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ORIGINAL ARTICLE

# Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients

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# CLEAR OUTCOMES

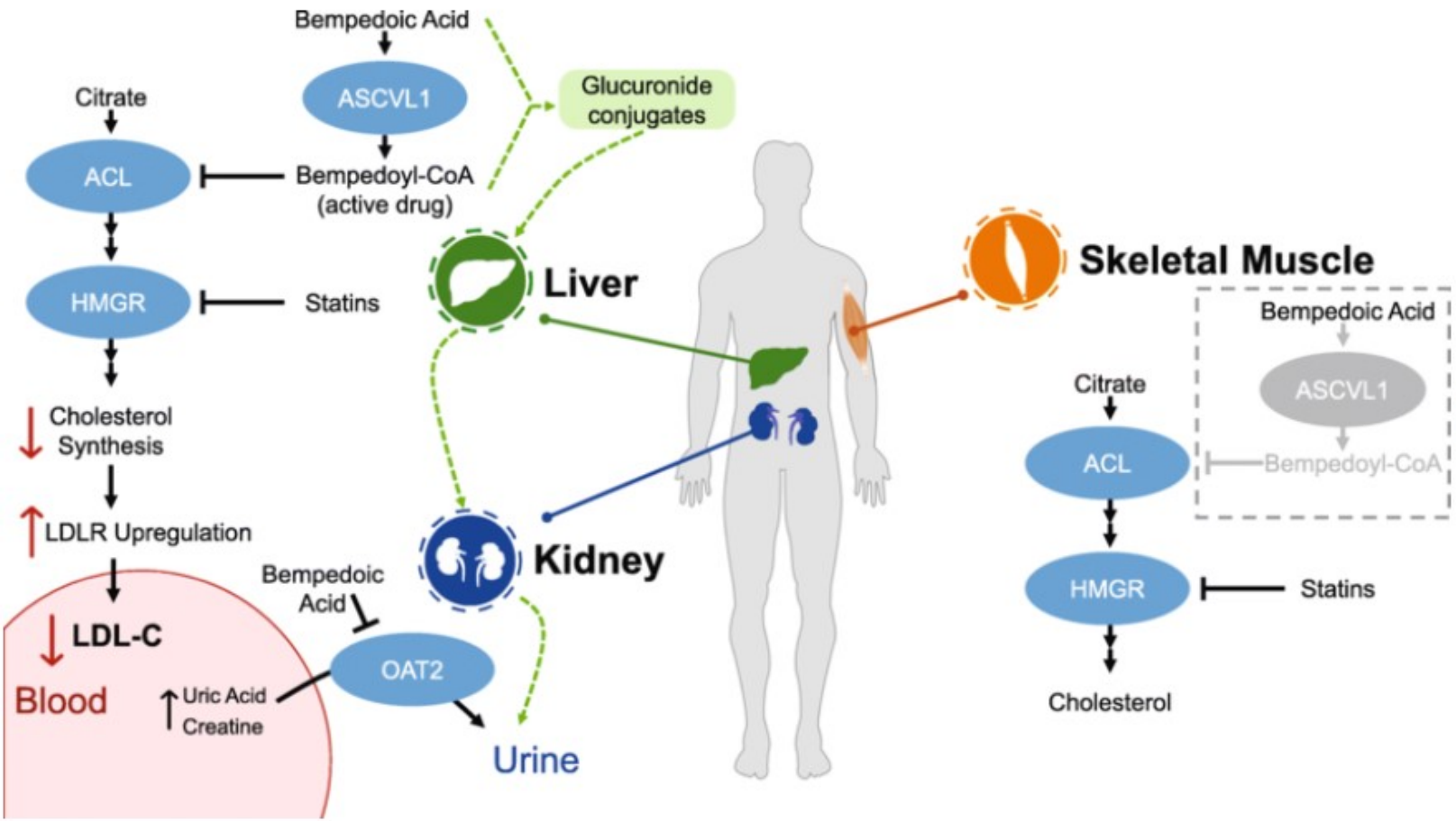
- Μαλκότς Μπελκίς
- Ειδικευόμενη Καρδιολογίας
- Πανεπιστημιακή Καρδιολογική Κλινική ΠΓΝΑ
- Διευθυντής: Καθ. Τζιακάς Δημήτριος

OBJECTIVE: To evaluate the effect of bempedoic acid on CV events in statin intolerant patients at high risk of or with established atherosl erotic CV disease (ASCVD)

