2023 to September 2024. The study's primary endpoints were the consistency and extent of LDL reduction after 3 months of therapy, and the effect of bempedoic acid on vascular function parameters. Endothelial function was assessed using the Reactive Hyperemia Index (RHI) via peripheral arterial tonometry (EndoPAT), while aortic stiffness was evaluated using pulse wave velocity (PWV), measured with the SphygmoCor system. Baseline measurements were compared with follow-up values at 3 months.

Results Seventy-five patients with hypercholesterolemia (mean age 71.4 ± 7.9 years; 60% men) were enrolled. At 3-month follow-up, bempedoic acid had significantly improved the lipid parameters: LDL decreased from 157.6 ± 19.2 to 77.4 ± 24.9 mg/dl (Δ = −80.2 ± 36.4, $P < 0.001$), HDL increased from 50 ± 9.2 to 54 ± 8.8 mg/dl (Δ = +4 ± 2.3, $P < 0.001$), triglycerides decreased from 160.8 ± 26.6 to 77.6 ± 14.9 mg/dl (Δ = −83.2 ± 30.9, $P < 0.001$), and total cholesterol from 239 ± 21 to 145 ± 39 mg/dl (Δ = −94 ± 45, $P < 0.001$). Endothelial function (RHI), improved from 1.36 ± 0.47 to 1.77 ± 0.40 (Δ = +0.41 ± 0.6, $P < 0.001$), and arterial stiffness (PWV) decreased from 10.1 ± 1.21 to 9.2 ± 1.26 m/s (Δ = −0.9 ± 0.4, $P < 0.001$). Correlation analysis showed that ΔRHI was inversely associated with ΔLDL reduction ($r = -0.391$, $P = 0.001$) and ΔTC reduction ($r = -0.359$, $P = 0.002$), and positively associated with HDL increase ($r = 0.367$, $P = 0.001$). Similarly, ΔPWV correlated positively with ΔLDL ($r = 0.260$, $P = 0.024$) and ΔTC reductions ($r = 0.342$, $P = 0.003$), and inversely with HDL increase ($r = -0.423$, $P < 0.001$). No significant changes in creatinine, uric acid, or glycemic parameters were observed, supporting the short-term safety of bempedoic acid.

Conclusion Bempedoic acid therapy significantly improved endothelial function and reduced arterial stiffness, in parallel with lipid profile improvement. These vascular benefits were achieved without adverse changes in renal function or uric acid levels, supporting the efficacy and short-term safety of bempedoic acid as a therapeutic option, particularly for statin-intolerant patients.

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Introduction

Oxidative stress and associated endothelial dysfunction, marked by reduced nitric oxide bioavailability due to endothelial nitric oxide synthase (eNOS) uncoupling and downregulation, have been implicated in the development and progression of arterial stiffness.[1] Clinically, endothelial dysfunction manifests as a diminished vasodilatory response to acetylcholine, a hallmark of early vascular impairment.[2] Arterial stiffness, now routinely assessed through noninvasive techniques such as pulse wave velocity (PWV), reflects the speed of pulse wave propagation along the arterial wall, which increases with greater vascular rigidity.[3] As such, PWV is widely recognized as a surrogate marker of vascular aging and is independently associated with major cardiovascular risk factors.[4] Aortic PWV, in particular, represents an integrated marker of cumulative vascular risk. With advancing age and repeated hemodynamic stress, elastic fibers within the arterial wall undergo progressive degradation and fragmentation, leading to vascular dilation and reduced compliance.[5] Recent

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models suggest that age-related arterial stiffening also involves dynamic intracellular ionic alterations, notably increased cytosolic calcium and decreased magnesium, which contribute independently to vascular smooth muscle tone and stiffness.[6] These changes predominantly affect elastic arteries (i.e. aorta and carotids), more so than muscular peripheral arteries, ultimately leading to a reversal of the normal central-to-peripheral stiffness gradient.[7] This gradient reversal disrupts the timing and efficiency of pulse wave reflection and contributes to elevated systolic pressure and increased cardiac workload. Among noninvasive measures, carotid–femoral PWV (cfPWV) remains the gold standard for assessing aortic stiffness.[7] Large-scale epidemiological studies have confirmed that PWV is an independent predictor of cardiovascular events, beyond traditional risk factors such as blood pressure, lipid profile, and glycemic status.[7,8] Indeed, increased arterial stiffness plays a central pathophysiological role in the progression of systolic hypertension, impaired coronary perfusion, and microvascular damage.[1] These alterations collectively lead to increased cardiovascular morbidity and mortality.[5] Furthermore, pro-inflammatory mediators and free fatty acids released by visceral adipose tissue, including interleukin-6, interleukin-1, and plasminogen activator inhibitor-1, contribute to atherosclerosis and endothelial dysfunction, both of which further promote arterial stiffness.[9]

