Circulation

Triple Versus Dual Lipid-Lowering Therapy in Acute Coronary Syndrome: The ES-BempedACS Randomized Clinical Trial

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BACKGROUND: Current guidelines recommend a stepwise strategy to achieve low-density lipoprotein cholesterol (LDL-C) goals after acute coronary syndrome (ACS). Earlier intensive strategies based on a combination of lipid-lowering therapies (LLTs) could be useful from the onset of ACS. However, the role of bempedoic acid in ACS, particularly when combined with high-intensity statins and ezetimibe, remains uncertain. The aim of ES-BempedACS (Efficacy and Security of Bempedoic Acid in Acute Coronary Syndrome) was to compare the efficacy and safety of triple LLT (high-dose, high-intensity statin+ezetimibe+bempedoic acid) versus standard of care (high-dose, high-intensity statin+ezetimibe) after ACS.

METHODS: ES-BempedACS is a multicenter, independent, pragmatic, prospective, randomized, open, blinded end point controlled trial conducted in 12 Spanish hospitals between November 2023 and October 2024. The primary end point was the proportion of patients achieving LDL-C <55 mg/dL (<1.4 mmol/L) at 8 weeks after ACS, comparing triple LLT with standard of care.

RESULTS: A total of 206 patients (59.5±10.9 years of age [mean±SD]; 21.4% women) were randomized within the first 72 hours of ACS to triple LLT or standard therapy of high-intensity statin+ezetimibe (ie, dual LLT). The baseline LDL-C level was 133.6±28.8 mg/dL. After 8 weeks, the LDL-C level was reduced to <55 mg/dL in 59.4% of patients in the triple LLT group compared with 53.1% in the control group (dual LLT; $P=0.376$). The percentage change in LDL-C level was 57.5±17.8% and 56.9±18.5% in the triple and dual LLT groups, respectively ($P=0.823$). Triple versus dual LLT showed similar results in reduction of non−high-density lipoprotein cholesterol levels (49.0±25.4 in triple LLT versus 49.1±31.2 in dual LLT; $P=0.970$) and triglyceride levels (14.9±36.9 in triple LLT versus 16.8±36.0 in dual LLT;) $P=0.718$), without differences in adverse events.

CONCLUSIONS: Both dual and triple LLT after ACS allow for high rates (>50%) of adequate LDL-C control (<55 mg/dL) at 8 weeks. Adding bempedoic acid to statin−ezetimibe therapy in the setting of ACS is safe but failed to improve the percentage of patients achieving the LDL-C goal (<55 mg/dL) at 8 weeks. Larger, randomized studies are needed to confirm our findings.

REGISTRATION: URL: https://www.clinicaltrialsregister.eu; Unique identifier: 2021-006550-31.

Key Words: 8-hydroxy-2,2,14,14-tetramethylpentadecanedioic acid ■ acute coronary syndrome ■ cholesterol, LDL ■ ezetimibe ■ hydroxymethylglutaryl-CoA reductase inhibitors

Clinical Perspective

What Is New?

- The addition of bempedoic acid to dual lipid-lowering therapy with high-intensity statin and ezetimibe does not improve lipid control at 8 weeks in patients discharged after an acute coronary syndrome.

What Are the Clinical Implications?

- After an acute coronary syndrome, dual lipid-lowering therapy (high-intensity statin+ezetimibe) allows early achievement of low-density lipoprotein cholesterol targets in more than half of patients.

Nonstandard Abbreviations and Acronyms

ACS	acute coronary syndrome
ES-BempedACS	Efficacy and Safety of Bempedoic Acid in Acute Coronary Syndrome
HDL-C	high-density lipoprotein cholesterol
ITT	intention-to-treat
LDL-C	low-density lipoprotein cholesterol
LLT	lipid-lowering therapy

Patients with acute coronary syndrome (ACS) are at high risk of recurrent atherosclerotic events, particularly in the first weeks after ACS.[1] A marked and early reduction of low-density lipoprotein cholesterol (LDL-C) levels has been associated with a reduction in the risk of ischemic events.[2] Despite the temporal importance of early LDL-C reduction in the context of ACS, clinical practice guidelines continue to promote a step-by-step therapeutic strategy.[3,4] In-hospital initiation of high-intensity statin treatment is the standard strategy promoted by current clinical practice guidelines, with the addition of ezetimibe considered as an optional therapy.[5] However, recent registries continue to show low rates of patients achieving LDL-C targets (ie, LDL-C <1.4 mmol/L [55 mg/dL]) early.[6,7] Given the high frequency of patients with ACS failing to achieve LDL-C goals with intensive statin therapy alone, and the increased risk of recurrence of ischemic events during the first weeks after ACS, it is logical to hypothesize that early initiation of a combination therapy with high-potency lipid-lowering drugs could have a potential therapeutic benefit in this setting.

