Bempedoic Acid and Cardiovascular

Statin Intolerant

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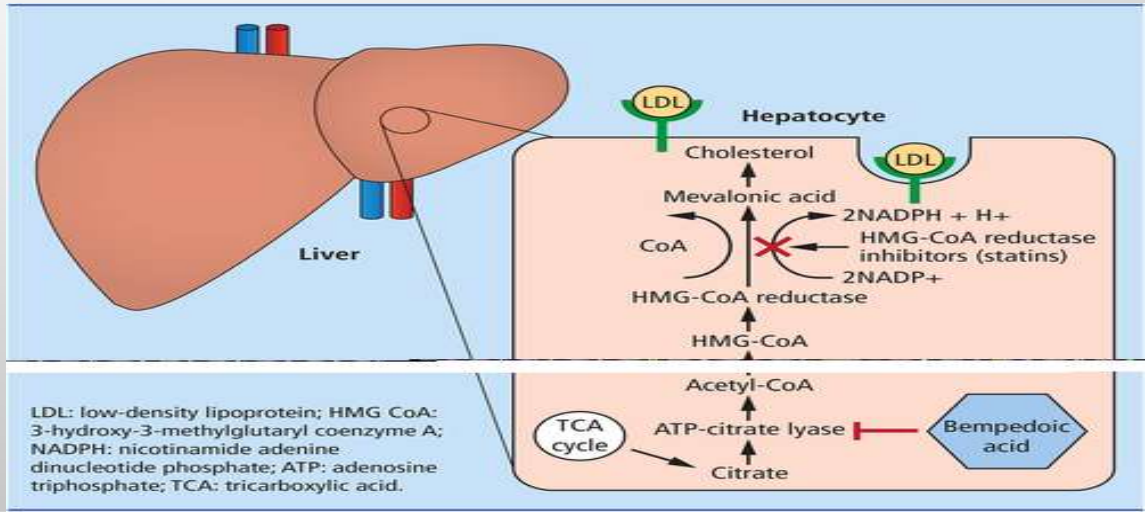
RESPECT TO THE FATHER OF NATION, BANGABANDHU SHEIKH MUJIBUR RAHMAN
AND ALL THE FREEDOM FIGHTERS

- **Bempedoic acid**, inhibits ATP citrate lyase (ACL), two steps upstream of HMG CoA reductase(Whereas statins inhibit HMG CoA reductase).

- Unlike statins, bempedoic acid is administered as a prodrug and is converted to active coenzyme- A form by enzymes found only in the liver and not in muscles.

- The lack of active metabolites of bempedoic acid in skeletal muscles makes it a promising alternative for patients with statin associated muscle symptoms (SAMS).

- Its effects on cardiovascular outcomes remain uncertain.



- In several studies, bempedoic acid reduced the level of LDL cholesterol by 17 to 28%, so in 2020, prompted its approval by the Food and Drug Administration(FDA) and the European Medicines Agency(EMA) for this indication.

- However, data from randomized, controlled trials on the effects of bempedoic acid on cardiovascular events are lacking.

- The CLEAR (Cholesterol Lowering via Bempedoic Acid [ECT1002], an ACL-Inhibiting Regimen) Outcomes trial to determine the effects of bempedoic acid on adverse cardiovascular events in a mixed population of patients for whom primary or secondary prevention is clinically indicated but who were unable or unwilling to take guideline recommended doses of statins.

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- Administration of statins to lower elevated levels of low-density lipoprotein (LDL) cholesterol is the cornerstone of contemporary therapy to reduce the risk of major adverse cardiovascular events in patients for whom primary or secondary prevention is clinically indicated.

- However, 7 to 29% of patients report adverse musculoskeletal effects that prevent them from using statins or limit their ability to receive guideline recommended doses.

- Withdrawal from statin therapy is associated with an increased risk of adverse cardiovascular event

- It conducted a double-blind, randomized, placebo-controlled trial involving patients who were unable or unwilling to take statins owing to unacceptable adverse effects (“statin-intolerant” patients) and had, or were at high risk for, cardiovascular diseases.

