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

Michelle C. Odden, PhD¹, Mark J. Pletcher, MD, MPH², Pamela G. Coxson, PhD³, Divya Thekkethala, B.S.¹, David Guzman, MS³, David Heller, MD³, Lee Goldman, MD, MPH⁴, and Kirsten Bibbins-Domingo, PhD, MD^{2,3}

¹School of Biological and Population Health Sciences, Oregon State University, Corvallis, OR

²Department of Epidemiology and Biostatistics, University of California, San Francisco, CA

³Department of Medicine, University of California, San Francisco, CA

⁴College of Physicians and Surgeons, Columbia University, New York, NY, USA

Abstract

BACKGROUND—Over 40% of adults 75 and older are taking statins, yet there is little evidence to guide primary prevention in this population.

OBJECTIVE—To project the population impact and cost-effectiveness of statin therapy in adults aged 75 years and older.

DESIGN—Forecasting study using the Cardiovascular Disease Policy Model, a Markov model.

DATA SOURCE—Trial, cohort, and nationally-representative data sources.

TARGET POPULATION—U.S. adults aged 75–94 years.

TIME HORIZON—10 years.

PERSPECTIVE—Health care system.

INTERVENTION—Statins for primary prevention based on: 1) Low density lipoprotein cholesterol 4.91 mmol/L (190 mg/dL), 2) 4.14 mmol/L (160 mg/dL), 3) 3.36 mmol/L (130 mg/dL), 4) diabetes, 5) 10-year risk score 7.5% (treat all).

Corresponding Author: Michelle C. Odden, PhD, Oregon State University, 141B Milam Hall, Corvallis, OR, 97331, Ph: 541-737-3184, Fax: 541-737-6914, Michelle.Odden@oregonstate.edu.

Kirsten Bibbins-Domingo is a member of the United States Preventive Services Task Force (USPSTF) and current co-Vice Chair. This work does not necessarily represent the views and policies of the USPSTF.

ADDRESS FOR REPRINT REQUESTS: Michelle C. Odden, PhD, Oregon State University, 141B Milam Hall, Corvallis, OR, 97331
MAILING ADDRESSES:

Dr. Odden and Ms. T Thekkethala: Oregon State University, 141B Milam Hall, Corvallis, OR, 97331

Dr. Pletcher: UCSF Box 0560, 185 Berry Street, Lobby 5, Suite 5700, San Francisco, CA 94107-1762

Drs. Coxson, Heller, and Bibbins-Domingo, and Mr. Guzman: 1001 Potrero Avenue, Building 10, W13, San Francisco, CA 94110
UCSF-SFGH Box# 1364

Dr. Goldman: Columbia University Medical Center, College of Physicians and Surgeons, 630 West 168th Street, 2nd Floor, Room 401, New York, NY 10032

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 at lgoldman@columbia.edu.

Data: All data are publically available and sources are listed in the references of the manuscript and supplemental content.

OUTCOME MEASURES—Myocardial infarction (MI), coronary heart disease (CHD) death, disability adjusted life years, costs

RESULT OF BASE-CASE ANALYSIS—All adults aged 75 and older in NHANES have a 10-year risk score >7.5%. If statins have no effect on functional limitation or cognitive impairment, all primary prevention strategies would prevent MIs and CHD deaths and be cost effective. The broadest strategy, treatment of all adults aged 75–94 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.

RESULT OF SENSITIVITY ANALYSIS—An increased relative risk of functional limitation or mild cognitive impairment in the range of 1.10 to 1.30 could offset the cardiovascular benefits.

LIMITATIONS—Limited trial evidence targeting primary prevention in adults 75 and older.

CONCLUSIONS—At effectiveness similar to trial findings, statins are projected to be cost-effective for primary prevention in adults age 75–94 years; however, even a small increase in geriatric specific side effects could offset the cardiovascular benefit. Improved data on the potential benefits and harms of statins are needed to inform decision-making.