International, multicenter, double-blind, randomized, placebo-controlled trial

1250 sites in 32 countries

7-29% of patients report adverse musculoskeletal effects with statins





Mechanism of action and physiologic sites of bempedoic acid metabolism, activation, biologic activity, and clearance. Following oral administration, bempedoic acid is converted to its active metabolite bempedoyl-CoA by ASCVL1 in the liver. Bempedoyl-CoA inhibits the cytoplasmic ACL enzyme, which converts citrate to acetyl-CoA in the cholesterol synthesis pathway, leading to upregulation of LDLR. ASCVL1 is not present in the muscle so is not converted to bempedoyl-CoA. Clearance of bempedoic acid and bempedoyl-CoA is primarily enacted by glucuronidation and subsequent renal elimination. Bempedoic acid is a weak inhibitor of OAT2, resulting in minor increases in plasma uric acid and creatinine. ACL ATP-citrate lyase, ASCVL1 very long-chain acyl-CoA syntheasae-1, HMGR 3-hydroxy-3-methylglutarate-CoA reductase, LDL-C low-density lipoprotein cholesterol, LDLR low-density lipoprotein receptor, OAT2 organic anion transporter-2

# Inclusion Criteria

- Age between 18 and 85 years
- History of, or at high risk for, cardiovascular disease (CVD) including coronary artery disease, symptomatic peripheral arterial disease, cerebrovascular atherosclerotic disease, or at high risk for a cardiovascular event
- Patient reported history of statin intolerance (inability to tolerate 2 or more statins, one at a low dose)
- Men and nonpregnant, nonlactating women
- Fasting blood LDL-cholesterol ≥ 100 mg/dl (2.6 mmol/L) at screening

# Exclusion Criteria

- Fasting blood triglycerides greater than 500 mg/dL (5.6 mmol/L) at screening
- Recent (within 90 days of screening) history of major cardiovascular events, transient ischemic attack (TIA), or unstable or symptomatic cardiac arrhythmia
- History of severe heart failure
- Uncontrolled hypertension or uncontrolled diabetes

# 3,970 patients

December 2016 and August 2019

6992 >bempedoic acid group

6978 >placebo group

median of follow-up was 40.6 months

mean LDL cholesterol level at baseline was 139.0 mg/dl

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 |

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

| Characteristic | Bempedoic Acid (N=6992) | Placebo (N=6978) |
|---|---|---|
| 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) |

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

| Characteristic | Bempedoic Acid (N=6992) | Placebo (N=6978) |
|---|---|---|
| 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) |

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

| Characteristic | Bempedoic Acid (N=6992) | Placebo (N=6978) |
|---|---|---|
| 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.

# Primary Endpoints

- CV death
- nonfatal myocardial infarction (MI)
- nonfatal stroke
- coronary revascularization

# Key secondary end points- hierarchical order

a three-component composite of death from cardiovascular causes, nonfatal stroke, or nonfatal myocardial infarction