In the contemporary management of dyslipidemia, residual cardiovascular risk persists despite optimal lipid lowering, partly driven by inflammatory pathways and endothelial dysfunction. In this context, therapeutic strategies targeting both lipid and inflammatory residual risk have gained increasing attention, particularly in patients with established coronary artery disease or those undergoing percutaneous coronary intervention, where persistent vascular inflammation contributes to adverse outcomes.[10] Recent evidence has highlighted the emerging role of nonstatin lipid-lowering therapies in improving cardiovascular risk profiles beyond LDL reduction alone, especially in statin-intolerant patients or in those requiring additional lipid lowering despite guideline-directed therapy.[11,12]

Bempedoic acid is a novel therapeutic agent recently approved for the treatment of hypercholesterolemia.[12,13] By inhibiting ATP citrate lyase (ACLY), an enzyme upstream of β-hydroxy β-methylglutaryl-CoA (HMG-CoA) reductase in the cholesterol biosynthesis pathway, bempedoic acid reduces hepatic acetyl-CoA availability, leading to decreased low-density lipoprotein (LDL) production and upregulation of LDL receptors.[11] In addition to its lipid-lowering effects, bempedoic acid activates AMP-activated protein kinase (AMPK), a central regulator of energy homeostasis, oxidative stress, and inflammation.[14] Preclinical data suggest that AMPK activation by bempedoic acid enhances endothelial function, reduces oxidative injury, and attenuates vascular remodeling.[15] Moreover, bempedoic acid also modulates inflammatory pathways by inhibiting monocyte activation and downregulating MAPK signaling, while reducing prostaglandin E2 synthesis through ACLY inhibition.[16]

Despite this promising mechanistic profile, the vascular bempedoic acid effects in humans remain largely unexplored. This study aims to evaluate the impact of bempedoic acid on PWV and endothelial function, as assessed by the Reactive Hyperemia Index (RHI) and PWV, in patients with hypercholesterolemia.

Materials and methods

Population of the study

The study was conducted from April 2023 to September 2024 at the Cardiology Department of Spedali Civili in Brescia.

A total of 75 patients with a confirmed diagnosis of hypercholesterolemia were enrolled in the study. Inclusion criteria comprised: Caucasian ethnicity; age at least 18 years; diagnosis of hypercholesterolemia as defined by current clinical guidelines[17]; no prior exposure to bempedoic acid; documented statin intolerance or patient refusal to initiate statin-based therapy. Exclusion criteria were: non-Caucasian ethnicity; age under 18 years; chronic renal failure stage V [estimated glomerular filtration rate (eGFR) < 15 ml/min/m^3], rheumatological or orthopedic diseases of the upper limbs that could interfere with the use of peripheral arterial tonometry (EndoPAT) or evaluation of arterial stiffness (SphygmoCor CvMS system, AtCor Medical, Sydney, Australia), homozygous familial hypercholesterolemia, pregnancy, prior bempedoic acid use, and acute coronary syndrome (ACS).

Demographic, clinical, and pharmacological data at the initiation of bempedoic acid therapy were collected from medical records.

Ethical approval was granted by the local ethics committee, and all participants provided written informed consent before enrollment.

Study design

This was a prospective, longitudinal, observational, single-center clinical study. All enrolled patients underwent instrumental assessments of endothelial function and arterial stiffness at baseline and after a 3-month follow-up period. Lipid profiles were evaluated both at the initiation of bempedoic acid therapy and at the follow-up visit.

Specifically, the study protocol included the following procedures performed at both time points: blood pressure

measurement, peripheral arterial tonometry (PAT) for the assessment of endothelial function, applanation tonometry for the evaluation of arterial stiffness, and fasting blood tests for comprehensive lipid panel analysis.

Blood pressure measurement

Blood pressure assessment was performed using an aneroid sphygmomanometer following the European Society of Hypertension (ESH) guidelines.[18] Hypertension was defined according to the European Society of Cardiology guidelines.[19]

Patients were seated comfortably and left to rest for 5 minutes in a quiet environment at a stable, comfortable room temperature. Subsequently, an appropriately sized cuff was placed above the antecubital fossa, with the arm extended and positioned at heart level. The procedure was then repeated on the contralateral arm to rule out any potential peripheral arterial disease.

Peripheral arterial tonometry

Endothelial function was assessed using the EndoPAT 2000 device (Itamar Medical Ltd, Israel), a noninvasive, operator-independent, and automated system designed to evaluate microvascular endothelial function. The technique measures reactive hyperemia-induced changes in digital pulse volume amplitude via finger-mounted pneumatic sensors connected to a computer-based analysis platform. This method provides a standardized and reproducible RHI, and has been previously described.[20]

Applanation tonometry

The noninvasive assessment of aortic stiffness parameters was performed using applanation tonometry with the SphygmoCor CvMS system (AtCor Medical, Sydney, Australia).

