Evolocumab for Treatment of High Cholesterol: Effectiveness and Value

New Evidence Update

September 11, 2017

NOTE: An earlier version of this document, posted on June 13, 2017, contained only clinical effectiveness analyses. This updated version contains both clinical and economic analyses, the former of which has remained unchanged from the original posting.

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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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The findings contained within this report are current as of the date of publication. Readers should be aware that new evidence may emerge following the publication of this report that could potentially influence the results. ICER may revisit its analyses in a formal update to this report in the future.

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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
ASCVD	Atherosclerotic cardiovascular disease
CHD	Coronary heart disease
CI	Confidence interval
CK	Creatinine kinase
CVD	Cardiovascular disease
CVDPM	Cardiovascular Disease Policy Model
HR	Hazard ratio
LDL-C	Low-density lipoprotein cholesterol
MACE	Major adverse cardiovascular event
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

CI: confidence interval, 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)

CI: confidence interval, 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-C < 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.

Long-term Cost Effectiveness

Overview & Methods

We also updated our estimates of the long-term cost-effectiveness of evolocumab based on data from the FOURIER trial as described above. Results were obtained using the Cardiovascular Disease Policy Model (CVDPM), which extrapolates data to the US population based on health behaviors and vital statistics captured in the National Health and Nutrition Examination Surveys (NHANES).[13] Structurally, the approach was identical to that previously described in ICER's final report on PCSK9 inhibitors developed as part of deliberations held by the New England Comparative Effectiveness Public Advisory Council in October 2015,[1] which was subsequently published in the peer-reviewed literature.[14] As before, the analyses adopted a health system perspective and assessed costs and outcomes over a lifetime horizon. Cost-effectiveness was presented in terms of cost per additional quality-adjusted life year (QALY) gained for adding evolocumab to statins in comparison to statins alone. Certain estimates were modified to more closely match the FOURIER population and results, however, as described in further detail below. Many of these changes are also summarized in a recently published, peer-reviewed research letter.[15]

As described in the research letter, the target population of interest was changed to include adults age 40-84 years with pre-existing atherosclerotic cardiovascular disease (ASCVD) who had an LDL-C level of ≥ 70 mg/dL (1.81 mmol/L) despite statin therapy, as in FOURIER (the original model focused on adults age 35-74 years). Second, reductions in the risk of MI and stroke were now estimated separately for years 1 and 2+ using data from the FOURIER landmark analyses as shown in Table 3, while the original model estimated reductions in these cardiovascular events per unit of reduction in LDL-C. We also updated all other healthcare costs to 2017 dollars using the medical care component of the US Consumer Price Index.[16]

There are several important differences between the analyses described in the research letter and those summarized in this evidence update, which are summarized in Table 4 below. Most importantly, the base-case analysis in the research letter assumed that the risk reductions for MI were applicable to all coronary heart disease (CHD) events, including chronic CHD deaths. Because no distinct cardiovascular mortality benefit was observed in FOURIER, we adopted a more conservative approach for our base case, assuming that any benefit would be restricted to deaths resulting directly from MI and stroke events only. However, we did not use the point estimates from FOURIER showing an actual increase in mortality (see Table 1), and so our base case is not as conservative as the data from FOURIER might suggest.

Second, consistent with our original analysis, the primary comparator for this update was statins alone, while the research letter compared combination therapy with PCSK9 inhibitors and statins to an ezetimibe-statin combination. While ezetimibe may be used in combination with statins in

patients with ASCVD, prior ezetimibe use is not required as part of the label for PCSK9 inhibitors, and it is not indicated for reductions in cardiovascular morbidity and mortality.[17] This update therefore remains consistent with the original ICER report in selecting statins alone as the primary comparator for the calculation of the cost-effectiveness of PCSK9 inhibitors.

Finally, while our original analysis assumed identical clinical outcomes for both currently-available PCSK9 inhibitors, and used an average of their wholesale acquisition costs (WACs) in the model, for this update only the costs and effects of evolocumab are modeled. In addition, our original analyses used only WAC prices, since the PCSK9 inhibitors had not yet been available for long enough to generate robust estimates of net prices. We also include calculations in this update that use net pricing estimates from SSR Health, LLC, which combine publicly-disclosed US sales figures that are net of discounts, rebates, concessions to wholesalers and distributors, and patient assistance programs, with data on unit sales to derive a net price. The current estimate of annual net price for evolocumab is approximately $8,970, nearly 40% lower than the WAC of $14,523.[18,19]