- The patients were assigned to receive oral **bempedoic acid**, **180 mg daily**, or **placebo.**

- The primary end point was a four component composite of major adverse cardiovascular events, defined as------

  Nonfatal myocardial infarction,
  Nonfatal stroke, or
  Coronary revascularization,
  Death from cardiovascular causes.

TRIAL POPULATION:

PATIENTS 18 TO 85 YEARS OF AGE ,IF THEY MET EITHER OF TWO CRITERIA FOR INCREASED CARDIOVASCULAR RISK —

- **A PREVIOUS CARDIOVASCULAR EVENT (SECONDARY PREVENTION PATIENTS)**

OR

- **CLINICAL FEATURES THAT PLACED THEM AT HIGH RISK FOR A CARDIOVASCULAR EVENT (PRIMARY PREVENTION PATIENTS).**

Table 1. Demographic and Baseline Patient Characteristics in the Intention-to-Treat Population.*

Characteristic	Bempedoic Acid (N = 6992)	Placebo (N = 6978)
Age		
Mean — yr	65.5±9.0	65.5±8.9
Distribution — no. (%)		
<65 yr	2859 (40.9)	2907 (41.7)
≥65 to <75 yr	3070 (43.9)	3027 (43.4)
≥75 yr	1063 (15.2)	1044 (15.0)
Female sex — no. (%)	3361 (48.1)	3379 (48.4)
White race — no. (%)†	6397 (91.5)	6335 (90.8)
Hispanic or Latinx — no. (%)†	1190 (17.0)	1143 (16.4)
Body-mass index‡	29.9±5.2	30.0±5.2
LDL cholesterol		
Mean value — mg/dl	139.0±34.9	139.0±35.2
Distribution — no. (%)		
<130 mg/dl	3074 (44.0)	3089 (44.3)
≥130 to <160 mg/dl	2213 (31.7)	2250 (32.2)
≥160 mg/dl	1705 (24.4)	1639 (23.5)
HDL cholesterol — mg/dl	49.6±13.3	49.4±13.3
Non-HDL cholesterol — mg/dl	173.8±39.5	173.9±40.2
Total cholesterol — mg/dl	223.5±40.6	223.3±41.1
Median triglycerides (IQR) — mg/dl	159.5 (118.0–216.5)	158.5 (118.0–215.0)
Median high-sensitivity CRP (IQR) — mg/liter	2.3 (1.2–4.5)	2.3 (1.2–4.5)
Estimated GFR — no. (%)		
≥90 ml/min/1.73 m^2	1216 (17.4)	1233 (17.7)
≥60 to <90 ml/min/1.73 m^2	4322 (61.8)	4282 (61.4)
≥30 to <60 ml/min/1.73 m^2	1437 (20.6)	1444 (20.7)
Cardiovascular risk category — no. (%)		
Primary prevention	2100 (30.0)	2106 (30.2)
Secondary prevention	4892 (70.0)	4872 (69.8)
Coronary artery disease	3574 (51.1)	3536 (50.7)
Peripheral arterial disease	794 (11.4)	830 (11.9)
Cerebrovascular atherosclerotic disease	1027 (14.7)	1040 (14.9)
Glycemic status — no. (%)		
Diabetes§	3144 (45.0)	3229 (46.3)
Inadequately controlled diabetes¶	1356 (19.4)	1369 (19.6)
Statin use — no. (%)	1601 (22.9)	1573 (22.5)
Ezetimibe use — no. (%)	803 (11.5)	809 (11.6)

* Plus–minus values are means ±SD. The intention-to-treat population included all the patients who underwent randomization. Percentages may not total 100 because of rounding. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. CRP denotes C-reactive protein, GFR glomerular filtration rate, HDL high-density lipoprotein, IQR interquartile range, and LDL low-density lipoprotein.

† Race and Hispanic or Latinx ethnic group were reported by the patient.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

§ At baseline, diabetes was defined as a medical history of type 2 diabetes, previous use of glucose-lowering medication, a glycated hemoglobin measurement of 6.5% or greater, or two or more fasting glucose measurements of 126 mg per deciliter (7.0 mmol per liter) or greater at baseline.

¶ Inadequately controlled diabetes was defined as diabetes and a glycated hemoglobin level of 7.0% or greater at baseline.

