Cost-effectiveness of simvastatin in the secondary prevention of coronary artery disease in Canada

Evidence

Études

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Abstract

Objective: To determine the cost-effectiveness of simvastatin in the secondary prevention of coronary artery disease (CAD) in Canada.

Design: Cost-effectiveness model based on results from the Scandinavian Simvastatin Survival Study (4S study) and cost and resource utilization data from Canadian sources to simulate the economic impact of long-term simvastatin treatment (15 years).

Patients: Subjects with mean age of 59.4 years at recruitment into 4S study.

Outcome measures: Overall death rate and incidence of 5 major nonfatal events associated with CAD: myocardial infarction, coronary artery bypass grafting, percutaneous transluminal coronary angioplasty, stroke and transient ischemic attack. Direct medical costs associated with CAD were assessed from the perspective of provincial ministries of health (i.e., costs borne by the ministries); the impact of simvastatin treatment on these costs was determined.

Results: The 4S study, with a median follow-up of 5.4 years, showed significantly reduced mortality and morbidity among the patients given simvastatin compared with the control subjects. Three premises were designed to predict the consequences of simvastatin treatment of CAD in Canada over 15 years, 10 years beyond the end of the 4S study. The 2 most probable premises, which assumed that the clinical benefits of simvastatin would be cumulative for either the first 10 years or the full 15 years of the model, had incremental costs per year of life gained (cost-effectiveness ratio) of $9867 and $6108 respectively.

Conclusion: This model suggests that simvastatin provides a cost-effective approach to the long-term prevention of secondary CAD in Canada.

Résumé

Objectif : Déterminer la rentabilité de la simvastatine dans la prévention secondaire de la coronaropathie au Canada.

Conception : Modèle de rentabilité fondé sur des résultats tirés de la Scandinavian Simvastatin Survival Study (étude 4S) et sur des données relatives aux coûts et à l'utilisation des ressources, tirées de sources canadiennes, afin de simuler l'impact économique d'un traitement de longue durée à la simvastatine (15 ans).

Patients : Sujets qui avaient en moyenne 59,4 ans lorsqu'ils ont été recrutés pour l'étude 4S.

Mesures des résultats : Taux global de mortalité et incidence de 5 événements majeurs non mortels associés à la coronaropathie : infarctus du myocarde, pontage aorto-coronarien, angioplastie coronarienne transluminale percutanée, accident cérébrovasculaire et ischémie transitoire. On a évalué les coûts médicaux directs liés à la coronaropathie dans l'optique des ministères provinciaux de la Santé (c.-à-d. des coûts assumés par les ministères) et déterminé l'impact du traitement à la simvastatine sur ces coûts.

Résultats : L'étude 4S, au cours de laquelle le suivi médian s'est établi à 5,4 ans, a révélé une réduction importante de la mortalité et de la morbidité chez les pa-

tients qui ont reçu de la simvastatine comparativement aux sujets témoins. On a établi 3 prémisses pour prévenir les conséquences du traitement par la simvastatine de la coronaropathie au Canada sur 15 ans, 10 ans après la fin de l'étude 4S. Les 2 prémisses les plus probables, conformément auxquelles on a supposé que les avantages cliniques de la simvastatine seraient cumulatifs soit sur les 10 premières années, soit sur toute la période de 15 ans du modèle, entraînaient une augmentation des coûts par année de vie gagnée (ratio coût-efficacité) de 9867 $ et 6108 $ respectivement.

Conclusion : Ce modèle indique que la simvastatine constitue un moyen rentable de prévention à long terme de la coronaropathie secondaire au Canada.

As in other developed countries, the leading cause of death in Canada is cardiovascular disease. In 1992, 38% of all deaths were due to this disease,[1] and the associated direct costs have been estimated at $8.3 billion (1993 dollars).[1] Epidemiologic studies have firmly established a direct relation between elevated serum cholesterol levels and the incidence of cardiovascular disease.[2–4] In addition, there are substantial cardiovascular benefits associated with the lowering of cholesterol.[5,6] Strong evidence suggests that these benefits are related in part to a reduction in the low-density lipoprotein (LDL) cholesterol level and to an increase in the high-density lipoprotein (HDL) cholesterol level.[7]

A number of medical interventions that lower cholesterol have been used in the primary and secondary prevention of coronary artery disease (CAD).[2,6] Secondary prevention is particularly important, since patients with pre-existing cardiovascular disease are 8 times more likely to die from CAD than people without such a history.[8,9]

