Medical Xpress

Darapladib falls short in chronic coronary heart disease

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The novel inflammation inhibitor darapladib showed no primary-endpoint advantage over placebo in patients with chronic coronary heart disease treated with a high level of background care, although it did suggest possible benefits for more specific coronary artery-related endpoints, according to research presented at the American College of Cardiology's 63rd Annual Scientific Session. STABILITY is the first study to test this inflammation-prevention mechanism for reducing the likelihood that plaque will become an artery-blocking clot.

Darapladib strongly inhibits Lp-PLA2, a biomarker of inflammation in blood vessels. In the bloodstream, Lp-PLA2 is generally found on LDL cholesterol. High Lp-PLA2 levels are a risk factor for coronary heart disease and, in animal models, are linked with vulnerable plaque, an unstable waxy buildup in arterial walls that is associated with heart attacks and strokes.

In this international, phase III double-blind trial, 15,828 patients with chronic coronary heart disease (median age 65 years) were randomly assigned to receive a 160-mg darapladib tablet or placebo once daily. No major safety concerns arose; median follow-up was 3.7 years. The primary endpoint of time to first heart attack, stroke and death from cardiovascular causes was not met. Darapladib showed no significant benefit, with 769 events (9.7 percent) compared with 819 events (10.4 percent) for placebo. However, a secondary endpoint looking at a reduction in major coronary events related to the arteries (heart attack, urgent need for angioplasty or bypass surgery, or death) was nominally

significant. The darapladib group had a 10 percent relative risk reduction, with 737 events (9.3 percent) in major coronary events compared with 814 events (10.3 percent) in the placebo group.

"These events are clinically important, with substantial consequences for patients," said Harvey D. White, M.D., director of Coronary Care Unit, Green Lane Cardiovascular Unit, Auckland City Hospital, New Zealand, and a co-chair of the study. "The effects on these endpoints could support the hypothesis that inhibition of Lp-PLA2 with darapladib may alter the composition of atherosclerotic plaques to a less vulnerable state and reduce ischemic events related to coronary artery plaque progression and rupture."

Researchers were surprised to see the high rate of background care in this patient population. At baseline, 93 percent of patients were taking aspirin, 97 percent statins, 79 percent beta-blockers and 77 percent ACE inhibitors or angiotensin receptor blockers, compared with similar rates at the end of the study. "We set out to test the incremental effect of darapladib on top of optimal treatment," White said.

One intriguing finding emerged from subgroup analyses: smokers had a greater decrease in major adverse cardiovascular events than non-smokers.

"Previous studies showed that smokers have higher Lp-PLA2 levels, and it's plausible that smokers may be more responsive to Lp-PLA2 inhibition, but this finding may have occurred by chance and should be considered hypothesis generating," White said.

Ongoing analysis of biomarkers, including Lp-PLA2 levels, and genetic sub-studies of STABILITY may help provide insight about darapladib's potential effects on the prevention of coronary events in patients with stable coronary heart disease. "As with statins, it may take some time for

the anti-inflammatory effect of darapladib to alter the composition of coronary artery plaque, resulting in less vulnerability and fewer coronary events," White said. The modest effect of darapladib on coronary artery-related events seen in this study may heighten interest in SOLID-TIMI 52, a phase III study of darapladib in patients with recent experience of acute coronary disease.

More information: This study will be simultaneously published online in the *New England Journal of Medicine* at the time of presentation.

Provided by American College of Cardiology