From: "[redacted]"
To: Lesley Groff <[redacted]>
Subject: Fwd: FOURIER: Significant LDL Reduction with Evolocumab
Date: Fri, 24 Mar 2017 11:17:36 +0000

Lesley please forward to Jeffrey
rs

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Begin forwarded message:

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Reply-To: Cardiology Alert <[redacted]>

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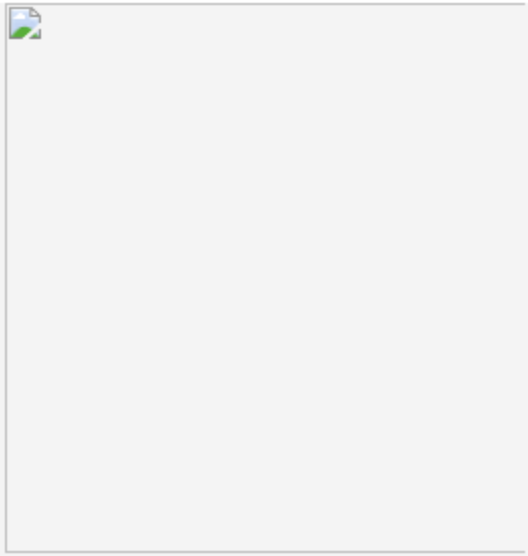
FOURIER: Significant LDL Reduction with Evolocumab

New data from the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) study, presented at the 2017 American College of Cardiology Scientific Session in Washington, [redacted], suggested that evolocumab was associated with significant reductions in LDL cholesterol in patients with atherosclerotic cardiovascular disease and elevated LDL.

The PCSK9 inhibitor evolocumab was the subject of the study. The research team sought to determine the safety and clinical efficacy of the drug when added to statin therapy in patients who have clinically evident atherosclerotic



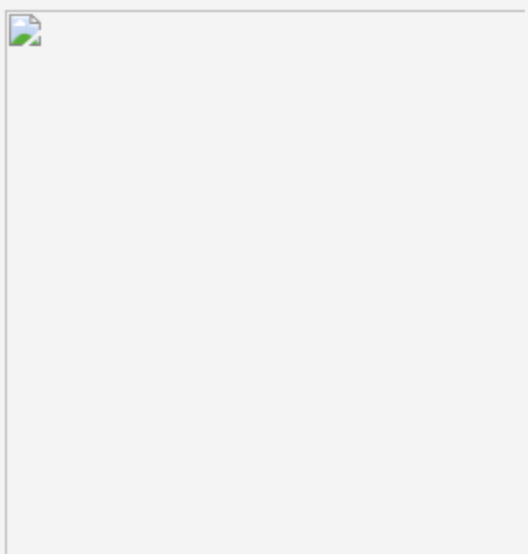
cardiovascular disease. The trial included patients from 1,242 sites in 49 countries.

The double-blind, placebo-controlled study included 27,564 patients who had clinically evident atherosclerotic cardiovascular disease and with a fasting LDL level of 70 mg/dL or higher. All patients were on high-intensity or low-intensity statin therapy. Patients were randomized 1:1 to subcutaneous evolocumab at either 140 mg every two weeks (or 420 mg monthly based on patient preference; n = 13,784) or to placebo (n = 13,780). The primary efficacy endpoint was major cardiovascular events (composite of cardiovascular death, myocardial infarction (MI), stroke, hospitalization for unstable angina, or coronary revascularization). Key secondary efficacy endpoints included a composite of cardiovascular death, MI, or stroke.

Lower LDL, No Effect on Cardiovascular Mortality

The researchers reported that the least-squares mean percentage reduction in LDL cholesterol levels was 59% in patients assigned to evolocumab. The mean absolute reduction from the media LDL baseline of 92 mg/dL down to 30 mg/dL in the evolocumab group ($P < 0.001$). The observed reduction remained steady throughout the trial. For patients in the evolocumab group, LDL was reduced to 70 mg/dL or lower in 87% of the patients and 40 mg/dL or less in 67% of the group, and down to 25 mg/dL in 42% of the patients. These reductions were significantly more substantial than those seen in the placebo group (18%, 0.5% and 0.1% respectively; $P < 0.001$ for all comparisons). In addition, patients in the evolocumab group saw lowered related atherosclerotic lipid measures, such as a 52% reduction in non-HDL cholesterol levels and a 49% reduction in apolipoprotein E levels ($P < 0.001$ for both).

For the primary study endpoint (which occurred in 1,344 patients in the evolocumab group and 1,563 in the placebo group; HR, 0.85; 95% CI, ,0.79-0.92; $P < 0.001$), evolocumab was associated with a significant reduction in the risk for the primary composite endpoint of cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization. Also observed was a significant reduction in the risk for the secondary composite endpoint. The key secondary endpoint occurred in 816 patients (5.9%) in the evolocumab group versus 1,013 (7.4%) in the placebo group (HR, 0.80; 95% CI, 0.73 to 0.88; $P < 0.001$). The beneficiary effect appeared to increase over time in both groups, and were also consistent across quartiles of baseline LDL level (highest, 126 mg/dL to lowest, 74 mg/dL).



"We've never been able to plumb these depths before," lead author Marc S. Sabatine, MD, of Brigham and Women's Hospital and Harvard Medical School, said in a conference press release. "These data strongly suggest that patients benefit from lowering LDL cholesterol well below current targets."

Regarding individual outcomes, no observed effect on cardiovascular mortality was reported by the study team. The P values, they said, should therefore be considered exploratory. The study reported between 21% and 27% reductions in the risk for MI, stroke, and coronary revascularization, but there remained no observed effects on hospitalization rates for unstable angina, cardiovascular death or hospitalization for worsening heart failure, or death from any cause. There were no significant differences between groups in adverse events, serious adverse events, or adverse events thought to be related to the study agent, signaling that evolocumab was well-tolerated and safe. No neutralizing antibodies were reported to develop.

Some Takeaways from FOURIER

One of the issues raised by FOURIER was the issue of decreasing LDL levels to below current recommended target levels.

"These findings show that patients with atherosclerotic cardiovascular disease benefit from the lowering of LDL cholesterol levels below current targets," they wrote in their conclusion.

The major study limitation, the researchers wrote, was the short follow-up period.

"The major limitation of this trial was a relatively short duration of follow-up as compared with that in other lipid-lowering trials, in which follow-up periods have averaged approximately 5 years," the authors wrote. "Although the median follow-up period in FOURIER was originally planned to be approximately 4 years, an event rate that was approximately 50% higher than had been postulated led to a shorter required duration of follow-up to accrue the prespecified number of events."

Dr. Sabatine emphasized the importance of aggressive LDL-lowering treatment in the future.

"We need to treat LDL cholesterol more aggressively, and now we have a new validated means to do so," he said in the press release. "People with atherosclerotic disease should discuss their LDL cholesterol with their physician and consider whether they need to lower it further."

Reference

Sabatine MS, Giugliano RP, Keech AC, et al. *N Engl J Med.* 2017;doi:NEJMoa1615664

http://www.nejm.org/doi/pdf/10.1056/NEJMoa1615664

Sabatine M. *Primary Results of the Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) Trial.* March 17. Presented at: American College of Cardiology 2017 Scientific Session in Washington, D.C.