fatal or nonfatal myocardial infarction

coronary revascularization

fatal or nonfatal stroke

death from cardiovascular causes

death from any cause

# RESULTS

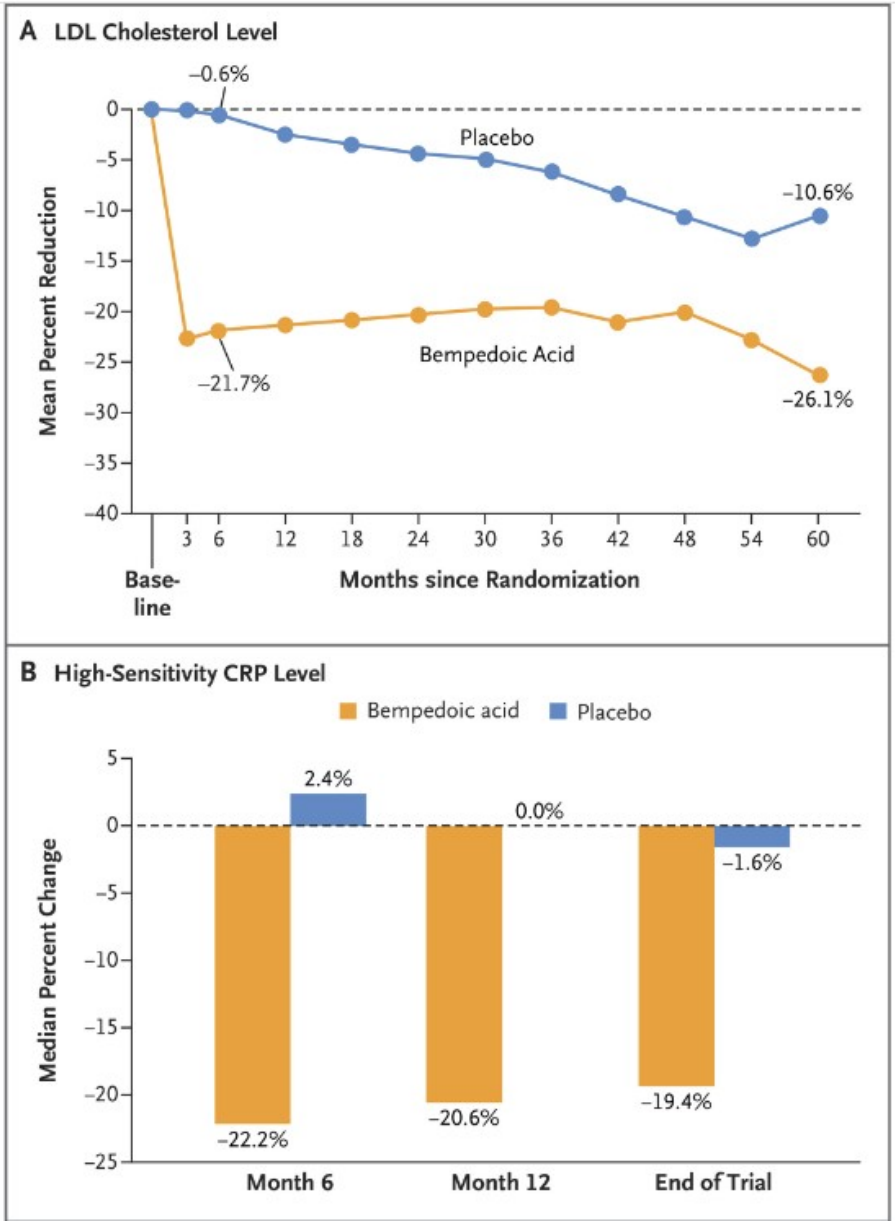



**Figure 1. Changes in LDL Cholesterol and High-Sensitivity CRP Levels over Time.**

**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) | |

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

| Outcome | Bempedoic Acid (N=6992) | Placebo (N=6978) | Difference (95% CI)* | P Value† |
|---|---|---|---|---|
| **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) | |

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

| Outcome | Bempedoic Acid (N=6992) | Placebo (N=6978) | Difference (95% CI)* | P Value† |
|---|---|---|---|---|
| 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,