INTRODUCTION

Statins are commonly used in adults aged 75 and older. (1) Despite the widespread use of statins, the evidence for their effectiveness for primary prevention in elderly adults remains unclear, and guidelines for their use in the elderly 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 and 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 atherosclerotic cardiovascular disease;” and suggesting that comorbidities, 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 and older as a part of the American Board of Internal Medicine Choosing Wisely campaign. (3) This recommendation was based on the lack of association of high cholesterol levels and outcomes in older adults, as well as the potential for an increased risk of statin-related adverse events, including cognitive impairment, falls, neuropathy, and muscle damage. (3)

The variation in these treatment recommendations reflects uncertainty regarding the balance between the benefits and risks of statin in older adults compared with younger adults, as well as the more limited evidence base in this population. Adults aged 75 years and 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 the associations between LDL-cholesterol and outcomes are attenuated in older adults. (4–7) Although the baseline risk of cardiovascular disease is increased in older adults, their life expectancy is shorter and their risks of competing mortality are greater. Finally, there has

been concern about geriatric-specific side effects, especially functional limitation due to muscle pain, weakness, and mild cognitive impairment. (8–16)

In the presence of uncertainty regarding 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 of harms. We evaluated the population benefit and cost-effectiveness of statins in persons aged 75 years and 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 aged 75–94 years over the next 10 years.

METHODS

The Model

The Cardiovascular Disease Policy Model (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 75–94 years. The model is composed of three 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, based on age, sex, systolic blood pressure, smoking, high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol, diabetes, body-mass index (BMI), 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 subjects with cardiovascular disease, stratified according to age, sex, and history of cardiovascular disease events. Additionally, persons may exit the model at any stage through a non-CHD, non-stroke 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) Hospitalized stroke and CHD costs and acute stroke rehabilitation costs were estimated using California hospital data, (18) deflated using cost to 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 the year 2014 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 given in the Appendix.

Simulation Inputs

We modeled the effect of statins on LDL cholesterol based on the PROspective Study of Pravastatin in the Elderly at Risk of Vascular Disease (PROSPER) trial, a randomized, placebo controlled trial of 5,804 men and women aged 70–82 years. (25) In this trial, the

mean LDL cholesterol lowering was 34% for participants with an average initial LDL cholesterol of 147 mg/dL, consistent with the estimated effect of a moderate dose statin in the 2013 ACA/AHA guideline. (2) We included three estimates for the effectiveness of LDL-cholesterol lowering on events. The main estimates were derived from extrapolating the age-stratified effect sizes of a 1.0 mmol/L reduction in LDL cholesterol from the Cholesterol Treatment Trialists' (CTT) meta-analysis. (26) We fit a regression line to the three age-strata reported in the CTT analysis (< 60 years, 60– 70 years, and 70 and older) to estimate the effect sizes at 80 and 90 years of age. As 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 on major coronary events in the meta-analysis. We used a low estimate based on the effect size of from PROSPER for primary prevention. (25)

Statin costs were derived from the National Average Drug Acquisition Cost (NADAC) database. (27) Our main cost estimate (\$5.59 for 30-day supply) is an average of the NADAC for the 4 moderate dose statins that are available in generic form: atorvastatin 10 mg, simvastatin 20 mg, pravastatin 40 mg, and lovastatin 40mg. This cost estimate is \$5.00 when indexed to 2010 dollars based on the medical component of the consumer price index. (18) Additionally, we used a low cost estimate of \$4/month, based on the price of generic statins from multiple discount retailers (e.g. Walmart, Target, Walgreens, etc). As a high cost estimate, we used \$30/30 day supply; the low and high cost estimates have been used similarly in other contemporary cost-effectiveness analyses. (28, 29) Adults age 65 years and older are on a median of 4 medications; therefore, we estimated the cost of an additional 0.25 physician visits per year for statin use, assuming that medication management could be covered in one visit. (30) We estimated one lipid panel per year for monitoring. (31, 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 there have been a number of major and minor adverse effects reported to be associated with statin use, we focused on two 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 (MCI). (8–16) Both of these conditions are prevalent in older adults and can have substantial impact on quality of life and ability to live independently. A recent review of late life activity limitations in the U.S. reported data on participants in five nationally representative surveys. The prevalence of activity of daily living (ADL) limitation was 27% in adults 75–84, and 45% in 85 years and older. (33) The population weighted average of these estimates is 32% for adults 75–94 years. A wide variety of prevalence estimates for MCI have been reported due to the differential measures of this condition, as well as the differences between populations. A recent review reported a range of 19–28% for the prevalence of MCI in studies of older U.S. adults; we used the average of the four U.S. studies which was 25%. (34) Disability adjusted life-years for the corresponding states were calculated as 1- the disability weights reported in the Global Burden of Disease Study. (24) Since the statin-associated relative risk of these adverse effects is uncertain, we assumed no elevated risk of 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 that would be required to offset the cardiovascular benefit. In sensitivity analyses, we