Table 4. Key Differences Between Original ICER Report, JAMA Research Letter, and ICER New Evidence Update

Data Element	Original ICER Analysis[1]	JAMA Research Letter[15]	ICER New Evidence Update
Population	Adults with pre-existing ASCVD or familial hypercholesterolemia who require additional lipid lowering or are statin-intolerant	Adults with pre-existing ASCVD who require additional lipid lowering	Adults with pre-existing ASCVD who require additional lipid lowering
Age Range	35-74	40-84	40-84
Interventions	PCSK9 inhibitors with or without statins	PCSK9 inhibitors with statins	Evolocumab with statins
Comparators	Statins alone (base case), ezetimibe with statins	Ezetimibe with statins	Statins alone
Treatment Effects in Base Case	Reduction in MI, stroke, and CVD death per unit of LDL-C-lowering	Reduction in MI and stroke based on FOURIER landmark analysis Extrapolation of MI risk reductions to all CHD events, including chronic CHD deaths	Reduction in MI and stroke based on FOURIER landmark analysis Mortality benefit restricted to MI and stroke case fatalities
Annual Intervention Costs	$14,350	$14,542	$14,523 (WAC price) $8,970 (net price)

ASCVD: atherosclerotic cardiovascular disease; CVD: cardiovascular disease; MI: myocardial infarction; LDL-C: Low-density lipoprotein cholesterol; CHD: coronary heart disease

Results

Model results are presented in Table 5 as generalized to the US population. Applying the entry criteria for FOURIER to the NHANES database produced a population of 8.8 million adults in the United States, with a mean age of 66 years, 39% female, and a mean LDL-C of 104 mg/dL (2.69 mmol/L). In comparison to the actual patients enrolled in FOURIER, this modeled population was slightly older, more likely to be female, and had a slightly higher baseline LDL-C (mean LDL-C in FOURIER was 92 mg/dL).

Despite these small differences in baseline characteristics, the model accurately reproduced the combined rates of MI, stroke, and cardiovascular mortality seen in FOURIER. For example, the year 1 rate for statins alone in FOURIER was 3.7% versus 3.6% in this application of the CVDPM; year 2+ rates were 3.7% and 3.8% respectively.

Cost-effectiveness results using both WAC and net pricing are presented in Table 5 on the following page. Over a lifetime time horizon, the addition of evolocumab would avert nearly 4 million of the major adverse cardiovascular events (MACE) of interest in this evaluation versus statins alone, yielding a number needed to treat (NNT) during the first five years of 28. These clinical benefits would translate into over 2 million QALYs gained. However, despite substantial cost offsets from averted events, drug costs and overall costs would increase substantially.

The balance of clinical benefits and higher costs yielded an incremental cost-effectiveness ratio for evolocumab + statins versus statins alone of approximately $1.34 million per QALY gained using WAC prices, a number substantially higher than our original report estimate of $302,000 per QALY gained. Using net prices, the cost-effectiveness ratio was approximately $800,000 per QALY. Even when we used net prices and conducted a sensitivity analysis extending the mortality benefit from MI and stroke only to all acute and chronic CHD deaths, the cost-effectiveness estimate was approximately $210,000 per QALY, greater than commonly cited cost-effectiveness thresholds of $50,000-$150,000 per QALY gained.

Table 5. Base Case Clinical and Economic Outcomes Among Patients with a Prior History of ASCVD and LDL-C ≥ 70mg/dL on Statin Therapy.*

	Total MACE averted	NNT_5†	QALYs gained‡	Incremental Drug Costs‡ (million $)	Incremental Costs, Other CV Care‡ (million $)	Incremental Costs, Non-CV Care‡ (million $)	ICER ($/QALY)
Statin Alone	*comparator*						
Statin + Evolocumab (WAC Price)	3,879,016	28	2,347,613	$3,293,232	-$209,212	$52,910	$1,336,221
Statin + Evolocumab (Net Price)	3,879,016	28	2,347,613	$2,033,445	-$209,212	$52,910	$799,596

Abbreviations: CV: cardiovascular, ICER: incremental cost-effectiveness ratio, LDL-C: low-density lipoprotein cholesterol, MACE: major adverse cardiovascular event (nonfatal and fatal MI, nonfatal and fatal stroke, and other cardiovascular death), NNT: number-needed-to-treat, QALY: quality-adjusted life year.

* In the base case, patients with pre-existing CVD and LDL-C ≥ 70mg/dL on statin therapy received incremental therapy with evolocumab. The analytic horizon was lifetime (defined as until patients reached the age of 95 years).

