

Supplementary Online Content

Pandya A, Sy S, Cho S, Weinstein MC, Gaziano TA. Cost-effectiveness of 10-year risk thresholds for initiation of statin therapy for primary prevention of cardiovascular disease. *JAMA*. doi:10.1001/jama.2015.6822.

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

eMethods

The Cardiovascular Disease Policy Model (CVDPM)

The CVDPM, coded in C++, integrates information on the associations between CVD risk factors and incidence, the prevalence of risk factors in the population, the natural and treated history of disease, and the effects of CVD on survival, quality of life, and medical care cost. The model is designed to be able to evaluate a wide range of cardiovascular disease prevention and treatment policies. It is designed to produce results for cost-effectiveness, comparative effectiveness, and projection analyses.

Model Population

The model is populated with a list of individuals with accompanying risk factor data. The CVD risk factors necessary to run the model are: sex, age, systolic blood pressure, total cholesterol, HDL cholesterol, body-mass index (BMI), smoking status, and diabetes status. We included history of CVD, LDL cholesterol, and race (African American or other) for this analysis. The model samples from the patient list, taking the initial set of patient risk factor characteristics for a drawn individual and simulating every subsequent year of the individual's life using Monte Carlo micro-simulation techniques and common random numbers.¹ Three main events occur each model cycle (one-year cycle length): 1) updating of the risk factors (e.g. an increase in systolic blood pressure); 2) potential transitions into a CVD health state; and 3) preventative interventions (i.e. screening and medication). Costs and health state utilities are also computed for each individual every year. After an individual's remaining lifespan is simulated with the model, a new individual is selected and added to the model population. Model population characteristics based on weighted sampling (with replacement) of individuals from the fasting data samples of the 2005-2006, 2007-2008, and 2009-2010 waves of the nationally representative National Health and Nutrition Examination Surveys (NHANES) are shown in eTable 1.²

Risk factors

Risk factors for all individuals update each model cycle. These updates were based on regressions from nine waves of cross-sectional NHANES data (data collected between 1973-2010).³ Systolic blood pressure, total and HDL cholesterol, and diabetes (statin-induced or otherwise) update every cycle (i.e., year) in the model. Updates were based on regression coefficients for age and year from the NHANES analysis. Systolic blood pressure and total cholesterol decrease with time and increase with age; HDL cholesterol and the risk of diabetes increase with time and age. For example, holding all other factors constant, a 60-year-old individual in 2010 would be expected to have higher systolic blood pressure compared to an identical 60-year-old individual in 2020; similarly, a 60-year-old individual in 2020 would be expected to have higher systolic blood pressure compared to an identical (except for age) 50-year-old individual in 2020. All other individual characteristics, such as smoking and blood pressure treatment, do not change from baseline in the model.

Transitions

The health states in the CVDPM are: Disease Free (DF), Coronary Heart Disease (CHD) or Cerebrovascular Accident (CVA) events, and death. The CHD events we modeled are myocardial infarction (MI), angina, and resuscitated cardiac arrest (RCA). The MI and angina health states are further classified to with and without revascularization, either with percutaneous coronary intervention (PTCI) or coronary artery bypass graft (CABG). At any given point in time, a simulated individual can only be in one health state. We also classify disease states as acute or post 1st-year (or chronic), with the first year a patient is in a disease state considered acute, and every subsequent year a patient remains in the same disease state as post 1st-year. A patient cannot return to the DF state after transitioning into a chronic CVD state. eFigures 1a and 1b show simplified schematics of how a DF individual can transition into other health states in the model. There are no repeat RCA events due to lack of data sources needed to inform this specific model input and because of the high case fatality of RCA events.

