Letters

RESEARCH LETTER

Updated Cost-effectiveness Analysis of PCSK9 Inhibitors Based on the Results of the FOURIER Trial

A cost-effectiveness analysis of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors based on their lowering of low-density lipoprotein cholesterol (LDL-C) demonstrated that the 2015 price of PCSK9 inhibitors would need to be reduced by more than two-thirds (to $4536 per year) to meet generally accepted cost-effectiveness thresholds.[1] Since that report, the Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) trial found the PCSK9 inhibitor evolocumab reduced risk of major adverse cardiovascular events (MACE; myocardial infarction, stroke, or cardiovascular death).[2] This study assessed how the cost-effectiveness of PCSK9 inhibitors is altered by the FOURIER results and current prices.

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Methods | As with the prior analysis,[1] the Cardiovascular Disease Policy Model (CVDPM) was used to estimate the cost-effectiveness of PCSK9 inhibitors or ezetimibe added to statin therapy among US adults with atherosclerotic cardiovascular disease (ASCVD) from a health system perspective and a lifetime analytic horizon. The primary outcome was the

Table 1. Comparison of Input Parameters for the Prior Cost-effectiveness Analyses Using LDL-C Lowering vs the Current Analysis Based on FOURIER Trial Criteria

Input Parameter	Prior Analysis Using LDL-C Lowering[1]	Updated Analysis Using FOURIER Trial Criteria
Population sample[a]	US adults with heterozygous familial hypercholesterolemia or preexisting atherosclerotic cardiovascular disease who require additional lipid lowering, either in addition to ongoing statin therapy or as monotherapy among those deemed statin intolerant	US adults with preexisting atherosclerotic cardiovascular disease who need additional lipid lowering in addition to ongoing statin therapy
Sample size at baseline, No.[b]	8 500 000	8 800 000
Age range at baseline, y	35-74	40-84[c]
Interventions	Statins alone; statins + ezetimibe; statins + PCSK9 inhibitors	Statins alone; statins + ezetimibe; statins + PCSK9 inhibitors
Effect size	Model based on LDL-C reduction (ie, percentage of reduction in LDL-C as seen in trials)[d]	Model based on hard clinical events (ie, calibrated rate ratio for coronary events and stroke events in FOURIER)[e]
Annual cost of ezetimibe, $[f]	2878	3818
Annual cost of PCSK9 inhibitors, $[f]	14 350	14 542
Key outcomes[g]	MACE; number needed to treat for 5 y to avoid 1 adverse event; ICER (US dollars per QALY); drug price at which PCSK9 inhibitors would become cost-effective relative to the next optimal strategy at an ICER of $100 000 per QALY; budget impact (change in total health care expenditures) over 5 years	MACE; number needed to treat for 5 y to avoid 1 adverse event; ICER (US dollars per QALY); drug price at which PCSK9 inhibitors would become cost-effective relative to the next optimal strategy at an ICER of $100 000 per QALY
Additional analyses[h]		Ezetimibe and PCSK9 inhibitors were assumed not to lower risk of cardiovascular death except as a direct result of myocardial infarction or stroke
Perspective	Health system	Health system
Analytic horizon	Lifetime	Lifetime

Abbreviations: FOURIER, Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events; NHANES, National Health and Nutrition Examination Survey; PCSK9, proprotein convertase subtilisin/kexin type 9; QALY, quality-adjusted life-year; RR, relative risk.

[a] The population analyzed in the research letter approximates the study population of the FOURIER trial; therefore, patients with familial hypercholesterolemia and those unable to tolerate statins were excluded from the new analysis.

[b] Estimated from NHANES based on inclusion criteria.

[c] To approximate the study population of the FOURIER trial. Baseline characteristics derived from NHANES based on inclusion criteria, age, and sex.

[d] Consistent with the LDL hypothesis, the base case assumed a constant relative reduction in the risk of coronary heart disease and stroke for each millimole per liter reduction in LDL-C, independent of the agent or agents used to lower LDL-C (statin, statin + ezetimibe, or statin + PCSK9 inhibitor). RR for coronary heart disease per 1-mmol/L reduction in LDL-C was 0.76; RR for stroke per 1-mmol/L reduction in LDL-C was 0.85.

[e] The updated analysis models the effectiveness of PCSK9 inhibitors based on event rates observed in the FOURIER trial. Different risk ratios were used for the first and subsequent years to reflect the increasing effectiveness of PCSK9 inhibitors seen in FOURIER. RR for coronary heart disease for statin + PCSK9 inhibitors relative to statins alone was 0.80 for year 1, and 0.65 for years 2 or more. RR for stroke for statin + PCSK9 inhibitors relative to statins alone was 0.83 for year 1, and 0.76 for years 2 or more. The effectiveness of statin alone and that of statin + ezetimibe were unchanged from the prior analysis.

