Appendix: Detailed methods of cost-utility analysis

Target population

In the reference case, we evaluated a simulated cohort of middle-aged patients at low cardiovascular risk. On average, simulated patients were 59 years old (the mean age of participants in the statin trials) and matched the definition of "low risk" used in the accompanying systematic review (i.e., a 10-year risk of cardiovascular-related death or nonfatal myocardial infarction of < 20%).[1] This approximates risk in patients free from cardiovascular disease and diabetes at baseline. Since there is controversy regarding what constitutes low risk, we also considered the cost-effectiveness of statins using other definitions of "low cardiovascular risk," including a projected average 10-year risk of cardiovascular-related death or nonfatal myocardial infarction < 10%.[2]

Treatment comparators

We categorized low-potency statins (fluvastatin, lovastatin, pravastatin and simvastatin) as those that lowered low-density lipoprotein (LDL) cholesterol by about 27%, and high-potency statins (atorvastatin and rosuvastatin) as those that lowered LDL cholesterol by about 55%.[3,4] We modeled three strategies: 1) no statin use, 2) use of low-potency statins and 3) use of high-potency statins. All strategies also included dietary and lifestyle advice.

Analytical approach

Our analysis was performed according to existing Canadian guidelines.[5] We used the perspective of Canada's publicly funded health care system, in which direct costs to the health care system and the patient, including time and travel costs, were included, consistent with current Canadian guidelines.[5] Costs to patients, including time and travel costs, were included where relevant differences were expected between the groups (i.e., additional visits for laboratory testing in the statin group). For the primary analysis, we used mathematical Markov modelling of a low-risk patient cohort over their lifetime (see Figure 1 in the main article), discounting costs and health outcomes at 5%.[5] The model included clinical states reflective of the outcomes reported in the randomized trials, such as nonfatal stroke and nonfatal myocardial infarction, unstable angina necessitating hospital admission, and death. Because adverse events or intolerance to statins can also develop, or patients may simply stop using statins, we included health states where patients discontinued statins. Model outcomes included cost, quality-adjusted life-years (QALYs) gained, and the cost per QALY gained.

Cardiovascular events with and without statins

For patients managed without statins, we calculated a pooled event rate, using a random-effects model, based on the event rates in control arms reported in the randomized trials included in a recent systematic review.[6] For patients receiving low- and high-potency statins, we modeled the risk of cardiovascular and adverse events, using the relevant pooled relative risk from the systematic review.

Because randomized trials reported the occurrence of nonfatal cardiovascular events and death separately, in our reference case, we modeled the occurrence of cardiovascular

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events and death independently for the initial three years of the model (reflecting the mean duration of the randomized trials). After three years, for patients not experiencing a cardiovascular event, and for those who continued to adhere to statin therapy, we assumed that statin therapy and the clinical benefits of statin treatment continued indefinitely. After the first three years, the survival and risk of cardiovascular events for patients in the event-free group in each of the strategies were extrapolated from the results of the systematic review and adjusted to account for the increasing age of the cohort based on Statistics Canada mortality tables.[7]

For patients experiencing a nonfatal cardiovascular event, in all three treatment strategies, we assumed that patients would subsequently be prescribed a high-potency statin.[8] Survival of these patients after three years was based on a cohort of nondiabetic people who survived myocardial infarction taken from the Alberta Provincial Project for Outcomes Assessment in Coronary Heart (APPROACH) disease database; a geographically defined cohort of patients undergoing cardiac catheterization.[9] We used this cohort to define subsequent outcomes because it provided long-term survival estimates and costs (up to 15 years), including utility estimates for survivors of first myocardial infarction and unstable angina. Moreover, because information on hospital readmission, costs and survival is available for all patients in this cohort, our analysis includes the impact of recurrent events.