One of the most effective classes of agents for lowering serum cholesterol are the 3-hydroxy-3-methylglutaryl–coenzyme A (HMG–CoA) reductase inhibitors.[10–12] Four such inhibitors are available: fluvastatin, lovastatin, pravastatin and simvastatin.[10] Although all HMG–CoA reductase inhibitors are effective in lowering LDL cholesterol, simvastatin consistently demonstrates greater reduction in serum levels than equal doses of the other inhibitors.[10,13–19]

A recent trial[20,21] has shown that clinical intervention to decrease serum cholesterol and, in turn, the incidence of CAD[2,8] has a positive effect on overall mortality. In this double-blind randomized trial (the Scandinavian Simvastatin Survival Study [4S study])[20] 4444 patients (mean age 59.4 years) with angina pectoris or previous myocardial infarction (MI) and a serum cholesterol level of 5.5–8.0 mmol/L were randomly assigned to either treatment with simvastatin (2221 patients [82% men]) or usual care (2223 patients [81% men]). Over the course of the study (median duration 5.4 years) the total and LDL cholesterol levels decreased by 25% and 35% respectively in the treatment group, and the HDL cholesterol level increased by 8%. The rate of death from CAD was 42% lower and the rate of nonfatal MI and the need for revascularization 37% lower in the simvastatin group than in the control group. The overall mortality, the primary end point of the 4S study, was 30% lower in the simvastatin group than in the control group; the reduction was due primarily to the decreased incidence of fatal CAD.[2,20] The 4S study also provided evidence that simvastatin was effective in reducing the incidence of fatal and nonfatal cerebrovascular events.[14,20]

The benefits of simvastatin observed in the 4S study suggest that long-term use of this drug may have positive clinical and economic implications for the treatment of CAD. With respect to the economic benefits, recent studies have shown that extrapolation of the 4S data to the United States and Sweden, for the same period as the clinical trial (5.4 years), would lead to decreases of 31% and 32% respectively in hospital care costs associated with cardiovascular disease.[22,23]

To evaluate the economic consequences of long-term simvastatin therapy in Canada, we used the results from the 4S study to develop a model that would project the expected benefits of simvastatin for 15 years. From this model, we were then able to calculate cost-effectiveness ratios for the long-term use of simvastatin. Our primary objective was to assess the cost-effectiveness of simvastatin therapy versus usual care in the secondary prevention of CAD in Canada. Our secondary objective was to determine the structure of the costs associated with major coronary and cerebrovascular events in Canada.

Methods

Model

To accomplish the primary objective we constructed a model to establish the survival function in the simvastatin and usual-care arms over a 15-year period using the results of the 4S study.[20,21] We designed the model to project the effectiveness of simvastatin treatment 10 years beyond the end of the 4S study. By the end of the 10 years the population originally recruited for the study (mean age at recruitment 59.4 years) would be expected to be 75 years.

We determined the observed probabilities of survival at the beginning of each 6-month period for the simvastatin and usual-care groups in the 4S study using the data in the published report.[20,21] The hazard function for the same period was estimated using the life-table method.[24] The hazard function showed different trends between the first period (up to 2.5 years) and the last period (3.0–5.4 years) of the 4S study. The different trends may reflect the 1-year lag observed in the 4S study before simvastatin begins to have a significant effect on CAD.[20] Since the last period of the trial provided a more accurate portrayal of the lasting effects of simvastatin, we used it to estimate the survival functions. Parameters of commonly used survival distributions, such as Weibull,[24] Gompertz–Makeham[25] and exponential[24] distributions, were all estimated; the Gompertz–Makeham distribution provided the best fit for the period 3.0–5.4 years in both arms of the 4S trial.

The survival curve for the usual-care group was extended to 15 years following Gompertz–Makeham distribution patterns. Extension of the survival curve for the simvastatin group was carried out in 3 ways, according to different assumptions for the efficacy of the drug over the 10-year period beyond the 4S study period. The 3 premises are as follows.

