Annals of Internal Medicine ORIGINAL RESEARCH

Cost-Effectiveness and Population Impact of Statins for Primary Prevention in Adults Aged 75 Years or Older in the United States

Michelle C. Odden, PhD; Mark J. Pletcher, MD, MPH; Pamela G. Coxson, PhD; Divya Thekkethala, BS; David Guzman, MS; David Heller, MD; Lee Goldman, MD, MPH; and Kirsten Bibbins-Domingo, MD, PhD

Background: Evidence to guide primary prevention in adults aged 75 years or older is limited.

Objective: To project the population impact and cost-effectiveness of statin therapy in adults aged 75 years or older.

Design: Forecasting study using the Cardiovascular Disease Policy Model, a Markov model.

Data Sources: Trial, cohort, and nationally representative data sources.

Target Population: U.S. adults aged 75 to 94 years.

Time Horizon: 10 years.

Perspective: Health care system.

Intervention: Statins for primary prevention based on low-density lipoprotein cholesterol threshold of 4.91 mmol/L (190 mg/dL), 4.14 mmol/L (160 mg/dL), or 3.36 mmol/L (130 mg/dL); presence of diabetes; or 10-year risk score of at least 7.5%.

Outcome Measures: Myocardial infarction (MI), coronary heart disease (CHD) death, disability-adjusted life-years, and costs.

Results of Base-Case Analysis: All adults aged 75 years or older in the National Health and Nutrition Examination Survey have a 10-year risk score greater than 7.5%. If statins had no effect on functional limitation or cognitive impairment, all primary prevention strategies would prevent MIs and CHD deaths and be cost-effective. Treatment of all adults aged 75 to 94 years would result in 8 million additional users and prevent 105 000 (4.3%) incident MIs and 68 000 (2.3%) CHD deaths at an incremental cost per disability-adjusted life-year of $25 200.

Results of Sensitivity Analysis: An increased relative risk for functional limitation or mild cognitive impairment of 1.10 to 1.29 could offset the cardiovascular benefits.

Limitation: Limited trial evidence targeting primary prevention in adults aged 75 years or older.

Conclusion: At effectiveness similar to that in trials, statins are projected to be cost-effective for primary prevention; however, even a small increase in geriatric-specific adverse effects could offset the cardiovascular benefit. Improved data on the potential benefits and harms of statins are needed to inform decision making.

Primary Funding Source: American Heart Association Western States Affiliate, National Institute on Aging, and the National Institute for Diabetes on Digestive and Kidney Diseases.

Ann Intern Med. 2015;162:533-541. doi:10.7326/M14-1430 **www.annals.org**
For author affiliations, see end of text.

Statins are commonly used in adults aged 75 years or older (1). Despite their widespread use, evidence for their effectiveness for primary prevention in elderly adults is unclear, and guidelines for their use in this population are inconsistent. The recently published American College of Cardiology/American Heart Association (ACC/AHA) Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults gave limited recommendations for statin use for primary prevention in adults aged 75 years or older (2), noting that "few data were available to indicate an atherosclerotic cardiovascular disease event reduction benefit in primary prevention among individuals >75 years of age who do not have clinical year atherosclerotic cardiovascular disease," and suggesting that comorbid conditions, safety, and priorities of care are recommended for joint provider and patient decision making. The American Medical Directors Association, a professional group of long-term care providers, recommended that statins not be routinely prescribed in adults aged 70 years or older as part of the American Board of Internal Medicine Choosing Wisely campaign (3). This recommendation was based on the lack of an association between high cholesterol levels and outcomes in older adults as well as the potential for an increased risk for statin-related adverse events, including cognitive impairment, falls, neuropathy, and muscle damage (3).

The variation in these treatment recommendations reflects uncertainty about the balance between the benefits and risks of statin use in older adults compared with younger adults as well as the more limited evidence base in this population. Adults aged 75 years or older have been underrepresented in trials of statins for primary prevention, so the effectiveness of statins is less clear in this population. Results from observational studies suggest that the associations between low-density lipoprotein (LDL) cholesterol levels and outcomes are attenuated in older adults (4–7). Although the baseline risk for cardiovascular disease is increased in older adults, their life expectancy is shorter and their risks for competing mortality are greater. Finally, there has been concern about geriatric-specific adverse effects, especially functional limitation due to muscle pain, weakness, and mild cognitive impairment (8–16).

See also:

Editorial comment 590
Summary for Patients I-28

EDITORS' NOTES

Context

Clinical guidelines provide conflicting recommendations about whether to prescribe statins in persons aged 75 years or older for primary prevention of unwanted cardiovascular outcomes.

Contribution

This study used information from clinical trials to model the tradeoffs between benefits and harms and found that using statins in all persons aged 75 to 94 years would prevent new myocardial infarctions and deaths from coronary heart disease at an acceptable cost.

Caution

Small increases in the frequency or severity of harms would negate the benefits.

Implication

Additional research is warranted to better understand the tradeoffs between benefits and harms in this age group.

In the presence of uncertainty about the risk–benefit tradeoff, computer simulations can provide estimates of the potential benefits of various treatment strategies as well as the costs and potential risk for harms. We evaluated the population benefit and cost-effectiveness of statins in persons aged 75 years or older without a history of cardiovascular disease in the United States. This investigation was conducted using the Cardiovascular Disease Policy Model (CVDPM), a Markov model of the U.S. population (17). We simulated the impact of statins for primary prevention based on treatment of the high-risk groups identified by the ACC/AHA guidelines, the associated costs, and potential harms that could offset the potential cardiovascular benefits in the U.S. population of adults aged 75 to 94 years over the next 10 years.

METHODS

The Model

The CVDPM is an established state-transition (Markov) model of the incidence, prevalence, mortality, and cost of CHD and stroke in U.S. residents aged 35 to 94 years (17). The present study was limited to adults aged 75 to 94 years. The model comprises 3 components. First, the demographic-epidemiologic submodel estimates the incidence of coronary heart disease (CHD) (cardiac arrest, myocardial infarction [MI], angina, or CHD death), ischemic stroke, and death from other causes on the basis of age, sex, systolic blood pressure, smoking, high-density lipoprotein and LDL cholesterol levels, diabetes, body mass index, and statin use. Second, the bridge submodel characterizes the initial CHD or stroke event and related events in the subsequent 30 days. Third, the disease-history submodel predicts the number of subsequent CHD and stroke events, revascularization procedures, and deaths among patients with cardiovascular disease, stratified according to age, sex, and history of cardiovascular disease events. In addition, persons may exit the model at any stage through a non-CHD, nonstroke mortality function, allowing for competing risk. Modifiable components of the model include population distributions, risk factor levels, risk factor coefficients, event rates, case-fatality rates, costs, and disability adjustments (17). Costs for stroke requiring hospitalization, CHD, and acute stroke rehabilitation were estimated using California hospital data (18) and were deflated using cost–charge ratios and the ratio of the U.S. national average costs to the California average (19, 20). Age- and sex-specific background health care costs were estimated using national data (21). All model costs were inflated to 2014 costs by using the medical component of the Consumer Price Index (22). All disability weights associated with the CHD and stroke event states were based on the Global Burden of Disease Study (23, 24). Additional details are provided in the **Appendix** (available at www.annals.org).

Simulation Inputs

We modeled the effect of statins on LDL cholesterol level based on PROSPER (Prospective Study of Pravastatin in the Elderly at Risk of Vascular Disease), a randomized, placebo-controlled trial of 5804 men and women aged 70 to 82 years (25). In that trial, the mean reduction in LDL cholesterol level was 34% for participants with an average initial level of 147 mg/dL, consistent with the estimated effect of a moderate-dose statin in the 2013 ACC/AHA guideline (2). We included 3 estimates for the effectiveness of a decrease in LDL cholesterol level on events. The primary estimates were derived by extrapolating the age-stratified effect sizes of a 1.0-mmol/L reduction in LDL cholesterol level from the Cholesterol Treatment Trialists' meta-analysis (26). We fit a regression line to the 3 age strata reported in that analysis (≤60 years, >60 to ≤70 years, and >70 years) to estimate the effect sizes at ages 80 and 90 years. In a sensitivity analysis, we used a high estimate based on the age-pooled estimate of effect of a 1.0-mmol/L reduction in LDL cholesterol level on major coronary events in the meta-analysis. We used a low estimate based on the effect size from PROSPER for primary prevention (25). Statin costs were derived from the National Average Drug Acquisition Cost (NADAC) database (27). Our primary cost estimate ($5.59 for a 30-day supply) was the average of the NADAC costs for the 4 moderate-dose statins that are available in generic form: atorvastatin, 10 mg; simvastatin, 20 mg; pravastatin, 40 mg; and lovastatin, 40 mg. This cost estimate was $5.00 when indexed to 2010 dollars based on the medical component of the Consumer Price Index (22). In addition, we used a low cost estimate of $4 per month, based on the price of generic statins from multiple discount retailers (such as Walmart, Target, and Walgreens). For a high cost estimate, we used $30 for a

30-day supply; the low and high cost estimates have been used similarly in other contemporary cost-effectiveness analyses (28, 29). Adults aged 65 years or older use a median of 4 medications; therefore, we estimated the cost of an additional 0.25 physician visit per year for statin use, assuming that medication management could be covered in 1 visit (30, 31). We estimated 1 lipid panel per year for monitoring (32). Event rates for myopathy and hemorrhagic stroke were estimated as 0.001 per statin-year of use, based on the ACC/AHA guideline statement (2).

