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RESEARCH LETTER

Impact of Bempedoic Acid on Cardiovascular Outcomes by Sex

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Lipid lowering therapies are crucial to reduce cardiovascular risk, yet outcomes data in women are limited. Further, women are less likely to have hypercholesterolemia diagnosed or treated and more likely to report statin intolerance.[1] CLEAR (Cholesterol Lowering via Bempedoic Acid [ECT1002], an ACL-Inhibiting Regimen) Outcomes showed patients with, or at high risk for, cardiovascular disease who are unable or unwilling to take guideline-recommended doses of statins had a significantly lower risk of major adverse cardiovascular events (MACE) with bempedoic acid, an ATP citrate lyase inhibitor, than with placebo.[2] CLEAR Outcomes is notable for having 48% (n=6740) female subjects—the highest percentage enrollment of females among contemporary lipid-lowering outcomes trials—affording the opportunity to assess whether improvements in cardiovascular risk seen with bempedoic acid varied by sex.[2,3]

CLEAR Outcomes methods have been previously published.[2] In brief, it was a double-blind, randomized, placebo-controlled trial that enrolled 13 970 patients at 1250 sites in 32 countries.[2] The study was approved by individual site institutional review committees, and participants gave informed consent. Participants were randomized to 180 mg oral bempedoic acid daily or placebo and followed for a median of 3.4 years. Approximately 91% of participants enrolled identified as white race, and 17% as Hispanic/Latinx ethnicity.

STATISTICAL ANALYSIS

A prespecified subgroup analysis based on patient-reported sex was performed for the primary efficacy end point (MACE-4: death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization) and key secondary end point (MACE-3: death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke). The hazard ratio (HR) for the treatment effect was estimated, with placebo as the reference group, within each sex by a Cox regression model and adjusted post hoc for common demographics and baseline characteristics. The proportional hazard assumption was evaluated and not violated. An intent-to-treat population was analyzed for efficacy, and the treated population was analyzed for safety.

The data will not be made publicly available.

EFFICACY END POINT

Bempedoic acid reduced cardiovascular risk and LDL-C similarly in both females and males (Figure). In females, the primary end point of MACE-4 occurred in 8.4% of females on bempedoic acid versus 9.7% on placebo (adjusted HR, 0.89 [95% CI, 0.75–1.04]). For males, MACE-4 occurred in 14.8% on bempedoic acid versus 16.6% on placebo (adjusted HR, 0.86 [95% CI, 0.77–0.97]). In females, MACE-3 occurred in 6.1% on bempedoic acid versus 7.2% on placebo (HR, 0.88 [95% CI, 0.73–1.06]).

Key Words: bempedoic acid ■ cardiovascular risk ■ hypercholesterolemia ■ sex

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Nonstandard Abbreviations and Acronyms

CLEAR	Cholesterol Lowering via Bempedoic Acid (ECT1002), an ACL-Inhibiting Regimen
HR	hazard ratio
MACE	major adverse cardiovascular events

For males, MACE-3 occurred in 10.2% on bempedoic acid versus 11.6% on placebo (HR, 0.84 [95% CI, 0.73–0.97]). The interaction *P* values for sex were not statistically significant for MACE-4 (*P*=0.82) and MACE-3 (*P*=0.84). These adjusted HRs are similar to the unadjusted reported previously.[2]

SAFETY

The overall incidences of serious adverse events, adverse events (eg, discontinuation because of myalgias, repeated and confirmed aminotransferase elevations in alanine aminotransferase or aspartate aminotransferase >3 times upper limit of normal, gout, and cholelithiasis), and changes in laboratory parameters (mean changes in uric acid and serum creatinine from baseline to 6 months) did not differ meaningfully between females and males. These events occurred at a similar frequency or magnitude