Individuals with no prior history of CVD enter into the model as DF, and those with prior history enter into the chronic state of that particular CVD event. The probability that a DF individual transitions into a CVA or CHD health state is derived from calibrated risk equations stemming from the Framingham Study, which factor in individual's risk factors, and are subsequently converted to an event probability for the model.^{4,5} Individuals can die from a non-CVD cause while in any health state, as well as a CVD-specific cause while in a CVD state. Individuals can also have repeat CVD events while in a CVD state. Transitions in the model are hierarchical, in which an individual faces the probability of the more severe events before less severe ones. For example, a DF individual would first face the probability of a non-CVD death, then a CVA event, and finally a CHD event. Likewise, an individual in the chronic MI state would first face the probability of a non-CVD death, then a chronic (post 1st-year) MI death, then a CVA event, and finally a repeat MI event. If an individual has had multiple CVD events, the individual remains in the health state of the more severe event. Although there are some combination health states (MI-CABG and Angina-CABG), we did not include all possible health state combinations. However, the micro-simulation model does track history of multiple events (for example, if a patient has an MI and stroke), and this specific disease history can affect factors such as post-1st year mortality in a CVD health state. Transition probabilities are either applied uniformly to all individuals or are age- and/or sex-specific. eTable 2 lists the transition probabilities used in the CVDPM.

Interventions

Adults without CVD are eligible to be screened for ASCVD risk at baseline and every five years in the model. The screening compliance rate (60%) came from a study that analyzed the National Ambulatory Medical Care Survey (NAMCS) data.⁶ The study reported screening rates for different preventative services provided at physician offices to patients, which we considered to be the same as screening compliance. Since the study reported cholesterol screening rates for both patients at risk of CVD and patients without risk, we calculated the weighted average for use in our model. Screened

individuals with 10-year ASCVD risk greater than the threshold being evaluated (current recommendations set the threshold at >7.5%) are eligible for statin therapy. Statin compliance in the primary prevention was estimated using the Greving JP, et al, study.^{7,8} The article presents a trial-based compliance rate and a real-world compliance rate for the 1st, 2nd, and 3rd year (values of 67%, 53%, and 45%, respectively). We divided the real-world compliance by the trial-based compliance for each year:

$$\text{Statin compliance rate} = \frac{\text{real - world compliance rate}}{\text{trial - based compliance rate}}$$

We divided these (inflated) compliance rates because the relative risks from statin trials includes non-compliance. Benefits, risks, and costs of statin treatment were all adjusted for compliance rates. We also applied the costs of a general practitioner and laboratory test every year for patients taking statins; these costs were not affected by compliance rates.

We used two approaches for modeling statin effectiveness. In our base-case analysis, we assumed the average reduction in LDL cholesterol (1.09 absolute mmol/L reduction) from the Cholesterol Treatment Trialists' (CTT) Collaborators meta-analysis on large statin trials; this approach corresponds to relative risk reductions of 0.25 and 0.19 for CHD and stroke, respectively.⁹ In a sensitivity analysis, we applied a proportional reduction in LDL cholesterol (29% reduction on LDL level) and applied relative risk reductions of 0.23 (CHD) and 0.17 (stroke) for each mmol/L LDL reduced (all data from the CTT meta-analysis). Therefore, individuals with higher LDL would experience more statin benefit (larger relative risk reductions) compared to individuals with lower LDL levels using the second approach described above. The differences of using these approaches for a model-based cost-effectiveness analysis have been previously evaluated by van Kempen et al., who found no difference optimal statin initiation policies using either approach.¹⁰

Model calibration and validation

Current disease modeling recommendations highlight the importance of model calibration and validation for assessing model quality.¹¹ Calibration is the systematic process of adjusting model inputs that were estimated with some uncertainty such that the resulting modeling outputs better reflect setting-specific observed disease outcomes.¹² Internal validity is considered a necessary condition for model quality; it assesses the ability of the model to replicate the data that was directly used to estimate key model inputs.¹¹ External validation, which is one of the strongest forms of validation^{11,13}, is the process of directly comparing model-generated results with observed outcomes (without adjusting the model to correct for any deviations from targets).