Although many major and minor adverse effects have been reported to be associated with statin use, we focused on 2 that are important to geriatric populations and that have generated concern in the scientific literature: functional limitation due to muscle pain and weakness, and mild cognitive impairment (8–16). Both are prevalent in older adults and can have a substantial effect on quality of life and the ability to live independently. A recent review of late-life activity limitations in the United States reported data on participants in 5 nationally representative surveys. The prevalence of limitations in activities of daily living was 27% in adults aged 75 to 84 years and 45% in those aged 85 years or older (33). The population-weighted average of these estimates is 32% for adults aged 75 to 94 years. Widely varying prevalence estimates for mild cognitive impairment have been reported due to the differential measures of this condition and the differences between populations. A recent review reported prevalence of mild cognitive impairment of 19% to 28% in studies of older U.S. adults; we used the average of the 4 U.S. studies, which was 25% (34). Disability-adjusted life-years for the corresponding states were calculated as 1 minus the disability weights reported in the Global Burden of Disease Study (24). Because the statin-associated relative risk for these adverse effects is uncertain, we assumed no elevated risk for these adverse effects in our base-case scenario. The goal of this investigation was not to evaluate the strength of the literature regarding the presence of these adverse effects but to identify the magnitude of the potential effects required to offset the cardiovascular benefit. In sensitivity analyses, we estimated the magnitude of this relative risk by using the following equation: $[(P_{AE} \times RR_{AE}) - P_{AE}] \times DALY_{AE} = DALY\ loss$, where P_{AE} equals the prev-

Table 1. Inputs for Simulation

Input	Effect Size	Reference
Effectiveness		
Statin-associated LDL-C decrease (95% CI), %	34 (20.4–47.6)	2, 25
β-coefficient per 1-mg/dL decrease in LDL-C level		
Stroke	0	25
CHD base case	Age 75–84 y: 0.004* Age 85–94 y: 0.003*	26
CHD low sensitivity	0.001	25
CHD high sensitivity	0.007	26
Cost		
Medication, *$ per 30 d*		
Base case	5.00	27
Low sensitivity	4.00	29
High sensitivity	30.00	29
1 physician visit every 4 y, *$*	67.00	31
Lipid panel, *$*	19.00	32
3 creatine kinase measurements per myopathy case, *$*	9.33	32
Hospitalization for stroke, *$*	15 000.00	18–20
Adverse effects		
Myopathy events per statin-year	0.001	2
Hemorrhagic stroke events per statin-year	0.001	2
Time to recover from myopathy, *mo*	2	Clinical judgment
QALY reduction of myopathy†	0.606	24
QALY reduction of stroke‡	0.312	24
Geriatric-specific adverse effects		
Statin-associated disability-adjusted life-year reduction due to functional limitation or mild cognitive impairment		
Base case	0.00	Clinical judgment
Sensitivity	0.00–0.01	Clinical judgment
Functional limitation		
Prevalence, %	32	33
Disability-adjusted life-year reduction	0.076	24
Mild cognitive impairment		
Prevalence, %	25	34
Disability-adjusted life-year reduction	0.082	24
10-y CVD risk, %	>7.5 for all aged ≥75 y	35

CHD = coronary heart disease; CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; QALY = quality-adjusted life-year.
* SD for each, 0.0006.
† Severe musculoskeletal problems.
‡ Moderate stroke with cognition problems.

Table 2. Population Impact of Multiple Strategies for Statin Use in U.S. Adults, 2014 to 2023

Treatment Strategy	Primary Prevention Treated in First Year, *n*	MIs, *n*	CHD Deaths, *n*	Total DALYs, *n*	Reduction in MIs, *n (%)*	Reduction in CHD Deaths, *n (%)*	Increase in DALYs, *n (%)*
Status quo	–	2 483 000	3 099 000	179 779 000	–	–	–
Secondary prevention compared with status quo	–	2 430 000	3 014 000	180 048 000	53 000 (2.1)	85 000 (2.7)	269 000 (0.15)
Primary compared with secondary prevention							
LDL-C level ≥4.91 mmol/L (≥190 mg/dL)	312 000	2 422 000	3 008 000	180 065 000	8000 (0.3)	6000 (0.2)	17 000 (0.01)
LDL-C level ≥4.14 mmol/L (≥160 mg/dL)	1 219 000	2 404 000	2 997 000	180 098 000	26 000 (1.1)	17 000 (0.6)	50 000 (0.03)
LDL-C level ≥3.36 mmol/L (≥130 mg/dL)	3 248 000	2 374 000	2 978 000	180 156 000	56 000 (2.3)	36 000 (1.2)	108 000 (0.06)
Diabetic patients	1 500 000	2 401 000	2 995 000	180 103 000	29 000 (1.2)	19 000 (0.6)	55 000 (0.03)
All	7 937 000	2 325 000	2 946 000	180 245 000	105 000 (4.3)	68 000 (2.3)	197 000 (0.11)

CHD = coronary heart disease; DALY = disability-adjusted life-year; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction.

alence of the adverse effects in the population, RR_{AE} equals the relative risk for the adverse effects associated with statin use, $DALY_{AE}$ equals the disability-adjusted life-year decrement of the adverse effects, and *DALY loss* equals the total disability-adjusted life-year decrement per statin-year of use. The total disability-adjusted life-year decrement per statin-year of use was varied from zero to 0.01.

Simulations

We used the CVDPM to run a 10-year simulation of U.S. adults aged 75 to 94 years in 2014 and followed through 2023. We modeled an open cohort, which allowed younger persons to age into the population. We did not model treatment among the few who reached age 95 years because data are insufficient to model cardiovascular disease in adults aged 95 years or older. We first conducted a simulation to estimate the effect of statin use for secondary prevention by modeling the addition of a statin in all adults aged 75 to 94 years who had a history of cardiovascular disease and were not currently using a statin; we assumed the current rate of statin use for older adults without a history of cardiovascular disease. Subsequently, we conducted simulations to compare the effect of primary prevention of the 3 remaining groups identified in the ACC/AHA guidelines: persons with an LDL cholesterol level of at least 4.91 mmol/L (≥190 mg/dL), those with diabetes, and those with a 10-year cardiovascular disease risk of at least 7.5%. Ten-year cardiovascular disease risk was assessed by using the 2013 ACC/AHA cardiovascular risk equation (35). We also explored the potential effect of statins for primary prevention by using 2 alternative LDL cholesterol thresholds: 4.14 mmol/L (160 mg/dL) or greater and 3.36 mmol/L (130 mg/dL) or greater.

In a sensitivity analysis, we extended follow-up for an additional 10 years (from 2024 to 2033) to evaluate the primary prevention strategies beyond the initial inception years. We conducted sensitivity analyses of both high and low estimates of effectiveness and analyses that used a high and low cost estimate and the effect of no or 1 physician visit per year. We further explored the statin-associated reduction in quality-adjusted life-years required to offset the cardiovascular disease benefit of statin use by varying the reduction from 0 to 0.01. Finally, we used probabilistic sensitivity analyses to vary the effectiveness parameters (LDL cholesterol–reducing effect of statins and the β-coefficient on risk for CHD for a 1-mg/dL reduction in LDL cholesterol level) over the range observed in the published literature (Table 1).