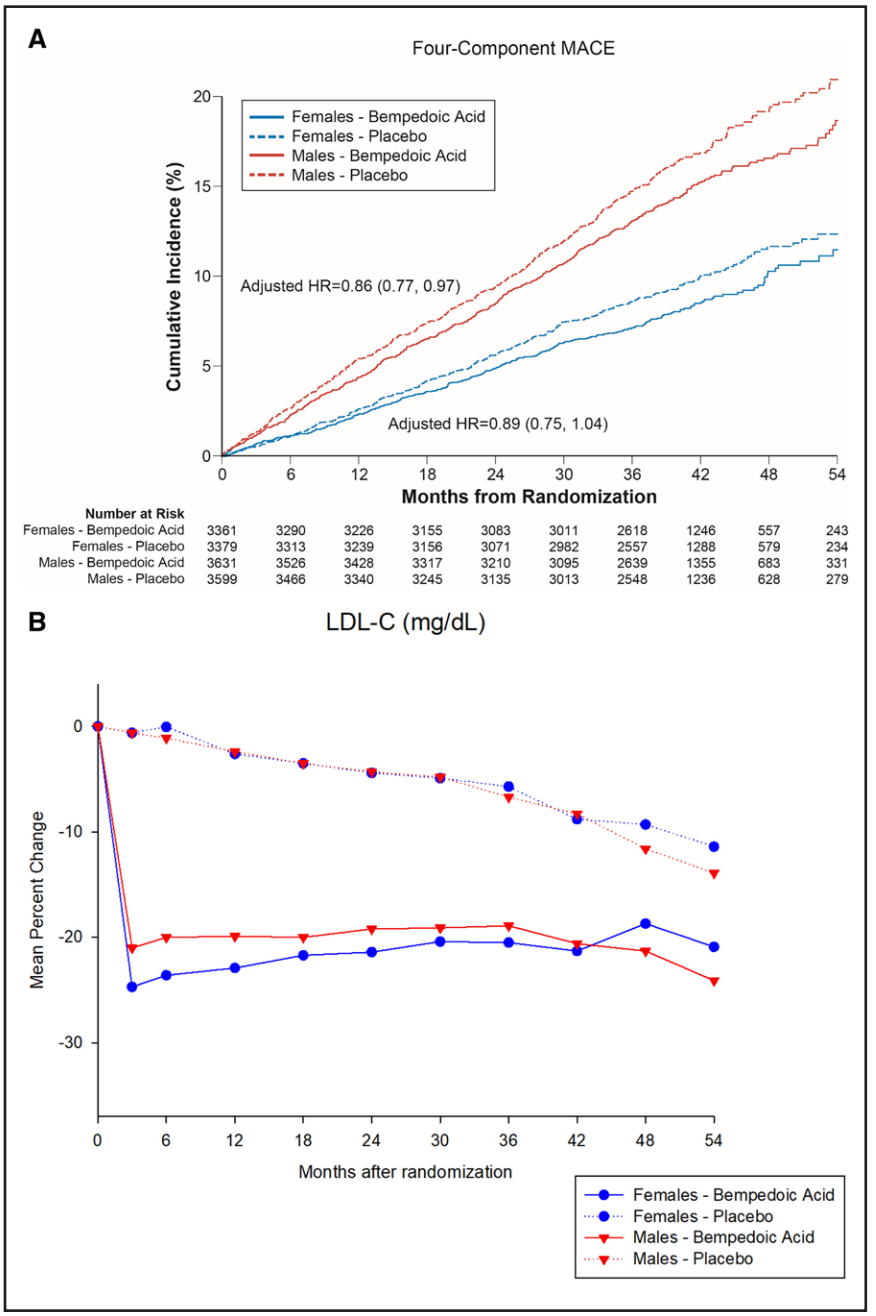

Figure. Cumulative incidence of four-component major adverse cardiovascular events (MACE) and change in LDL cholesterol over time by sex.
A, Cumulative incidence of four-component MACE. **B**, Change in LDL-C over time by sex. HR indicates hazard ratio; LDL-C, low-density lipoprotein cholesterol; and MACE, major adverse cardiovascular events.

as those previously reported in the overall population for bempedoic acid versus placebo regardless of sex.[2] At month 6, the mean (SD) changes in serum creatinine from baseline for bempedoic acid versus placebo were 0.05 (0.16) versus 0.01 (0.14) mg/dL for females, respectively, and 0.05 (0.18) versus 0.01 (0.21) mg/dL for males, respectively. Mean (SD) changes in uric acid were 0.76 (1.15) versus −0.01 (0.96) mg/dL for females and 0.77 (1.28) versus −0.04 (1.08) mg/dL for males.

In CLEAR Outcomes, the risk of a primary end point event, MACE-4, was similarly reduced for patients on bempedoic acid compared with placebo for both females and males. Like other cardiovascular trials, specifically cholesterol lowering trials, the overall cardiovascular event rates in both study arms were lower for females compared with males. Encouragingly, no difference was seen in the rate of adverse events in females enrolled in CLEAR Outcomes versus males.

Although the concept of statin intolerance remains controversial and is a limitation of this study, clinical data and experience have established that some patients are unable or unwilling to take a statin at all or at the recommended dose. Alternative nonstatin lipid modifying therapies, given alone or in combination, are needed to manage patients to guideline-recommended low-density lipoprotein cholesterol thresholds, especially using agents that have demonstrated a reduction in cardiovascular risk and events.[4,5]

CONCLUSIONS

Irrespective of sex in CLEAR Outcomes, similar efficacy and tolerability with bempedoic acid compared with placebo were reported, making bempedoic acid an important option for health care providers and patients to reduce cardiovascular risk.

ARTICLE INFORMATION

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT02993406.

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Dr Cho reported serving on the steering committee for the CLEAR Outcomes trial. Dr Plutzky reported clinical trial support from Esperion, including the steering committee for the CLEAR Outcomes trial, Boehringer Ingelheim (grant support, clinical trial), Novo Nordisk (consultant, SELECT Steering Committee), New Amsterdam, Novartis (grant support), Myome (consultant), and Altimmune (consultant). Prof Nicholls reported receiving grants from Esperion, AstraZeneca, New Amsterdam Pharma, Amgen, Anthera, Eli Lilly, Esperion, Novartis, Cerenis, The Medicines Company, Resverlogix, InfraReDx, Roche, Sanofi-Regeneron, and LipoScience; receiving honoraria to his institution from AstraZeneca, Amarin, Akcea, Eli Lilly, Anthera, Omthera, Merck, Takeda, Resverlogix, Sanofi-Regeneron, CSL Behring, Esperion, Boehringer Ingelheim, Vaxxinity, and Sequiris; and being a named inventor on a patent for PCSK9 inhibitors and atherosclerosis. Dr Lincoff reported receiving Esperion research funding for this trial; receiving grants from Eli Lilly, AbbVie, CSL, AstraZeneca, and Novartis; and receiving personal fees from Novo Nordisk, Glaxo, Akebia, Endologix, Fibrogen, Provention, and Becton Dickson. Dr Nissen reported receiving grants to perform clinical trials from AbbVie, AstraZeneca, Amgen, Arrowhead Pharmaceuticals, Bristol Myers Squibb, Eli Lilly, Esperion Therapeutics Inc, Medtronic, MyoKardia, New Amsterdam Pharmaceuticals, Novartis, and Silence Therapeutics. Dr Louie reported he was an employee of Esperion Therapeutics Inc during the conduct of the study. Dr Lei, Ms Robinson, and Dr Powell are employees of Esperion Therapeutics Inc. The other author reports no conflicts.

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