- *Premise A:* In this one-time effect scenario, patients continue to take simvastatin for all 15 years of the model, but the full clinical effects of the drug are assumed to be observed at 5.4 years, the end point of the 4S study. Therefore, the survival curve for the simvastatin group is extended in parallel to the curve for the usual-care group, and the 2 curves continue in parallel for the 15 years.
- *Premise B:* In this semicontinuous scenario, the full effects of simvastatin are assumed to be cumulative, and the survival curve for the simvastatin group would continue to diverge from the curve for the usual-care group. However, with increasing age, morbidity and mortality from other diseases are assumed to increase, and the overall clinical benefit of simvastatin treatment would be diluted. Therefore, in this premise the survival curves for both groups diverge up to the 10-year point and then continue in parallel to the 15-year end point. The absolute difference in survival between the 2 groups is therefore constant from the 10- to 15-year point of the model.
- *Premise C:* In this continuous scenario, the beneficial effects of simvastatin are assumed to continue for the full 15 years, and the survival curves for the 2 groups would diverge for the 15 years.

The Kaplan–Meier survival curves[24] for the usual-care group and the curves predicted for the simvastatin group, are shown in Fig. 1. The curves for the simvastatin group to the 5.4-year point were derived directly from the 4S study and are therefore common to all 3 premises.

Clinical data

The standard daily dose of simvastatin in the 4S study was 20 mg, although 37% of the patients had their dose raised to 40 mg during the first 6 months. There were 231 and 288 dropouts from the simvastatin and usual-care groups respectively, because of either adverse events or patient reluctance to continue. For our study, we assumed that the number of dropouts was equal in the 20- and 40-mg simvastatin groups.

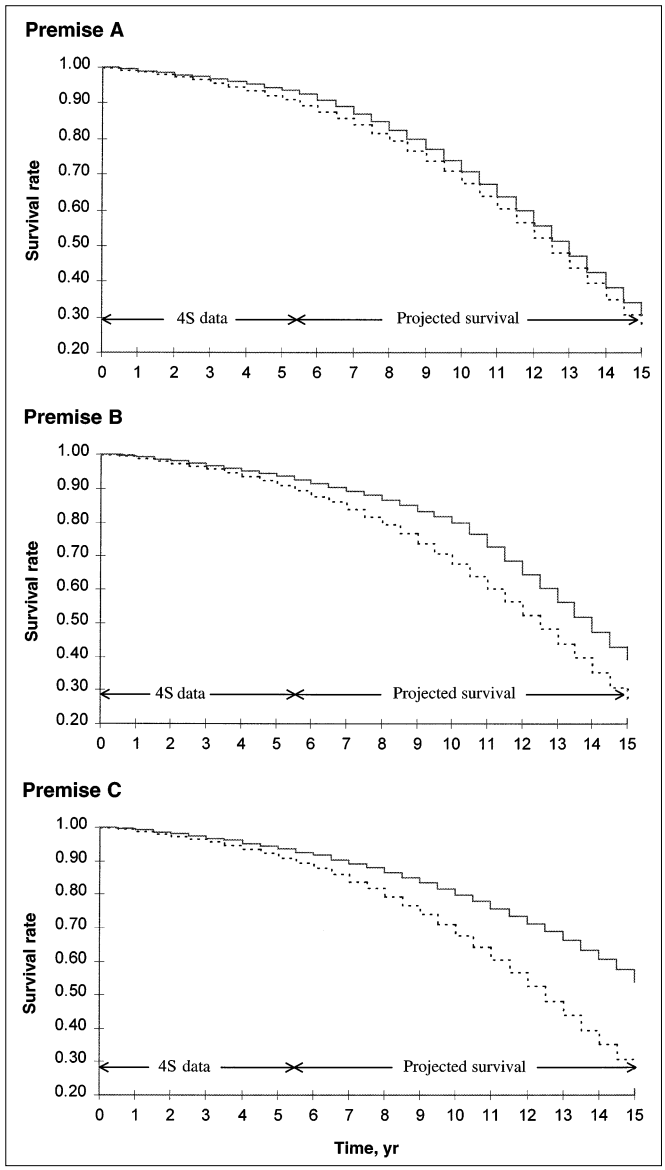

Fig. 1: Predicted survival curves for the long-term effects of simvastatin (solid line) compared with usual care (broken line) based on results from the Scandinavian Simvastatin Survival Study (4S study).[20,21] Survival curves for the simvastatin group were plotted according to 3 assumptions for the efficacy of the drug over the 10 years beyond the termination of the 4S study. Premise A = one-time clinical effect, premise B = semicontinuous clinical effect, premise C = continuous clinical effect (see Methods for details).