➢ RANDOMIZATION, PATIENT CHARACTERISTICS, AND FOLLOW-UP

- BETWEEN DECEMBER 2016 AND AUGUST 2019, A TOTAL OF 13,970 PATIENTS UNDERWENT RANDOMIZATION;
- 6992 WERE ASSIGNED TO THE BEMPEDOIC ACID GROUP AND
- 6978 TO THE PLACEBO GROUP.
- THE BASELINE CHARACTERISTICS OF THE PATIENTS IN THE TRIAL GROUPS WERE SIMILAR.

- **THE MEAN (±SD) AGE WAS 65.5±9.0 YEARS,** 6740 PATIENTS **(48.2%) WERE FEMALE,** 6373 **(45.6%) HAD DIABETES,** 9764 (**69.9%) HAD A PREVIOUS CARDIOVASCULAR EVENT,** 3174 (**22.7%**) **WERE TAKING A STATIN,** AND **1612 (11.5%**) **WERE RECEIVING EZETIMIBE.**

- THE MEAN LDL-CHOLESTEROL LEVEL WAS 139.0 MG PER DECILITER (3.59 MMOL PER LITER), THE MEAN HIGH-DENSITY LIPO- PROTEIN CHOLESTEROL LEVEL 49.5 MG PER .

- DIFFERENCES IN EFFECTS WERE ALSO OBSERVED BETWEEN BEMPEDOIC ACID AND STATINS OR OTHER LIPID LOWERING NONSTATIN THERAPIES.

- UNLIKE STATINS, BEMPEDOIC ACID, AS COMPARED WITH PLACEBO, **DID NOT INCREASE GLYCATED HEMOGLOBIN LEVELS OR THE INCIDENCE OF NEW ONSET DIABETES.**

- **SIX MONTHS OF TREATMENT** WITH BEMPEDOIC ACID RESULTED IN A **21.6% REDUCTION IN THE HIGH-SENSITIVITY CRP LEVEL RELATIVE TO PLACEBO**.

- FURTHER STUDY IS NEEDED TO DETERMINE WHETHER THE REDUCTION IN THE HIGH-SENSITIVITY CRP LEVEL WITH BEMPEDOIC ACID CONTRIBUTED TO THE OBSERVED BENEFITS.

Table 2. Efficacy End Points in the Intention-to-Treat Population.*

Outcome	Bempedoic Acid (N=6992)	Placebo (N=6978)	Difference (95% CI)*	P Value†
Primary efficacy end point				
Four-component MACE — no. (%)‡	819 (11.7)	927 (13.3)	0.87 (0.79 to 0.96)	0.004
Key secondary efficacy end points				
Three-component MACE — no. (%)§	575 (8.2)	663 (9.5)	0.85 (0.76 to 0.96)	0.006
Fatal or nonfatal myocardial infarction — no. (%)	261 (3.7)	334 (4.8)	0.77 (0.66 to 0.91)	0.002
Coronary revascularization — no. (%)	435 (6.2)	529 (7.6)	0.81 (0.72 to 0.92)	0.001
Fatal or nonfatal stroke — no. (%)	135 (1.9)	158 (2.3)	0.85 (0.67 to 1.07)	0.16
Death from cardiovascular causes — no. (%)	269 (3.8)	257 (3.7)	1.04 (0.88 to 1.24)	
Death from any cause — no. (%)	434 (6.2)	420 (6.0)	1.03 (0.90 to 1.18)	
Additional secondary end points				
Death from any cause, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization — no. (%)	962 (13.8)	1062 (15.2)	0.89 (0.82 to 0.97)	
Five-component MACE — no. (%)¶	831 (11.9)	952 (13.6)	0.86 (0.78 to 0.94)	
Hospitalization for unstable angina — no. (%)	91 (1.3)	137 (2.0)	0.66 (0.50 to 0.86)	
New-onset type 2 diabetes mellitus — no./total no. (%)‖	429/3848 (11.1)	433/3749 (11.5)	0.95 (0.83 to 1.09)	
Change from baseline in secondary lipid and biomarker efficacy end points				
Mean percent change in mean LDL cholesterol level at 6 mo (95% CI)**	−21.1 (−21.6 to −20.5)	−0.8 (−1.4 to −0.2)	−20.3 (−21.1 to −19.5)	
Median percent change in high-sensitivity CRP level at 6 mo (95% CI)	−22.2 (−23.5 to −20.8)	2.4 (0.0 to 4.2)	−21.6 (−23.7 to −19.6)	
Mean percentage-point change in glycated hemoglobin level at 12 mo in patients with inadequately controlled type 2 diabetes mellitus (95% CI)**††	−0.04 (−0.12 to 0.03)	−0.01 (−0.09 to 0.06)	−0.03 (−0.14 to 0.08)	

