Supplementary Online Content

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eAppendix

Additional Modeling Details

eTables

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eAppendix: Additional Modeling Details

Input Parameters and Model Calibration

The present version of the CVD Policy Model includes data from prior versions as well as many updates and upgrades.[1-3] The 2010 U.S. Census provided the baseline population [4] and number of 35 year-olds projected to enter the model population from 2010-2060.[5,6] CHD and stroke deaths in 2010 were extracted from U.S. Vital Statistics.[7] Deaths were categorized according to the International Classification of Diseases (ICD) 10 codes:[8] I20-I25 and two-thirds of I49, I50, and I51 were used to estimate coronary heart disease deaths,[9] I60-I69 were used to estimate stroke deaths, and all other deaths were considered non-CVD deaths.

Statin use among US adults was estimated from contemporary survey data (National Health and Nutrition Examination Survey [NHANES], 2005-2012). Statin use in the model was stratified by age, gender, and history of cardiovascular disease. Further, the model incorporated the bivariate distribution of LDL and statin-use estimated directly from the NHANES 2005-12 series. Model input parameters regarding statin use among patients with atherosclerotic cardiovascular disease are shown in eTable 1.

The incidence of coronary heart disease and stroke were based on competing risk Cox proportional hazards analysis of the Framingham Heart Study[10] and the Framingham Offspring Study[11] 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 angina pectoris, hospitalized myocardial infarction, or cardiac arrest. Prevalence, joint distributions and means of U.S. risk factor values were estimated from pooled, survey design-weighted U.S. National Health and Nutrition Examination Survey (NHANES), 2007-12.[12] Annual

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transition rates between risk factor levels were calculated to preserve age-range trends. Risk function betas were estimated separately for the risk of incident coronary heart disease events, incident strokes, and non-CVD deaths, using examinations 1-8 of the Framingham Offspring cohort and accounting for competing risk across the three outcomes.[11] The Framingham coefficients have been found to be useful for predicting CVD risk relationships across many populations.[13-16] Risk factors were assumed to affect the incidence of myocardial infarction, arrest, and angina in proportion to the overall incidence of coronary heart disease, except tobacco smokers were assumed to have a higher relative risk for infarction and arrest ([17]; 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[18] but not to influence angina.

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)[19] adjusted for likely miscoding,[20] such as patients who were discharged alive after two days or fewer without a percutaneous coronary intervention, and transfer patients. Case-fatality rates and rates of myocardial infarction in subgroups were estimated from national data[19] and a variety of complementary sources.[21-23] Patients with pre-hospital arrest deaths were estimated from the U.S. Vital Statistics,[24] and patients with out-of-hospital cardiac arrests surviving to hospital discharge were estimated from national data.[19] Survival after a coronary heart disease event was estimated using California data on the ratio of in-hospital survival to 30 day survival[25] and data from Medicare and Seattle, Washington.[26,27] Rates of coronary revascularizations were estimated from the National Hospital Discharge Survey,[19] with mortality estimated from aggregated historical data.

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Atherosclerotic CVD event rates in the baseline simulation were modeled as a function of the history of age-range, gender and prior CVD events (e.g., rate of MI in the population with prior MI is higher than in the population with angina only; eTable 2). Rates of these events were also assumed to be higher in the first year after an incident CVD event. Case fatality rates were a function of age-range, gender and prior CVD history.

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, eTable 3).

Stroke incidence was assumed to 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. Positive predictive values of specific ICD-9 stroke hospital diagnosis codes (inclusive of ICD 9 codes 430-438) were derived by pooling several studies of stroke incidence that compared hospital diagnoses with a gold standard (e.g., stroke ascertained by Atherosclerosis in Communities Study, the Rochester Epidemiology Study or similar criteria).[28] 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[29,30] yielded annual mortality rate estimates within the range of stroke rates reported by the U.S. Centers for Disease Control (CDC Wonder) for 2010. Incidence calibration assumed that 77% of all strokes are incident (first ever),[31] 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

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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[32] and the probability of coronary heart disease in stroke patients was based on natural history studies.[33-38]

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,[39] assuming that the imperfect positive predictive value of survey data is offset by its imperfect sensitivity.[40-42] 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.

The LDL-C lowering effect assumptions were validated in a simulation of West of Scotland Coronary Prevention Study.[43,44] The study enrolled men 45-64 years of age with elevated cholesterol but no history of myocardial infarction and randomized them to daily treatment with 40 mg pravastatin once per day (n=3302) or placebo (n=3293).[44] WOSCOPS participants were followed over 5 years for the primary endpoint, a composite measure of nonfatal myocardial infarction or death from coronary heart disease. The CVD Policy Model was used to simulate the WOSCOPS intervention among all US adults age 45-64 years by selecting those who would qualify according to cholesterol level inclusion criteria in WOSCOPS, imposing the pre- and post-intervention LDL-C and HDL cholesterol levels recorded in the West of Scotland Study 9 for the treatment and placebo groups,[44] and evaluating model-produced estimates of

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key clinical outcomes including the WOSCOP Study primary endpoint (cumulative CHD mortality or first MI) and the ratio of events in participants treated with statins compared to placebo.[43] The model produced estimates that were within one percentage point of the numbers observed in the trial (eTable 4).

Hospitalized stroke and coronary heart disease costs and acute stroke rehabilitation costs were estimated using California hospital data,[45] deflated using cost-to-charge ratios,[46] and the ratio of the U.S. national average costs to the California average.[47] Chronic outpatient CVD 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, as were average annual non-cardiovascular (background) costs.[48] All costs were indexed to the year 2015 using the medical component of the U.S. Consumer Price Index.[49]

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 CHD states and non-CVD costs. For instance, approximately a quarter of patients who have an AMI develop heart failure after the initial hospitalization. The CVDPM currently assumes a rate of heart failure hospitalizations proportional to CHD mortality, so when an intervention such as PCSK9 inhibitor therapy reduces CHD events, cost related to subsequent complications such as heart failure is also reduced.

This study modeled the LDL Hypothesis, i.e., that statins, ezetimibe, and PCSK9 inhibitors produce identical reductions in cardiovascular outcomes per unit reduction in LDL-C.[50,51] As shown below, this assumption is supported not only by the wealth of clinical trial data for

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statins and an analysis of IMPROVE-IT (The Improved Reduction of Outcomes: Vytorin Efficacy International Trial) for ezetimibe, but also by the limited available data on PCSK9 inhibitors.[51-60] The IMPROVE-IT trial investigators demonstrated a linear relationship between reduction in the rate of major cardiovascular events and LDL-C reduction, and showed that the point-estimate of the IMPROVE-IT study lies on this line, suggesting that LDL-C reduction by ezetimibe likely has a similar effect on cardiovascular outcomes as that achieved by statins.[51] The results of IMPROVE-IT and ten published PCSK9 inhibitor trials[52-60] were used to examine the relationship between LDL-C reduction and major coronary events (the endpoint used in this study, CHD mortality + nonfatal MI). For ezetimibe, a mean reduction in LDL-C of 12.8 mg/dL (0.33mmol/L) was assumed, as reported by the IMPROVE-IT study investigators after imputation for missing data (similar to the method used by the Cholesterol Treatment Trialists for statin analyses). For PCSK9 inhibitors a fixed-effect meta-analysis was performed based on nine publications reporting randomized trials examining the effect of alirocumab and evolocumab on major coronary events: DESCARTES[52] (Evolocumab 420 mg vs. placebo every 4 weeks added to diet and statin ± ezetimibe 10mg in patients with hypercholesterolemia), LAPLACE-TIMI57[53] (Evolocumab 140 mg every two weeks or evolocumab 420 mg every four weeks or placebo added to stable-dose statin ± ezetimibe 10 mg in patients with nonfamilial hyperlipidemia and hypercholesterolemia); ODYSSEY-ALTERNATIVE[54] (Alirocumab 75-150 mg every two weeks compared with ezetimibe 10mg in patients with hypercholeterolemia); ODYSSEY-COMBO I[55] (Alirocumab 75-150 mg every two weeks or placebo in addition to intensive statin therapy in patients with hypercholesterolemia) and ODYSSEY-COMBO II[56] (Alirocumab 75-150 mg every 2 weeks or ezetimibe 10mg in addition to intensive statin therapy in patients with hypercholesterolemia); ODYSSEY FHI and FHII[57] (Alirocumab 75-150 mg or placebo every two weeks in addition to intensive statin therapy in heterozygous familial hypercholesterolemia); ODYSSEY-LONGTERM[58] (Alirocumab 150 mg or placebo every two weeks in addition to

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intensive statin therapy in heterozygous familial hypercholesterolemia or hypercholesterolemia); ODYSSEY-OPTIONS I[59] and ODYSSEY-OPTIONSII[60] (Alirocumab 75-150 mg or ezetimibe 10mg every two weeks in addition to statin therapy for patients with hypercholesterolemia). See Navarese et al. for a summary of the included studies.[61] There were three key differences between our analysis and that by Navarese and colleagues: 1) Our outcome of interest was major coronary events, defined as a composite of non-fatal MI and death from coronary heart disease; 2) We included all patients in the treatment and control arms of the relevant trials, irrespective of the dose or dosing frequency tested; 3) Since CV events were included in the safety analyses of the relevant trials (rather than efficacy analyses), we included in the denominator only those patients for whom safety data were available. In other words, patients who were randomized but were lost to follow-up so that safety data were not available were not included in our analysis. Fourteen studies were excluded from the analysis because they did not report at least one event of interest in either arm of the study.[62-75]

As done by Navarese and colleagues, the OSLER trial was excluded because enrolled patients were derived from previous RCTs.[76] The nine publications (reporting 10 randomized trials) provided safety data on 6,607 patients. One reported a phase 2 study and the remainder reported phase 3 RCTs. Follow-up ranged from 12 to 52 weeks. As reported by Navarese and colleagues, all studies were randomized, double-blinded, with adequate allocation concealment, systematic adjudication outcomes, and without evidence of selective outcome reporting.[61]

Heterogeneity was evaluated using the I^2 statistic. Since the heterogeneity was deemed to be low (I^2<50%), pooled relative risk was calculated using a fixed-effects model (see Deeks et al. for a description of the Maentel Hanzel method employed in this meta-analysis).[77] Sparse events were handled by applying a standard continuity correction of 0.5 to empty cells.[78,79]

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eTable 5 summarizes PRISMA information related to our meta-analysis[80] and eFigure 2 presents the results of the meta-analysis. The meta-analysis results were adjusted for the LDL-C reduction observed in the included clinical trials (57.50 mg/dL or 1.49 mmol/L) to estimate risk reduction in major coronary events per mmol/L reduction LDL-C (eTable 6). Note that there were too few strokes in the short-term PCSK9 inhibitor trials included in this analysis to meaningfully estimate the effect of PCSK9 inhibitors on stroke.