Ezetimibe added to statin therapy after ACS has been shown to achieve a greater reduction in LDL-C levels, and consequently to reduce the composite of cardiovascular death and ischemic events.[8] However, the efficacy of adding bempedoic acid to combined statin−ezetimibe

therapy in achieving the current LDL-C target (<1.4 mmol/L [55 mg/dL]) after ACS has not yet been evaluated. Moreover, the effect of bempedoic acid on LDL-C levels may be reduced in the setting of high-intensity statin use.[9] We conducted a randomized controlled trial to compare the impact of triple lipid-lowering therapy (LLT; high-intensity statin+ezetimibe+bempedoic acid) versus standard of care (high-intensity statin+ezetimibe) in the early achievement of LDL-C targets after ACS.

METHODS

Data Sharing

The data, analytic methods, and study materials supporting the findings of this study will be made available to other researchers upon reasonable request. For new analyses related to ES-BempedACS (Efficacy and Safety of Bempedoic Acid in Acute Coronary Syndrome), qualified researchers should submit a request that includes the research objectives, end points or outcomes of interest, statistical analysis plan, data requirements, publication plan, and qualifications of the researchers. Requests will be reviewed by an internal committee. If approved, the data necessary to address the research question will be provided under the terms of a data-sharing agreement. Requests may be submitted to bempedacs@gmail.com.

Study Design

ES-BempedACS is a multicenter, independent, pragmatic, prospective, randomized, open, blinded end point controlled trial conducted at 12 centers across Spain. The trial design has been described previously.[10] ES-BempedACS was an independent trial designed and overseen by a steering committee. This investigator-initiated clinical trial was promoted by the Spanish Society of Cardiology. The protocol was approved by the Spanish Agency of Medicines and Medical Devices and the Galician Clinical Research Ethics Committee (approval 2021/534), as well as the investigational review boards at each of the participating sites. The trial was registered in the European Clinical Trials Database (EUDRACT 2021-006550-31) and followed the principles outlined in the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. The steering committee developed the study protocol and the Clinical Research Unit of Hospital Alvaro Cunqueiro (Vigo, Spain) monitored the progress of the trial, had full access to the complete database, and independently generated all analyses. The authors take full responsibility for the accuracy and completeness of the data and analyses, as well as for ensuring that the trial and this report faithfully reflect the protocol. This report adhered to the CONSORT (Consolidated Standards of Reporting Trials) reporting guidelines (Supplemental Material).

Patients

We included consecutive patients admitted with ACS with clinically significant coronary artery disease (defined by invasive coronary angiography as >50% stenosis of the left main stem or >70% stenosis in another coronary vessel) whose LDL-C levels were ≥3 mmol/L (≥115 mg/dL) in statin-naive patients,

≥2.6 mmol/L (≥100 mg/dL) in patients under treatment with low-potency statins or high-potency statins at submaximal doses, or ≥1.8 mmol/L (≥70 mg/dL) despite treatment with high-potency statins at high doses. Atorvastatin (80 mg) and rosuvastatin (20 to 40 mg) were considered high-potency statins at high doses. Exclusion criteria were any contraindication to statins, bempedoic acid, or ezetimibe; concomitant therapy with fibrates, inclisiran, or any PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitor; history of gout; or uric acid levels ≥9.0 mg/dL, triglycerides ≥400 mg/dL, or a glomerular filtration rate (estimated by the Chronic Kidney Disease Epidemiology Collaboration equation) <30 mL·min·1.73 m² or dialysis. A complete list of the inclusion and exclusion criteria is provided in Table S1. All participants provided written informed consent.

Randomization, Procedures, and Study Interventions

Eligible patients were randomly assigned in a 1:1 ratio to receive triple LLT (high-potency statin+ezetimibe+bempedoic acid) versus standard of care (high-potency statin±ezetimibe). Because all patients were at very high cardiovascular risk (ie, secondary prevention after ACS) and had poor LDL-C control, the physicians were strongly encouraged to prescribe ezetimibe, in combination with high-potency statin, in the control group (ie, standard of care). Because all patients in the standard-of-care group ultimately received high-potency statins combined with ezetimibe from the time of randomization, this group was also referred to as the dual LLT group. Randomization was performed in stabilized patients within the first 72 hours after hospital admission. It was conducted using a secure web-based system and stratified according to sex, LLT on admission before randomization (with or without high-potency, high-dose statin therapy), and baseline LDL-C values (<2.6 or ≥2.6 mmol/L [≥100 mg/dL]). Blood samples for assessment of fasting lipids were obtained within the first 72 hours after hospital admission, and LDL-C was assessed locally at each site to determine eligibility. The LDL-C level was calculated with the use of the Friedewald formula. Treatment began at the time of randomization. Enrolled patients were treated for the ACS event in accordance with current guidelines, including in-hospital medical therapy and coronary revascularization. The assessment of lipid levels, clinical outcomes, and adherence to triple or dual LLT group was conducted at the control visit scheduled at 8 weeks. Treatment adherence was assessed through patient self-report at the 8-week follow-up.

