# Cost-effectiveness of 3-Hydroxy-3-Methylglutaryl–Coenzyme A Reductase Inhibitors in the Secondary Prevention of Cardiovascular Disease

## *Forecasting the Incremental Benefits of Preventing Coronary and Cerebrovascular Events*

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**Objective:** To forecast the long-term benefits and cost-effectiveness of lipid modification in the secondary prevention of cardiovascular disease.

**Methods:** A validated model based on data from the Lipid Research Clinics cohort was used to estimate the benefits and cost-effectiveness of lipid modification with 3-hydroxy-3-methylglutaryl–coenzyme A reductase inhibitors (statins) based on results from the Scandinavian Simvastatin Survival Study (4S), including a 35% decrease in low-density-lipoprotein (LDL)–cholesterol levels and an 8% increase in high-density-lipoprotein (HDL)–cholesterol levels. After comparing the short-term outcomes predicted for the 4S with the results actually observed, we forecast the long-term risk of recurrent myocardial infarction, congestive heart failure, transient ischemic attacks, arrhythmias, and strokes and the need for surgical procedures such as coronary artery bypass grafting, catheterization, angioplasty, and pacemaker insertions. Outpatient follow-up care costs were estimated, as were the costs of hospital care and drug therapy. All costs were expressed in 1996 US dollars.

**Results:** The short-term outcomes predicted for the 4S were consistent with the observed results. The long-term benefits of lipid modification among low-risk subjects (normotensive nonsmokers) with a baseline LDL/HDL ratio of 5 but no other risk factors ranged from $5424 to $9548 per year of life saved for men and $8389 to $13 747 per year of life saved for women. In high-risk subjects (hypertensive smokers) with an LDL/HDL ratio of 5, the estimated costs ranged from $4487 to $8532 per year of life saved in men and $5138 to $8389 per year of life saved in women. Assuming that lipid modification has no effect on the risk of stroke, cost-effectiveness increased by as much as 100%.

**Conclusions:** These long-term cost estimates are consistent with the short-term economic analyses of the published 4S results. The long-term treatment of hyperlipidemia in secondary prevention is forecasted to be cost-effective across a broad range of patients between 40 and 70 years of age. Recognizing the additional effects of lipid changes on cerebrovascular events can substantially improve the cost-effectiveness of treating hyperlipidemia.

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CARDIOVASCULAR disease (CVD), including coronary heart disease (CHD) and stroke, is the leading cause of death in most industrialized countries.[1] Accordingly, much attention has been focused on recent clinical trials demonstrating that lipid modification with 3-hydroxy-3-methylglutaryl–coenzyme A reductase inhibitors (statins) can reduce the morbidity and mortality of secondary events among adults diagnosed as having CHD.[2-4]

The scientific proof that lipid modification is clinically effective in secondary prevention provides a strong rationale for evaluating all patients with coronary artery disease for hyperlipidemia. Statistically significant trial results among specific patient groups, however, do not necessarily prove that all of these patients will benefit clinically from lipid therapy. For instance, persons with shortened life expectancies or other major medical problems are less likely to benefit substantially from modifying specific risk factors for CHD. The costs of lipid therapy or managing other risk factors for CHD are also substantial enough that patients and third-party payers will increasingly ask whether the costs of long-term treatment are justified by the anticipated benefits.[5-10]

A recent pharmacoeconomic analysis of the Scandinavian Simvastatin Survival Study (4S)[6] has calculated the cost-effectiveness of statin therapy in secondary prevention. Based directly on the 4S data, this analysis included a 5-year period. For most patients, however, treatment will be

## METHODS

The CVD life-expectancy model is designed to estimate the benefits and costs associated with modifying risk factors for CVD. Although this model can be used in both primary and secondary prevention settings,[5] this analysis focuses on the benefits and cost-effectiveness of lipid modification achieved following treatment with a statin in the secondary prevention of CVD. The benefits of modifying CVD risk factors are estimated as years of life saved (YOLS). The economic perspective is that of a third party providing comprehensive coverage of all health care services. Estimated health care costs include hospitalization costs occurring either as a consequence of cardiovascular events or related procedures, the yearly costs associated with prevention measures, and the medical follow-up of patients with symptomatic CVD.