estimated the magnitude of this relative risk, based on the following equation: $[(P_{AE} \times RR_{AE}) - P_{AE}] \times DALY_{AE} = DALY\ loss$, where P_{AE} = prevalence of the adverse effects in the population, RR_{AE} = the relative risk of the adverse effects associated with statin use, $DALY_{AE}$ = disability adjusted life-year decrement of the adverse effects, and $DALY\ loss$ = 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 75–94 years in 2014, followed through 2023. We modeled an open cohort which allows younger persons to age into the population. We did not model treatment among the few survivors who reached age 95 years because there are insufficient data to model cardiovascular disease in adults ages 95 years and older. We first conducted a simulation to estimate the impact of statin use for secondary prevention by modeling addition of a statin in all adults 75–94 years with a history of cardiovascular disease and currently not on 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 impact of primary prevention of the three remaining groups identified in the ACC/AHA guidelines: 1) LDL-cholesterol 4.91 mmol/L (190 mg/dL), 2) diabetics, and 3) 10-yr cardiovascular disease risk 7.5%. Ten-year cardiovascular disease risk was assessed by the 2013 ACC/AHA cardiovascular risk equation. (35) We also explored the potential impact of statins for primary prevention based on two alternative LDL-cholesterol thresholds, 4.14 mmol/L (160 mg/dL) and 3.36 mmol/L (130 mg/dL).

As a sensitivity analysis, we extended follow-up for an additional 10 years, from 2024–2033 to evaluate the primary prevention strategies beyond the initial inception years. We conducted sensitivity analyses of both a high and low estimate of effectiveness, as well as analyses that used a high and low cost estimate and the impact of no or one physician visit per year. We further explored the statin-associated reduction in QALYs that would be required to offset the cardiovascular disease benefit of statin use by varying the statin QALY reduction from zero to 0.01. Finally, we used probabilistic sensitivity analyses to vary the effectiveness parameters (LDL cholesterol lowering effect of statins, and the beta-coefficient on risk of CHD for a 1mg/dL lower LDL cholesterol) over the range observed in the published literature (Table 1).

Costs were calculated from the healthcare system perspective. All costs were inflated to 2014 dollars by using the Bureau of Labor Statistics Consumer Price Index for Medical Care Costs. (22) Costs and disability adjusted life-years were discounted at 3%/year. An intervention was defined to be of high value if the cost to extend one disability adjusted life-years was less than \$50,000, intermediate value if the cost was \$50,000 to less than \$150,000, and low value if the cost were greater than or equal to \$150,000. (36)

Role of Funding Source

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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 U.S. are aged 75–94 years, and 30% already have cardiovascular disease. Over the next 10 years with current rates of statin use, this population is projected to experience 2.5 million MIs and 3.1 million CHD deaths, and accrue costs due to cardiovascular disease of \$881 billion (Table 2 & 3). If all adults age 75–94 years with a history of cardiovascular disease who are not currently on 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 decline by approximately \$14 billion.

The potential impact of statins for primary prevention varies by treatment strategy. All adults age 75–94 years in NHANES have an estimated 10-year cardiovascular disease risk of 7.5%, so treatment based on this risk threshold does not discriminate in this population. Adding a statin in currently untreated adults aged 75–94 years with LDL-cholesterol 4.91 mmol/L (190 mg/dL) is 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. (Table 2 & 3) Further lowering the LDL-cholesterol treatment threshold to 4.14 mmol/L (160 mg/dL), which is also projected to be cost saving, would treat substantially more elders, and the number of events prevented would increase accordingly. At a threshold of 3.36 mmol/L (130 mg/dL), over 3 million currently untreated older adults would be treated with statins for primary prevention, and this strategy would prevent 56,000 MIs and 36,000 CHD deaths, and save 108,000 disability adjusted life-years at an estimated cost-effectiveness of \$5,300 per disability adjusted year of life compared with a threshold of 4.14 mmol/L (160 mg/dL). Treatment of all diabetics is dominated by extension and would not be considered a cost-effective alternative to the other strategies presented. If all older adults without a history of cardiovascular disease and not currently on statins were treated, statin use in these estimated 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 3.36 mmol/L (130 mg/dL) threshold.