Table 3. Cost-Effectiveness of Multiple Strategies for Statin Use in U.S. Adults, 2014 to 2023

Treatment Strategy	Total Cost, *million $*	CVD Costs, *million $*	Rank*	ICER, *$*†‡	CER Compared With Treating Secondary Prevention, *$*‡
Status quo	4 351 900	880 900	–	–	–
Secondary prevention compared with status quo	4 346 200	866 900	1	Cost-saving	–
Primary compared with secondary prevention					
LDL-C level ≥4.91 mmol/L (≥190 mg/dL)	4 346 000	866 100	2	Cost-saving	Cost-saving
LDL-C level ≥4.14 mmol/L (≥160 mg/dL)	4 345 900	862 400	3	Cost-saving	Cost-saving
LDL-C level ≥3.36 mmol/L (≥130 mg/dL)	4 346 200	861 600	5	5300	400
Diabetic patients	4 346 200	864 200	4	Dominated	460
All	4 348 500	856 900	6	25 200	11 600

CER = cost-effectiveness ratio; CVD = cardiovascular disease; ICER = incremental cost-effectiveness ratio; LDL-C = low-density lipoprotein cholesterol.
* Based on fewest (1) to most (6) disability-adjusted life-years gained.
† Compared with next least effective nondominated strategy.
‡ Calculations may not be exact due to rounding.

Costs were calculated from the health care system perspective. All costs were inflated to 2014 dollars by using the medical component of the Consumer Price Index (22). Costs and disability-adjusted life-years were discounted at 3% per year. An intervention was defined as high-value if the cost to extend 1 disability-adjusted life-year was less than $50 000, intermediate-value if the cost was $50 000 to less than $150 000, and low-value if the cost was at least $150 000 (36).

Role of the Funding Source

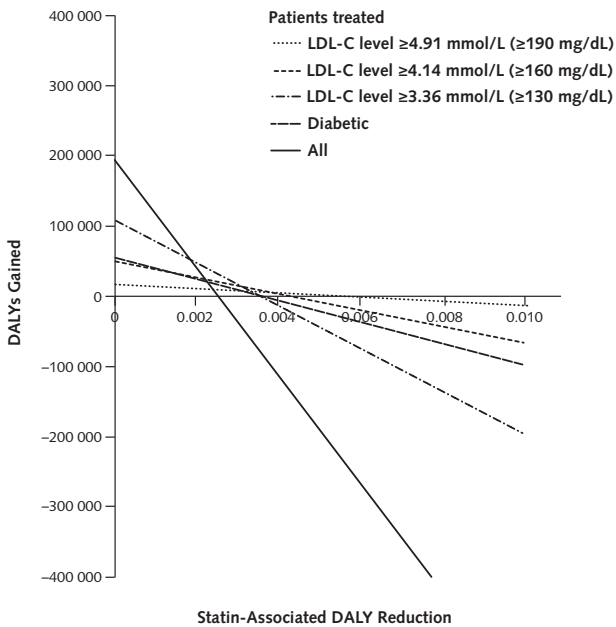
Funding for this study was provided by the American Heart Association Western States Affiliate and the National Institute on Aging, which had no role in the study design or conduct or the reporting of data. The Institutional Review Board at Oregon State University determined that this study does not meet the definition of "research involving human subjects."

RESULTS

In 2014, an estimated 19 million adults in the United States were aged 75 to 94 years, and 30% had cardiovascular disease. Over the ensuing 10 years, at current rates of statin use, this population was projected to have 2.5 million MIs and 3.1 million CHD deaths and accrue cardiovascular disease costs of $881 billion (Tables 2 and 3). If all adults aged 75 to 94 years with a history of cardiovascular disease who were not currently using a statin were treated with a statin over the next 10 years, approximately 53 000 MIs and 85 000 CHD deaths would be prevented, an estimated 269 000 disability-adjusted life-years would be gained, and the societal costs of cardiovascular disease would decrease by approximately $14 billion.

The potential effect of statins for primary prevention varied by treatment strategy. All adults aged 75 to 94 years in NHANES (National Health and Nutrition Examination Survey) have an estimated 10-year cardiovascular disease risk of at least 7.5%, so treatment based on this risk threshold does not discriminate in this population. Adding a statin in currently untreated adults aged 75 to 94 years with an LDL cholesterol level of at least 4.91 mmol/L (≥190 mg/dL) was projected to be cost-saving but would have a minimal impact on prevention of MIs and CHD deaths in the overall population because this risk group comprises a small proportion of the population (Tables 2 and 3). Decreasing the LDL cholesterol treatment threshold to 4.14 mmol/L (160 mg/dL), which was also projected to be cost-saving, would allow for treatment of substantially more elderly adults, and the number of events prevented would increase accordingly. At a threshold of 3.36 mmol/L (130 mg/dL), more than 3 million currently untreated older adults would receive statins for primary

Figure. Sensitivity analysis of magnitude of statin-associated DALY reduction needed to offset cardiovascular benefit.



The value of the statin-associated DALY reduction at which the lines cross the *x*-axis is the magnitude needed to offset the cardiovascular benefit and result in no net DALYs gained. DALY = disability-adjusted life-year; LDL-C = low-density lipoprotein cholesterol.

Table 4. Cost-Effectiveness of Multiple Strategies for Statin Use in U.S. Women and Men, Aged 75 to 84 y and 85 to 94 y (2014 to 2023)

Treatment Strategy	Women Aged 75-84 y		Men Aged 75-84 y		Women Aged 85-94 y		Men Aged 85-94 y	
	DALYs Gained	CER, $*	DALYs Gained	CER, $*	DALYs Gained	CER, $*	DALYs Gained	CER, $*
Secondary prevention compared with status quo	56 000	Cost-saving	55 000	Cost-saving	97 000	3700	62 000	138
Primary compared with secondary prevention								
LDL-C level ≥4.91 mmol/L (≥190 mg/dL)	5000	Cost-saving	2000	Cost-saving	7000	2100	3000	Cost-saving
LDL-C level ≥4.14 mmol/L (≥160 mg/dL)	15 000	Cost-saving	8000	Cost-saving	18 000	5400	9000	Cost-saving
LDL-C level ≥3.36 mmol/L (≥130 mg/dL)	30 000	8600	22 000	Cost-saving	39 000	9200	17 000	Cost-saving
Diabetic patients	15 000	6500	11 000	Cost-saving	20 000	8000	8000	Cost-saving
All	48 000	31 400	43 000	Cost-saving	67 000	15 500	39 000	100

CER = cost-effectiveness ratio; DALY = disability-adjusted life-year; LDL-C = low-density lipoprotein cholesterol.
* All primary prevention strategies compared with secondary prevention.

Table 5. Cost-Effectiveness of Multiple Strategies for Statin Use in U.S. Adults Extended for a Second Decade of Follow-up (2024 to 2033)

Treatment Strategy	Total Cost, *million $*	CVD Costs, *million $*	DALYs Gained	Rank*	ICER,$†‡	CER for Comparison With Secondary Prevention,$‡
Status quo	4 403 800	885 800	–	–	–	–
Secondary prevention compared with status quo	4 405 300	874 600	445 000	1	3200	–
Primary compared with secondary prevention						
LDL-C level ≥4.91 mmol/L (≥190 mg/dL)	4 405 200	873 600	33 000	2	Cost-saving	Cost-saving
LDL-C level ≥4.14 mmol/L (≥160 mg/dL)	4 405 500	870 200	107 000	3	3900	2500
LDL-C level ≥3.36 mmol/L (≥130 mg/dL)	4 406 400	867 600	236 000	5	4700	5000
Diabetic patients	4 405 900	871 000	124 000	4	Dominated	5300
All	4 409 800	861 300	436 000	6	17 100	10 600

CER = cost-effectiveness ratio; CVD = cardiovascular disease; DALY = disability-adjusted life-year; ICER = incremental cost-effectiveness ratio; LDL-C = low-density lipoprotein cholesterol.
* Based on fewest (1) to most (6) DALYs gained.
† Compared with next least effective nondominated strategy.
‡ Calculations may not be exact due to rounding.

prevention, and this strategy would prevent 56 000 MIs and 36 000 CHD deaths and would save 108 000 disability-adjusted life-years at an estimated cost-effectiveness of $5300 per disability-adjusted year of life compared with a threshold of 4.14 mmol/L (160 mg/dL). Treatment of all diabetic patients was dominated by extension and would not be considered a cost-effective alternative to the other strategies presented. If all older adults who had no history of cardiovascular disease and were not currently using statins were treated, statin use in these nearly 8 million new users would prevent about 105 000 MIs and 68 000 CHD deaths and save 197 000 disability-adjusted life-years at an incremental cost per disability-adjusted life-year of $25 200 compared with treatment at a threshold of 3.36 mmol/L (130 mg/dL).

