JAMA | Original Investigation

Cost-effectiveness of PCSK9 Inhibitor Therapy in Patients With Heterozygous Familial Hypercholesterolemia or Atherosclerotic Cardiovascular Disease

Dhruv S. Kazi, MD, MSc, MS; Andrew E. Moran, MD, MPH; Pamela G. Coxson, PhD; Joanne Penko, MS, MPH; Daniel A. Ollendorf, PhD; Steven D. Pearson, MD, MSc; Jeffrey A. Tice, MD; David Guzman, MSPH; Kirsten Bibbins-Domingo, PhD, MD, MAS

IMPORTANCE Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors were recently approved for lowering low-density lipoprotein cholesterol in heterozygous familial hypercholesterolemia (FH) or atherosclerotic cardiovascular disease (ASCVD) and have potential for broad ASCVD prevention. Their long-term cost-effectiveness and effect on total health care spending are uncertain.

OBJECTIVE To estimate the cost-effectiveness of PCSK9 inhibitors and their potential effect on US health care spending.

DESIGN, SETTING, AND PARTICIPANTS The Cardiovascular Disease Policy Model, a simulation model of US adults aged 35 to 94 years, was used to evaluate cost-effectiveness of PCSK9 inhibitors or ezetimibe in heterozygous FH or ASCVD. The model incorporated 2015 annual PCSK9 inhibitor costs of $14 350 (based on mean wholesale acquisition costs of evolocumab and alirocumab); adopted a health-system perspective, lifetime horizon; and included probabilistic sensitivity analyses to explore uncertainty.

EXPOSURES Statin therapy compared with addition of ezetimibe or PCSK9 inhibitors.

MAIN OUTCOMES AND MEASURES Lifetime major adverse cardiovascular events (MACE: cardiovascular death, nonfatal myocardial infarction, or stroke), incremental cost per quality-adjusted life-year (QALY), and total effect on US health care spending over 5 years.

RESULTS Adding PCSK9 inhibitors to statins in heterozygous FH was estimated to prevent 316 300 MACE at a cost of $503 000 per QALY gained compared with adding ezetimibe to statins (80% uncertainty interval [UI], $493 000-$1 737 000). In ASCVD, adding PCSK9 inhibitors to statins was estimated to prevent 4.3 million MACE compared with adding ezetimibe at $414 000 per QALY (80% UI, $277 000-$1 539 000). Reducing annual drug costs to $4536 per patient or less would be needed for PCSK9 inhibitors to be cost-effective at less than $100 000 per QALY. At 2015 prices, PCSK9 inhibitor use in all eligible patients was estimated to reduce cardiovascular care costs by $29 billion over 5 years, but drug costs increased by an estimated $592 billion (a 38% increase over 2015 prescription drug expenditures). In contrast, initiating statins in these high-risk populations in all statin-tolerant individuals who are not currently using statins was estimated to save $12 billion.

CONCLUSIONS AND RELEVANCE Assuming 2015 prices, PCSK9 inhibitor use in patients with heterozygous FH or ASCVD did not meet generally acceptable incremental cost-effectiveness thresholds and was estimated to increase US health care costs substantially. Reducing annual drug prices from more than $14 000 to $4536 would be necessary to meet a $100 000 per QALY threshold.

JAMA. 2016;316(7):743-753. doi:10.1001/jama.2016.11004

Author Video Interview

Supplemental content

CME Quiz at jamanetworkcme.com

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Kirsten Bibbins-Domingo, PhD, MD, MAS, University of California, San Francisco, Division of General Internal Medicine, Zuckerberg San Francisco General Hospital, PO Box 1364, San Francisco, CA 94143-1364 (kirsten.bibbins-domingo@ucsf.edu).

Proprotein convertase subtilisin/kexin type 9 (PCSK9) facilitates the degradation of low-density lipoprotein (LDL) receptors, reducing the clearance of circulating LDL particles.[1] PCSK9 activity is inversely related to LDL cholesterol (LDL-C) level: gain-of-function PCSK9 gene mutations are one cause of elevated LDL-C and cardiovascular risk in familial hypercholesterolemia (FH),[2] whereas loss-of-function mutations cause low LDL-C and reduced risk of atherosclerotic cardiovascular disease (ASCVD).[3] These observations spurred the development, testing, and US Food and Drug Administration (FDA) approval of 2 therapeutic agents that inhibit PCSK9 and lower LDL-C.[1]

In clinical trials of 3 to 12 months' duration, 2 PCSK9 inhibitors, alirocumab and evolocumab, reduced mean LDL-C levels by 47.5% (95% CI, 25.3%-69.6%).[4,5] Although these trials were not powered for clinical outcomes, ASCVD events appeared to be reduced with PCSK9 inhibitor treatment (odds ratio for myocardial infarction [MI], 0.49; 95% CI, 0.26-0.93).[4] Based on these data, PCSK9 inhibitors were approved for use in patients with FH or preexisting ASCVD who require additional lowering of LDL-C despite maximally tolerated doses of statins.[1] If clinical benefits seen in short-term trials are sustained in the longer term, PCSK9 inhibitors could become an important option for patients at high risk of ASCVD, potentially lowering health care costs through preventing ASCVD events. However, with a mean US price in 2015 of more than $14 000 per patient per year, their cost-effectiveness and effect on national health care spending are uncertain. The goal of this study was to assess the value of PCSK9 inhibitors from the health system perspective by conducting a cost-effectiveness analysis and examining potential effects on total US health care spending using an established simulation model of ASCVD in the US population.

Key Points

Question What are the cost-effectiveness and potential effect on health care spending of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor treatment in heterozygous familial hypercholesterolemia and atherosclerotic cardiovascular disease?

Findings In this simulation model of US adults aged 35 to 94 years, adding PCSK9 inhibitor therapy to current statin regimens was estimated to cost $423 000 per quality-adjusted life-year (QALY) gained compared with adding ezetimibe and increased US health care costs by $565 billion over 5 years (including a 38% increase in annual prescription drug expenditures over 2015 levels). Price reductions from more than $14 000 annually to $4536 would be necessary to meet a $100 000 per QALY threshold.

Meaning Assuming 2015 prices, PCSK9 inhibitor use did not meet generally accepted cost-effectiveness thresholds and was estimated to increase US health care costs substantially.

Methods

The institutional review boards of the University of California, San Francisco, and Columbia University approved the analyses of Framingham data. All other analyses were conducted on publicly available data.

Model Structure

The Cardiovascular Disease Policy Model is an established simulation model of coronary heart disease and stroke incidence, prevalence, mortality, and costs in the US population aged 35 years or older (eFigure 1 in the Supplement).[6-8] In the population without ASCVD, the model predicts incidence of coronary heart disease, stroke, and death due to noncardiovascular causes as a function of age, sex, and conventional ASCVD risk factors (systolic blood pressure, smoking status, diabetes mellitus, body mass index, high-density lipoprotein cholesterol, and LDL-C). In those who develop ASCVD, the model characterizes the initial event (cardiac arrest, MI, angina, or stroke) and its sequelae, including cardiovascular death, for 30 days. In the populations with a history of ASCVD, the model predicts subsequent cardiovascular events, coronary revascularization procedures, and cardiovascular or noncardiovascular mortality as a function of age, sex, and clinical history.

The model included the entire population of US adults aged 35 to 74 years in 2015 and followed them over their lifetime (until death or survival to 95 years of age). The prevalence of cardiovascular risk factors was estimated from population-weighted National Health and Nutrition Examination Surveys (NHANES) from 2005-2012.[9] Utilities and costs were assigned to each clinical event and health state in annual cycles and discounted at 3% annually[10] (**Table 1**). The model assumed the health system perspective, considering all direct health care costs (including immediate and downstream costs associated with disease progression or longer life expectancy). Extensive deterministic and probabilistic sensitivity analyses were conducted to account for input parameter uncertainty. The model adhered to recommendations of the Panel on Cost-Effectiveness in Health and Medicine.[10] Additional modeling details, including estimation of input parameters and calibration of the model, are in eFigures 1 and 2 and eTables 1 through 9 in the Supplement.