Outcomes

The primary end point was the percentage of patients achieving LDL-C <1.4 mmol/L (<55 mg/dL) at 8 weeks of treatment. The following secondary end points were established: absolute change in LDL-C level from baseline at 8 weeks of treatment; percentage change in non–high-density lipoprotein cholesterol (HDL-C) level from baseline at 8 weeks of treatment; and percentage change in HDL-C and triglyceride levels from baseline at 8 weeks of treatment. Clinical cardiovascular events—including a composite of cardiovascular death, ACS, nonelective coronary revascularization, and ischemic stroke— were assessed with blinding as a complementary analysis,

although they were not prespecified end points in the original trial protocol. Safety end points were adverse events from baseline to 8 weeks, including any adverse event leading to discontinuation of the trial therapy, general allergic reaction, musculoskeletal pain, gout, hyperuricemia (uric acid >6.9 mg/dL), alanine aminotransferase/aspartate aminotransferase increase >3× upper limit of normal, cholelithiasis, new-onset diabetes, or cancer.

Statistical Analysis

The study was designed as a superiority trial powered for the primary end point. Assuming that the rate of patients achieving the LDL-C goal <1.4 mmol/L (55 mg/dL) was 30% in the standard of care group and 50% in the triple LLT group, a total sample size of 186 patients would provide 80% power to detect a statistically significant effect at a 5% significance level using a 2-sided statistical test. Anticipating a dropout rate of 10% at 8 weeks, enrollment of 206 patients was planned. Comparisons of baseline characteristics were performed using Student t tests and χ^2 tests. Efficacy and safety analyses were performed based on the intention-to-treat principle, analyzing all patients according to their assigned randomization group. Missing data were not imputed because only 5 baseline variables (left ventricular ejection fraction, hemoglobin, creatinine, alanine aminotransferase, and uric acid) had missing values and missingness was <5% for all of them except uric acid (18.9% of missingness; see footnote in Table 1). Adverse events were summarized by treatment group using descriptive statistics (Fisher exact test because small number of events). Prespecified subgroup analyses were performed by sex, prerandomization statin treatment, and baseline LDL-C ≥2.6 mmol/L (≥100 mg/dL). Tests are 2-sided throughout and a P value <0.05 was considered significant. Analyses were performed with SPSS version 25 and Stata version 15.

RESULTS

From November 2023 through October 2024, a total of 206 consecutive patients were randomly assigned to triple LLT (n=101) or standard of care (n=105) at 12 centers in Spain (Table S2; Figure S1). The mean age was 59.5±10.9 years, and 21.4% of participants were women. The mean calculated LDL-C levels at baseline were 3.5±0.7 mmol/L (133.6±28.8 mg/dL), and 67.0% of patients were statin-naive. In the intervention group (triple LLT), all patients received a high-potency statin (50.5% atorvastatin 80 mg and 49.5% rosuvastatin 20–40 mg), 10 mg of ezetimibe, and bempedoic acid, whereas in the control group (standard of care), all patients received a high-potency statin (44.8% atorvastatin 80 mg and 55.2% rosuvastatin 20–40 mg) plus 10 mg of ezetimibe. Half of the patients (50%) participated in cardiac rehabilitation after myocardial infarction. Patient characteristics and baseline therapies were well-balanced between groups at baseline (Table 1).

Only one patient discontinued the assigned treatment arm before the control visit (8 weeks). Besides that patient (who stopped bempedoic acid because of gout),

Table 1.   Patient Characteristics at Baseline

Characteristics	Intervention group, triple LLT (n=101)	Control group, dual LLT (n=105)	P value
Age, y	60.2±10.6	58.8±11.2	0.364
Female sex	23 (22.8)	21 (20.0)	0.627
Cardiovascular disease history and risk factors			
Smoking	49 (48.5)	52 (49.5)	0.885
Hypertension	48 (47.4)	49 (46.7)	0.902
Diabetes type 2	14 (13.9)	21 (20.0)	0.241
Previous myocardial infarction	6 (5.9)	7 (6.7)	0.830
Peripheral artery disease	2 (2.0)	2 (1.9)	0.969
Atrial fibrillation	1 (1.0)	3 (2.9)	0.332
Previous LLT			
Baseline (on admission) statin therapy	31 (30.7)	37 (35.2)	0.488
High potency	10 (9.9)	10 (9.5)	0.927
Not high potency	21 (20.8)	27 (25.7)	0.403
Baseline (on admission) ezetimibe therapy	4 (4.0)	7 (6.7)	0.388
Current admission			
Type of ACS			0.994
STEMI	52 (51.5)	54 (51.4)	
NSTEMI	49 (48.5)	51 (48.6)	
Left ventricular ejection fraction, %*	54.1±8.8	55.0±10.0	0.496
Multivessel coronary artery disease	38 (37.6)	37 (35.2)	0.722
Complete revascularization	80 (79.2)	92 (87.6)	0.104
Laboratory data			
Hemoglobin, g/dL†	14.7±1.5	14.5±1.5	0.272
Creatinine, mg/dL‡	0.9±0.2	0.9±0.2	0.887
Total cholesterol, mg/dL	201.6±36.0	201.6±29.8	0.997
LDL-C, mg/dL	132.2±29.8	135.0±27.9	0.486
HDL-C, mg/dL	41.9±13.9	43.5±14.2	0.442
Triglycerides, mg/dL	146.2±72.1	139.5±66.2	0.499
ALT, mg/dL§	32.1±20.8	37.3±32.6	0.178
Uric acid, mg/dL‖	5.5±2.8	5.3±1.3	0.466
Medical therapy at discharge			
Acetylsalicylic acid	101 (100.0)	102 (97.1)	0.087
P2Y12 inhibitor	101 (100.0)	104 (99.0)	0.326
Beta-blockers	56 (55.4)	68 (64.8)	0.172
Renin-angiotensin system inhibitor	67 (66.3)	75 (71.4)	0.430
SGLT2 inhibitor	20 (19.8)	22 (21.0)	0.838
High-potency statin after ACS			0.410
Rosuvastatin 20–40 mg	50 (49.5)	58 (55.2)	
Atorvastatin 80 mg	51 (50.5)	47 (44.8)	
Ezetimibe after ACS	101 (100)	105 (100)	1.000
Cardiac rehabilitation	59 (49.5)	53 (50.5)	0.889