When the population was stratified by age and sex, all primary prevention strategies were cost-saving or high-value in men and women aged 75 to 84 years and 85 to 94 years compared with secondary prevention alone. Almost all primary prevention strategies were cost-saving in men, and all strategies were high-value in women compared with secondary prevention (Table 4). In the second decade of implementation of these statin therapy strategies (2024 to 2033), secondary prevention was projected to no longer be cost-saving but continued to be high-value. In addition, the incremental cost-effectiveness ratios between primary and secondary prevention were modestly attenuated (Table 5).

The benefit observed in the primary prevention strategies was sensitive to assumptions about the magnitude of potential harms. Based on a strategy of treating persons with an LDL cholesterol level of at least 4.91 mmol/L (≥190 mg/dL), the magnitude of the statin-associated disability-adjusted life-year reduction necessary to offset the cardiovascular benefit would be 0.006 (Figure). Of note, the magnitude of a statin-associated disability-adjusted life-year reduction required to offset the cardiovascular benefit would be smaller for the other primary prevention strategies (Figure). This reduction translated to relative risks that ranged from 1.10 to 1.24 for functional limitation and from 1.12 to 1.29 for mild cognitive impairment (Table 6).

One-way sensitivity analyses showed that the cost-effectiveness ratios of the primary prevention strategies were sensitive to effectiveness and cost estimates for statins (Table 7). At a lower estimate of effectiveness or a statin cost of $30 per month, treating only adults with an LDL cholesterol level of at least 4.91 mmol/L (≥190 mg/dL) continued to be high-value. In contrast, if effectiveness of statins in adults aged 75 years or older was similar to that observed in a younger population or if older adults were able to obtain statins for $4 per month, all primary prevention strategies were cost-saving or very-high-value.

Based on probabilistic sensitivity analyses, the findings for the primary prevention strategies seemed consistent. Compared with treating adults with a history of cardiovascular disease only, treating those with an LDL cholesterol level of at least 4.91 mmol/L (≥190 mg/dL) was projected to prevent 8000 MIs (95% CI, 6000 to 11 000), treating those with an LDL cholesterol level of at least 4.14 mmol/L (≥160 mg/dL) was projected to prevent 26 000 MIs (CI, 17 000 to 35 000), treating

Table 6. Hypothetical Relative Risk for Adverse Effects Required to Offset CVD Benefit Under Base-Case Assumptions*

Variable	LDL-C Level ≥4.91 mmol/L (≥190 mg/dL)	LDL-C Level ≥4.14 mmol/L (≥160 mg/dL)	LDL-C Level ≥3.36 mmol/L (≥130 mg/dL)	Diabetic Patients	All
Functional limitation	1.24 (1.02–1.41)	1.18 (0.79–1.64)	1.15 (0.84–1.42)	1.15 (1.02–1.30)	1.10 (0.84–1.34)
Mild cognitive impairment	1.29 (1.02–1.48)	1.21 (0.75–1.76)	1.17 (0.81–1.50)	1.18 (1.02–1.35)	1.12 (0.81–1.41)

CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol.
* Values are relative risks (95% CIs).

Table 7. One-Way Sensitivity Analyses Varying Effectiveness and Cost Parameters

Variable	CER Compared With Secondary Prevention, *$/DALY*				
	LDL-C Level ≥4.91 mmol/L (≥190 mg/dL)	LDL-C Level ≥4.14 mmol/L (≥160 mg/dL)	LDL-C Level ≥3.36 mmol/L (≥130 mg/dL)	Diabetic Patients	All
Base case	Cost-saving	Cost-saving	400	460	11 600
Effectiveness*					
Low	41 400	61 000	77 900	67 900	109 600
High	Cost-saving	Cost-saving	Cost-saving	Cost-saving	Cost-saving
Monthly statin cost, $†					
High ($30/mo)	46 800	72 400	96 500	95 000	144 900
Low ($4/mo)	Cost-saving	Cost-saving	Cost-saving	Cost-saving	6400
Physician visit‡					
Annual	Cost-saving	7500	16 200	16 000	33 600
None	Cost-saving	Cost-saving	Cost-saving	Cost-saving	4200

CER = cost-effectiveness ratio; DALY = disability-adjusted life-year; LDL-C = low-density lipoprotein cholesterol.
* Base case: β-coefficient = 0.004 per 1-mg/dL decrease in LDL-C level for persons aged 75–84 y and 0.003 for those aged 85–94 y (low, 0.001; high, 0.007).
† Base case: $5 per 30-d supply.
‡ Base case: 0.25 physician visit per year.

those with an LDL cholesterol level of at least 3.36 mmol/L (≥130 mg/dL) was projected to prevent 56 000 MIs (CI, 39 000 to 74 000), treating those with diabetes was projected to prevent 29 000 MIs (CI, 22 000 to 37 000), and treating all was projected to prevent 105 000 MIs (CI, 75 000 to 135 000). Of the primary prevention strategies, 70% of the simulations for treating adults at an LDL cholesterol threshold of 4.91 mmol/L (190 mg/dL), 51% of the simulations for a threshold of 4.14 mmol/L (160 mg/dL), 32% of the simulations for a threshold of 3.36 mmol/L (130 mg/dL), and 21% of the simulations for treating all adults were cost-saving, and 99%, 94%, 83%, and 81%, respectively, were high-value, with a cost per disability-adjusted life-year less than $50 000.

DISCUSSION

On the basis of available data, we project that generic statins are cost-effective for primary prevention in adults aged 75 to 94 years, and strategies that treat a greater proportion of the population have the potential to prevent similarly higher numbers of MIs and CHD deaths. Although these findings are promising, even a small increased risk for functional limitation or cognitive impairment could offset the cardiovascular benefit. In addition, our estimates of the value of statin use for primary prevention were susceptible to varying assumptions about effectiveness and cost. Because of the sensitivity of our findings to these parameters, studies to quantify the potential benefits and harms of statin use in older adults are paramount.

The ACC/AHA guideline recommends patient–provider discussion of the potential benefits, risk for adverse effects, and patient preferences before statin initiation for primary prevention. In the absence of clear evidence, individualized treatment decision making is warranted. However, for treatment decisions that are vulnerable to variations in effectiveness, cost, and potential risks, more precise and reliable data on these parameters are needed to inform the decision process. Whereas effectiveness data are available from clinical trials, fewer systematic data exist on the potential risks of statins. Clinical trials are likely to include participants who are healthier than those in the general population, so the risks of an intervention in a representative patient population are uncertain. In addition, mild to moderate adverse effects may be underreported in postmarketing surveillance systems intended to identify rare and serious adverse events. We focused on functional limitation due to muscle pain and weakness and mild cognitive impairment because these conditions are prevalent in older adults and can have an important and immediate effect on quality of life and independence (8–16). Unlike previous analyses that showed that a large theoretical increase in adverse effects would be required to counterbalance the cardiovascular benefits in the general population (28), our analysis showed that, in older adults, even a small increase in the risk for functional limitation and mild cognitive impairment from statins could result in net harm. In our simulations, a 10% to 30% increased risk for these adverse effects would offset the cardiovascular benefit. Our results provide strong motivation for further investigations into the incidence of adverse effects from statins in a diverse group of elderly adults, including those who are frail and have complex comorbidity. Because of the sample size required to identify potential risks in a diverse population, pragmatic trials and improved postmarketing surveillance are the most promising approaches for this goal.

We focused on geriatric-specific conditions with an immediate impact on quality of life, although other potential harms and benefits have been considered. Serious adverse effects, including rhabdomyolysis, liver failure, and peripheral neuropathy, seem to be rare (37), and prior simulations have suggested that the rarity of

these events results in a risk–benefit ratio that favors statin use (28, 38, 39). The risk for statin-associated diabetes is modest (37, 39), and the time interval from the incidence of diabetes to a clinically observable event is generally delayed and may be less concerning in older adults than the immediate risk for a coronary event. We also did not include the potential benefit of statins on kidney function and peripheral arterial disease because, as with diabetes, the time interval between the incidence of these conditions and a clinically observable event is likely to be several years. Our results underscore both the tremendous potential benefit of statin use and the tenuous balance of benefits and harms and highlight the need to quantify and adequately account for all health effects of the use of these medications for primary prevention in older adults.