* The patients were followed for a median of 40.6 months. Differences are given as the hazard ratio for the primary efficacy end point, the key secondary efficacy end points, and the additional secondary end points and as the percentage-point difference for the changes from baseline in secondary lipid and biomarker efficacy end points.

† As prespecified in the hierarchical testing procedure, all P values after the first nonsignificant P value are not presented.

‡ The primary efficacy end point was a four-component composite of adjudicated major adverse cardiovascular events (MACE), defined as death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization, as assessed in a time-to-first-event analysis.

§ The first key secondary end point was a three-component MACE, defined as death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.

¶ The five-component MACE was defined as death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina.

‖ New-onset type 2 diabetes mellitus was defined as a glycated hemoglobin level of 6.5% or greater or two or more fasting glucose measurements of 126 mg per deciliter (7.0 mmol per liter) or greater in patients with a baseline glycemic status of no diabetes.

** Results were adjusted for baseline LDL cholesterol or glycated hemoglobin levels with the use of a pattern-mixture model for missing data.

†† Inadequately controlled type 2 diabetes was defined as type 2 diabetes and a glycated hemoglobin level of 7% or greater at baseline.

Results:

- The mean LDL cholesterol level after 6 months of treatment with bempedoic acid was 107.0 mg per deciliter (2.77 mmol per liter), as compared with 136.0 mg per deciliter (3.52 mmol per liter) with placebo.

- The observed difference in the percent reductions was 21.1 percentage points (95% confidence interval [CI], 20.3 to 21.9) in favor of bempedoic acid.

- The difference in the percent reductions was 15.9 percentage points in favor of bempedoic acid.

- Among the patients in the placebo group, 15.6% received additional lipid-lowering therapy, as compared with 9.4% of the patients in the bempedoic acid group.

- At 6 months, the difference in the percent change in the median high-sensitivity CRP level was -21.6 percentage,points (95% CI, −23.7 to −19.6) in favor of bempedoic acid.