Using data from the published report of the 4S study we also constructed survival curves for each of the 5 major events associated with CAD: MI, coronary artery bypass grafting (CABG), percutaneous transluminal coronary angioplasty (PTCA), stroke and transient ischemic attack (TIA). When the survival data for each event were fitted to the survival distribution patterns described earlier, plots of the hazard function for each event showed a linear exponential distribution for all the determined points. For each event, the survival curves for the usual-care group were extended for 15 years and the corresponding curves for the simvastatin group were extended according to the 3 premises. On the basis of the model characteristics, we determined the number of occurrences of each of the 5 events in the 2 groups for each premise over the 15 years. Data regarding events from the 4S study were available only for patients who experienced 1 or more events; the actual number of events each patient experienced was not given.

Resource utilization

To determine the impact of CAD in Canada, we collected health care utilization data for acute events associated with CAD from 5 provinces: British Columbia, Alberta, Ontario, Quebec and New Brunswick. We interviewed 19 experts, including academic and community cardiologists, neurologists and general practitioners, about the use of resources in the treatment of such events using a questionnaire specifically designed for the assessment. Resources utilized were determined for a 3-month period and therefore included the initial hospital care and some of the subsequent rehabilitation. We assessed the following resources: number of ambulance trips, length of stay in hospital; inpatient and outpatient physician consultations; inpatient and outpatient laboratory and diagnostic tests; inpatient and outpatient procedures (e.g., angiography, CT scanning); outpatient rehabilitation; and outpatient prescriptions.

Costs were ascribed to each resource consumed, according to the perspective of provincial ministries of health (i.e., costs borne by the ministries), and were obtained from hospitals, formularies and the schedule of benefits for each province. The hospital costs were obtained from the Canadian Institute for Health Information for 1995–96, and a national average was applied in all provinces. The cost per case mix group was all inclusive except for physician fees. In the case of MI and CABG, an average cost was determined from the ratio of the number of cases of MI, with and without complications, and on the ratio of the number of cases of CABG, with and without catheterization. We measured the cost for long-term care and hospital care for rehabilitation by applying the per diem rate provided by the provincial ministry of health. Physician fees were taken from the schedule of benefits in each province.

We obtained costs of outpatient procedures from the schedule of benefits in each province. We estimated costs of more complicated tests and procedures that could only be performed in hospital using hospital costs. The costs of outpatient allied health services were estimated from the average compensation for allied health workers from each province. For outpatient rehabilitation programs following hospitalization we determined the cost of a single day visit. We used market data to determine the most commonly prescribed outpatient drugs in CAD. We calculated the corresponding costs for the drugs from the formularies of each province and provincial reimbursement rates. Pharmacist fees, mark-up fees and copayments were included in the cost of each prescription for simvastatin and other concomitant medications. If the costs for specific resources were not available for a province, we used an average cost, determined from information in other provinces.

In each province, resource utilization data and the subsequent cost for each acute event were weighted according to the patient population of the specialist or general practitioner that was interviewed. In addition, resource utilization and costing data were also weighted to reflect the population of each province with respect to the total Canadian population to determine a national average.

Cost structure

To accomplish the secondary objective, the resources used for each event were assigned a cost, and the cost structure representing the total average cost per event was determined for a 3-month period for each of the 5 provinces. A national weighted average is presented.

Cost-effectiveness analysis

To determine the cost-effectiveness ratio, we first calculated the total treatment cost for CAD in Canada by multiplying the number of expected events in both the simvastatin and usual-care groups over the 15 years by the cost per event. Costs were adjusted to reflect the yearly dropout rate in the first 5.4 years. For the cost-effectiveness ratio, we divided the difference in total treatment costs between the 2 groups by the estimated number of years of life gained (YLGs) with simvastatin. The number of YLGs were based on the predictions of the 15-year survival curves for each premise. In all the calculations, we discounted cost and effectiveness outcomes at 5% annually. For a sensitivity analysis, costs were varied by 20% to test the robustness of the results.

Results

The resource utilization values for each of the 5 major events associated with CAD in Canada are shown in Table 1. The average number of visits by allied health care workers was greatest for stroke and was the largest form of resource consumption overall, although not the costliest. The average length of hospital stay was also greater for stroke than for the other events.

Length of hospital stay was the main cost determinant for all the acute events (Table 2), constituting 86% of the total cost on average. In contrast, drug costs had an almost insignificant impact on the total cost of care for all the events, ranging from 0.6% for stroke to 4.0% for TIA. Although length of hospital stay was the main cost determinant, other aspects of patient care had a strong impact. For example, in the TIA group, the cost of physician consultations, laboratory investigations and procedures, and drugs amounted to 28% of the total cost. Overall, stroke was the most expensive acute event, followed closely by CABG; TIA was the least expensive.