Target Population

Base-case simulations modeled the cost-effectiveness of PCSK9 inhibitors in 2 target adult populations defined using NHANES to approximate current FDA-approved indications[38,39]:

- Heterozygous FH: either (1) family history of premature coronary heart disease and LDL-C level of at least 190 mg/dL (4.91 mmol/L) without statin therapy or LDL-C level of at least 150 mg/dL (3.88 mmol/L) with statin therapy (in line with the recent consensus statement of the American Heart Association)[40,41] or (2) no family history of premature coronary disease and LDL-C level of at least 250 mg/dL (6.46 mmol/L) without statin therapy or LDL-C level of at least 200 mg/dL (5.17 mmol/L) with statin therapy
- Preexisting ASCVD: history of angina, MI, or stroke, with LDL-C level of at least 70 mg/dL (1.81 mmol/L) despite maximally tolerated statin therapy

The base-case assumption was that 10% of each population was "statin intolerant," but the size of this population varied in sensitivity analyses.[42,43]

Table 1. Key Input Parameters in the Cardiovascular Disease Policy Model

Parameters	Base-Case Value (Range for Probabilistic Sensitivity Analyses)	Distribution[a]	Source
Effect Size			
Reduction in LDL-C, %			
PCSK9 inhibitor			
Without background statin therapy	53.65 (47.78-59.51)	β	Navarese et al, 2015[4]
Added to mixed low- and high-intensity statin therapy	65.24 (60.02-70.46)	β	Navarese et al, 2015[4]
Added to high-intensity statin therapy	57.93 (54.91-60.95)	β	Navarese et al, 2015[4]
Ezetimibe			
Without background statin therapy	18.56 (17.44-19.68)	β	Ara et al, 2008[11]
Added to mixed low- and high-intensity statin therapy	23.60 (21.7-25.6)	β	Navarese et al, 2015[4]; Mikhailidis et al, 2007[12]
Added to high-intensity statin therapy	23.60 (21.7-25.6)	β	Navarese et al, 2015[4]; Mikhailidis et al, 2007[12]
Relative risk of nonfatal myocardial infarction or CHD mortality per 1-mmol/L reduction in LDL-C[b]			
Statin	0.76 (0.73-0.79)	Log normal	Fulcher et al, 2010[13]
Ezetimibe	0.76 (0.61-0.94)	Log normal	Fulcher et al, 2010[13]; Cannon et al, 2015[14]
PCSK9 inhibitor	0.76 (0.58-1.04)	Log normal	Fulcher et al, 2010[13]; individual PCSK9 trials[15-23]
Relative risk of stroke per 1-mmol/L reduction in LDL-C[c]			
Statin	0.85 (0.80-0.89)	Log normal	Fulcher et al, 2010[13]
Ezetimibe	0.85 (0.80-0.89)	Log normal	Fulcher et al, 2010[13]; Cannon et al, 2015[14]
PCSK9 inhibitor	0.85 (0.80-1.00)	Log normal	Fulcher et al, 2010[13]; assumed
Common Adverse Events With PCSK9 Inhibitors			
Injection-site reactions, %	5 (0-10)	β	Blom et al[15]; Moriarty et al[17]; Kereiakes et al[18]; Robinson et al[21]; Raal et al[24]; Sabatine et al[25]
Drug Costs			
Annual drug costs, 2015 US $[d]			
Ezetimibe	2878 (1437-5756)	NA	Red Book Online[26]
PCSK9 inhibitor[e]	14 350 (7175-28 700)	NA	Red Book Online[26]
Cardiovascular Costs			
Costs of CHD care, 2015 US $[f]			
Acute fatal MI hospitalization	53 565 (44 638-64 278)	Log normal	California OSHPD, 2008[27,28]; US Census Bureau[29]; Bureau of Labor Statistics[30]
Acute nonfatal MI hospitalization	38 766 (32 305-46 519)	Log normal	California OSHPD, 2008[27,28]; US Census Bureau[29]; Bureau of Labor Statistics[30]
Acute nonfatal MI and CABG	99 092 (82 577-118 910)	Log normal	California OSHPD, 2008[27,28]; US Census Bureau[29]; Bureau of Labor Statistics[30]
Acute MI posthospitalization year 1 costs	12 338 (10 282-14 806)	Log normal	California OSHPD, 2008[27,28]; US Census Bureau[29]; Bureau of Labor Statistics[30]
CHD costs, subsequent years	2520 (2100-3024)	Log normal	AHRQ[31]; Bureau of Labor Statistics[30]
Costs of heart failure care, 2015 US $			
Heart failure hospitalization	19 512 (16 260-23 414)	Log normal	California OSHPD, 2008[27,28]; US Census Bureau[29]; Bureau of Labor Statistics[30]
Costs of stroke care, 2015 US $			
Fatal stroke hospitalization	26 699 (22 249-32 039)	Log normal	California OSHPD, 2008[27,28]; US Census Bureau[29]; Bureau of Labor Statistics[30]
Nonfatal stroke hospitalization	19 732 (16 443-23 678)	Log normal	California OSHPD, 2008[27,28]; US Census Bureau[29]; Bureau of Labor Statistics[30]
Poststroke cost, months 2-11	34 712 (28 927-41 654)	Log normal	California OSHPD, 2008[27,28]; US Census Bureau[29]; Bureau of Labor Statistics[30]
Poststroke cost, annual, subsequent years	5305 (4421-6366)	Log normal	AHRQ[31]; Bureau of Labor Statistics[30]
Utility Weights			
No history of cardiovascular disease	1.0000		Assumed
History of angina	0.9064 (0.8667-0.9393)	β	Moran et al, 2014[32,33]; Murray et al, 2012[34]
History of MI	0.9648 (0.9505-0.9758)	β	Moran et al, 2014[32,33]; Murray et al, 2012[34]
History of stroke	0.8835 (0.8414-0.9108)	β	Moran et al, 2014[32,33]; Murray et al, 2012[34]
History of MI and stroke	0.8524 (0.7998-0.8888)	β	Moran et al, 2014[32,33]; Murray et al, 2012[34]

(continued)

Table 1. Key Input Parameters in the Cardiovascular Disease Policy Model (continued)

Parameters	Base-Case Value (Range for Probabilistic Sensitivity Analyses)	Distribution[a]	Source
Transient utility tolls for acute events			
Angina	0.0078 (0.0051-0.0111)	β	Moran et al, 2014[32,33]; Murray et al, 2012[34]
Percutaneous revascularization	0.0096 (0.0041-0.0192)	β	Kazi et al, 2014[35]
Surgical revascularization	0.0192 (0.0096-0.0396)	β	Kazi et al, 2014[35]
Acute MI	0.0079 (0.0051-0.0112)	β	Moran et al, 2014[32,33]; Murray et al, 2012[34]
Acute stroke	0.0113 (0.0084-0.0154)	β	Moran et al, 2014[32,33]; Murray et al, 2012[34]
Injection site adverse reactions	0.0003 (0.0000-0.0020)	β	Khazeni et al, 2009[36,37]

Abbreviations: AHRQ, Agency for Healthcare Research and Quality; CABG, coronary artery bypass graft; CHD, coronary heart disease; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; NA, not applicable; OSHPD, Office of Statewide Health Planning and Development; PCSK9, proprotein convertase subtilisin/kexin type 9.

[a] In multiway probabilistic sensitivity analyses, model parameters varied randomly by predefined statistical distributions. To limit the degrees of freedom, some parameters were assumed to be correlated (all drug costs, all other health care costs).

[b] Consistent with the LDL hypothesis, the base case assumed a constant relative reduction in the risk of nonfatal myocardial infarction or CHD mortality for each millimole per liter of reduction in LDL-C, independent of the agent used to lower LDL-C (statin, ezetimibe, or PCSK9 inhibitor). This was estimated from the most recent meta-analysis from the Cholesterol Treatment Trialists.[13] Sensitivity analyses explored the range of uncertainty in this end point as seen in IMPROVE-IT for ezetimibe[14] and in a meta-analysis of PCSK9 trials that reported that end point.[15-23] See the eAppendix in the Supplement for details.