### CARDIOVASCULAR LIFE-EXPECTANCY MODEL

Among persons with diagnosed CVD, including CHD, cerebrovascular disease, or peripheral vascular disease, the model describes the yearly transitions to secondary CVD end points such as nonfatal myocardial infarction (MI), congestive heart failure (CHF), transient ischemic attack (TIA), and stroke, as well as fatal end points such as fatal MI, sudden coronary death, stroke death, and death from other causes. The yearly probabilities associated with transitions to fatal events are estimated using multivariate logistic regression coefficients derived from the Lipid Research Clinics Program prevalence and follow-up data.[11-15]

This study[14] was conducted from 1972 to 1976 in 10 North American clinics and focused on an "abnormal lipid" group and a representative 15% random sample to determine the prevalence of dyslipoproteinemias and related factors. The cardiovascular life-expectancy model was derived using data from the 15% random sample. At baseline, persons were classified as having CVD (5% of subjects) if they had definite coronary artery disease or myocardial ischemia at study entry, suffered a stroke or TIA, or reported symptoms consistent with peripheral vascular disease.[11,14,16]

The model has been previously described[5] in detail. Briefly, multivariate logistic regression equations were developed for coronary death, stroke death, and death from other causes incorporating independent covariates such as age, sex, mean blood pressure (two thirds the diastolic pressure and one third the systolic pressure), the natural logarithm transformation of the low-density-lipoprotein (LDL)– over high-density-lipoprotein (HDL)–cholesterol levels, and the presence of cigarette smoking or glucose intolerance.

All subjects were assumed to have CVD at entry into the model and could suffer nonfatal secondary events, including MI, CHF, TIA, and strokes. Because we assumed that lipid therapy reduces the risk of fatal and nonfatal events to the same extent, the probabilities of nonfatal events were estimated from the ratio of nonfatal to fatal events based on the reported results averaged across both arms of the 4S.[2] Age- and sex-specific probabilities of CHF developing were derived from Framingham Study reports.[17]

### ESTIMATING THE BENEFITS OF LIPID MODIFICATION

A cohort of patients with CVD (N = 1000) is entered into the model at a given age with specified levels of risk factors. Each year, subjects can either die of coronary artery disease following an MI or sudden coronary death, die of cerebrovascular disease following a stroke, die of other causes, or survive with or without experiencing another CVD event. Subjects surviving are aged 1 year and reenter the model for the following year. This process continues until all subjects have died or have reached 102 years of age. At this point, the remaining subjects are assumed to die, and mean life expectancy can be calculated by summing across the total person years of life enjoyed by the cohort and dividing by the cohort size at entry into the model (ie, 1000).

When comparing treatments having a differential effect on risk factors, the benefits associated with one treatment over the other are calculated as the YOLS due to the "first" treatment over the "second" treatment. This value is computed as $YOLS = LE_{first} - LE_{second}$, in which LE indicates life expectancy.

### ESTIMATING HEALTH CARE COSTS

Treatment costs were assigned to each of the following acute, nonsurgical events: sudden death, fatal MI, nonfatal MI (with or without cardiac catheterization), CHF (with or without complications), arrhythmia (with or without complications), stroke, and TIA. Treatment costs for each CVD medical event included the costs of hospitalization, physician fees, and outpatient and emergency services when applicable.

Hospital costs for each medical event were estimated using the Canadian Institute for Health Information methods.[18] The medical records of more than 85% of all Canadian patients discharged from acute care hospitals (4.5 million patient records per year) are categorized into case-mix groups that are the equivalents of the US diagnosis-related groups. Each case-mix group is assigned a relative cost based on the intensity of resource use (the corresponding resource-intensity weight for that case-mix group). The resource-intensity weights were developed by the Canadian Institute for Health Information to adjust hospital inpatient costs for the systematic differences in resource use across diagnoses. The Maryland hospital inpatient database was used to derive resource-intensity weights in Canada.

Costs of surgical hospital inpatient care for patients experiencing CVD events also included probability-weighted costs of the following procedures: coronary artery bypass grafting (with or without catheterization, complications, and comorbidities), angioplasty (with or without complications and comorbidities), coronary artery catheterization (with or without complex diagnoses), permanent and temporary pacemaker insertion, and pacemaker replacement (with or without complications and comorbidities). Costs per admission for surgical procedures were calculated as previously described for acute medical care hospital admissions.

