Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease (FOURIER)

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Trial Summary

Despite advances in treatment, patients with cardiovascular disease remain at high risk for major adverse cardiovascular events. Low-density lipoprotein cholesterol, or LDL-C, is a well-established modifiable cardiovascular risk factor.[1] Evolocumab is a fully humanized monoclonal antibody that inhibits the binding of proprotein convertase subtilisin/kexin type 9 (PCSK9) to LDL receptors, which increases the number of LDL receptors available to clear LDL-C from the blood, thus lowering LDL-C levels.[2] FOURIER was a randomized, double blind, placebo-controlled, multinational clinical trial involving 1,242 sites in 49 countries. Eligible patients received subcutaneous injections of evolocumab (either 140 mg every 2 weeks or 420 mg every month, according to patient preference) or matching placebo. The study's objective was to investigate the clinical efficacy and safety of evolocumab when added to high- or moderate-intensity statin therapy in patients with clinically evident atherosclerotic cardiovascular disease (ASCVD) and an LDL-C level ≥70 mg/dL or a non-HDL-C level ≥100 mg/dL. The median follow-up duration was 2.2 years.[1]

From February 2013 through June 2015, a total of 27,564 patients underwent randomization to either the evolocumab group (13,784 patients) or the placebo group (13,780 patients). At 48 weeks, the mean percentage reduction in LDL-C levels with evolocumab compared to placebo was 59% to a median level of 30 mg/dL (mean absolute reduction of 56 mg/dL). The primary efficacy endpoint of cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization occurred in 1,344 patients (9.8%) in the evolocumab group and in 1,563 patients (11.3%) in the placebo group ($p < 0.001$), resulting in a 15% risk reduction. The key secondary efficacy endpoint of cardiovascular death, MI, or stroke occurred in 816 patients (5.9%) in the evolocumab group and in 1,013 patients (7.4%) in the placebo group ($p < 0.001$), resulting in a 20% risk reduction. Overall, 74 patients would need to be treated over a period of two years to prevent one cardiovascular death, MI, or stroke. Evolocumab had no effect on the individual outcome of cardiovascular mortality so other outcomes should be considered exploratory.[1]

Rates of muscle-related events, rhabdomyolysis, cataracts, new-onset diabetes, neurocognitive adverse events, and allergic reactions did not differ significantly between the two groups. Injection-site reactions were more frequent with evolocumab compared to placebo (2.1% vs. 1.6%). However, only 0.1% of patients in each group stopped receiving the study drug due to an injection-site reaction. Evolocumab-binding antibodies were seen in 43 patients (0.3%), but development of neutralizing antibodies did not occur in any patient.[1]

In conclusion, evolocumab, in addition to statin therapy, lowered LDL-C levels to a median of 30 mg/dL and reduced the risk of cardiovascular events in patients with clinically evident ASCVD. The benefits of evolocumab were consistent across all quartiles of baseline LDL-C levels, and the magnitude of risk reduction was shown to increase over time.[1] The major limitation of this trial was its short duration of follow-up, but there is currently an open-label extension being conducted that will include additional safety data.[3] Therapy with evolocumab is approximately $14,000 per year, whereas a generic statin costs only $250 per year.[4] Therefore, the ideal patient will need to be determined. It is uncertain how these results will influence the guidelines and whether they will revert to the theory that "lowest is best."

Follow-Up Questions

1. **How can we translate the NNT=74 clinically, taking into consideration the cost and the non-significant effect of the drug on mortality?**

Despite the intense lowering of LDL-C, the clinical efficacy of evolocumab appeared modest in this high-risk population, with an absolute benefit of 1.5% driven primarily by non-fatal MI, stroke, and coronary revascularization.[1] A NNT of 74 would translate into ~2 million dollars spent to reduce one event over two years. Additionally, the lack of mortality benefit and the large price tag of evolocumab therapy propagate controversy regarding its clinical utility.

2. **Few patients were also on ezetimibe in this trial. Comparing these results with those of IMPROVE-IT, should we be trying ezetimibe first before a PCSK9 inhibitor?**

Yes, I believe so. The IMPROVE-IT trial of 18,144 patients with ACS showed that simvastatin plus ezetimibe led to a statistically significant reduction in the primary composite endpoint of death from cardiovascular causes, major coronary event, or nonfatal stroke compared to simvastatin alone (32.7% vs. 34.7%, p=0.016, NNT 50).[5] The 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk suggested that the PCSK9 inhibitors may be considered if the goals of therapy have not been achieved on maximally tolerated statin and ezetimibe therapy in higher-risk patients with clinical ASCVD or familial hypercholesterolemia.[6]

3. **Based on these results, do you recommend a more aggressive approach to LDL-lowering for all of our CAD patients?**

Yes, I would recommend a more aggressive approach to LDL-lowering in most CAD patients. The FOURIER trial showed that even when LDL-C was reduced to very low levels, patients still experienced cardiovascular benefit without a statistically significant increase in adverse events. This trial suggested the benefit was related to the absolute reduction in LDL-C and that lower is better.[1]

4. **What are your thoughts on use in post-ACS patients intolerant to statins? Are there any trials pending for using PCSK9 inhibitors without statins?**

I believe post-ACS patients with a true intolerance to statins achieving <50% reduction in LDL-C on a statin ± ezetimibe may receive benefit from evolocumab. The ODYSSEY ALTERNATIVE trial compared alirocumab with ezetimibe in patients at moderate to high cardiovascular risk with statin intolerance and found a mean LDL-C reduction of 45% with alirocumab versus 14.5% reduction with ezetimibe after 24 weeks of treatment. When compared to patients rechallenged with atorvastatin, skeletal muscle-related events were less frequent with those in the alirocumab group.[7] Additionally, the GAUSS-3 trial found a statistically significant reduction in LDL-C levels after 24 weeks in statin intolerant patients treated with evolocumab compared to ezetimibe.[8] However, neither trial assessed long-term efficacy and safety.[7,8]

5. **What was the definition and how were neurocognitive events collected?**

Little information is provided regarding the definition and collection of neurocognitive adverse events in FOURIER. The supplementary appendix stated that neurocognitive events were categorized by the TIMI Safety Desk according to lower level MedDRA terms.[1] However, EBBINGHAUS, a cognitive study of a subset of patients enrolled in the FOURIER trial, shared additional insight. The primary objective of the study was to evaluate the change in executive function over 20 months utilizing the Cambridge Neuropsychological Test Automated Battery (CANTAB), which is a validated, computerized assessment tool designed to evaluate cognitive function by testing numerous domains, such as working memory, reaction time, and attention. The study found no statistically significant differences between evolocumab and placebo across various cognitive tests, with patient-reported daily cognition, and with investigator-reported neurocognitive adverse events, even in patients with LDL-C levels below 25 mg/dL.[9]

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*Results are available from the presentation at the American College of Cardiology 66th Annual Scientific Session Late-Breaking Clinical Trial on March 18, 2017. Slides can be accessed online at www.timi.org.