[c] The base case assumed a constant relative reduction in the risk of stroke for each millimole per liter of reduction in LDL-C, independent of the agent used to lower LDL-C (statin, ezetimibe, or PCSK9 inhibitor). This was estimated from the most recent meta-analysis from the Cholesterol Treatment Trialists.[13] Sensitivity analyses explored the range of uncertainty in this end-point as seen in IMPROVE-IT for ezetimibe.[14] There were too few strokes in the short-term PCSK9 trials, so the range was extended to include no evidence of benefit with PCSK9 inhibitors. See the eAppendix in the Supplement for details.

[d] Drug costs were included in 1-way sensitivity analyses but not in the probabilistic analysis.

[e] In the base case, the cost of a PCSK9 inhibitor was assumed to be the average of the wholesale acquisition price of alirocumab ($14 600) and evolocumab ($14 100).

[f] In the probabilistic sensitivity analysis, the population mean for health care costs was varied by −20% to +25% because confidence intervals were not available from the primary data sources.

Treatment Strategies

Three treatment strategies were modeled: (1) status quo, defined by statin use as identified in the 2005-2012 NHANES; (2) incremental treatment with ezetimibe; and (3) incremental treatment with PCSK9 inhibitors. In each case, the incremental drug was added to statin therapy or was used as monotherapy among those intolerant to statins.

The degree of LDL-C reduction with ezetimibe and PCSK9 inhibitors was estimated from the published literature (Table 1). Statins, ezetimibe, and PCSK9 inhibitors were each assumed to reduce the risk of cardiovascular events by an identical amount per milligram per deciliter of LDL-C reduction.[13,14] Alternative assumptions were modeled in sensitivity analyses.

Among patients receiving PCSK9 inhibitor therapy, 5% were assumed to develop mild injection site reactions resulting in a small disutility, without an increase in costs or treatment discontinuation.[15,17,18,21,24]

Costs and Utilities

Age- and sex-specific health care costs were estimated using national data (Table 1).[27-31] Annual drug costs were assumed to be equal to their wholesale acquisition costs[26]; in the case of PCSK9 inhibitors, this was assumed to be the mean of the 2015 annual costs of alirocumab ($14 600) and evolocumab ($14 100).[26,44] Health-related quality-of-life weights and severity distributions for ASCVD states were based on the Global Burden of Disease 2010 study.[32-34]

Main Outcomes and Measures

The primary outcome was the incremental cost-effectiveness ratio (ICER; cost per quality-adjusted life-year [QALY]) over the lifetime analytic horizon.[10] Secondary outcomes were (1) incremental cost per life-year gained; (2) the number of patients that would need to be treated for 5 years to avert 1 major adverse cardiovascular event (MACE, defined as a composite of cardiovascular death, nonfatal MI, or nonfatal stroke); (3) the price at which the drugs became cost-effective at a willingness-to-pay threshold of $100 000 per QALY; (4) the total effect on the US health care budget over the next 5 years if all eligible patients were to receive PCSK9 inhibitors (compared with receipt of ezetimibe); and (5) the net monetary benefit of incremental therapy with a PCSK9 inhibitor at willingness-to-pay thresholds ranging from $50 000 to $1 000 000 per additional QALY.

Sensitivity Analyses

One-way sensitivity analyses for key input parameters were performed by varying one input at a time while holding others constant at their base-case estimates. Several prespecified scenario analyses were also performed, including (1) using higher LDL-C thresholds to define heterozygous FH (LDL-C ≥250 mg/dL [6.46 mmol/L] without statin therapy or LDL-C ≥200 mg/dL [5.17 mmol/L] with statin therapy) and assuming a higher ASCVD risk than predicted by LDL-C level (2 times the risk for individuals with heterozygous FH compared with individuals without FH for the same LDL-C level); (2) modeling the main effect of ezetimibe and PCSK9 inhibitors on cardiovascular outcomes as seen in clinical trials (rather than based on the LDL-C hypothesis; eTable 6 in the Supplement)[14-23]; (3) initiating PCSK9 inhibitors only after incident MI (by simulating addition of PCSK9 inhibitors among those with incident MI in the base year); (4) initiating PCSK9 inhibitor

monotherapy among all patients with heterozygous FH or ASCVD requiring additional lipid lowering and not currently taking a statin or unable to tolerate statins; (5) varying the prevalence of statin intolerance between 3% and 20%; (6) modeling a 0.5% incidence of mild neurocognitive defects in patients receiving PCSK9 inhibitor therapy; and (7) treating all currently untreated, statin-tolerant individuals with statins.

Probabilistic sensitivity analyses simultaneously varied multiple input parameters across prespecified statistical distributions in 1000 iterations. Table 1 shows the range and type of distribution used for each input parameter. The results of these simulations captured the uncertainty in key outcomes and are presented as (1) 80% uncertainty intervals (UIs) around the point estimate for clinical and economic outcomes and (2) acceptability curves showing the proportion of simulations in which PCSK9 inhibitor therapy was the optimal treatment strategy at various willingness-to-pay thresholds. Of note, 80% (rather than 95%) UIs were chosen to avoid issues related to extreme outliers such as flipped ordering of strategies or negative ICERs. See the eAppendix in the Supplement for additional methodologic details.

The CVD Policy Model is programmed in Lahey Fortran 95. Modeled outcomes were analyzed using QuickBasic64 and Excel 2011 (Microsoft) and statistical analyses were performed using SAS version 9.4 (SAS Institute Inc) and Stata version 13 (StataCorp).

Results

Base-Case Analysis

Of 1.7 million individuals aged 35 to 74 years who met criteria for heterozygous FH, 1.1 million (61%) were either taking a statin or designated as statin intolerant and thus eligible for ezetimibe or PCSK9 inhibitor treatment (**Table 2**). Mean age was 51 years and mean LDL-C level was 207 mg/dL (5.36 mmol/L). Addition of ezetimibe to statin therapy was estimated to avert 214 400 MACE and generate 475 100 additional QALYs at an ICER of $152 000 per QALY (**Table 3** and eTable 10 in the Supplement). Compared with adding ezetimibe, adding a PCSK9 inhibitor was estimated to result in 316 300 fewer MACE and 628 500 additional QALYs. The number needed to treat over 5 years to prevent 1 MACE in patients with heterozygous FH currently taking statins or statin intolerant was estimated to be 72 for ezetimibe relative to status quo and 59 for PCSK9 inhibitors relative to ezetimibe. Treating the entire 35- to 74-year-old FH population taking statins or statin intolerant with PCSK9 inhibitors over their lifetime was estimated to cost $323 billion more than treating with ezetimibe; an estimated $17 billion would be offset by decreased cost of cardiovascular care due to averted events, leading to a net of $582 000 per life-year gained or $503 000 per QALY (Table 3).

Among the 13.0 million individuals with ASCVD, 8.5 million (65%) either were taking a statin with an LDL-C level higher than 70 mg/dL or were statin intolerant; mean age was 61 years and mean LDL-C level was 109 mg/dL (2.82 mmol/L) (Table 2). Addition of ezetimibe to statin therapy was estimated to avert 2.7 million MACE and generate 5.3 million QALYs at an ICER of $154 000 per QALY (**Table 4** and eTable 10 in the Supplement). In contrast, addition of a PCSK9 inhibitor to statin therapy was estimated to avert an additional 4.3 million MACE and produce 7.9 million additional QALYs (compared with ezetimibe plus statin). The number needed to treat over 5 years to prevent 1 MACE among those with ASCVD and not meeting the LDL-C goal despite maximally tolerated statin therapy was estimated to be 51 for ezetimibe compared with status quo and 35 for PCSK9 inhibitors relative to ezetimibe. PCSK9 inhibitor therapy over the lifetime in this population was projected by the model to cost $3.3 trillion more than treating with ezetimibe, but $155 billion was estimated to be offset by decreased cost of cardiovascular care due to averted events, for a net of $378 000 per life-year gained or $414 000 per QALY (Table 3).

