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Authors

Waters, David D
Hsue, Priscilla Y

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PCSK9 Inhibition to Reduce Cardiovascular Risk Tempering Expectations

David D. Waters, Priscilla Y. Hsue

Evolocumab and clinical outcomes in patients with cardiovascular disease

Sabatine et al

N Engl J Med. Published online ahead of print March 17, 2017.

Cardiovascular efficacy and safety of bococizumab in high-risk patients

Ridker et al

N Engl J Med. 2017;376:1527–1539.

The first large clinical outcomes trials of proprotein convertase subtilisin–kexin type 9 (PCSK9) inhibitors have demonstrated that these drugs, when taken with statins, reduce cardiovascular events by 15% to 20% more than statins alone. However, this event reduction is less than expected for such a large decrease in low-density lipoprotein cholesterol (LDL-C), and the reasons for this disconnect between LDL-C lowering and cardiovascular events remain unclear. Future trials should clarify the degree of clinical benefit to be expected from PCSK9 inhibitors.

Two years ago, in these pages, we discussed the results of very early clinical outcome trials of the PCSK9 monoclonal antibodies evolocumab and alirocumab.¹ These drugs both reduced LDL-C levels by slightly >60% on top of statin therapy and reduced cardiovascular events by ≈50%.^{2,3} We noted that although these results engendered great expectations, both of these studies were preliminary, with a small number of end points, short follow-up, and other important limitations.¹

As often happens with life in general, our great expectations have been tempered by 2 recent reports. The FOURIER trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) enrolled 27 564 patients with atherosclerotic cardiovascular disease and LDL-C levels ≥70 mg/dL who were receiving statin therapy.⁴ Patients were randomly assigned to receive double-blind treatment with evolocumab (either 140 mg every 2 weeks or 420 mg

monthly) or placebo as subcutaneous injections. The primary composite end point was cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization and the median duration of follow-up was 2.2 years. At 48 weeks, LDL-C levels were reduced by 59%, from a median of 92 to 30 mg/dL.

The primary end point was reduced by evolocumab, 9.8% compared with 11.3% (hazard ratio, 0.85; 95% confidence interval, 0.79–0.92; $P<0.001$). For the key secondary end point of cardiovascular death, myocardial infarction, or stroke, the corresponding event rates were 5.9% and 7.4% (hazard ratio, 0.80; 95% confidence interval, 0.73–0.88; $P<0.001$).

Unlike evolocumab and alirocumab, which are fully humanized monoclonal antibodies, bococizumab is a humanized monoclonal antibody with ≈3% murine sequence remaining in the antigen-binding complementarity-determining regions.⁵ The bococizumab program consisted of 6 trials with LDL-C end points, the SPIRE (Studies of PCSK9 Inhibition and the Reduction of Vascular Events) program, and 2 large trials, SPIRE-1 and SPIRE-2, with cardiovascular event end points.

In the lipid-lowering trials, bococizumab lowered LDL-C by 54.2% at 12 weeks, but by 52 weeks, this reduction was attenuated to 40.4%. At 1 year, 48% of bococizumab-treated patients had detectable antidrug antibodies, and a titer-dependent attenuation in LDL-C reduction was noted, along with wide variability in the amount of LDL-C-lowering irrespective of antidrug antibody status. Faced with these results, the sponsor discontinued the development of bococizumab on November 1, 2016.

The demise of bococizumab resulted in the very early termination of SPIRE-1 and SPIRE-2.⁶ These were 2 parallel, double-blinded trials where 27 438 patients were randomized to bococizumab 150 mg subcutaneously or placebo every 2 weeks. The primary composite end point consisted of cardiovascular death, myocardial infarction, stroke, or hospitalization for unstable angina requiring urgent revascularization.

In SPIRE-1, which involved lower-risk patients, an LDL-C inclusion of ≥70 mg/dL and a median follow-up of 7 months, the primary end point occurred in 3% of patients in both treatment groups. In SPIRE-2, which involved higher-risk patients, an LDL-C inclusion of ≥100 mg/dL, and a median follow-up of 12 months, the primary end point occurred in 179 and 224 patients, respectively (hazard ratio, 0.79; 95% confidence interval, 0.65–0.97; $P=0.02$).