The relative risk of CHD mortality and nonfatal MI per mmol/L reduction in LDL-C was found to be nearly identical across the three agents: 0.76 for statins (95% confidence interval [CI], 0.73-0.79); 0.75 for ezetimibe (95% CI, 0.61-0.94); and 0.78 for PCSK9 inhibitors (95% CI, 0.58-1.04). As would be expected, the confidence intervals were widest for PCSK9 inhibitors, because only short-term clinical trials with relatively few clinical events are currently available for these drugs. These findings were consistent with the US FDA's approval of PCSK9 inhibitors based on the intuition that LDL-C reduction would be expected to improve cardiovascular outcomes in the long-term. However, the large confidence intervals for the effect of ezetimibe and PCSK9 inhibitors reflect the uncertainty arising from the small number of events in PCSK9 inhibitor and ezetimibe trials.

In light of these new data, a scenario analysis was performed based on drug-specific risk reductions (i.e., average effect observed in trials, not tied to the choice of agent). In order to capture the uncertainty in clinical outcomes with ezetimibe and PCSK9 inhibitor therapy, the wider confidence intervals were incorporated into the probabilistic sensitivity analysis. Additional input parameters that were used in sensitivity analyses are shown in eTables 7 and 8.

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Prior to final submission of this manuscript we conducted an updated review of the literature in MEDLINE, Embase, and Google Scholar using the search terms employed by Navarese and colleagues.[61] We found one additional randomized trial that examined the effect of alirocumab or evolocumab on cardiovascular outcomes: Nissen and colleagues reported 2 major adverse cardiovascular events relevant to our analysis in the GAUSS-3 trial (1 each in the treatment and control arm).[81] Other trials of alirocumab or evolocumab published in the interim reported no major coronary events and were therefore excluded from the meta-analysis.[82-84] Finally, the online supplement to one study that was already included in our meta-analysis (ODYSSEY FH-I and FH-II) provided information about 3 non-fatal events (2 in the control arm and 1 in the treatment arm).[56] Including this information in the meta-analysis did not materially alter our point-estimate or uncertainty intervals (relative risk reduction in major coronary events per mmol/L lowering of LDL-C changed from 0.778 [95% CI, 0.583-1.040] to 0.774 [95% CI, 0.596 – 1.006]), and thus did not alter our results or conclusions.

Drug costs were estimated from published average wholesale acquisition costs.[85] For the sensitivity analysis of statin therapy among patients eligible for statins but not currently receiving them, we estimated the cost of statin-related adverse events based on a prior publication of the CVD Policy Model (eTable 8).[86]

Sullivan and Ghushchyan have previously estimated quality-of-life estimates for a variety of chronic medication conditions, based on data from the Medical Expenditure Panel Survey (2000-2002).[87] In general, Sullivan's effect size estimates are lower (less severe) than those estimated by the Global Burden of Disease study from which the base case quality-of-life estimates were derived (eTable 8). A scenario analysis was performed to explore the effect of using these quality-of-life estimates to estimate the cost-effectiveness of PCSK9 inhibitor therapy.

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The base case did not model disutility related to taking a daily pill (for patients receiving ezetimibe) or a monthly subcutaneous injection (for patients receiving PCSK9 inhibitor therapy). A probabilistic sensitivity analysis was performed to explore the effect of treatment-related disutilities assuming the following input parameters:

- Pill disutility (0.00104[88] [0.0004[assumed]-0.0038[89]]) applied to the ezetimibe arm.
- Injection disutility applied to the PCSK9 inhibitor arm, assumed to be equivalent to needing to take a monthly subcutaneous bisphosphonate: 0.0040 (0.0008-0.0080).[90]

The frequency and severity of adverse events related to PCSK9 inhibitors are uncertain because of the absence of long-term safety data. Simulation modeling offers the opportunity to explore how the cost-effectiveness of PCSK9 inhibitors would change if future investigations showed up additional adverse events. The base case modeled a small disutility for injection-site reactions (which have been seen to affect 5% of patients in numerous clinical trials, are generally minor, and do not require discontinuation of the drug). A sensitivity analysis explored the effect of minor neurocognitive deficits in 0.5% of the population (eTable 8).

The probabilistic sensitivity analysis incorporated 1000 Monte Carlo microsimulations that simultaneously varied key input parameters across pre-specified statistical distributions (see Table 1). The results of the probabilistic sensitivity analysis are presented in several ways to facilitate interpretation:

- 80% uncertainty intervals around the base case estimate for key outcomes such as major adverse cardiovascular events, costs, QALYs, etc.;
- acceptability curves, which plot the proportion of simulations that are cost-effective across a range of willingness-to-pay thresholds; and
- using the net monetary benefit framework (because the net monetary benefit metric has more stable statistical properties than the ICER).

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The rationale behind the choice of 80% uncertainty intervals was as follows. Since microsimulations typically assume that input parameters vary independently, the uncertainty intervals can appear to be substantially wider than would be expected in the real world. Uncertainty intervals from simulations should therefore not be considered equivalent to confidence intervals from empirical data. Reporting wide uncertainty intervals poses additional challenges when more than two strategies are being examined because the ICER becomes unstable when the denominator approaches zero. At the extremes, the ICER may even become negative and therefore nonsensical. Even when ICERs remain positive, the order of preference among the strategies may flip at the extreme, so that ICERs become considerably more difficult to interpret. Several of the above issues were relevant to our analysis: 95% uncertainty intervals were expected to be wide (given the uncertainty in the effect of PCSK9 inhibitors on cardiovascular outcomes), with the possibility of flipped ordering of the strategies at the extreme, which would make ICERs both statistically unstable and challenging to interpret. We therefore chose to present 80% uncertainty intervals, and focused on the use of acceptability curves as a preferred way to capture the uncertainty in our estimates.

An alternative metric of cost-effectiveness is net monetary benefit (NBM), where:

NMB = (Willingness-to-pay)(Effectiveness of an intervention) – (Cost of the intervention)*

The key advantage of NMB it has more stable statistical properties compared with the ICER, which, being a ratio, becomes unstable as the denominator approaches zero. Multiple strategies can be depicted in a single NMB graph: the steeper the curve, the more efficient the strategy. At any willingness-to-pay threshold, the highest strategy above the x-axis is the optimal strategy, and the vertical distance between two strategies is a measure of the incremental NMB of one strategy over the other (eFigure 5).

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Model Validation

The model accurately predicted MACE rates observed in the high-intensity statin arms of the trials included in the Cholesterol Treatment Trialists Collaboration meta-analysis (eTable 9).

Additional Results

Results from additional sensitivity analyses are presented in eTables 10-19 and eFigures 3-5.

Of note, one scenario analysis examined the effect of using utilities derived from the Medical Expenditure Panel Survey by Sullivan et al (eTable 14).[87] Since the baseline quality-of-life after a cardiovascular event was lower (e.g., 0.778 after an MI vs. 0.9648 in the Global Burden of Disease Study from which the base case estimates were derived), PCSK9 inhibitors were estimated to be more cost-effective in the FH population (where the drugs reduce the incidence of a first event) and less cost-effective in the ASCVD population (where everyone has a prior history of CVD, and therefore a lower baseline quality-of-life; eTable 14). Overall, the results did not meaningfully differ from the base case.

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eTable 1. Statin Use in the CVD Policy Model. Bivariate distribution of statin use and LDL-cholesterol level among individuals with a history of coronary heart disease or stroke was estimated from NHANES 2005-2012.

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

Abbreviations: CVD, cardiovascular disease; LDL-C, Low-density lipoprotein cholesterol; NHANES, National Health and Nutrition Examination Survey

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eTable 2. 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

Abbreviations: CVD, cardiovascular disease; MI, myocardial infarction.

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eTable 3. 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%	

Abbreviations: CHD, coronary heart disease; NHDS, National Hospital Discharge Survey.

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eTable 4. Validation of the CVD Policy Model Against Data from the West of Scotland Coronary Prevention Study. Comparing the cumulative proportions of persons with a first major coronary event (nonfatal MI or death from coronary heart disease) in WOSCOPS with estimates from the CVD Policy Model.

	WOSCOPS[a]			CVD Policy Model[b]		
Year	Placebo (dietary counseling only)	Intervention (40 mg pravastatin/day)	Ratio	Placebo	Intervention	Ratio
1	1.70%	1.20%	0.73	1.60%	1.10%	0.67
2	3.20%	2.20%	0.68	3.30%	2.20%	0.67
3	4.90%	3.30%	0.68	5.10%	3.40%	0.67
4	6.50%	4.30%	0.67	7.00%	4.60%	0.66
5	9.20%	6.40%	0.7	8.80%	5.90%	0.67

Abbreviations: CVD, cardiovascular disease; MI, myocardial infarction; WOSCOPS, West of Scotland Study.

[a] The WOSCOPS trial randomized 45-64 year old men with elevated LDL to once daily treatment with 40 mg pravastatin (n=3302) or placebo (n=3293); results presented here were generated with Kaplan-Meier survival adjustment for censored data.[44]

[b] The CVD Policy Model was used to simulate the WOSCOPS trial in US adults age 45-64 years by selecting qualifying adults according to WOSCOPS cholesterol eligibility criteria and modeling the LDL-C and HDL-C changes observed for the treatment and placebo groups in WOSCOPS.[43]

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eTable 5. PRISMA information for Meta-analysis to Estimate Effect of PCSK9 Inhibitor Therapy on Relative Risk of Major Coronary Events. [80]

#	Section/Topic	Information
1	Title	This work is identified in the eAppendix as a meta-analysis that builds on the prior publication by Navarese and colleagues, Annals 2015.[61]
2	Abstract	N/A
3	Rationale	The meta-analysis by Navarese and colleagues examined the effect of PCSK9 inhibitor therapy on the following clinical end-points: (1) myocardial infarction, (2) angina, and (3) cardiovascular mortality.[61] We sought to estimate the effect of the PCSK9 inhibitors alircocumab and evolocumab on Major Coronary Events (a composite of fatal and non-fatal myocardial infarctions and deaths from coronary heart disease), which is the relevant input parameter for the CVD Policy Model.
4	Objectives	To evaluate the effect of PCSK9 inhibitor therapy with evolocumab or alirocumab compared with statin therapy or ezetimibe on major coronary events among adults with hypercholesterolemia.
5	Protocol and Registration	Per Navarese and colleagues.[61]
6	Eligibility Criteria	Phase 2 or 3 randomized clinical trials comparing evolocumab or alirocumab with no PCSK9 antibody in adults with hypercholesterolemia, in which at least one major coronary event was reported in either the treatment or control arms. We included all doses of alirocumab, evolocumab, or control therapies that were studied in these trials. We only included the patients for whom safety data were available (since cardiovascular events were reported as safety events in these studies).
7	Information Sources	Key sources: MEDLINE, Cochrane Central Registry of Controlled Trials, Embase, and Google Scholar. See Navarese, et al. for details.[61]
8	Search	Our main analysis was restricted to studies included by Navarese and colleagues. For the sensitivity analysis described below, we updated the literature search using MEDLINE, Embase, and Google Scholar, and applying the same search terms used by Navarese and colleagues.
9	Study Selection	Similar to Navarese and colleagues, we included all studies that reported at least one major coronary event in either the treatment arm or the control arm of the study.
10	Data collection process	Two investigators (DSK and PGC) independently abstracted the data. Discrepancies were resolved by consensus.
11	Data items	1. Number of nonfatal MIs, fatal MIs, and other deaths adjudicated as related to coronary heart disease (collectively termed Major Coronary Events) in the treatment and control arms 2. The number of patients included in the safety analysis in the treatment and control arms.
12	Risk of bias in individual studies	Per Navarese and colleagues, using methods described in the Cochrane Collaboration guidelines.[61]
13	Summary measures	Relative risk for Major Coronary Events among patients receiving alirocumab or evolocumab relative to patients receiving the control treatment (which varied by study), with 95% confidence intervals.
14	Synthesis of Results	We performed a fixed-effects meta-analysis using the Mantel-Haenzel method,[77] and using a standard continuity correction of 0.5 for sparse events.[78,79] Heterogeneity was evaluated using the I^2 statistic. If the heterogeneity was low to moderate (I^2<50%), pooled relative risk

