Supplement

Impact of Money-Back Guarantees on the Cost-Effectiveness of Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitors

Table of Contents

Supplement Tables

7. Sensitivity Analysis: Clinical and economic outcomes of PCSK9 Inhibitor therapy in atherosclerotic cardiovascular disease over the lifetime analytic horizon assuming drug costs based on the Federal Supply Schedule.
8. Sensitivity Analysis: Clinical and economic outcomes of PCSK9 Inhibitor therapy in atherosclerotic cardiovascular disease over the lifetime analytic horizon assuming complete market capture by generic ezetimibe.

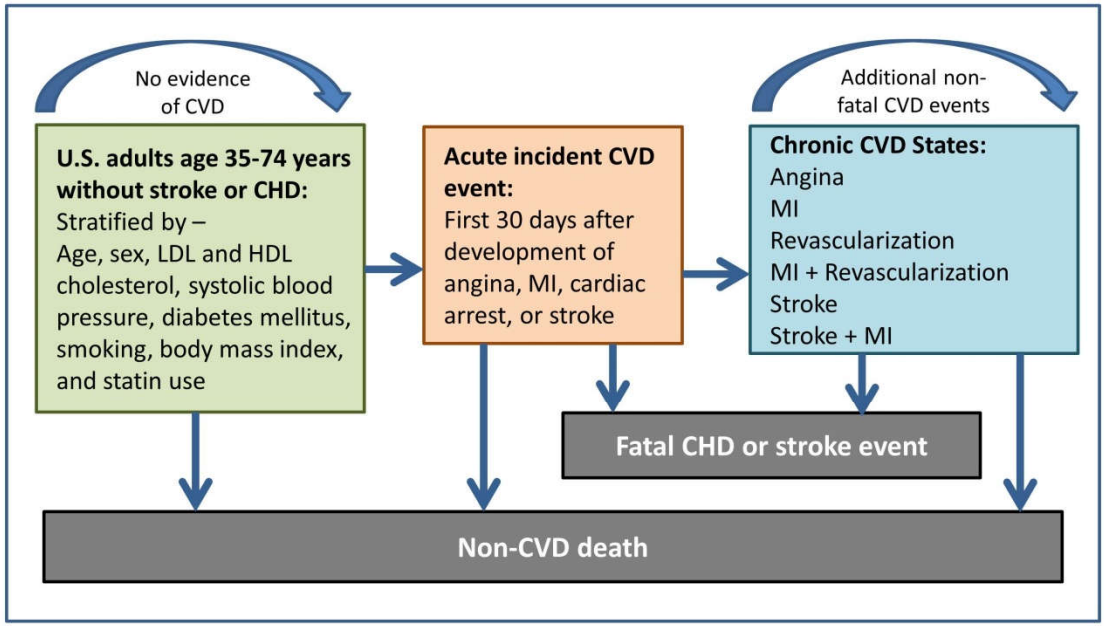
Supplement Figures

1. Schematic of the Cardiovascular Disease Policy Model.

Technical Details

Overview of Model Structure

The Cardiovascular Disease Policy Model is a state-transition Markov model of cardiovascular disease (CVD) among US adults age 35-94 (1-4). The structure and transitions in the CVD Policy Model are shown in Supplement Figure 1. The population included in this analysis reflects the cohort of US adults age 40-84 years in 2015, with demographics defined using the US census (5, 6). The baseline cohort was followed by the model in one-year cycles, beginning in 2015 and ending when cohort members either die or reach the age of 94 years (whichever comes first).



Appendix Figure 1. Schematic of the Cardiovascular Disease Policy Model. The structure and transitions in the CVD Policy Model are shown here. The model has been extensively validated across national and clinical-trial data.

Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MI, myocardial infarction.

Persons without a prior diagnosis of CVD (defined as angina, myocardial infarction, cardiac arrest, or stroke, shown in the green box in Supplement Figure 1) experience an annual rate of incident coronary heart disease, stroke, or non-CVD death based on their underlying risk factor profile (age, sex, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, diabetes mellitus, smoking, and body mass index) and statin use. In the first 30 days after an acute CVD event (the "bridge" state, shown in orange in Supplement Figure 1), patients face the increased short-term costs and QALY penalties associated with the acute event, as well as an increased probability of mortality. Patients who survive 30 days after the incident CVD event enter one of the chronic CVD states as defined by the initial event (shown in blue in Supplement Figure 1), where they can then experience recurrent events with transition probabilities defined by age, sex, prior CVD history, and smoking status. At all stages in the model, patients can experience death from cardiovascular and non-cardiovascular causes. The model tracks major adverse cardiovascular events (MACE), survival (life-years), quality-adjusted survival (quality-adjusted life years or QALYs), and costs (including intervention costs, outpatient and inpatient cardiovascular costs, and costs related to non-cardiovascular care). This analysis takes a

health system perspective over a lifetime analytic horizon. Future costs and QALYs are discounted at 3% a year.

Input Parameters and Model Calibration

A summary of key input parameters used in this study is shown in Table 1 in the manuscript, with more detailed inputs described in Supplement Table 1 and full citations in the Reference section at the end of this Supplement (7-21).

Supplement Table 1. Input Parameters for Cardiovascular Disease Policy Model Simulations