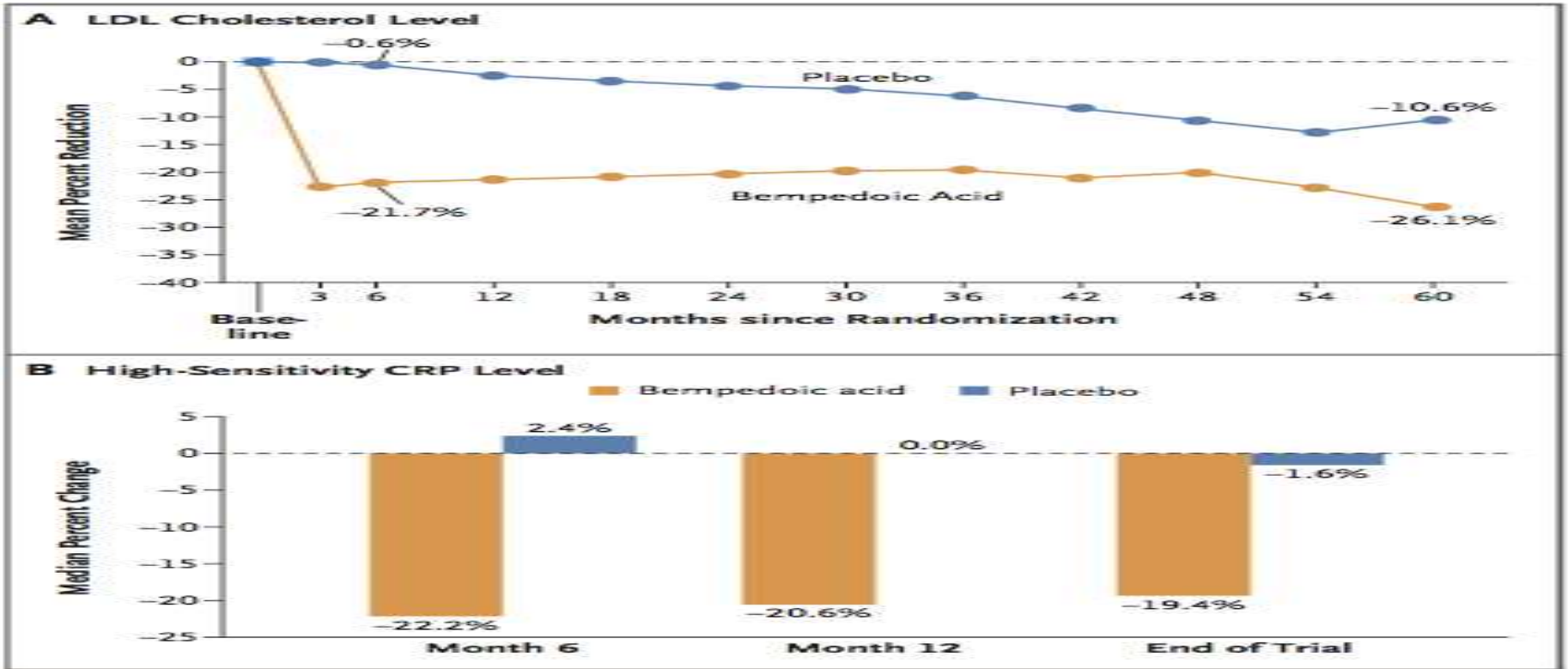

Figure 1. Changes in LDL Cholesterol and High-Sensitivity CRP Levels over Time.

Panel A shows the percent changes from baseline in the low-density lipoprotein (LDL) cholesterol level in the bempedoic acid group and placebo group throughout the trial. The mean baseline LDL cholesterol level in both groups was 139.0 mg per deciliter. The time-averaged difference in the reduction in LDL cholesterol level between the bempedoic acid group and the placebo group over the duration of the trial was −22.0 mg per deciliter (−0.57 mmol per liter); the difference in percent reduction was 15.9 percentage points in favor of bempedoic acid. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. Panel B shows the changes from baseline in the high-sensitivity C-reactive protein (CRP) level in the bempedoic acid group and placebo group at several time points during the trial. The median baseline high-sensitivity CRP was 2.3 mg per liter.