When the population is stratified by age and sex, all primary prevention strategies are cost-saving or of high value in men and women aged 75–84 and 85–94 years compared with secondary prevention alone. The primary prevention strategies in men are nearly all cost-saving, and all strategies are of high value in women compared with secondary prevention. (Table e1) In the second decade of implementation of these statin therapy strategies (2024–2033), secondary prevention is projected to be no longer cost saving, but remains of high value. Additionally, the ICERs between primary prevention and secondary prevention are modestly attenuated. (Table e2)

The benefit observed in the primary prevention strategies is sensitive to assumptions regarding the magnitude of potential harms. Based on a strategy of treating those with an LDL-cholesterol 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 1). Notably, 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 1) This reduction translates into a relative risks that range from 1.10 to 1.24 for functional limitation and 1.12 to 1.29 for mild cognitive impairment (Table 4).

One-way sensitivity analyses demonstrate that the cost-effectiveness ratios of the primary prevention strategies are sensitive to effectiveness and cost estimates for statins. (Table 5) At a lower estimate of effectiveness or a statin cost of \$30/month, only treating those with an LDL-cholesterol 4.91 mmol/L (190 mg/dL) remains of high value. In contrast, if effectiveness of statins in adults 75 years and older is comparable to that observed a younger population, or if older adults are able to obtain statins for \$4/month, then any primary preventions strategy would be cost-saving or of very high value.

Based on probabilistic sensitivity analyses, the findings for the primary prevention strategies appear consistent. Compared with treating those with a history of cardiovascular disease only, the treat LDL-cholesterol 4.91 mmol/L (190 mg/dL) strategy is projected to prevent 8,000 MIs (95% CI: 6,000,11,000), the 4.14 mmol/L (160 mg/dL) strategy, 26,000 MIs (95% CI: 17,000, 35,000), the 3.36 mmol/L (130 mg/dL) strategy, 56,000 MIs (95% CI: 39,000, 74,000), the treat DM strategy, 29,000 MIs (95% CI: 22,000, 37,000), and the treat all strategy, 105,000 MIs (95% CI: 75,000, 135,000). Of the primary prevention strategies, 70% of the treat LDL-cholesterol 4.91 mmol/L (190 mg/dL) simulations, 51% of the 4.14 mmol/L (160 mg/dL) simulations, 32% of the 3.36 mmol/L (130 mg/dL) simulations, and 21% of the treat all simulations were cost saving; and 99%, 94%, 83%, and 81% were of high value with a cost per disability adjusted life-year of <\$50,000.

DISCUSSION

Based on currently available data, we project that generic statins are cost-effective for primary prevention in adults aged 75–94 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 of functional limitation or cognitive impairment could offset the cardiovascular benefit. Additionally, our estimates of the value of statin use for primary prevention were susceptible to varying assumptions regarding effectiveness and cost. Due to the sensitivity of our findings to these parameters, studies to quantify both 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 of 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 through clinical trials, less systematic data exist on the potential risks of statins. Clinical trials are likely to include healthier participants compared with the general population, so the risks of an intervention in a representative patient population are uncertain. Additionally, mild-to-moderate adverse effects may be underreported in post-marketing 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 impact on quality of life and independence. (8–16). Unlike previous analyses which showed that a large theoretical adverse effect would be required to counterbalance the cardiovascular benefits in the general population (28), our analysis showed that in older adults even a small adverse effect of statins on functional limitation and mild cognitive impairment could result in net harm. In our simulations, a 10–30% increased risk of these side effects would offset the cardiovascular benefit. Our results provide strong motivation for further investigations into the incidence of side effects from statins in a diverse group of elders, including those who are frail and have complex comorbidity. Due to the sample size required to identify potential risks in a diverse population, pragmatic trials and improved post-marketing 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 side effects, including rhabdomyolysis, liver failure, and peripheral neuropathy appear to be rare, (37) and prior simulations have suggested that the rarity of these events results in a risk-to-benefit ratio that favors statin use. (28, 38, 39) The risk of statin-associated diabetes is modest, (37, 39) and the time interval from the incidence of diabetes and clinically observable events is generally delayed and may be less concerning in older adults compared with the immediate risk of a coronary event. We also did not include the potential benefit of statins on kidney function and peripheral arterial disease because, similar to diabetes, the time interval from the incidence of these conditions until 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 both 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, as there will always be unpredicted changes that can impact results. Our projections have limitations that should be considered when interpreting the findings. The primary limitation, as has been noted by professional groups, is the lack of high-quality evidence targeting primary prevention in adults 75 and 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 worse if older adults use newer agents that have yet to become generic. Additionally, pleiotropic effects or a

beneficial effect of statins on kidney function or peripheral arterial disease, or a harmful effect on diabetes risks could alter our estimates of the benefit to harm ratio.