Input Parameter	Base case values	Range for Monte Carlo simulations	Distribution	Source*
Intervention effect sizes				
Ezetimibe† (% reduction in LDL-C)	23.6	21.7 – 25.6	Beta	13,17
PCSK9i (relative rate of coronary events) †				
Year 1	0.80	0.68 - 0.94	Log-normal	19
Year 2+	0.65	0.55 - 0.77	Log-normal	19
PCSK9i (relative rate of stroke events) ‡				
Year 1	0.83	0.63 - 1.08	Log-normal	19
Year 2+	0.76	0.60 - 0.97	Log-normal	19
Effect of 1 mmol/L reduction in LDL-C				
Incidence of coronary heart disease	0.76	0.73 – 0.79	Log-normal	9
Incidence of stroke	0.85	0.80 – 0.89	Log-normal	9
Costs, 2017 US$				
Annual drug costs				
Ezetimibe	1,440.84	7,20.42-2,881.68	Log-normal	20
PCSK9 inhibitor	9,162.00	4,581.00-19,324.00	Log-normal	20
Costs of coronary heart disease				
Acute fatal MI hospitalization	55,172	45,977 – 66,206	Log-normal	7, 8
Acute non-fatal MI hospitalization	39,929	33,274 – 47,915	Log-normal	7, 8
Acute non-fatal MI and CABG	102,065	85,054 – 122,477	Log-normal	7, 8
Acute MI post-hospitalization (year 1)	12,708	10,590 – 15,250	Log-normal	7, 8
Coronary heart disease costs, subsequent years	2,596	2,163 – 3,115	Log-normal	7,21
Costs of heart failure				
Heart failure hospitalization	20,097	16,748 – 24,116	Log-normal	7, 8
Costs of stroke care				
Hospitalized fatal stroke	27,500	22,916 – 33,000	Log-normal	7, 8

Hospitalized non-fatal stroke	20,324	16,936 – 24,388	Log-normal	7, 8
Post-stroke cost, months 2-11	35,753	29,795 – 42,904	Log-normal	7, 8
Post-stroke cost, subsequent years	5,464	4,554 – 6,557	Log-normal	7,21
Quality-of-Life				
Quality-of-life for chronic conditions				
No history of cardiovascular disease	1.0000	-	-	Assumed
History of angina	0.9000	0.8667-0.9393	β	14-16
History of revascularization for angina[§]	0.9864	0.9819-0.9917	β	10, 14-16
History of MI	0.9648	0.9505-0.9758	β	14-16
History of stroke	0.8835	0.8414-0.9108	β	14-16
History of MI and stroke	0.8524	0.7997-0.8888	β	14-16
Quality-of-life deductions for acute events (days)				
Angina	0.40	11.1-24.36	β	14-16
Revascularization[‖]	5.11	2.56-7.67	β	10
Acute MI	2.89	1.86-4.09	β	14-16
Acute MI and revascularization[¶]	8.00	4.42-11.76	β	Estimated
Acute stroke	4.13	3.07-5.62	β	14-16
Injection site adverse reactions	0.11	0.00-0.73	β	11,12

CABG = coronary artery bypass grafting; FOURIER = Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; PCSK9i = proprotein convertase subtilisin/kexin type 9 inhibitors.

[†] Effect of Ezetimibe in addition to ongoing statin therapy, with percent reduction in LDL assumed to be the same each year of the simulation.

[‡] The effect of PCSK9i was modeled by calibrating the rate ratio for coronary and stroke events based on outcome analysis of the FOURIER trial (6). We used different risk ratios for the first and subsequent years based on increasing effectiveness of PCSK9i seen in FOURIER. The model assumes a constant risk reduction in MI and stroke beyond year 1, equal to the risk reduction observed in year 2 of the FOURIER trial.

[§] Estimated by linear interpolation between the quality of life with angina and perfect health.

[‖] Weighted average of disutility related with percutaneous and surgical revascularization.

[¶] Acute disutility for MI and revascularization is the sum of disutilities associated with an MI and a revascularization procedure.

Transition Probabilities

The present version of the CVD Policy Model includes data from prior versions as well as many updates and upgrades (1-4). The 2010 U.S. Census provided the baseline population

(5) and number of 35 year-olds projected to enter the model population from 2010-2060 (5, 22).

Prevalence and joint distributions of cardiovascular risk factors in the US population were estimated from pooled, survey design-weighted U.S. National Health and Nutrition Examination Survey (NHANES), 2007-12 (23). Annual transition rates between risk factor levels were calculated to preserve age-range trends. Statin use among US adults was estimated from contemporary survey data (National Health and Nutrition Examination Survey [NHANES], 2005-2012) (23). Statin use in the model was stratified by age, gender, and history of cardiovascular disease. Further, the model incorporated the bivariate distribution of LDL-C and statin-use estimated directly from the NHANES 2005-12 series. Model input parameters regarding statin by age and gender among patients with atherosclerotic CVD are shown in Supplement Table 2.

The incidence of coronary heart disease and stroke were based on Cox proportional hazards analysis of the Framingham Heart Study (24) and the Framingham Offspring Study (25) cohorts from 1988-2007, with further adjustment for risk factor differences between the

Framingham cohorts and NHANES. Incident coronary heart disease events were allocated to three groups: angina pectoris, hospitalized myocardial infarction, or cardiac arrest. Risk function betas were estimated separately for the risk of incident coronary heart disease, incident strokes, and non-CVD deaths, using examinations 1-8 of the Framingham Offspring cohort and accounting for competing risk across the three outcomes (25). The Framingham coefficients have been found to be useful for predicting CVD risk relationships across many populations (26-29). Risk factors were assumed to affect the incidence of myocardial infarction, cardiac arrest, and angina in proportion to the overall incidence of coronary heart disease, except among tobacco smokers who were assumed to have a higher relative risk for infarction and arrest ((30); personal communication, Sean Coady, National Heart, Lung, and Blood Institute, February, 2006) and a proportionately lower coefficient for angina. Environmental tobacco exposure was assumed to carry a relative risk of 1.26 for myocardial infarction and cardiac arrest compared with non-exposed non-smokers (31) but not to influence angina.

