Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

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eMethods

Background, Model Structure, Model Inputs, and CVD Policy Model Microsimulation Version Discrimination and Recalibration

Background: microsimulation version of the Cardiovascular Disease Policy Model

Motivated by the need to choose between competing interventions for coronary heart disease, Weinstein and colleagues published the Coronary Heart Disease Policy Model in 1987.[1] This decision-analytic cohort simulation model was developed to forecast coronary heart disease incidence, prevalence, mortality, and cost in the US population. The form of the model is "compartmental", and groups of individuals who share similar average characteristics (age, sex, risk factor exposure levels, and cardiovascular health states) are simulated together; interventions to alter risk factor exposures or treat disease states are also applied at the level of the group. Developed to study epidemiology and policy related to coronary heart disease alone, the original model now predicts the health and cost outcomes of interventions that affect both coronary heart disease and stroke incidence in the U.S. population. The model is now named the Cardiovascular Disease (CVD) Policy Model. Inputs have also been updated regularly, as has the Fortran software platform on which the model runs.

The model has been redeveloped to perform simulations of individual life time cardiovascular health histories (microsimulation). In contrast to the traditional CVD Policy Model, the microsimulation version both simulates individual risk factor exposures and cardiovascular health histories, and simulated preventive interventions are applied at the individual level. This new iteration of the model was developed using TreeAge software (TreeAge Inc, Williamstown, MA, U.S.A.) using data inputs from the traditional CVD Policy Model and was validated using the traditional model. Hereafter in this document, this new model version will be referred to as the CVD Policy Model microsimulation version.

The CVD Policy Model microsimulation version was developed for three specific purposes:

1. Quantifying the effect of life-course, cumulative exposures to CVD risk factors, and estimating health and cost outcomes attributable to interventions that reduce such exposures.

2. Use in clinical practice as a tool which helps physicians and their patients understand lifetime risk and the benefits and risks of intervening of exposures at different stages of the life-course in a competing risk framework.

3. Flexible "switch out" of simulation cohorts and their characteristics, allowing for long-term simulations of lifetime benefits and risks of hypothetical interventions on observational cohorts (e.g., the MESA study cohort), or extension of short-term clinical trials (e.g., SPRINT or BARBER trials).

Model Structure

The CVD Policy Model microsimulation version simulates coronary heart disease (CHD) and stroke incidence and prevalence in the US population aged 20 and older. The model's primary outputs are CVD event rates, life years, quality-adjusted life years (QALYs), and direct health care costs. The default perspective adopted in the CVD Policy Model microsimulation version is that of the U.S. health care sector. Analyses therefore account for all health gains in the population and all direct and indirect medical costs borne by U.S. payers (e.g., patients, third-party payers).

Figure 1 in the manuscript shows the model structure and CVD-related state transitions that may occur annually. Each year, individuals can transition one time between the following five health states: (1) No CVD, (2) Chronic CHD, (3) Chronic Stroke, (4) Chronic CHD + Stroke, and (5) Death. Possible transitions are illustrated by the arrows. **eFigure 1** shows the clinical events that may occur within each model cycle that determine the health state transitions. Individuals first are at risk for having an acute CVD event or non-CVD death. If individuals do not have an acute CVD event and do not experience a non-CVD death, they remain in their current health state that cycle. If individuals have either an acute CHD event or an acute stroke, that event may be fatal or non-fatal. If non-fatal, they

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may have a second event of the same type. If they do not have a recurrent event, they may also have the other cardiovascular disease event type.

A large input dataset containing time-varying risk factor information for each individual is used to run the model. For each "run" of the model, a cohort of patients is randomly selected with replacement from the input dataset. Each profile is used in the model to determine the probability that individuals experience CVD events and progress through the model's health states over their remaining lifetime. Each health state has an attributed health-related quality of life (i.e., utility – an overall assessment of well-being on a scale from 0 [death] to 1 [perfect health]) and cost. Based on the individual's specific 'history' through the model, cost and health outcomes are estimated. This information allows cost-effectiveness and other decision-analytic metrics to be calculated for the population.

Model Inputs

Probability of first-ever, incident CVD

The annual probabilities of first-ever CVD event (i.e., acute myocardial infarction, unstable or stable angina pectoris, cardiac arrest, or acute stroke) and the competing probability of non-CVD death are estimated with risk functions derived from analysis of the NHLBI Pooled Cohorts Project at Columbia University.[2] The Pooled Cohorts Project contains data from six U.S. National Institutes of Health (NIH)-funded observational cohort studies: Atherosclerotic Risk in Communities (ARIC) Study, Cardiovascular Risk Development in young Adults (CARDIA) Study, Cardiovascular Health Study (CHS), Framingham Heart Study Offspring Cohort (FHS-O), Health, Aging, and Body Composition (Health ABC) Study, Multi-Ethnic Study of Atherosclerosis (MESA) Study.[3–8] All studies regularly collected information on participants CVD risk factors, and prospectively detailed incident CVD events. Each of these studies obtained informed consent from study participants. Columbia University entered into data use agreements with each cohort's coordinating center and pooled cohorts analysis plans were approved by the cohort study investigators.

Probabilities of first CVD event and probability of non-CVD death are operationalized in a logistic risk function that takes the following form:

$$rate_{k,i} = \frac{\exp(\alpha + x\beta)}{1 + \exp(\alpha + x\beta)}.$$

In this equation, $rate_{k,i}$ denotes the annual probability of disease-free individual i experiencing primary CVD event k. The value α represents the underlying event rate for k in the Pooled Cohorts population (or more specifically the intercept in the null model). The term x is a vector of CVD risk factors. The risk factors included in the base model are: continuous age, systolic blood pressure (SBP), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C), tobacco smoking (cigarettes per day), body mass index (BMI), and categorical diabetes status (fasting glucose ≥126 mg/dl [7.0 mmol/L] or taking anti-diabetes medications). The term β is a vector of coefficients where each coefficient represents the additive increase in log odds of event k associated with a risk factor in x. Therefore, an individual's annual incident CVD event risk is increased or decreased compared to the population average in accordance with their risk factor profile. Green and Symons have shown that the regression coefficients of the logistic model approximate to those of a proportional hazards model which has a constant underlying hazard rate.[9]

The pooled cohorts logistic risk equations are presented in **eTable 1**. The overall population incidence was re-calibrated to replicate incidence output from the traditional CVD Policy Model and contemporary cause-specific CVD and non-CVD death rates.

Simulation Cohort

The model is populated by a cohort of individuals from the 1999-2014 National Health and Nutrition Examination Survey (NHANES) that are matched to participants in the NHLBI Pooled Cohort Project at Columbia University.[10] NHANES is a large-scale, cross-sectional nationwide survey of health and nutritional status in which individuals are

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selected for inclusion using a complex, multistage probability sampling design. The probability sampling design allowed for oversampling of low-response demographics. The weighted NHANES-based estimates reflect the civilian, non-institutionalized U.S. population. We used survey, examination, and laboratory data for key CVD risk factors from NHANES respondents aged 20-85 years.

We used the following inclusion criteria to select participants from NHANES and the NHLBI Pooled Cohort Project. For both NHANES and NHLBI Pooled Cohort, we only included individuals who self-reported to be free from CVD (i.e., no history of myocardial infarction, angina, heart failure, or stroke) at the time of NHANES examination or at the baseline visit for the CU-NHLBI Pooled Cohort. For NHANES, we further selected individuals with complete data for the following CVD risk factors: age, SBP, diastolic blood pressure (DBP), current antihypertensive medication use (yes/no), LDL-C, HDL-C, total cholesterol, current lipid-lowering medication use (yes/no), tobacco smoking (cigarettes per day), BMI, serum glucose, diabetes status (yes/no) and serum creatine. Similarly, from the Pooled Cohort, we further selected individuals with at least one non-missing value for each of the above-mentioned CVD risk factors during any study visit.

Fitting risk factor exposure trajectories from age 20 years until age 89 years or death

We imputed lifetime trajectories (each year from age 18 to 99 years) for each of the CVD risk factors described above in individuals in the NHLBI Pooled Cohort Project. The details of this approach are described elsewhere.[11,12] Briefly, we leveraged the risk factor patterns observed in the younger cohorts to impute unobserved early adult exposures in the older cohorts and vice versa. We used a series of linear mixed models to estimate latent trajectories underlying the observed values for each participant, and imputed risk factor levels annually from age 18 years until age 99 or death for each participant. To account for estimation error in imputed risk factors trajectories, we used multiple imputation techniques to obtain 15 imputed datasets for the Pooled Cohort.

For modeling lipid-lowering medications, we also calculated the untreated LDL-C, HDL-C, and total cholesterol by subtracting the beta-coefficient for lipid-lowering medication from the linear mixed model used for multiple imputation (i.e., we assumed that the beta-coefficient represented the potential reduction in cholesterol associated with use of lipid-lowering medication use) (**eFigure 3**). For example, an individual who started lipid-lowering medication at age 60, with an imputed LDL-C of 125 mg/dL at age 60 and a beta-coefficient of -0.26 for lipid-lowering medication use, would have an estimated untreated LDL-C:

$$Untreated\ LDL = e^{LN(125)-(-0.26)} = 162\ mg/dL$$

Note: cholesterols were log-transformed in the imputation models.

Matching NHANES and NHLBI Pooled Cohort Project participants

After applying the inclusion criteria, 14,917 NHANES participants were available to match to 35,544 unique individuals in the NHLBI Pooled Cohort Project. Since we created 15 imputed datasets for each Pooled Cohort participants, this resulted in 533,160 participant trajectories available for matching. We randomly matched NHANES participants 1:1 to Pooled Cohort participants with replacement. We matched on CVD risk factors using the values observed at the NHANES examination visit and the imputed values for the Pooled Cohort. We required exact matches for baseline age, race (white, black, or other), sex, diabetes diagnosis, current smoking status, current antihypertensive medication use, and current lipid-lowering medication use. Additionally, based on clinical experience, we required matches to be within defined thresholds for the following continuous CVD risk factors. We required the NHLBI Pooled Cohort imputed SBP and DBP to be within 5 mm Hg of NHANES observed values, LDL-C to be within 10 mg/dL, and 10-year atherosclerotic CVD risk to be within 2.5%.

We matched 12,096 NHANES participants to CU-NHLBI Pooled Cohort participants. Overall, the mean (standard deviation) baseline age of the matched cohort was 46.1 (17.3) years and 54.0% were female. At the baseline age, mean SBP was 120.0 (15.2), mm Hg, DBP was 70.5 (9.4) mm Hg, LDL-C was 117.2 (31.3) mg/dL, and 10-year atherosclerotic CVD risk was 7.0% (11.5%). Participants were well-matched on these CVD risk factors (**eTable 2**).

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Probability of survival to 30 days after an acute CVD event

The model incorporates the risk of 30-day case fatality in individuals experiencing coronary heart disease and stroke events, stratified by age and sex (**eTable 3**). The 30-day case fatality rate for coronary heart disease events differs between primary and recurrent coronary heart disease events. For stroke, 30-day case fatality rates were assumed to be equal for primary and secondary events.

Probability of recurrent CVD events in the population living with chronic CVD

The risk of recurrent CVD events and chronic CVD health state transitions among the population living with chronic CVD states are based on natural history studies of community-dwelling patients living with chronic CVD or on hospital-based CVD case registries (**eTable 3)**. These secondary events include: recurrent CHD event within a year of a prior occurrence, recurrent CHD event after a year of a prior occurrence, stroke after CHD, CHD after stroke within 10 years, and CHD proceeding stroke after 10 years.

Treatment effects

The health benefit associated with treatment may be employed in two key ways within the structure of the model. Firstly, a primary intervention which changes the value of a patient's risk factor may be modelled directly (e.g. 15 mm Hg reduction in SBP, 30% reduction in LDL-C). These effects will then affect the individual's probability of developing CVD within the model via the risk equations which determine probability of incident event. An individual's risk of experiencing an event within the model may also be modulated by a relative risk. Modulating probability of event with a unitary relative risk across all patients implicitly assumes that the relative risk associated with treatment is consistent across patient subpopulations. Cost of treatment and patient monitoring can be added to patients receiving treatment in the model, as can screening costs.

Health-related quality of life according to health state

Health benefits are accumulated through health-related quality of life assigned to health states. Details of the value and source of the health-related quality of life inputs are included in **eTable 4**. QALYs are used to reflect health-related quality of life in the model. This measure reflects both quality and longevity of health, where 1.0 represents perfect health, and QALYs less than 1.0 represent health loss due to illness or imperfect health. These are a useful metric for assessment of the health effects of preventive interventions for CVD as CVD-related events can reduce both quality and longevity of life.

Health-related quality of life inputs were derived from a combination of data regarding CVD event rates in the US[13,14] and utility weights derived from international analysis.[15] Each health state has attributed an annual QALY penalty. Additionally, all acute events in the model (e.g., hospitalizations, fatalities) have an associated acute (30-day) QALY penalty. All outcome values are age-differentiated to account for age-based heterogeneity in costs and health-related quality of life. While receiving a treatment, individuals may experience treatment-related disutility. Such disutility is applied in the model by subtracting an annual treatment-related QALY decrement from an individual's total QALYs in each cycle of the model that they receive treatment.