We calibrated our model-generated CHD and stroke incidence outcomes to observed rates from large U.S. cohort studies. Specifically, we used the Framingham Offspring Cohort (observation years 1980-2003) and Atherosclerosis Risk in Communities (ARIC, observation years 1987-2001) as benchmarks for age- and sex-specific CHD and stroke incidence rates.¹⁴ The composite CHD endpoint for the Framingham Offspring cohort was more inclusive (MI, angina pectoris, coronary insufficiency, or death from CHD) than CHD incidence accounted for in the model (MI, angina, cardiac arrest, or death from CHD within one year from the event); the corresponding CHD from ARIC (MI or death from CHD) was more restrictive than our model. Similarly, the criteria for stroke incidence were relatively more inclusive for Framingham (occurrence of a stroke either in-hospital examination or physician review of hospital records) than ARIC (ischemic stroke based on expert committee review of hospital records). Therefore, when model-generated rates fell outside of the upper (Framingham Offspring) and lower (ARIC) observed point estimates, we manually calibrated sex-specific CHD and/or stroke incidence parameters such that the resulting model incidence rates fell between the observed ranges. Consistent with other CHD simulation models^{15,16}, we started our calibration exercise by adjusting coefficients related to baseline risk (i.e., intercept coefficients) for the underlying CHD and stroke risk functions.^{4,5}

Beta coefficients for age were also calibrated if further adjustments were needed to meet calibration targets.

Prior to model calibration, model results under-predicted CHD (in females) and stroke (in males and females) incidence compared to the target outcomes. Specifically, model results for CVD incidence fell within 8 out of 16 age- and sex-specific observed ranges. For males, only the intercept term for the stroke risk function was adjusted during calibration. For females, the intercept terms for the CHD and stroke risk functions were adjusted, in addition to the age and age-sex interaction beta coefficients for the CHD risk function. After model calibration, 13 out of the 16 incidence targets were met. eFigures 2-5 show the sex- and age-specific incidence results for CHD and stroke before and after model calibration.

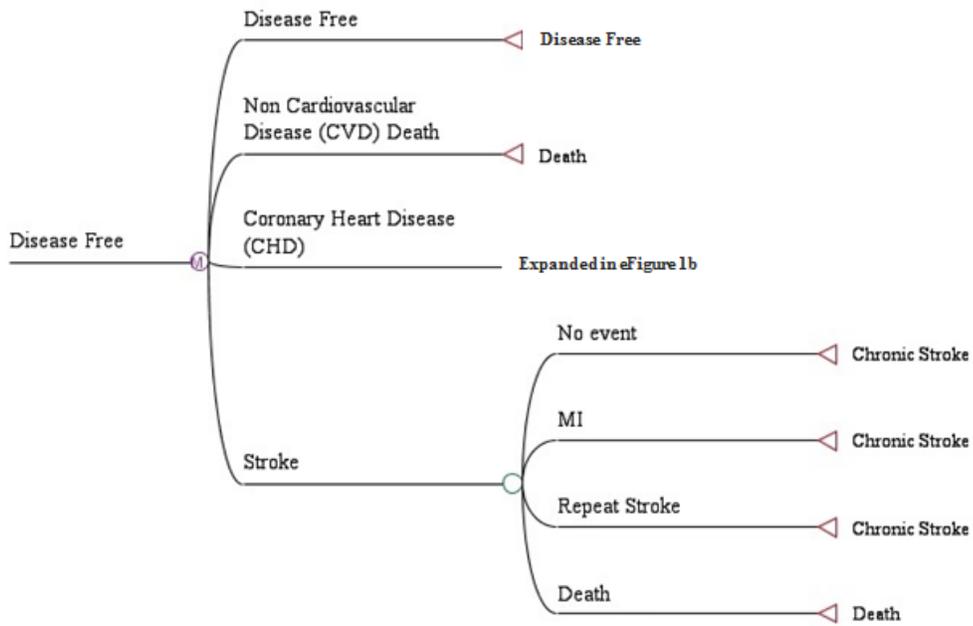
eTable 3 shows the internal and external validation results for the calibrated simulation model compared to observed mortality outcomes. Model-predicted total mortality results were within 3% of all targets with the exception of 10-year total mortality compared to the NHANES III compared, which had a 7.1% deviation (model predicted 10-year death for 8.1% of the population compared to 7.6% in the NHANES III population). CVD mortality observed in the NHANES III cohort fell within the model-predicted ranges at 5 and 10 years. We used ranges for model-predicted CVD mortality because of how mortality was estimated in chronic CVD states. Specifically, we applied multipliers to all-cause life tables for individuals in CHD and CVA health states, which do not allow for parsing of non-CVD-related and CVD-related mortality for individuals that died in chronic CVD health states. Therefore, we used acute CVD mortality (i.e., individuals that died within one year of a CVD event) and any post-event death (which includes both non-CVD-related and CVD-related mortality at any point after a CVD event) as the range for model-predicted CVD mortality in our validation analyses.