Supplement Table 2. Bivariate distribution of statin use and low-density lipoprotein cholesterol level among individuals with a history of coronary heart disease or stroke in the CVD Policy Model, estimated from NHANES 2005-2012.*

		Men		Women	
		On Statin	Not on Statin	On Statin	Not on Statin
Age 35-44	LDL-C <70 mg/dL	0.1159	0.0738	0.0000	0.0295
	LDL-C 70-100 mg/dL	0.1112	0.0708	0.1680	0.3318
	LDL-C >100 mg/dL	0.2723	0.3560	0.0488	0.4219
Age 45-54	LDL-C <70 mg/dL	0.1581	0.0629	0.0252	0.0216
	LDL-C 70-100 mg/dL	0.1963	0.1604	0.2351	0.1881
	LDL-C >100 mg/dL	0.1473	0.2750	0.1121	0.4179
Age 55-64	LDL-C <70 mg/dL	0.1999	0.0045	0.0366	0.0073
	LDL-C 70-100 mg/dL	0.3063	0.0861	0.3413	0.0664
	LDL-C >100 mg/dL	0.1662	0.2370	0.2757	0.2727
Age 65-74	LDL-C <70 mg/dL	0.1652	0.0440	0.2307	0.0641
	LDL-C 70-100 mg/dL	0.3042	0.0612	0.2404	0.0493
	LDL-C >100 mg/dL	0.2610	0.1644	0.1282	0.2873
Age 75-84	LDL-C <70 mg/dL	0.1915	0.0273	0.1672	0.0050
	LDL-C 70-100 mg/dL	0.4020	0.1301	0.1790	0.0798
	LDL-C >100 mg/dL	0.0943	0.1548	0.1958	0.3732
Age 84-95	LDL-C <70 mg/dL	0.1915	0.0273	0.1672	0.0050
	LDL-C 70-100 mg/dL	0.4020	0.1301	0.1790	0.0798
	LDL-C >100 mg/dL	0.0943	0.1548	0.1958	0.3732
Incoming, Age 35	LDL-C <70 mg/dL	0.1019	0.0649	0.0000	0.1259
	LDL-C 70-100 mg/dL	0.0978	0.0622	0.1224	0.3434
	LDL-C >100 mg/dL	0.2394	0.4338	0.0356	0.3727

CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; NHANES = National Health and Nutrition Examination Survey.

* To convert LDL-C levels from mg/dL to SI units, multiply by 0.02586

The number of patients with hospitalized myocardial infarctions was obtained from discharges coded as ICD-9 code 410 in the 2010 National Hospital Discharge Survey (NHDS) (32) adjusted for likely miscoding (33), and excluding patients who were discharged alive after two days or fewer without a percutaneous coronary intervention, and transfer patients (Supplement Table 3). Case-fatality rates and rates of myocardial infarction in age/gender subgroups were estimated from national data (34) with subpopulation (e.g. prior MI vs not) relative rates derived from complementary sources (35-37). Patients with pre-hospital arrest deaths were estimated from the U.S. Vital Statistics (34), and patients with out-of-hospital cardiac arrests surviving to hospital discharge were estimated from national data (34). Survival after a coronary heart disease event was estimated using California data on the ratio of in-hospital survival to 30 day survival (21) and data from Medicare and Seattle, Washington (38, 39). Rates of coronary revascularizations were estimated from the National Hospital Discharge Survey (34), with mortality estimated from aggregated historical data.

Deaths from coronary heart disease and stroke in 2010 were extracted from U.S. Vital Statistics (34). Deaths were categorized according to the International Classification of Diseases (ICD) 10 codes (40): I20-I25 and two-thirds of I49, I50, and I51 were used to

estimate coronary heart disease deaths (41), I60-I69 were used to estimate stroke deaths, and all other deaths were considered non-CVD deaths.

Although heart failure is not a distinct health state in the current version of the CVD Policy Model, the costs and quality of life penalties due to ischemic and non-ischemic heart failure are incorporated into chronic coronary heart disease states and non-CVD costs. For instance, approximately a quarter of patients who have an AMI develop heart failure after the initial hospitalization. The CVD Policy Model currently assumes a rate of heart failure hospitalizations proportional to coronary heart disease mortality, so when an intervention such as PCSK9 inhibitor therapy reduces coronary heart disease events, cost related to subsequent complications such as heart failure is also reduced.

Supplement Table 3. 2010 Rates of Myocardial Infarction in the CVD Policy Model, Conditional on Age, Gender, and Health State.

	Health State				
	History of Angina	**History of MI**	**History of Stroke**	**MI in current year**	**Stroke in current year**
Men age 35-44	0.0014	0.0091	0.0014	0.0307	0.0030
Men age 45-54	0.0049	0.0143	0.0049	0.0485	0.0104
Men age 55-64	0.0059	0.0127	0.0059	0.0430	0.0125
Men age 65-74	0.0079	0.0152	0.0079	0.0516	0.0167
Men age 75-84	0.0098	0.0187	0.0098	0.0635	0.0206
Men age 85-94	0.0193	0.0364	0.0193	0.1234	0.0406
Women age 35-44	0.0008	0.0058	0.0008	0.0196	0.0017
Women age 45-54	0.0019	0.0078	0.0019	0.0265	0.0040
Women age 55-64	0.0046	0.0122	0.0046	0.0413	0.0098
Women age 65-74	0.0066	0.0138	0.0066	0.0469	0.0139
Women age 75-84	0.0115	0.0198	0.0115	0.0673	0.0242
Women age 85-94	0.0234	0.0322	0.0234	0.1093	0.0494

CVD = cardiovascular disease; MI = myocardial infarction.

Stroke incidence was assumed to be independent of the risk of new onset coronary heart disease in the same year. The number of hospitalized strokes was also obtained from the 2010 NHDS (32). We applied positive predictive values of specific ICD-9 stroke hospital diagnosis codes (inclusive of ICD 9 codes 430-438) according to methods described in Williams et al (1999) (42), which involved pooling published data from four cohort studies of stroke incidence that compared hospital diagnoses with a gold standard (43-46). The positive predictive values were applied to age- and sex-specific NHDS cases in order to estimate total stroke event rates (inclusive of first-ever and recurrent stroke events).

Applying 30-day case fatality rates based on the Atherosclerosis in Communities Study (46, 47) yielded annual mortality rate estimates within the range of stroke rates reported by the U.S. Centers for Disease Control (CDC Wonder) for 2010 (48). Incidence calibration assumed that 77% of all strokes are incident (first ever) (49), but it was assumed that the proportion first ever/total diminished with age (i.e., >90% of all strokes are first strokes in 35-44 year olds and 50% are first strokes in 85-94 year olds). The resulting incidence of hospitalized stroke approximated age- and sex- specific stroke incidence rates observed in U.S. stroke cohort and surveillance studies. The annual probabilities of stroke after myocardial infarction (50) and the probability of coronary heart disease in stroke patients was based on natural history studies (51-56).