This technique involves applying a Millar tonometer over the artery of interest, allowing a digital recording of the pulse wave over a 10-s interval. The device's software automatically analyzes the waveform to calculate indices related to aortic stiffness. Prior to the measurement, patient-specific data, including weight (in kilograms), height (in centimeters), date of birth, sex, and SBP and DBP, are entered into the software. In the first phase of the procedure, pulse wave analysis (PWA) is performed by placing the tonometer on the right radial artery for 10 s, obtaining the corresponding pressure waveform. In the second phase, the PWV is measured. The distance used to calculate the aortic transit time is estimated by measuring, with a standard measuring tape, the length in millimeters between the carotid pulse site and the sternal notch, and then from the sternal notch to the femoral pulse site. These values are entered into the software to approximate the surface projection of the aortic path. Electrodes are then applied to record an ECG, which is used to time-align the pressure waveforms obtained at the two arterial sites.[21]

Statistical analysis

The normality of distribution of the parameters was assessed by using the Kolmogorov–Smirnov test. Continuous variables with Gaussian distribution were reported as mean ± standard deviation and compared by using the Student's *t*-test, whereas variables with nonnormal distribution were reported as median [interquartile range] and compared by using the Mann–Whitney *U* test.

Categorical variables are presented as number (percentage) and comparisons were made with Fisher's exact test when the expected frequency was below 5, otherwise the chi squared test (Yates corrected). A Pearson's correlation analysis was conducted to evaluate the association between changes in endothelial function (ΔRHI) and arterial stiffness (ΔPWV) with changes in lipid parameters (Δ cholesterol values) over the 3-month follow-up period.

A *P* value less than 0.05 in two-sided tests was considered statistically significant.

Statistical analysis was performed using SPSS (version 25, IBM Corp., Armonk, New York, USA).

Results

Total population characteristics

The study population included 75 patients with hypercholesterolemia, with a mean age of 71.4 ± 7.9 years. The cohort exhibited a high burden of cardiovascular risk factors: 100% had dyslipidemia, 69% were hypertensive, 37% had established coronary artery disease, and 12% had diabetes mellitus. The mean BMI was 26.0 ± 4.3 kg/m^2. the average SBP and DBP were 125.7 ± 13.9 and 71.2 ± 10.5 mmHg, respectively. The mean heart rate was 67 ± 11 bpm, and 27% of patients were active smokers. Laboratory evaluation showed preserved renal function, with a mean serum creatinine of 1.04 ± 0.3 mg/dl and an eGFR of 65.8 ± 17.2 ml/min/1.73 m^2. the hemoglobin levels averaged 12.8 ± 1.6 g/dl, while the fasting glucose and HbA1c values were 92 mg/dl [84–102] mg/dl and 5.8 ± 0.5%, respectively. Echocardiographic data indicated preserved systolic function with a median ejection fraction of 56% [54–60], normal chamber dimensions (EDD: 47 mm [44–52]), and a median left atrial volume index (LAVi) of 30 ml/m^2 [26–40]. Diastolic parameters and pulmonary pressures were within normal range. Mild-to-moderate mitral and tricuspid regurgitation were common, but no patients exhibited severe valvular disease. Regarding pharmacological therapy, 72% were treated with aspirin, 32% with

P2Y12 inhibitors, and 21% received dual antiplatelet therapy (DAPT). Beta-blockers were prescribed in 71% of cases, ACE inhibitors or ARBs in 89%, and SGLT2 inhibitors in 33%.

Sex-based population characteristics

Among the total population, 60% ($n=45$) were men and 40% ($n=30$) were women. There were no significant differences in age between the sexes (71.1 ± 8.1 vs. 71.9 ± 7.7 years, $P=0.667$). However, the men were significantly taller (169 ± 0.1 vs. 163 ± 0.1 cm, $P=0.005$) and heavier (75.1 ± 12.1 vs. 68.0 ± 15.9 kg, $P=0.032$). Creatinine levels were higher in men (1.1 ± 0.3 vs. 0.94 ± 0.2 mg/dl, $P=0.013$), although eGFR was not significantly different.

No sex-related differences were observed in blood pressure, heart rate, smoking status, or major comorbidities such as coronary artery disease, diabetes, or atrial fibrillation.

Notably, women had a significantly larger left atrial volume index (LAVi: 37 [29–41] vs. 29 [26–32] ml/m^2, $P=0.002$), and a trend toward higher right ventricular systolic velocities (right ventricular S': 13 [12–14] vs. 12 [10–12] cm/s, $P=0.055$).

Pharmacological treatments were largely comparable between the sexes, with no statistically significant differences in the use of antiplatelet agents, beta-blockers, or renin-angiotensin system inhibitors. Table 1 summarizes the baseline characteristics.

Lipid profile

At the 3-month follow-up, bempedoic acid treatment was associated with a significant and consistent improvement in the lipid panel profile across the total population (Table 2).

The LDL levels decreased markedly from a baseline of 157.6 ± 19.2 to 77.4 ± 24.9 mg/dl, corresponding to a mean absolute reduction of -80.2 ± 36.4 mg/dl ($P<0.001$). The high-density lipoprotein cholesterol (HDL) levels increased significantly from 50 ± 9.2 to 54 ± 8.8 mg/dl (Δ: $+4 \pm 2.3$ mg/dl, $P<0.001$). Triglycerides were also significantly reduced, decreasing from 160.8 ± 26.6 to 77.6 ± 14.9 mg/dl, with a mean change of -83.2 ± 30.9 mg/dl ($P<0.001$).

Similarly, total cholesterol (TC) dropped from 239 ± 21 to 145 ± 39 mg/dl (Δ: -94 ± 45 mg/dl, $P<0.001$).