In summary, statins are projected to be cost effective for primary prevention of cardiovascular disease in a 75 to 94 year old population that derives a relative benefit similar to what was observed in randomized controlled trials, assuming a low monthly cost of statins. More research on effectiveness and potential harms in a diverse population of elders is needed to inform decision-making in populations of older adults who may be frail or have multiple chronic health conditions. Since 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 needs and care goals, and the critical need to give patients and providers tools to make healthcare decisions that balance both potential benefits and potential harms, studies that leverage existing infrastructure may prove most useful for providing this important data in a timely manner.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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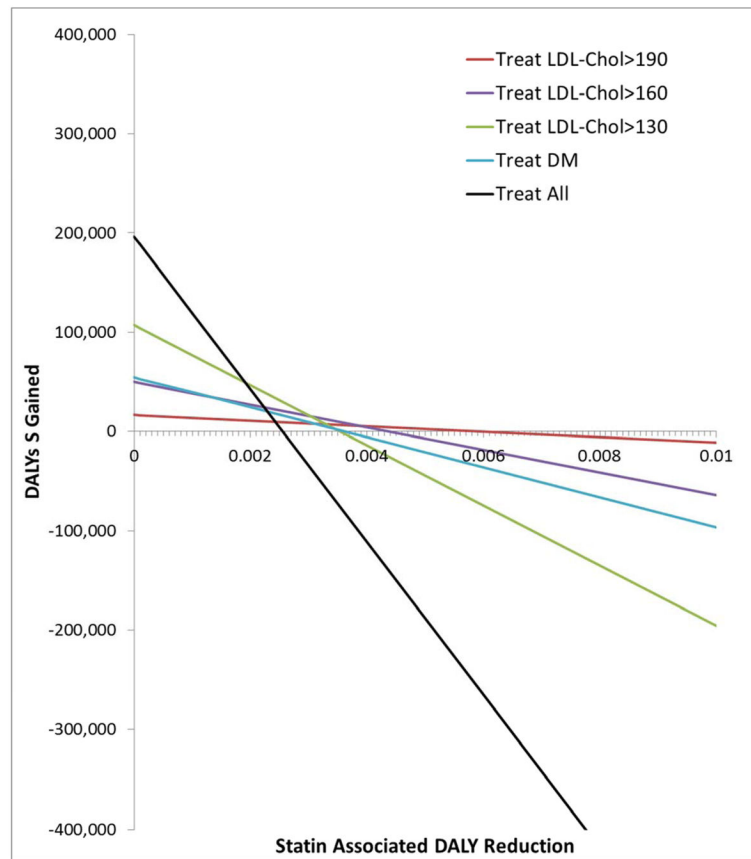


Figure 1. Sensitivity analysis of magnitude of statin associated disability adjusted life-year reduction that would be needed to offset the cardiovascular benefit. The value of the statin-associated disability adjusted life-year reduction at which the lines cross the x-axis is the magnitude needed to offset the cardiovascular benefit and result in no net disability adjusted life-years gained.

Table 1

Inputs for simulation

Input		Effect Size	Reference
EFFECTIVENESS			
LDL-C Lowering from statins		34% (95% CI: 20.4, 47.6)	(2, 25)
Beta-Coefficient, per mg/dL of LDL-C			
	Stroke	0	(25)
	CHD Base Case	0.004 (SD 0.0006) 0.003 (SD 0.0006)	(26)
	CHD Low Sensitivity	0.001	(25)
	CHD High Sensitivity	0.007	(26)
COST			
Medication Costs			
	Base Case	\$5/30/days	(27)
	Low Sensitivity	\$4/30 days	(29)
	High Sensitivity	\$30/30 days	(29)
Physician Visit	1 every 4 years	\$67	(31)
Lipid Panel		\$19	(32)
Creatine Kinase	3 tests per myopathy case	\$9.33	(32)
Hospitalization from stroke		\$15,000	(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		2 Months	Clinical judgment
QALY Reduction of Myopathy	(musculoskeletal problems, severe)	0.606	(24)
QALY Reduction of Stroke	(moderate plus cognition problems)	0.312	(24)
GERIATRIC-SPECIFIC			
ADVERSE EFFECTS			
Statin Associated Disability	Base Case	0	Clinical judgment
Adjusted Life-Year Reduction due to Functional Limitation or Mild Cognitive Impairment	Sensitivity	0–0.01	Clinical judgment
Prevalence of Functional Limitation		32%	(33)
Disability Adjusted Life-Year Reduction of Functional Limitation		0.076	(24)
Prevalence of Mild Cognitive Impairment		25%	(34)
Disability Adjusted Life Year Reduction of Mild Cognitive Impairment		0.082	(24)
10-YEAR CVD RISK		>7.5% for all 75 years	(35)

