Evolocumab for Treatment of High Cholesterol: Clinical Effectiveness

New Evidence Update

June 13, 2017

NOTE: The New Evidence Update will be released in two parts. This portion covers new information about the comparative clinical effectiveness of evolocumab that has been released since the original ICER report on PCSK9 inhibitors was issued in 2015, including an analysis of newly-released evidence from the FOURIER trial. In the coming months, ICER will release an updated economic analysis based on the FOURIER trial data that will include a revised value-based price benchmark for evolocumab.

As described in this document, the FOURIER trial showed that evolocumab combined with statins is effective in reducing the incidence of cardiovascular events such as heart attack and stroke, but did not show a statistically significant reduction in cardiovascular mortality. The revised value-based price benchmark is expected to be lower than the previous benchmark of $5,404-$7,735 annually because the cost-effectiveness analysis in ICER's 2015 review had assumed a mortality benefit that was not found in the FOURIER study.

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DATE OF PUBLICATION: June 13, 2017

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent non-profit research organization that evaluates medical evidence and convenes public deliberative bodies to help stakeholders interpret and apply evidence to improve patient outcomes and control costs. ICER receives funding from government grants, non-profit foundations, health plans, provider groups, and health industry manufacturers. For a complete list of funders, visit http://www.icer-review.org/about/support/. Through all its work, ICER seeks to help create a future in which collaborative efforts to move evidence into action provide the foundation for a more effective, efficient, and just health care system. More information about ICER is available at http://www.icer-review.org

Clinical Expert Input

In the development of this new evidence update, ICER's researchers consulted with several clinical experts, a patient advocacy organization, and several drug manufacturers. The following clinical experts provided input that helped guide the ICER team as we shaped the document. None of these individuals is responsible for the final contents of this report or should be assumed to support any part of this report, which is solely the work of the ICER team and its affiliated researchers.

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List of Acronyms Used in this Report

AHRQ	Agency for Healthcare Research and Quality
ALT	Alanine aminotransferase
ARR	Absolute risk reduction
CI	Confidence interval
CK	Creatinine kinase
CVD	Cardiovascular disease
CVDPM	Cardiovascular Disease Policy Model
HR	Hazard ratio
LDL-C	Low-density lipoprotein cholesterol
MI	Myocardial infarction
NHANES	National Health and Nutrition Examination Surveys
NNT	Number needed to treat
PCSK9	Proprotein convertase subtilisin-kexin type 9
QALY	Quality-adjusted life-year
RR	Relative risk
RRR	Relative risk reduction
SC	Subcutaneous

Background

ICER reviewed the comparative clinical effectiveness and cost-effectiveness of proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors at the October 8, 2015 public meeting of the New England Comparative Effectiveness Public Advisory Council.[1] At that time, the evidence clearly demonstrated that both evolocumab and alirocumab reduced low-density lipoprotein cholesterol (LDL-C) levels by more than 50% when added to maximally tolerated statin therapy. A meta-analysis that combined data from all randomized trials of the two agents suggested that the PCSK9 inhibitors reduced the rate of myocardial infarction (MI), stroke, and death from cardiovascular disease (CVD) by 50% when added to maximally tolerated statin therapy, but with wide confidence intervals.[2] This was because prior studies were not powered to detect changes in hard clinical endpoints, which were relatively rare. The 2015 report therefore concluded, with moderate certainty, that the net health benefit for patients of the PCSK9 inhibitors was either incremental or substantial (promising but inconclusive) and that treatment with PCSK9 inhibitors generates incremental cost-effectiveness ratios that far exceed commonly-accepted willingness-to-pay thresholds, such as $100,000 per quality-adjusted life-year (QALY) gained.[3] Achieving incremental cost-effectiveness at a threshold of $100,000 per QALY relative to maximally tolerated statin therapy was estimated to require price reductions of 60% to 63%.

Uptake of the PCSK9 inhibitors has been slow, with their high cost and limited data on hard CVD outcomes dampening enthusiasm for the drugs. The initial approval rates by payers have been low (17%), with an additional 26% of requests approved after appeal.[4] The top three reasons for denial are inadequate documentation of familial hypercholesterolemia, the patient not receiving maximally-tolerated statin therapy, and the drug not being on the formulary.[5] In addition, high co-pays (mean ~$250 per 30-day prescription) may explain why 25-40% of patients do not fill the PCSK9 inhibitor prescription once approved.[6] The goal of this report is to update the prior assessment based on the recently published Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial, which assessed the effect of evolocumab on CVD events.[7]

Clinical Evidence

FOURIER Trial Results[7]