The background prevalence of CVD by age, sex, and CVD disease state (stroke, coronary heart disease, or both stroke and coronary heart disease) in 2010 was estimated from the National Health Interview Survey data from 2009-2011 (57), assuming that the imperfect positive predictive value of survey data is offset by its imperfect sensitivity (58-60), Age-specific prevalence for individual CVD disease states were fitted with polynomial or spline functions of age to obtain smooth, monotonically increasing prevalence. The background

prevalence of prior coronary revascularization was estimated from revascularizations before 2010 and estimated survival after revascularization, while model projections were used to infer the distribution of revascularization by CVD state.

Costs

Costs related to hospitalizations for coronary heart disease and stroke and rehabilitation cost after an acute stroke were estimated using California hospital data (8, 18), deflated using cost-to-charge ratios (8), and the ratio of the U.S. national average costs to the California average (61). Chronic outpatient CVD costs and annual non-cardiovascular (background) costs were estimated for patients with a stroke or coronary heart disease diagnosis surveyed in the U.S. Medical Expenditure Panel Surveys pooled from 1998-2008 (21). All costs were indexed to the year 2017 using the medical component of the U.S. Consumer Price Index (7).

Quality-of-Life Preference Weights

The Global Burden of Disease 2010 study was used for health-related quality-of-life weights and severity distributions for cardiovascular disease states (Table 1 in the manuscript) (14-16).

Model Validation

The model has been extensively validated across national and clinical-trial data. (1-4, 62) CVD Policy Model estimates for the year 2010 were within 1% of estimates from the national vital statistics (stroke deaths, CHD deaths, and deaths from all causes) and the US National Hospital Discharge Survey (total MIs and strokes, Supplement Table 4).

Supplement Table 4. Model Validation. Comparisons of selected Cardiovascular Disease Policy Model simulation outputs for 2010 (model base year) with national targets for 2010.

Age and sex category	Total myocardial infarctions		Total strokes		CHD deaths		Stroke deaths		All-cause deaths	
	Target source: NHDS		Target source: NHDS		Target source: national vital statistics		Target source: national vital statistics		Target source: national vital statistics	
	Target	**Model**	**Target**	**Model**	**Target**	**Model**	**Target**	**Model**	**Target**	**Model**
Males										
35-44	13,979	13,839	16,535	16,553	4,783	4,862	1,027	1,031	43,345	43,335
45-54	56,129	55,811	43,493	43,710	19,489	19,594	3,298	3,301	111,981	111,933
55-64	77,992	77,395	67,863	68,497	38,032	38,065	6,159	6,133	190,845	190,629
65-74	75,804	75,689	79,450	79,239	45,700	46,096	9,350	9,265	231,327	231,231
75-84	62,982	63,063	76,205	76,436	64,610	65,097	16,215	16,240	312,778	312,873
85-94	37,568	37,483	38,943	39,247	64,071	63,958	15,318	14,742	264,705	263,235
Females										
35-44	6,259	6,144	6,390	6,387	1,710	1,822	873	875	26,538	26,619
45-54	17,071	17,035	36,952	37,083	6,858	6,969	2,609	2,764	71,145	71,352
55-64	40,246	40,403	42,966	43,222	15,122	15,265	4,622	4,605	122,502	122,546
65-74	43,843	43,898	69,473	69,659	24,964	25,137	8,504	8,308	178,530	178,342
75-84	60,097	60,043	93,040	93,434	53,247	53,600	21,492	21,541	313,803	313,894
85-94	57,661	57,403	77,481	77,883	99,680	98,988	35,416	36,233	448,864	447,244
Deviation from target	-0.26%		0.39%		0.27%		0.12%		-0.14%	

CHD = coronary heart disease; NHDS = National Hospital Discharge Survey.

Specific Model Adaptations for the Present Analysis

Summary of the FOURIER Trial

This study simulated effectiveness of PCSK9 inhibitors based on outcome data from the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial (19). The FOURIER trial enrolled 27,564 patients with ASCVD and LDL-C levels of >= 1.81 mmol/L (70 mg/dL) on statin therapy. Patients were randomly assigned to receive subcutaneous injections of evolocumab (either 140 mg every 2 weeks or 420 mg monthly) or matching placebo. The primary efficacy end point was the composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization. Over a median follow-up of 2.2 years, evolocumab reduced LDL-C levels by 59%, from a median baseline value of 2.38 mmol/L (92 mg/dL) to 0.78 mmol/L (30 mg/dL, p<0.001). Treatment with evolocumab relative to placebo significantly reduced the risk of the primary end point (9.8% vs. 11.3%; hazard ratio, 0.85; 95% confidence interval, 0.79 to 0.92; p<0.001). The results were consistent across subgroups, and, in landmark analyses, there appeared to be a greater effect in year 2 compared with year 1. There was no significant increase in adverse events with the exception of injection-site reactions, which

were more common with evolocumab (2.1% vs. 1.6%).

Model Adaptations

For this analysis, we adapted the CVD Policy Model to simulate the experience with evolocumab observed in the FOURIER trial, following from prior work (63, 64). We modeled a cohort of US adults that would have qualified for the FOURIER trial (adults 40-80 years old who have a prior history of atherosclerotic cardiovascular disease, are on statin therapy, and have LDL-C levels ≥ 1.81 mmol/L [70 mg/dL]) (63, 64). The starting cohort was defined using NHANES surveys from 2005-2012 (23) and estimated to include 8.8 million adults. Among patients receiving PCSK9i therapy in addition to maximally tolerated statin therapy, we modeled separate risk ratios for year 1 and years 2 and beyond to reflect improved outcomes seen over time in FOURIER trial results.

Model Calibration

We confirmed that event rates projected by the CVD Policy Model closely approximated those observed at years 1 and 2 in the FOURIER trial (Supplement Table 5).