Non-healthcare costs

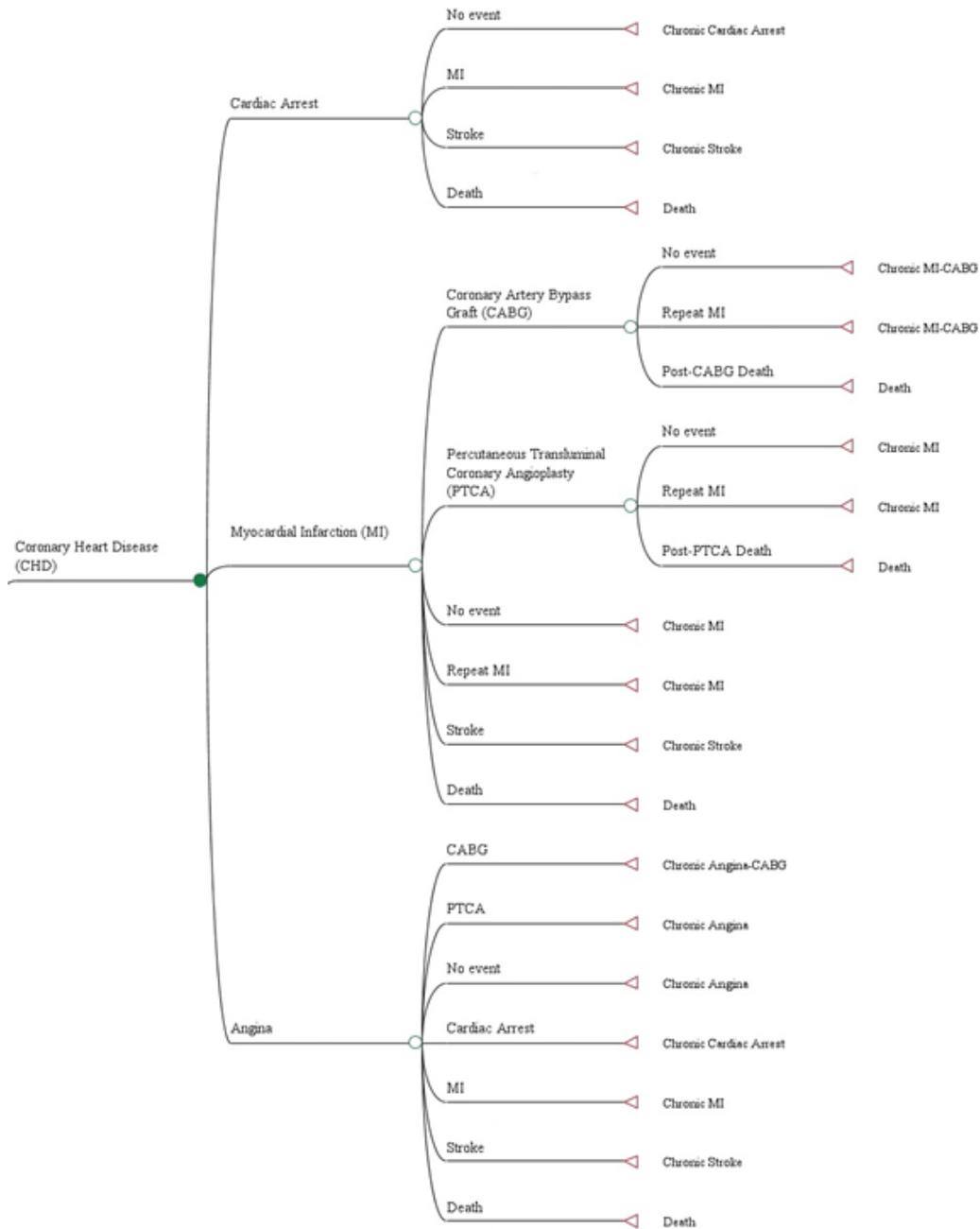
In addition to costs for screening, acute and post-1st year CVD events, and drug costs, the model includes patient travel and waiting time costs. Specifically, average travel (35 minute) and waiting times