Table 2. Baseline Clinical Characteristics and Modeled MACE Rates Among Treatment Populations Included in the Model (US Adults Aged 35-74 Years in 2015 Eligible for Additional Lipid-Lowering Therapy)

	Heterozygous FH (n = 1 065 000)[a]	History of ASCVD, LDL-C ≥70 mg/dL (n = 8 531 000)[a]
Baseline clinical characteristics[b]		
Age, mean (95% CI), y	51 (50-53)	61 (60-62)
Female, % (95% CI)	72 (63-81)	38 (31-45)
LDL-C, mean (95% CI), mg/dL	207 (202-212)	109 (105-114)
HDL-C, mean (95% CI), mg/dL	55 (53-57)	51 (49-52)
Body mass index, mean (95% CI)[c]	29 (28-30)	31 (30-32)
Systolic blood pressure, mean (95% CI), mm Hg	128 (122-135)	127 (125-130)
Hypertension, % (95% CI)	49 (36-63)	68 (58-78)
Diabetes mellitus, % (95% CI)	26 (17-36)	32 (26-38)
Modeled MACE rates per 100 patient-years[d]		
Nonfatal myocardial infarction	0.39	0.99
Nonfatal stroke	0.43	1.01
CHD death	0.20	0.88
Death due to vascular causes	0.24	1.02
All MACE	1.06	3.02

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; FH, familiar hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse clinical events (nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death).

[a] Sample size refers to the number of individuals in the CVD Policy Model who meet the definition of heterozygous familial hypercholesterolemia or ASCVD.

[b] Derived from continuous US National Health and Nutrition Examination Survey (NHANES) 2005-2012 using examination weights and operational definitions of treatment populations as described in study methods. No risk factor trends were assumed, so the CVD Policy Model simulations incorporated the age- and sex-specific multivariate risk factor distribution estimated from existing NHANES data. Reported 95% CIs are based on standard errors.

[c] Calculated as weight in kilograms divided by height in meters squared.

[d] The standard error for MACE in the source data from which these rates were derived was approximately 3%. The numbers presented here are the MACE event rates observed in the calibrated model over the first 5 years.

One-Way and Probabilistic Sensitivity Analyses

In 1-way sensitivity analyses varying drug cost, analytic horizon, discount factor, magnitude of LDL-C reduction, and the proportion of statin-intolerant individuals, cost-effectiveness of PCSK9 inhibitor therapy and ezetimibe was highly sensitive

Table 3. Modeling Results: Clinical and Economic Outcomes Over the Lifetime Analytic Horizon[a]

Treatment Strategy	Total No. of MACE Averted	NNT_5	Life-Years Gained	QALYs Gained	Incremental Cost, 2015 US $, in Millions			ICER, $	
					Drug	Cardiovascular Care	Noncardiovascular Care[b]	Per Life-Year	Per QALY
Current US Population With Heterozygous FH for Whom Additional Lipid-Lowering Therapy Is Indicated[c]									
Current statin use[d]	Comparator								
Incremental treatment with ezetimibe[e]	214 400 (110 600-322 300)	72 (55-113)	415 200 (243 500-579 900)	475 100 (258 300-692 600)	76 758 (74 945-78 440)	−12 323 (−18 450 to −6122)	7640 (4300-10 915)	174 000 (122 000-305 000)	152 000 (102 000-287 000)
Incremental treatment with PCSK9 inhibitor (vs ezetimibe plus statin)[e]	316 300 (185 200-405 400)	59 (46-107)	543 200 (316 600-678 400)	628 500 (183 900-648 400)	323 096 (311 363-331 405)	−17 043 (−21 042 to −10 700)	10 268 (6069-12 836)	582 000 (475 000-970 000)	503 000 (493 000-1 737 000)[f]
Current US Population With ASCVD for Whom Additional Lipid-Lowering Therapy Is Indicated[g]									
Current statin use[d]	Comparator								
Incremental treatment with ezetimibe[e]	2 727 000 (1 407 300-4020 400)	51 (35-102)	5 762 900 (2 983 400-8 394 400)	5 255 500 (2 708 100-7 566 200)	802 253 (797 515-806 888)	−101 166 (−150 528 to −52 599)	107 801 (56 051-157 315)	140 000 (97 000-269 000)	154 000 (107 000-297 000)
Incremental treatment with PCSK9 inhibitor (vs ezetimibe plus statin)[e]	4 281 200 (1 136 400-6 839 200)	35 (23-83)	8 676 300 (2 232 900-13 374 100)	7 919 400 (2 090 600-12 061 300)	3 272 730 (3 199 542-3 331 767)	−155 000 (−246 237 to −39 323)	164 144 (43 683-255 114)	378 000 (251 000-1 435 000)	414 000 (277 000-1 539 000)[h]

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; FH, familial hypercholesterolemia; ICER, incremental cost-effectiveness ratio; MACE, major adverse cardiovascular events (nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death); NNT_5, number needed to treat for 5 years to avert 1 MACE; 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% per year. To reflect the precision of the model, person-years of treatment are rounded to the nearest 100 000; MACE and QALYs are rounded to the nearest 100; costs are rounded to the nearest million; and incremental cost-effectiveness ratios to the nearest 1000. All reported values are point estimates from the base case with 80% uncertainty intervals. Additional modeling details are available in the eAppendix in the Supplement.

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

[c] This analysis included patients who met the operational definition of heterozygous FH and were either already receiving statin therapy or deemed statin intolerant (n = 1 065 000 in 2015) and involved 43.0 million person-years of incremental treatment with ezetimibe or 45.6 million person-years of incremental treatment with a PCSK9 inhibitor.

[d] The comparator was statin therapy (as treated) among patients who were statin tolerant and no lipid-lowering therapy among patients who were statin intolerant.

[e] Statin plus ezetimibe is compared with current statin use, whereas statin plus PCSK9 inhibitor is compared with statin plus ezetimibe (the next best alternative).

[f] This is the ICER of incremental PCSK9 inhibitor therapy relative to ezetimibe among patients with heterozygous FH. For reference, the ICER of PCSK9 inhibitor relative to status quo was $352 000 per QALY.

[g] This analysis included patients with a history of ASCVD and low-density lipoprotein-cholesterol ≥70 mg/dL (≥1.81 mmol/L; taking statin therapy if tolerated or not taking statin therapy among patients who were statin intolerant; n = 8 531 000 in 2015) and involved 489.0 million person-years of incremental treatment with ezetimibe or 500.6 million person-years of incremental treatment with a PCSK9 inhibitor.

[h] This is the ICER of incremental PCSK9 inhibitor therapy relative to ezetimibe among patients with ASCVD. For reference, the ICER of PCSK9 inhibitor relative to status quo was $310 000 per QALY.

Table 4. Effect of PCSK9 Inhibitors on Total Health Care Spending Over 5 Years[a]

Treatment Strategy	Incremental Cost, 2015 US $, in Millions			Net Health Care Cost, $, in Millions
	Drug	Cardiovascular Care	Noncardiovascular Care[b]	
Current US Population With Heterozygous FH for Whom Additional Lipid-Lowering Therapy Is Indicated[c]				
Current statin use[d]	Comparator			
Incremental treatment with ezetimibe[e]	16 467 (16 406-16 520)	−1543 (−2011 to −989)	83 (59-103)	15 007 (14 587-15 492)
Incremental treatment with PCSK9 inhibitor[e]	66 077 (65 752-66 286)	−1868 (−2346 to −994)	95 (47-119)	64 304 (63 986-64 876)
Current US Population With ASCVD for Whom Additional Lipid-Lowering Therapy Is Indicated[f]				
Current statin use[d]	Comparator			
Incremental treatment with ezetimibe[e]	134 673 (134 519-134 809)	−19 076 (−27 495 to −9467)	1175 (579-1684)	116 772 (109 008-125 634)
Incremental treatment with PCSK9 inhibitor[e]	539 039 (536 665-540 647)	−27 723 (−41 051 to −6077)	1699 (37-2503)	513 014 (502 101-530 850)

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; FH, familial hypercholesterolemia; PCSK9, proprotein convertase subtilisin/kexin type 9.

[a] The model assumed the health system perspective and a 5-year analytic horizon and discounted future costs and QALYs at 3% a year. To reflect the precision of the model, person-years of treatment are rounded to the nearest 100 000, costs are rounded to the nearest million, and incremental cost-effectiveness ratios to the nearest 1000. All costs are reported in 2015 US dollars. All reported values are point estimates from the base case with 80% uncertainty intervals. Additional modeling details are available in the eAppendix in the Supplement.