The age- and sex-specific probabilities of undergoing each surgical procedure were based on the relative annual

separations for surgical procedures compared with the number of hospital admissions for acute MI in Canada (Statistics Canada, Ontario, special tabulation, November 1996). Because these proportions change as persons grow older, and given the number of estimated MI episodes over the lifetime of patients with CVD from our model, we calculated the number of surgical procedures performed on patients with CVD over time, stratified by sex. We chose the MI episodes as the critical denominator because these events are based on relatively reliable diagnoses.

The mean costs of physician services for emergency, inpatient and outpatient care, and laboratory services were based on reimbursement fee schedules from Quebec and Ontario.[19-21] All costs were calculated in 1996 Canadian dollars, using the Canadian hospital expenditure implicit price indices when applicable (Statistics Canada, National Accounts and Environment Division, written communication, November 1996). All costs were then converted to US dollars at the 1996 exchange rate (US $1 = Can $1.36).[22]

Outpatient care costs included costs of outpatient physician visits, diagnostic tests, and drugs. Outpatient care costs for survivors of CVD events included separate cost estimates for the first year after the event and the subsequent years. The annual health care costs of nonacute care were estimated separately for patients with CHD alone, CHD and TIA, and CHD and stroke.

The cost of stroke, in addition to hospital admission and outpatient care costs, included the costs of first-year poststroke rehabilitation and of ongoing care for those discharged to long-term care facilities. The age- and sex-specific data on discharge destinations after an initial episode of stroke were obtained from the Quebec hospital discharge database (Nancy Mayo, PhD, Division of Clinical Epidemiology, Royal Victoria Hospital, Montreal, written communication, April 1994). We assumed that among men and women younger than 65 years who underwent rehabilitation, 95% would return home and 5% would be transferred to long-term care facilities. The success of rehabilitation would decrease to 85% for those 65 to 79 years old and to 75% for those aged 80 years or older.

The cost of rehabilitation therapy was estimated at $24 874 per episode. This estimate was based on a mean length of stay of 72.3 days in specialized rehabilitation centers by 129 Quebec patients with stroke[23] and on a mean cost of $344 per day spent in rehabilitation hospitals.[24] We calculated the cost of care in the long-term care facilities at $25 965 per year, based on a mean cost of $71 per day.[25]

The frequencies of outpatient visits and diagnostic tests for patients with CHD were based on reasonable estimates of the use of these services. The frequencies of poststroke outpatient visits and of diagnostic tests for those receiving ticlopidine hydrochloride therapy were based on the clinical trial of ticlopidine and recent treatment guidelines.[26,27]

## DRUG COSTS

All drug costs were provided by IMS of Canada, Ltd.[28] We chose the most commonly prescribed medications in each class of CVD-therapy drugs. Annual costs were based on mean retail prices, including dispensing fees for an average monthly prescription.

The mean use of CHD medications, including diuretics, β-blockers, angiotensin-converting enzyme inhibitors, calcium channel blockers, vasodilators, digitalis preparations, antiarrhythmia agents, anticoagulants, and aspirin, was based on a recent literature review (the list of articles is available on request). The annual mean medication cost for patients with CHD was calculated at $576.

The regimens of post-TIA and poststroke drug therapies were taken from published guidelines[29,30] for the management of patients with TIA or stroke. We assumed that those who subsequently had a stroke or TIA would have aspirin or ticlopidine added to their daily drug regimen.

The mean simvastatin dose was taken from the results of the 4S[7]: 61.6% of patients were given 20 mg of simvastatin daily, 31.6% were given 40 mg/d, 0.1% were taking 10 mg/d, and 6.7% discontinued the medication. The annual cost of simvastatin was accordingly estimated at $667.