For all treatment strategies, a proportion of low-risk patients acquire additional cardiovascular risk factors (e.g., diabetes) and thus move to a higher cardiovascular risk status. In the reference case, transition to high-risk cardiovascular status was based on the development of diabetes, because this risk was accurately reported within the randomized trials. Higher rates of transition to high-risk status were considered in sensitivity analyses. We assumed that all high-risk patients would begin to receive high-potency statins, with subsequent survival based on the reported risk of death among diabetic patients receiving statins in a meta-analysis of 14 randomized trials.[3]

Non-adherence and intolerance to statin therapy

We assumed patients may stop taking statins for three broad reasons. First, they may develop serious adverse events, including rhabdomyolysis or liver toxicity; this risk is very small and was taken from the accompanying systematic review (see Table 1 of the main article). Alternatively, patients may discontinue statin therapy because of intolerance (e.g., due to myalgias), or simply fail to adhere to therapy for a variety of other reasons. Because it is difficult to distinguish this in practice, we took the proportion of patients who become intolerant of statins or nonadherent from a systematic review of observational studies,[10] considering a wide range of values within sensitivity analyses.

Health-related quality of life

Because our systematic review found no trials reporting quality of life in participants,[6] the reference case assumed no difference in utility of health care resources for statin users. However, because tatins might preserve quality of life by avoiding functional limitations associated with stroke or myocardial infarction, we completed a focused literature search to estimate utility among patients surviving a cardiovascular event, with preference given to studies that used a validated utility measure and studies performed in

a Canadian (or similar) setting (eTable 1). The utility among survivors of stroke is driven primarily by the proportion of patients with severe stroke, which was taken from a prospective study documenting the proportion of stroke survivors at baseline and one year[11] (see Table 1 of the main article).

Estimation of costs

The most accurate method of determining average drug costs is controversial since dosing used in clinical trials is often driven by protocol, and does not reflect actual clinical practice. To determine real-world utilization of the various types and doses of statins, we used data from a provincial research database [Alberta Kidney Disease Network (AKDN)].[12] From a cohort of participants who were ≥65 years in 2006 (and thus had available data on prescription drug use, n=1,532,600), we selected a low risk cohort by excluding all patients with diabetes, cardiovascular disease, congestive heart failure, and peripheral vascular disease using claims data and validated algorithms.[13,14] Of the remainder (n=1,324,447), 73,339 patients were prescribed at least one statin in 2006. The cost of low- and high-potency statins was taken from Alberta Blue Cross (the provincial drug insurer for Alberta Health and Wellness[15]). We estimated the annual cost of low- and high-potency statins by weighting the annual cost for each statin and dose formulation by the proportion of patients receiving each treatment. The weighted annual cost of low- and high-potency statins for these 73,339 low-risk statin users, including dispensing fees, was $527 and $790, respectively.

Guidelines recommend monitoring liver function and creatine kinase,[16] which we assumed would occur at baseline and annually thereafter. The direct cost for this laboratory monitoring is $38 per test,[17] while the indirect costs relating to travel and time costs for laboratory monitoring was $36. We assumed an additional physician visit each year for reviewing laboratory tests and renewing the statin prescription ($35) (see Table 2 in the main article).

Given a lack of published Canadian estimates, we utilized several local databases to estimate ongoing costs of care (see Table 2 in the main article). The APPROACH database[9] provided costs for non-fatal myocardial infarction, hospitalization for unstable angina, revascularization, and the cost of caring for long-term survivors after a cardiovascular event. The Calgary Health Region administrative costing database provided information on the costs on nonfatal stroke.[18]

Budget impact analysis

We used the 2007 Canadian Community Health Survey (18) to estimate the proportion of Canadians who might fit various criteria for low cardiovascular risk. We used various definitions ranging from very low to low risk: a) age >40, no heart disease, diabetes or stroke; b) men aged >50, women aged >60, no heart disease, diabetes or stroke, and; c) men aged >50, women aged >60, without heart disease, diabetes or stroke but with either hypertension or who smoke. Since medication use and LDL-C levels were not available from the Canadian Community Health Survey, we used the results of the National Health and Nutrition Examination Survey, a nationally representative longitudinal survey of the US population, to estimate statin use and LDL-C levels in

these different risk groups defined by the Canadian Community Health Survey.[20] To determine the incremental number of Canadians who would meet criteria for a statin, we combined the population estimates from the Canadian Community Health Survey with data from National Health and Nutrition Examination Survey reporting the proportion of low-risk patients currently not taking a statin. Since it is uncertain whether physicians would also take LDL-C levels into account when prescribing statins for patients not on statins in the National Health and Nutrition Examination Survey dataset, we stratified the sample into patients with LDL-C levels <2.5, 2.5–4.5 and >4.5 mmol/L.