[f] Source: Truven Health Analytics' Red Book Online (http://truvenhealth.com/products/micromedex/product-suites/clinical-knowledge/red-book/about).

[g] The original analysis reported costs in 2015 US dollars. The updated analysis updates all costs to 2017 US dollars using the Consumer Price Index Inflation calculator.

[h] The updated analysis explores the effect on the ICER of the finding in FOURIER that PCSK9 inhibitor therapy did not lower cardiovascular or all-cause mortality.

Table 2. Clinical and Economic Outcomes of Treatment Strategies in ASCVD[a]

	Statin + Ezetimibe Relative to Statin Alone, Difference (80% Uncertainty Interval)	Statin + PCSK9 Inhibitor Relative to Statin + Ezetimibe, Difference (80% Uncertainty Interval)
Total MACE averted[b]	2 164 000 (1 305 300 to 2 913 100)	2 893 500 (1 647 600 to 4 295 800)
NNT, No. (80% uncertainty interval)[c]	41 (30 to 67)	37 (25 to 65)[d]
Life-years gained	4 849 000 (2 924 100 to 6 491 900)	6 087 500 (3 390 400 to 9 081 200)
QALYs gained	4 423 700 (2 661 900 to 5 938 100)	5 558 400 (3 085 600 to 8 333 700)
Incremental costs, $ millions[e]		
Drugs	870 084 (866 573 to 873 118)	2 485 684 (2 470 148 to 2 501 282)
Cardiovascular care	−85 540 (−115 905 to −51 262)	−109 478 (−162 994 to −60 892)
Noncardiovascular care[f]	97 002 (58 462 to 129 960)	123 415 (69 214 to 184 453)
Incremental cost-effectiveness ratio		
Per life-year gained	182 000 (137 000 to 299 000)	411 000 (277 000 to 721 000)
Per QALY gained (primary outcome)	199 000 (150 000 to 328 000)	450 000 (301 000-787 000)[g]

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; MACE, major adverse cardiovascular events; NNT, number needed to treat; PCSK9, proprotein convertase subtilisin/kexin type 9; QALY, quality-adjusted life-year.

[a] The model assumed the health system perspective and a lifetime analytic horizon, and discounted future costs and QALYs at 3% a year. To reflect the precision of the model, MACE and QALYs are rounded to the 100s; costs are rounded to the millions; and incremental cost-effectiveness ratios to the 1000s. This analysis included patients with a history of ASCVD and low-density lipoprotein cholesterol of 70 mg/dL or more taking statin therapy (n = 8 947 000 in 2015).

[b] MACE was defined as a composite of nonfatal myocardial infarction, nonfatal stroke, and death from cardiovascular causes.

[c] No. of patients that would need to be treated for 5 years to avert 1 MACE.

[d] This is the number of patients that would have to be treated for 5 years with statin + PCSK9 inhibitor compared with statin + ezetimibe to avoid 1 MACE. For context, 20 patients would have to be treated for 5 years with statin + PCSK9 inhibitor compared with statin alone to avoid 1 MACE.

[e] All costs are reported in 2017 US dollars.

[f] Noncardiovascular costs include age-specific background health care costs (ie, health care costs unrelated to management of cardiovascular disease).

[g] For reference purposes, the incremental cost-effectiveness ratio of the statins + PCSK9 inhibitor group relative to statin therapy was $339 000/QALY (80% uncertainty interval, $284 000 to $430 000).

incremental cost-effectiveness ratio (ICER; incremental health care costs per quality-adjusted life-year [QALY] gained). The secondary outcome was the drug cost at which PCSK9 inhibitors would become cost-effective at a willingness-to-pay threshold of $100 000/QALY.

The simulation cohort in this update approximated the FOURIER inclusion criteria (US adults aged 40-80 years with ASCVD and LDL-C ≥70 mg/dL [to convert to mmol/L, multiply by 0.0259] despite statin therapy, based on 2005-2012 National Health and Nutrition Examination Surveys [NHANES]).[3] Reductions in myocardial infarction and stroke risk were estimated from FOURIER, with separate hazard ratios for the first year and subsequent years to account for the increasing effectiveness over time observed in the trial (**Table 1**). Drug costs were based on current wholesale acquisition costs ($3818 for ezetimibe [32% increase between 2015 and 2017] and $14 542 for PCSK9 inhibitors [1% increase between 2015 and 2017])[4]; all other health care costs were inflated to 2017 US dollars. Because PCSK9 inhibitors did not reduce risk of cardiovascular death in FOURIER, we conducted an additional analysis with no effect on cardiovascular death except as a direct result of lowering myocardial infarction or stroke risk. Table 1 compares the approach in the prior analysis and this update.