CVD and background direct medical costs

Costs for stroke hospitalization, CHD hospitalization, and acute stroke rehabilitation, which account for hospital bed, provider, medication, and procedural costs, were estimated using Californian hospital data, deflated using cost-to-charge ratios and the ratio of US national-to-Californian average costs.16,17 Outpatient costs incurred by patients with chronic CVD were estimated with pooled 1998-2008 Medical Expenditure Panel Survey (MEPS) data.[18] Every

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simulated individual accrues annual age-specific "background" cost, or "non-CVD" cost (i.e., non-CHD and non-stroke cost). Background costs were also estimated from MEPS. All costs were indexed to the year 2019 using the medical component of the US Consumer Price Index.[19] Details of the value and source of the model's cost inputs are included in **eTable 5**.

Alternative sources of cost data

Costs and utilization of health services can vary across the US. Hence, the sources employed to assign health state and acute event costs in the model may lead to biased results. It is therefore useful to compare costs employed in the model with other sources of CVD-related health costs. In 2011, O'Sullivan et al. analyzed administrative claims data from around 21.5 million commercial and Medicare Advantage members from across the US to estimate costs associated with a range of CVD-related events.[21] These costs have been used to define health state and acute health costs in a previously-published cost-effectiveness analyses of preventive interventions for CVD.[22] The costs employed in the CVD Policy Model microsimulation version and O'Sullivan et al.'s estimates are presented in **eTable 6**.

Chronic, acute, and fatal health costs were estimated according to regression equations provided in the supplemental appendix of O'Sullivan et al.'s analysis of administrative claims data. These were converted into a form which would enable comparison with the CVD Policy Model microsimulation version. Age-based non-fatal MI and angina costs from O'Sullivan et al. were weighted and combined into a unitary CHD cost. Similarly, ischemic and hemorrhagic stroke were weighted and combined to replicate the CVD Policy Model microsimulation version's stroke state. Costs were also age-stratified or averaged across age-groups where appropriate.

For chronic and acute CHD events, the policy model's inputs were similar to those derived from the regression equations. However, the regression-based CHD costs tended to drop in later life, while the CVD Policy Model microsimulation version costs generally increase with age. O'Sullivan et al. do not detail the age-groups in which their regression models are valid. It is possible that their model should not be used to predict costs in elderly individuals.

When compared with the regression-based costs, the CVD Policy Model microsimulation version inputs generally assumes higher costs for CHD mortality, chronic stroke, and acute stroke events. For chronic stroke in particular, regression-based costs appear improbable. For example, in years following a stroke event, the aggregated regression-based cost for chronic stroke is lower for cases than controls. If the CVD Policy Model microsimulation version is systematically over-predicting CVD-related costs, it is possible that the model overstates the cost-effectiveness of interventions which reduce incidence of CHD and stroke. This must be weighed against the fact that the model assigns a lower cost to stroke mortality than O'Sullivan et al.'s equations

Annual statin medication costs

We used the 2015 Prescribed Medicines File from the Medical Expenditure Panel Survey (MEPS)[20] available from the Agency for Healthcare Research and Quality (AHRQ) to estimate the cost of moderate- and high-intensity statins. When weighted appropriately, cost estimates from MEPS are considered nationally representative and include all US payers (e.g., Medicare, Medicaid, private, Veterans Affairs, patients). We identified moderate- and high-intensity statins, regardless of brand or generic products, by the drug name and dose combinations shown in **eTable 7**. We excluded records that did not include the prescription name, strength, or quantity dispensed. We also excluded non-tablet formulations. Due to a small number of records with "partial" tablets dispensed (e.g., 2.5 entered as the quantity), we only included records with at least 7 tablets dispensed.

We assumed once per day dosing and calculated the annual cost for each statin fill as the (cost to all payers/quantity dispensed)*365 days. As generic statin prices have decreased since 2015 and rosuvastatin is now generically available, we attempted to account for these temporal changes in cost by: (1) only including the lowest cost statin fill for each individual when estimating the survey-weighted costs and (2) using the median rather than the mean survey-weighted cost. We then determined the annual survey-weighted cost separately for moderate- and high-intensity statins and used the survey-weighted standard error to represent uncertainty in these estimates. Upper and lower bounds for statin costs used in sensitivity analysis were derived from the 25th and 75th percentile of statin costs in MEPS, respectively.

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CVD Policy Model Microsimulation Version Discrimination and Recalibration

The traditional CVD Policy Model is regularly validated against US national estimates of stroke mortality, CHD mortality, and all-cause mortality. These model outcomes were within 1% of estimates from 2010 US national vital statistics and the US National Hospital Discharge Survey (NHIS).

eFigure 2 shows the validation of the CVD Policy Model microsimulation version by comparing its incidence rates with the traditional CVD Policy Model, cumulative mortality rates with reports from the Centers for Disease Control and Prevention's Wide-ranging ONline Data for Epidemiologic Research (WONDER) data,[23] and overall survival with US lifetables.

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eTable 1. Logistic Risk Functions Determining Incident Event Probability in the CVD Policy Model Microsimulation Version

Parameter	Description	Hazard Ratio (95% CI)	Beta Value (95% CI)	Source
Risk function: Incident CHD event				
Age	Years[a]	1.107 (1.090, 1.125)	0.10156 (0.08578, 0.11734)	CU-NHLBI Pooled Cohorts Dataset
African American	Binary	0.885 (0.826, 0.949)	-0.12189 (-0.19158, -0.05220)	
BMI	kg/m^2	1.006 (1.000, 1.012)	0.00597 (0.00046, 0.01147)	
Former smoker	Binary	1.204 (1.134, 1.278)	0.18574 (0.12603, 0.24545)	
Current smoker	Binary	1.683 (1.496, 1.893)	0.52051 (0.40291, 0.63811)	
Cigarettes per day	-	1.006 (1.001, 1.011)	0.00604 (0.00126, 0.01083)	
Systolic blood pressure	mmHg	1.013 (1.012, 1.014)	0.01289 (0.01149, 0.01429)	
Diabetes	Binary	1.916 (1.789, 2.052)	0.65028 (0.58172, 0.71884)	
HDL-C	mg/dL	0.985 (0.983, 0.988)	-0.01488 (-0.01727, -0.01250)	
LDL-C	mg/dL	1.005 (1.005, 1.006)	0.00543 (0.00466, 0.00619)	
eGFR	$mL/min/1.73^2$	0.993 (0.992, 0.995)	-0.00676 (-0.00849, -0.00504)	
Age x current smoker	-	0.987 (0.982, 0.991)	-0.01349 (-0.01841, -0.00856)	
Age x systolic blood pressure	-	1.000 (1.000, 1.000)	-0.00031 (-0.00040, -0.00021)	
Age x diabetes	-	0.990 (0.985, 0.995)	-0.01027 (-0.01511, -0.00544)	
Age x HDL-C	-	1.000 (1.000, 1.000)	0.00033 (0.00018, 0.00049)	
Age x LDL-C	-	1.000 (1.000, 1.000)	-0.00019 (-0.00025, -0.00014)	
Risk function: Incident stroke event				
Age	Years	1.146 (1.123, 1.170)	0.13656 (0.11627, 0.15686)	CU-NHLBI Pooled Cohorts Dataset
African American	Binary	1.605 (1.430, 1.802)	0.47326 (0.35738, 0.58914)	
Current smoker	Binary	1.868 (1.667, 2.094)	0.62513 (0.51121, 0.73906)	
Systolic blood pressure	mmHg	1.020 (1.018, 1.022)	0.01988 (0.01773, 0.02202)	
Diabetes	Binary	1.950 (1.751, 2.171)	0.66772 (0.56039, 0.77505)	
HDL-C	mg/dL	0.995 (0.992, 0.998)	-0.00472 (-0.00779, -0.00165)	

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Parameter	Description	Hazard Ratio (95% CI)	Beta Value (95% CI)	Source
LDL-C	mg/dL	1.002 (1.000, 1.003)	0.00172 (0.00049, 0.00295)	
eGFR	mL/min/1.73^2	0.996 (0.993, 0.998)	-0.00421 (-0.00691, -0.00152)	
Age x African American	-	0.977 (0.969, 0.986)	-0.02280 (-0.03126, -0.01435)	
Age x current smoker	-	0.990 (0.982, 0.999)	-0.00955 (-0.01772, -0.00138)	
Age x systolic blood pressure	-	1.000 (0.999, 1.000)	-0.00042 (-0.00056, -0.00028)	
Age x diabetes	-	0.984 (0.977, 0.991)	-0.01607 (-0.02356, -0.00858)	
Risk function: Non-CVD mortality				
Age	Years	1.104 (1.097, 1.111)	0.09916 (0.09289, 0.10543)	CU-NHLBI Pooled Cohorts Dataset
African American	Binary	1.501 (1.404, 1.605)	0.40643 (0.33944, 0.47342)	
BMI	kg/m^2	0.905 (0.886, 0.925)	-0.09962 (-0.12093, -0.07832)	
BMI^2	-	1.001 (1.001, 1.002)	0.00137 (0.00106, 0.00168)	
Former smoker	Binary	1.296 (1.228, 1.369)	0.25967 (0.20511, 0.31422)	
Current Smoker	Binary	1.985 (1.792, 2.200)	0.68585 (0.58327, 0.78842)	
Cigarettes per day	Among current smokers	1.020 (1.016, 1.025)	0.02027 (0.01601, 0.02452)	
Systolic blood pressure	mmHg	1.001 (1.000, 1.002)	0.00113 (-0.00010, 0.00236)	
Diabetes	Binary	1.542 (1.441, 1.650)	0.43303 (0.36525, 0.50081)	
eGFR	mL/min/1.73^2	0.993 (0.992, 0.995)	-0.00660 (-0.00815, -0.00506)	
Age x African American	-	0.985 (0.980, 0.989)	-0.01530 (-0.01998, -0.01061)	
Age x BMI^2	-	1.000 (1.000, 1.000)	0.00002 (0.00001, 0.00002)	
Age x diabetes	-	0.989 (0.984, 0.994)	-0.01144 (-0.01647, -0.00641)	

[a]Years centered around age 55

BMI – body mass index, CI – confidence interval, CU-NHLBI – Columbia University-National Heart Lung and Blood Institute, CVD – cardiovascular disease, eGFR – Estimated Glomerular Filtration Rate, HDL-C – high-density lipoprotein cholesterol, LDL-C – low-density lipoprotein cholesterol

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eTable 2. Difference between NHANES Observed and NHLBI Pooled Cohort Imputed CVD Risk Factors

CVD Risk Factor	Mean Difference (NHANES – NHLBI Pooled Cohort)	95% CI
Systolic Blood Pressure	0.21 mm Hg	0.16 to 0.26
Diastolic Blood Pressure	-0.43 mm Hg	-0.48 to -0.38
Low-density lipoprotein cholesterol	-0.37 mg/dL	-0.48 to -0.27
10-year atherosclerotic CVD risk	-0.05%	-0.07% to -0.04%

NHLBI Pooled Cohort – National Heart, Lung, and Blood Institute Pooled Cohorts Project at Columbia University; CVD – cardiovascular disease; NHANES – National Health and Nutrition Examination Survey; 95% CI – 95% confidence interval.

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eTable 3. Probabilities for Non-incident CHD and Stroke Events in the CVD Policy Model Microsimulation Version

Parameter	Base Case Value (%)	Source
Following CHD event (annual probability)		
Recurrent[a] CHD event within 1 year of previous CHD even		
Men		24–27
40-44 years	3.53	
45-54 years	4.74	
55-64 years	6.49	
65-74 years	7.96	
75+ years	12.8	
Women		
40-44 years	2.26	
45-54 years	3.96	
55-64 years	4.98	
65-74 years	8.29	
75+ years	13.55	
Recurrent CHD event after 1 year of previous CHD event		
Men		24–28
40-44 years	1.22	
45-54 years	1.6	
55-64 years	2.23	
65-74 years	2.79	
75+ years	4.53	
Women		
40-44 years	0.96	
45-54 years	1.25	
55-64 years	1.63	
65-74 years	2.72	
75+ years	4.66	
Stroke after CHD		
Men		29,30
40-44 years	0.55	
45-54 years	0.55	

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Parameter	Base Case Value (%)	Source
55-64 years	0.79	
65-74 years	0.83	
75+ years	0.92	
Women		
40-44 years	0.55	
45-54 years	0.55	
55-64 years	0.77	
65-74 years	0.87	
75+ years	0.89	
Following stroke event (annual probability)		
Recurrent stroke event	3.60	[31]
CHD after stroke within 10 years	2.50	[32]
CHD after stroke after 10 years	2.20	[33]
30-day case fatality rates		
Incident CHD		
Men		
40-44 years	6.62	
45-54 years	10.31	
55-64 years	12.31	
65-74 years	14.66	
75-85 years	13.00	
85+ years	17.50	[27,34–38]
Women		
40-44 years	5.00	
45-54 years	6.94	
55-64 years	9.29	
65-74 years	12.69	
75-85 years	10.57	
85+ years	17.09	
Recurrent CHD		
Men		
40-44 years	1.58	[27,34–38]
45-54 years	5.54	

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Parameter	Base Case Value (%)	Source
55-64 years	6.98	
65-74 years	9.15	
75-85 years	10.31	
85+ years	17.50	
Women		
40-44 years	5.00	
45-54 years	6.94	
55-64 years	9.29	
65-74 years	12.69	
75-85 years	10.57	
85+ years	17.09	
Any stroke		
Men		
40-44 years	5.94	
45-54 years	7.20	
55-64 years	8.53	
65-74 years	13.23	
75-85 years	20.20	
85+ years	35.74	
Women		[38,39]
40-44 years	13.06	
45-54 years	7.10	
55-64 years	10.15	
65-74 years	11.36	
75-85 years	21.94	
85+ years	44.31	
Other		
Maximum annual number of CVD events per cycle	2	Assumption