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

[c] This analysis included patients who met the operational definition of heterozygous FH and were either already receiving statin therapy or deemed statin intolerant (n = 1 065 000 in 2015) and involved 5.7 million person-years of incremental treatment with ezetimibe or 5.8 million person-years of incremental treatment with a PCSK9 inhibitor.

[d] The comparator was statin therapy (as treated) among patients who were statin tolerant and no lipid-lowering therapy among patients who were statin intolerant.

[e] Statin plus ezetimibe is compared with current statin use, whereas statin plus PCSK9 inhibitor is compared with statin plus ezetimibe (the next best alternative).

[f] This analysis included patients with a history of ASCVD and low-density lipoprotein-cholesterol ≥70 mg/dL (≥1.81 mmol/L; taking statin therapy if tolerated or not taking statin therapy among patients who were statin intolerant; n = 8 531 000 in 2015) and involved 46.8 million person-years of incremental treatment with ezetimibe or 46.9 million person-years of incremental treatment with a PCSK9 inhibitor.

only to the cost of the drug and the time horizon (with the lifetime horizon in the base analysis the most optimistic scenario) (eFigure 3 in the Supplement). In probabilistic sensitivity analyses, at 2015 US prices PCSK9 inhibitors were estimated to be cost-effective in 0% of simulations at thresholds of $50 000 per QALY, $100 000 per QALY, and $150 000 per QALY (**Figure 1** and eFigure 4 in the Supplement).[45,46]

Threshold Analyses and Effect on Health Care Spending

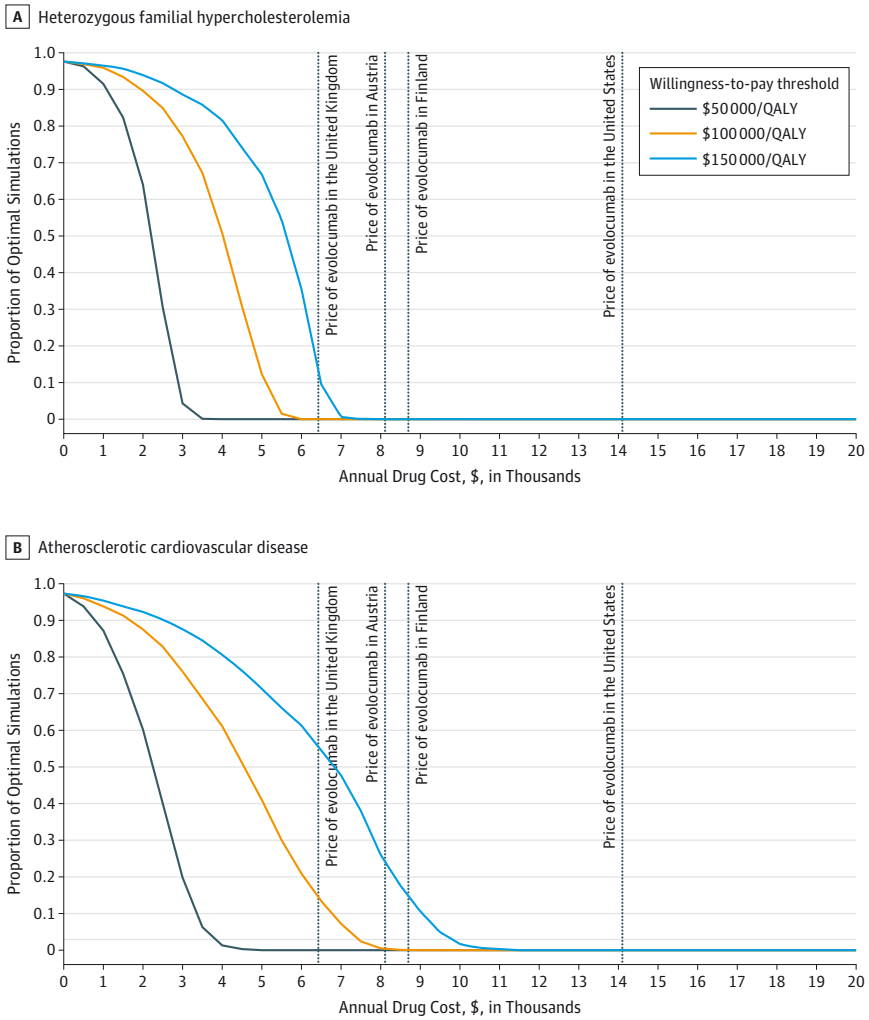
A cost-effectiveness threshold of $100 000 per QALY was achieved when the annual price of PCSK9 inhibitors was reduced by 68% to 70% to $4536 (**Figure 2** and eTable 11 and eFigure 4 in the Supplement). Simulations that modeled the use of PCSK9 inhibitors instead of ezetimibe among all currently eligible patients resulted in an estimated $592 billion increase in drug spending over 5 years (Table 4 and eTable 12 in the Supplement). Although cardiovascular costs were estimated to decrease by $29 billion over the same period, there was an estimated net increase of $568 billion in health care spending. Adding PCSK9 inhibitor therapy to status quo statin therapy was estimated to generate the greatest net monetary benefit if the willingness-to-pay threshold was at least $423 000 per QALY (eFigure 5 in the Supplement). For willingness-to-pay thresholds ranging from at least $155 000 per QALY to less than $423 000 per QALY, the greatest net monetary benefit was estimated to result from adding ezetimibe to status quo statin therapy. At any level of willingness to pay less than $155 000 per QALY, neither strategy was estimated to yield a net monetary benefit, and the comparator, status quo statin therapy, was projected by the model to be the optimal choice.

Scenario Analyses

Most scenarios resulted in the same or economically less favorable ICERs for PCSK9 inhibitors, including (1) modeling the effects on ASCVD as estimated from drug-specific clinical trials rather than the LDL hypothesis (eTable 13 in the Supplement); (2) incorporating alternative quality-of-life estimates (eTable 14 in the Supplement); (3) stopping incremental therapy at age 75 years (eTable 15 in the Supplement); and (4) modeling a decrement in quality of life related to subcutaneous injections or additional adverse drug reactions (eTables 16 and 17 in the Supplement).

A few scenarios resulted in more economically favorable ICERs or budget projections. Defining the heterozygous FH population using higher LDL-C thresholds resulted in 460 000 fewer adults eligible for PCSK9 inhibitor therapy, a lower ICER ($435 000 per QALY), and a smaller increase in estimated spending ($28.6 billion over 5 years); assuming those with FH have a 2-fold higher ASCVD risk than that predicted by their LDL-C level improved the ICER to $175 000 per QALY. Restricting PCSK9 inhibitor therapy to statin-intolerant patients in the heterozygous FH and ASCVD populations resulted in ICER estimates of $282 000 per QALY and $346 000 per QALY, respectively (eTable 18 in the Supplement). Restricting PCSK9 inhibitor therapy to patients with an incident MI lowered the ICER to an estimated $304 000 per QALY (eTable 19 in the Supplement). Reducing the prevalence of statin intolerance from 10% to 3% resulted in 974 000 fewer individuals eligible for PCSK9 therapy with an estimated decrease in health care spending of $10.2 billion over 5 years. Initiating statin treatment among all individuals with heterozygous FH or ASCVD not currently

Figure 1. Probabilistic Sensitivity Analyses Showing the Proportion of Optimal Simulations as a Function of Drug Price



At 2015 US prices and a threshold of $100 000 per quality-adjusted life-year (QALY), proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors were not cost-effective among patients with heterozygous familial hypercholesterolemia or atherosclerotic cardiovascular disease. Lowering the drug price or increasing the cost-effectiveness threshold would increase the proportion of simulations that are cost-effective. Vertical dotted lines show the list price of a 1-year supply of evolocumab in the United States ($14 100), the United Kingdom ($6427; the National Health Service receives an additional discount), Austria ($8110), and Finland ($8700).[45,46]

taking statins resulted in an estimated 214 500 fewer MACE over 5 years, with a net cost savings estimated at $12 billion over 5 years compared with status quo.