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eTable 1: Utility estimates

Health state	Utility	Confidence interval	Source
Low cardiovascular risk patient	0.92	(0.91-0.93)	Levy et al.[21]
Myocardial infarction, year 1	0.85	(0.84-0.86)	APPROACH[9]
Post-hospitalization for unstable angina	0.77	(0.74-0.80)	APPROACH[9]
Mild/moderate stroke (Modified Rankin score 0-3)	0.76	(0.72-0.80)	Gage et al.[22]
Severe stroke (Modified Rankin score 4-6)	0.39	(0.36-0.42)	Gage et al.[22]
Longterm survivors of cardiovascular event	0.85	(0.82-0.87)	APPROACH[9]
Patients with diabetes	0.88	(0.87-0.89)	Levy et al.[21]

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eTable 2: Annual predicted drug expenditures in Canada for statin use in low risk patients using various definitions for low risk

Population		Treat regardless of LDL-C	Treat only if LDL-C > 2.5 mmol/L	Treat only if LDL-C > 4.5 mmol/L
Age > 40 yr, no heart disease, diabetes or stroke and not currently on a statin	No. of Canadians who would be eligible for therapy	11.6 M	9.6 M	1.1 M
	Financial impact – all patients use low-potency statins ($)	6.12 B	5.08 B	577.3 M
	Financial impact – all patients use high-potency statins ($)	9.17 B	7.62 B	865.0 M
	Financial impact – all patients use generic atorvastatin at 45% of brand price ($)*	4.79B	3.98B	451.8 M
Men > 50 yr, women > 60 yr, no heart disease diabetes or stroke and not currently on a statin	No. of Canadians who would be eligible for therapy	5.17 M	4.43 M	538,348
	Financial impact – all patients use low-potency statins ($)	2.72 B	2.33 B	283.8 M
	Financial impact – all patients use high-potency statins ($)	4.08 B	3.50 B	425.3 M
	Financial impact – all patients use generic atorvastatin at 45% of brand price ($)*	2.13 B	1.83 B	222.1 M
Men > 50 yr, women > 60 yr, no heart disease diabetes or stroke and either hypertensive or smoker and not currently on a statin	No. of Canadians who would be eligible for therapy	4.03 M	3.41 M	374,014
	Financial impact – all patients use low-potency statins ($)	2.13 B	1.79 B	197.2 M
	Financial impact – all patients use high-potency statins ($)	3.19 B	2.69 B	295.5 M
	Financial impact – all patients use generic atorvastatin at 45% of brand price ($)*	1.67 B	1.41 B	154.3 M

B = billions; M = millions.
Note: this table does not take into account any potential savings from averted cardiovascular events, or additional costs related to additional survivors resulting from statin use.
*Price for generic atorvastatin per dose reported in Alberta (www.ab.bluecross.ca/dbl/publications.html), and assuming that the clinical effectiveness of atorvastatin is representative of the high-potency statins as a class.