[a]Recurrent event occurs subsequent to primary CHD or stroke event

CHD – coronary heart disease, CVD – cardiovascular disease

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eTable 4. Chronic and Acute Utilities Used in CVD Policy Model Microsimulation Version

Parameter	Base Case Value (QALYs)	Source
CHD		
Age 40-44	0.9348	[13–15]
Age 45-54	0.9374	
Age 55-64	0.9376	
Age 65-74	0.9372	
Age 75-84	0.9364	
Age 85+	0.9358	
Stroke		
All ages	0.8835	[13–15]
Acute (30-day) CHD		
Age 40-44	0.8970	[13–15]
Age 45-54	0.8862	
Age 55-64	0.8669	
Age 65-74	0.8351	
Age 75-84	0.7946	
Age 85+	0.6829	
Acute (30-day) stroke		
All ages	0.8662	[13–15]

CHD – coronary heart disease, CVD – cardiovascular disease events

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eTable 5. Health State and Acute Event Costs Used in CVD Policy Model Microsimulation Version

Subgroup	Cost (2019 USD)	Source
Background health cost		
Men		[18]
40-49 years	3,689	
50-59 years	4,849	
60-69 years	6,461	
70-79 years	9,609	
80-89 years	14,541	
90+ years	27,874	
Women		
40-49 years	5,183	
50-59 years	7,034	
60-69 years	10,120	
70-79 years	12,426	
80-89 years	18,528	
90+ years	32,515	
CHD first year		
Aged 40-69	13,273	[18]
Aged 70+	20,284	
CHD subsequent years		
Aged 40-89	2,711	[18]
Aged 90+	4,262	
Acute (30-day) CHD		
Men		[16,17]
40-49 years	8,317	
50-59 years	14,135	
60-69 years	20,454	
70-79 years	24,131	
80-89 years	25,174	
90+ years	26,258	
Women		
40-49 years	6,608	

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Subgroup	Cost (2019 USD)	Source
50-59 years	8,874	
60-69 years	17,312	
70-79 years	22,112	
80-89 years	25,957	
90+ years	34,502	
CHD Mortality		
Men		[16,17]
40-49 years	64,209	
50-59 years	67,520	
60-69 years	73,412	
70-79 years	64,513	
80-89 years	54,473	
90+ years	46,475	
Women		
40-49 years	64,614	
50-59 years	56,959	
60-69 years	69,176	
70-79 years	63,939	
80-89 years	54,640	
90+ years	46,274	
Stroke first year		
All ages	20,538	[18]
Stroke subsequent years		
All ages	5,707	[18]
Acute (30-day) stroke		
Men		[16,17]
40-49 years	26,171	
50-59 years	22,736	
60-69 years	21,228	
70-79 years	17,915	
80+ years	19,144	
Women		
40-49 years	25,278	

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Subgroup	Cost (2019 USD)	Source
50-59 years	21,842	
60-69 years	20,336	
70-79 years	17,023	
80+ years	18,251	
Stroke Mortality		
Men		
40-49 years	32,344	
50-59 years	30,070	
60-69 years	28,724	
70-79 years	25,763	
80+ years	26,861	[16,17]
Women		
40-49 years	32,344	
50-59 years	29,272	
60-69 years	27,926	
70-79 years	24,965	
80+ years	26,063	
Inflation factor		
$US2010 to $US2019	1.2587	[19]

CHD – coronary heart disease

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eTable 6. Comparison of CVD Policy Model Microsimulation Version and O'Sullivan et al's Health Care Costs[21]

Parameter	CVD Policy Model Microsimulation Version Costs (2019 USD)	O'Sullivan et al. Costs (2019 USD)
Background health cost		
Men		
Aged 40-49 years	3,689	9,521
Aged 50-59 years	4,849	10,895
Aged 60-69 years	6,461	10,391
Aged 70-79 years	9,609	8,243
Aged 80-89 years	14,541	4,195
Women		
Aged 40-49 years	5,183	9,411
Aged 50-59 years	7,034	10,759
Aged 60-69 years	10,120	10,260
Aged 70-79 years	12,426	8,141
Aged 80-89 years	18,528	4,149
CHD first year		
Aged 40-69 years	13,273	11,083
Aged 70+ years	20,284	9,701
CHD subsequent years		
Aged 40-89 years	2,711	792
Acute (30-day) CHD		
Men		
Aged 40-49 years	8,317	25,664
Aged 50-59 years	14,135	29,126
Aged 60-69 years	20,454	27,112
Aged 70-79 years	24,131	19,752
Aged 80-89 years	25,174	17,116
Women		
Aged 40-49 years	6,608	23,524
Aged 50-59 years	8,874	27,309
Aged 60-69 years	17,312	25,753
Aged 70-79 years	22,112	18,886
Aged 80-89 years	25,957	19,337
CHD Mortality		
Men		
Aged 40-49 years	64,209	45,467

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Parameter	CVD Policy Model Microsimulation Version Costs (2019 USD)	O'Sullivan et al. Costs (2019 USD)
Aged 50-59 years	67,520	50,447
Aged 60-69 years	73,412	45,401
Aged 70-79 years	64,513	33,357
Aged 80-89 years	54,473	20,045
Women		
Aged 40-49 years	64,614	40,709
Aged 50-59 years	56,959	45,268
Aged 60-69 years	69,176	40,768
Aged 70-79 years	63,939	29,961
Aged 80-89 years	54,640	18,006
Stroke first year		
All ages	20,538	2,840
Stroke subsequent years		
All ages	5,707	-463
Acute (30-day) stroke		
Men		
Aged 40-49 years	26,171	14,474
Aged 50-59 years	22,736	9,804
Aged 60-69 years	21,228	4,944
Aged 70-79 years	17,915	1,782
Aged 80+ years	19,144	414
Women		
Aged 40-49 years	25,278	13,550
Aged 50-59 years	21,842	10,578
Aged 60-69 years	20,336	6,105
Aged 70-79 years	17,023	2,378
Aged 80+ years	18,251	570
Stroke Mortality		
Men		
Aged 40-49 years	32,344	93,127
Aged 50-59 years	30,070	67,650
Aged 60-69 years	28,724	57,906
Aged 70-79 years	25,763	58,173
Aged 80+ years	26,861	70,710
Women		
Aged 40-49 years	32,344	100,245

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Parameter	CVD Policy Model Microsimulation Version Costs (2019 USD)	O'Sullivan et al. Costs (2019 USD)
Aged 50-59 years	29,272	72,388
Aged 60-69 years	27,926	61,912
Aged 70-79 years	24,965	62,511
Aged 80+ years	26,063	76,495

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eTable 7. Statin-Intensity Classifications

	High-intensity	Moderate-intensity
Statins	Atorvastatin 40-80 mg Rosuvastatin 20-40 mg	Atorvastatin 10-20 mg Lovastatin 40 mg Pravastatin 40 mg Rosuvastatin 5-10 mg Simvastatin 40 mg

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eTable 8. Characteristics of the Simulation Cohort at Ages 40, 50, and 60 Years without Statin Treatment

Characteristics	Women Simulation baseline age			Men Simulation baseline age			Total Simulation baseline age		
	40	50	60	40	50	60	40	50	60
N CVD-free	500,000	475,192	432,687	500,000	453,465	381,872	1,000,000	928,630	814,131
Mortality from age 40 (%)	0.0	1.7	5.8	0.0	3.1	10.2	0.0	2.4	8.0
CVD event from age 40 (%)	0.0	3.6	8.8	0.0	7.0	16.3	0.0	5.3	12.6
Ten-year ASCVD risk (%)									
Mean	1.0	1.9	4.5	2.5	5.2	10.6	1.8	3.5	7.4
Category									
<2.5 %	89.5	78.7	20.8	64.5	13.0	0.0	77.0	46.7	11.0
2.5-4.9 %	8.5	15.9	52.8	23.0	47.6	2.1	15.7	31.4	29.1
5.0-7.4 %	1.6	3.8	14.6	9.9	21.9	22.8	5.8	12.6	18.5
≥7.5%	0.3	1.6	11.8	2.6	17.4	75.1	1.5	9.3	41.5
LDL Cholesterol (mg/dL)									
Mean	122.8	125.8	123.8	128.9	127.9	120.5	125.8	126.9	122.3
Category									
<100 mg/dL	24.1	23.0	24.1	19.4	21.5	26.8	21.7	22.2	25.4
100-129 mg/dL	36.7	34.8	36.8	33.6	33.8	38.1	35.1	34.3	37.4
130-159 mg/dL	27.5	27.0	25.3	30.4	27.8	24.2	29.0	27.4	24.8
≥160 mg/dL	11.7	15.3	13.8	16.6	16.9	10.8	14.1	16.1	12.4
HDL Cholesterol (mean, mg/dL)	54.6	56.7	58.4	43.8	44.6	45.9	49.2	50.8	52.5
Cigarettes Per Day (mean)	4.6	3.0	1.6	7.4	4.1	2.0	6.0	3.5	1.8
Systolic Blood Pressure (mean, mm Hg)	114.4	119.1	124.1	119.7	121.9	124.1	117.1	120.5	124.2
African American (%)	11.3	11.1	10.7	10.5	10.2	9.8	10.9	10.7	10.3
Diabetes (%)	2.7	6.8	13.1	2.8	8.1	16.2	2.8	7.4	14.5

ASCVD – atherosclerotic cardiovascular disease, CVD – cardiovascular disease, HDL – high-density lipoprotein cholesterol, LDL – low-density lipoprotein cholesterol.

Notes: All individuals started the simulation at age 40. Estimates at ages 50 and 60 years represent a scenario assuming that no individuals started statin treatment.

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eTable 9. Number of ASCVD Events Prevented Over 10 Years for Risk- and Cholesterol-Based Statin Treatment Strategies

Policy	Total ASCVD Events	ASCVD Events Prevented
Women		
Standard Care	20,384	Reference
Add AR_{10} 5.0-7.4% & LDL-C 160-189 mg/dL	20,331	53
Add AR_{10} 5.0-7.4% & LDL-C 130-159 mg/dL	20,293	91
Add remainder AR_{10} ≥5.0%	20,275	109
Men		
Standard Care	40,037	Reference
Add AR_{10} 5.0-7.4% & LDL-C 160-189 mg/dL	39,844	193
Add AR_{10} 5.0-7.4% & LDL-C 130-159 mg/dL	39,528	509
Add remainder AR_{10} ≥5.0%	39,284	753
Combined women and men		
Standard Care	60,421	Reference
Add AR_{10} 5.0-7.4% & LDL-C 160-189 mg/dL	60,175	246
Add AR_{10} 5.0-7.4% & LDL-C 130-159 mg/dL	59,821	600
Add remainder AR_{10} ≥5.0%	59,559	862

Cohort includes 500,000 U.S. men and 500,000 U.S. women aged 40 years at baseline.

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eTable 10. Scenario Analyses Showing the Costs, QALYs, and ICERs When Changing Model Assumptions

Scenario	Cost (2019 USD)				QALYs			
	SC	A	B	C	SC	A	B	C
Women								
Base case	125,046,215,620	125,044,868,352	125,048,146,932	125,060,057,499	2,309,786	2,309,798	2,309,818	2,309,917
No monitoring costs	124,896,551,652	124,890,109,674	124,879,012,762	124,873,887,014	11,582,459	11,582,673	11,582,850	11,583,006
Myalgia[a]	125,046,215,620	125,044,868,352	125,048,146,932	125,060,057,499	11,581,615	11,581,911	11,582,130	11,582,092
Statin Cost: $1,520[b]	128,219,707,649	128,329,107,200	128,515,004,130	128,841,891,397	11,582,459	11,582,673	11,582,850	11,583,006
Statin Cost: $3,040[b]	131,651,087,145	131,878,788,899	132,265,868,358	132,934,182,686	11,582,459	11,582,673	11,582,850	11,583,006
Time horizon: 10 years	26,828,969,558	26,829,991,372	26,831,369,218	26,831,216,213	4,296,105	4,296,093	4,296,096	4,296,097
Time horizon: 20 years	54,809,393,337	54,811,330,418	54,814,269,002	54,817,199,631	7,397,990	7,398,013	7,398,008	7,398,018
Time horizon: 30 years	81,219,095,147	81,221,362,487	81,227,372,050	81,244,784,005	9,535,694	9,535,730	9,535,668	9,535,610
Time horizon: 40 years	105,224,249,254	105,221,865,863	105,224,787,519	105,236,407,146	10,895,864	10,896,034	10,896,203	10,896,193
Full Adherence	125,095,312,285	125,099,748,824	125,111,515,004	125,143,935,281	11,587,880	11,588,599	11,589,241	11,589,781
Men								
Base case	90,574,138,606	90,562,851,415	90,558,695,685	90,581,623,102	2,170,436	2,170,641	2,170,940	2,171,203
No monitoring costs	90,450,643,674	90,437,248,250	90,417,941,299	90,402,809,391	10,914,126	10,915,020	10,916,180	10,917,063
Myalgia[a]	90,574,138,606	90,562,851,415	90,558,695,685	90,581,623,102	10,913,484	10,914,352	10,915,458	10,916,246
Statin Cost: $1,520[b]	95,459,924,539	95,651,271,081	96,061,038,352	96,787,395,093	10,914,126	10,915,020	10,916,180	10,917,063
Statin Cost: $3,040[b]	100,639,873,478	101,039,887,538	101,887,042,846	103,371,112,738	10,914,126	10,915,020	10,916,180	10,917,063
Time horizon: 10 years	19,691,419,027	19,693,529,415	19,700,079,764	19,712,246,483	4,266,764	4,266,804	4,266,708	4,266,614
Time horizon: 20 years	39,592,522,000	39,593,444,718	39,608,368,166	39,642,565,685	7,272,948	7,273,176	7,273,270	7,273,116
Time horizon: 30 years	59,576,426,780	59,571,776,700	59,578,923,247	59,611,671,677	9,268,829	9,269,188	9,269,961	9,270,153
Time horizon: 40 years	78,010,207,671	78,001,948,115	77,998,313,761	78,015,922,769	10,438,582	10,439,111	10,439,775	10,439,998