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		was calculated using a fixedo effects model.
15	Risk of bias across studies	Per Navarese and colleagues, using methods described in the Cochrane Collaboration guidelines. Funnel plots were used by Navarese and colleagues to assess publication bias. [61]
16	Additional Analyses	Immediately prior to publication, we performed an updated literature search to identify additional studies relevant to our meta-analysis. We searched MedLine, EMBASE, and Google Scholar for any new randomized clinical trials examining the effect of alirocumab or evolocumab on major coronary events that were published after the completion of the Navarese analysis. We evaluated newly reported randomized trials as well as any additional events reported by the trials already included in the meta-analysis.
17	Study selection	In the main analysis, we identified nine publications that reported RCT results with at least one major coronary event in either arm.[52-60] As done by Navarese and colleagues, the OSLER trial was excluded because enrolled patients were derived from previous RCTs.[76] Thus results from nine publications were included in our main-analysis.
18	Study Characteristics	The nine publications taken together provided safety data on 6607 patients. One reported a phase 2 study and the remainder reported phase 3 randomized clinical trials. Follow-up ranged from 12 to 52 weeks.
19	Risk of bias within studies	As reported by Navarese and colleagues, all studies were randomized, double-blinded, with adequate allocation concealment, systematic adjudication outcomes, and without evidence of selective outcome reporting. [61]
20	Results of individual studies	See eFigure 2. Full publications of three studies (Odyssey Combo II,[56] Odyssey FH-I and FH-II,[57] Odyssey OPTIONS-I[59] and OPTIONS-II[60]) were available that had not been released at the time of the Navarese meta-analysis. This resulted in the identification of additional events, particularly in Odyssey COMBO-II,[56] where 15 MIs were not included in the Navarese analysis: 12 in the PCSK9 inhibitor arm, 3 in the control arm.
21	Synthesis of results	We estimated a relative risk of 0.689 (95% CI: 0.448-1.060). See eFigure 2.
22	Risk of bias across studies	Funnel plots published by Navarese and collegues showed no evidence of publication bias. Egger bias analysis for individual endpoints showed p-values >0.05 for all relevant endpoints studied by Navarese and colleagues.[61]
23	Additional analysis	In the updated literature search, we found one randomized trial that examined the effect of alirocumab or evolocumab on cardiovascular outcomes (as with the other studies, it included CV outcomes in safety rather than effectiveness analyses). GAUSS-3 reported 1 myocardial infarction each in the treatment and control arms.[81] Of note, other randomized trials of alirocumab or evolocumab published in the interim reported no major coronary events in either arm and were therefore excluded from the analysis.[82-84] One study that was previously included in the analysis (ODYSSEY FH-I and FH-II) provided information about 3 additional non-fatal MIs (two in the control arm and one in the treatment arm).[56] After adjusting for the observed LDL-C reduction, the inclusion of the additional events did not materially alter our estimate (relative risk for major coronary events per mmol/L reduction in LDL-C changed from from 0.778 [95% CI: 0.583-1.040] to 0.774 [CI:0.596 – 1.006]), and thus did not alter our results or conclusions.

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24	Summary of evidence	We present our summary estimate for the effect of PCSK9 inhibitors on major coronary events as well as place this in the context of the risk reduction observed in trials with statins and ezetimibe.
25	Limitations	Included trials were of limited duration, and coronary events are rare. Strokes are even less frequently observed, so we did not attempt to perform a meta-analysis for that outcome. Definitive trials powered to study cardiovascular outcomes are currently ongoing.
26	Conclusions	This meta-analysis, performed as a part of a larger cost-effectiveness analysis, generated the relevant input parameter for the CVD Policy Model. This was not used in the base case (which modeled the LDL hypothesis), but was tested in a scenario analysis (eTable 13). The confidence intervals generated by this meta-analysis, which are necessarily wide given the relatively few events in the trials thus far, were incorporated into our Monte Carlo simulations.
27	Sources of funding and role of funders	Sources of funding and role of funders are clearly stated in the acknowledgements section of the manuscript.

Abbreviations: CI, confidence interval; LDL-C, Low density lipoprotein cholesterol; MI, myocardial infarction; PCSK9, proprotein convertase subtilisin/kexin type 9; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

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eTable 6. Reduction in risk of a major CHD event among patients receiving a high-intensity statin, ezetimibe, or a PCSK9 inhibitor.

Drug	Data Source	Risk of major CHD event, per mmol/L reduction in LDL-C	95% Confidence Interval
Statin	CTT 2015[a]	0.76	(0.73 – 0.79)
Ezetimibe	IMPROVE-IT[b]	0.75	(0.61 – 0.94)
PCSK9 Inhibitor	Updated meta-analysis[c]	0.78	(0.58 – 1.04)

Abbreviations: CHD, coronary heart disease; CTT, Cholesterol Treatment Trialists; IMPROVE-IT, The Improved Reduction of Outcomes: Vytorin Efficacy International Trial;[51] LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9.

[a] Based on hazard ratios reported in Lancet 2015; 385: 1397-405.[50]

[b] Mean reduction in LDL-C in the IMPROVE-IT trial[51] was 12.8 mg/dL (0.33mmol/L) with imputation for missing data similar to the method used by the Cholesterol Treatment Trialists for statin analyses.

[c] Based on primary data from nine PCSK9 inhibitor trials that reported cardiovascular outcomes in sufficient detail: DESCARTES, LAPLACE-TIMI57, ODYSSEY-ALTERNATIVE, ODYSSEY-COMBOI, ODYSSEY-COMBOII, ODYSSEY FHI and FHII, ODYSSEY-LONGTERM, ODYSSEY-OPTIONSI, ODSSEY-OPTIONSII.[52-60] A fixed-effect meta-analysis was performed using additional clinical details regarding cardiovascular events that were not available to the investigators of the Annals meta-analysis (based on papers that have been published since). The risk ratio estimated from the meta-analysis (0.689 [0.448-1.060]) was then adjusted for the mean LDL-C reduction observed in the included clinical trials (57.50 mg/dL or 1.49 mmol/L) to estimate risk reduction per mmol/L lowering in LDL-C.

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eTable 7. Pre-Specified One-Way Sensitivity Analyses

One-Way Sensitivity Analyses	Base-Case Value	Range
LDL-C lowering by ezetimibe and PCSK9 inhibitors	see Table 1	see Table 1
Relative risk of stroke among patients receiving PCSK9 inhibitors, per 1 mmol/L reduction in LDL-C	0.85	0.85-1.00
Prevalence of statin-intolerance in the FH and atherosclerotic CVD populations	10%	3-20%
Annual drug cost for PCSK9 inhibitors, per patient per year	$14,350	$7,175-$28,700
Analytic horizon	lifetime	20 years-lifetime
Discount factor	3%	0-5%

Abbreviations: CVD, cardiovascular disease; FH, familial hypercholesterolemia; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9.

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eTable 8. Additional Input Parameters for Sensitivity Analyses

Parameter	Point-Estimate for Sensitivity Analysis	Range for Sensitivity Analyses	Source
Probabilities			
Mild neurocognitive deficits among patients receiving PCSK9 inhibitor therapy	0.05	-	Robinson, et al, 2015;[58] Sabatine, et al, 2015[76]
Annual Costs, *US dollars*			
High-intensity statin therapy	$814.00[a]	-	Red Book, 2015[85]
Statin-related adverse events	$96.17[b]	-	Pletcher, et al, 2009[86]
Utility Weights			
Estimated from Medical Expenditure Panel Survey			Sullivan, et al, 2006[87]
History of Angina	0.7680	-	
History of Myocardial Infarction	0.7780	-	
History of Stoke	0.7680	-	
History of Myocardial Infarction and Stroke	0.7270	-	
Annual disutility related to taking one additional pill	0.0010	0.0004-0.0038	Fontana, et al, 2014;[88] Pletcher, et al, 2014[89]
Annual disutility related to taking a subcutaneous injection once a month	0.0040	0.0008-0.0080	Matza, et al, 2013[90]
Statin-related adverse events	0.000034	-	Pletcher, et al, 2009[86]
Neurocognitive deficits related to PCSK9 inhibitor therapy[c]	0.1586	0.0000-0.2700	Moran, et al, 2014; [91,92] Murray, et al, 2012[93]

Abbreviations: CVD, cardiovascular disease; FH, familial hypercholesterolemia; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9.

[a] Wholesale acquisition price of generic atorvastatin = $180.21 per year; wholesale acquisition price of branded Lipitor = $3351.43; market share for branded Lipitor was assumed to be 20%.

[b] Includes a probability-weighted cost of statin-induced myopathy and hepatitis related to high-intensity statin therapy.

[c] This scenario analysis assumed that 0.5% of patients receiving PCSK9 inhibitor therapy experience mild neurocognitive deficits that produce disutility equivalent to a mild stroke.

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eTable 9. Model Validation. Comparison of Predicted MACE Rates Among the Atherosclerotic Cardiovascular Disease Population with Observed MACE Rates in Statin Trials[a]

	MACE rates predicted by the CVD Policy Model among individuals with a history of atherosclerotic CVD, on statin therapy or intolerant, requiring additional lipid-lowering therapy[b]	MACE rates observed in the treatment arm of trials included in the Cholesterol Treatment Trialists meta-analysis[c]
	(number of individuals = 7,271,000)	(number of individuals = 169,138)
MACE rates, per 100 patient-years		
Nonfatal MI	0.99	0.9-1.3
Nonfatal MI + CHD death	1.87	1.3-1.9
Stroke[d]	1.15	0.6-0.7
Cardiovascular death[e]	1.02	1.0

Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; MI, myocardial infarction.