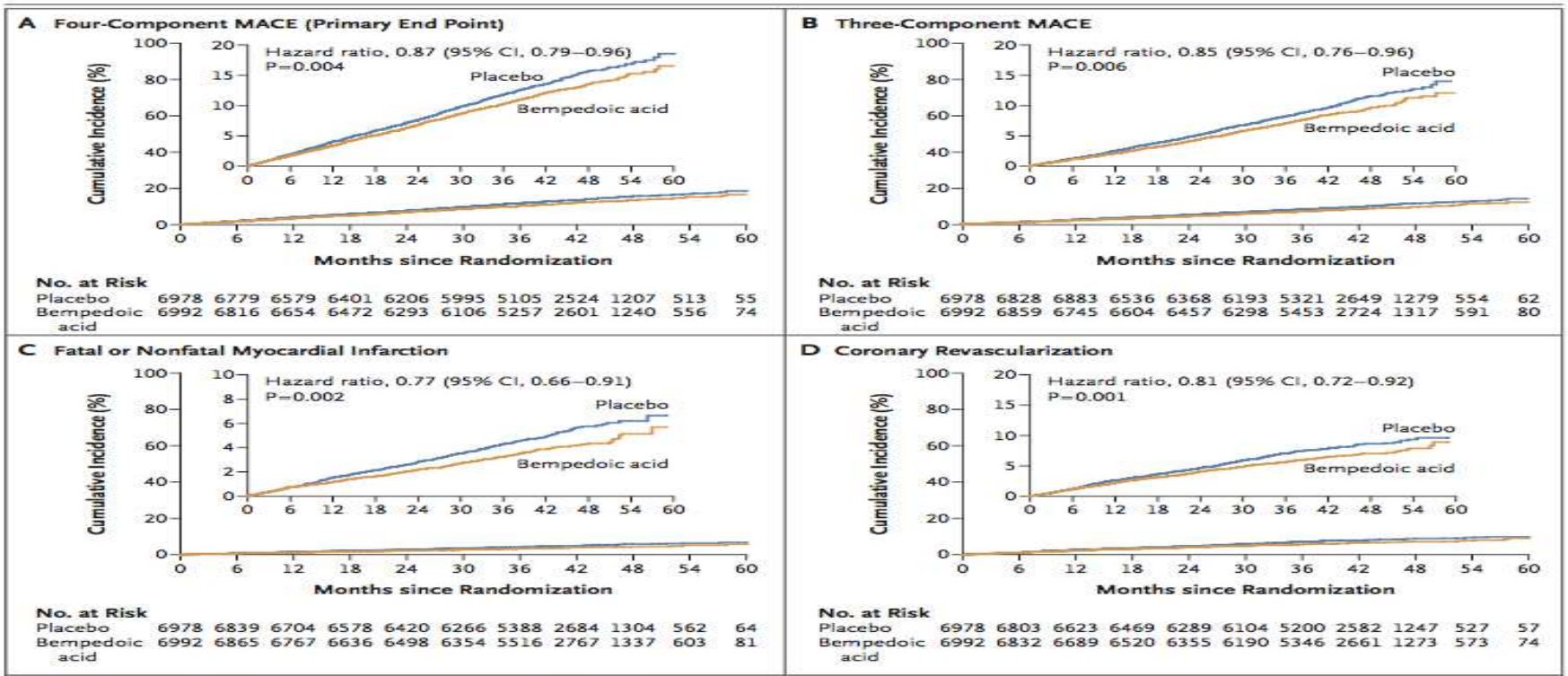

Figure 2. Cumulative Incidence of Cardiovascular Events.

Panel A shows the cumulative incidence of a primary end-point event, a four-component composite of major adverse cardiovascular events (MACE), defined as death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization. Panel B shows the cumulative incidence of a three-component MACE, defined as death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke (the first key secondary end point). Panel C shows the cumulative incidence of fatal or nonfatal myocardial infarction (the second key secondary end point). Panel D shows the cumulative incidence of coronary revascularization (the third key secondary end point). The definitions of all end points are provided in the Supplementary Appendix. In each panel, the inset shows the same data on an enlarged y axis. The P values were calculated with the use of the log-rank test.

DISCUSSION

- **THE RISK OF A PRIMARY END-POINT EVENT (DEATH FROM CARDIOVASCULAR CAUSES, NONFATAL MYOCARDIAL INFARCTION, NONFATAL STROKE, OR CORONARY REVASCULARIZATION) WAS SIGNIFICANTLY LOWER BY 13% WITH BEMPEDOIC ACID THAN WITH PLACEBO AFTER A MEDIAN OF 40.6 MONTHS OF FOLLOWUP, WITH AN ABSOLUTE BETWEEN GROUP DIFFERENCE IN INCIDENCE OF 1.6 PERCENTAGE POINTS.**

- **THE RISK OF DEATH FROM CARDIOVASCULAR CAUSES, NONFATAL STROKE, OR NONFATAL MYOCARDIAL INFARCTION (THE FIRST KEY SECONDARY END POINT) WAS 15% LOWER WITH BEMPEDOIC ACID THAN WITH PLACEBO, AND THE RISKS OF FATAL OR NONFATAL MYOCARDIAL INFARCTION AND CORONARY REVASCULARIZATION WERE 23% LOWER AND 19% LOWER, RESPECTIVELY.**

- **At 6 months, the observed reduction in mean LDL cholesterol level in the bempedoic acid group was greater than that in the placebo group, and bempedoic acid reduced the high- sensitivity CRP level as compared with placebo.**