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Scenario	Cost (2019 USD)				QALYs			
	SC	A	B	C	SC	A	B	C
Full Adherence	90,588,280,900	90,578,538,237	90,592,747,589	90,657,399,704	10,925,778	10,927,150	10,929,226	10,930,520
Combined women and men								
Base case	215,620,354,226	215,607,719,767	215,606,842,617	215,641,680,601	4,480,222	4,480,439	4,480,759	4,481,120
No monitoring costs	215,347,195,327	215,327,357,925	215,296,954,062	215,276,696,405	22,496,585	22,497,693	22,499,030	22,500,068
Myalgia[a]	215,620,354,226	215,607,719,767	215,606,842,617	215,641,680,601	22,495,099	22,496,263	22,497,587	22,498,338
Statin Cost: $1,520[b]	223,679,632,188	223,980,378,282	224,576,042,482	225,629,286,491	22,496,585	22,497,693	22,499,030	22,500,068
Statin Cost: $3,040[b]	232,290,960,623	232,918,676,437	234,152,911,204	236,305,295,424	22,496,585	22,497,693	22,499,030	22,500,068
Time horizon: 10 years	46,520,388,585	46,523,520,787	46,531,448,982	46,543,462,696	8,562,870	8,562,897	8,562,804	8,562,712
Time horizon: 20 years	94,401,915,337	94,404,775,135	94,422,637,169	94,459,765,316	14,670,938	14,671,189	14,671,278	14,671,134
Time horizon: 30 years	140,795,521,927	140,793,139,186	140,806,295,297	140,856,455,682	18,804,523	18,804,919	18,805,629	18,805,763
Time horizon: 40 years	183,234,456,925	183,223,813,978	183,223,101,281	183,252,329,916	21,334,446	21,335,145	21,335,978	21,336,190
Full Adherence	215,683,593,185	215,678,287,061	215,704,262,593	215,801,334,985	22,513,659	22,515,749	22,518,467	22,520,301

[a]Utility decrements applied to persistent statin users for mild and severe adverse events

[b]Statin cost per year

A – standard care plus treat all borderline risk with LDL-C 160-189 mg/dL, B - standard care plus treat all borderline risk with LDL-C 130-159 mg/dL, C - standard care plus treat all borderline risk

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eTable 11. Scenario Analyses Showing the ICERs When Changing Model Assumptions

Scenario	ICER ($ per QALY gained)			
	SC	A	B	C
Women				
Base case	Ref	Cost-Saving	18,487	76,576
No monitoring costs	Ref	Cost-Saving	Cost-Saving	Cost-Saving
Myalgia[a]	Ref	Cost-Saving	14,988	Str Dominated
Statin Cost: $1,520[b]	Ref	510,965	1,048,214	2,101,641
Statin Cost: $3,040[b]	Ref	1,063,511	2,182,618	4,296,761
Time horizon: 10 years	Ref	Str Dominated	Str Dominated	Str Dominated
Time horizon: 20 years	Ref	85,417	Str Dominated	1,179,389
Time horizon: 30 years	Ref	62,125	Str Dominated	Str Dominated
Time horizon: 40 years	Ref	Cost-Saving	17,258	Str Dominated
Full Adherence	Ref	6,171	18,334	60,069
Men				
Base case	Ref	Cost-Saving	Cost-Saving	25,977
No monitoring costs	Ref	Cost-Saving	Cost-Saving	Cost-Saving
Myalgia[a]	Ref	Cost-Saving	Cost-Saving	29,073
Statin Cost: $1,520[b]	Ref	213,928	353,296	822,973
Statin Cost: $3,040[b]	Ref	447,221	730,406	1,681,473
Time horizon: 10 years	Ref	52,962	Str Dominated	Str Dominated
Time horizon: 20 years	Ref	4,051	159,295	Str Dominated
Time horizon: 30 years	Ref	Cost-Saving	9,250	170,592
Time horizon: 40 years	Ref	Cost-Saving	Cost-Saving	79,175
Full Adherence	Ref	Cost-Saving	6,844	49,933
Combined women and men				
Base case	Ref	Cost-Saving	Cost-Saving	33,558
No monitoring costs	Ref	Cost-Saving	Cost-Saving	Cost-Saving
Myalgia[a]	Ref	Cost-Saving	Cost-Saving	46,410
Statin Cost: $1,520[b]	Ref	271,298	445,460	1,014,549
Statin Cost: $3,040[b]	Ref	566,251	923,007	2,073,308
Time horizon: 10 years	Ref	113,690	Str Dominated	Str Dominated
Time horizon: 20 years	Ref	11,419	201,162	Str Dominated
Time horizon: 30 years	Ref	Cost-Saving	18,525	374,098
Time horizon: 40 years	Ref	Cost-Saving	Cost-Saving	137,950
Full Adherence	Ref	Cost-Saving	Cost-Saving	52,915

[a]Utility decrements applied to persistent statin users for mild and severe adverse events
[b]Statin cost per year

A – standard care plus treat all borderline risk with LDL-C 160-189 mg/dL, B - standard care plus treat all borderline risk with LDL-C 130-159 mg/dL, C - standard care plus treat all borderline risk, ICER – incremental cost-effectiveness ratio, SC – standard care, Str Dominated – strictly dominated

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eTable 12. Cost-Effectiveness of Statins for Borderline Risk Individuals with Chronic Kidney Disease[a]

Policy	Years of Treatment Eligibility	ASCVD Events	Discounted QALYs	Discounted Costs (2019 USD)	ICER ($/QALY)
Women					
Standard Care	8,485,471	354,209	11,582,459	125,046,215,620	Reference
Add AR_{10} 5.0-7.4% & CKD	8,670,735	353,921	11,582,669	125,048,782,218	12,220
Men					
Standard Care	11,153,224	480,658	10,914,126	90,574,138,606	Reference
Add AR_{10} 5.0-7.4% & CKD	11,216,220	480,590	10,914,233	90,574,361,157	2,080
Combined women and men					
Standard Care	19,638,695	834,867	22,496,585	215,620,354,226	Reference
Add AR_{10} 5.0-7.4% & CKD	19,886,955	834,511	22,496,902	215,623,143,375	8,798

AR_{10} – 10-year absolute atherosclerotic cardiovascular disease risk, ASCVD – atherosclerotic cardiovascular disease, CKD – chronic kidney disease, defined as eGFR<60 mL/min/1.73 m^2, ICER – incremental cost-effectiveness ratio, QALY – quality-adjusted life years.
[a]eGFR <60 mL/min/1.73 m^2

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eTable 13. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) Statement

Section/item	Item No	Recommendation	Reported on page, line number(s), figure, table
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as “cost-effectiveness analysis”, and describe the interventions compared.	Title page (Page 1) (line 1)
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	page 3, lines 1-43
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study.	page 4, lines 3-20
		Present the study question and its relevance for health policy or practice decisions.	page 4, lines 20-26
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	page 6, lines 17-22 page 6, lines 31-41 page 7, lines 1-3 page 7, lines 5-7 supplement, eTable 8
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	page 6, lines 31-37
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	page 8, lines 1-8
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	page 6, line 31 - page 7, line 7
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	page 5, line 22 page 5, line 35

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Section/item	Item No	Recommendation	Reported on page, line number(s), figure, table
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	page 8, line 5
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	page 4, line 30 page 8, line 1 eMethods, page 7 …lines 20-25
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	Not applicable
	11b	*Synthesis-based estimates*: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	page 7, lines 9-38
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	page 6, lines 11-13 eMethods, page 7 …lines 26-32 eTable 4
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	not applicable
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	page 4, lines 34-46 eMethods, page 7 (lines 34-42) eMethods, page 8 (lines 16-40) supplement, eTable 7

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Section/item	Item No	Recommendation	Reported on page, line number(s), figure, table
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	page 8, line 1 supplement, page 7 (lines 40-42) eTable 5
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	page 5, lines 30 -page 6, line 13 Figure 1 eFigure 1
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	page 5, lines 30-40 Table 1 eMethods
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	page 6, lines 15-27 page 8, lines 16-27 eMethods
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	page 7, lines 9-38 Table 1
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	page 9, line 31 -page 9, line 13 Table 2
	20a	*Single study-based economic evaluation:* Describe the effects of sampling	not applicable

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Section/item	Item No	Recommendation	Reported on page, line number(s), figure, table
Characterising uncertainty		uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	page 10, lines 1-25 eFigures 5-8
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	page 9, lines 16-39 figure 2 figure 3
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	page 10, lines 27 -page 12, line 17
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	page 12, lines 28-33
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	page 12, lines 35-39

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eTable 14. Cross-Validation of the CVD Policy Model Microsimulation Version vs Pandya et al's ASCVD Risk Threshold Statin Cost-Effectiveness Analysis[22]

Policy	Patient-Years of Treatment Eligibility	ASCVD Events	Discounted QALYs	Discounted Costs (2013 USD)	ICER[a] ($/QALY)	Pandya et al.'s ICER
Combined cohort of women and men (n=1,000,000)						
AR_{10} ≥20%	11,559,746	824,563	19,312,248	16,940,016,282	Reference	Reference
AR_{10} ≥10%	16,806,964	813,328	19,320,212	17,040,121,459	12,570	9,300
AR_{10} ≥7.5%	19,442,914	808,759	19,324,540	17,124,933,191	19,593	15,000
AR_{10} ≥5.0%	22,974,469	803,055	19,331,053	17,268,427,077	22,033	27,000

[a]Incremental to prior most effective, non-dominated strategy

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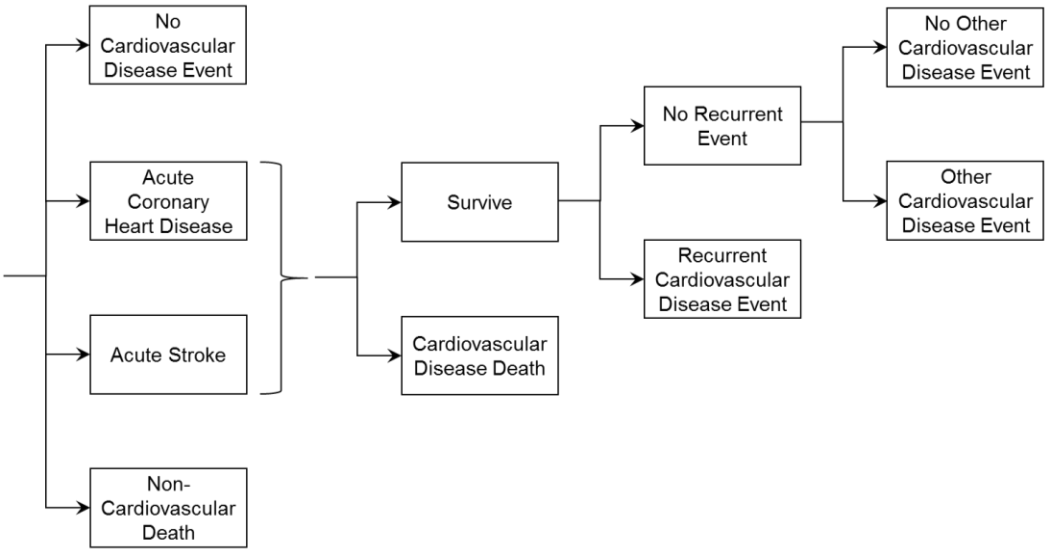
eFigure 1. CVD Policy Model Microsimulation Version Structure, Within-Cycle Events



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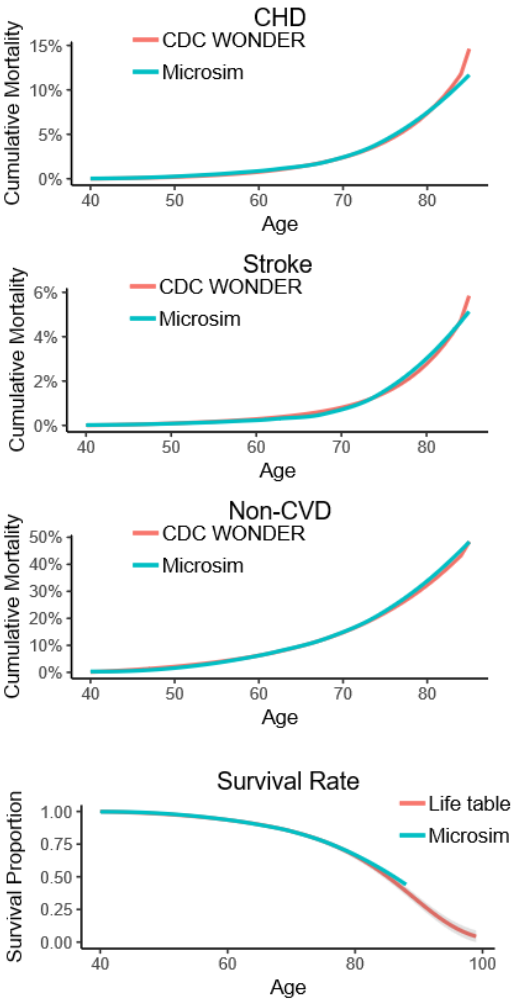
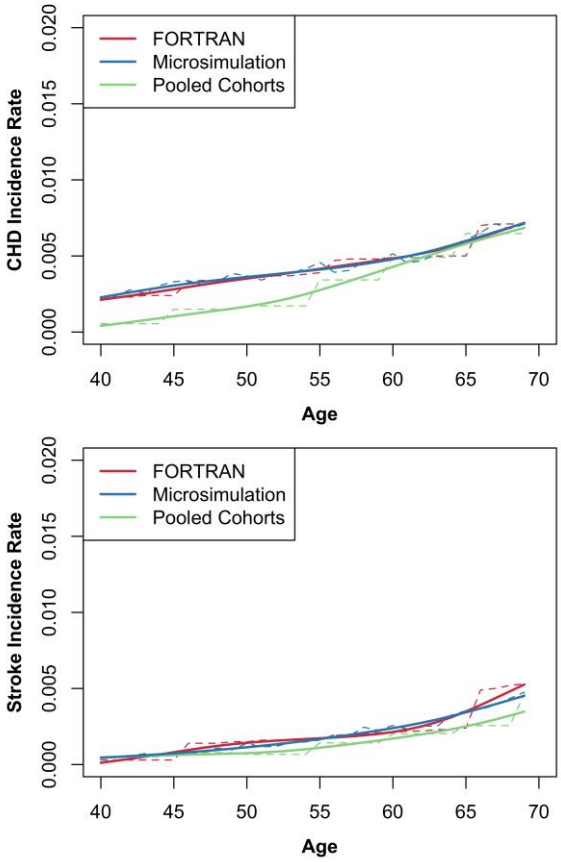
eFigure 2. Validation of the CVD Policy Model Microsimulation Version

A) Women





CDC WONDER – Centers for Disease Control and Prevention's Wide-ranging ONline Data for Epidemiologic Research, CHD – coronary heart disease, CVD – cardiovascular disease.