The 3 premises we developed (Fig. 1) permitted us to predict the long-term effects of simvastatin on mortality and morbidity associated with CAD. In the usual-care group, the Kaplan–Meier probability of survival was 87.7% at the end of the 4S trial; after extension of the survival curve, we predicted a probability of survival of 26.6% at 15 years. In the simvastatin group, the probability of survival at the end of the 4S study was 91.3%, and the predicted values at the end of the 15 years were 29.7% (premise A), 38.7% (premise B) and 54.4% (premise C).

By applying these cost data to the model for the long-term effect of simvastatin, we were able to determine the cost-effectiveness ratios for each premise (Table 3). The ratios for premises B and C ($9867 and $6108 per YLG respectively) were 3 and 5 times more cost-effective respectively than the ratio for premise A ($29 888 per YLG). For sensitivity analyses we varied the cost for each premise by 20%. The resulting variations of 24%, 29% and 34% in cost-effectiveness ratios for premises A, B and C respectively suggested that the model was relatively robust (Table 3).

Discussion

Using data from the 4S study[20,21] as a basis we were able to model the long-term effect of simvastatin by calculating cost-effectiveness ratios using 3 patterns of long-term efficacy. The discriminating factor in the 3 premises is the point at which the clinical advantages of simvastatin begin to diminish. In the 4S study, although there were reductions in acute events at 6 months or earlier,[14] there was lit-

Table 1: Average resource utilization values for 5 major cardiovascular events* associated with coronary artery disease (CAD) in Canada over a 3-month period

Variable	MI	CABG	PTCA	Stroke	TIA
No. of ambulance trips	1	0	0	1	0
Length of hospital stay, d	8	9	3	37	2
No. of physician consultations	11	15	6	19	6
No. of visits by allied health care workers	3	7	1	69	0
No. of laboratory investigations and procedures	17	16	9	9	9
No. of outpatient prescriptions	11	10	2	7	7
Total	51	57	21	142	24

*MI = myocardial infarction, CABG = coronary artery bypass grafting, PTCA = percutaneous transluminal coronary angioplasty, TIA = transient ischemic attack.

Table 2: Total cost per major cardiovascular event associated with CAD over a 3-month period

	CAD-related event; cost, $*				
Variable	MI	CABG	PTCA	Stroke	TIA
Ambulance trips	94	10	17	144	22
Hospital care	8 900	19 371	8 696	19 911	2 200
Physician consultations	335	408	201	495	212
Visits by allied health care workers	90	143	49	1 702	0
Laboratory investigations and procedures	231	968	605	148	532
Outpatient prescriptions	140	173	196	126	125
Total	9 790	21 073	9 764	22 526	3 091

*In 1995–96.

tle or no impact on survival for the first 1 or 2 years of the trial. However, at the end of the 5 years, there was a significant impact, and survival curves continued to diverge.[20,26]

On this basis, premise A, the one-time effect scenario, is unlikely, since the benefits of simvastatin are likely to continue to accumulate. Premise B, the semicontinuous model, assumes that the clinical benefits of simvastatin would continue to the 10-year point in the model, when the patients would be 70 years old on average. However, the long-term benefits of simvastatin may continue beyond this point. Although there are no available data on the long-term benefits of cholesterol reduction in elderly patients with CAD, Law and associates,[27] in a meta-analysis of primary prevention trials, showed that a reduction of 10% in the serum cholesterol concentration is associated with decreases of 27%, 20% and 19% in the risk of ischemic heart disease at age 60, 70 and 80 respectively. They also demonstrated that the decrease in the incidence of CAD became more apparent with increasing duration of reduction in cholesterol. Their observations suggest that there is a considerable reduction in the risk of CAD between the ages of 70 and 80, even with modest reductions in cholesterol, and this reduction in risk may be even higher in patients with pre-existing heart disease. Therefore, in premise C we hypothesized that the clinical benefits of simvastatin would continue for the full 15 years of the model.

In the absence of clinical trial data on the effect of long-term simvastatin treatment in older patients, premises B and C, therefore, provide a range for cost-effectiveness of simvastatin in Canada, with a high value of $9867 per YLG (premise B) to a low, or more cost-effective, value of $6108 per YLG (premise C). Although the definition of an acceptable cost-effectiveness ratio is debated, these values are favourable when compared with those for other currently funded medical interventions such as renal dialysis, for which the ratio varies from US$20 000 to US$74 000 (1993 dollars).[28]

We found length of hospital stay to be the main cost determinant for all 5 major events associated with CAD, and stroke and CABG to be the most expensive events. Previously published costs of treating stroke in Toronto ($27 500 in 1991–92[29]) and of performing CABG in Vancouver ($10 982 to $33 676 in 1989[1]) are similar to the costs of $22 526 and $21 073 determined for stroke and CABG in our study.