Laboratory parameters

In addition to lipid assessment, a panel of routine blood tests was performed to evaluate the short-term safety and tolerability of bempedoic acid (Table 3). No clinically relevant alterations in hepatic, renal, or glycemic parameters were observed over the 3-month period. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) showed modest, nonsignificant increases (ALT: from 20 ± 8 to 24 ± 9 U/l, $P=0.120$; AST: from 23 ± 7 to 25 ± 8 U/l, $P=0.354$). Total bilirubin rose slightly from 0.45 [0.29–0.65] to 0.58 [0.42–0.81] mg/dl ($P=0.208$). Glycemic control remained unchanged, with HbA1c stable at 5.8 ± 0.5 vs. 5.7 ± 0.6% ($P=0.829$), and uric acid levels showed a nonsignificant trend toward increasing (5.9 ± 0.6–6.2 ± 0.7 mg/dl, $P=0.064$).

These findings indicate that bempedoic acid exerted substantial effects on lipid metabolism without significantly altering hepatic enzymes, glycemic status, or uric acid levels over the short-term observation period.

Endothelial function and arterial stiffness

Over the 3-month follow-up period (mean days 96 ± 3), a significant improvement in both endothelial function and arterial stiffness was observed in the overall study cohort ($n=75$). RHI, as assessed by PAT, significantly increased from a baseline value of 1.36 ± 0.47 to 1.77 ± 0.40 at 3 months (ΔRHI: $+0.41 \pm 0.5$, $P<0.001$), indicating a substantial enhancement in microvascular endothelial function (Table 4).

In parallel, PWV, measured via applanation tonometry, demonstrated a significant reduction, reflecting improved arterial compliance. The mean PWV decreased from 10.1 ± 1.21 m/s at baseline to 9.2 ± 1.26 m/s at 3 months (ΔPWV: -0.9 ± 0.4 m/s, $P<0.001$) (Table 5).

Correlation between changes in endothelial function and lipid profile

In the total study population, changes in RHI over the 3-month follow-up were significantly associated with modifications in specific lipid fractions. A robust inverse correlation was observed between ΔRHI and ΔLDL ($r=-0.391$, $P=0.001$), indicating that greater LDL reductions were linked to more pronounced improvements in endothelial function. Similarly, ΔRHI showed a significant inverse correlation with ΔTC ($r=-0.359$, $P=0.002$), indicating that larger reductions in TC paralleled greater endothelial function gains.

Conversely, ΔRHI demonstrated a significant positive correlation with ΔHDL ($r=0.367$, $P=0.001$), suggesting that increases in HDL were also associated with enhanced endothelial responsiveness. No significant relationship emerged between ΔRHI and changes in triglyceride levels ($r=-0.059$, $P=0.615$) (Table 6 and Fig. 1).