Finally, we calculated the incremental costs per YOLS of simvastatin therapy as prescribed in the 4S by calculating the difference between lifetime medical costs with and without simvastatin divided by the difference in the forecasted life expectancies. Because the costs and the health outcomes occur at different times, we discounted both by 3% annually according to the latest recommendations of the Panel on Cost-Effectiveness in Health and Medicine.[31]

## MODEL VALIDATION AND SIMULATIONS

Reported baseline and follow-up risk factor values from the placebo and simvastatin arms of the 4S[2] were used in the model to predict fatal and nonfatal CVD outcomes. These values were then compared with observed results. We then performed simulations on low- and high-risk men and women aged 40, 50, 60, and 70 years for LDL-cholesterol levels of 5.46 mmol/L (211 mg/dL), 4.34 mmol/L (168 mg/dL), and 3.85 mmol/L (149 mg/dL) at baseline. The HDL-cholesterol level was assumed to be 1.1 mmol/L (43 mg/dL) for all simulations. Low-risk persons were defined as nonsmokers with a blood pressure of 120/80 mm Hg, and those at high risk were defined as smokers with a blood pressure of 160/100 mm Hg. For all simulations, we assumed that subjects did not have diabetes mellitus. The treatment effect on lipid values was taken to be that reported in the 4S,[2] ie, a reduction in LDL-cholesterol levels of 35% and an increase of 8% in HDL-cholesterol levels. Given the absence of clinical trial results among elderly persons, we conservatively assumed that the benefits of lipid modification would cease at age 75 years but that the costs of lipid treatment would continue until death.

By including the natural logarithm of the LDL/HDL ratio in the logistic equation for stroke, we explicitly assumed that lipid modification therapy affects the risk of fatal and nonfatal stroke.[32] In a sensitivity analysis, we used a second set of logistic coefficients that excluded the natural logarithm of the LDL/HDL ratio from the model for fatal stroke, thereby ignoring the potential effect of lipids on the risk of stroke.

We validated the model using the results of primary and secondary randomized clinical trials.[5] The predicted results in both the intervention and control groups of the

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9 randomized trials correlate strongly with those that were actually observed ($R = 0.96$; $P < .001$). Furthermore, the predicted benefits of intervention fell within the 95% confidence interval of the observed results for 25 (96%) of 26 outcomes. Similar results were obtained for the model forecasting stroke death ($R = 0.68$; $P = .004$) and total deaths ($R = 0.92$; $P < .001$). Accordingly, it appears that the results of primary and secondary prevention trials can be predicted on the basis of actual changes in LDL-cholesterol levels, HDL-cholesterol levels, mean blood pressure, and smoking habits across different therapeutic interventions and patient populations. These results confirm the ability of the model to forecast the net effects of risk factor modification on cardiovascular and total mortality.

### SENSITIVITY ANALYSES

After assuming that lipid therapy reduces the risk of coronary and cerebrovascular events consistently across all age groups, we recalculated the cost-effectiveness of lipid therapy over the entire lifetime. We also evaluated the effects of increasing the discount rate from 3% to 5%.

Finally, to evaluate the robustness of our results based on Canadian data, we compared the cost-effectiveness of statin therapy using health care costs from Sweden and the United States. For Sweden, the reported hospital costs, expressed in US dollars, were provided by a sample of Swedish hospitals by Johannesson et al.[6] Swedish drug costs and physician fees were based on the mean difference between Canadian and Swedish hospital costs.

To calculate the US results, we used American health care utilization estimates provided by the 4S investigators.[7] These included diagnosis-related group–based hospital admission charges for CVD and the wholesale acquisition costs of simvastatin. To calculate the costs of physician care, we used a ratio of physician fees between the United States and Canada, based on a detailed analysis by Fuchs and Hahn.[33]

long-term, as will the costs and anticipated benefits of this treatment. The analysis also explicitly ignored the post hoc observation that the incidence of cerebrovascular events was reduced 30% in the intervention group.

We have developed and validated a cardiovascular life-expectancy model to forecast the long-term benefits of risk factor intervention.[5] This model can also be used to estimate the effects of reducing the incidence of cerebrovascular events on the cost-effectiveness of secondary prevention. This model is now used to estimate the cost-effectiveness of statin therapy in secondary prevention based on the published results of 4S.[2]

## RESULTS

The model estimates closely approximated all fatal and nonfatal events observed in both arms of the 4S[2] (**Table 1**). The observed rates of CHD deaths were 85.02 (per 1000) and 49.98 in the placebo and treatment groups, whereas the model predicted 85.69 CHD deaths and 49.63, respectively. The numbers of predicted stroke deaths and total deaths were also consistent with the observed results.