[a] This includes patients in the statin arm of the statin v. placebo trials and the high-intensity statin arm of the high- v. moderate-intensity statin therapy trials included in the Cholesterol Treatment Trialists Meta-analysis.[50]

[b] Predicted MACE rates refers to the event rates observed in the CVD Policy Model in the first five years of the analysis.

[c] Lancet 2015;385:1397-405.[53]

[d] Includes all strokes - fatal and nonfatal ischemic and hemorrhagic strokes.

[e] Includes deaths from CHD and stroke.

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eTable 10. Additional Clinical and Economic Outcomes[a]

	Number of MACE Averted			Incremental Life-Years	Incremental Health Care Cost (Discounted, $ millions)[b]
	CV death	nonfatal MI	nonfatal stroke		
Current U.S. Population with Familial Hypercholesterolemia[c]					
Current statin use[d]	*comparator*				
Incremental treatment with ezetimibe[e]	84,600	79,200	50,600	968,200	72,074
Incremental treatment with a PCSK9 inhibitor[e]	124,800	111,100	80,400	1,296,900	316,321
Current U.S. Population with Atherosclerotic CV Disease for Whom Additional Lipid-Lowering Therapy is Indicated[f]					
Current statin use	*comparator*				
Incremental treatment with ezetimibe[e]	1,321,600	869,200	536,100	13,068,900	808,888
Incremental treatment with a PCSK9 inhibitor[e]	2,085,300	1,291,800	904,100	19,812,300	3,281,876

Abbreviations: CV, cardiovascular; MACE, major adverse cardiovascular event (nonfatal MI, non-fatal stroke, and cardiovascular death); MI, myocardial infarction; PCSK9, proprotein convertase subtilisin/kexin type 9.

[a] The model assumed the health system perspective and a lifetime analytic horizon, and discounted future costs at 3% a year. Life-years reported here are undiscounted. To reflect the precision of the model, MACE and life-years are rounded to the 100s and costs are rounded to the millions.

[b] This includes all health care costs in 2015 U.S. dollars.

[c] This analysis included patients who met the operational definition of FH and were either already receiving statin therapy or deemed statin-intolerant (n=1,065,000 in 2015).

[d] The statin + ezetimibe arm is compared with the current statin use arm, whereas the statin + PCSK9 inhibitor arm is compared with the statin + ezetimibe arm (the next best alternative).

[e] Both statin+ezetimibe and statin+PCSK9 inhibitor arms are compared with the statin (as treated) arm.

[f] This analysis included patients with a history of atherosclerotic CV disease and low-density lipoprotein-cholesterol ≥ 70mg/dL (on statin therapy if tolerated or off statin therapy among patients who were deemed statin-intolerant; n = 8,531,000 in 2015).

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eTable 11. Threshold Analyses. Annual drug cost and percentage discount of current wholesale acquisition cost at which PCSK9 inhibitors would be cost-effective in high-risk subpopulations under varying willingness-to-pay thresholds.[a,b]

Patient Subpopulation	Willingness-to-Pay Threshold		
	$50,000/QALY	$100,000/QALY	$150,000/QALY
Current U.S. population with FH[c]	2,392 (83%)	4,372 (70%)	6,353 (56%)
Current U.S. population with atherosclerotic CVD for whom additional lipid-lowering therapy is indicated[d]	2,264 (84%)	4,584 (68%)	6,904 (52%)
Current U.S. population with FH or atherosclerotic CVD for whom additional lipid-lowering therapy is indicated[d]	2,261 (84%)	4,536 (68%)	6,810 (53%)

Abbreviations: CVD, cardiovascular disease; FH, familial hypercholesterolemia; PCSK9, proprotein convertase subtilisin/kexin type 9; QALY, quality-adjusted life year.

[a] The model assumed the health system perspective and a lifetime analytic horizon, and discounted future costs and QALYs at 3% a year. To reflect the precision of the model, threshold drug costs are rounded to the 100s. Values in parenthesis indicate the percentage discount from current wholesale acquisition cost that would be required to make PCSK9 inhibitor therapy cost-effective at that willingness-to-pay threshold. Since the base-case incremental cost-effectiveness ratios of ezetimibe exceed $150,000 per QALY in each of the above scenarios, ezetimibe is eliminated by extended dominance and PCSK9 inhibitor therapy is compared with *status quo* statin therapy.

[b] All costs are reported in 2015 U.S. dollars.

[c] Patients who met the operational definition of FH and were either already receiving statin therapy or deemed statin-intolerant (10% of the population) received incremental therapy with a PCSK9 inhibitor (n = 1,065,000 in 2015).

[d] Patients with pre-existing CVD and LDL-C ≥ 70mg/dL on statin therapy or off statin therapy if deemed statin-intolerant received incremental therapy with a PCSK9 inhibitor (n = 8,531,000 in 2015).

[e] In this scenario analysis, patients who had an incident (first-ever) MI in 2015 and were either receiving statin therapy or deemed statin-intolerant received incremental therapy with a PCSK9 inhibitor (n =169,000).

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eTable 12. Additional Modeling Results: Combined Analysis of Patients with Familial Hypercholesterolemia or Atherosclerotic CV Disease[a]

A. Cost-Effectiveness over the Life-Time Analytic Horizon

Treatment Strategy	Person-Years of Treatment (millions)	Total MACE Averted[b]	NNT_5[c]	QALYs Gained	Incremental Drug Cost[d] (millions, $)	Incremental Cost of CV Care[d] (millions, $)	Incremental Cost of non-CV Care[d] (millions, $)	Incremental Cost-Effectiveness Ratio ($/QALY)[e]
Current statin use[f]	*Comparator*							
Incremental treatment with ezetimibe[g]	523.9	2,881,900	54	5,579,600	864,280	-110,747	112,624	155,000
Incremental treatment with a PCSK9 inhibitor[g]	538.2	4,523,400	37	8,374,100	3,537,073	-168,793	171,133	423,000[h]

B. Effect of PCSK9 Inhibitors on Total U.S. Healthcare Spending over 5 Years.

Treatment Strategy	Person-Years of Treatment (millions)	Incremental Drug Cost (millions, $)[d]	Incremental Cost of CV Care (millions, $)[d]	Incremental Costs of Non-CV Care (millions, $)[d]	Net Health Care Cost (millions, $)[d]
Current statin use[f]	Comparator				
Incremental treatment with ezetimibe[g]	51.4	147,820	-19,853	1,207	129,174
Incremental treatment with a PCSK9 inhibitor[g]	51.5	591,882	-28,884	1,738	564,736

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Abbreviations: CV, cardiovascular; MACE, major adverse cardiovascular event (nonfatal MI, non-fatal stroke, and cardiovascular death); NNT, number-needed-to-treat; PCSK9, proprotein convertase subtilisin/kexin type 9; QALY, quality-adjusted life year; UI, uncertainty interval.

[a] This analysis included patients who met the operational definition of FH and were either already receiving statin therapy or deemed statin-intolerant (n=1,065,000 in 2015) as well as patients with a history of atherosclerotic CV disease and low-density lipoprotein-cholesterol ≥ 70mg/dL (1.81 mmol/L; on statin therapy if tolerated or off statin therapy among patients who were deemed statin-intolerant; n = 8,531,000 in 2015). The model assumed the health system perspective 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. Note that these results mirror the results presented in Tables 2 and 3 of the manuscript, presenting a life-time analytic horizon for estimating incremental cost-effectiveness and a 5-year horizon to estimate effect on total U.S. healthcare spending.

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

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

[d] All costs are reported in 2015 U.S. dollars.

[e] The incremental cost-effectiveness ratio is estimated as the incremental cost in 2015 US dollars divided by the incremental quality-adjusted life years of the intervention relative to the comparator.

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

[g] The statin + ezetimibe arm is compared with the current statin use arm, whereas the statin + PCSK9 inhibitor arm is compared with the statin + ezetimibe arm (the next best alternative).

[h] This compares the addition of PCSK9 inhibitor therapy to statin therapy with addition of ezetimibe to statin therapy. For reference purposes, the incremental cost-effectiveness of PCSK9 inhibitor + statin relative to *status quo* was $316,000/QALY.

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eTable 13. Scenario Analysis: Modeling Effect Sizes Observed in Clinical Trials (rather than the LDL Hypothesis).[a]

Treatment Strategy	Person-Years of Treatment (millions)	Total MACE Averted[b]	NNT_5[c]	QALYs Gained	Incremental Drug Cost[d] (millions, $)	Incremental Cost of CV Care[d] (millions, $)	Incremental Cost of non-CV Care[d] (millions, $)	Incremental Cost-Effectiveness Ratio ($/QALY)[e]
Current U.S. Population with Familial Hypercholesterolemia for whom Additional Lipid-Lowering Therapy is Indicated[f]								
Current statin use[g]	*comparator*							
Incremental treatment with ezetimibe[h]	43.1	224,100	69	495,600	76,869	-12,864	7,971	145,000
Incremental treatment with a PCSK9 inhibitor[h]	45.3	265,000	69	530,000	320,845	-14,336	8,649	595,000
Current U.S. Population with Atherosclerotic CV Disease for whom Additional Lipid-Lowering Therapy is Indicated[i]								
Current statin use	*comparator*							
Incremental treatment with ezetimibe[h]	489.0	2,852,600	49	5,493,500	802,703	-105,776	112,707	147,000
Incremental treatment with a PCSK9 inhibitor[h]	499.0	3,568,500	42	6,618,400	3,262,204	-129,386	137,111	494,000
Current U.S. Population for whom Additional Lipid-Lowering Therapy is Indicated (Combined Analysis of Patients with Familial Hypercholesterolemia or Atherosclerotic CV Disease)								
Current statin use	*comparator*							
Incremental treatment with ezetimibe[h]	524.3	3,014,700	52	5,831,900	864,841	-115,785	117,746	149,000
Incremental treatment with a PCSK9 inhibitor[h]	536.3	3,770,900	44	7,000,900	3,524,301	-140,968	142,977	504,000

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Abbreviations: CV, cardiovascular; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular event (nonfatal MI, non-fatal stroke, and cardiovascular death); NNT, number-needed-to-treat; PCSK9, proprotein convertase subtilisin/kexin type 9; QALY, quality-adjusted life year.

[a] In contrast to the LDL hypothesis that was modeled in the base case, this sensitivity analysis models drug-specific betas: from the cholesterol treatment trialists' meta-analysis (for statin therapy), Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT, for ezetimibe),[51] and a meta-analysis of published PCSK9 inhibitor trials (see eFigure 2 for details).[52-60] As in the base case, this sensitivity analysis 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.

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

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

[d] All costs are reported in 2015 U.S. dollars.

[e] The incremental cost-effectiveness ratio (ICER) is defined as the increased cost incurred in a given strategy per quality-adjusted life year gained relative to the comparator.

[f] This analysis included patients who met the operational definition of FH and were either already receiving statin therapy or deemed statin-intolerant (n=1,065,000 in 2015).