Supplement Table 5. FOURIER Model Validation. Rates of major adverse cardiovascular events (per 100 patient years) observed in the FOURIER trial and projected using the CVD Policy Model at the end of year 1 and year 2.

Trial Arm	Year 1		Year 2	
	FOURIER Trial	CVD Policy Model	FOURIER Trial	CVD Policy Model
Statin only	3.7	3.6	3.7	3.8
Statin + PCSK9 inhibitor	3.1	3.0	2.7	2.7

CVD = cardiovascular disease; FOURIER = Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk ; PCSK9i = proprotein convertase subtilisin/kexin type 9 inhibitors.

Input Parameters: Costs

Base-case drug costs were assumed to be the U.S. average net costs (i.e., costs net of rebates and discounts, to approximate costs actually paid). As seen in Supplement Table 6, the average net costs represent substantial discounts over the wholesale acquisition costs. We obtained net pricing estimates from SSR Health, LLC, which combine data on unit sales with publicly-disclosed US sales figures that are net of discounts, rebates, concessions to wholesalers and distributors, and patient assistance programs, to derive a net price (20). We estimated net prices by comparing rolling averages of both net prices and wholesale acquisition cost per unit for the most recent four quarters of available data to arrive at a mean discount from wholesale acquisition cost for the drug. Finally, we applied this average discount to the most recent wholesale acquisition cost (Truven Health Analytics, 2017. Redbook Online. November 2017) (65) to arrive at an estimated net price per unit. In a

sensitivity analysis, we assumed the drug costs to be equal to those in the Federal Supply Schedule (FSS, version January 1, 2018) (66). The FSS Service awards multi-year, multiple award federal contracts that are available for use by eligible government agencies. Pricing is negotiated based on how vendors do business with their commercial customers and is made publicly available twice a month by the Office of Acquisition and Logistics in the Department of Veterans' Affairs (66).

Supplement Table 6. Drug Costs.

Drug	Wholesale Acquisition Cost, per year, $	Average Net Cost, per year,* $	Effective Discount (%)	Federal Supply Schedule, $†	Comments
Evolocumab	$14,523.08	$9,259.88	36	13809.84	Base-case annual cost of PCSK9i therapy = mean of net average cost of evolocumab and alirocumab = $9162.00 per year.
Alirocumab	$14,560.00	$9,064.12	38	8810.09	
Brand-name ezetimibe (Zetia™)	$3,820.52	$1,440.84	62	2967.46	The marked discount on brand-name ezetimibe is due to price competition from generic formulations approved since 2016. In a sensitivity analysis, the annual cost of ezetimibe was assumed to be equal to the median price of all available generic formulations ($307.28).

PCSK9i = proprotein convertase subtilisin/kexin type 9 inhibitors.

* Average price paid for the drug net of discounts and rebates. See text for methodological details.

Input Parameters: Utilities

In addition to quality-of-life penalties associated with acute CVD events, the model

incorporated a small disutility for injection-site reactions (which affect 5% of patients in clinical trials, are generally minor, and do not require discontinuation of the drug).

Sensitivity Analyses

Since US net average costs are not publicly available, we performed a sensitivity analysis that incorporated the cost of PCSK9i and brand-name ezetimibe from the Federal Supply Schedule (66) (Supplement Table 7).

Given the increasing uptake of generic ezetimibe over the past year, we performed a deterministic sensitivity analysis in which we assumed the cost of ezetimibe to be the median cost of generic formulations of ezetimibe as of November 2017 (Supplement Table 8).

We also conducted probabilistic sensitivity analyses in order to construct uncertainty intervals around point estimates from model output. We conducted 1000 Monte Carlo iterations, each taking random draws from pre-specified distributions of the varied parameters (Supplement Table 1). Model output from each simulation was stored and the

1000 results were used to construct 95% Uncertainty Intervals (95% UIs).

Supplement Table 7. Clinical and Economic Outcomes of PCSK9 Inhibitor Therapy in Atherosclerotic Cardiovascular Disease over the Lifetime Analytic Horizon* using drug prices listed in the Federal Supply Schedule.[*]

	Clinical Outcomes		Economic Outcomes			Cost-Effectiveness
Treatment Strategy	**Total MACE Averted (number)** [†]	**QALYs Gained**	**Incremental Drug Cost**[‡] **(millions,$)**	**Incremental Cost of CV Care**[‡] **(millions, $)**	**Incremental Cost of non-CV Care**[‡,§] **(millions, $)**	**ICER ($/QALY)**
Statin + Ezetimibe[‖]	2,164,000 (1,019,500-3,170,800)	4,423,700 (2,113,800-6,391,200)	676,272 (672,644-679,348)	-85,540 (-40,636 to -124,156)	97,002 (46,316-139,799)	155,000 (109,000-321,000)
Statin + PCSK9 Inhibitor[¶]						
Current Payment Method	2,893,500 (1,169,200-4,647,600)	5,558,400 (2,227,000-8,865,600)	1,933,743 (1,917,311-1,948,944)	-109,478 (-44,728 to -175,420)	123,415 (49,138-196,511)	350,000 (220,000-821,000)
Reimbursement of 1-year of drug costs incurred prior to MACE[†]	Same as above	Same as above	1,919,476 (1,901,981-1,935,847)	Same as above	Same as above	348,000 (219,000-814,000)
Reimbursement of all drug costs incurred prior to MACE[†]	Same as above	Same as above	1,896,773 (1,877,183-1,915,126)	Same as above	Same as above	344,000 (216,000-804,000)
Reimbursement of all drug costs incurred prior to MACE and direct inpatient costs resulting from MACE[†]	Same as above	Same as above	Same as above	-136,055 (-73,145 to -200,758)	Same as above	339,000 (214,000-791,000)

* The analysis included 8.9 million US adults age 40-84 years with ASCVD and low-density lipoprotein cholesterol level > 1.81 mmol/L (70mg/dL) despite statin therapy. It 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, person-years of treatment are rounded to the nearest 100,000s; MACE and QALYs are rounded to the 100s; costs are rounded to the millions; and incremental cost-effectiveness ratios to the 1000s. All reported values are point-estimates from the base case and the 95% uncertainty interval. CV denotes cardiovascular, ICER incremental cost-effectiveness ratio, MACE major adverse cardiovascular event (nonfatal MI, non-fatal stroke, and cardiovascular death), PCSK9 proprotein convertase subtilisin/kexin type 9, QALY quality-adjusted life year.