Expectations and Explanations

Expectations for cholesterol-lowering trials were set by the Cholesterol Treatment Trialists' Collaborators, who reported in 2005 that for each 1 mmol/L (38.6 mg/dL) reduction in LDL-C, cardiovascular events were reduced by a mean of 22% across 14 large statin trials.⁷ This relationship, depicted

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From the Division of Cardiology, San Francisco General Hospital, CA; and Department of Medicine, University of California, San Francisco.

Correspondence to David D. Waters, MD, Division of Cardiology, Room 5G1, San Francisco General Hospital, 1001 Potrero Ave, San Francisco, CA 94114. E-mail David.Waters@ucsf.edu

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in the Figure, holds true for most other interventions that lower LDL-C, including ezetimibe, niacin, fibrates, diet, bile acid sequestrants, and ileal bypass surgery.⁸

PCSK9 inhibitors also reduce cardiovascular events; however, as shown in the Figure, the reductions in FOURIER and SPIRE fall well below what would be expected, based on the degree of LDL-C lowering. Potential explanations for these less-than-anticipated results are listed in the Table.

The most obvious and likely explanation is that the duration of follow-up in FOURIER and SPIRE was too short. In 27 statin trials, the reduction in vascular events per mmol/L reduction in LDL-C in the first year was 9%, compared with 24% in years 1 to 5.⁹ It is possible that with longer follow-up, the relative risk reduction from PCSK9 inhibitors would increase. Inspection of the Kaplan–Meier curves from FOURIER does not entirely support this assertion because the relative risk reduction at years 1, 2, and 3 for the primary end point is approximately the same. (For the key secondary end point, some increase in the relative risk reduction is seen, as the authors note.) In contrast, risk reductions of ≈50% were observed in OSLER (Open-Label Study of Long-Term Evaluation Against LDL Cholesterol) and ODYSSEY (Long-Term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients With Hypercholesterolemia Not Adequately Controlled With

Table. Potential Reasons for the Less-Than-Expected CV Event Rate Reduction in FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) and SPIRE (Studies of PCSK9 Inhibition and the Reduction of Vascular Events)

Short follow-up period
Less benefit at lower on-treatment LDL-C levels
Less benefit in statin-treated patients
PCSK9 inhibitors lack the potent anti-inflammatory effects of statins
Increased LDL-C variability with PCSK9 inhibitors
Suboptimal choice of trial end points
Antidrug antibodies (bococizumab)

CV indicates cardiovascular; LDL-C, low-density lipoprotein cholesterol; and PCSK9, proprotein convertase subtilisin–kexin type 9.

Their Lipid Modifying Therapy), where the duration of follow-up was shorter than in FOURIER.

Inflammation contributes to atherogenesis and to the initiation of cardiovascular events, and statins reduce inflammation, as evidenced by a reduction in inflammatory markers, including C-reactive protein. PCSK9 inhibitors do not reduce C-reactive protein levels. Anti-inflammatory effects possibly explain why statins might reduce events more or have an earlier benefit, compared with PCSK9 inhibitors. A large clinical trial nearing completion with canakinumab, a human monoclonal antibody that targets interleukin-1β, and subsequent trials of other specific anti-inflammatory drugs will be informative in this regard.¹⁰

Cardiovascular event reduction with statins is independent of baseline LDL-C level,⁷ and in FOURIER event reduction was similar across quartiles of baseline LDL-C ranging from 74 to 126 mg/dL. However, in SPIRE-1 and SPIRE-2, mean LDL-C levels at baseline were 94 and 134 mg/dL, respectively, and cardiovascular event reduction was seen only in the trial with higher baseline LDL-C levels.

At the other end of the scale, incremental reductions in LDL-C at very low LDL-C levels may not produce incremental reductions in cardiovascular events. Across statin trials, cardiovascular event reduction has been observed at on-treatment LDL-C levels <50 mg/dL¹¹; however, in FOURIER, 42% of patients had an LDL-C level ≤25 mg/dL at 48 weeks,⁴ and in SPIRE, the corresponding rate at 14 weeks was 28%.⁵ With LDL-C levels this low, it may be unrealistic to expect a further reduction in event rates.

Almost all patients in FOURIER and SPIRE were receiving statins during the trial, usually at moderate or high doses, and many patients had probably been treated with these drugs for years. Another possibility is that cardiovascular event reduction achieved by LDL-C reduction is attenuated among individuals whose atherosclerotic plaques have already been stabilized by long-term statin therapy.

Although a mechanism has not been established, variability in LDL-C levels has been associated with an increase in cardiovascular events in 2 large statin trials.^{12,13} Administration of PCSK9 inhibitors results in a saw-tooth pattern of LDL-C levels, with high LDL-C variability that could theoretically lead to an increase in cardiovascular events.