- **The observed lower incidence of cardiovascular events suggests that bempedoic acid is among the medications that lower the LDL cholesterol level and have clinically meaningful cardiovascular benefits.**

Adverse events:

Table 3. Investigator-Reported Adverse Events and Laboratory Safety-Related Findings in the Safety Population.*

Event	Bempedoic Acid (N = 7001)	Placebo (N = 6964)
Any adverse event that started or worsened after the first dose of a trial agent — no. (%)	6040 (86.3)	5919 (85.0)
Serious adverse event that started or worsened after the first dose of a trial agent — no. (%)	1767 (25.2)	1733 (24.9)
Adverse event leading to discontinuation of the trial regimen — no. (%)	759 (10.8)	722 (10.4)
Prespecified adverse events of special interest		
Myalgia — no. (%)	393 (5.6)	471 (6.8)
Discontinuation of the trial regimen because of myalgia — no. (%)	124 (1.8)	129 (1.9)
New-onset diabetes in patients without diabetes at baseline — no./total no. (%)	621/3856 (16.1)	640/3740 (17.1)
New-onset diabetes in patients with prediabetes at baseline — no./total no. (%)†	569/2918 (19.5)	586/2877 (20.4)
New-onset diabetes in patients with normoglycemia at baseline — no./total no. (%)†	52/938 (5.5)	54/863 (6.3)
Worsening hyperglycemia — no./total no. (%)‡	713/3145 (22.7)	746/3224 (23.1)
Hypoglycemia — no. (%)	304 (4.3)	267 (3.8)
Metabolic acidosis — no. (%)	13 (0.2)	11 (0.2)
Elevated hepatic-enzyme level — no. (%)	317 (4.5)	209 (3.0)
Renal impairment — no. (%)	802 (11.5)	599 (8.6)
Neurocognitive disorders — no. (%)	58 (0.8)	69 (1.0)
Atrial fibrillation — no. (%)	229 (3.3)	246 (3.5)
Adjudicated tendon rupture — no. (%)	86 (1.2)	66 (0.9)
Tendinopathies — no. (%)	118 (1.7)	128 (1.8)
Malignant conditions — no. (%)	321 (4.6)	341 (4.9)
Other adverse events — no. (%)		
Hyperuricemia	763 (10.9)	393 (5.6)
Gout	215 (3.1)	143 (2.1)
Cholelithiasis	152 (2.2)	81 (1.2)
Laboratory results after 6 mo — mg/dl		
Change from baseline in uric acid level	0.76±1.2	−0.03±1.0
Change from baseline in creatinine level	0.05±0.2	0.01±0.2
Laboratory results after 12 mo		
Change from baseline in glycated hemoglobin level — %§	0.04±0.74	0.06±0.70
Abnormal enzyme level at any visit — no. (%)		
Creatine kinase level >5× ULN, single occurrence	45 (0.6)	40 (0.6)
Creatine kinase level >5× ULN, repeated and confirmed	8 (0.1)	8 (0.1)
Creatine kinase level >10× ULN, single occurrence	18 (0.3)	15 (0.2)
Creatine kinase level >10× ULN, repeated and confirmed	2 (<0.1)	4 (0.1)
Alanine aminotransferase level >3× ULN¶	83 (1.2)	53 (0.8)
Aspartate aminotransferase level >3× ULN¶	80 (1.1)	43 (0.6)

Limitations:

- A major limitation of the trial was the inclusion of only patients who had reported that they were unable or unwilling to take statins, a factor that resulted in a high mean LDL cholesterol level at baseline.

- The effects of bempedoic acid on cardiovascular events in populations with lower LDL cholesterol levels and in patients taking conventional therapeutic doses of statins were not studied.

Similar articles

•Efficacy and Safety of Bempedoic Acid in Patients With Hypercholesterolemia and Statin Intolerance.Laufs U, Banach M, Mancini GBJ, Gaudet D, Bloedon LT, Sterling LR, Kelly S, Stroes ESG.J Am Heart Assoc. 2019 Apr 2;8(7):e011662. doi: 10.1161/JAHA.118.011662.PMID: 30922146 Free PMC article. Clinical Trial.