Table 1 Baseline population characteristics

	Total population = 75	Male = 45	Female = 30	*P*
General characteristics				
Age (years)	71.4 ± 7.9	71.1 ± 8.1	71.9 ± 7.7	0.667
Height (cm)	166 ± 0.1	169 ± 0.1	163 ± 0.1	**0.005**
Weight (kg)	72.2 ± 13.9	75.1 ± 12.1	68 ± 15.9	**0.032**
BMI (kg/m^2)	26 ± 4.3	26.5 ± 4	25.4 ± 4.6	0.310
SBP (mmHg)	125.7 ± 13.9	125 ± 13.7	126.8 ± 14.7	0.600
DBP (mmHg)	71.2 ± 10.5	71.4 ± 10.9	70.9 ± 10.2	0.871
HR (bpm)	67 ± 11	66 ± 12	70 ± 10	0.151
Smoker, *n* (%)	20 (27)	14 (31)	6 (20)	0.069
Dyslipidemia, *n* (%)	75 (100)	45 (100)	30 (100)	1
Diabetes, *n* (%)	9 (12)	3 (6)	6 (20)	0.082
Hypertension, *n* (%)	52 (69)	32 (71)	20 (66)	0.683
Coronary artery disease, *n* (%)	28 (37)	17 (37)	11 (37)	0.922
Prior myocardial infarction, *n* (%)	6 (8)	19 (42)	19 (63)	0.918
Peripheral artery disease, *n* (%)	5 (7)	3 (6)	2 (6)	1
Atrial fibrillation, *n* (%)	11 (15)	4 (8)	7 (23)	0.105
CKD, *n* (%)	5 (7)	4 (8)	1 (3)	0.345
COPD, *n* (%)	16 (21)	9 (20)	7 (23)	0.730
Blood tests				
Hb (g/dl)	12.8 ± 1.6	12.7 ± 1.6	12.9 ± 1.6	0.763
PLT (10_3/μl)	222 ± 60	216 ± 59	231 ± 62	0.296
Creatinine (mg/dl)	1.04 ± 0.3	1.1 ± 0.3	0.94 ± 0.2	**0.013**
eGFR (ml/min/m^3)	65.8 ± 17.2	64.3 ± 18.6	68.3 ± 14.9	0.351
Na (mEq/l)	140.9 ± 3.3	140.8 ± 3.2	141.2 ± 3.4	0.647
K (mEq/l)	4.4 ± 0.5	4.4 ± 0.5	4.4 ± 0.4	0.856
ALT (U/l)	20 ± 8	20.2 ± 9	19.7 ± 7.4	0.818
AST (U/l)	23 ± 7	25 ± 7.5	21 ± 6.5	0.058
Total bilirubin (mg/dl)	0.45[0.29–0.65]	0.45 [0.31–0.50]	0.47 [0.27–0.75]	0.691
Fasting blood glucose (mg/dl)	92 [84–102]	95 [85–104]	91 [83–98]	0.308
HbA1c (%)	5.8 ± 0.5	5.8 ± 0.6	5.7 ± 0.4	1
Uric acid (mg/dl)	5.9 ± 0.6	5.9 ± 0.5	5.9 ± 0.7	0.783
Echocardiography parameters				
EDD (mm)	47 [44–52]	50 [44–52]	45 [43–50]	0.046
EF (%)	56 [54–60]	56 [54–60]	56 [54–60]	**0.991**
E/A	0.8 [0.6–1.2]	0.7 [0.6–1.1]	0.8 [0.6–1.2]	0.609
E/E	9.6 [7.6–10.5]	9.9 [8.2–10.5]	9.3 [7.6–10.5]	0.207
MR grade, *n* (%)	75 (100)	45 (100)	30 (100)	0.368
None	12 (16)	7 (16)	5 (16)	
Mild	33 (44)	18 (40)	15 (50)	
Moderate	30 (40)	20 (26)	10 (33)	
LAVi (ml/m^2)	30[26–40]	29[26–32]	37 [29–41]	**0.002**
TAPSE (mm)	22[20–24]	22[20–24]	23[20–24]	0.245
RV S' (cm/s)	12[11–13]	12[10–12]	13[12–14]	0.055
PASP (mmHg)	27 ± 6	27 ± 5	28 ± 7	0.794
TR grade, *n* (%)	75 (100)	45 (100)	30 (100)	0.239
None	5 (6)	3 (6)	2 (6)	
Mild	40 (53)	22 (48)	18 (60)	
Moderate	30 (40)	20 (26)	10 (33)	
Massive	0 (0)	0 (0)	0 (0)	
Torrential	0 (0)	0 (0)	0 (0)	
AR grade, *n* (%)	75 (100)	45 (100)	30 (100)	0.133
None	65 (87)	37 (82)	28 (93)	
Mild	10 (13)	8 (18)	2 (6) 0 (0)	
Moderate	0 (0)	0 (0)		
Drugs therapy				
Anticoagulant, *n* (%)	11 (15)	6 (13)	5 (16)	0.689
Aspirin, *n* (%)	54 (72)	33 (73)	21 (70)	0.753
P2Y12, *n* (%)	24 (32)	15 (33)	9 (30)	0.762
DAPT, *n* (%)	16 (21)	10 (22)	6 (20)	0.818
PPI, *n* (%)	57 (76)	35 (77)	22 (73)	0.659
Beta-blocker, *n* (%)	53 (71)	31 (68)	22 (73)	0.679
Calcium channel blocker, *n* (%)	9 (12)	6 (13)	3 (10)	0.663
ACEi/ARB, *n* (%)	67 (31)	38 (84)	29 (97)	0.345
SGLT2i, *n* (%)	13 (17)	8 (18)	5 (16)	0.167

Values are expressed as mean ± standard deviation or median [interquartile range].ACEi, ACE inhibitor; ALT, alanine transaminase; AR, aortic regurgitation; ARB, angiotensin receptor blocker; AST, aspartate transaminase; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DAPT, dual antiplatelet therapy; EDD, end-diastolic diameter; EF, ejection fraction; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; HbA1c, glycated hemoglobin; HR, heart rate; LAVi, left atrial volume index; MR, mitral regurgitation; PASP, pulmonary artery systolic pressure; PLT, platelet; PPI, proton pump inhibitors; RV, right ventricle; SGLT2i, sodium-glucose cotransporter-2 inhibitors; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

Table 2 Changes in lipid profile

Lipid panel profile	Baseline	3 months	ΔValues	P
LDL (mg/dl)	157.6 ± 19.2	77.4 ± 24.9	−80.2 ± 36.4	**<0.001**
HDL (mg/dl)	50 ± 9.2	54 ± 8.8	4 ± 2.3	**<0.001**
TG (mg/dl)	160.8 ± 26.6	77.6 ± 14.9	−83.2 ± 30.9	**<0.001**
TC (mg/dl)	239 ± 21	145 ± 39	−94 ± 45	**<0.001**

Values are expressed as mean ± standard deviation.HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

Table 3 Blood test variations

Blood tests	Baseline	3 months	P
ALT (U/l)	20 ± 8	24 ± 9	0.120
AST (U/l)	23 ± 7	25 ± 8	0.354
Total bilirubin (mg/dl)	0.45 [0.29–0.65]	0.58 [0.42–0.81]	0.208
HbA1c (%)	5.8 ± 0.5	5.7 ± 0.6	0.829
Uric acid (mg/dl)	5.9 ± 0.6	6.2 ± 0.7	0.064

Values are expressed as mean ± standard deviation or median [interquartile range]ALT, alanine transaminase; AST, aspartate transaminase; HbA1c, glycated hemoglobin.