Values are mean±SD or n (%). Percentages may not sum to 100 because of rounding. There were no significant differences between the 2 groups for any variable except for coronary artery disease. ACS indicates acute coronary syndrome; ALT, alanine aminotransferase; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NSTEMI, non–ST-segment–elevation myocardial infarction; P2Y12, purinergic P2Y12 receptor; SGLT2, sodium-glucose cotransporter 2; and STEMI, ST-segment–elevation myocardial infarction.

*Data were missing for 5 patients in the triple lipid-lowering therapy (LLT) group and 4 patients in the dual LLT group.

†Data were missing for 3 patients in the triple LLT group and 2 patients in the dual LLT group.

‡Data were missing for 3 patients in the triple LLT group and one patient in the dual LLT group.

§Data were missing for 2 patients in the triple LLT group and 4 patients in the dual LLT group.

‖Data were missing for 17 patients in the triple LLT group and 22 patients in the dual LLT group.
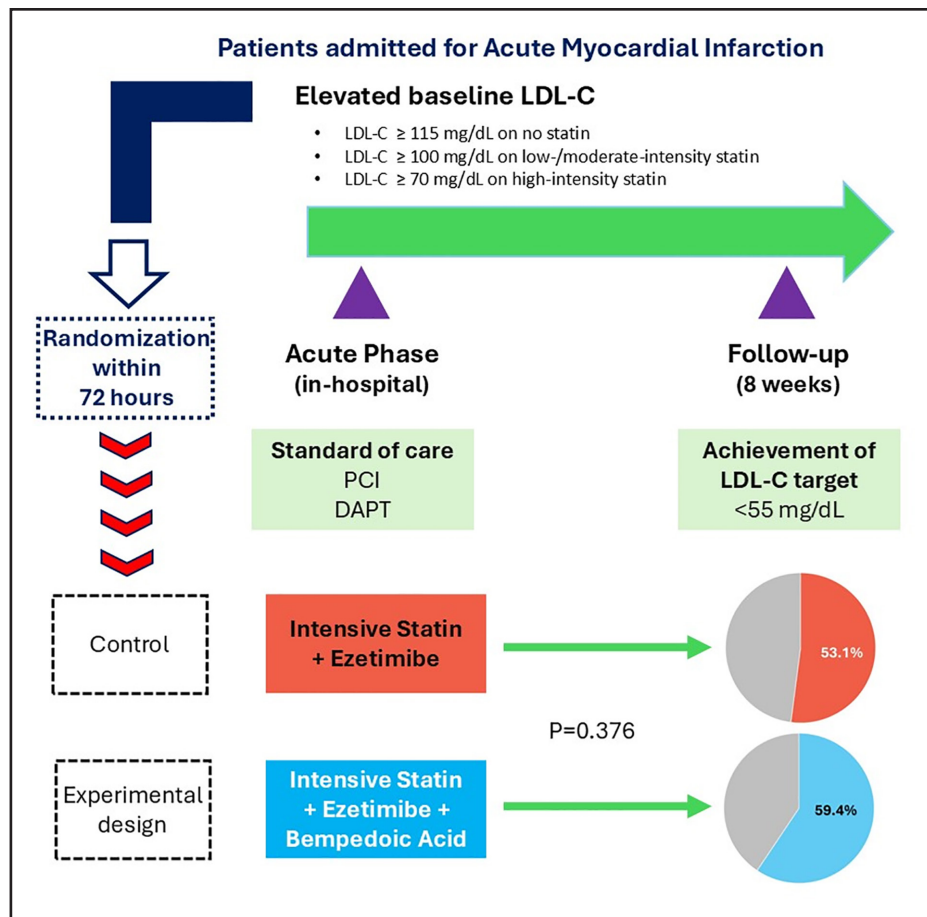
Figure 1. Triple lipid-lowering therapy in patients with acute coronary syndrome.
DAPT indicates dual antiplatelet therapy; LDL-C, low-density lipoprotein cholesterol; and PCI, percutaneous coronary intervention.

no crossovers were detected between the arms during the study period.