(42 minutes) for outpatient visits were based on results from the American Time Use Survey (ATUS) by Russell et al.¹⁷ We applied these costs once per CVD screening visit (occurs once every five years for individuals in the Disease Free state), once per year for individuals in the Disease Free state taking statins (this was adjusted for statin compliance), three times in the first year of a CVD event, and two times per year for all years post-1st year after CVD events. We monetized patient time using the average wage for individuals over the age of 45 from the Bureau of Labor Statistics (\$14.40 per hour).¹⁸

eFigure 1a. Simplified depiction of CVDPM health states

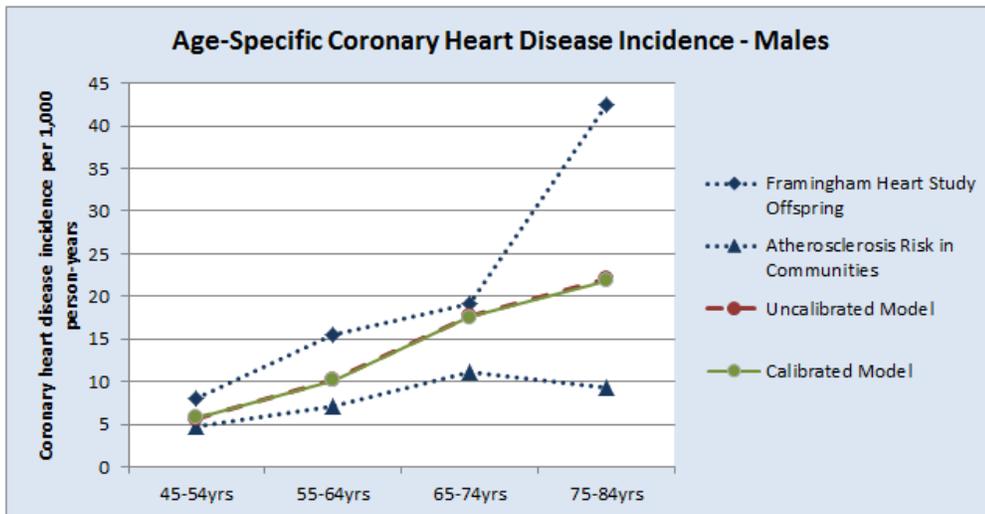


eFigure 1b. Simplified depiction of transitions from the Coronary Heart Disease (CHD) health state

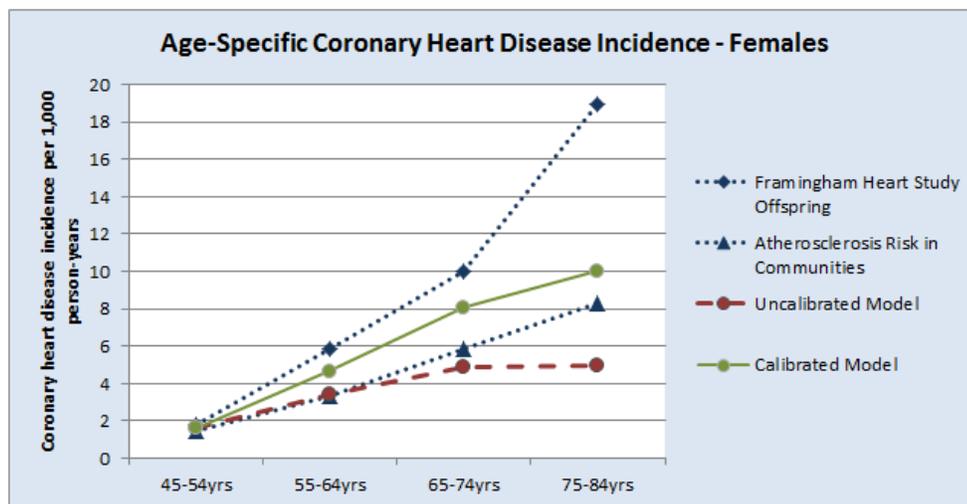


Notes: eFigures 1a and 1b were created using TreeAge Pro[®] (for illustration purposes only). In the figures, open green circles are chance nodes, which indicate events with several potential outcomes. Red triangles are terminal nodes, which show every potential ending health state for each model cycle. "Chronic" CVD events (Chronic Cardiac Arrest, Chronic MI, Chronic Angina, Chronic Stroke, etc.) refer to all time spent in cardiovascular disease health states post 1st-year of the events.