Table 4 Reactive Hyperemia Index variation in general population

Total population	RHI basal	RHI at 3 months	ΔRHI basal at 3 months	P
	1.36 ± 0.47	1.77 ± 0.40	0.41 ± 0.6	<0.001

Values are expressed as mean ± standard deviationRHI, Reactive Hyperemia Index.

Table 5 Pulse wave velocity variation in general population

Total population	PWV basal	PWV at 3 months	ΔPWV basal at 3 months	P
	10.1 ± 1.21	9.2 ± 1.26	0.9 ± 0.4	<0.001

Values are expressed as mean ± standard deviation.PWV, pulse wave velocity.

Correlation between changes in arterial stiffness and lipid parameters

For arterial stiffness, assessed by changes in ΔPWV, a significant positive correlation was observed for ΔLDL ($r = 0.260$, $P = 0.024$) and ΔTC ($r = 0.342$, $P = 0.003$), indicating that larger reductions in these lipid fractions were associated with greater decreases in arterial stiffness. ΔHDL exhibited a strong inverse correlation with ΔPWV ($r = -0.423$, $P < 0.001$), suggesting that increases in HDL were linked to reductions in PWV, reflecting improved vascular compliance. ΔTG was not significantly correlated with ΔPWV ($r = 0.042$, $P = 0.722$) (Table 7 and Fig. 2).

Table 6 Correlation between endothelial function and lipid profile

ΔRHI correlation	r	P
ΔLDL	−0.391	**0.001**
ΔHDL	0.367	**0.001**
ΔTG	−0.059	0.615
ΔTC	−0.359	**0.002**

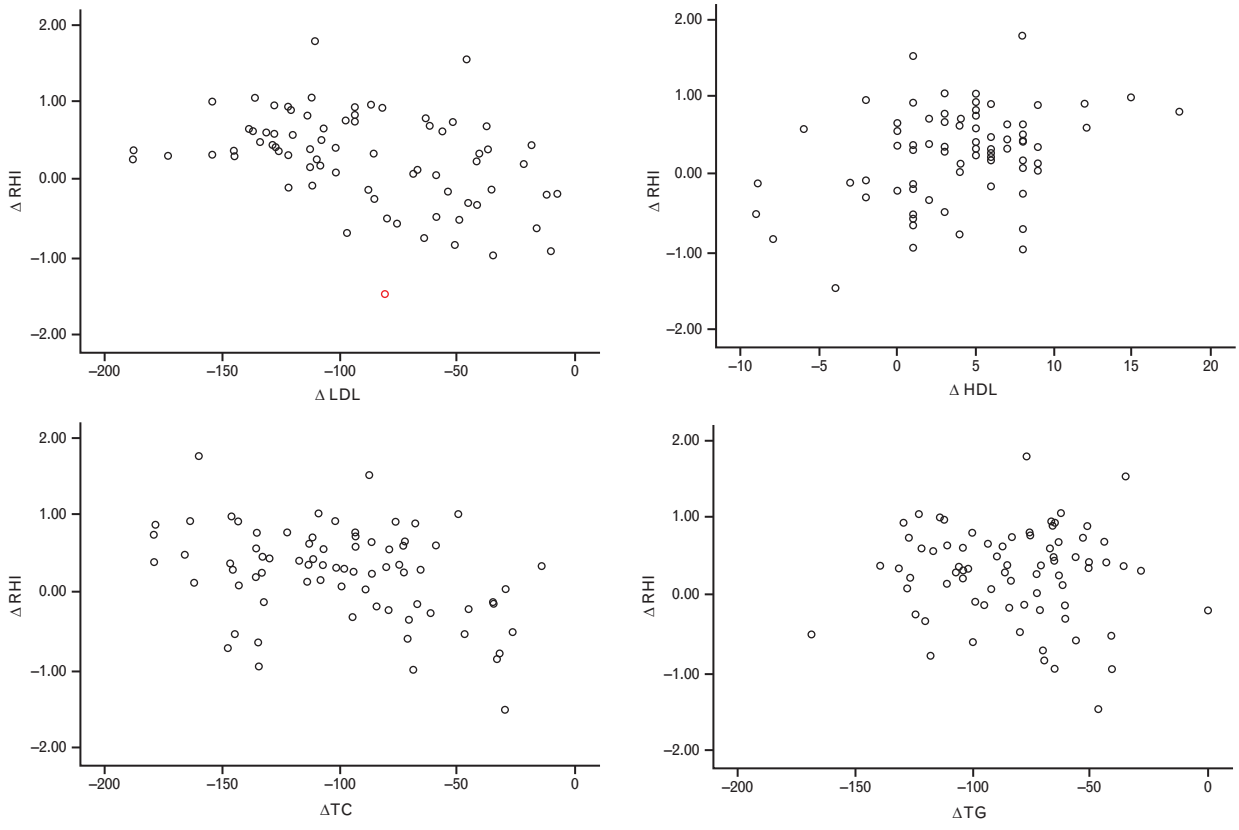
HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; RHI, reactive hyperemia index; TC, total cholesterol; TG, triglycerides. Overall, ΔRHI appears significantly associated with changes in LDL, HDL, and total cholesterol, but not with triglycerides.