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

[h] The statin + ezetimibe arm is compared with the current statin use arm, whereas the statin + PCSK9 inhibitor arm is compared with the statin + ezetimibe arm (the next best alternative).

[i] This analysis included patients with a history of atherosclerotic CV disease and low-density lipoprotein-cholesterol ≥ 70mg/dL (1.81 mmol/L; on statin therapy if tolerated or off statin therapy among patients who were deemed statin-intolerant; n = 850,000 in 2015).

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eTable 14. Scenario Analysis: Modeling Quality-of-Life Estimates Derived from the Medical Expenditure Panel Survey.[a]

Treatment Strategy	Person-Years of Treatment (millions)	Total MACE Averted[b]	NNT_5[c]	QALYs Gained	Incremental Drug Cost[d] (millions, $)	Incremental Cost of CV Care[d] (millions, $)	Incremental Cost of non-CV Care[d] (millions, $)	Incremental Cost-Effectiveness Ratio ($/QALY)[e]
Current U.S. Population with Familial Hypercholesterolemia for whom Additional Lipid-Lowering Therapy is Indicated[f]								
Current statin use[g]	*comparator*							
Incremental treatment with ezetimibe[h]	43.0	214,400	72	573,300	76,758	-12,323	7,640	126,000
Incremental treatment with a PCSK9 inhibitor[h]	45.6	316,300	59	765,100	323,096	-17,043	10,268	413,000
Current U.S. Population with Atherosclerotic CV Disease for whom Additional Lipid-Lowering Therapy is Indicated[i]								
Current statin use	*comparator*							
Incremental treatment with ezetimibe[h]	489.0	2,727,000	51	4,414,000	802,253	-101,166	107,801	183,000
Incremental treatment with a PCSK9 inhibitor[h]	500.6	4,281,200	35	6,646,800	3,272,730	-155,000	164,144	494,000
Current U.S. Population for whom Additional Lipid-Lowering Therapy is Indicated (Combined Analysis of Patients with Familial Hypercholesterolemia or Atherosclerotic CV Disease)								
Current statin use	*comparator*							
Incremental treatment with ezetimibe[h]	523.9	2,881,900	54	4,859,900	864,280	-110,747	112,624	178,000
Incremental treatment with a PCSK9 inhibitor[h]	538.2	4,523,400	37	7,265,700	3,537,073	-168,793	171,133	487,000

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Abbreviations: CV, cardiovascular; MACE, major adverse cardiovascular event (nonfatal MI, non-fatal stroke, and cardiovascular death); NNT, number-needed-to-treat; PCSK9, proprotein convertase subtilisin/kexin type 9; QALY, quality-adjusted life year.

[a] This analysis modeled quality-of-life estimates derived from the Medical Expenditure Panel Survey (2000-2002) by Sullivan, et al. Med Decis Making 2006; 26:410-420.[87] See eTable 8 for details. The model assumed the health system perspective and a lifetime analytic horizon, and discounted future costs and QALYs at 3% a year. To reflect the precision of the model, 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.

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

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

[d] All costs are reported in 2015 U.S. dollars.

[e] The incremental cost-effectiveness ratio (ICER) is defined as the increased cost incurred in a given strategy per quality-adjusted life year gained relative to the comparator.

[f] This analysis included patients who met the operational definition of FH and were either already receiving statin therapy or deemed statin-intolerant (n=1,065,000 in 2015).

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

[h] The statin + ezetimibe arm is compared with the current statin use arm, whereas the statin + PCSK9 inhibitor arm is compared with the statin + ezetimibe arm (the next best alternative).

[i] This analysis included patients with a history of atherosclerotic CV disease and low-density lipoprotein-cholesterol ≥ 70mg/dL (1.81 mmol/L; on statin therapy if tolerated or off statin therapy among patients who were deemed statin-intolerant; n = 8,531,000 in 2015).

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eTable 15. Scenario Analysis: Modeling the Effect of Stopping PCSK9 inhibitor Therapy at Age 75 Years.[a]

Treatment Strategy	Person-Years of Treatment (millions)	Total MACE Averted[b]	QALYs Gained	Incremental Drug Cost[d] (millions, $)	Incremental Cost of CV Care[d] (millions, $)	Incremental Cost of non-CV Care[d] (millions, $)	Incremental Cost-Effectiveness Ratio ($/QALY)[e]
Current U.S. Population with Familial Hypercholesterolemia for whom Additional Lipid-Lowering Therapy is Indicated[f]							
Current statin use[g]	*comparator*						
Incremental treatment with ezetimibe[h]	31.7	109,900	349,100	62,781	-9,319	4,692	167,000
Incremental treatment with a PCSK9 inhibitor[h]	32.7	142,600	431,700	258,241	-12,105	5,712	583,000
Current U.S. Population with Atherosclerotic CV Disease for whom Additional Lipid-Lowering Therapy is Indicated[i]							
Current statin use	*comparator*						
Incremental treatment with ezetimibe[h]	259.4	777,300	2,512,900	499,019	-56,964	37,411	191,000
Incremental treatment with a PCSK9 inhibitor[h]	261.8	1,158,400	3,652,300	2,009,272	-84,245	54,382	542,000
Current U.S. Population for whom Additional Lipid-Lowering Therapy is Indicated (Combined Analysis of Patients with Familial Hypercholesterolemia or Atherosclerotic CV Disease)							
Current statin use	*comparator*						
Incremental treatment with ezetimibe[h]	284.7	851,500	2,744,600	549,160	-63,981	40,246	191,000
Incremental treatment with a PCSK9 inhibitor[h]	288.0	1,259,500	3,955,100	2,217,103	-93,707	58,099	552,000

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Abbreviations: CV, cardiovascular; MACE, major adverse cardiovascular event (nonfatal MI, non-fatal stroke, and cardiovascular death); NNT, number-needed-to-treat; PCSK9, proprotein convertase subtilisin/kexin type 9; QALY, quality-adjusted life year.

[a] In the absence of effectiveness or safety data in the elderly, it is conceivable that patients and providers may be reluctant to use the drug in patients older than 75 years. This analysis models that therapy is stopped at age 75 years, although all patients are followed until death or surviving to 75 years of age. The model assumed the health system perspective and a lifetime analytic horizon, and discounted future costs and QALYs at 3% a year. To reflect the precision of the model, 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. Additional modeling details are available in the eAppendix.

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

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

[d] All costs are reported in 2015 U.S. dollars.

[e] The incremental cost-effectiveness ratio (ICER) is defined as the increased cost incurred in a given strategy per quality-adjusted life year gained relative to the comparator.

[f] This analysis included patients who met the operational definition of FH and were either already receiving statin therapy or deemed statin-intolerant (n=1,065,000 in 2015).

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

[h] The statin + ezetimibe arm is compared with the current statin use arm, whereas the statin + PCSK9 inhibitor arm is compared with the statin + ezetimibe arm (the next best alternative).

[i] This analysis included patients with a history of atherosclerotic CV disease and low-density lipoprotein-cholesterol ≥ 70mg/dL (1.81 mmol/L; on statin therapy if tolerated or off statin therapy among patients who were deemed statin-intolerant; n = 8,531,000 in 2015).

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eTable 16. Two-Way Sensitivity Analysis on Pill Disutility vs Injection Disutility.[a]

Treatment Strategy	Costs (millions)[b]	QALYs gained	Incremental Cost-Effectiveness Ratio ($/QALY)[c]	95% uncertainty interval
Current U.S. Population with Familial Hypercholesterolemia for whom Additional Lipid-Lowering Therapy is Indicated[d]				
Current statin use[e]	*comparator*			
Incremental treatment with ezetimibe[f]	72,074	450,000	160,000	155,000-165,00
Incremental treatment with a PCSK9 inhibitor[f]	316,321	553,300	572,000	517,000 – 604,000
Current U.S. Population with Atherosclerotic CV Disease for whom Additional Lipid-Lowering Therapy is Indicated[g]				
Current statin use[e]	*comparator*			
Incremental treatment with ezetimibe[f]	808,888	5,054,400	160,000	156,000 – 163,000
Incremental treatment with a PCSK9 inhibitor[f]	3,281,876	7,304,200	449,000	422,000 – 464,000

Abbreviations: CV, cardiovascular; PCSK9, proprotein convertase subtilisin/kexin type 9; QALY, quality-adjusted life year.

[a] The base case assumed that there was no disutility with taking a pill or receiving a subcutaneous injection. This probabilistic analysis assumed a small disutility associated with taking a daily pill for the ezetimibe arm (0.0010, range: 0.0004-0.0038) and a slightly larger disutility with taking a monthly subcutaneous injection for PCSK9 inhibitor therapy (0.0040, range: 0.0008-0.0080). As with the base case, this analysis 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, QALYs are rounded to the 100s; costs are rounded to the millions; and incremental cost-effectiveness ratios to the 1000s.

[b] All costs are reported in 2015 U.S. dollars.

[c] The incremental cost-effectiveness ratio (ICER) is defined as the increased cost incurred in a given strategy per quality-adjusted life year gained relative to the comparator.

[d] This analysis included patients who met the operational definition of FH and were either already receiving statin therapy or deemed statin-intolerant (n=1,065,000 in 2015).

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

[f] The statin + ezetimibe arm is compared with the current statin use arm, whereas the statin + PCSK9 inhibitor arm is compared with the statin + ezetimibe arm (the next best alternative).

[g] This analysis included patients with a history of atherosclerotic CV disease and low-density lipoprotein-cholesterol ≥ 70mg/dL (1.81 mmol/L; on statin therapy if tolerated or off statin therapy among patients who were deemed statin-intolerant; n = 8,531,000 in 2015).

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eTable 17. Scenario Analysis: Modeling Mild Neurocognitive Deficit as an Adverse Event.[a]

Treatment Strategy	Person-Years of Treatment (millions)	Total MACE Averted[b]	QALYs Gained	Incremental Drug Cost[d] (millions, $)	Incremental Cost of CV Care[d] (millions, $)	Incremental Cost of non-CV Care[d] (millions, $)	Incremental Cost-Effectiveness Ratio ($/QALY)[e]
Current U.S. Population with Familial Hypercholesterolemia for whom Additional Lipid-Lowering Therapy is Indicated[f]							
Current statin use[g]	*comparator*						
Incremental treatment with ezetimibe[h]	43.0	214,400	475,100	76,758	-12,323	7,640	152,000
Incremental treatment with a PCSK9 inhibitor[h]	45.6	316,300	608,900	323,096	-17,043	10,268	520,000
Current U.S. Population with Atherosclerotic CV Disease for whom Additional Lipid-Lowering Therapy is Indicated[i]							
Current statin use	*comparator*						
Incremental treatment with ezetimibe[h]	489.0	2,727,000	5,255,500	802,253	-101,166	107,801	154,000
Incremental treatment with a PCSK9 inhibitor[h]	500.6	4,281,200	7,756,900	3,272,730	-155,000	164,144	423,000
Current U.S. Population for whom Additional Lipid-Lowering Therapy is Indicated (Combined Analysis of Patients with Familial Hypercholesterolemia or Atherosclerotic CV Disease)							
Current statin use	*comparator*						
Incremental treatment with ezetimibe[h]	523.9	2,881,900	5,579,600	864,280	-110,747	112,624	155,000
Incremental treatment with a PCSK9 inhibitor[h]	538.2	4,523,400	8,195,600	3,537,073	-168,793	171,133	431,900

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Abbreviations: CV, cardiovascular; MACE, major adverse cardiovascular event (nonfatal MI, non-fatal stroke, and cardiovascular death); NNT, number-needed-to-treat; PCSK9, proprotein convertase subtilisin/kexin type 9; QALY, quality-adjusted life year.