Efficacy

Calculated LDL-C levels were available at baseline and at 8 weeks for assessment of the primary end point in 194 patients (94.2%). At 8 weeks, the LDL-C level was reduced to <1.4 mmol/L (<55 mg/dL) in 59.4% of patients in the triple LLT group compared with 53.1% in the control (dual LLT) group (Figure 1; Figure S2). Percentage change in LDL-C level from baseline to 8 weeks was 57.5±17.8% in the triple LLT group (from mean 132.5 to 54.6 mg/dL) versus 56.9±18.5% in the control (dual LLT) group (from mean 134.6 to 55.3 mg/dL; Figures 2 and 3; Figure S3). Triple LLT showed similar results in reduction of other atherogenic lipid particles (eg, non-LDL-C, triglycerides) compared with the control group (dual LLT; Table 2). The effect of triple versus dual LLT on the primary outcome was consistent across different subgroups (Table 3). There were no differences between the groups (triple and dual LLT) by tertiles of baseline LDL-C levels (Table S3). Results were consistent after using other equations to estimate the LDL-C level (Martin-

Hopkins and Sampson-NIH equations versus the Friedewald formula; see Table S4).

Safety

The percentage of patients who experienced adverse events was similar between the groups (Table 4). Only one patient presented an adverse event leading to study drug discontinuation (one gout episode in the triple LLT group). Asymptomatic hyperuricemia was the most common reported adverse event, occurring in 7 patients (7.3%) in the triple LLT and 5 patients (5.1%) in the control (dual LLT) group (P=0.527). Only one patient had gout (in the triple LLT group). No death was reported. Adjudicated cardiovascular events did not differ significantly between groups. In total, 4 patients (4.2%) in the triple LLT group and 2 patients (2.0%) in the control (dual LLT) group experienced cardiovascular events.

DISCUSSION

In this study, the first randomized controlled trial evaluating the addition of bempedoic acid to statin−ezetimibe therapy in the setting of ACS, adding bempedoic
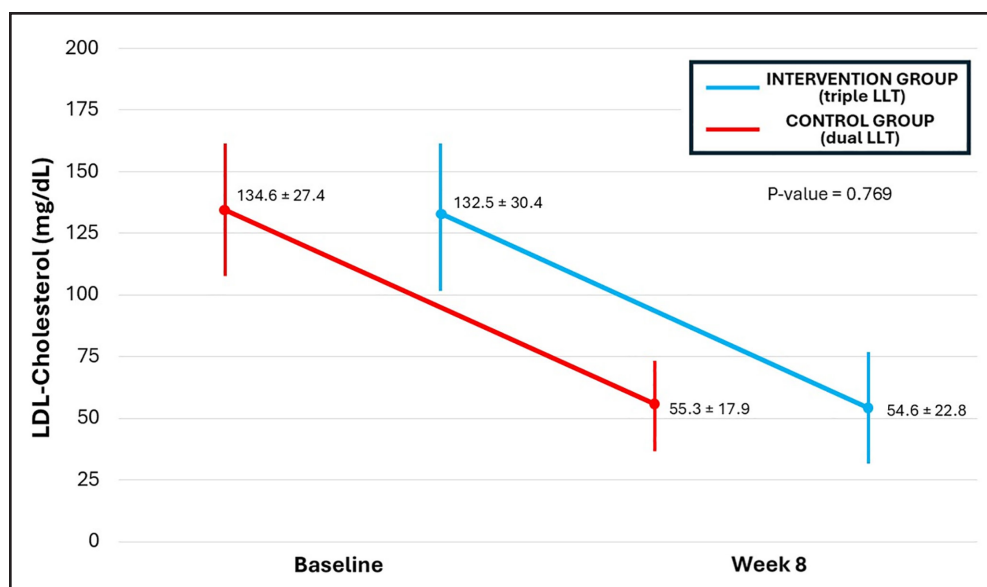
Figure 2. Changes in low-density lipoprotein cholesterol levels from baseline to 8 weeks with triple or dual lipid-lowering therapy.
LDL indicates low-density lipoprotein; and LLT, lipid-lowering therapy.

acid was safe but did not significantly reduce LDL-C, non−HDL-C, or triglyceride levels at 8 weeks in patients treated with high-potency statins and ezetimibe. In both groups (dual and triple LLT), a high proportion of patients with ACS achieved LDL-C <55 mg/dL (>50%), non−HDL-C <85 mg/dL (>70%), and triglycerides <150 mg/dL (>80%).

The current strategy for lipid management after ACS consists of a stepwise approach of early initiation of high-intensity statin, followed by addition of ezetimibe±bempedoic acid during follow-up, and further consideration of PCSK-9 inhibitors or inclisiran if LDL-C