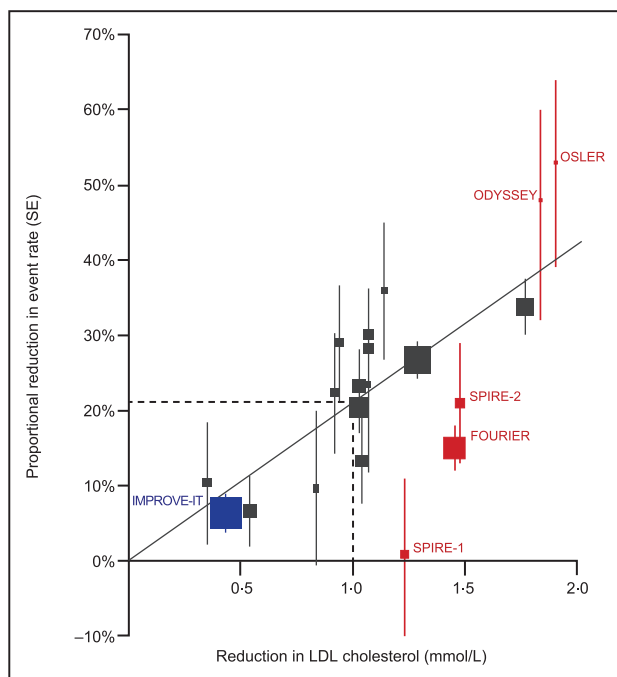


Figure. Relationship between reduction in LDL-C in mmol/L (x axis) and percentage reduction in vascular events (y axis) in 14 clinical trials with statins (black), 1 trial with ezetimibe (blue) and 5 trials with PCSK9 inhibitors. The sizes of the boxes are proportional to the number of cardiovascular (CV) events in each trial. The statin and ezetimibe trials exhibit a relationship where each mmol/L reduction in LDL-C is associated with a 22% reduction in CV events. The FOURIER and the SPIRE trials do not conform to this pattern. Adapted from Baigent et al⁷ with permission of the publisher. Copyright ©2005, Elsevier. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation. LDL-C indicates low-density lipoprotein cholesterol; and PCSK9, proprotein convertase subtilisin–kexin type 9.

A combination of these explanations, and others, could account for the less-than-expected cardiovascular event reduction in FOURIER and SPIRE. Although these drugs reduce cardiovascular events, the relationship between LDL-C lowering and event reduction has now been uncoupled, at least for PCSK9 inhibitors, so that the degree of benefit with these drugs is no longer predictable.

Safety

The adverse event that had drawn the most scrutiny in earlier PCSK9 inhibitor studies was neurocognitive defects. This term covers an array of symptoms, including amnesia, memory impairment, delirium, confusion, and other related conditions.

To further investigate potential neurocognitive issues, EBBINGHAUS (Evaluating PCSK9 Binding Antibody Influence on Cognitive Health in High Cardiovascular Risk Subjects) was a noninferiority trial assessing cognitive function embedded in FOURIER. EBBINGHAUS enrolled 1974 FOURIER patients without cognitive problems at baseline.¹⁴ The Cambridge Neuropsychological Test Automated Battery was applied at baseline and multiple times during a mean follow-up of about 19 months. No differences were detected between the treatment groups (P for noninferiority <0.0001), and exploratory analyses found no differences for patients who attained very low LDL-C levels.

Although these findings are reassuring, longer trials with PCSK9 inhibitors are needed to address safety definitively. In comparison, several reports of long-term follow-up after statin trials have raised no safety issues and indeed indicate that a legacy effect of this class of drugs continues to confer benefit ≤ 20 years.⁹

Next Steps

The ODYSSEY Outcomes trial, in which 18 000 statin-treated patients with a recent acute coronary syndrome have been randomized to alirocumab or placebo, is nearing completion. Inclisiran, a small interfering RNA that targets PCSK9 messenger RNA has recently been reported in a phase 2 trial to reduce LDL-C at 180 days by 27.9% to 41.9% after a single dose and by 35.5% to 52.6% after 2 doses.¹⁵ Inclisiran has the advantages of a very long dosing interval and stable LDL-C levels compared with the monoclonal antibodies. A large outcomes trial with inclisiran is expected to begin later this year. Other monoclonal antibodies to PCSK9 are in earlier stages of development.

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