[a] In short-term trials of PCSK9 inhibitors, 0.5% of patients develop neurocognitive deficit. This adverse event was not associated with LDL-C levels and has not been consistently observed in larger trials. This scenario analysis assumed that 0.5% of patients receiving PCSK9 inhibitor therapy develop mild neurocognitive dysfunction. These patients are assigned a disutility of 0.1586 (equivalent to the disutility of a mild stroke as estimated by the Global Burden of Disease Study investigators). See eAppendix for details. As with the base case, this analysis 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.

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

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

[d] All costs are reported in 2015 U.S. dollars.

[e] The incremental cost-effectiveness ratio (ICER) is defined as the increased cost incurred in a given strategy per quality-adjusted life year gained relative to the comparator.

[f] This analysis included patients who met the operational definition of FH and were either already receiving statin therapy or deemed statin-intolerant (n=1,065,000 in 2015).

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

[h] The statin + ezetimibe arm is compared with the current statin use arm, whereas the statin + PCSK9 inhibitor arm is compared with the statin + ezetimibe arm (the next best alternative).

[i] This analysis included patients with a history of atherosclerotic CV disease and low-density lipoprotein-cholesterol ≥ 70mg/dL (1.81 mmol/L; on statin therapy if tolerated or off statin therapy among patients who were deemed statin-intolerant; n = 8,531,000 in 2015).

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eTable 18. Scenario Analysis: Modeling Patients with Statin Intolerance.[a]

Treatment Strategy	Person-Years of Treatment (millions)	Total MACE Averted[b]	NNT_5[c]	QALYs Gained	Incremental Drug Cost[d] (millions, $)	Incremental Cost of CV Care[d] (millions, $)	Incremental Cost of non-CV Care[d] (millions, $)	Incremental Cost-Effectiveness Ratio ($/QALY)[e]
Current U.S. Population with Familial Hypercholesterolemia for whom Additional Lipid-Lowering Therapy is Indicated[f]								
Current statin use[g]	*comparator*							
Incremental treatment with ezetimibe[h]	3.0	19,200	58	43,500	5,509	-1,044	768	120,000
Incremental treatment with a PCSK9 inhibitor[h]	3.0	34,700	33	77,100	22,211	-1,874	1,360	282,000
Current U.S. Population with Atherosclerotic CV Disease for whom Additional Lipid-Lowering Therapy is Indicated[i]								
Current statin use	*comparator*							
Incremental treatment with ezetimibe[h]	77.8	434,500	53	823,600	126,420	-15,230	17,372	156,000
Incremental treatment with a PCSK9 inhibitor[h]	78.1	786,400	30	1,473,300	506,219	-27,312	31,204	346,000

Abbreviations: CV, cardiovascular; MACE, major adverse cardiovascular event (nonfatal MI, non-fatal stroke, and cardiovascular death); NNT, number-needed-to-treat; PCSK9, proprotein convertase subtilisin/kexin type 9; QALY, quality-adjusted life year.

[a] This analysis restricted the use of PCSK9 inhibitor therapy to patients with heterozygous familial hypercholesterolemia or atherosclerotic cardiovascular disease with statin intolerance. The model assumed the health system perspective and a lifetime analytic horizon, and discounted future costs and QALYs at 3% a year. To reflect the precision of the model, 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.

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

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

[d] All costs are reported in 2015 U.S. dollars.

[e] The incremental cost-effectiveness ratio (ICER) is defined as the increased cost incurred in a given strategy per quality-adjusted life year gained relative to the comparator.

[f] This analysis included patients who met the operational definition of FH and were deemed statin-intolerant.

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

[h] The statin + ezetimibe arm is compared with the current statin use arm, whereas the statin + PCSK9 inhibitor arm is compared with the statin + ezetimibe arm (the next best alternative).

[i] This analysis included patients with a history of atherosclerotic CV disease and low-density lipoprotein-cholesterol ≥ 70mg/dL (1.81 mmol/L) who were deemed statin-intolerant.

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eTable 19. Scenario Analysis: Modeling a High Risk Population (US Adults age 35-74 years who experienced their first-ever MI in 2015).[a]

Treatment Strategy	Person-Years of Treatment (millions)	Total MACE Averted[b]	NNT_5[c]	QALYs Gained	Incremental Drug Cost[d] (millions, $)	Incremental Cost of CV Care[d] (millions, $)	Incremental Cost of non-CV Care[d] (millions, $)	Incremental Cost-Effectiveness Ratio ($/QALY)[e]
Current U.S. Population with Atherosclerotic CV Disease for whom Additional Lipid-Lowering Therapy is Indicated[i]								
Current statin use[f]	*comparator*							
Incremental treatment with ezetimibe[g]	3.3	17,000	36	63,300	6,849	-1,075	1,036	108,000
Incremental treatment with a PCSK9 inhibitor[g]	3.5	26,700	26	93,600	28,456	-1,617	1,561	304,000

Abbreviations: CV, cardiovascular; MACE, major adverse cardiovascular event (nonfatal MI, non-fatal stroke, and cardiovascular death); NNT, number-needed-to-treat; PCSK9, proprotein convertase subtilisin/kexin type 9; QALY, quality-adjusted life year.

[a] In order to examine the cost-effectiveness of PCSK9 inhibitor therapy in a high-risk population, this scenario analysis restricted incremental therapy with ezetimibe or a PCSK9 inhibitor to patients who experience their first-ever MI in 2015 (n=169,000 in 2015). The model assumed the health system perspective and a lifetime analytic horizon, and discounted future costs and QALYs at 3% a year. To reflect the precision of the model, 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. Additional modeling details are available in the eAppendix.

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

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

[d] All costs are reported in 2015 U.S. dollars.

[e] The incremental cost-effectiveness ratio (ICER) is defined as the increased cost incurred in a given strategy per quality-adjusted life year gained relative to the comparator.

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

[g] The statin + ezetimibe arm is compared with the current statin use arm, whereas the statin + PCSK9 inhibitor arm is compared with the statin + ezetimibe arm (the next best alternative).

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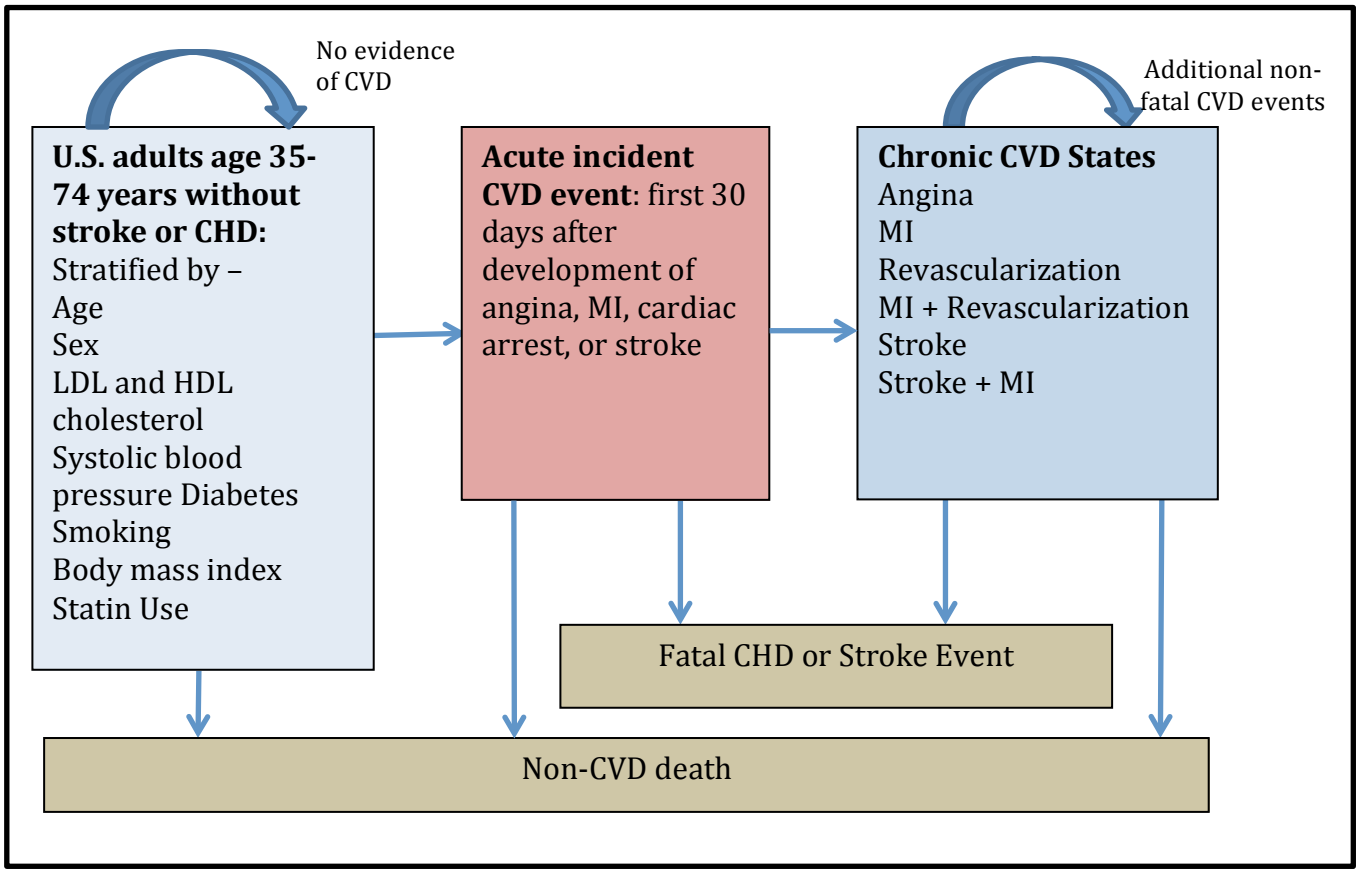
eFigure 1. Schematic of the Cardiovascular Disease Policy Model. The structure and transitions in the CVD Policy Model are shown here. The model has been extensively validated across national and clinical-trial data.