levels remain ≥55 mg/dL (1.4 mmol/L). With this approach, most patients need months to achieve LDL-C levels within the recommended targets. In ES-BempedACS, we found that with both dual and triple LLT more than half of the patients achieved the target LDL-C level (<55 mg/dL [1.4 mmol/L]) early (within 8 weeks after an ACS). This is important because the risk of recurrent cardiovascular events is high, particularly during the first weeks after an admission for ACS.[1] However, previous data from patients treated with standard therapy based on statin monotherapy after ACS showed poor LDL-C control, clearly worse than what we observed in our study,
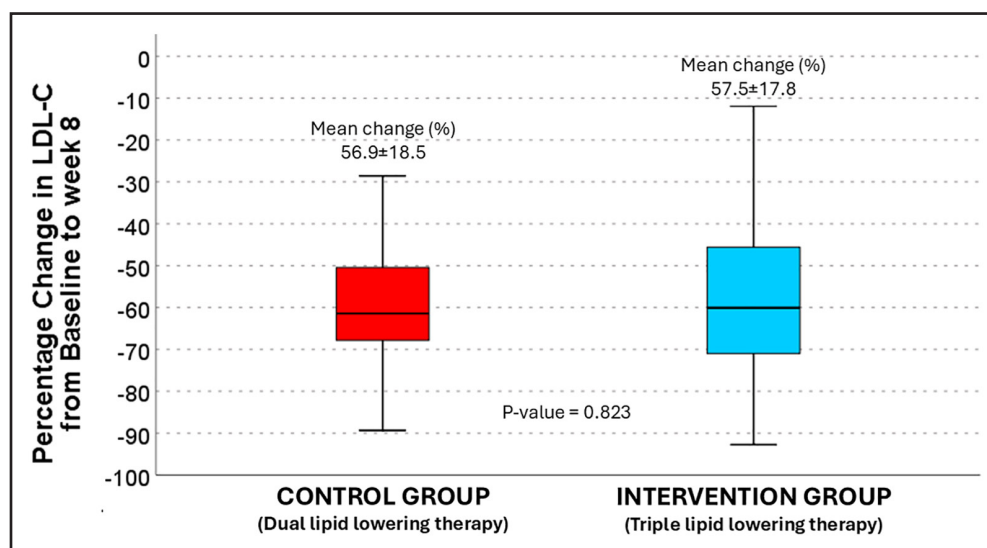

Figure 3. Percentage reduction in low-density lipoprotein cholesterol levels from baseline to 8 weeks with triple versus dual lipid-lowering therapy.
LDL-C indicates low-density lipoprotein cholesterol.

Table 2. Efficacy Outcomes

Outcomes	Intervention group, triple LLT (n=96)	Control group, dual LLT (n=98)	P value
LDL-C			
Baseline, mg/dL	132.5±30.4	134.6±27.4	0.626
Week 8, mg/dL	54.6±22.8	55.3±17.9	0.822
Absolute change from baseline, mg/dL	77.9±32.5	79.3±32.4	0.769
% Change from baseline	57.5±17.8	56.9±18.5	0.823
Patients with LDL <55 mg/dL at week 8	57 (59.4)	52 (53.1)	0.376
Non–HDL-C			
Baseline, mg/dL	160.4±37.7	158.2±30.5	0.664
Week 8, mg/dL	76.9±24.1	74.7±19.1	0.480
Absolute change from baseline, mg/dL	83.4±39.5	83.5±36.7	0.989
% Change from baseline	49.0±25.4	49.1±31.2	0.970
Patients with non–HDL-C <85 mg/dL at week 8	69 (71.9)	72 (73.5)	0.803
Triglycerides			
Baseline, mg/dL	146.5±71.3	138.3±63.9	0.401
Week 8, mg/dL	113.5±54.2	107.4±67.3	0.492
Absolute change from baseline, mg/dL	33.0±66.9	30.9±63.7	0.821
% Change from baseline	14.9±36.9	16.8±36.0	0.718
Patients with triglycerides <150 mg/dL at week 8	81 (84.4)	85 (86.7)	0.640

Values are mean±SD or n (%). HDL-C indicates high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; and LLT, lipid-lowering therapy.

Table 3. Subgroup Analysis for the Primary End Point*

Subgroups	Intervention group, triple LLT (n=96)	Control group, dual LLT (n=98)	P value	P_interaction
Sex				0.940
Male	45 (60.0)	42 (54.5)	0.497	
Female	12 (57.5)	10 (47.6)	0.535	
Age, y				0.981
<65	37 (58.7)	36 (53.7)	0.566	
≥65	20 (60.6)	16 (51.6)	0.469	
Diabetes				0.811
Yes	7 (58.3)	10 (55.6)	0.880	
No	50 (59.5)	42 (52.5)	0.365	
Previous statin therapy				0.175
Naive	43 (63.2)	32 (51.6)	0.180	
Non-naive	14 (50.0)	20 (55.6)	0.659	
Baseline LDL-C, mg/dL				0.143
<130	38 (66.7)	26 (55.5)	0.291	
≥130	19 (48.7)	26 (50.0)	0.904	
Type of acute coronary syndrome				0.666
STEMI	29 (56.9)	30 (57.7)	0.932	
NSTEMI	28 (62.2)	22 (47.8)	0.168	
Cardiac rehabilitation				0.752
Yes	29 (58.0)	26 (51.0)	0.590	
No	28 (60.9)	26 (55.3)	0.588	

Values are n (%). LDL-C indicates low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; NSTEMI, non–ST-segment–elevation myocardial infarction; and STEMI, ST-segment–elevation myocardial infarction.