Notes: The figures compare the outputs of the CVD Policy Model microsimulation version to: (1) estimated incidence rate of CHD and stroke from the traditional CVD Policy Model, base year: 2010 (upper two left panels), (2) cumulative CHD and stroke mortality from CDC WONDER data (upper two right panels), 1999-2016 (3) survival rate in US life tables (lower left panel), base year: 2014 and (4) incidence rate of non-CVD mortality from CDC Wonder data, 1999-2014.

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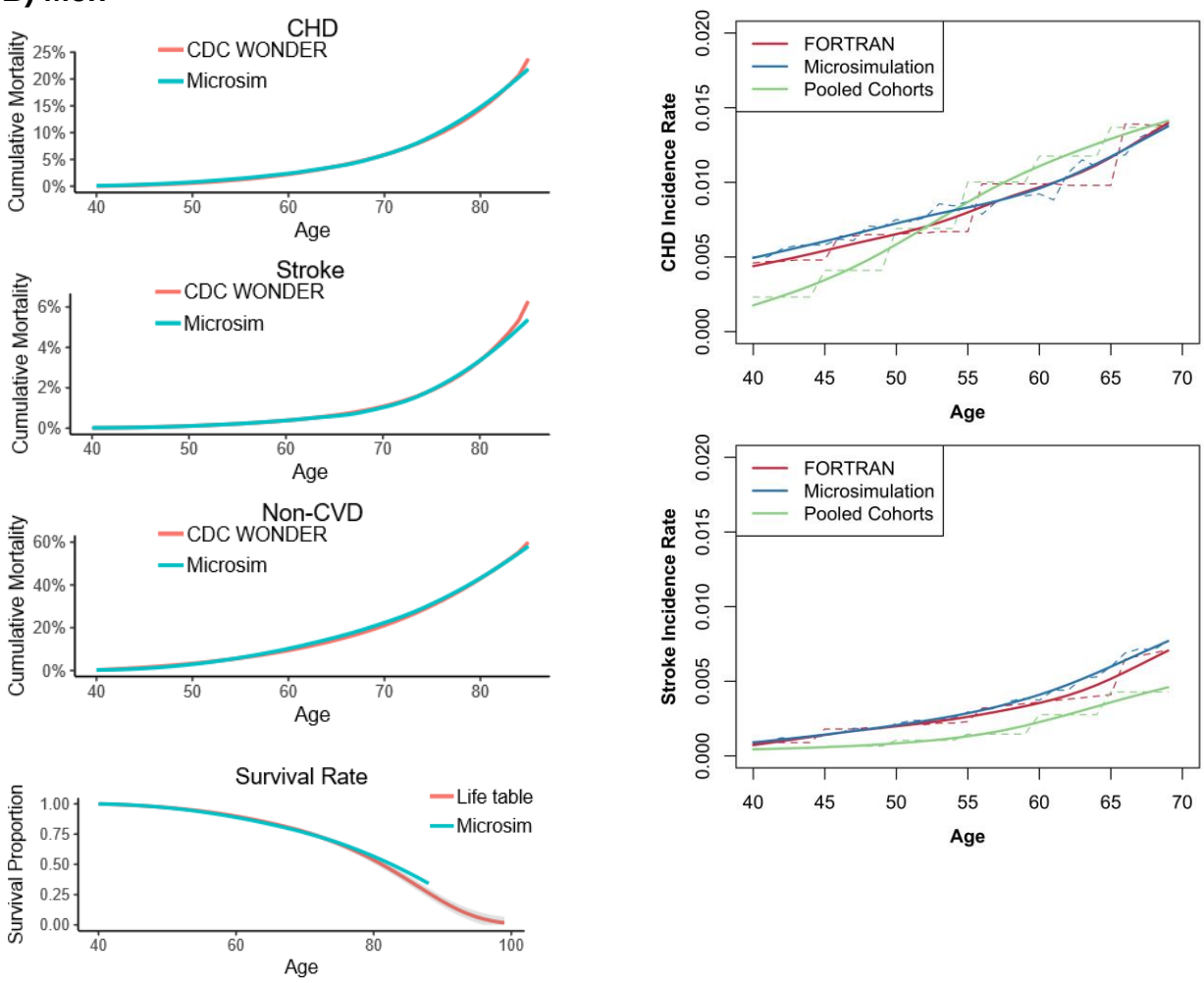
B) Men



CDC WONDER – Centers for Disease Control and Prevention's Wide-ranging ONline Data for Epidemiologic Research, CHD – coronary heart disease, CVD – cardiovascular disease.

Notes: The figures compare the outputs of the CVD Policy Model microsimulation version to: (1) estimated incidence rate of CHD and stroke from the traditional CVD Policy Model (upper two left panels), (2) cumulative CHD and stroke mortality from CDC WONDER data (upper two right panels), (3) survival rate in US life tables (lower left panel), and (4) incidence rate of non-CVD mortality from CDC Wonder data.

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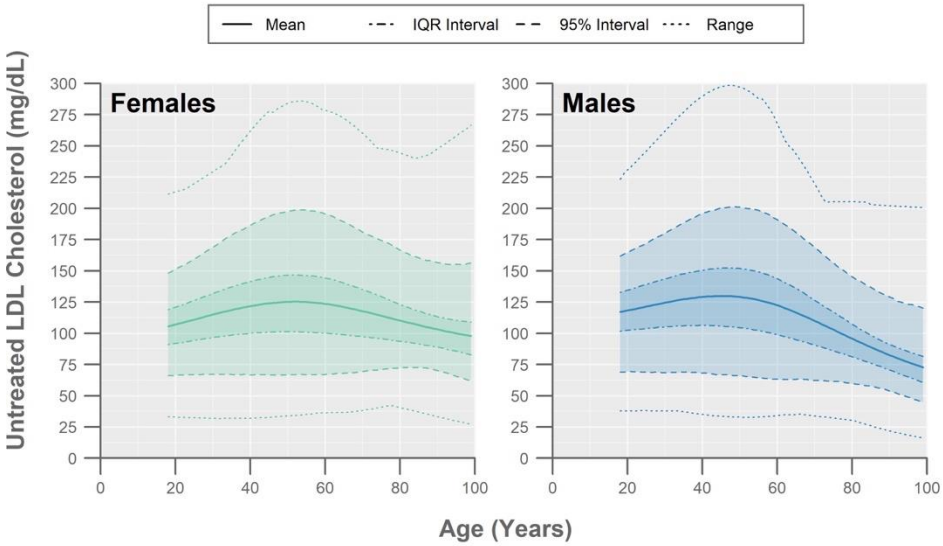
eFigure 3. Untreated LDL Cholesterol Lifetime Trajectory



IQR – Interquartile Range; LDL – low-density lipoprotein; 95% Interval – 2.5th to 97.5th percentile.

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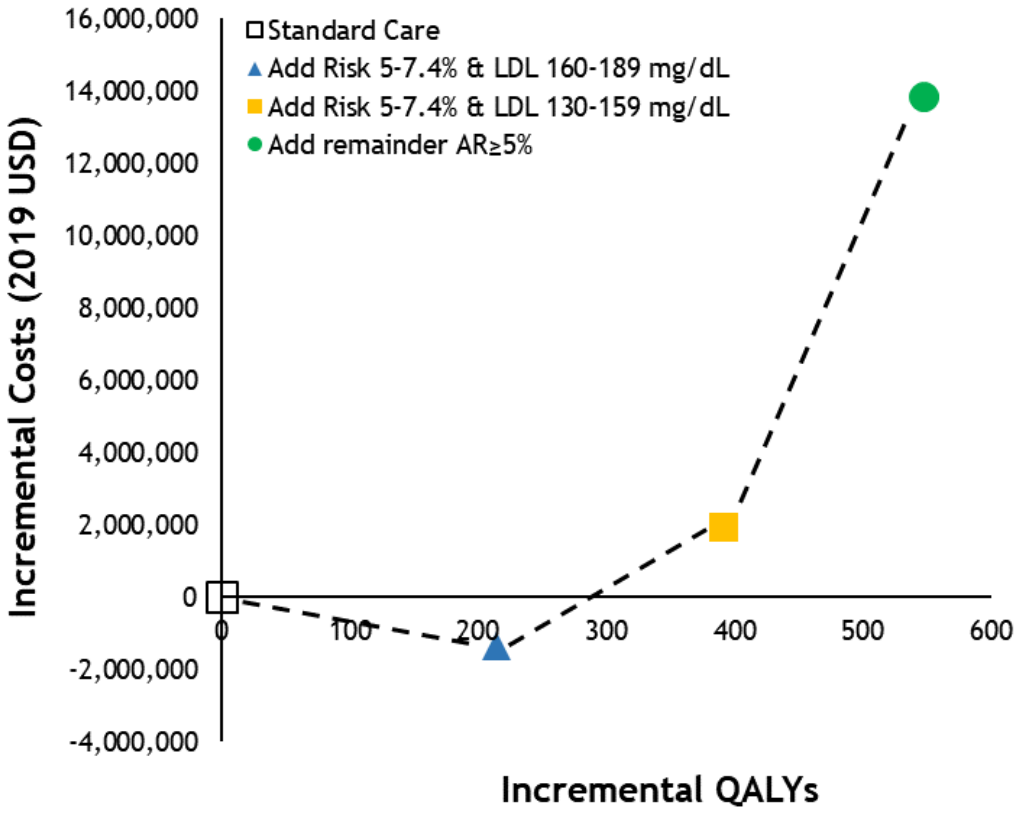
eFigure 4. Cost-Effectiveness Plane for Base Case Analysis

A) Women



AR_{10} – 10-year atherosclerotic cardiovascular disease risk, LDL-C low-density lipoprotein cholesterol, QALYs – quality-adjusted life years.

Figure shows the incremental costs and quality-adjusted life years of each strategy compared to standard care. Strategies that are in the fourth quadrant are cost-saving relative to standard care; strategies in the first quadrant cost more and are more effective than standard care. The slope of the line between each strategy indicates the incremental cost-effectiveness ratio.

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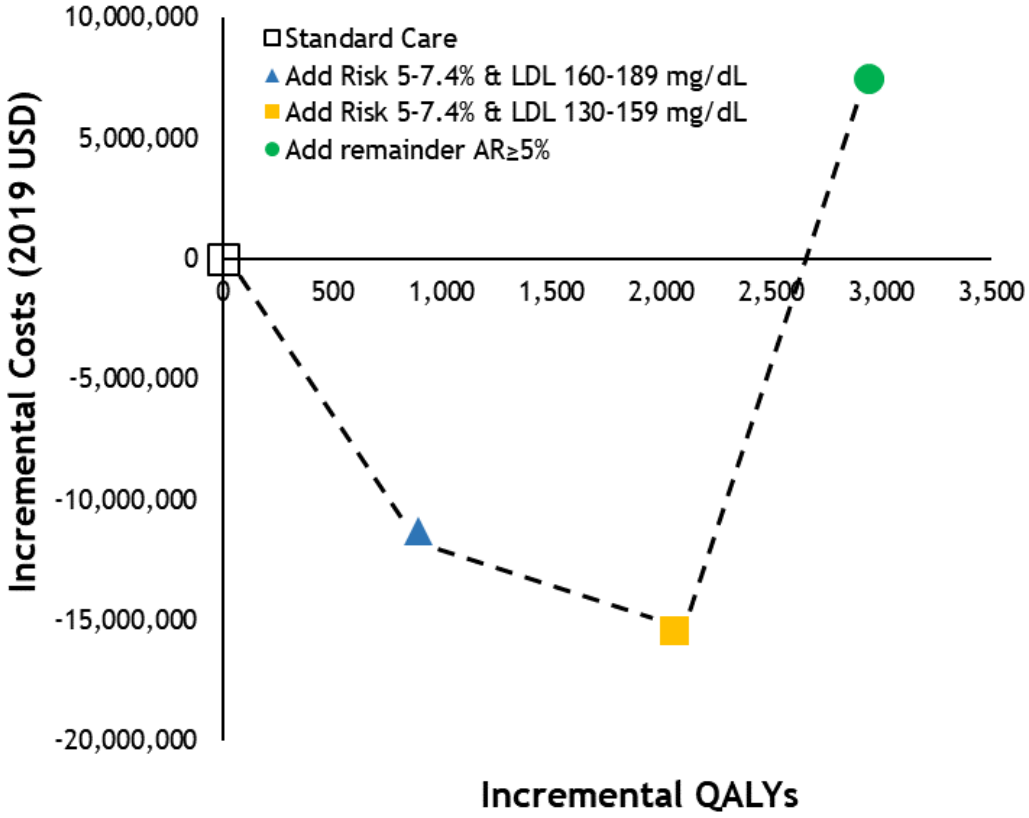
B) Men



AR_{10} – 10-year atherosclerotic cardiovascular disease risk, LDL-C low-density lipoprotein cholesterol, QALYs – quality-adjusted life years.