The CVDPM is programmed in Fortran 95 (Lahey Computer Systems). Outcomes were analyzed using QuickBasic 64 and Excel 2011 (Microsoft); statistical analyses were performed using SAS (SAS Institute), version 9.4, and Stata (StataCorp), version 13.

Results | Approximately 8.9 million US adults meet the age, ASCVD, LDL-C, and statin treatment criteria of FOURIER. Based on NHANES, this population is 61% men (95% CI, 55%-67%), with a mean age of 66 years (95% CI, 65-68), mean LDL-C of 104 mg/dL (95% CI, 100-108), and diabetes proportion of 33% (95% CI, 28%-39%). The CVDPM accurately reproduced FOURIER MACE rates (statin only: FOURIER estimate, 3.7% in year 1, 3.7% in year 2; CVDPM, 3.6% in year 1, 3.8% in year 2; statin plus PCSK9 inhibitors: FOURIER estimate, 3.1% in year 1, 2.7% in year 2; CVDPM, 3.0% in year 1, 2.7% in year 2). Adding PCSK9 inhibitors to statins was estimated to prevent 2 893 500 more MACE compared with adding ezetimibe, at an ICER of $450 000/QALY (80% uncertainty interval, $301 000-$787 000) (**Table 2**). Reducing annual drug costs by 71% (to ≤$4215) would be needed for PCSK9 inhibitors to be cost-effective at a threshold of $100 000/QALY. Assuming no direct effect on cardiovascular death as observed in FOURIER, the ICER increased to $1 795 000/QALY.

Discussion | PCSK9 inhibitor use in patients with ASVCD was not cost-effective at 2017 prices, and these updated analyses based on FOURIER estimates suggest that even greater price reductions than previously reported are required to meet cost-effectiveness thresholds. The 71% price reduction required to make PCSK9 inhibitor therapy cost-effective is greater than the 25% to 30% discounts typically offered by manufacturers.[5] A rebate model proposed by 1 PCSK9 inhibitor manufacturer[6] (refunding the drug costs if patients experience MACE while receiving PCSK9 inhibitor therapy) is also unlikely to meaningfully reduce drug expenditures given the low overall MACE rate (approximately 3% per year). Although computer simulations that synthesize data from observational studies and clinical trials may not precisely reflect clinical effectiveness that may be observed in practice over time, these updated results continue to demonstrate

that reducing the price of PCSK9 inhibitors remains the best approach to delivering the potential health benefits of PCSK9 inhibitors therapy at an acceptable cost.

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Medication-Assisted Treatment and Opioid Use Before and After Overdose in Pennsylvania Medicaid

For every fatal opioid overdose, there are approximately 30 nonfatal overdoses. Nonfatal overdoses that receive medical attention represent intervention opportunities for clinicians to mitigate risk by reducing opioid prescribing or advocating addiction treatment. Studies evaluating commercially insured patients suggest these potential interventions are underutilized. For example, a 2000-2012 study[1] reported high rates of opioid prescribing for patients even after they had sustained a nonfatal opioid overdose. Another study[2] of patients with opioid use disorder (OUD) showed low rates of buprenorphine treatment after hospitalization for overdose. However, little is known about how opioid prescribing and medication-assisted treatment (MAT) changes from before to after overdose among Medicaid enrollees, who have a 3-times higher risk of opioid overdose.[3] We used data from a large Medicaid program to compare (1) prescription opioid use, (2) duration of opioid use, and (3) rates of MAT (buprenorphine, methadone, or naltrexone) among enrollees before and after an overdose event.[4]

Methods | This study was deemed exempt by the University of Pittsburgh institutional review board. We conducted a retrospective cohort analysis using 2008-2013 claims data for all Pennsylvania Medicaid enrollees aged 12 to 64 years with a heroin or prescription opioid overdose who were identified using *International Classification of Diseases, Ninth Revision*, codes (965.00-965.02, 965.09, E.850.1-E.850.2) in inpatient, outpatient, and professional claims. We included patients with 6 months of continuous enrollment in Medicaid before and after the overdose claim (limiting our analyses to nonfatal opioid overdoses). We measured all nonparenteral prescription opioid use in pharmacy claims. We used *Current Procedural Terminology* codes (H0020, J1230) in professional claims to capture methadone dispensed for OUD in an opioid treatment program (as opposed to prescriptions for pain management). We used National Drug Codes in pharmacy claims to identify OUD-approved buprenorphine and naltrexone. We used a logistic regression model with generalized estimating equations for correlated data to estimate differences from before to after overdose in prescription opioid use (any use and receipt of ≥90 cumulative days duration) and differences in receiving MAT (overall and each medication separately). Analyses were stratified by overdose type (prescription opioid vs heroin) and conducted using SAS (SAS Institute), version 9.4, and STATA (StataCorp), version 14. We considered 2-sided