*Percentage of patients with low-density lipoprotein cholesterol (LDL-C) <1.4 mmol/L (<55 mg/dL).

with only 1 in 3 patients achieving optimal LDL-C levels.[11,12] Several studies have shown that an earlier and higher reduction of LDL-C levels is associated with a lower rate of cardiovascular events during follow-up.[8,13,14] Therefore, early optimal LDL-C control may improve prognosis considerably in these complex cases, as was shown in the SWEDEHEART Registry (Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies).[15]

Considering that patients with ACS frequently fail to achieve recommended treatment targets despite high-intensity statin, there is an unmet need for early, intensive reduction of atherogenic lipids in patients in this very-high-risk clinical setting. EVOPACS (Evolocumab for Early Reduction of LDL-Cholesterol Levels in Patients With Acute Coronary Syndromes) showed that the addition of a PCSK-9 inhibitor, compared with statin alone, resulted in a substantially greater reduction in LDL-C levels after 8 weeks.[16] ES-BempedACS tested a novel approach of early initiation of high-intensity LLT, but based exclusively on oral therapy, comparing triple LLT versus standard of care (dual LLT in our trial). Ezetimibe

is increasingly being used in the context of discharge after ACS, given the medium- to long-term results shown in IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial).[8] However, evidence on the use of bempedoic acid early after ACS is scarce, and primarily based on patients with statin intolerance.

Bempedoic acid is a recently developed lipid-lowering drug that reduces cholesterol biosynthesis,[17] thus increasing the expression of LDL receptors and leading to a clinically significant reduction of LDL-C blood levels. Safety and efficacy of bempedoic acid has been tested in different randomized clinical trials in stable patients with or without cardiovascular disease,[18–22] describing a significant reduction of LDL-C levels between 17.4% and 28.5%, depending on baseline lipid-lowering strategy. However, most of the patients from those trials were statin-intolerant or received low or moderate doses of statins. Therefore, bempedoic acid plays a relevant role in patients who are statin-intolerant or in clinical settings in which injectable therapies such as PCSK9 inhibitors or inclisiran are not accessible.[23–25]

Data from our pragmatic clinical trial showed that the addition of bempedoic acid to a high-intensity

Table 4. Investigator-Reported Adverse Events and Laboratory Safety-Related Findings

Event	Intervention group, triple LLT (n=96)	Control group, dual LLT (n=98)	P value
Stop treatment	1 (1.1)	0 (0.0)	0.495
Safety outcomes			
Adverse event leading to discontinuation of the trial regimen	1 (1.1)	0 (0.0)	0.495
General allergic reaction	0 (0.0)	0 (0.0)	–
Musculoskeletal pain	4 (4.2)	1 (1.0)	0.209
Gout	1 (1.1)	0 (0.0)	0.495
Hyperuricemia	7 (7.3)	5 (5.1)	0.566
ALT increase >3× ULN	3 (3.1)	5 (5.1)	0.721
Cholelithiasis	0 (0.0)	0 (0.0)	–
New-onset diabetes	0 (0.0)	0 (0.0)	–
Cancer	0 (0.0)	0 (0.0)	–
Clinical outcomes			
All-cause death	0 (0.0)	0 (0.0)	–
Cardiovascular death	0 (0.0)	0 (0.0)	–
Myocardial infarction	0 (0.0)	1 (1.1)	0.505
Hospitalization for recurrent ACS	1 (1.1)	1 (1.1)	1.000
Unplanned coronary revascularization	1 (1.0)	2 (2.0)	0.508
Cerebrovascular event (stroke or TIA)	0 (0.0)	0 (0.0)	–

ACS indicates acute coronary syndrome; ALT, alanine aminotransferase; LLT, lipid-lowering therapy; TIA, transient ischemic attack; and ULN, upper limit of normal.

statin+ezetimibe did not further reduce LDL-C levels at 8 weeks. Although the proportion of patients achieving optimal LDL-C control was slightly higher among the triple LLT group compared with the dual LLT group, this difference was not statistically significant. Likewise, no significant differences were observed between the groups (dual and triple LLT) regarding LDL-C change at 8 weeks. These unexpected results can be explained by several factors.

Mechanistic redundancy and pharmacodynamic interactions likely explain the modest effect of bempedoic acid on LDL-C levels in our study. Both bempedoic acid and statins act on the same cholesterol synthesis pathway, and previous studies have shown that the LDL-C–lowering effect of bempedoic acid is greatest in statin-naive patients and diminishes as statin dose and intensity increase.[26] Dose–response models indicate that the effect of bempedoic acid is markedly reduced in patients receiving high-intensity statins, such as 80 mg of atorvastatin or 20 to 40 mg of rosuvastatin,[9] which were the regimens used in our trial.