The CVDPM is tested and updated regularly to reflect changes in risk factor distributions, population estimates, risk factor associations, event rates, case-fatality rates, and costs. However, projections from any forecasting model should be viewed with caution because unpredicted changes can impact results. Our projections have limitations that should be considered during interpretation of the findings. The primary limitation, as has been noted by professional groups, is the lack of high-quality evidence targeting primary prevention in adults aged 75 years or older. We used the best available evidence for our simulations and provide high- and low-effect sensitivity analyses. We used pharmaceutical cost data for generic statins; the cost-effectiveness of statin use may be substantially lower if older adults use newer agents that have yet to become generic. In addition, pleiotropic or beneficial effects of statins on kidney function or peripheral arterial disease or a harmful effect on diabetes risks could alter our estimates of the benefit–harm ratio.

In summary, statins are projected to be cost-effective for primary prevention of cardiovascular disease in a population of adults aged 75 to 94 years that derives a relative benefit similar to what was observed in randomized, controlled trials if a low monthly cost of statins is assumed. More research on effectiveness and potential harms in a diverse population of elderly adults is needed to inform decision making in populations of older adults who are frail or have multiple chronic health conditions. Because even a modest increase in harm could offset the cardiovascular benefit in some populations, large studies of statin users are needed to identify the magnitude of any statin-associated risks. Given the growing population of older adults, the heterogeneity of their health requirements and care goals, and the critical need to give patients and providers tools to make health care decisions that balance potential benefits and potential harms, studies that leverage existing infrastructure may prove most useful for providing these important data in a timely manner.

From Oregon State University, Corvallis, Oregon; University of California, San Francisco, San Francisco, California; and Columbia University, New York, New York.

Disclaimer: Dr. Bibbins-Domingo is currently co-vice chair of the U.S. Preventive Services Task Force (USPSTF). This work does not necessarily represent the views and policies of the USPSTF. This manuscript was prepared using Framingham Cohort and Framingham Offspring Research Materials obtained from the NHLBI Biologic Specimen and Data Repository Information Coordinating Center and does not necessarily reflect the opinions or views of the Framingham Cohort, Framingham Offspring, or the NHLBI.

Grant Support: By the American Heart Association Western States Affiliate (11CRP7210088), the National Institute on Aging (K01AG039387), and the National Institute for Diabetes and Digestive and Kidney Diseases (K24DK103992).

Disclosures: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M14-1430.

Reproducible Research Statement: *Study protocol:* Not available. *Statistical code:* Persons interested in joining the Intellectual Property Commons that is committed to improving the model and using it for scientific purposes should contact Dr. Goldman (e-mail, lgoldman@columbia.edu). *Data set:* All data are publicly available, and sources are listed in the references and the Appendix.

Requests for Single Reprints: Michelle C. Odden, PhD, Oregon State University, 141B Milam Hall, Corvallis, OR 97331.

Current author addresses and author contributions are available at www.annals.org.

References

1. **Lo-Ciganic WH, Boudreau RM, Gray SL, Zgibor JC, Donohue JM, Perera S, et al.** Changes in cholesterol-lowering medications use over a decade in community-dwelling older adults. Ann Pharmacother. 2013;47:984-92. [PMID: 23780807] doi:10.1345/aph.1S050

2. **Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines.** 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129:S1-45. [PMID: 24222016] doi:10.1161/01.cir.0000437738.63853.7a

3. **Society for Post-Acute and Long-Term Care Medicine.** Five Things Physicians and Patients Should Question. Columbia, MD: Society for Post-Acute and Long-Term Care Medicine; 2013. Accessed at www.amda.com/tools/choosingwisely.cfm on 22 April 2014.

4. **Kronmal RA, Cain KC, Ye Z, Omenn GS.** Total serum cholesterol levels and mortality risk as a function of age. A report based on the Framingham data. Arch Intern Med. 1993;153:1065-73. [PMID: 8481074]

5. **Krumholz HM, Seeman TE, Merrill SS, Mendes de Leon CF, Vaccarino V, Silverman DI, et al.** Lack of association between cholesterol and coronary heart disease mortality and morbidity and all-cause mortality in persons older than 70 years. JAMA. 1994;272:1335-40. [PMID: 7772105]

6. **Schatz IJ, Masaki K, Yano K, Chen R, Rodriguez BL, Curb JD.** Cholesterol and all-cause mortality in elderly people from the Honolulu Heart Program: a cohort study. Lancet. 2001;358:351-5. [PMID: 11502313]