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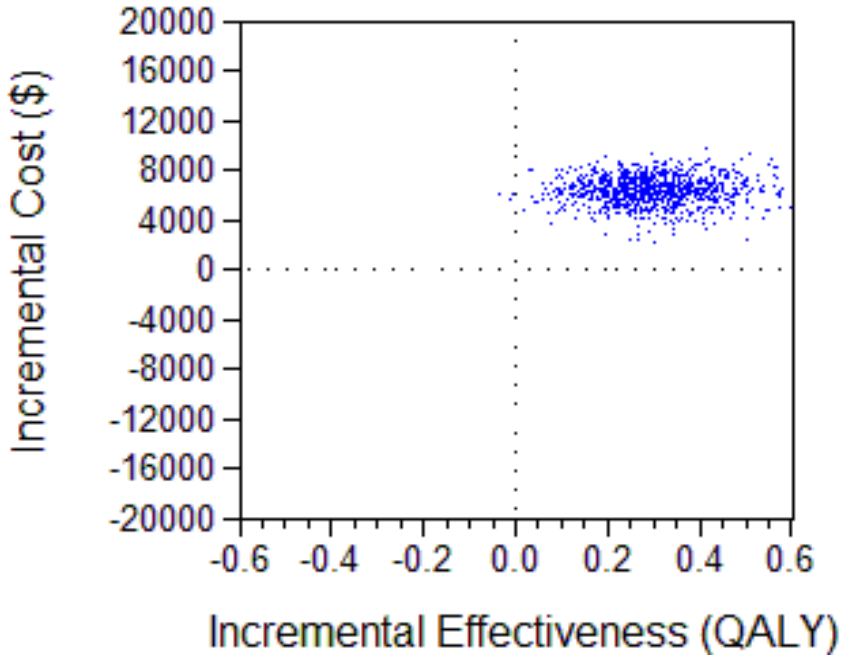
eFigure 1: Scatterplot of incremental cost-effectiveness of treatment with high-potency statin compared with no statin.



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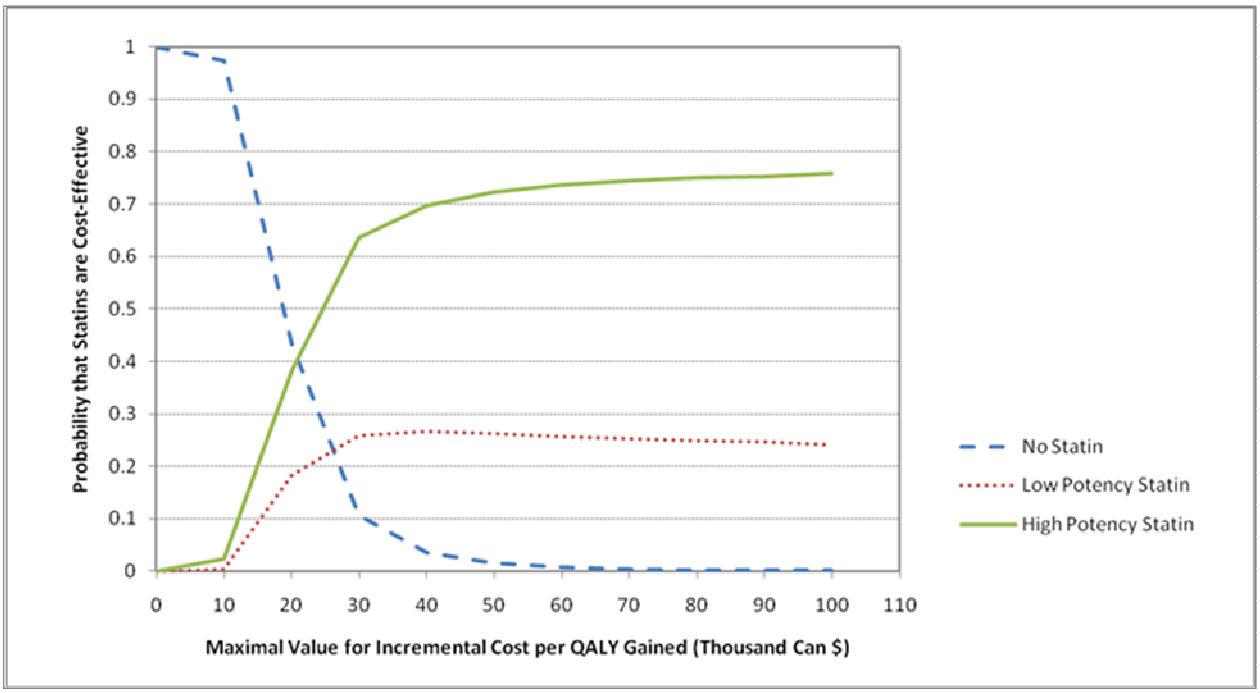
eFigure 2: Cost-effectiveness acceptability curves for treatment with low- and high-potency statins.



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