**Table 1. Scandinavian Simvastatin Survival Study: Observed and Predicted Event Rates (per 1000)***

| | Placebo | | Simvastatin | |
|---|---|---|---|---|
| Events | Observed | Predicted | Observed | Predicted |
| Cause of death | | | | |
| CHD | 85.02 | 85.69 | 49.98 | 49.63 |
| Sudden coronary | 35.09 | 37.54 | 20.71 | 21.86 |
| MI | 49.93 | 48.15 | 29.27 | 27.77 |
| Stroke | 5.40 | 9.54 | 6.30 | 5.47 |
| Other | 24.74 | 26.38 | 25.64 | 26.11 |
| All deaths | 115.16 | 121.61 | 81.92 | 81.21 |
| Nonfatal | | | | |
| MI | 248.76 | 248.56 | 171.09 | 148.35 |
| TIA | 13.05 | 16.63 | 8.55 | 9.67 |
| Stroke | 33.29 | 42.70 | 25.66 | 24.81 |

**CHD indicates coronary heart disease; MI, myocardial infarction; and TIA, transient ischemic attack.*

### BENEFITS OF SIMVASTATIN THERAPY IN SUBJECTS WITH CVD

The benefits of lipid modification in low-risk subjects with a baseline LDL/HDL ratio of 5 (LDL-cholesterol level of 5.46 mmol/L [211 mg/dL] and HDL-cholesterol level of 1.1 mmol/L [43 mg/dL]) were estimated at 3.84 undiscounted YOLS for 40-year-old men (**Table 2**). These benefits decreased to 3.10, 2.05, and 0.74 YOLS, respectively, for 50-, 60-, and 70-year-old low-risk men. The forecasted benefits for women were less than for men, ranging from 2.58 to 0.58 YOLS. At lower baseline levels of LDL-cholesterol levels, the benefits of treatment declined accordingly. For instance, among 40-year-old men with LDL/HDL ratios of 3.9 and 3.5, the estimated YOLS were 3.19 and 2.86, respectively.

### COST-EFFECTIVENESS OF SIMVASTATIN THERAPY

The cost-effectiveness of simvastatin therapy in the secondary prevention of CVD in low-risk men (**Table 3**) with an LDL/HDL ratio of 5 was estimated at $7797 per YOLS at age 40 years, $6050 per YOLS at age 50 years, $5424 per YOLS at age 60 years, and $9548 per YOLS at age 70 years. These estimated costs per YOLS for low-risk men with an LDL/HDL ratio of 3.9 were higher, ranging from $6875 to $11 761. When baseline LDL/HDL ratios were only 3.5, the estimated costs rose higher but still remained at less than $14 000 per YOLS.

For low-risk women with an elevated LDL/HDL ratio of 5, the estimated costs per YOLS were $13 090, $9926, $8389, and $13 747 for those aged 40, 50, 60, and 70 years, respectively. As for men, costs per YOLS increased as the LDL/HDL ratio decreased.

In high-risk subjects, the estimated costs per YOLS across different LDL/HDL ratios remained comparable for

**Table 2. Estimated Benefits of Statin Therapy Among Persons With Cardiovascular Disease: Lipid Modification Reduces Coronary and Stroke Risk***

| Baseline Lipid Levels, mmol/L (mg/dL) | | | | | YOLS, by Age, y | | | |
|---|---|---|---|---|---|---|---|---|
| Chol | LDL | LDL/HDL Ratio | Risk | Sex | 40 | 50 | 60 | 70 |
| 7.8 (302) | 5.46 (211) | 5.0 | Low | M | 3.84 | 3.10 | 2.05 | 0.74 |
| | | | | F | 2.58 | 2.15 | 1.50 | 0.58 |
| | | | High | M | 4.65 | 3.32 | 1.91 | 0.65 |
| | | | | F | 4.39 | 3.39 | 2.13 | 0.75 |
| 6.2 (240) | 4.34 (168) | 3.9 | Low | M | 3.19 | 2.61 | 1.77 | 0.65 |
| | | | | F | 2.02 | 1.70 | 1.20 | 0.47 |
| | | | High | M | 4.55 | 3.37 | 2.02 | 0.70 |
| | | | | F | 3.99 | 3.17 | 2.06 | 0.75 |
| 5.5 (213) | 3.85 (149) | 3.5 | Low | M | 2.86 | 2.36 | 1.61 | 0.60 |
| | | | | F | 1.76 | 1.48 | 1.05 | 0.41 |
| | | | High | M | 4.43 | 3.34 | 2.04 | 0.72 |
| | | | | F | 3.74 | 3.01 | 1.99 | 0.74 |

*Chol indicates total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; and YOLS, years of life saved.