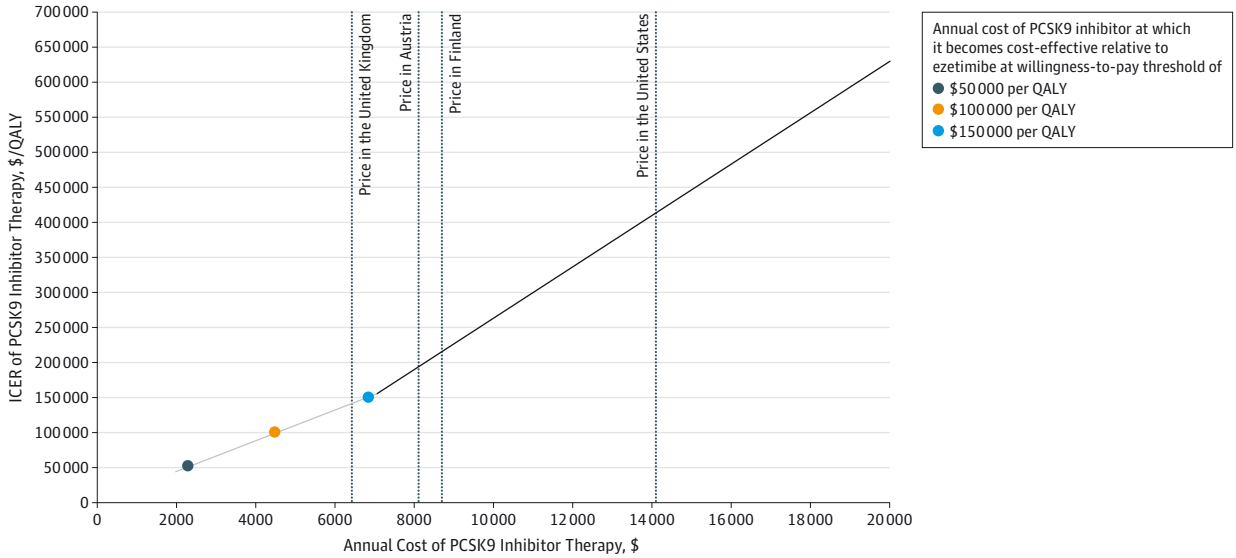
Discussion

This economic evaluation of PCSK9 inhibitors from the US health system perspective demonstrates that their use as indicated could substantially reduce MIs, strokes, and cardiovascular deaths. However, even if they prove highly effective in preventing ASCVD, PCSK9 inhibitors are not cost-effective at 2015 prices, and achieving commonly accepted cost-effectiveness thresholds would require price reductions by more than two-thirds.[47] At 2015 prices, PCSK9 inhibitor use in eligible individuals between the ages of 35 and 74 years was estimated to increase annual prescription spending by approximately $125 billion over ezetimibe use (a 38% increase from the approximately $329 billion spent on prescription drugs in 2015) and US health care expenditures by about $120 billion (a 4% increase from the $2.8 trillion dollars in total US health care spending in 2015).[48]

The effect of a new medication on health care spending is determined by the size of the target population, duration and effectiveness of therapy, drug price, and costs of care.[49] Although new, expensive therapies indicated for short duration or for treatment of rare conditions have thus far been absorbed by the budgets of health systems, the high cost of PCSK9 inhibitors is uniquely challenging. This is because PCSK9 inhibitors are meant to be lifelong therapy not only for the relatively small number of patients with FH but also for a large and growing population with ASCVD. As a result, the potential increase in health care expenditures at current or even moderately discounted prices could be staggering, despite cost savings from averted ASCVD events.

Restricting the population treated with PCSK9 inhibitors is one strategy for containing costs. Higher-risk patient subgroups (such as those with a recent MI or heterozygous FH patients with higher LDL-C levels) would likely derive greater benefit from PCSK9 inhibitors; use in a smaller number of

Figure 2. Incremental Cost-effectiveness Ratio (ICER) of PCSK9 Inhibitor Therapy Among Patients With Heterozygous Familial Hypercholesterolemia or Atherosclerotic Cardiovascular Disease



The ICER for proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor therapy increases with the annual cost of PCSK9 inhibitor therapy. Blue, orange, and black data markers indicate the price at which PCSK9 inhibitor therapy would become cost-effective in the United States at willingness-to-pay thresholds of $150 000 per quality-adjusted life-year (QALY) ($6810), $100 000 per QALY ($4536), and $50 000 per QALY ($2261), respectively. In the base case, status quo statin plus PCSK9 inhibitor therapy is compared with status quo statin plus ezetimibe (black line). When PCSK9 inhibitor therapy costs less than $7049 per year (inflection in the graph), ezetimibe is eliminated by extended dominance and status quo statin plus PCSK9 inhibitory therapy is compared directly with status quo statin therapy (gray line). For reference, vertical lines include the list price of a 1-year supply of evolocumab in the United States and 3 European countries.

higher-risk patients lowers total spending, but PCSK9 inhibitor therapy is still not cost-effective in these groups at current prices. Identifying patients with true statin intolerance (by rechallenging patients with statins[50] or performing n-of-1 trials to assess statin tolerability[51]) could also reduce the number of individuals eligible for PCSK9 inhibitors and lower total costs.

The results of multiple scenario analyses suggest that reducing the price of PCSK9 inhibitors remains the primary approach to improving the value of these therapies. Although biologic agents are inherently more expensive to study and manufacture compared with small molecules, these costs may not be the ultimate driver of pricing.[52] Furthermore, the US prices of biologic agents have not declined over time and have increased 6% to 12% a year for top-selling rheumatoid arthritis drugs.[53] Although generic biosimilars may eventually lower drug costs, their entry has often been delayed by complex manufacturing and approval requirements, extending the effective market exclusivity of the pioneer drugs and reducing price competition after patent expiration.[54] Biosimilars of other therapies currently available in the European Union cost 25% to 30% less than the reference biologic agent[55]; if the US experience with PCSK9 inhibitors is comparable, biosimilar versions of PCSK9 inhibitors would still not be cost-effective. These results are consistent with those of the National Institute for Health and Care Excellence in the United Kingdom: although PCSK9 inhibitors were initially introduced in the United Kingdom at a price less than half that in the United States (Figure 1), they were approved for use in the National Health Service only after manufacturers agreed to an additional price discount.[56]

In the face of limited health care resources, payers must consider the potential trade-off between paying for new drug treatments like PCSK9 inhibitors and investing in interventions known to improve access, physician prescription rates, and patient adherence to statin therapy among those at high ASCVD risk. Nationally representative data from NHANES indicate that more than one-third of both FH and ASCVD patients who have an LDL-C level of at least 70 mg/dL are not currently receiving statins, despite evidence of long-term effectiveness, safety, and cost-effectiveness.[57] Fully treating these populations that have an indication for statins but are currently not receiving them would actually save an estimated $12 billion over 5 years.

This analysis has several limitations. First, no long-term data on clinical outcomes exist for PCSK9 inhibitors. Although the short-term trials suggest lower rates of MI and cardiovascular death, these were not powered for clinical outcomes, and several nonstatin medications that lower LDL-C have not shown clinical benefit in long-term trials.[58] If ongoing clinical trials demonstrate that the drugs do not improve clinical outcomes as predicted by their effect on LDL-C, this model will have overestimated their cost-effectiveness. Second, the effect of PCSK9 inhibitors on total health care spending in the community setting will depend on uptake and adherence, which may vary based on age, educational status,

comorbidities, and cost sharing. The long-term effect of missed doses of PCSK9 inhibitor therapy on clinical effectiveness is currently unknown, although from an economic standpoint, patients who stop taking the drug accrue neither costs nor benefits and therefore do not alter the cost-effectiveness of the drug. Third, because LDL-C–lowering treatment in FH may begin in childhood or young adulthood to prevent premature coronary heart disease, the model may not have captured the entire clinical and economic burden of FH or the benefits of LDL-C lowering in childhood or young adulthood. However, there are no data about the efficacy or safety of PCSK9 inhibitors in children and there are limited data in young adults, and PCSK9 inhibitors are currently approved for use only among adults. The base case assumed that the elevated cardiovascular risk among patients with FH is mediated by their high levels of LDL-C along with other known cardiovascular risk factors. Although contemporary data on cardiovascular risk in heterozygous FH are limited, a patient with FH may have higher ASCVD risk than predicted by their LDL-C level, perhaps because of the early-life exposure to high LDL-C. In a sensitivity analysis, doubling ASCVD risk related to LDL-C levels in FH resulted in an improved ICER that was still above the $100 000 per QALY threshold.

