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CLEAR Outcomes Trial and Cardiovascular Outcomes

Announcer:
Welcome to CME on ReachMD. This episode is part of our MinuteCME curriculum.

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Dr. Nissen:
I'm Dr. Steven Nissen. I am the Chief Academic Officer of the Heart, Vascular, Thoracic Institute at the Cleveland Clinic. And I'm going to talk with you about the CLEAR Outcomes trial.

This is a trial performed in patients that were statin intolerant, and they had to complain of intolerance to two or more statins, or one statin if unwilling to attempt a second statin, or advised by a physician not to attempt a second statin. The patients were either primary or secondary prevention patients with an LDL cholesterol greater than 100, randomize to bempedoic acid 180 milligrams per day or matching placebo. This was an event-driven trial to 1,620 primary 4-component MACE endpoints. And 810 3-component MACE endpoints with greater than 24 months of follow-up.

The primary and key secondary endpoints are shown here. The primary endpoint was 4-component MACE, nonfatal MI, nonfatal stroke, coronary revascularization, or cardiovascular death. There was hierarchical testing of the key secondary endpoints to preserve study wise alpha at 0.5. That included 3-component MACE, nonfatal and fatal MI, coronary revascularization, fatal and nonfatal stroke, cardiovascular death, and all-cause mortality.

The baseline characteristics, importantly, 48% of these patients were women. We had 30% high-risk primary prevention, and 70% secondary prevention, nearly half were diabetic. The drug, bempedoic acid, reduced LDL cholesterol at the 6-month point, which was where we specified we would measure by 21.7%. The drug also reduced high sensitivity CRP by 22%. The LDL differences between placebo and bempedoic acid narrowed over time but maintained a gradient between the two treatment arms.

This is the primary and first key secondary endpoint, 4-component MACE had a hazard ratio of 0.87 with a P-value of 0.004. Number needed to treat was 63 to prevent one event, and the Kaplan-Meier curve was separated early. 3-component mace had a hazard ratio of 0.85, P was 0.006 with an absolute risk reduction of 1.3%. The big effect was on fatal and nonfatal MI, which was reduced 23%, hazard ratio of 0.77, also highly significant. On the right, coronary revascularization, that's stenting or bypass surgery, hazard ratio of 0.81, highly significant.

There was no effect of the trial regimens on either cardiovascular death or all-cause mortality. All of the recent trials over the last decade of LDL-lowering therapies have failed to show an effect on mortality. Presumably this is because our conjunctive therapies are particularly effective, and death is a late effect of coronary disease events; doesn't occur after the first MI but may occur after the second or third myocardial infarction.

There were some adverse events, but importantly, these patients who were statin intolerant did not withdraw from the bempedoic acid

group in a higher rate than the placebo group. Importantly, new-onset diabetes was not more common. As you know, in statin trials, there was an increase in the risk of diabetes that was not observed with bempedoic acid. There was a 1% absolute increase in gout and a 1% absolute increase in cholelithiasis.

So what did we conclude? Bempedoic acid was well tolerated in a mixed population of primary and secondary prevention patients unable or unwilling to take a statin. The drug lowered LDL cholesterol by 21.7% and CRP by 22.2%, with small increases in the incidence of gout and cholelithiasis. The primary endpoint 4-component MACE was reduced by 13%; 3-component MACE by 15%, myocardial infarction by 23%, and coronary revascularization by 19%. These findings established bempedoic acid as an effective approach to reduce major cardiovascular events in statin-intolerant patients.

Thank you for your attention.

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