Figure shows the incremental costs and quality-adjusted life years of each strategy compared to standard care. Strategies that are in the fourth quadrant are cost-saving relative to standard care; strategies in the first quadrant cost more and are more effective than standard care. The slope of the line between each strategy indicates the incremental cost-effectiveness ratio.

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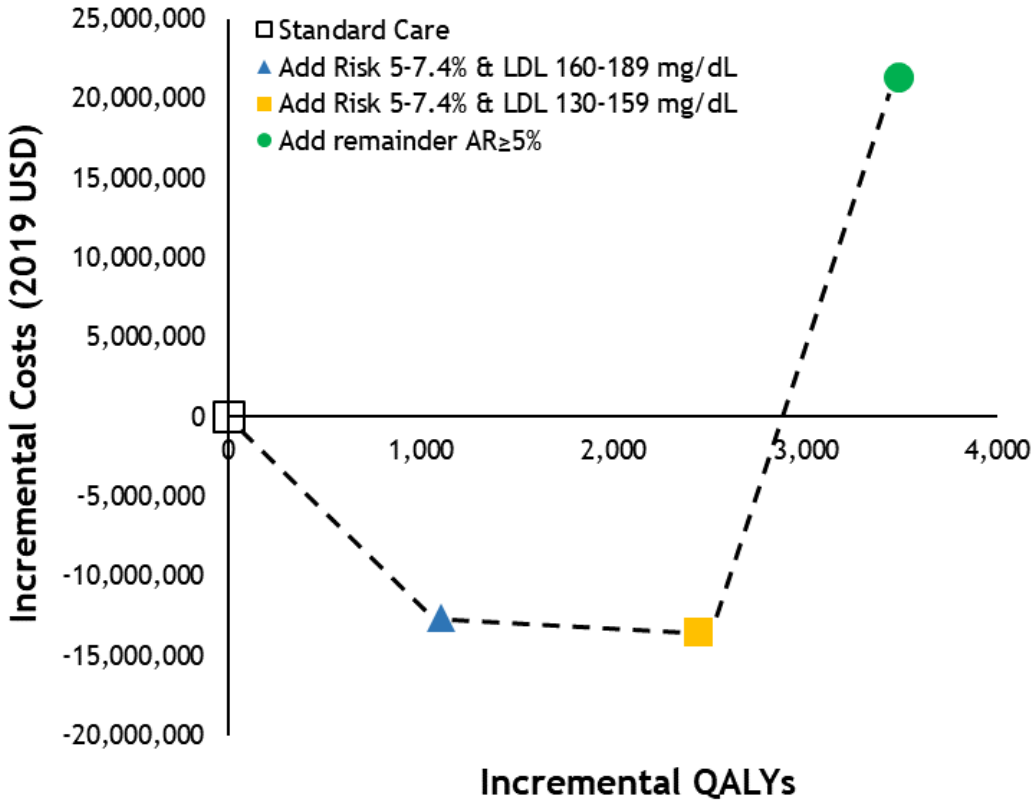
C) Combined women and men



AR_{10} – 10-year atherosclerotic cardiovascular disease risk, LDL-C low-density lipoprotein cholesterol, QALYs – quality-adjusted life years.

Figure shows the incremental costs and quality-adjusted life years of each strategy compared to standard care. Strategies that are in the fourth quadrant are cost-saving relative to standard care; strategies in the first quadrant cost more and are more effective than standard care. The slope of the line between each strategy indicates the incremental cost-effectiveness ratio.

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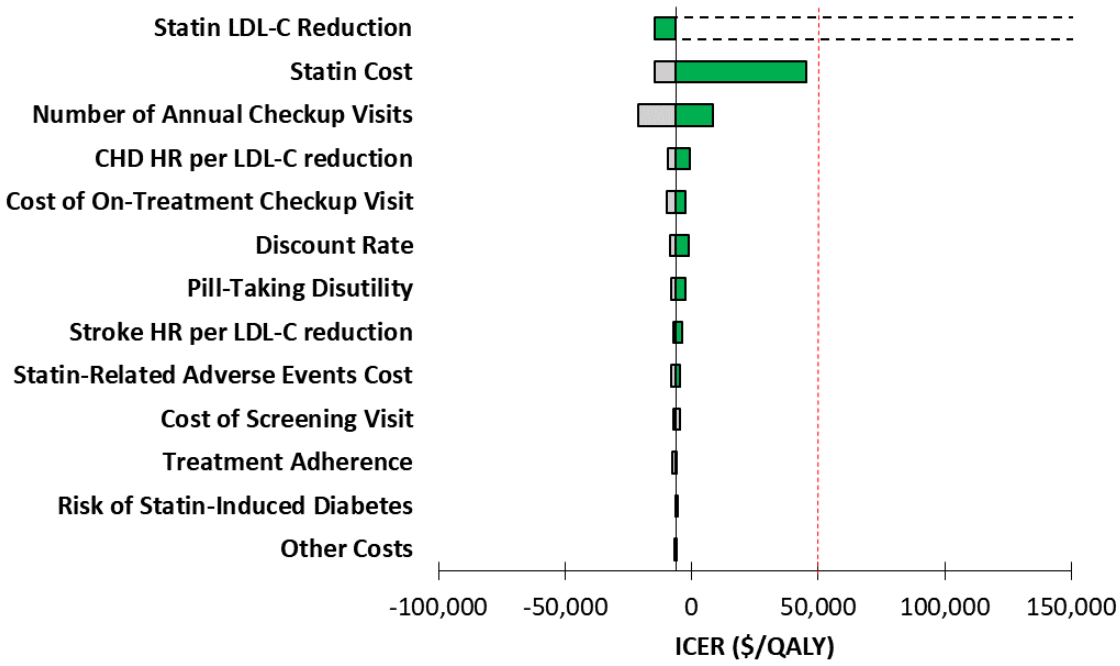
eFigure 5. One-Way Sensitivity Analysis Tornado Diagram

A) Women: Standard care (SC; treat AR_{10} ≥7.5%, LDL-C ≥190 mg/dL, and diabetes) vs. SC + treat borderline risk (AR_{10} 5.0-7.4%) with LDL-C 160-189 mg/dL.



AR_{10} – 10-year atherosclerotic cardiovascular disease risk, CHD – coronary heart disease, HR – hazard ratio, ICER – incremental cost-effectiveness ratio, LDL-C low-density lipoprotein cholesterol, QALY – quality-adjusted life years, SC – standard care.

Notes: The tornado diagrams show the impact that independently changing the model parameters has on the incremental cost-effectiveness ratio (ICER) between two strategies. Upper and lower values employed in analysis presented in main text Table 1. Green bars represent ICER for upper parameter input value, white bars represent ICER for lower parameter input value. Dotted red line shows willingness-to-pay of $50,000 per QALY gained. Treatment decision was strictly dominated (more costs, less QALYs) when applying the lower estimate for LDL-C reduction from statin therapy.

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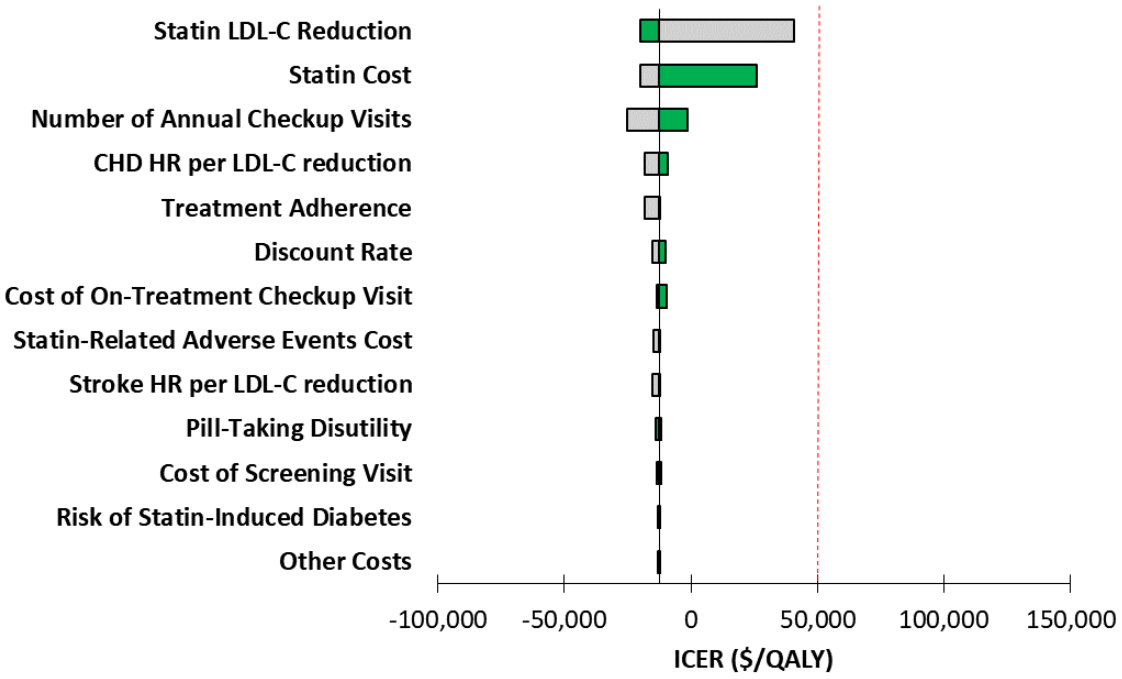
B) Men: SC vs. SC + treat borderline risk (AR_{10} 5.0-7.4%) with LDL-C 160-189 mg/dL.



AR_{10} – 10-year atherosclerotic cardiovascular disease risk, CHD – coronary heart disease, HR – hazard ratio, ICER – incremental cost-effectiveness ratio, LDL-C low-density lipoprotein cholesterol, QALY – quality-adjusted life years, SC – standard care.

Notes: The tornado diagrams show the impact that independently changing the model parameters has on the incremental cost-effectiveness ratio (ICER) between two strategies. Upper and lower values employed in analysis presented in main text Table 1. Green bars represent ICER for upper parameter input value, white bars represent ICER for lower parameter input value. Dotted red line shows willingness-to-pay of $50,000 per QALY gained.

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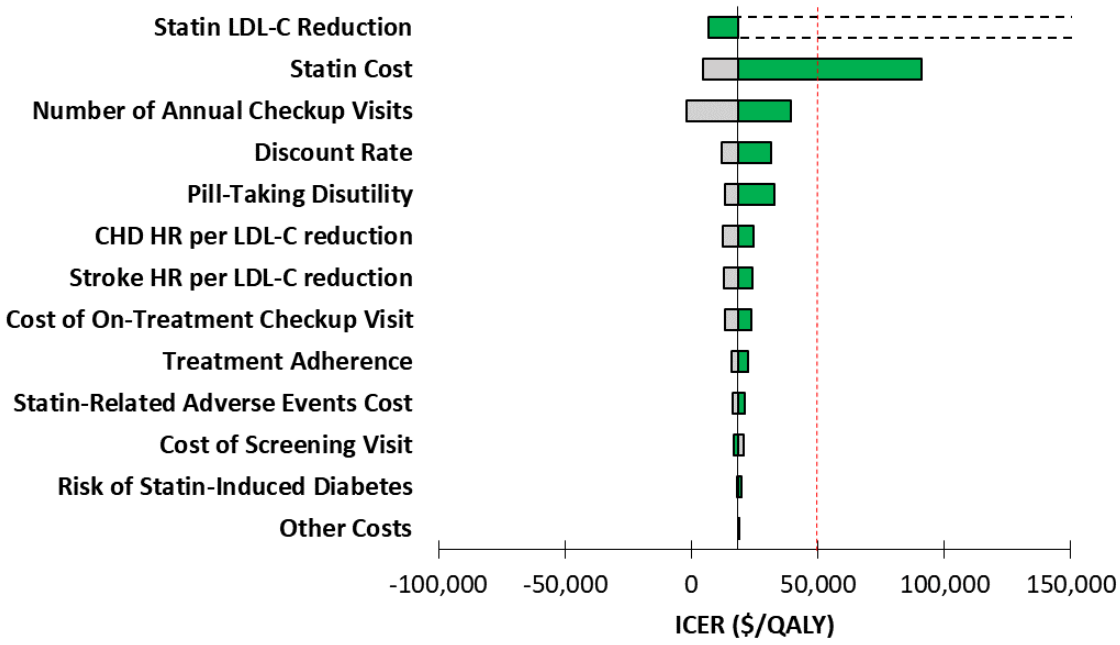
C) Women: SC + treat borderline risk with LDL-C 160-189 mg/dL vs. SC + treat borderline risk with LDL-C 130-159 mg/dL.