[†] MACE was defined as a composite of non-fatal MI, non-fatal stroke, and death from cardiovascular causes.

[‡] All costs are reported in 2017 U.S. dollars

[§] Noncardiovascular costs include age-specific background healthcare costs, i.e., health care costs unrelated to management of cardiovascular disease.

[‖] The comparator for the statin + ezetimibe arm was *status quo* statin therapy (as observed in the National Health and Nutrition Examination Survey 2005-2012).

[¶] The statin + PCSK9 inhibitor arm is compared with the statin + ezetimibe arm (the next best alternative).

Supplement Table 8. Sensitivity Analysis. Clinical and Economic Outcomes of PCSK9 Inhibitor Therapy in Atherosclerotic Cardiovascular Disease over the Lifetime Analytic Horizon Assuming Complete Market Capture by Generic Ezetimibe.[*]

Treatment Strategy	Clinical Outcomes		Economic Outcomes			Cost-Effectiveness
	Total MACE Averted (number) [†]	QALYs Gained	Incremental Drug Cost[‡] (millions,$)	Incremental Cost of CV Care[‡] (millions, $)	Incremental Cost of non-CV Care[‡,§] (millions, $)	ICER ($/QALY)
Statin + Ezetimibe[‖]	2,164,000 (1,019,500-3,170,800)	4,423,700 (2,113,800-6,391,200)	70,028 (69,652-70,346)	-85,540 (-40,636 to -124,156)	97,002 (46,316-139,799)	18,000 (13,000-36,000)
Statin + PCSK9 Inhibitor[¶]						
Current Payment Method	2,893,500 (1,169,200-4,647,600)	5,558,400 (2,227,000-8,865,600)	2,044,297 (2,030,795-2,057,209)	-109,478 (-44,728 to -175,420)	123,415 (49,138-196,511)	370,000 (232,000-870,000)
Reimbursement of 1-year of drug costs incurred prior to MACE[†]	Same as above	Same as above	2,032,740 (2,018,303-2,046,721)	Same as above	Same as above	368,000 (231,000-864,000)
Reimbursement of all drug costs incurred prior to MACE[†]	Same as above	Same as above	2,014,349 (1,998,527-2,029,941)	Same as above	Same as above	365,000 (229,000-856,000)
Reimbursement of all drug costs incurred prior to MACE and direct inpatient costs resulting from MACE[†]	Same as above	Same as above	Same as above	-136,055 (-73,145 to -200,758)	Same as above	360,000 (226,000-843,000)

* The analysis included 8.9 million US adults age 40-84 years with ASCVD and low-density lipoprotein cholesterol level > 1.81 mmol/L (70mg/dL) despite statin therapy. It 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, person-years of treatment are rounded to the nearest 100,000s; MACE and QALYs are rounded to the 100s; costs are rounded to the millions; and incremental cost-effectiveness ratios to the 1000s. All reported values are point-estimates from the base case and the 95% uncertainty interval. CV denotes cardiovascular, ICER incremental cost-effectiveness ratio, MACE major adverse cardiovascular event (nonfatal MI, non-fatal stroke, and cardiovascular death), PCSK9 proprotein convertase subtilisin/kexin type 9, QALY quality-adjusted life year.

† MACE was defined as a composite of non-fatal MI, non-fatal stroke, and death from cardiovascular causes.

‡ All costs are reported in 2017 U.S. dollars

§ Non-cardiovascular costs include age-specific background healthcare costs, i.e., health care costs unrelated to management of cardiovascular disease.

‖ The comparator for the statin + ezetimibe arm was *status quo* statin therapy (as observed in the National Health and Nutrition Examination Survey 2005-2012). This sensitivity analysis assumes the use of generic ezetimibe, costing $307.28 per year.

¶ The statin + PCSK9 inhibitor arm is compared with the statin + ezetimibe arm (the next best alternative).

REFERENCES

1. Bibbins-Domingo K, Coxson P, Pletcher MJ, Lightwood J, Goldman L**.** Adolescent overweight and future adult coronary heart disease. N Engl J Med. 2007;357:2371-9.
2. Hunink MGM, Goldman L, Tosteson ANA, Mittleman MA, Goldman PA, Williams LW, et al. The recent decline in mortality from coronary heart disease, 1980-1990: the effect of secular trends in risk factors and treatment. JAMA. 1997;277:535-42.
3. Weinstein MC, Coxson PG, Williams LW, Pass TM, Stason WB, Goldman L**.** Forecasting coronary heart disease incidence, mortality, and cost: the Coronary Heart Disease Policy Model. Am J of Public Health. 1987;77:1417-26.
4. Moran AE, Odden MC, Thanataveerat A, Tzong KY, Rasmussen PW, Guzman D, et al. Cost-effectiveness of hypertension therapy according to 2014 guidelines. N Engl J Med. 2015;372:447-55.
5. U.S. Census Bureau Population Division**.** Monthly Postcensal Resident Population by Single Year of Age, Sex, Race and Hispanic Origin for the United States: July 1, 2010 to December 1 2010 (NC-EST2011-ALLDATA-R-File02). Washington D.C.; 2011.

6. U.S. Census Bureau Population Division**.** Projected Population by Single Year of Age, Sex, Race, and Hispanic Origin for the United States: 2012 to 2060 (NP2012_D1). Washington, D.C.; 2012.

7. United States Department of Labor. Bureau of Labor Statistics. Consumer Price Index for All Urban Consumers: Medical Care. Accessed at http://data.bls.gov/cgi-bin/surveymost?cu on July 15, 2015.