Methods and Patient Population

The FOURIER trial randomized 27,564 patients between 40 and 85 years of age who had clinically-evident CVD and LDL-C levels ≥ 70 mg/dL on moderate- to high-intensity statin therapy.[7] The study participants had a mean age of 63 years, 25% were female, 85% were white, 81% had prior MI, 19% had prior stroke, and 13% had symptomatic peripheral artery disease. The geographic distribution included 17% in North America, 63% in Europe, 7% in Latin America, and 14% in Asia/South Africa. The participants were randomized to evolocumab or identical placebo injections. Participants were allowed to choose between doses of 140 mg subcutaneous (SC) every 2 weeks or 420 mg SC every month, but the two doses were analyzed together. The primary outcome was the time to first major cardiovascular event defined as the composite of cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization. The secondary endpoint was the composite of cardiovascular death, MI, or stroke. The median follow-up was 26 months (interquartile range 22 to 30 months).

The quality of the trial was good. There was appropriate 1:1 randomization with allocation concealment and blinding. The primary outcomes were clinical outcomes that matter to patients and the final outcomes assessment was performed by a central, blinded, clinical events committee. The groups were comparable at randomization and loss to follow-up was very low (<1%). The study measurements were equal and valid and all key outcomes were assessed and reported. The intervention was clearly defined. The analysis was appropriate and used a strict intention-to-treat approach.

Cardiovascular Disease Outcomes

The median LDL-C in the treatment group decreased from 92 mg/dL to 30 mg/dL at 48 weeks (mean reduction 56 mg/dL, 59%). The primary outcome occurred in 9.8% of the evolocumab group and 11.3% of the placebo group (absolute risk reduction [ARR] 1.5%; number needed to treat [NNT] 67; relative risk reduction [RRR] 15%, hazard ratio [HR] 0.85, 95% CI 0.79-0.92, p<0.001). The outcomes are summarized in Table 1 below.

Table 1. Key Outcomes Including Pre-Specified Secondary Outcomes

Outcome	Events Placebo	Events Evolocumab	HR (95% CI)	p-value
Primary				
CVD death, MI, stroke, unstable angina, revascularization	1563	1344	0.85 (0.79-0.92)	<0.001
Secondary				
MI, Stroke, CVD death	1013	816	0.80 (0.73-0.88)	<0.001
CVD death	240	251	1.05 (0.88-1.25)	0.62
Other (exploratory)				
All cause death	426	444	1.04 (0.91-1.19)	0.54
MI	639	468	0.73 (0.68-0.82)	<0.001
Stroke	262	207	0.79 (0.66-0.95)	0.01
Unstable Angina	239	236	0.99 (0.82-1.18)	0.89
Revascularization	965	759	0.78 (0.71-0.86)	<0.001
CHD death, MI, stroke, revascularization	1512	1271	0.83 (0.77-0.90)	<0.001
Hemorrhagic stroke	25	29	1.16 (0.68-1.98)	NR

CHD: congestive heart disease, CVD: cardiovascular disease, HR: hazard ratio, MI: myocardial infarction

There were no significant interactions for the primary and secondary endpoints by age, sex, race, region, type of CVD at entry, baseline LDL-C, baseline statin intensity, or dosing regimen.

The observed reductions in all-cause mortality, death from cardiovascular disease, and unstable angina in the FOURIER trial were lower than expected based on the reduction in LDL-C[8] and the meta-analysis of earlier trials of the PCSK9 inhibitors (Table 2 below).[2] However, the observed reductions in heart attacks, strokes, and revascularization in the FOURIER trial were similar to those expected based on changes in LDL-C.[8]

Table 2. Expected and Observed Treatment Effects of PCSK9 Inhibitors

Outcome	Expected Effect of PCSK9 Inhibitor Therapy Based on 60mg/dL reduction in LDL-C,* RR	Expected Effect of PCSK9 Inhibitor Therapy Based on MA of Earlier Trials,† RR	Observed Effect of PCSK9 Inhibitor Therapy in the FOURIER Trial, HR
All-cause death	0.86 (0.81-0.89)	0.48 (0.27-0.85)	1.04 (0.91-1.19)
CVD death	0.81 (0.75-0.86)	0.49 (0.23-1.07)	1.05 (0.88-1.25)
MI	0.58 (0.52-0.66)	0.49 (0.26-0.93)	0.73 (0.65-0.82)
Stroke	0.75 (0.67-0.83)	NR	0.79 (0.66-0.95)
Unstable Angina	NR	0.51 (0.05-4.86)	0.99 (0.82-1.18)
Revascularization	0.61 (0.57-0.66)	NR	0.78 (0.71-0.86)