Table 3: Estimated cost-effectiveness ratios for long-term (15-year) simvastatin treatment in Canada according to 3 premises of clinical benefit

Premise*	Cost per YLG,† $	Cost per YLG ± 20%,‡ $	
		−20%	+20%
A (one-time benefit)	29 888	22 695	37 081
B (semicontinuous benefit)	9 867	7 044	12 690
C (continuous benefit)	6 108	4 030	8 186

*See Methods for descriptions of premises.
†YLG = year of life gained.
‡Costs are varied by 20% for sensitivity analysis.

Three recent studies also used the data from the 4S study to estimate the economic impact of using statins to lower cholesterol on the health care systems in the United States,[22] Sweden[23] and the United Kingdom.[30] In the United States and Sweden simvastatin use was associated with a 32% savings in CAD-related hospitalization over the 5.4-year period of the 4S study. Although no cost-effectiveness ratio was determined for the United States, in Sweden the savings in hospitalization resulted in a ratio of £5502 (Can$11 644) per YLG. For this ratio, it was assumed that simvastatin therapy stopped after the 5.4 years and cost-savings were determined for this period. In contrast, the investigators calculated years of life saved over 15.5 years, using an average life expectancy of 10 years beyond the end of the 4S study period and disregarding future treatment effects.[23] However, we believe that this therapeutic pattern is unlikely to reflect normal medical practice, since patients would likely continue to take simvastatin beyond the initial 5.4 years, as defined in the 3 premises described in our study.

In the UK study, Pharoah and Hollingworth,[30] using the 4S data together with other clinical data, assessed the cost-effectiveness of statins in lowering cholesterol in patients with and without pre-existing CAD over 10 years. They used a life-table method to estimate YLGs with treatment. The cost-effectiveness ratios determined were highly dependent on patient group risk factors and varied from £6000 (Can$12 698) for men 55–64 years of age with CAD to £137 000 (Can$290 000) for men 45–64 years of age without CAD but with an elevated cholesterol level. Their findings confirm those of a previous study,[31] which showed better cost-effectiveness ratios for patients with pre-existing CAD. The lowest ratio for CAD patients in the United Kingdom was higher than the ratios we determined for premises B and C, partly because the models differed and because the patients in the UK study were only 59 years of age at the end of the 10-year model. In addition, differences in patterns of treatment in the United Kingdom and Canada will also affect cost-effectiveness ratios.

A possible limitation of our study is in the estimated number of occurrences of each major CAD-related event. Publication of the results from the 4S study provided data only for the number of patients experiencing each event one or more times and not for the actual number of occurrences of each event. Therefore, the actual totals may have been underestimated, which, in turn, would have led

to an underestimation of the cost-effectiveness of simvastatin. In addition, the cost-effectiveness ratios we determined depend solely on the 4S data and the risk of CAD in the patients recruited. The placebo cohort in the 4S study had a risk of CAD of only 23% over 6 years,[20] a risk that may be lower than that in a typical CAD population in North America. In a recent US study of carotid stenosis[32] 43% of men with CAD (average age 63.9 years) had a subsequent cardiac event over the 4-year study period. If the 4S study patients were at unusually low risk for secondary cardiovascular events, this would also tend to underestimate the cost-effectiveness ratios obtained for simvastatin. Finally, our study was confined to the direct medical costs associated with CAD from a single perspective. Indirect costs were not considered. By preventing acute CAD-related events and decreasing the disability associated with CAD, simvastatin would be likely to have a positive effect on indirect costs. In addition, we have preliminary data (on file) that suggest favourable cost-effectiveness ratios for simvastatin treatment of CAD patients in Canada, from the perspective of a third-party payer. From this perspective, ratios of $4734 and $3485 were calculated for premises B and C respectively when death benefits, long-term disability and drug reimbursement were considered. In-depth assessment of these additional factors would enhance the overall cost-effectiveness of simvastatin in Canada.

The model we used is a well-recognized technique for predicting medical outcomes in the absence of primary data.[33] The cost-effectiveness ratios we determined using this method suggest that long-term use of simvastatin would be an economically feasible approach to the prevention of secondary heart disease in Canada.

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