•Bempedoic Acid: a cholesterol lowering agent with a novel mechanism of action.Nguyen H, Akamnonu I, Yang T.Expert Rev Clin Pharmacol. 2021 May;14(5):545-551. doi: 10.1080/17512433.2021.1901579. Epub 2021 Mar 18.PMID: 33691561 Review.

•Efficacy and safety of bempedoic acid added to ezetimibe in statin-intolerant patients with hypercholesterolemia: A randomized, placebo-controlled study.Ballantyne CM, Banach M, Mancini GBJ, Lepor NE, Hanselman JC, Zhao X, Leiter LA.Atherosclerosis. 2018 Oct;277:195-203. doi: 10.1016/j.atherosclerosis.2018.06.002. Epub 2018 Jun 12.PMID: 29910030 Clinical Trial.

•Association of Bempedoic Acid Administration With Atherogenic Lipid Levels in Phase 3 Randomized Clinical Trials of Patients With Hypercholesterolemia.Banach M, Duell PB, Gotto AM Jr, Laufs U, Leiter LA, Mancini GBJ, Ray KK, Flaim J, Ye Z, Catapano AL.JAMA Cardiol. 2020 Oct 1;5(10):1124-1135. doi: 10.1001/jamacardio.2020.2314.PMID: 32609313 Free PMC article.

•Clinical development of bempedoic acid: phase 2 and phase 3 clinical trials.Lekuona I, Pintó X.Clin Investig Arterioscler. 2021 May;33 Suppl 1:58-64. doi:

REFERENCES

1. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. Circulation 2019;139(25):e1082-e1143.
2. Stroes ES, Thompson PD, Corsini A, et al. Statin-associated muscle symptoms: impact on statin therapy — European Atherosclerosis Society Consensus Panel statement on assessment, aetiology and management. Eur Heart J 2015;36:1012-22.
3. Bytyçi I, Penson PE, Mikhailidis DP, et al. Prevalence of statin intolerance: a meta-analysis. Eur Heart J 2022;43:3213-23.
4. Hovingh GK, Gandra SR, McKendrick J, et al. Identification and management of patients with statin-associated symptoms in clinical practice: a clinician survey. Atherosclerosis 2016;245:111-7.
5. Zhang H, Plutzky J, Shubina M, Turchin A. Continued statin prescriptions after adverse reactions and patient outcomes: a cohort study. Ann Intern Med 2017;167:221-7.
6. 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.
7. Thompson PD, Rubino J, Janik MJ, et al. Use of ETC-1002 to treat hypercholesterolemia in patients with statin intolerance. J Clin Lipidol 2015;9:295-304.
8. Ballantyne CM, Davidson MH, Macdougall DE, et al. Efficacy and safety of a novel dual modulator of adenosine triphosphate-citrate lyase and adenosine monophosphate-activated protein kinase in patients with hypercholesterolemia: results of a multicenter, randomized, double-blind, placebo-controlled, parallel-group trial. J Am Coll Cardiol 2013;62:1154-62.
9. Ray KK, Bays HE, Catapano AL, et al. Safety and efficacy of bempedoic acid to reduce LDL cholesterol. N Engl J Med 2019;380:1022-32.
10. Goldberg AC, Leiter LA, Stroes ESG, et al. Effect of bempedoic acid vs placebo added to maximally tolerated statins on low-density lipoprotein cholesterol in patients at high risk for cardiovascular disease: the CLEAR Wisdom randomized clinical trial. JAMA 2019;322:1780-8.
11. Ballantyne CM, Banach M, Mancini GBJ, et al. Efficacy and safety of bempedoic acid added to ezetimibe in statin-intolerant patients with hypercholesterolemia: a randomized, placebo-controlled study. Atherosclerosis 2018;277:195-203.
12. Laufs U, Banach M, Mancini GBJ, et al. Efficacy and safety of bempedoic acid in patients with hypercholesterolemia and statin intolerance. J Am Heart Assoc 2019;8(7):e011662-112.
13. Nicholls SJ, Lincoff AM, Bays HE, et al. Rationale and design of the CLEAR-out-


THREE THANKS
1.FOR ARRANGING THE SESSION
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