8. California Office of Statewide Health Planning & Development**.** Hospital financial data for cost to charge ratio, CA inpatinet discharage data hospital annual financial data, pivot profiles. 1999-2000.

9. Cholesterol Treatment Trialists C, Fulcher J, O'Connell R, Voysey M, Emberson J, Blackwell L, et al. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. Lancet. 2015;385:1397-405.

10. Kazi DS, Garber AM, Shah RU, Dudley RA, Mell MW, Rhee C, et al. Cost-effectiveness of genotype-guided and dual antiplatelet therapies in acute coronary syndrome. Ann Intern Med. 2014;160:221-32.

11. Khazeni N, Hutton DW, Garber AM, Hupert N, Owens DK**.** Effectiveness and cost-effectiveness of vaccination against pandemic influenza (H1N1) 2009. Ann Intern Med. 2009;151:829-39.

12. 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;151:840-53.

13. Mikhailidis DP, Sibbring GC, Ballantyne CM, Davies GM, Catapano AL**.** Meta-analysis of the cholesterol-lowering effect of ezetimibe added to ongoing statin therapy. Curr Med Res Opin. 2007;23:2009-26.

14. Moran AE, Forouzanfar MH, Roth G, Mensah G, Ezzati M, Murray CJ, et al. Temporal Trends in Ischemic Heart Disease Mortality in 21 World Regions, 1980-2010: The Global Burden of Disease 2010 Study. Circulation. 2014.

15. Moran AE, Forouzanfar MH, Roth G, Mensah GA, Ezzati M, Flaxman A, et al. The Global Burden of Ischemic Heart Disease in 1990 and 2010: The Global Burden of Disease 2010 Study. Circulation. 2014.

16. Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a

systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380:2197-223.

17. Navarese EP, Kolodziejczak M, Schulze V, Gurbel PA, Tantry U, Lin Y, 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;163:40-51.

18. California Office of Statewide Health Planning and Development**.** California Public Patient Discharge Data, 2008. In: Development OoSHPa, ed. Sacramento, California: Office of Statewide Health Planning and Development 2008.

19. Sabatine MS, Giugliano RP, Wiviott SD, Raal FJ, Blom DJ, Robinson J, et al. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. N Engl J Med. 2015;372:1500-9.

20. SSR Health. US Brand Rx Net Price (access restricted document). 2017.

21. Medical Expenditure Panel Survey**.** Medical Expenditure Panel Survey Public Use Files 1998-2008.

22. U.S. Census Bureau Population Division**.** Methodology and Assumptions for the 2012 National Projections. December 2012 ed. Washington D.C.; 2012.

23. National Center for Health Statistics**.** National Health and Nutrition Examination Survey, 2005-2012.

24. Dawber TR**.** *The Framingham Study: the epidemiology of atherosclerotic disease.* Cambridge, MA: Harvard University Press; 1980.

25. Feinleib M, Kannel WB, Garrison RJ, McNamara PM, Castelli WP**.** The Framingham Offspring Study. Design and preliminary data. Prev Med. 1975;4:518-25.

26. Brindle P, Emberson J, Lampe F, Walker M, Whincup P, Fahey T, et al. Predictive accuracy of the Framingham coronary risk score in British men: prospective cohort study. BMJ. 2003;327:1267-70.

27. D'Agostino RB, Grundy S, Sullivan LM, Wilson PW**.** Validation of the Framingham Coronary Heart Disease Prediction Scores. JAMA. 2001;286:180-7.

28. Liu J, Hong Y, D'Agostino RBS, Wu Z, Sun J, Wilson PW, et al. Predictive value for the Chinese population of the Framingham CHD risk assessment tool compared with the Chinese Multi-Provincial Cohort Study. JAMA. 2004;291:2591-9.

29. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershaltz H, Kannel WB**.** Prediction of coronary heart disease using risk factor categories. Circulation. 1998;97:1837-47.

30. Parish S, Collins R, Peto R, Youngman L, Barton J, Jayne K, et al. Cigarette smoking, tar yields, and non-fatal myocardial infarction: 14,000 cases and 32,000 controls in the United Kingdom. The International Studies of Infarct Survival (ISIS) Collaborators. BMJ. 1995;311:471-7.

31. Law MR, Morris JK, Wald NJ**.** Environmental tobacco smoke exposure and ischaemic heart disease: an evaluation of the evidence. BMJ. 1997;315:973-80.

32. National Center for Health Statistics**.** National Hospital Discharge Survey. Accessed at ftp://ftp.cdc.gov/pub/Health_Statistics/NCHS/Datasets/NHDS/ on March 29, 2012.

33. Petersen LA, Wright S, Normand S-LT, Daley J**.** Positive predictive value of the diagnosis of acute myocardial infarction in an administrative database. J Gen Intern Med. 1999;14:555-8.

34. Centers for Disease Control and Prevention; National Center for Health Statistics**.** Underlying cause of death 1999-2010 on CDC WONDER online database, released 2012. 2012.

35. Canto JG, Rogers WJ, Goldberg RJ, Peterson ED, Wenger NK, Vaccarino V, et al. Association of age and sex with myocardial infarction symptom presentation and in-hospital mortality. JAMA. 2012;307:813-22.

36. Rieves D, Wright G, Gupta G, Shacter E**.** Clinical trial (GUSTO-1 and INJECT) evidence of earlier death for men than women after acute myocardial infarction. Am J Cardiol. 2000;85:147-53.

37. Vaccarino V, Parsons L, Peterson ED, Rogers WJ, Kiefe CI, Canto J**.** Sex differences in mortality after acute myocardial infarction: changes from 1994 to 2006. Arch Intern Med. 2009;169:1767-74.

38. Groeneveld PW, Heidenreich PA, Garber AM**.** Racial disparity in cardiac procedures and mortality among long-term survivors of cardiac arrest. Circulation. 2003;108:286-91.

39. Rea TD, Crouthamel M, Eisenberg MS, Becker LJ, Lima AR**.** Temporal patterns in long-term survival after resuscitation from out-of-hospital cardiac arrest. Circulation. 2003;108:1196-201.