AR_{10} – 10-year atherosclerotic cardiovascular disease risk, CHD – coronary heart disease, HR – hazard ratio, ICER – incremental cost-effectiveness ratio, LDL-C low-density lipoprotein cholesterol, QALY – quality-adjusted life years, SC – standard care.

Notes: The tornado diagrams show the impact that independently changing the model parameters has on the incremental cost-effectiveness ratio (ICER) between two strategies. Upper and lower values employed in analysis presented in main text Table 1. Green bars represent ICER for upper parameter input value, white bars represent ICER for lower parameter input value. Dotted red line shows willingness-to-pay of $50,000 per QALY gained. Treatment decision was strictly dominated (more costs, less QALYs) when applying the lower estimate for LDL-C reduction from statin therapy.

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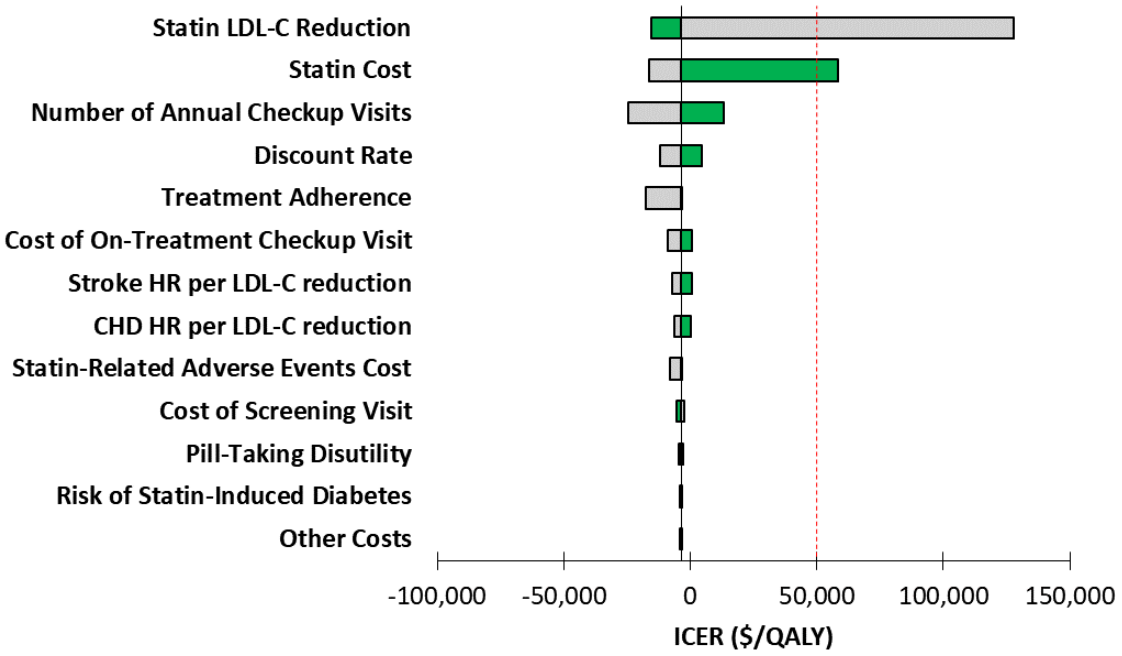
D) Men: SC + treat borderline risk with LDL-C 160-189 mg/dL vs. SC + treat borderline risk with LDL-C 130-159 mg/dL.



AR_{10} – 10-year atherosclerotic cardiovascular disease risk, CHD – coronary heart disease, HR – hazard ratio, ICER – incremental cost-effectiveness ratio, LDL-C low-density lipoprotein cholesterol, QALY – quality-adjusted life years, SC – standard care.

Notes: The tornado diagrams show the impact that independently changing the model parameters has on the incremental cost-effectiveness ratio (ICER) between two strategies. Upper and lower values employed in analysis presented in main text Table 1. Green bars represent ICER for upper parameter input value, white bars represent ICER for lower parameter input value. Dotted red line shows willingness-to-pay of $50,000 per QALY gained.

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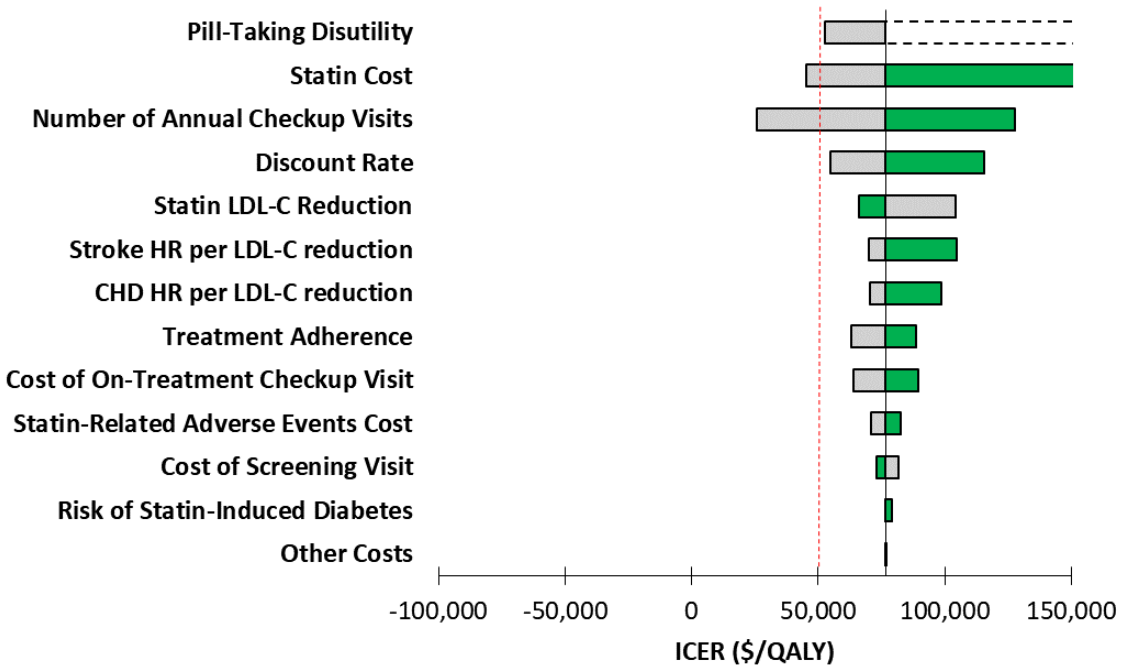
E) Women: SC + treat borderline risk with LDL-C 160-189 mg/dL vs. SC + treat all borderline risk.



AR_{10} – 10-year atherosclerotic cardiovascular disease risk, CHD – coronary heart disease, HR – hazard ratio, ICER – incremental cost-effectiveness ratio, LDL-C low-density lipoprotein cholesterol, QALY – quality-adjusted life years, SC – standard care.

Notes: The tornado diagrams show the impact that independently changing the model parameters has on the incremental cost-effectiveness ratio (ICER) between two strategies. Upper and lower values employed in analysis presented in main text Table 1. Green bars represent ICER for upper parameter input value, white bars represent ICER for lower parameter input value. Dotted red line shows willingness-to-pay of $50,000 per QALY gained. Treatment decision was strictly dominated (more costs, less QALYs) when applying the upper estimate for pill-taking disutility. ICER associated with upper estimate of statin cost was $673,700 per QALY gained.

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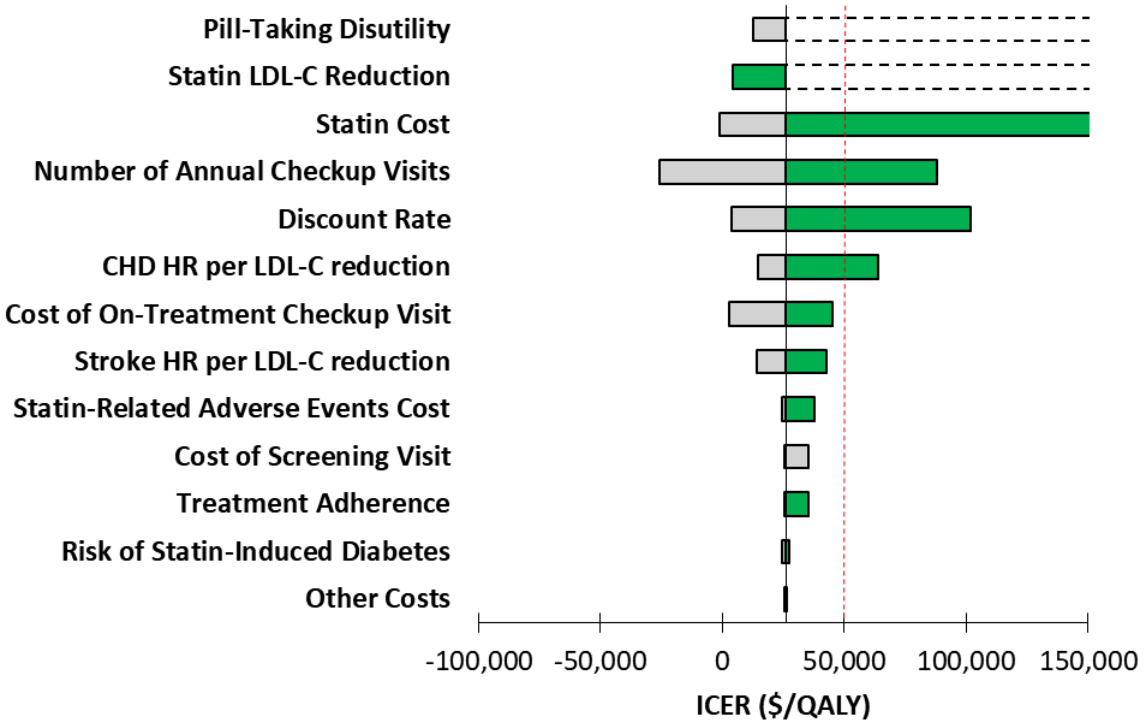
F) Men: SC + treat borderline risk with LDL-C 160-189 mg/dL vs. SC + treat all borderline risk.



AR_{10} – 10-year atherosclerotic cardiovascular disease risk, CHD – coronary heart disease, HR – hazard ratio, ICER – incremental cost-effectiveness ratio, LDL-C low-density lipoprotein cholesterol, QALY – quality-adjusted life years, SC – standard care.

Notes: The tornado diagrams show the impact that independently changing the model parameters has on the incremental cost-effectiveness ratio (ICER) between two strategies. Upper and lower values employed in analysis presented in main text Table 1. Green bars represent ICER for upper parameter input value, white bars represent ICER for lower parameter input value. Dotted red line shows willingness-to-pay of $50,000 per QALY gained. Treatment decision was strictly dominated (more costs, less QALYs) when applying the upper estimate for pill-taking disutility and lower estimate for LDL-C reduction from statin therapy. ICER associated with upper estimate of statin cost was $373,600 per QALY gained.

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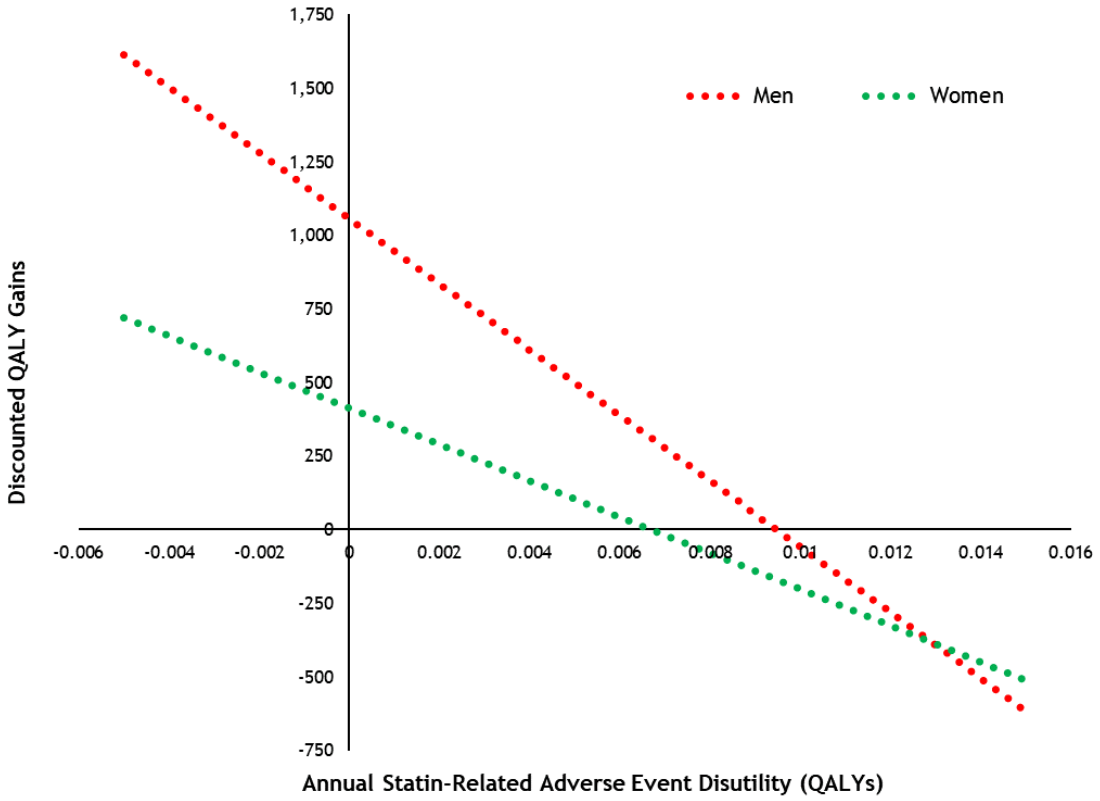
eFigure 6. One-Way Sensitivity Analysis of Statin-Related Adverse Event Disutility on Discounted QALY Gains for Standard Care vs Standard Care Plus Treat LDL 160-189 mg/dL



LDL-C – low-density lipoprotein cholesterol, QALY – quality-adjusted life years.