Scarce evidence exists regarding the combination of bempedoic acid with high-intensity statins, particularly in the post-ACS setting. No randomized trials have compared high-potency statin+ezetimibe+bempedoic acid versus high-potency statin+ezetimibe, and most studies were conducted in statin-intolerant patients or those receiving low- to moderate-intensity statins. In CLEAR Outcomes (Evaluation of Major Cardiovascular Events in Participants With, or at High Risk for, Cardiovascular Disease Who Are Statin Intolerant Treated With Bempedoic Acid [ETC-1002] or Placebo),[27] only patients on very low daily statin doses could be enrolled. In CLEAR Harmony (Evaluation of Long-Term Safety and Tolerability of ETC-1002 in High-Risk Patients With Hyperlipidemia and High CV Risk),[28] <50% of patients received high-intensity statins. In CLEAR Wisdom (Evaluation of Long-Term Efficacy of Bempedoic Acid [ETC-1002] in Patients With Hyperlipidemia at High Cardiovascular Risk),[27] only 53% of high-risk patients were on high-intensity statins. In a study by Ballantyne et al,[22] the fixed-dose combination of bempedoic acid+ezetimibe significantly reduced LDL-C levels compared with placebo or monotherapy, but only about one third of patients were on high-potency statins. Previous trials excluded patients with recent ACS, leaving the safety and efficacy of bempedoic acid in this high-risk population largely unknown. To our knowledge, ES-BempedACS is the first randomized trial designed to assess bempedoic acid on top of currently recommended LLT in the early post-ACS setting. All patients in our study were treated within 72 hours of ACS and followed for 8 weeks, a period of highest risk but also of heightened adherence and lifestyle attention.[1] Approximately 50% of patients participated in cardiac rehabilitation programs, further ensuring adherence and optimal management of health and lifestyle, which may influence the observed LDL-C response. Moreover, participation bias in a clinical trial may further contribute to high early adherence, providing an additional explanation for the modest LDL-C reduction observed.

Besides the neutral result of our trial, it is worth highlighting the high proportion (>50%) of patients reaching optimal LDL-C control at 8 weeks in both groups (dual or triple LLT), which is clearly higher than previous studies showing ≈30% of patients with optimal lipidic control.[16] The high grade of good LDL-C control in ES-BempedACS might be attributable, at least in part, to the potent lipid-lowering strategy in both groups (dual and triple LLT), including both high-potency, high-dose statins and ezetimibe in all patients, along with a high rate of inclusion in cardiac rehabilitation programs. In ES-BempedACS, the mean reduction in LDL-C was >55% in both groups. In EVOPACS, the percentage change in LDL-C was 35% in patients treated with statins alone and 77% in patients treated with evolocumab.[12] Despite this good control in both groups, ≈3% to 4% of patients had LDL-C levels >100 mg/dL (2.6 mmol/L) at 8 weeks after ACS in ES-BempedACS, highlighting the potential need for more potent parenteral LLT for reducing risk in this complex scenario.

The rate of side effects was low, and similar in both groups. Although asymptomatic hyperuricemia was more frequently observed among patients in the triple LLT group versus the control (dual LLT) group, the difference was not significant. Therefore, a good safety profile of bempedoic acid in patients with recent ACS also treated with high-dose statins+ezetimibe was observed. The short follow-up period likely underestimated issues related to adherence and tolerability, which are frequently reported with statin therapy over the medium to long term. This is particularly relevant given that in patients with statin intolerance, bempedoic acid has been shown not only to improve lipid control but also to reduce cardiovascular event rates.[27]

The low rate of clinical cardiovascular events observed in patients from the BempedACS trials is probably related to this optimal control and management and the short follow-up. This low cardiovascular event rate, combined with significant LDL-C reduction, also suggests strong adherence and a high-quality care environment. However, the study was not powered for cardiovascular outcomes or serious adverse events. Therefore, whether early initiation of triple LLT versus dual LLT during the acute ACS phase might translate into an incremental clinical benefit remains to be determined in properly designed studies.

This trial has several limitations, including its pragmatic and open-label trial nature. The trial was conducted only in Spain, limiting the generalization of the results. Race and ethnicity data were not collected in this study; however, given that the trial was conducted exclusively in Spain, it is expected that the majority of participants were White. In addition, most of the study population consisted of men, which may further restrict the applicability of the results to broader populations. The moderate simple size only has powerful to detect changes in the percentage of patients with good LDL-C control. Because more than half of the centers enrolled <10 patients, a reliable center-specific analysis is not feasible, and we cannot rule out that low recruitment by center may have influenced the results. Moreover, we did not strictly monitor adherence beyond patient self-reporting at the 8-week follow-up. However, given that we are analyzing the first 2 months after an ACS, high adherence is expected.[29] In addition, given the real-world approach, certain laboratory measures of potential interest, such as C-reactive protein, lipoprotein(a), and apolipoprotein B, were not systematically collected. The study was not powered for observing differences in clinical events, with a modest study size and a short study duration. Based on the current results, larger and longer-term studies should further investigate the addition of bempedoic acid to statin–ezetimibe therapy in the acute ACS setting, assessing potential effects on clinical outcomes. Despite those limitations, this trial reports novel and important data regarding the role of bempedoic acid on top of high-intensity, high-dose statins and ezetimibe for reaching optimal LDL-C control after a recent admission for ACS. Improving management of these high-risk patients may have important clinical, economic, and social consequences.

Conclusions

Bempedoic acid initiated within 72 hours after ACS on top of a combination of high-intensity statin and ezetimibe therapy was well-tolerated, but did not result in higher percentages of patients with LDL <1.4 mmol/L (<55 mg/dL). Further studies are needed not only to confirm whether adding bempedoic acid to high-potency statin+ezetimibe is beneficial in achieving early LDL-C reduction after ACS, but also to evaluate the effect of triple therapy on clinical outcomes.

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