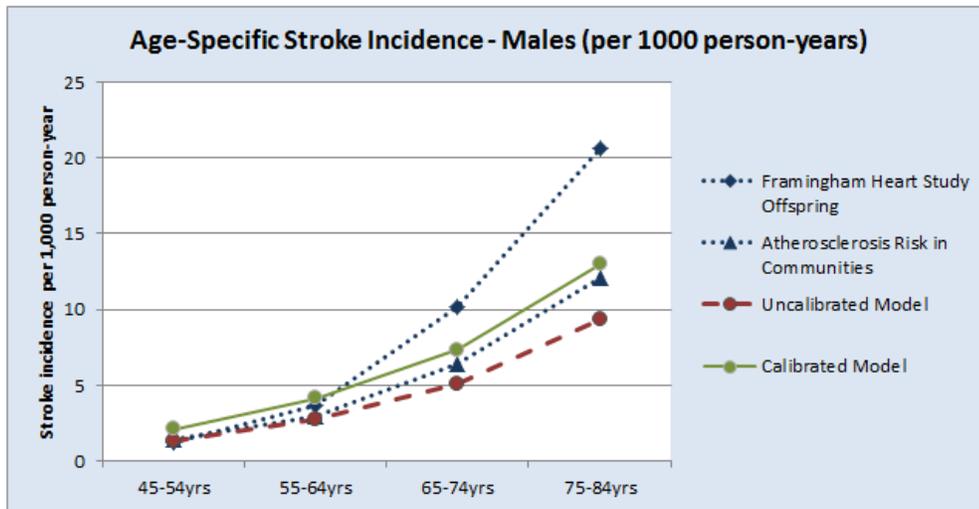
eFigure 2. Calibration results for coronary heart disease incidence, men



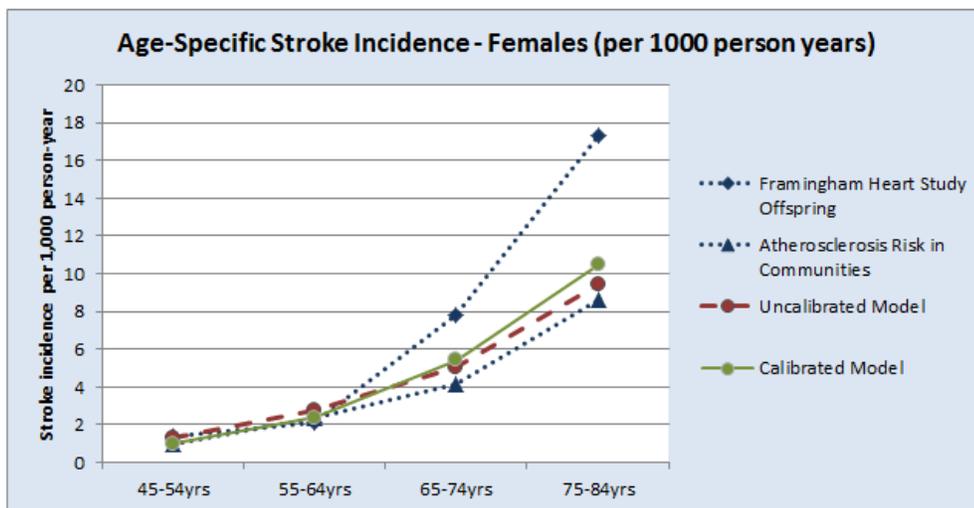
eFigure 3. Calibration results for coronary heart disease incidence, women



eFigure 4. Calibration results for stroke incidence, men



eFigure 5. Calibration results for stroke incidence, women



eTable 1. Model population characteristics (at baseline)

Sample size (n)	3,879
Female (%)	51.6
Age (years)	54.4 (9.6)
History of CVD (%)	6.6
History of diabetes (%)	14.7
LDL cholesterol >190 mg/dL(%)	3.5
10-year ASCVD risk (%)	34.0
African American (%)	9.9
Currently smoker (%)	18.7
Blood pressure treatment (%)	34.6
Systolic blood pressure (mmHg)	122.9 (18.6)
Total cholesterol (mg/dL)	202.4 (40.9)
HDL cholesterol (mg/dL)	55.7 (16.6)