The figure shows the impact changing the annual statin-related adverse event disutility has on the lifetime discounted quality-adjusted life years gained in cohort of 500,000 women and 500,000 men, respectively, when comparing initiation of statins under standard care to standard care plus AR_{10} ≥5% and an LDL-C 160-189 mg/dL.

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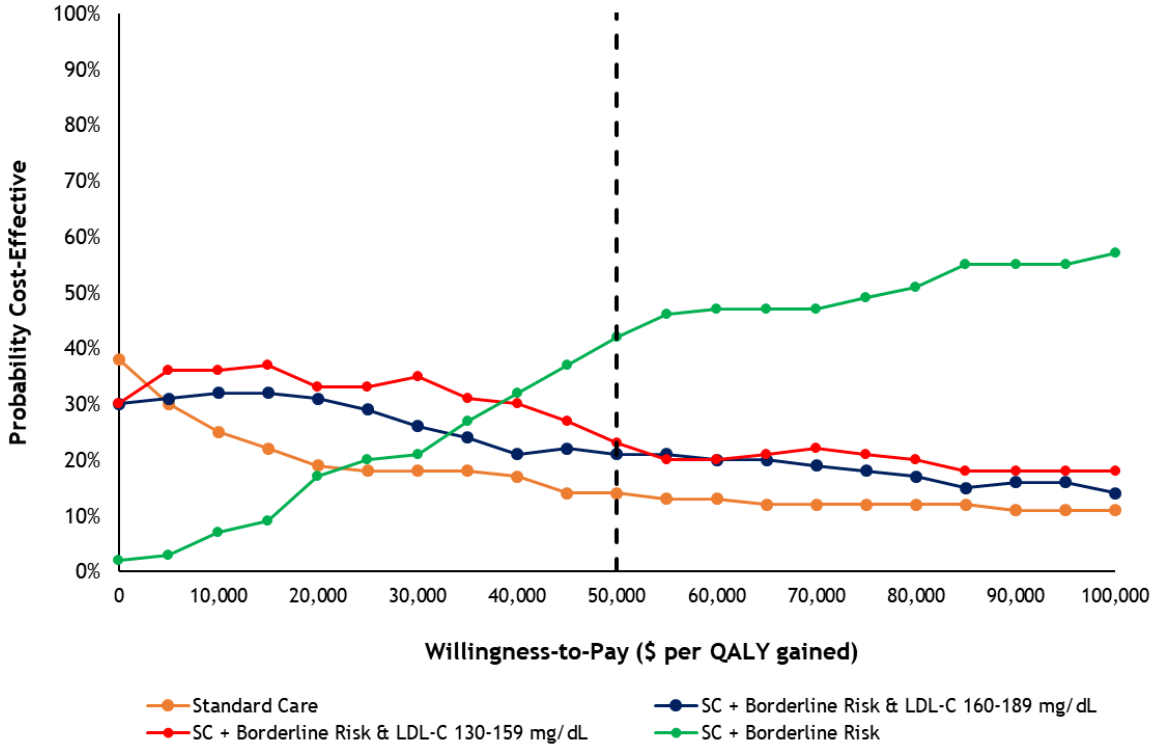
eFigure 7. Cost-Effectiveness Acceptability Curve

A) Women



AR_{10} – 10-year atherosclerotic cardiovascular disease risk, Borderline risk - AR_{10} 5.0-7.4%, LDL – low-density lipoprotein cholesterol, QALY – quality-adjusted life year, SC – standard care.

The figures show the probability that each strategy is cost-effective as the willingness to pay for a quality-adjusted life year (QALY) changes. The dashed black line indicates the commonly accepted willingness-to-pay threshold of $50,000/QALY.

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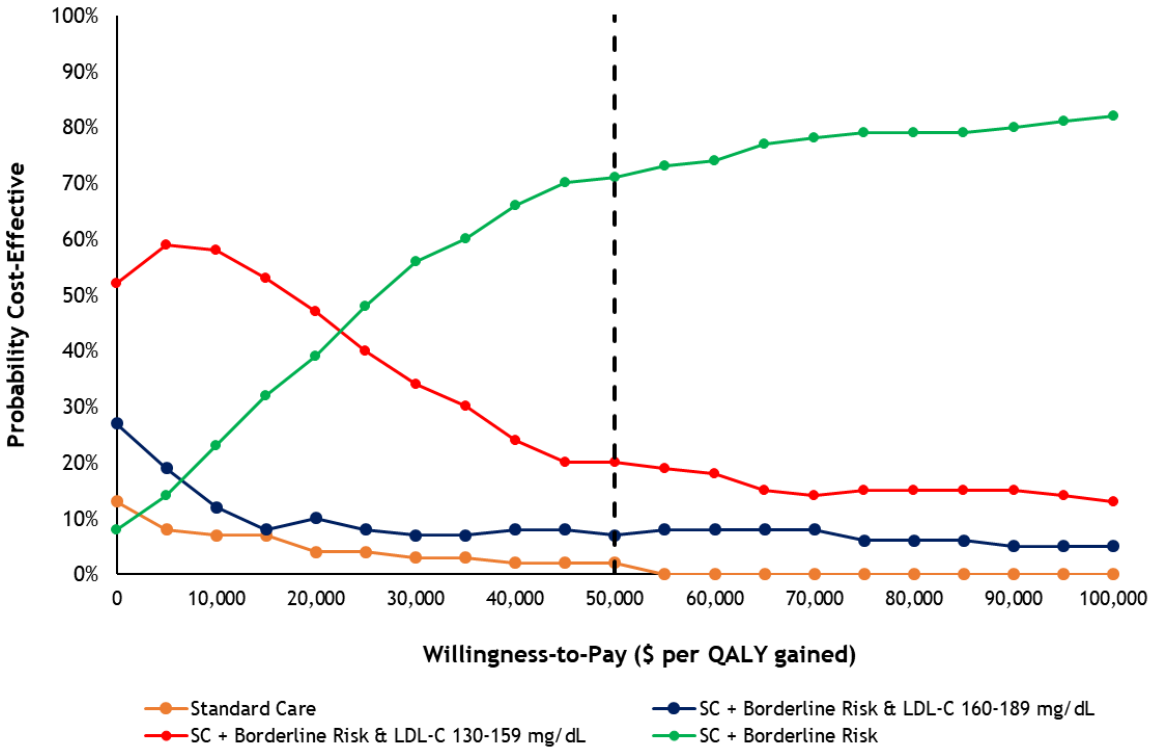
B) Men



AR_{10} – 10-year atherosclerotic cardiovascular disease risk, Borderline risk - AR_{10} 5.0-7.4%, LDL – low-density lipoprotein cholesterol, QALY – quality-adjusted life year, SC – standard care.

The figures show the probability that each strategy is cost-effective as the willingness to pay for a quality-adjusted life year (QALY) changes. The dashed black line indicates the commonly accepted willingness-to-pay threshold of $50,000/QALY.

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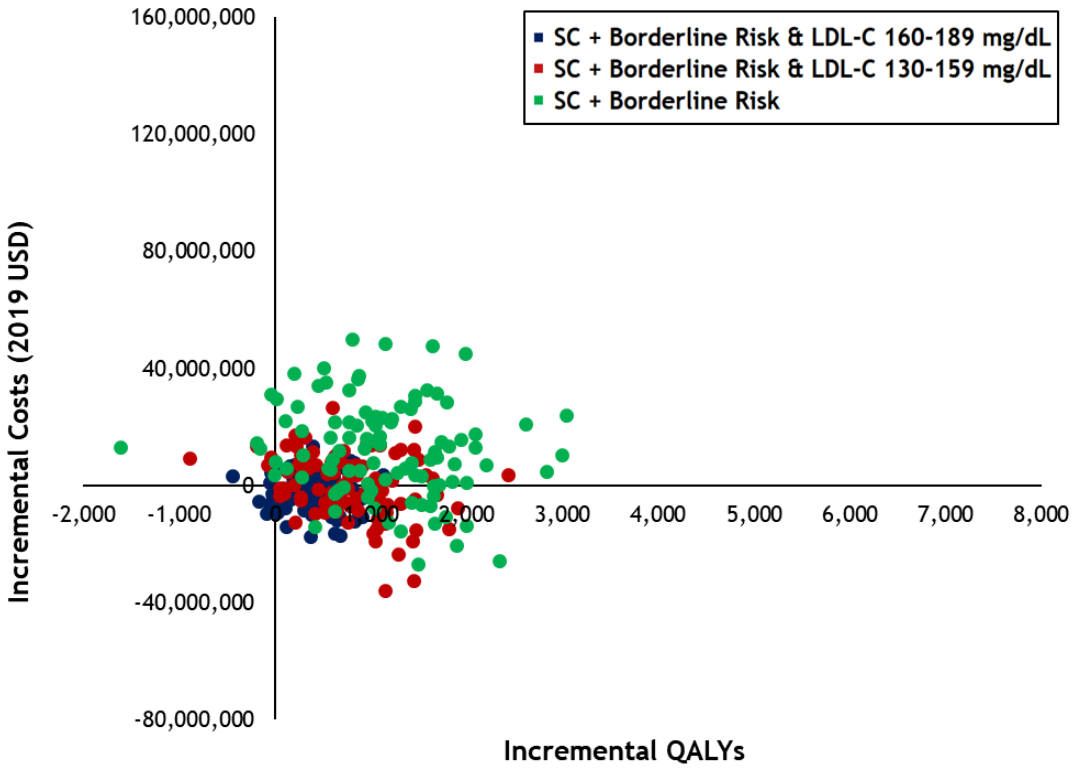
eFigure 8. Incremental Cost-Effectiveness Scatter Plot

A) Women



LDL – low-density lipoprotein cholesterol, QALYs – quality-adjusted life years, SC – standard care.

Notes: The figures show the results of the 500 probabilistic iterations of the model. Each dot indicates the incremental costs and incremental effectiveness of the strategy relative to standard care in one iteration of the model.

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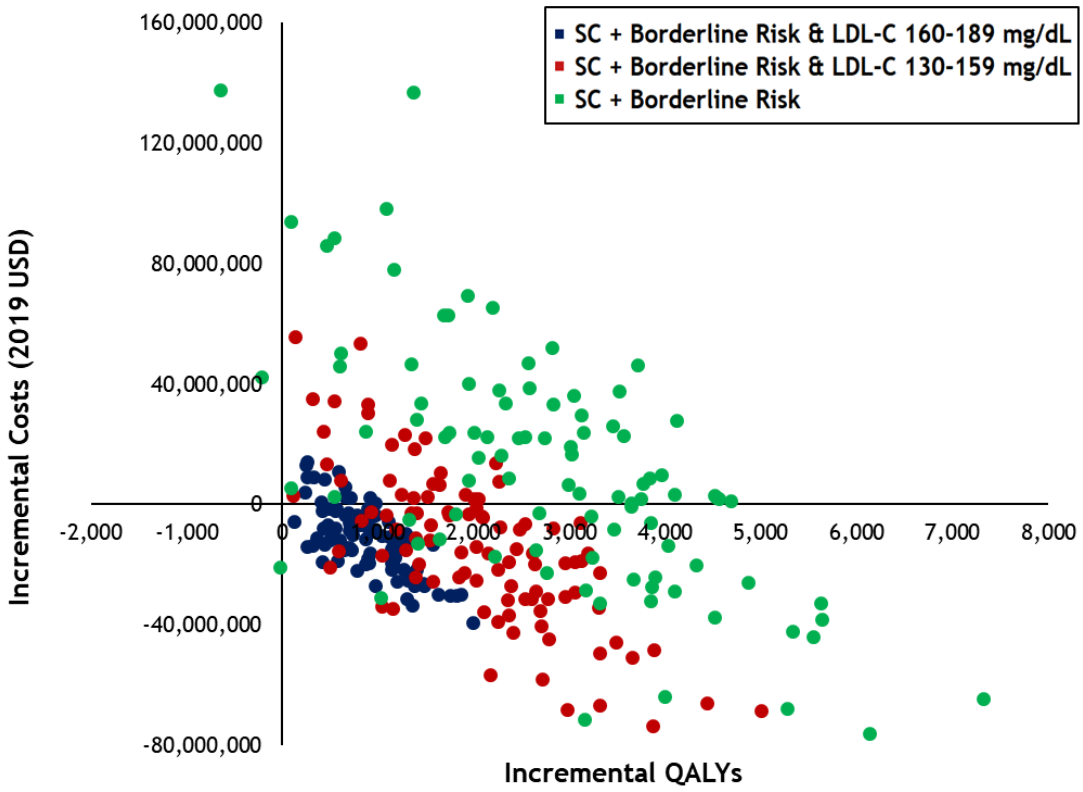
B) Men



LDL – low-density lipoprotein cholesterol, QALYs – quality-adjusted life years, SC – standard care.

Notes: The figures show the results of the 500 probabilistic iterations of the model. Each dot indicates the incremental costs and incremental effectiveness of the strategy relative to standard care in one iteration of the model.

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