Conclusions

Assuming 2015 prices, PCSK9 inhibitor use in patients with heterozygous familial hypercholesterolemia or ASCVD did not meet generally acceptable incremental cost-effectiveness thresholds and was estimated to increase US health care costs substantially. Reducing annual drug prices from more than $14 000 to $4536 would be necessary to meet a $100 000 per QALY threshold.

ARTICLE INFORMATION

Author Affiliations: Department of Medicine, Center for Vulnerable Populations, University of California, San Francisco (Kazi, Coxson, Penko, Guzman, Bibbins-Domingo); Department of Medicine, University of California, San Francisco (Kazi, Coxson, Penko, Tice, Bibbins-Domingo); Department of Epidemiology and Biostatistics, University of California, San Francisco (Kazi, Bibbins-Domingo); Center for Healthcare Value, University of California, San Francisco (Kazi); Division of Cardiology, Zuckerberg San Francisco General Hospital, San Francisco, California (Kazi); Division of General Internal Medicine, Columbia University Medical Center, New York, New York (Moran); College of Physicians and Surgeons, Columbia University, New York, New York (Moran); Division of General Internal Medicine, Zuckerberg San Francisco General Hospital, San Francisco, California (Coxson, Bibbins-Domingo); Institute for Clinical and Economic Review, Boston, Massachusetts (Ollendorf, Pearson).

Author Contributions: Drs Kazi and Bibbins-Domingo had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Kazi, Moran, Ollendorf, Pearson, Tice, Bibbins-Domingo.
Acquisition, analysis, or interpretation of data: Kazi, Moran, Coxson, Penko, Ollendorf, Tice, Guzman, Bibbins-Domingo.
Drafting of the manuscript: Kazi, Penko, Bibbins-Domingo.
Critical revision of the manuscript for important intellectual content: Kazi, Moran, Coxson, Ollendorf, Pearson, Tice, Guzman, Bibbins-Domingo.
Statistical analysis: Kazi, Moran, Tice, Guzman, Bibbins-Domingo.
Obtaining funding: Ollendorf, Bibbins-Domingo.
Administrative, technical, or material support: Kazi, Penko, Ollendorf, Tice.
Study supervision: Kazi, Moran, Pearson, Bibbins-Domingo.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Drs Ollendorf and Pearson are employees of the Institute for Clinical and Economic Review, an independent organization that evaluates the evidence on the value of health care interventions, which is funded by grants from the Laura and John Arnold Foundation, Blue Shield of California Foundation, and the California Healthcare Foundation. The organization's annual summit is supported by dues from Aetna, America's Health Insurance Plans, Anthem, Blue Shield of California, CVS Caremark, Express Scripts, Harvard Pilgrim Health Care, Omeda Rx, United Healthcare, Kaiser Permanente, Premera Blue Cross, AstraZeneca, Genentech, GlaxoSmithKline, Johnson & Johnson, Merck, National Pharmaceutical Council, Takeda, Pfizer, Novartis, Eli Lilly, and Humana. Dr Tice reports receiving grant funding from the Institute for Clinical and Economic Review. No other disclosures are reported.

Funding/Support: Portions of this work were presented to the New England Comparative Effectiveness Public Advisory Council, a program of the Institute for Clinical and Economic Review that is supported by grants from the New England States Consortium Systems Organization and the Laura and John Arnold Foundation.

Role of the Funder/Sponsor: Funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

Disclaimers: Dr Bibbins-Domingo is the chair of the US Preventive Services Task Force (USPSTF). This article is the original work of its authors and does not represent the position or recommendation of the USPSTF. The Framingham Cohort and Framingham Offspring Research Materials were obtained from the US National Heart, Lung, and Blood Institute (NHLBI) Biologic Specimen and Data Repository Information Coordinating Center. The manuscript does not necessarily reflect the opinions or views of the Framingham Cohort, Framingham Offspring, or NHLBI.

REFERENCES

1. Giugliano RP, Sabatine MS. Are PCSK9 inhibitors the next breakthrough in the cardiovascular field? *J Am Coll Cardiol*. 2015;65(24):2638-2651.

2. Hunt SC, Hopkins PN, Bulka K, et al. Genetic localization to chromosome 1p32 of the third locus for familial hypercholesterolemia in a Utah kindred. *Arterioscler Thromb Vasc Biol*. 2000;20(4):1089-1093.

3. Cohen J, Pertsemlidis A, Kotowski IK, et al. Low LDL cholesterol in individuals of African descent resulting from frequent nonsense mutations in PCSK9. *Nat Genet*. 2005;37(2):161-165.

4. Navarese EP, Kolodziejczak M, Schulze V, et al. Effects of proprotein convertase subtilisin/kexin type 9 antibodies in adults with hypercholesterolemia: a systematic review and meta-analysis. *Ann Intern Med*. 2015;163(1):40-51.

5. Tice JA, Kazi D, Ollendorf DA, et al. *PCSK9 Inhibitors for Treatment of High Cholesterol: Effectiveness, Value, and Value-Based Price Benchmarks Draft Report*. Boston, MA: Institute for Clinical and Economic Review; September 8, 2015.

6. Moran AE, Odden MC, Thanataveerat A, et al. Cost-effectiveness of hypertension therapy according to 2014 guidelines. *N Engl J Med*. 2015;372(5):447-455.

7. Bibbins-Domingo K, Coxson P, Pletcher MJ, Lightwood J, Goldman L. Adolescent overweight and future adult coronary heart disease. *N Engl J Med*. 2007;357(23):2371-2379.

8. Weinstein MC, Coxson PG, Williams LW, et al. Forecasting coronary heart disease incidence, mortality, and cost. *Am J Public Health*. 1987;77(11):1417-1426.

9. National Center for Health Statistics. National Health and Nutrition Examination Survey, 2005-2012. http://www.cdc.gov/nchs/nhanes/nhanes_questionnaires.htm. Accessed June 8, 2015.

10. Gold MR, Siegel JE, Russel LB, eds. *Cost-Effectiveness in Health and Medicine*. New York, NY: Oxford University Press; 1996.

11. Ara R, Tumur I, Pandor A, et al. Ezetimibe for the treatment of hypercholesterolaemia. *Health Technol Assess*. 2008;12(21):iii, xi-xiii, 1-212.

12. Mikhailidis DP, Sibbring GC, Ballantyne CM, et al. Meta-analysis of the cholesterol-lowering effect of ezetimibe added to ongoing statin therapy. *Curr Med Res Opin*. 2007;23(8):2009-2026.

13. Fulcher J, O'Connell R, Voysey M, et al. Efficacy and safety of LDL-lowering therapy among men and women. *Lancet*. 2015;385(9976):1397-1405.

14. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med*. 2015;372(25):2387-2397.

15. Blom DJ, Hala T, Bolognese M, et al. A 52-week placebo-controlled trial of evolocumab in hyperlipidemia. *N Engl J Med*. 2014;370:1809-1819.

16. Giugliano RP, Desai NR, Kohli P, et al. Efficacy, safety, and tolerability of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 in combination with a statin in patients with hypercholesterolaemia (LAPLACE-TIMI 57). *Lancet*. 2012;380(9858):2007-2017.

17. Moriarty PM, Thompson PD, Cannon CP, et al. Efficacy and safety of alirocumab vs ezetimibe in statin-intolerant patients, with a statin rechallenge arm. *J Clin Lipidol*. 2015;9(6):758-769.

18. Kereiakes DJ, Robinson JG, Cannon CP, et al. Efficacy and safety of the proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab among high cardiovascular risk patients on maximally tolerated statin therapy. *Am Heart J*. 2015;169(6):906-915.