**Table 3. Estimated Cost-effectiveness of Statin Therapy Among Persons With Cardiovascular Disease: Lipid Modification Reduces Coronary and Stroke Risk***

| Baseline Lipid Levels, mmol/L (mg/dL) | | | | | Estimated Cost,† per YOLS, by Age, y | | | |
|---|---|---|---|---|---|---|---|---|
| Chol | LDL | LDL/HDL Ratio | Risk | Sex | 40 | 50 | 60 | 70 |
| 7.8 (302) | 5.46 (211) | 5.0 | Low | M | 7797 | 6050 | 5424 | 9548 |
| | | | | F | 13 090 | 9926 | 8389 | 13 747 |
| | | | High | M | 4675 | 4487 | 5016 | 8532 |
| | | | | F | 5841 | 5182 | 5138 | 8389 |
| 6.2 (240) | 4.34 (168) | 3.9 | Low | M | 10 072 | 7775 | 6875 | 11 761 |
| | | | | F | 17 745 | 13 477 | 11 412 | 18 397 |
| | | | High | M | 4996 | 4430 | 4573 | 7738 |
| | | | | F | 6573 | 5420 | 4947 | 8042 |
| 5.5 (213) | 3.85 (149) | 3.5 | Low | M | 11 665 | 9010 | 7947 | 13 404 |
| | | | | F | 20 987 | 15 984 | 13 582 | 21 719 |
| | | | High | M | 5241 | 4471 | 4419 | 7447 |
| | | | | F | 7072 | 5629 | 4927 | 7991 |

*Abbreviations are explained in the footnote to Table 2.
†1996 US dollars.

men and women of all ages. Furthermore, the estimated costs among these groups were particularly low, usually less than $8000 per YOLS.

Assuming that lipid modification has no effect on the risk of stroke, the estimated costs of simvastatin therapy per YOLS increased for all simulations (**Table 4**). For example, the estimated costs per YOLS increased from $7797 to $8691 (an 11% increase) in 40-year-old low-risk men with an LDL/HDL ratio of 5. The largest increases occurred, however, in high-risk women with lower baseline LDL/HDL ratios, reflecting the higher clinical burden of cerebrovascular disease among women than among men.[1]

## SENSITIVITY ANALYSES

Assuming that the benefits of lipid therapy do not diminish with age but remain constant, the estimated costs per YOLS drop further by as much as $18 000, as outlined in **Table 5**. Treatment among older persons is particularly sensitive to this assumption.

Using a 5% discount rate, the cost-effectiveness ratios increased substantially by as much as 34% among 40-year-old low-risk men and women. The effect of the higher discount rate diminished with advancing age for low-risk persons and had a negligible effect on high-risk adults aged 50 to 70 years.

Finally, we evaluated the sensitivity of these analyses to health care utilization and cost data across countries. We, therefore, calculated the results for Sweden and the United States, based on the results of 4S. The cost-effectiveness ratios did not change substantially (**Figure**). For example, for low-risk men with an LDL/HDL ratio of 5, the estimated costs per YOLS changed marginally after substituting Swedish or US cost and utilization data for Canadian data. The Swedish costs for lipid medication and cardiac events were marginally lower but closely approximated Canada's so that the esti-

**Table 4. Estimated Cost-effectiveness of Statin Therapy Among Persons With Cardiovascular Disease: Lipid Modification Reduces Only Risk of Coronary Disease***