7. **Weverling-Rijnsburger AW, Blauw GJ, Lagaay AM, Knook DL, Meinders AE, Westendorp RG.** Total cholesterol and risk of mortality in the oldest old. Lancet. 1997;350:1119-23. [PMID: 9343498]
8. **Muldoon MF, Ryan CM, Sereika SM, Flory JD, Manuck SB.** Randomized trial of the effects of simvastatin on cognitive functioning in hypercholesterolemic adults. Am J Med. 2004;117:823-9. [PMID: 15589485]
9. **Padala KP, Padala PR, Potter JF.** Statins: a case for drug withdrawal in patients with dementia [Letter]. J Am Geriatr Soc. 2010;58:1214-6. [PMID: 20722868] doi:10.1111/j.1532-5415.2010.02889.x
10. **Wagstaff LR, Mitton MW, Arvik BM, Doraiswamy PM.** Statin-associated memory loss: analysis of 60 case reports and review of the literature. Pharmacotherapy. 2003;23:871-80. [PMID: 12885101]
11. **Schiattarella GG, Perrino C, Magliulo F, Ilardi F, Serino F, Trimarco V, et al.** Statins and the elderly: recent evidence and current indications. Aging Clin Exp Res. 2012;24:47-55. [PMID: 23160507]
12. **Scott D, Blizzard L, Fell J, Jones G.** Statin therapy, muscle function and falls risk in community-dwelling older adults. QJM. 2009;102:625-33. [PMID: 19633029] doi:10.1093/qjmed/hcp093
13. **Joy TR, Hegele RA.** Narrative review: statin-related myopathy. Ann Intern Med. 2009;150:858-68. [PMID: 19528564]
14. **Bruckert E, Hayem G, Dejager S, Yau C, Bégaud B.** Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients–the PRIMO study. Cardiovasc Drugs Ther. 2005;19:403-14. [PMID: 16453090]
15. **Lee DS, Markwardt S, Goeres L, Lee CG, Eckstrom E, Williams C, et al.** Statins and physical activity in older men: the Osteoporotic Fractures in Men Study. JAMA Intern Med. 2014;174:1263-70. [PMID: 24911216] doi:10.1001/jamainternmed.2014.2266
16. **Sathasivam S.** Statin induced myotoxicity. Eur J Intern Med. 2012;23:317-24. [PMID: 22560377] doi:10.1016/j.ejim.2012.01.004
17. **Weinstein MC, Coxson PG, Williams LW, Pass TM, Stason WB, Goldman L.** Forecasting coronary heart disease incidence, mortality, and cost: the Coronary Heart Disease Policy Model. Am J Public Health. 1987;77:1417-26. [PMID: 3661794]
18. California Patient Discharge Data January 1–December 31, 2000, Public Version A-24 [CD-ROM]. Sacramento, CA: California Office of Statewide Health Planning and Development; 2000.
19. Average Cost to Community Hospitals per Patient, by State (Table 204). Statistical Abstract of the United States Bureau of the Census. Washington, DC: Government Printing Office; 1998:136.
20. **California Office of Statewide Health Planning and Development.** Annual Financial Data. Sacramento, CA: California Office of Statewide Health Planning and Development; 2008. Accessed at www.oshpd.ca.gov/HID/Products/Hospitals/AnnFinanData/PivotProfles/default.asp on 1 June 2010.
21. **Centers for Medicare & Medicaid Services.** Personal Health Care Spending by Type of Service, Age Group, and Source of Payment Distribution, Calendar Year 1999. Baltimore: Centers for Medicare & Medicaid Services; 2000. Accessed at www.cms.hhs.gov/NationalHealthExpendData/downloads/agetables.pdf on 1 June 2010.
22. **Bureau of Labor Statistics.** Consumer Price Index. Washington, DC: U.S. Department of Labor; 2014. Accessed at www.bls.gov/CPI on 1 April 2014.
23. **Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al.** Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380:2197-223. [PMID: 23245608] doi:10.1016/S0140-6736(12)61689-4
24. **Salomon JA, Vos T, Hogan DR, Gagnon M, Naghavi M, Mokdad A, et al.** Common values in assessing health outcomes from disease and injury: disability weights measurement study for the Global Burden of Disease Study 2010. Lancet. 2012;380:2129-43. [PMID: 23245605] doi:10.1016/S0140-6736(12)61680-8
25. **Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, et al; PROSPER study group.** PROspective Study of Pravastatin in the Elderly at Risk. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet. 2002;360:1623-30. [PMID: 12457784]
26. **Mihaylova B, Emberson J, Blackwell L, Keech A, Simes J, Barnes EH, et al; Cholesterol Treatment Trialists' (CTT) Collaborators.** The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet. 2012;380:581-90. [PMID: 22607822] doi:10.1016/S0140-6736(12)60367-5
27. **Centers for Medicare & Medicaid Services.** National Average Drug Acquisition Cost (NADAC). Baltimore: Centers for Medicare & Medicaid Services; 2014. Accessed at www.medicaid.gov/medicaid-chip-program-information/by-topics/benefits/prescription-drugs/pharmacy-pricing.html on 30 September 2014.
28. **Lazar LD, Pletcher MJ, Coxson PG, Bibbins-Domingo K, Goldman L.** Cost-effectiveness of statin therapy for primary prevention in a low-cost statin era. Circulation. 2011;124:146-53. [PMID: 21709063] doi:10.1161/CIRCULATIONAHA.110.986349
29. **Pletcher MJ, Pignone M, Earnshaw S, McDade C, Phillips KA, Auer R, et al.** Using the coronary artery calcium score to guide statin therapy: a cost-effectiveness analysis. Circ Cardiovasc Qual Outcomes. 2014;7:276-84. [PMID: 24619318] doi:10.1161/CIRCOUTCOMES.113.000799
30. **National Center for Health Statistics.** National Health and Nutrition Examination Survey 2009–2010. Atlanta, GA: Centers for Disease Control and Prevention; 2015. Accessed at http://wwwn.cdc.gov/nchs/nhanes/search/nhanes09_10.aspx on 19 February 2015.
31. **Centers for Medicare & Medicaid Services.** National Physician Fee Schedule, 2010B. Baltimore: Centers for Medicare & Medicaid Services; 2015. Accessed at www.cms.gov/apps/physician-fee-schedule/search/search-criteria.aspx on 4 April 2014.
32. **Centers for Medicare & Medicaid Services.** Clinical Lab Fee Schedule, 2010B. Baltimore: Centers for Medicare & Medicaid Services; 2014. Accessed at www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/ClinicalLabFeeSched/clinlab.html on 4 April 2014.
33. **Freedman VA, Spillman BC, Andreski PM, Cornman JC, Crimmins EM, Kramarow E, et al.** Trends in late-life activity limitations in the United States: an update from five national surveys. Demography. 2013;50:661-71. [PMID: 23104207] doi:10.1007/s13524-012-0167-z
34. **Ward A, Arrighi HM, Michels S, Cedarbaum JM.** Mild cognitive impairment: disparity of incidence and prevalence estimates. Alzheimers Dement. 2012;8:14-21. [PMID: 22265588] doi:10.1016/j.jalz.2011.01.002
35. **Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines.** 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129:S49-73. [PMID: 24222018] doi:10.1161/01.cir.0000437741.48606.98
36. **Anderson JL, Heidenreich PA, Barnett PG, Creager MA, Fonarow GC, Gibbons RJ, et al; ACC/AHA Task Force on Performance Measures.** ACC/AHA statement on cost/value methodology in clinical practice guidelines and performance measures: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures and Task Force on Practice Guidelines. Circulation. 2014;129:2329-45. [PMID: 24677315] doi:10.1161/CIR.0000000000000042
37. **Law M, Rudnicka AR.** Statin safety: a systematic review. Am J Cardiol. 2006;97:52C-60C. [PMID: 16581329]
38. **Pletcher MJ, Lazar L, Bibbins-Domingo K, Moran A, Rodondi N, Coxson P, et al.** Comparing impact and cost-effectiveness of primary prevention strategies for lipid-lowering. Ann Intern Med. 2009;150:243-54. [PMID: 19221376]
39. **Ridker PM, Pradhan A, MacFadyen JG, Libby P, Glynn RJ.** Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: an analysis from the JUPITER trial. Lancet. 2012;380:565-71. [PMID: 22883507] doi:10.1016/S0140-6736(12)61190-8

Current Author Addresses: Dr. Odden and Ms. Thekkethala: Oregon State University, 141B Milam Hall, Corvallis, OR 97331.
Dr. Pletcher: Department of Epidemiology and Biostatistics, University of California, San Francisco, UCSF Box 0560, 185 Berry Street, Lobby 5, Suite 5700, San Francisco, CA 94107-1762.
Drs. Coxson, Heller, and Bibbins-Domingo and Mr. Guzman: Department of Medicine, University of California, San Francisco, 1001 Potrero Avenue, Building 10, W13, UCSF-SFGH Box 1364, San Francisco, CA 94110.
Dr. Goldman: Columbia University Medical Center, College of Physicians and Surgeons, 630 West 168th Street, 2nd Floor, Room 401, New York, NY 10032.

Author Contributions: Conception and design: M.C. Odden, K. Bibbins-Domingo.
Analysis and interpretation of the data: M.C. Odden, M.J. Pletcher, P.G. Coxson, D. Thekkethala, D. Guzman, D. Heller, L. Goldman, K. Bibbins-Domingo.
Drafting of the article: M.C. Odden, K. Bibbins-Domingo.
Critical revision of the article for important intellectual content: M.C. Odden, M.J. Pletcher, P.G. Coxson, D. Thekkethala, D. Heller, L. Goldman, K. Bibbins-Domingo.
Final approval of the article: M.C. Odden, M.J. Pletcher, D. Heller, L. Goldman, K. Bibbins-Domingo.
Provision of study materials or patients: L. Goldman, K. Bibbins-Domingo.
Statistical expertise: M.C. Odden, P.G. Coxson, K. Bibbins-Domingo.
Obtaining of funding: M.C. Odden, K. Bibbins-Domingo.
Administrative, technical, or logistic support: M.C. Odden, D. Thekkethala, L. Goldman, K. Bibbins-Domingo.
Collection and assembly of data: M.C. Odden, D. Thekkethala, D. Guzman, K. Bibbins-Domingo.

Appendix: Additional Model Details

Structure

The CVDPM is a computer simulation, state-transition (Markov cohort) model of CHD and stroke incidence, prevalence, mortality, and costs in the population of U.S. adults older than 35 years (17, 40, 41). The demographic-epidemiologic submodel predicts CHD and stroke incidence and non–cardiovascular disease (CVD) mortality among patients without CVD, stratified by age, sex, and up to 8 additional categorized risk factors estimated from weighted NHANES data from 1999 to 2010 (**Appendix Figure**). After CVD develops, the bridge submodel characterizes the initial stroke or CHD event (cardiac arrest, MI, or angina) and its sequelae for 30 days. Then, the disease history submodel predicts subsequent CVD events, coronary revascularization procedures, CVD mortality, and non-CVD mortality among patients with CVD, stratified by age, sex, and history of events. The general chronic CVD categories are CHD only, stroke only, and combined prior CHD and prior stroke. Each state and event has an annual cost and quality-of-life adjustment as well as an annual probability of a repeated event and/or transition to a different CVD state. All population distributions, risk factor levels, coefficients, event rates, case-fatality rates, costs, and quality-of-life adjustments can be modified for forecasting simulations.

Data Sources

Version 4 of the CVDPM includes data from prior versions as well as many updates and upgrades (17, 40, 41). The 2010 U.S. Census provides the baseline population (42) and number of 35-year-old persons projected to enter the model population from 2010 to 2060 (43, 44). Deaths due to CHD and stroke in 2010 were extracted from U.S. Vital Statistics (45). Deaths were categorized according to codes from the 10th revision of the International Classification of Diseases (ICD) (46): I20 to I25 and two thirds of I49, I50, and I51 were used to estimate CHD deaths (47); I60 to I69 were used to estimate stroke deaths; and all other deaths were considered non-CVD deaths.