Abbreviations: LDL-C = low-density lipoprotein cholesterol; CHD = CHD

Table 2
Population impact of multiple strategies for statin use in U.S. adults (2014–2023)

Treatment Strategy	Primary Prevention Treated in First Year	MI	CHD Deaths	Total Disability Adjusted Life-Years	N (%) reduction in MI	N (%) reduction in CHD Deaths	N (%) increase in Disability Adjusted Life-Years
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 4.91 mmol/L (190 mg/dL)	312,000	2,422,000	3,008,000	180,065,000	8,000 (0.3%)	6,000 (0.2%)	17,000 (0.01%)
LDL-C 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 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%)
Diabetics	1,500,000	2,401,000	2,995,000	180,103,000	29,000 (1.2%)	19,000 (0.6%)	55,000 (0.03%)
Treat 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%)

Abbreviations: LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction, CHD = CHD; CVD = cardiovascular disease

Table 3
 Cost-effectiveness of multiple strategies for statin use in U.S. adults (2014–2023)

Treatment Strategy	Total Cost (millions)	CVD Costs (Millions)	Rank*	ICER ^{†‡}	CER Compared to 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	\$4,346,000	\$866,100	2	Cost saving	Cost saving
LDL-C 4.91 mmol/L (190 mg/dL)					
LDL-C 4.14 mmol/L (160 mg/dL)	\$4,345,900	\$862,400	3	Cost saving	Cost-Saving
LDL-C 3.36 mmol/L (130 mg/dL)	\$4,346,200	\$861,600	5	\$5,300	\$400
3.36 mmol/L (130 mg/dL)Diabetics	\$4,346,200	\$864,200	4	Dominated	\$460
Treat All	\$4,348,500	\$856,900	6	\$25,200	\$11,600

* Based on least (1) to most (6) disability adjusted life-years gained

† Compared with the next less effective non-dominated strategy

‡ Calculations may not work out exactly due to rounding

Abbreviations: LDL-C = low-density lipoprotein cholesterol; CVD = cardiovascular disease; ICER = incremental cost-effectiveness ratio; CER = cost-effectiveness ratio

Table 4
Hypothetical Relative Risk of Adverse Effects Required to Offset CVD Benefit under Base Case Assumptions

	LDL-C 4.91 mmol/L (190 mg/dL)	LDL-C 4.14 mmol/L (160 mg/dL)	LDL-C 3.36 mmol/L (130 mg/dL)	Diabetics	Treat 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)

Abbreviations: LDL-C = low-density lipoprotein cholesterol

Table 5

One-way sensitivity analyses varying effectiveness and cost parameters

	Cost-Effectiveness Ratio Compared with Secondary Prevention (\$ per disability adjusted life-year)						Treat All	
	LDL-C	4.91 mmol/L (190 mg/dL)	LDL-C	4.14 mmol/L (160 mg/dL)	LDL-C	3.36 mmol/L (130 mg/dL)		Diabetics
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/month)	\$ 46,800		\$ 72,400		\$ 96,500	\$ 95,000	\$ 144,900
	Low (\$4/month)	Cost Saving		Cost Saving		Cost Saving	Cost Saving	\$6,400
Physician Visit [‡]	Annual Physician Visit	Cost Saving		\$7,500		\$16,200	\$16,000	\$33,600
	No Physician Visit	Cost Saving		Cost Saving		Cost Saving	Cost Saving	\$4,200

* Base case: beta-coefficient = 0.004 per mg/dL LDL cholesterol for 75–84 years, 0.003 for 85–94 years; low: 0.001; high: 0.007

[†] Base case: \$5/30 day supply

[‡] Base case: 0.25 physician visit per year

Abbreviations: LDL-C = low-density lipoprotein cholesterol