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

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eFigure 2. Effect of PCSK9 Inhibitor Therapy on Major Coronary Events. In this meta-analysis, a fixed-effects model was used to estimate the effect of PCSK9 inhibitor therapy on the combined endpoint of death from coronary heart disease (CHD) and non-fatal myocardial infarction (MI) using primary data from nine PCSK9 inhibitor trials that reported these cardiovascular outcomes.[52-60] Fourteen studies were excluded.[62-75] Marker size is proportional to the weight allocated to the study in the meta-analysis (Mantel–Haenszel method).[77]

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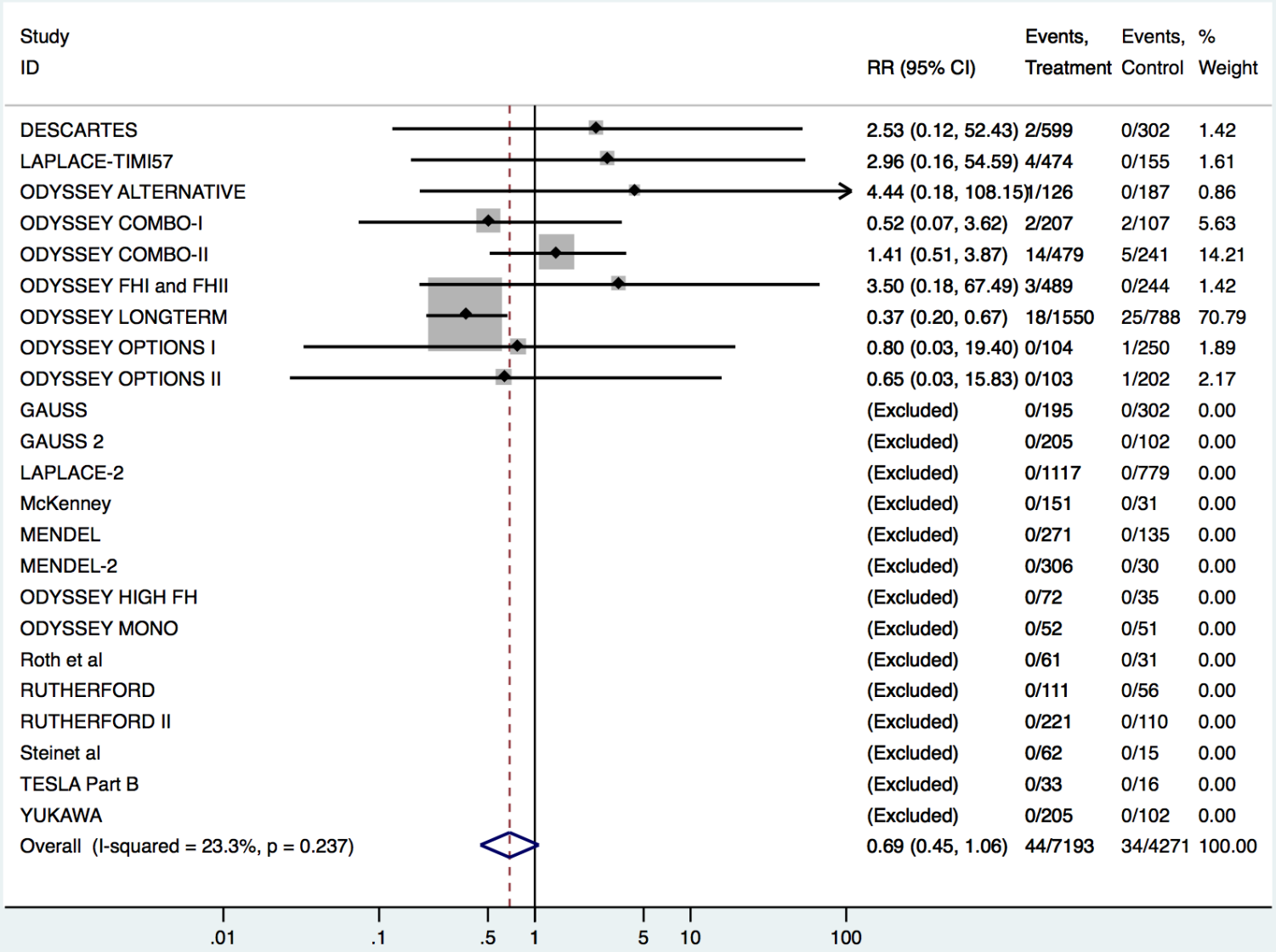

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eFigure 3. One-Way Sensitivity Analyses. Among patients with FH (panel A) and atherosclerotic CVD eligible for PCSK9 inhibitor therapy (panel B), the incremental cost-effectiveness of PCSK9 inhibitor therapy was very sensitive to changes in drug cost and the analytic horizon. One-way sensitivity analyses among patients with FH (panel C) and atherosclerotic CVD (panel D) receiving ezetimibe produced similar results, the incremental cost-effectiveness of ezetimibe was also very sensitive to changes in drug cost and the analytic horizon. In both cases, higher drug costs and shorter analytic horizons reduced the cost-effectiveness of the therapy. High- or low- LDLC effect refer to the upper and lower bounds of estimated LDL-C reduction with each drug. Abbreviations: CVD, cardiovascular disease; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; QALY, quality-adjusted life year.

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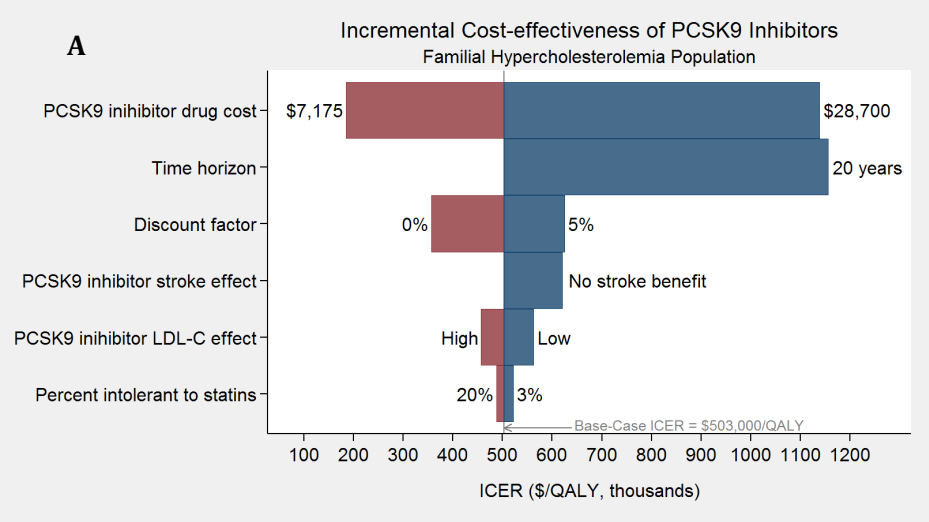

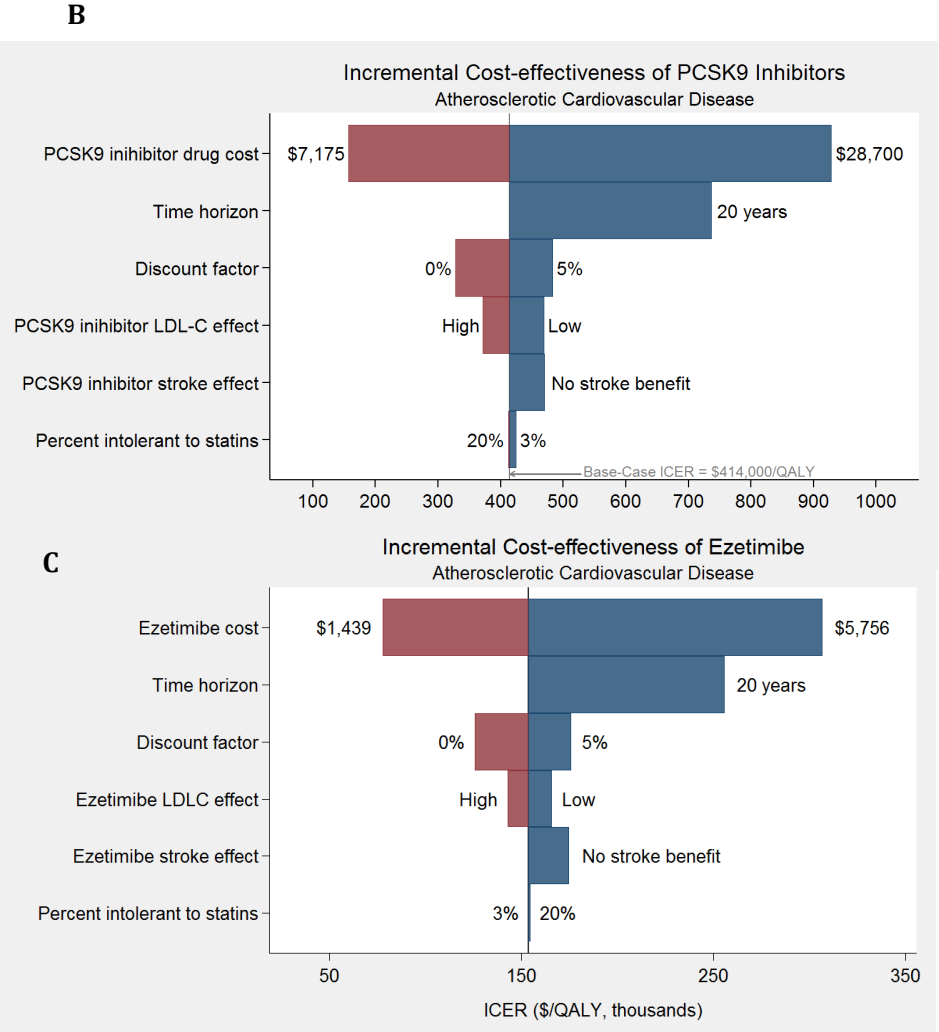

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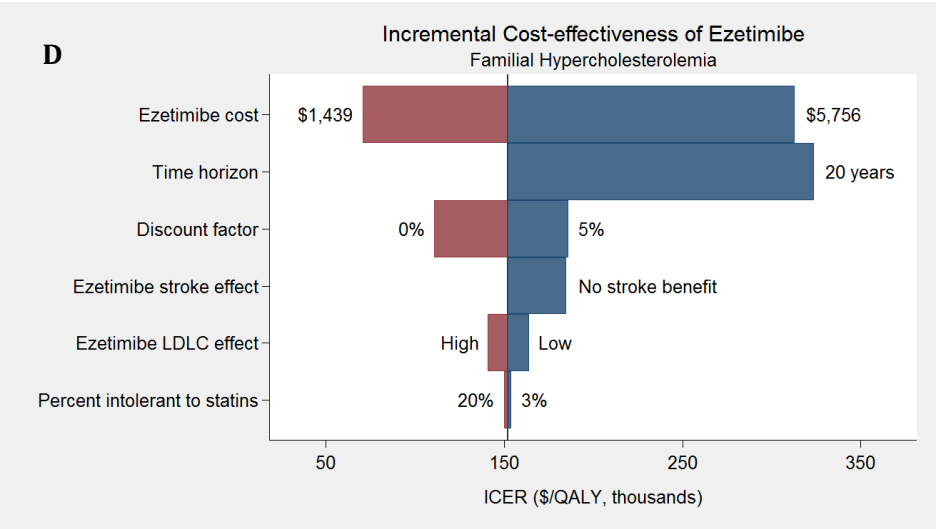

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eFigure 4. Probabilistic Sensitivity Analyses. Probabilistic sensitivity analyses analyzed 1000 simulations of the model (separately for patients with familial hypercholesterolemia [Panel A] and those with atherosclerotic cardiovascular disease [Panel B]) in which input parameters were randomly varied across pre-specified statistical distributions. Acceptability curves plot the probability that a given therapy is the "optimal" choice (y-axis) at a given willingness-to-pay threshold (x-axis). Note that at a willingness-to-pay threshold of $100,000/QALY, continuing background statin therapy without any incremental therapy is estimated to be the most cost-effective strategy. As the willingness-to-pay threshold increases, first ezetimibe and then PCSK9 inhibitors become the optimal choice. PCSK9 inhibitors were the optimal strategy in 80% of the simulations at thresholds of $905,000/QALY among FH patients and $785,000/QALY among patients with atherosclerotic CVD. Note that this analysis captures the uncertainty in clinical outcomes with PCSK9 inhibitors given the small numbers of clinical events in the currently available clinical trial results.