| Baseline Lipid Levels, mmol/L (mg/dL) | | | | | Estimated Cost,† per YOLS, by Age, y | | | |
|---|---|---|---|---|---|---|---|---|
| Chol | LDL | LDL/HDL Ratio | Risk | Sex | 40 | 50 | 60 | 70 |
| 7.8 (302) | 5.46 (211) | 5.0 | Low | M | 8691 | 7097 | 6875 | 12 284 |
| | | | | F | 16 161 | 13 331 | 12 728 | 21 025 |
| | | | High | M | 5352 | 5323 | 6781 | 13 345 |
| | | | | F | 7727 | 7295 | 8269 | 13 906 |
| 6.2 (240) | 4.34 (168) | 3.9 | Low | M | 11 408 | 9282 | 8834 | 15 135 |
| | | | | F | 22 183 | 18 260 | 17 295 | 27 984 |
| | | | High | M | 6217 | 5888 | 6945 | 12 671 |
| | | | | F | 9708 | 8847 | 9481 | 15 074 |
| 5.5 (213) | 3.85 (149) | 3.5 | Low | M | 13 281 | 10 802 | 10 220 | 17 200 |
| | | | | F | 26 316 | 21 650 | 20 446 | 32 818 |
| | | | High | M | 6822 | 6326 | 7196 | 12 638 |
| | | | | F | 11 038 | 9905 | 10 360 | 16 076 |

*Abbreviations are explained in the footnote to Table 2.
†1996 US dollars.

**Table 5. Estimated Cost-effectiveness of Statin Therapy Among Persons With Cardiovascular Disease: Risks of Coronary Disease and Stroke Reduced Over the Entire Lifetime***

| Baseline Lipid Levels, mmol/L (mg/dL) | | | | | Estimated Cost,† per YOLS, by Age, y | | | |
|---|---|---|---|---|---|---|---|---|
| Chol | LDL | LDL/HDL Ratio | Risk | Sex | 40 | 50 | 60 | 70 |
| 7.8 (302) | 5.46 (211) | 5.0 | Low | M | 6740 | 4939 | 3805 | 3488 |
| | | | | F | 10 060 | 6996 | 4759 | 3420 |
| | | | High | M | 4689 | 4517 | 5049 | 7379 |
| | | | | F | 5907 | 5315 | 5398 | 7815 |
| 6.2 (240) | 4.34 (168) | 3.9 | Low | M | 8244 | 5900 | 4315 | 3558 |
| | | | | F | 12 712 | 8640 | 5587 | 3514 |
| | | | High | M | 5003 | 4463 | 4622 | 6528 |
| | | | | F | 6613 | 5560 | 5245 | 7245 |
| 5.5 (213) | 3.85 (149) | 3.5 | Low | M | 9279 | 6588 | 4724 | 3711 |
| | | | | F | 14 550 | 9819 | 6245 | 3722 |
| | | | High | M | 5234 | 4497 | 4461 | 6138 |
| | | | | F | 7067 | 5745 | 5207 | 6959 |

*Abbreviations are explained in the footnote to Table 2.
†1996 US dollars.

mated costs per YOLS were no more than 8% lower than those in the Canadian data. The US costs, however, were much higher than Canadian costs for treating both hyperlipidemia and cardiac events. Accordingly, the lipid therapy costs and the health care savings associated with averted cardiac events moved in parallel so that the American costs per YOLS were no more than 13% higher than the Canadian costs.

## COMMENT

These analyses suggest that the treatment of hyperlipidemia in secondary prevention may be cost-effective across a broad range of patients. Despite conservative assumptions, the forecasted benefits of lipid modification are large enough to result in at least 1 YOLS for men and women aged 40 to 60 years. For persons aged 70 years or older, the estimated benefits range from 0.41 to 0.75 YOLS, reflecting the assumption that the benefits of lipid therapy would stop at age 75 years, but the costs of medication would continue until death. Nonetheless, the cost-effectiveness of treating 70-year-old men and women remained competitive, ranging from $7447 per YOLS to $21 719 per YOLS, which reflects the relatively short duration of therapy.

The estimated costs per YOLS forecasted for long-term lipid therapy are consistent with the short-term estimates, published by Johannesson et al,[6] that were based on the actual results of the 4S data. For instance, using a 3% discount rate and ignoring the potential effects of the risk of stroke, we forecast that the estimated costs of statin therapy per YOLS would range from $6781 to $6875 for men aged 60 years with a pretreatment total blood cholesterol level of 7.80 mmol/L (302 mg/dL) (Table 4). Using a 5% discount rate, Johannesson et al[6] estimated the costs per YOLS for men with an average age of 59 years and a pretreatment blood cholesterol level of 7.99 mmol/L (309 mg/dL) at $4200. For women with similar risk fac-

tors, they estimated a cost per YOLS of $7100 compared with our long-term forecasts of $8269 to $12 728. Both analyses conclude that the costs per YOLS are lower for men than for women and that treating lower baseline lipid values results in higher costs per YOLS.