19. Cannon CP, Cariou B, Blom D, et al. Efficacy and safety of alirocumab in high cardiovascular risk patients with inadequately controlled hypercholesterolaemia on maximally tolerated doses of statins. *Eur Heart J*. 2015;36(19):1186-1194.

20. Kastelein JJ, Ginsberg HN, Langslet G, et al. ODYSSEY FH I and FH II: 78 week results with alirocumab treatment in 735 patients with heterozygous familial hypercholesterolaemia. *Eur Heart J*. 2015;36(43):2996-3003.

21. Robinson JG, Farnier M, Krempf M, et al. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *N Engl J Med*. 2015;372(16):1489-1499.

22. Bays H, Gaudet D, Weiss R, et al. Alirocumab as add-on to atorvastatin vs other lipid treatment strategies. *J Clin Endocrinol Metab*. 2015;100(8):3140-3148.

23. Farnier M, Jones P, Severance R, et al. Efficacy and safety of adding alirocumab to rosuvastatin vs adding ezetimibe or doubling the rosuvastatin dose in high cardiovascular-risk patients. *Atherosclerosis*. 2016;244:138-146.

24. Raal FJ, Honarpour N, Blom DJ, et al. Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolaemia (TESLA Part B). *Lancet*. 2015;385(9965):341-350.

25. Sabatine MS, Giugliano RP, Wiviott SD, et al. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. *N Engl J Med*. 2015;372(16):1500-1509.

26. Truven Health Analytics. Red Book Online. http://www.redbook.com/redbook/about. Accessed July 1, 2015.

27. *California Public Patient Discharge Data, 2008*. Sacramento, CA: Office of Statewide Health Planning and Development; 2008.

28. *Hospital Financial Data, 1999-2000*. Sacramento, CA: Office of Statewide Health Planning and Development; 2003. http://www.oshpd.ca.gov/HID/Hospital-Financial.asp#Profile. Accessed January 1, 2016.

29. US Census Bureau. *Statistical Abstract of the United States: Average Cost to Community Hospitals Per Patient, by State (Table 204)*. Washington, DC: Government Printing Office; 1998:136.

30. Bureau of Labor Statistics. Consumer Price Index for All Urban Consumers. http://data.bls.gov/cgi-bin/surveymost?cu. Accessed July 15, 2015.

31. Agency for Healthcare Research and Quality. Medical Expenditure Panel Survey public use files 1998-2008. http://meps.ahrq.gov/mepsweb/. Accessed January 1, 2015.

32. Moran AE, Forouzanfar MH, Roth GA, et al. Temporal trends in ischemic heart disease mortality in 21 world regions, 1980 to 2010. *Circulation*. 2014;129(14):1483-1492.

33. Moran AE, Forouzanfar MH, Roth GA, et al. The global burden of ischemic heart disease in 1990 and 2010. *Circulation*. 2014;129(14):1493-1501.

34. Murray CJ, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010. *Lancet*. 2012;380(9859):2197-2223.

35. Kazi DS, Garber AM, Shah RU, et al. Cost-effectiveness of genotype-guided and dual antiplatelet therapies in acute coronary syndrome. *Ann Intern Med*. 2014;160(4):221-232.

36. Khazeni N, Hutton DW, Garber AM, et al. Effectiveness and cost-effectiveness of vaccination against pandemic influenza (H1N1) 2009. *Ann Intern Med*. 2009;151(12):829-839.

37. Khazeni N, Hutton DW, Garber AM, Owens DK. Effectiveness and cost-effectiveness of expanded antiviral prophylaxis and adjuvanted vaccination strategies for an influenza A (H5N1) pandemic. *Ann Intern Med*. 2009;151(12):840-853.

38. US National Library of Medicine. Label: Praluent—alirocumab injection, solution. http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=446f6b5c-0dd4-44ff-9bc2-c2b41f2806b4. Accessed September 2, 2015.

39. US National Library of Medicine. Label: Repatha—evolocumab injection, solution. http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=709338ae-ab8f-44a9-b7d5-abaabec3493a. Accessed September 2, 2015.

40. Gidding SS, Champagne MA, de Ferranti SD, et al. The agenda for familial hypercholesterolemia: a scientific statement from the American Heart Association. *Circulation*. 2015;132(22):2167-2192.

41. Singh S, Bittner V. Familial hypercholesterolemia—epidemiology, diagnosis, and screening. *Curr Atheroscler Rep*. 2015;17(2):482.

42. Grundy SM. Statin discontinuation and intolerance: the challenge of lifelong therapy. *Ann Intern Med*. 2013;158(7):562-563.

43. Zhang H, Plutzky J, Skentzos S, et al. Discontinuation of statins in routine care settings. *Ann Intern Med*. 2013;158(7):526-534.

44. Sanofi and Regeneron announce FDA approval of Praluent (alirocumab) injection, the first PCSK9 inhibitor in the US, for the treatment of high LDL cholesterol in adult patients. http://en.sanofi.com/NasdaQ_OMX/local/press_releases/sanofi_and_regeneron_announce_1941221_24-07-2015!21_24_28.aspx. Accessed August 1, 2015.

45. UK National Health Service Medicines Information. New drugs online report for evolocumab. http://www.ukmi.nhs.uk/applications/ndo/record_view_open.asp?newDrugID=5828. Accessed November 1, 2015.

46. Amgen debuts Repatha in UK, with price at a huge discount to that in the USA. February 9, 2015. http://www.thepharmaletter.com/article/amgen-debuts-repatha-in-uk-with-price-at-a-huge-discount-to-that-in-usa. Accessed November 1, 2015.

47. Anderson JL, Heidenreich PA, Barnett PG, et al. ACC/AHA statement on cost/value methodology in clinical practice guidelines and performance measures. *J Am Coll Cardiol*. 2014;63(21):2304-2322.

48. Office of the Assistant Secretary for Planning and Evaluation, Department of Health and Human Services. Observations on trends in prescription drug spending. https://aspe.hhs.gov/sites/default/files/pdf/187586/Drugspending.pdf. Accessed May 10, 2016.

49. Reinhardt U. Probing our moral values in health care: the pricing of specialty drugs. http://newsatjama.jama.com/2015/08/11/jama-forum-probing-our-moral-values-in-health-care-the-pricing-of-specialty-drugs/. Accessed August 17, 2015.

50. Newman CB, Tobert JA. Statin intolerance: reconciling clinical trials and clinical experience. *JAMA*. 2015;313(10):1011-1012.

51. Joy TR, Zou GY, Mahon JL. N-of-1 (single-patient) trials for statin-related myalgia. *Ann Intern Med*. 2014;161(7):531-532.

52. *The Price of Sovaldi and Its Impact on the US Health Care System*. http://www.finance.senate.gov/download/the-price-of-sovaldi-and-its-impact-on-the-us-health-care-system-full-report. Accessed May 10, 2016.

53. *Rheumatoid Arthritis: Background, New Development, Key Strategies*. http://www.optum.com.br/content/dam/optum/Images/Thought%20Leadership/Rx/rheumatoid-arthritis-insight-report/M53018_L_RA_Insight%20Report_Live%20Links_FINAL.pdf. Accessed July 1, 2016.

54. Blackstone EA, Joseph PF. The economics of biosimilars. *Am Health Drug Benefits*. 2013;6(8):469-478.

55. Mulcahy AW, Predmore Z, Mattke S. *The Cost Savings Potential of Biosimilar Drugs in the United States: RAND Corporation Perspective*. https://www.rand.org/content/dam/rand/pubs/perspectives/PE100/PE127/RAND_PE127.pdf. Accessed May 10, 2016.

56. NICE draft guidance recommends new drugs for cholesterol disorder. https://www.nice.org.uk/news/press-and-media/nice-draft-guidance-recommends-new-drugs-for-cholesterol-disorder. Accessed May 10, 2016.

57. Lazar LD, Pletcher MJ, Coxson PG, et al. Cost-effectiveness of statin therapy for primary prevention in a low-cost statin era. *Circulation*. 2011;124(2):146-153.

58. Everett BM, Smith RJ, Hiatt WR. Reducing LDL with PCSK9 inhibitors—the clinical benefit of lipid drugs. *N Engl J Med*. 2015;373(17):1588-1591.