† Number of patients that would need to be treated for 5 years to avert one MACE event.

‡ All costs are reported in 2017 US dollars. Future costs and QALYs are discounted 3% a year.

Value-based Benchmark Prices

ICER's value-based benchmark price is defined as the price that would yield cost-effectiveness ratios between $100,000 and $150,000 per QALY gained. These prices are shown in Table 6 below, and indicate that the updated value-based price benchmark for evolocumab is $1,725 to $2,242 for a year of treatment. This price range represents discounts of 85-88% from the WAC price, and is substantially lower than the range cited in our original analysis for ASCVD patients ($5,300 - $7,600)[1] and the stated threshold price to achieve $100,000 per QALY in the research letter ($4,215),[15] driven mainly by the different mortality assumptions and choice of comparator used in this update.

Table 6. Value-based Benchmark Prices* for Evolocumab Among Patients with a History of ASCVD, an LDL-C of ≥70 mg/dL, and Current Use of Statins.

Agent	WAC*	Cost to achieve $100k/QALY*	Cost to achieve $150K/QALY*	Discount from WAC to reach threshold*	Current net price discount sufficient?
Evolocumab	$14,523	$1,725	$2,242	85% to 88%	No

QALY: quality-adjusted life year, WAC: wholesale acquisition cost

*Annual prices

Summary and Comment

The cost-effectiveness of PCSK9 inhibitors was evaluated in our original report based on the assumed effects of LDL-C lowering on rates of MACE events. With the availability of data from FOURIER, we are now able to examine the economic impact of evolocumab based on its direct effects on MACE outcomes. However, the FOURIER findings represent truly mixed results—reductions in the rates of MI and stroke that improve over time, but no impact on cardiovascular mortality in either year 1 or year 2+ of study follow-up. As a result, and using WAC prices as we did in our original analyses, or net price estimates that are now available, our calculation of the cost-effectiveness of adding evolocumab to statins vs. statins alone in an ASCVD population is far less favorable than that in our original report: ~$1.3 million per QALY [WAC] or ~$800,000 per QALY [net price] versus the original report's finding of ~$300,000 per QALY gained [WAC].

These updated results greatly exceed commonly cited cost-effectiveness thresholds, and discounts from WAC of 85% to 88% would be required to reach such thresholds. We note that the manufacturer has recently discussed developing outcomes-based agreements that refund drug payments to payers if patients have a CVD event.[20] While we have not modeled the impact of such an agreement here, we note that others have, and have observed minimal savings due to the relatively low absolute reduction in events.[21]

We note that additional scenario and sensitivity analyses were conducted for our original report and/or the 2016 JAMA publication but were not replicated here. For example, we assessed questions of cost-effectiveness of immediate initiation of PCSK9 inhibitor therapy in an ASCVD subset with an incident, first-ever MI, to examine whether the higher baseline risk in this population would affect our findings. Other analyses involved use of alternative sets of health-state utilities for the ASCVD population. These analyses initially produced cost-effectiveness ratios that were higher than commonly-cited thresholds; we have no reason to believe that this pattern would change with our updated findings, given that the base case in this update is less favorable than that estimated initially. Since FOURIER only included patients with clinically-evident ASCVD on moderate- to high-intensity statin therapy, we did not update our prior estimates of cost-effectiveness among patients with heterozygous familial hypercholesterolemia or those intolerant of statins.[1,14,15]

In summary, our updated cost-effectiveness analyses, informed by the now-available clinical information from FOURIER, demonstrate worse cost-effectiveness than suggested in our original report. Our original report had assumed a greater mortality benefit from reduced LDL-C than was found in FOURIER, and this difference made the added costs with evolocumab treatment appear even more out of scale with the clinical benefits in this population. Studies of longer duration are needed to further evaluate the impact of evolocumab on cardiovascular and all-cause mortality, and additional evidence on alirocumab expected within the next year may help provide important information on this point and on the question of whether the clinical outcomes of the two PCSK9

inhibitors can be distinguished. Given the evidence available from FOURIER, however, our updated analyses suggested that to reasonably align with clinical benefit the annual price of evolocumab would need to drop by 85-88%, to a range between $1,725 and $2,242. To improve value, assure affordability for patients and health systems, and facilitate broader access to a medication that offers important clinical benefits to many patients, patient-centered outcomes data from the FOURIER trial demonstrates that substantial reductions in the price for evolocumab will be needed.

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