Discussion

To the best of our knowledge, this is the first study to report the potential effects of bempedoic acid on endothelial function and arterial stiffness in patients with hypercholesterolemia.

Data from this longitudinal, observational, single-center investigation demonstrated that a 3-month course of bempedoic acid was sufficient to yield significant improvements in both endothelial dysfunction and arterial stiffness. Moreover, changes in RHI and PWV were correlated with

Fig. 1



Correlation between Reactive Hyperemia Index and lipid profile. HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; RHI, Reactive Hyperemia Index; TC, total cholesterol; TG, triglycerides.

favorable modifications in the lipid profile, namely LDL reduction and HDL increase.

The effects of bempedoic acid have been extensively evaluated in the phase III CLEAR (Cholesterol Lowering via Bempedoic Acid, an ACL-Inhibiting Regimen) program, which includes five pivotal trials: CLEAR Harmony,[13] CLEAR Wisdom,[22] CLEAR Serenity,[23] CLEAR Tranquility,[24] and CLEAR Outcome.[25] The latter enrolled 6992 statin-intolerant patients treated with bempedoic acid and 6978 placebo recipients, showing a 21.1% greater LDL-C reduction in the bempedoic acid arm, together with a significant reduction in major cardiovascular events.[25]

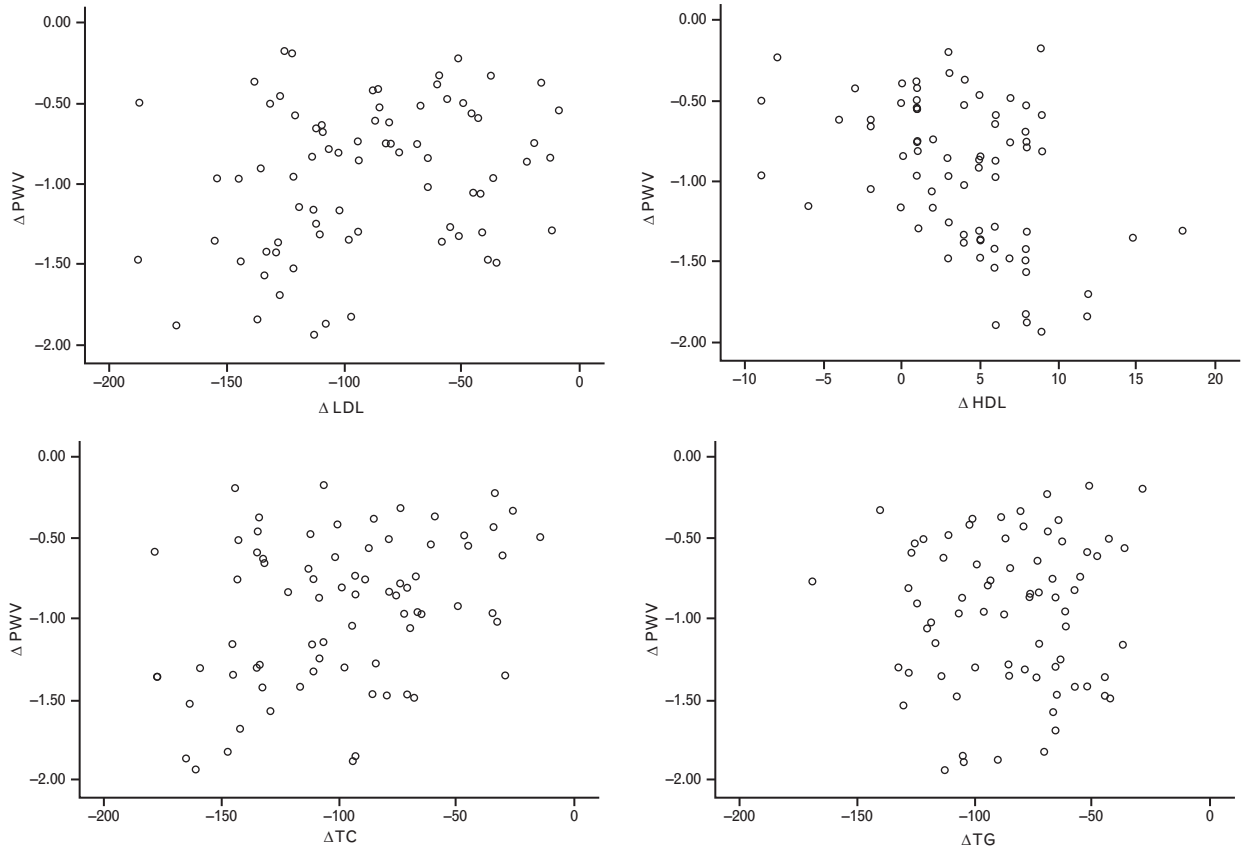
Moreover, a recent meta-analysis[26] confirmed the ability of bempedoic acid to lower LDL by 20.4% overall, with greater efficacy in lipid-lowering naive individuals (24.5%) compared with those already on maximal statin therapy (17.8%). The same analysis reported a reduction in cardiovascular events of between 11 and 21%, and suggested anti-inflammatory potential, as indicated by decreased plasma C-reactive protein (CRP) levels.[26] Our present findings align with these reports. In detail, we observed substantial LDL reductions, consistently with prior literature, along with improved vascular function. Mechanistically, bempedoic acid has been shown to maintain vascular integrity and counteract remodeling by inhibiting the ERK/TGF-β fibrotic pathway.[27] The improvement in RHI in our cohort correlated linearly with LDL reduction, suggesting a lipid-driven vascular benefit. However, experimental evidence points to additional pleiotropic effects: bempedoic acid may activate AMPK, enhancing eNOS activity and nitric oxide bioavailability, while also inhibiting gluconeogenesis via downregulation of G6Pase and