40. National Center for Health Statistics**.** ICD10 Codes. Accessed at http://ftp.cdc.gov/pub/Health_Statistics/NCHS/Publications/ICD10/each10.txt. 2004.

41. Consensus recommendations for the management of chronic heart failure. On behalf of the membership of the advisory council to improve outcomes nationwide in heart failure. Am J Cardiol. 1999;83:1A-38A.

42. Williams GR, Jiang JG, Matchar DB, Samsa GP**.** Incidence and occurrence of total (first-ever and recurrent) stroke. Stroke. 1999;30:2523-8.

43. Benesch C, Witter DM, Jr., Wilder AL, Duncan PW, Samsa GP, Matchar DB**.** Inaccuracy of the International Classification of Diseases (ICD-9-CM) in identifying the diagnosis of ischemic cerebrovascular disease. Neurology. 1997;49:660-4.

44. Broderick J, Brott T, Kothari R, Miller R, Khoury J, Pancioli A, et al. The Greater Cincinnati/Northern Kentucky Stroke Study: preliminary first-ever and total incidence rates of stroke among blacks. Stroke. 1998;29:415-21.

45. Leibson CL, Naessens JM, Brown RD, Whisnant JP**.** Accuracy of hospital discharge abstracts for identifying stroke. Stroke. 1994;25:2348-55.

46. Rosamond WD, Folsom AR, Chambless LE, Wang CH, McGovern PG, Howard G, et al. Stroke incidence and survival among middle-aged adults: 9-year follow-up of the Atherosclerosis Risk in Communities (ARIC) cohort. Stroke. 1999;30:736-43.

47. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators. Am J Epidemiol. 1989;129:687-702.

48. Centers for Disease Control and Prevention; National Center for Health Statistics. Underlying cause of death 1999-2010 on CDC WONDER online database, released 2012. 2012.

49. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, et al. Heart disease and stroke statistics--2014 update: a report from the American Heart Association. Circulation. 2014;129:e28-e292.

50. Witt BJ, Brown RD, Jr., Jacobsen SJ, Weston SA, Yawn BP, Roger VL. A community-based study of stroke incidence after myocardial infarction. Ann Intern Med. 2005;143:785-92.

51. Amarenco P, Bogousslavsky J, Callahan A, 3rd, Goldstein LB, Hennerici M, Rudolph AE, et al. High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med. 2006;355:549-59.

52. Appelros P, Gunnarsson KE, Terent A. Ten-year risk for myocardial infarction in patients with first-ever stroke: a community-based study. Acta Neurol Scand. 2011;124:383-9.

53. Behar S, Tanne D, Abinader E, Agmon J, Barzilai J, Friedman Y, et al. Cerebrovascular accident complicating acute myocardial infarction: incidence, clinical significance and

short- and long-term mortality rates. The SPRINT Study Group. Am J Med. 1991;91:45-50.

54. Lakshminarayan K, Schissel C, Anderson DC, Vazquez G, Jacobs DR, Jr., Ezzeddine M, et al. Five-year rehospitalization outcomes in a cohort of patients with acute ischemic stroke: Medicare linkage study. Stroke. 2011;42:1556-62.

55. Prosser J, MacGregor L, Lees KR, Diener HC, Hacke W, Davis S**.** Predictors of early cardiac morbidity and mortality after ischemic stroke. Stroke. 2007;38:2295-302.

56. Touze E, Varenne O, Chatellier G, Peyrard S, Rothwell PM, Mas JL**.** Risk of myocardial infarction and vascular death after transient ischemic attack and ischemic stroke: a systematic review and meta-analysis. Stroke. 2005;36:2748-55.

57. National Center for Health Statistics**.** National Health Interview Survey, 2009-2011. Accessed at ftp://ftp.cdc.gov/pub/Health_Statistics/NCHS/Datasets/NHIS/ on June 12, 2012.

58. Bergmann MM, Byers T, Freedman DS, Mokdad AH**.** Validity of self-reported diagnoses leading to hospitalization: a comparison of self-reports with hospital records in a prospective study of American adults. Am J Epidemiol. 1998;147:969-77.

59. Ford ES, Giles WH**.** Changes in prevalence of nonfatal coronary heart disease in the United States from 1971-1994. Ethnicity and Disease. 2003;13:85-93.

60. Gross R, Bentur N, Elhayany A, Sherf M, Epstein L**.** The validity of self-reports on chronic disease: characteristics of underreporters and implications for the planning of services. Public Health Reviews. 1996;24:167-82.

61. Average cost to community hospitals per patient, by state (Table 204). Statistical Abstract of the United States. Bureau of the Census. Washington, D.C.: Government Printing Office; 1998:136.

62. Lazar LD, Pletcher MJ, Coxson PG, Bibbins-Domingo K, Goldman L**.** Cost-effectiveness of statin therapy for primary prevention in a low-cost statin era. Circulation. 2011;124:146-53.

63. Kazi DS, Moran AE, Coxson PG, Penko J, Ollendorf DA, Pearson SD, et al. Cost-effectiveness of PCSK9 Inhibitor Therapy in Patients With Heterozygous Familial Hypercholesterolemia or Atherosclerotic Cardiovascular Disease. JAMA. 2016;316:743-53. doi: 10.1001/jama.2016.11004.

64. Kazi DS, Penko J, Coxson PG, Moran AE, Ollendorf DA, Tice JA, et al. Updated Cost-effectiveness Analysis of PCSK9 Inhibitors Based on the Results of the FOURIER Trial. JAMA. 2017;318:748-50. doi: 10.1001/jama.2017.9924.

65. Truven Health Analytics. Red Book Online. Accessed at www.redbook.com/redbook/about on November 14, 2017.

66. U.S. Department of Veterans Affairs Office of Acquisition and Logistics**.** Federal Supply Schedule (FSS) pharmaceutical prices. Washington, D.C.: US Department of Veterans Affairs; 2018. Accessed at https://www.va.gov/oal/business/fss/pharmPrices.asp on Jan 14, 2018.