* Based on LDL-C reduction of 60 mg/dL or 1.55 mmol/L and the relative risks for clinical events per 1 mmol/L reduction estimated by the Cholesterol Treatment Trialists' Collaboration[8]

† Meta-analysis combining events from all doses of both alirocumab and evolocumab[2]

CVD: cardiovascular disease, LDL-C: low-density lipoprotein cholesterol, MA: meta-analysis, MI: myocardial infarction, NR: not reported, RR: relative risk

The investigators suggested that the overall trial results underestimate the long-term benefits of therapy with evolocumab. They point to evidence from the Cholesterol Treatment Trialists' Collaboration suggesting that there may be greater relative risk reductions for all outcomes in the second and subsequent years of therapy with statins than is observed in the first year.[8] The results of the FOURIER trial separated into year one outcomes and subsequent outcomes are summarized in Table 3 below.

Table 3. Landmark Analyses for Individual Outcomes in the FOURIER Trial

Outcome	Year 1 HR (95% CI)	Years 2+ HR (95% CI)
All cause death	NR	NR
CVD death	0.96 (0.74-1.25)	1.12 (0.88-1.42)
MI	0.80 (0.68-0.94)	0.65 (0.55-0.77)
Stroke	0.83 (0.63-1.08)	0.76 (0.60-0.97)
Unstable Angina	0.97 (0.77-1.22)	0.99 (0.75-1.30)
Revascularization	0.84 (0.74-0.96)	0.72 (0.63-0.82)

CVD: cardiovascular disease HR: hazard ratio, MI: myocardial infarction, NR: not reported

As was reported in the meta-analysis of statin randomized trials, the reduction in MIs, strokes, and revascularization was greater in years 2+ than in the first year of therapy. However, the lack of reduction in CVD death overall and in years 2+ is concerning. Similar findings have been observed in other trials of intensification therapy. For instance, in the IMPROVE-IT trial, the addition of ezetimibe reduced cardiovascular disease event rates, but did not reduce CVD mortality (HR 1.00, 95% CI 0.89-1.13).[9]

Harms / Safety Concerns

There were no significant differences in the incidence of diabetes, neurocognitive outcomes, muscle-related events, rhabdomyolysis, creatinine kinase (CK) elevation, alanine aminotransferase (ALT) elevation, any adverse events (AEs), serious AEs, or AEs leading to discontinuation.[7] There were slightly more injection site reactions with evolocumab (2.1% versus 1.6%, p<0.001). The detailed neurologic outcomes evaluated in the EBBINGHAUS sub-study within FOURIER have been presented, but not published.[10] There were no differences on detailed neurocognitive testing between the groups receiving evolocumab and placebo including the subgroup with LDL < 25 mg/dL.[11] However, it may take longer for neurocognitive harms to appear. Up to 4 years of follow-up (mean 44 months) of patients in the original lipid-lowing clinical trials has not identified any unexpected AEs.[12] There may also be rare, significant harms which have yet to be identified.

Summary and ICER Evidence Rating

The prior ICER rating for PCSK9 inhibitors was promising, but inconclusive (P/I) because of the uncertainties about both the clinical benefits and harms over time. In the much larger and longer FOURIER trial, we now have strong evidence of benefit for evolocumab in reducing heart attacks, strokes, and revascularization, but not unstable angina or CVD death in patients with clinical CVD on statin therapy. Apart from mild injection site reactions, no harms were identified in this very large trial nor were harms identified in the extension trials out to four or more years of follow-up. The major limitation of FOURIER, as the authors point out, was the relatively short duration of follow-up (26 of 48 months planned) because the event rate was substantially higher than expected. It is also concerning that there was no trend toward a reduction in death from cardiovascular disease and the increase in mortality was greater in years 2+ than it was in the first year of the trial. Studies of statin therapy for secondary prevention have consistently demonstrated a reduction in CVD and total mortality. Thus, we give evolocumab added to statin therapy an ICER rating of C+ (comparable or better) based on moderate certainty of a small net benefit compared to statin therapy alone. We considered a B+ rating (incremental or better), but the uncertainty introduced by the non-significant trend towards increased cardiovascular mortality in years 2+ of the trial (HR 1.12, 95% CI 0.88-1.42) led us to the more conservative assessment. We continue to assume a class effect for evolocumab and alirocumab because the degree of LDL-C lowering is similar and sustained, though acknowledge greater uncertainty about alirocumab because the hard CVD outcome study for alirocumab is still in progress. The longer outcomes trial for alirocumab may shine additional light on the concerns about cardiovascular mortality.

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