Note: standard deviations shown for continuous variables shown in parentheses

eTable 2. Disease progression inputs used in the CVD micro-simulation model

Parameter	Value	Source
<i>From Disease Free State</i>		
Non-CVD death	Age- and sex-specific table	NCHS 2010 ¹⁹
CHD and stroke events	Risk factor-based equations	Wolf 1991 ⁴ , Anderson 1991 ⁵
% Cardiac Arrest	Age- and sex-specific table	Weinstein 1987 ¹⁵
% MI (males)	0.35	NHLBI 2006 ¹⁴
% MI (females)	0.20	NHLBI 2006 ¹⁴
<i>Chronic mortality (i.e., post-1st year) multipliers(i.e., relative risks) for CVD health states</i>		
Post-CHD, men <2 CHD events	1.6	Smolina 2012 ²⁰
Post-CHD, men ≥2 CHD events	3.4	Smolina 2012 ²⁰
Post-CHD, women <2 CHD events	2.1	Smolina 2012 ²⁰
Post-CHD, women ≥2 CHD events	2.5	Smolina 2012 ²⁰
Post-stroke	2.3	Dennis 1993 ²¹
<i>From Cardiac Arrest State</i>		
Acute (within 1 year) death	0.954	Nichol 2008 ²²
MI event	0.064	Assumption: same as MI
<i>From MI State</i>		
Immediate death	0.15	Go 2014 ²³
Acute death (days 30-365)	Age- specific table	Weinstein 1987 ¹⁵
Acute CABG	0.082	Fang 2010 ²⁴
Acute PTCA	0.300	Fang 2010 ²⁴
% Procedure death	0.009	Dorros 1984 ²⁵
Acute 2 nd MI (no PTCA)	0.060	Capewell 2006 ²⁶
Acute 2 nd MI (after PTCA)	0.052	BARI 1996 ²⁷
Repeat MI	0.064	Jokhadar 2004 ²⁸
<i>From MI and CABG State</i>		
Acute post-CABG death	0.027	Peterson 2004 ²⁹
Acute 2 nd MI (i.e., 2 nd MI within the one year of first MI)	0.051	BARI 1996 ²⁷
Repeat MI (i.e., repeat MIs post 1 st -year)	0.039	Jokhadar 2004 ²⁸
<i>From Angina State</i>		
Acute death	0.045	Capewell 2006 ²⁶
Acute cardiac arrest	0.006	Hsia 2008 ³⁰
Acute MI	0.035	Hemingway 2003 ³¹
Acute CABG	0.200	Ford 2007 ³²
Acute PTCA	0.300	Ford 2007 ³²
<i>From Angina and CABG State</i>		
Chronic (post 1 st -year) death	0.018	Law 2002 ³³
MI event	0.021	Hemingway 2003 ³¹
<i>From Stroke State</i>		
Acute death	0.140	Lee 2010 ³⁴
Repeat stroke event	0.040	Hardie 2004 ³⁵
MI event	0.022	Touze 2005 ³⁶

eTable 3. Model validation results

Outcome	CVD simulation model*	NHANES III**	Life table projection***
5-year total mortality	3.4%	3.5%	3.4%
10-year total mortality	8.1%	7.6%	8.0%
20-year total mortality	24.7%	n/a	24.2%
30-year total mortality	43.1%	n/a	42.6%
5-year CVD mortality	0.6-1.4%	1.0%	n/a
10-year CVD mortality	1.4-3.6%	2.2%	n/a
Life expectancy (years)	77.7	n/a	77.8

*Results from the CVD simulation model populated with the NHANES III cohort

**Observed outcomes from the NHANES III cohort

***Predicted outcomes applying 1996 sex-specific life tables to the NHANES III cohort

eTable 4. Optimal ASCVD treatment threshold as a function of statin price

WTP*	Annual statin price (2013 U.S. dollars per year)												
	\$0	\$50	\$68**	\$100	\$150	\$250	\$267	\$500	\$750	\$1000	\$1250	\$1500	\$2000
\$50,000/QALY	3.0%	4.0%	4.0%	4.0%	5.0%	7.5%	7.5%	10.0%	None****	None****	None****	None****	None****
\$100,000/QALY	3.0%	3.0%	3.0%	3.0%	3.0%	4.0%	4.0%	5.0%	7.5%	10.0%	None****	None****	None****
\$150,000/QALY	3.0%	3.0%	3.0%	3.0%	3.0%	3.0%	3.0%	4.0%	5.0%	7.5%	7.5%	10.0%	None****