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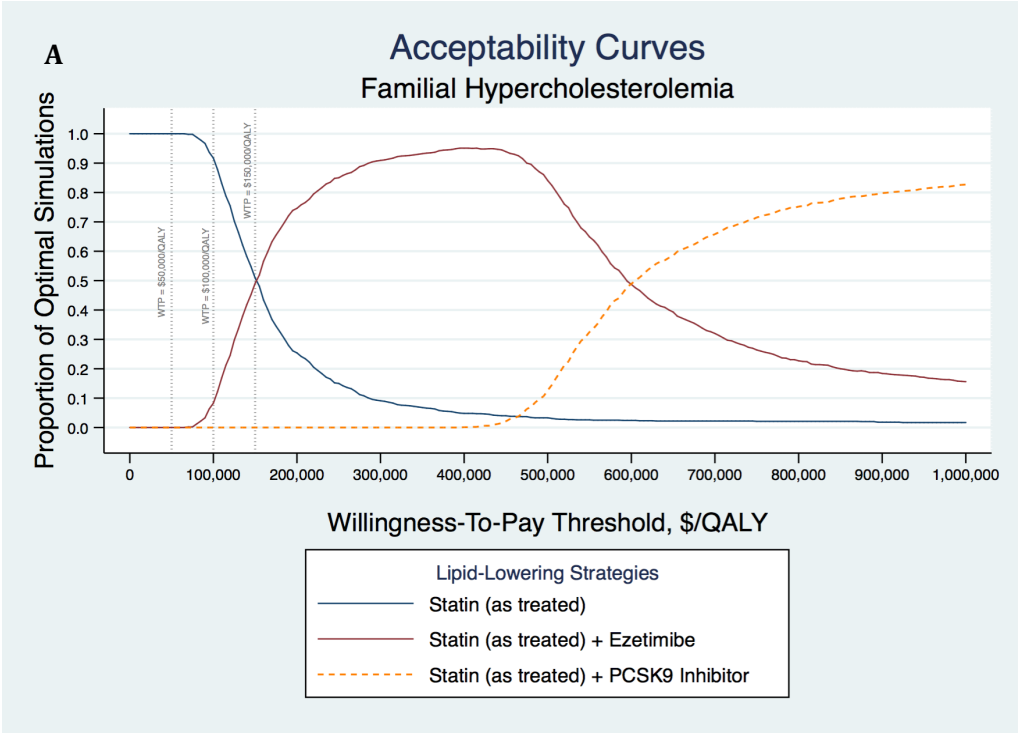

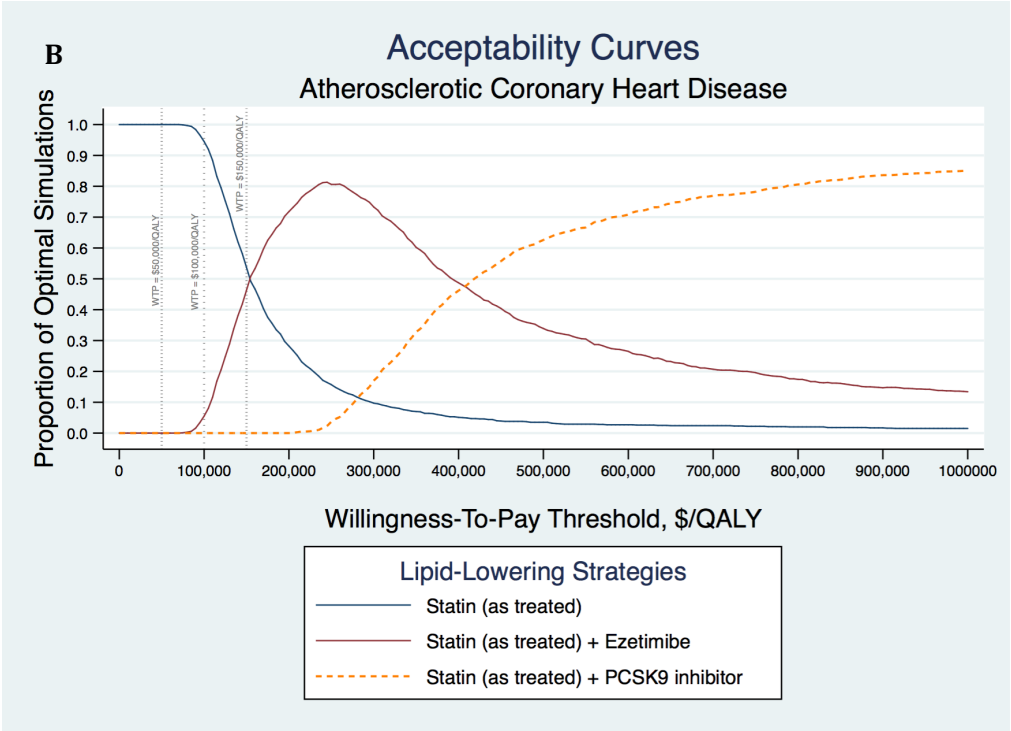

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eFigure 5. Net Monetary Benefit of Ezetimibe and PCSK9 Inihibitor Therapy Among Patients with Heterozygous Familial Hypercholesterolemia or Atherosclerotic Cardiovascular Disease on *Status Quo* Statin Therapy. If the willingness-to-pay threshold was ≥$423,000, the addition of PCSK9 inhibitor therapy to *status quo* statin therapy was estimated to generate the greatest net monetary benefit (NMB) and is the optimal strategy (solid orange line). If the willingness-to-pay threshold was ≥$155,000/QALY but <$423,000/QALY, addition of ezetimibe to *status quo* statin therapy was estimated to generate the greatest NMB (solid blue line). At any level of willingness-to-pay <155,000, neither strategy is estimated to generate a net monetary benefit (and the comparator, *status quo* statin therapy, would be the optimal choice). The vertical distance between the two strategies indicates the incremental NMB, with the higher of the two strategies being the optimal choice.
Abbreviations: QALY, quality-adjusted life year; PCSK9, proprotein convertase subtilisin/kexin type 9.

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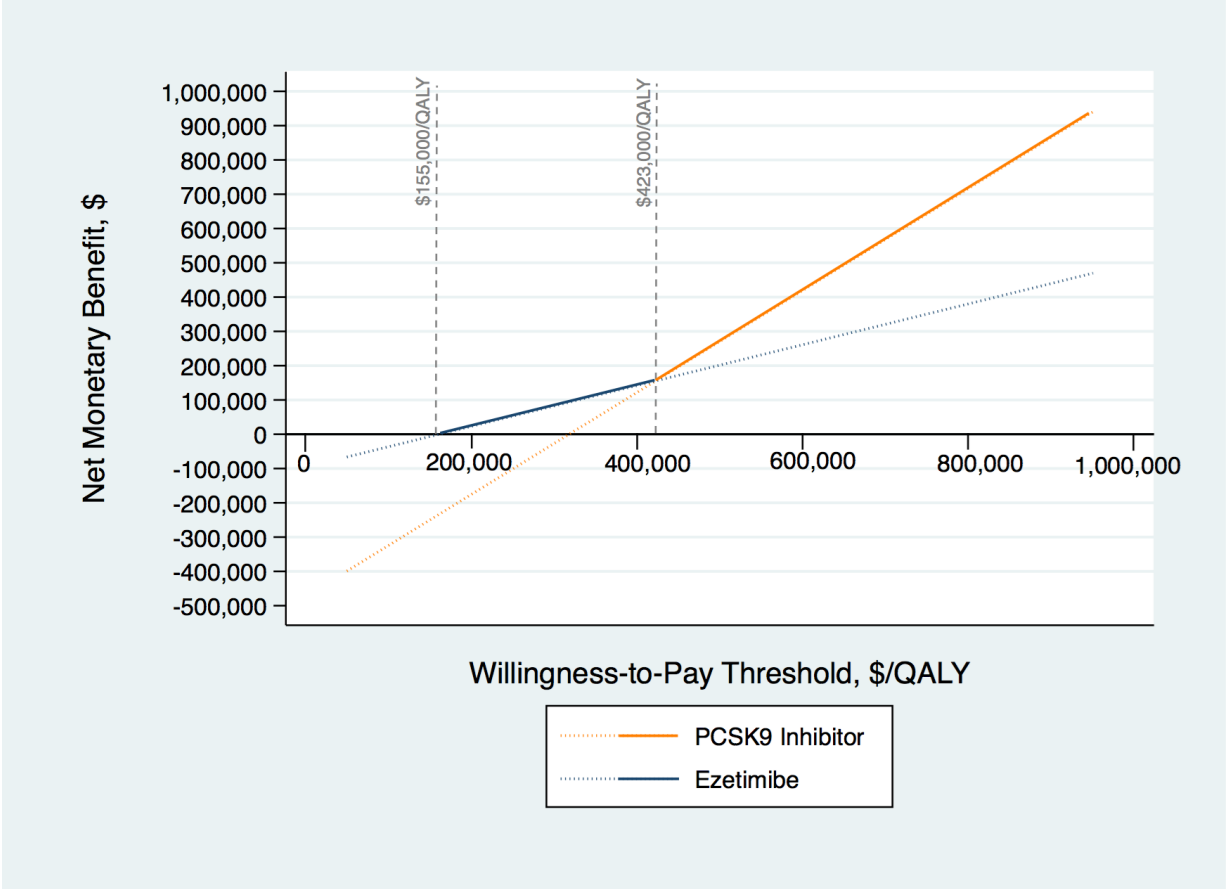

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