The incidence of CHD and stroke were based on competing-risk Cox proportional hazards analysis of the Framingham Heart Study (48) and the Framingham Offspring Study cohorts from 1988 to 2007 (49), with further adjustment for risk factor differences between the Framingham cohorts and the contemporary U.S. population represented by NHANES. Incident CHD events were allocated to angina pectoris, MI requiring hospitalization, or cardiac arrest. Prevalence, joint distributions, and means of U.S. risk factor values were estimated from pooled, survey design–weighted NHANES data from 1999 to 2010 (30). Annual transition rates between risk factor levels were calculated to preserve age range trends. Risk function β-coefficients for all risk factors except LDL cholesterol level were estimated separately for the risk for incident CHD events, incident strokes, and non-CVD deaths, using examinations 1 to 8 of the Framingham Offspring cohort (49). The Framingham coefficients have been useful across many populations (50–53). Risk factors were assumed to affect the incidence of MI, arrest, and angina in proportion to the overall incidence of CHD, but tobacco smokers were assumed to have a higher relative risk for infarction and arrest (54) (Coady S. Personal communication) and a proportionately lower coefficient for angina. Environmental tobacco exposure was assumed to carry a relative risk of 1.26 for MI and cardiac arrest compared with nonexposed nonsmokers (55) but was assumed not to influence angina.

The number of MIs requiring hospitalization was obtained from discharges with ICD-9 code 410 in the 2010 National Hospital Discharge Survey (NHDS) (56) with adjustment for likely miscoding (57), such as transfer patients and patients who were discharged alive after 2 days or fewer without a percutaneous coronary intervention. Case-fatality rates and rates of MI in subgroups were estimated from national data (56) and var-

ious complementary sources (58–60). Prehospital arrest deaths were estimated from U.S. Vital Statistics (45), and patients with out-of-hospital cardiac arrests who survived to hospital discharge were estimated from national data (56). Survival after a CHD event was estimated using California data on the ratio of in-hospital survival to 30-day survival (18) and data from Medicare and Seattle, Washington (61, 62). Rates of coronary revascularization were estimated from the National Hospital Discharge Survey (56), with mortality rates estimated from aggregated historical data.

Stroke incidence was assumed to be independent of the risk for new-onset CHD in the same year. The number of strokes requiring hospitalization was also obtained from the 2010 NHDS. Positive predictive values of specific ICD-9 stroke hospital diagnosis codes (430 to 438) were derived by pooling several studies of stroke incidence that compared hospital diagnoses with a gold standard (such as stroke ascertained by the Atherosclerosis Risk in Communities Study, the Rochester Epidemiology Study, or similar criteria) (63). The positive predictive values were applied to age- and sex-specific NHDS cases to estimate total stroke event rates (inclusive of first-ever and recurrent stroke events). Applying 30-day case-fatality rates based on the Atherosclerosis Risk in Communities Study (64, 65) yielded annual mortality rate estimates within the range of stroke rates reported by the Centers for Disease Control and Prevention for 2010. Incidence calibration assumed that 77% of all strokes are incident (first-ever) (66) but that the proportion of first-ever strokes diminished with age (that is, >90% of all strokes are first strokes in persons aged 35 to 44 years and 50% are first strokes in those aged 85 to 94 years). The resulting incidence of stroke requiring hospitalization approximated age- and sex-specific stroke incidence rates observed in U.S. stroke cohort and surveillance studies. The annual probabilities of stroke after MI (67) and the probability of CHD in patients with stroke were based on natural history studies (68–73).

The background prevalence of CVD by age, sex, and CVD disease state (stroke, CHD, or both) in 2010 was estimated from National Health Interview Survey data from 2009 to 2011 (74), with the assumption that the imperfect positive predictive value of survey data is offset by its imperfect sensitivity (75–77). Age-specific prevalences for individual CVD disease states were fitted with polynomial or spline functions of age to obtain smooth, monotonically increasing prevalence. The background prevalence of prior coronary revascularization was estimated from revascularizations done before 2010 and estimated survival after revascularization, and model projections were used to infer the distribution of revascularization by CVD state.

Age- and sex-specific health care costs were estimated using national data (21). Costs for stroke requiring hospitalization, CHD, and acute stroke rehabilitation were estimated by using California hospital data (18) and were deflated using cost–charge ratios and the ratio of the U.S. national average costs to the California average (19, 20). Outpatient costs for chronic CVD in addition to average background health care costs for the first year after the event and for subsequent years were estimated for patients with stroke or CHD diagnosis surveyed in the U.S. Medical Expenditure Panel Survey (MEPS) pooled from 1998 to 2008. Average annual noncardiovascular (background) costs were also estimated from the MEPS (78). All model costs were indexed to 2010 by using the medical component of the Consumer Price Index (22). Disability weights and severity distributions for disease states were based on the Global Burden of Disease disability weights study (23, 24, 79, 80). Individual 10-year atherosclerotic cardiovascular disease risk was assessed by using the 2013 ACC/AHA cardiovascular risk equation (35).

Web-Only References

40. **Bibbins-Domingo K, Coxson P, Pletcher MJ, Lightwood J, Goldman L.** Adolescent overweight and future adult coronary heart disease. N Engl J Med. 2007;357:2371-9. [PMID: 18057339]

41. **Hunink MG, Goldman L, Tosteson AN, Mittleman MA, Goldman PA, Williams LW, et al.** The recent decline in mortality from coronary heart disease, 1980–1990. The effect of secular trends in risk factors and treatment. JAMA. 1997;277:535-42. [PMID: 9032159]

42. **U.S. Census Bureau.** Monthly Postcensal Resident Population by Single Year of Age, Sex, Race and Hispanic Origin for the United States: July 1, 2010 to December 1, 2010 (NC-EST2011-ALLDATA-R-File02). Washington, DC: U.S. Census Bureau; 2011.

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

44. **U.S. Census Bureau.** Methodology and Assumptions for the 2012 National Projections. Washington, DC: U.S. Census Bureau; 2012.

45. **National Center for Health Statistics.** CDC WONDER Database. Underlying Cause of Death, 1999–2010. Atlanta, GA: Centers for Disease Control and Prevention; 2012. Accessed at http://wonder.cdc.gov/ucd-icd10.html on 25 February 2015.

46. **National Center for Health Statistics.** ICD-10 Codes. Atlanta, GA: Centers for Disease Control and Prevention; 2004. Accessed at http://ftp.cdc.gov/pub/Health_Statistics/NCHS/Publications/ICD10/allvalid2011%20(detailed%20titles%20headings).pdf on 25 February 2015.

47. Consensus recommendations for the management of chronic heart failure. On behalf of the membership of the Advisory Council to Improve Outcomes Nationwide in Heart Failure. Am J Cardiol. 1999;83:1A-38A. [PMID: 10072251]

48. **Dawber TR.** The Framingham Study: The Epidemiology of Atherosclerotic Disease. Cambridge, MA: Harvard Univ Pr; 1980.

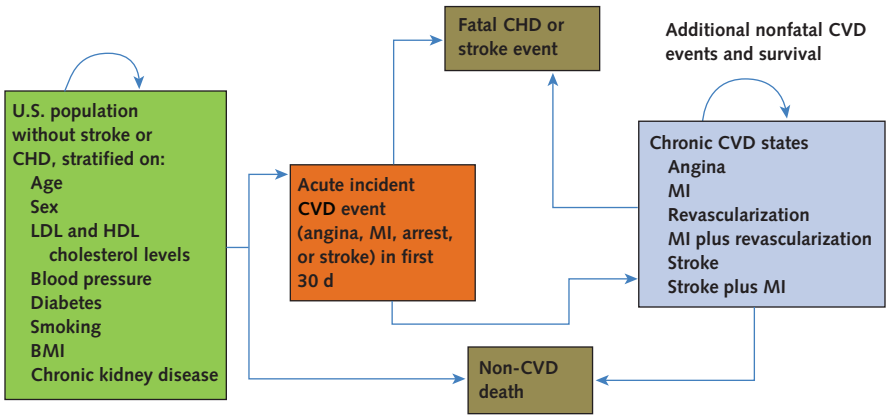
49. **Feinleib M, Kannel WB, Garrison RJ, McNamara PM, Castelli WP.** The Framingham Offspring Study. Design and preliminary data. Prev Med. 1975;4:518-25. [PMID: 1208363]