*WTP stands for willingness-to-pay, which represents various societal willingness-to-pay for health values (i.e., cost-effectiveness thresholds)

**Generic statin price

***Blended statin price

****Strategy of using no ASCVD treatment threshold

eTable 5. Optimal ASCVD treatment threshold as a function of statin-induced diabetes risk

	Odds ratio for statin-induced diabetes										
WTP*	1.000	1.025	1.050	1.075	1.090*	1.100	1.150	1.250	1.500	1.750	2.000
\$50,000/QALY	3.0%	4.0%	5.0%	7.5%	7.5%	7.5%	10.0%	15.0%	None***	None***	None***
\$100,000/QALY	2.0%	3.0%	3.0%	4.0%	4.0%	4.0%	5.0%	7.5%	15.0%	None***	None***
\$150,000/QALY	1.0%	2.0%	3.0%	3.0%	3.0%	4.0%	5.0%	7.5%	15.0%	20.0%	None***

*WTP stands for willingness-to-pay, which represents various societal willingness-to-pay for health values (i.e., cost-effectiveness thresholds)

**Base-case value

***Strategy of using no ASCVD treatment threshold

eTable 6. Additional sensitivity analysis results: lifetime per-person quality-adjusted life years (QALYs), costs (\$), and incremental cost-effectiveness ratios (\$/QALY) for alternative acute cardiovascular disease mortality and statin effectiveness results

ACC-AHA ASCVD risk threshold	Acute CVD mortality reduced by 20% scenario			Statin effectiveness based on proportional LDL reductions scenario		
	QALYs ^B	Costs ^B	ICER (\$/QALY)	QALYs ^B	Costs ^B	ICER (\$/QALY)
No ASCVD threshold	17.334	\$21,884	Reference	17.276	\$21,313	Reference
≥30.0%	17.344	\$22,218	Extended dominance ^D	17.285	\$21,668	Extended dominance ^D
≥20.0%	17.356	\$22,462	\$21,000/QALY	17.296	\$21,930	Extended dominance ^D
≥15.0%	17.366	\$22,669	\$22,000/QALY	17.304	\$22,149	\$31,000/QALY
≥10.0%	17.377	\$23,010	\$31,000/QALY	17.314	\$22,508	\$35,000/QALY
≥7.5% ^C	17.383	\$23,247	\$39,000/QALY	17.320	\$22,754	\$43,000/QALY
≥5.0%	17.388	\$23,586	\$62,000/QALY	17.325	\$23,106	\$70,000/QALY
≥4.0%	17.390	\$23,747	\$81,000/QALY	17.327	\$23,272	\$93,000/QALY
≥3.0%	17.392	\$23,954	\$150,000/QALY	17.328	\$23,486	\$270,000/QALY
≥2.0%	17.392	\$24,203	\$1,200,000/QALY	17.327	\$23,739	Strong dominance ^E
≥1.0%	17.391	\$24,497	Strong dominance ^E	17.327	\$24,036	Strong dominance ^E
Treat all adults with statins	17.389	\$24,771	Strong dominance ^E	17.325	\$24,312	Strong dominance ^E

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^Adefined as non-fatal or fatal: myocardial infarction, angina, cardiac arrest, or stroke

^Bdiscounted at 3%

^CASCVD risk threshold used in 2013 ACC-AHA guidelines

^DExtended dominance: other, more effective strategies have lower cost-effectiveness ratios than this strategy.

^EDominated: other strategies are less costly and more effective than this strategy. Based on recommendations, strategies that are dominated by either mechanism are eliminated from further consideration in a cost-effectiveness analysis.

Note: CVD stands for cardiovascular disease; QALYs stands for quality-adjusted life years; ICER stands for incremental cost-effectiveness ratio.

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