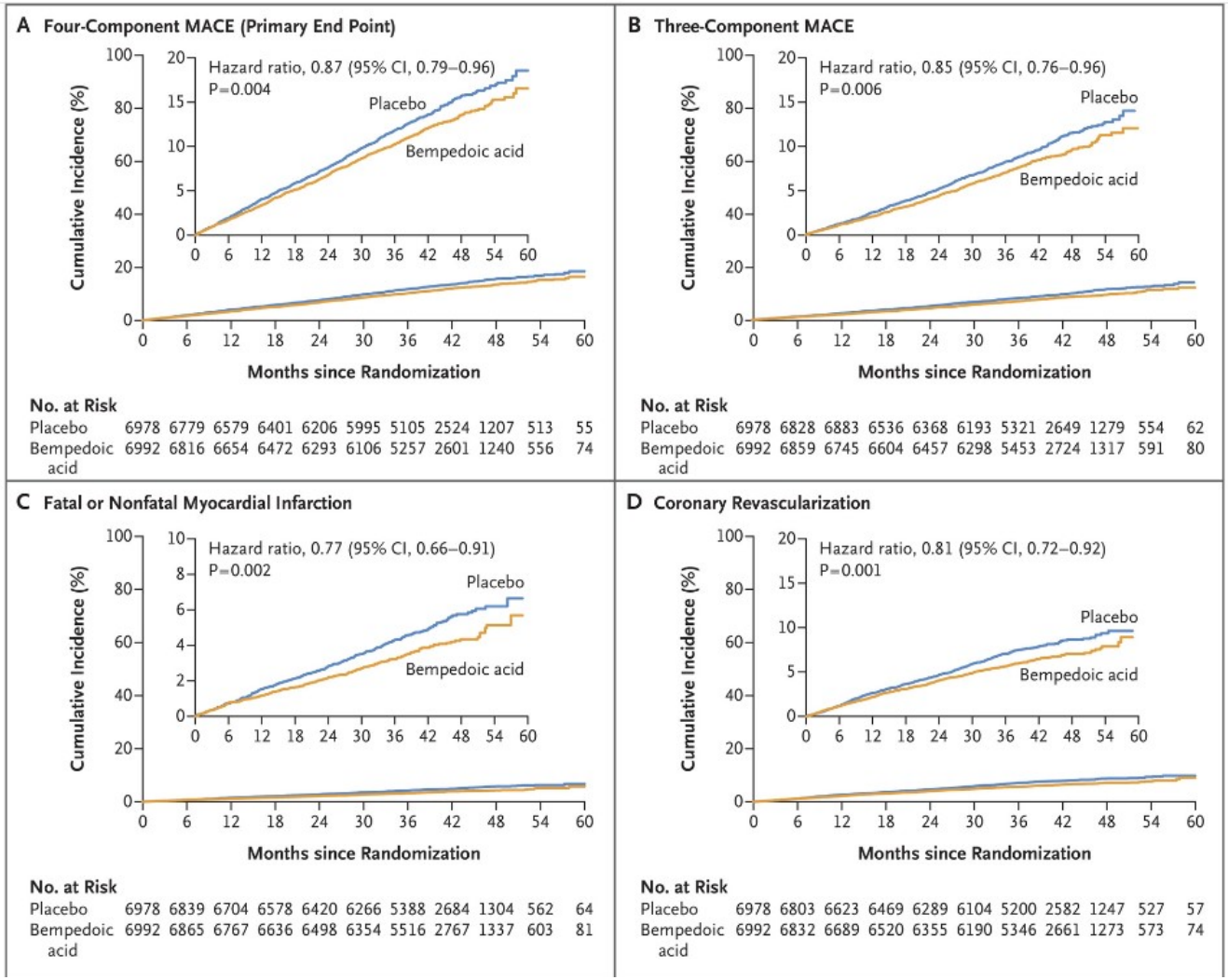



**Figure 2. Cumulative Incidence of Cardiovascular Events**

# 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) |

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

| Event | Bempedoic Acid (N=7001) | Placebo (N=6964) |
|---|---|---|
| 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) |

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

| Event | Bempedoic Acid (N=7001) | Placebo (N=6964) |
|---|---|---|
| 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) |

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

| Event | Bempedoic Acid (N=7001) | Placebo (N=6964) |
|---|---|---|
| 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) |

* Plus–minus values are means ±SD. The safety population included all patients who underwent randomization and received at least one dose of bempedoic acid or placebo; patients who received any dose of double-blind bempedoic acid were placed in the bempedoic acid group in the safety analyses. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for uric acid to micromoles per liter, multiply by 59.48. ULN denotes upper limit of the normal range.

† Prediabetes at baseline was defined as no medical history of diabetes plus a glycated hemoglobin level of 5.7 to less than 6.5% or one or more fasting glucose measurements of 100 mg per deciliter (5.6 mmol per liter) or greater but not more than one fasting glucose measurement of 126 mg per deciliter (7.0 mmol per liter) or greater. Patients with normoglycemia at baseline

# DISCUSSION

- None of LDL cholesterol–lowering nonstatin therapies(PCSK-9 inh., ezetimibe), including bempedoic acid, reduced the risk of death from cardiovascular causes, which may reflect the effectiveness of contemporary adjunctive therapies, the need for a longer treatment duration to reduce this risk, or a lack of effect of the drugs on mortality.

- Unlike statins, bempedoic acid, as compared with placebo, did not increase glycated hemoglobin levels or the incidence of new-onset diabetes

months of treatment with bempedoic acid resulted in a 21.6%
luction in the high-sensitivity CRP level relative to placebo.  statins
luce CRP level, but neither PCSK9 inhibitors nor ezetimibe
notherapy have shown reductions in biomarkers associated with
ammation

e concept of statin intolerance remains controversial, with some
ent studies suggesting that reported adverse effects represent an
ticipation of harm, often described as the nocebo effect

- A major limitation of trial>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

# CONCLUSIONS

- Among statin-intolerant patients, treatment with bempedoic acid was associated with a lower risk of major adverse cardiovascular events (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization)

# Ευχαριστώ