Table 7 Correlation between lipid profile and arterial stiffness

ΔPWV correlation	*r*	*P*
ΔLDL	0.260	0.024
ΔHDL	−0.423	<0.001
ΔTG	0.042	0.722
ΔTC	0.342	0.003

HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; PWV, pulse wave velocity; TC, total cholesterol; TG, triglycerides.

Fig. 2



Correlation between lipid profile and pulse wave velocity. HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; PWV, pulse wave velocity; TC, total cholesterol; TG, triglycerides.

PEPCK.[14] These actions may contribute to endothelial improvement independently of LDL lowering, mirroring early observations with statins. Furthermore, bempedoic acid has demonstrated the ability to suppress vascular smooth muscle cell proliferation and differentiation, processes central to hypertension, stiffness, and atherosclerosis, via AMPK signaling.[28] In our study, PWV reduced significantly, though the magnitude may have been tempered by relatively low baseline stiffness values, as greater changes are typically observed in individuals with higher initial PWV.

Although the observed improvements in endothelial function and arterial stiffness were statistically significant, their clinical interpretation requires careful consideration. The reduction in PWV of approximately 0.9 m/s over a relatively short follow-up period is notable; however, part of this change may reflect physiological variability or measurement-related factors, particularly in a population with relatively modest baseline PWV values.

Similarly, the increase in RHI from 1.36 to 1.77 suggests a shift toward improved endothelial responsiveness, yet this change should be interpreted in light of known intra-individual variability and the influence of autonomic tone, environmental conditions, and short-term physiological fluctuations on EndoPAT-derived measurements.

Furthermore, lifestyle modifications following therapy initiation, including changes in diet, physical activity, or treatment adherence, cannot be entirely excluded as contributing factors to vascular improvement in this observational setting. Therefore, while the parallel improvement in lipid parameters and vascular indices supports a biologically plausible association, causality cannot be established.

From a safety perspective, bempedoic acid was well tolerated. No significant increases in serum uric acid or creatinine levels were observed. This is clinically relevant, as elevated uric acid is implicated in endothelial dysfunction and hypertension through increased systemic vascular resistance and reduced nitric oxide bioavailability.[29]

Although statins, or β-hydroxy β-methylglutaryl-CoA (HMG-CoA) reductase inhibitors, are considered the first-line therapy for dyslipidemia due to their proven efficacy in lowering LDL and reducing cardiovascular events,[17] their use can be limited by adverse effects, including rhabdomyolysis, hepatic dysfunction, renal impairment, and other intolerance-related symptoms.[30] Therefore, given that endothelial dysfunction and arterial stiffness are early, potentially reversible hallmarks of atherosclerosis, the vascular improvements observed in this study, accompanying significant lipid profile changes, suggest that bempedoic acid may have a meaningful role not only in lipid management but also in broader vascular protection and long-term cardiovascular risk reduction with a safety profile.

Limitations

This study has several limitations that should be acknowledged. First, the observational, single-center design introduces an inherent risk of selection bias and limits the external validity of the findings, particularly with respect to different ethnic populations, healthcare systems, and clinical practice settings. Second, the relatively small sample size and the absence of an a priori power calculation for vascular endpoints may limit statistical robustness, particularly for subgroup analyses and correlation assessments, and preclude causal inference.

Third, the lack of a control group prevents differentiation between treatment-related effects and spontaneous variability over time. Measurements of endothelial function using PAT, although operator-independent, are known to be influenced by autonomic tone, environmental conditions, and short-term physiological variability, which may partially contribute to the observed changes in RHI. Similarly, PWV measurements may be affected by physiological fluctuations and blood pressure variability.

In addition, potential confounding factors such as lifestyle modifications following therapy initiation, including dietary changes or increased physical activity, were not systematically controlled for and may have influenced vascular outcomes. Finally, correlation analyses were limited to univariable models and no adjustment for multiple comparisons was performed, increasing the risk of type I error. Therefore, the present findings should be considered hypothesis-generating and require confirmation in larger, multicenter, prospective studies with appropriate control groups and multivariable statistical adjustment.

Conclusion

In patients with hypercholesterolemia, 3 months of bempedoic acid significantly improved endothelial function and reduced arterial stiffness, in parallel with marked lipid profile improvement.

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Conflicts of interest

There are no conflicts of interest.

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GRAPHICAL ABSTRACT