50. **Brindle P, Emberson J, Lampe F, Walker M, Whincup P, Fahey T, et al.** Predictive accuracy of the Framingham coronary risk score in British men: prospective cohort study. BMJ. 2003;327:1267. [PMID: 14644971]

51. **D'Agostino RB Sr, Grundy S, Sullivan LM, Wilson P; CHD Risk Prediction Group.** Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. JAMA. 2001;286:180-7. [PMID: 11448281]

52. **Liu J, Hong Y, D'Agostino RB Sr, Wu Z, Wang W, Sun J, et al.** Predictive value for the Chinese population of the Framingham CHD risk assessment tool compared with the Chinese Multi-Provincial Cohort Study. JAMA. 2004;291:2591-9. [PMID: 15173150]
53. **Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB.** Prediction of coronary heart disease using risk factor categories. Circulation. 1998;97:1837-47. [PMID: 9603539]
54. **Parish S, Collins R, Peto R, Youngman L, Barton J, Jayne K, et al.** Cigarette smoking, tar yields, and non-fatal myocardial infarction: 14,000 cases and 32,000 controls in the United Kingdom. The International Studies of Infarct Survival (ISIS) Collaborators. BMJ. 1995; 311:471-7. [PMID: 7647641]
55. **Law MR, Morris JK, Wald NJ.** Environmental tobacco smoke exposure and ischaemic heart disease: an evaluation of the evidence. BMJ. 1997;315:973-80. [PMID: 9365294]
56. **National Center for Health Statistics.** National Hospital Discharge Survey. Atlanta, GA: Centers for Disease Control and Prevention; 2010. Accessed at ftp://ftp.cdc.gov/pub/Health_Statistics/NCHS/Datasets/NHDS on 25 February 2015.
57. **Petersen LA, Wright S, Normand SL, Daley J.** Positive predictive value of the diagnosis of acute myocardial infarction in an administrative database. J Gen Intern Med. 1999;14:555-8. [PMID: 10491245]
58. **Canto JG, Rogers WJ, Goldberg RJ, Peterson ED, Wenger NK, Vaccarino V, et al; NRMI Investigators.** Association of age and sex with myocardial infarction symptom presentation and in-hospital mortality. JAMA. 2012;307:813-22. [PMID: 22357832] doi:10.1001/jama.2012.199
59. **Rieves D, Wright G, Gupta G, Shacter E.** Clinical trial (GUSTO-1 and INJECT) evidence of earlier death for men than women after acute myocardial infarction. Am J Cardiol. 2000;85:147-53. [PMID: 10955368]
60. **Vaccarino V, Parsons L, Peterson ED, Rogers WJ, Kiefe CI, Canto J.** Sex differences in mortality after acute myocardial infarction: changes from 1994 to 2006. Arch Intern Med. 2009;169:1767-74. [PMID: 19858434] doi:10.1001/archinternmed.2009.332
61. **Groeneveld PW, Heidenreich PA, Garber AM.** Racial disparity in cardiac procedures and mortality among long-term survivors of cardiac arrest. Circulation. 2003;108:286-91. [PMID: 12835222]
62. **Rea TD, Crouthamel M, Eisenberg MS, Becker LJ, Lima AR.** Temporal patterns in long-term survival after resuscitation from out-of-hospital cardiac arrest. Circulation. 2003;108:1196-201. [PMID: 12939219]
63. **Williams GR, Jiang JG, Matchar DB, Samsa GP.** Incidence and occurrence of total (first-ever and recurrent) stroke. Stroke. 1999;30: 2523-8. [PMID: 10582972]
64. **Rosamond WD, Folsom AR, Chambless LE, Wang CH, McGovern PG, Howard G, et al.** Stroke incidence and survival among middle-aged adults: 9-year follow-up of the Atherosclerosis Risk in Communities (ARIC) cohort. Stroke. 1999;30:736-43. [PMID: 10187871]
65. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators. Am J Epidemiol. 1989;129: 687-702. [PMID: 2646917]
66. **Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, et al; American Heart Association Statistics Committee and Stroke Statistics Subcommittee.** Heart disease and stroke statistics–2014 update: a report from the American Heart Association. Circulation. 2014;129:e28-e292. [PMID: 24352519] doi:10.1161/01.cir.0000441139.02102.80
67. **Witt BJ, Brown RD Jr, Jacobsen SJ, Weston SA, Yawn BP, Roger VL.** A community-based study of stroke incidence after myocardial infarction. Ann Intern Med. 2005;143:785-92. [PMID: 16330789]
68. **Amarenco P, Bogousslavsky J, Callahan A 3rd, Goldstein LB, Hennerici M, Rudolph AE, et al; Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators.** High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med. 2006;355:549-59. [PMID: 16899775]
69. **Appelros P, Gunnarsson KE, Terént A.** Ten-year risk for myocardial infarction in patients with first-ever stroke: a community-based study. Acta Neurol Scand. 2011;124:383-9. [PMID: 21355858] doi: 10.1111/j.1600-0404.2011.01500.x
70. **Behar S, Tanne D, Abinader E, Agmon J, Barzilai J, Friedman Y, et al.** Cerebrovascular accident complicating acute myocardial infarction: incidence, clinical significance and short- and long-term mortality rates. The SPRINT Study Group. Am J Med. 1991;91:45-50. [PMID: 1858828]
71. **Lakshminarayan K, Schissel C, Anderson DC, Vazquez G, Jacobs DR Jr, Ezzeddine M, et al.** Five-year rehospitalization outcomes in a cohort of patients with acute ischemic stroke: Medicare linkage study. Stroke. 2011;42:1556-62. [PMID: 21474798] doi:10.1161/STROKEAHA.110.605600
72. **Prosser J, MacGregor L, Lees KR, Diener HC, Hacke W, Davis S; VISTA Investigators.** Predictors of early cardiac morbidity and mortality after ischemic stroke. Stroke. 2007;38:2295-302. [PMID: 17569877]
73. **Touzé E, Varenne O, Chatellier G, Peyrard S, Rothwell PM, Mas JL.** Risk of myocardial infarction and vascular death after transient ischemic attack and ischemic stroke: a systematic review and meta-analysis. Stroke. 2005;36:2748-55. [PMID: 16254218]
74. **National Center for Health Statistics.** National Health Interview Survey, 2009–2011. Atlanta, GA: Centers for Disease Control and Prevention; 2012. Accessed at ftp://ftp.cdc.gov/pub/Health_Statistics/NCHS/Datasets/NHIS on 25 February 2015.
75. **Bergmann MM, Byers T, Freedman DS, Mokdad A.** Validity of self-reported diagnoses leading to hospitalization: a comparison of self-reports with hospital records in a prospective study of American adults. Am J Epidemiol. 1998;147:969-77. [PMID: 9596475]
76. **Ford ES, Giles WH.** Changes in prevalence of nonfatal coronary heart disease in the United States from 1971–1994. Ethn Dis. 2003; 13:85-93. [PMID: 12723017]
77. **Gross R, Bentur N, Elhayany A, Sherf M, Epstein L.** The validity of self-reports on chronic disease: characteristics of underreporters and implications for the planning of services. Public Health Rev. 1996;24: 167-82. [PMID: 8918183]
78. **Agency for Healthcare Research and Quality.** Medical Expenditure Panel Survey Public Use Files, 1998–2008. Rockville, MD: Agency for Healthcare Research and Quality; 2014. Accessed at http://meps.ahrq.gov/mepsweb on 25 February 2015.
79. **Moran AE, Forouzanfar MH, Roth GA, Mensah GA, Ezzati M, Murray CJ, et al.** Temporal trends in ischemic heart disease mortality in 21 world regions, 1980 to 2010: the Global Burden of Disease 2010 study. Circulation. 2014;129:1483-92. [PMID: 24573352] doi: 10.1161/CIRCULATIONAHA.113.004042
80. **Moran AE, Forouzanfar MH, Roth GA, Mensah GA, Ezzati M, Flaxman A, et al.** The global burden of ischemic heart disease in 1990 and 2010: the Global Burden of Disease 2010 study. Circulation. 2014;129:1493-501. [PMID: 24573351] doi:10.1161/CIRCULATIONAHA.113.004046

Appendix Figure. Cardiovascular Disease Policy Model structure and disease states.



BMI = body mass index; CHD = coronary heart disease; CVD = cardiovascular disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MI = myocardial infarction.