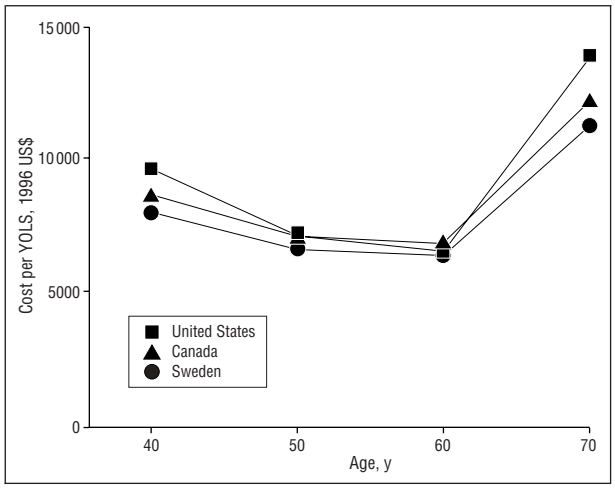
The cost-effectiveness estimates presented in our analyses were sensitive to the reduced risk of stroke predicted with lipid modification therapy. This reflects the presence of the LDL/HDL ratio as an independent risk factor for stroke death in the cardiovascular life-expectancy model and the actual reduction in the incidence of stroke observed in both the 4S and the Cholesterol and Recurrent Events trial.[2,3] If the effects of lipid modification on the risk of stroke are ignored, the costs per YOLS of lipid modification therapy increase substantially, by as much as 100%. Nonetheless, the cost estimates are still relatively low compared with those of other interventions: from $5323 per YOLS to $17 200 per YOLS for men and $7295 per YOLS to $32 818 per YOLS for women (Table 4).

Whereas lipid modification is cost-effective, it will save lives but not money among the groups analyzed herein. Some previous analyses[34] have suggested, however, that lipid therapy for secondary prevention may result in cost savings. For instance, Goldman et al[8] used the CHD policy model to estimate the cost-effectiveness of lovastatin therapy in secondary prevention. For men aged 35 to 54 years, the forecasted savings from future CHD outweighed the costs of treatment. These discrepancies between the 2 models reflect the different assumptions and covariates used in each model. More recent economic analyses of the 4S data by Pedersen et al[7] also confirm that, at least in the short term, statin therapy saved lives but not money. Nonetheless, both models suggest that statin therapy in secondary prevention will be cost-effective in adults aged 70 years or younger with significant hyperlipidemia.[5,8]

For persons older than 70 years, the cost-effectiveness of secondary prevention is particularly sensitive to assumptions regarding the benefits of treatment at older ages. Some epidemiological studies have demonstrated a weakening of the association between lipids and risk of coronary artery disease with increasing age.[35,36] Post hoc analyses of secondary prevention trials have not been able to demonstrate a statistically significant reduction in benefit with increasing age.[2,3] As contrasted in Tables 3 and 5, the cost-effectiveness among older persons will be largely driven by assumptions about treatment efficacy after age 75 years, underscoring the need for definitive outcome trials among elderly persons.

## CONCLUSIONS

These results support the cost-effectiveness of lipid modification among persons younger than 75 years with an LDL/HDL ratio of 3.5 or greater and known CVD, based on the results of the 4S. These conclusions are robust regardless of whether the effects of lipid modification on cerebrovascular events are considered. These results are also consistent across current health care costs and utilization rates of revascularization procedures among countries such as Sweden, the United States, and Canada.[37-39] Responding to these findings may require that health care providers allocate additional monies to secondary prevention. The net benefits appear to provide good value for the additional expenditures across a wide range of assumptions.




*The cost-effectiveness of statin therapy for hyperlipidemia (total, low-density-lipoprotein–, and high-density-lipoprotein–cholesterol levels of 7.80, 5.46, and 1.1 mmol/L [300, 211, and 42 mg/dL], respectively) among normotensive, nonsmoking men, given in 1996 US dollars. The costs per year of life saved (YOLS) are consistent using health care costs and revascularization rates from Sweden, Canada, and the United States.*

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