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The Cost-effectiveness of HMG-CoA Reductase Inhibitors to Prevent Coronary Heart Disease

Estimating the Benefits of Increasing HDL-C

Vivian H. Hamilton, PhD; Francois-Eric Racicot, MSc; Hanna Zowall, MA; Louis Coupal, MSc; Steven A. Grover, MD, MPA, FRCPC

Objective.—To evaluate the lifetime cost-effectiveness of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors for treatment of high blood cholesterol levels.

Design.—We added cost data to a validated coronary heart disease (CHD) prevention computer model that estimates the benefits of lifelong risk factor modification. The updated model takes into account the costs of cholesterol reduction, the savings in CHD health care costs attributable to intervention, the additional non-CHD costs resulting from patients' living longer, and the beneficial effects of reducing CHD risk by reducing total cholesterol and increasing high-density lipoprotein cholesterol (HDL-C).

Patients.—Men and women aged 30 to 70 years who were free of CHD, had total cholesterol levels equal to the 90th percentile of the US distribution in their age and sex group, had HDL-C levels equal to the mean of the US distribution in their age and sex group, and were either with or without additional CHD risk factors.

Intervention.—Use of 20 mg of lovastatin per day, which on average reduces total serum cholesterol by 17% and increases HDL-C by 7%.

Main Outcome Measures.—Cost per year of life saved after discounting benefits and costs by 5% annually.

Results.—The increase in HDL-C associated with lovastatin lowered cost-effectiveness ratios by approximately 40%, such that the treatment of hypercholesterolemia was relatively cost-effective for men (as low as $20 882 per year of life saved at age 50 years) and women ($36 627 per year of life saved at age 60 years) with additional risk factors. Non-CHD costs resulting from longer life expectancy after intervention added at most 23% to the cost-effectiveness ratios for patients who began treatment at age 70 years, and as little as 3% for patients at age 30 years.

Conclusion.—The cost-effectiveness of HMG-CoA reductase inhibitors varied widely by age and sex and was sensitive to the presence of non-lipid CHD risk factors. The additional non-CHD costs due to increased life expectancy may be significant for the elderly. Accounting for the drug effects of raising HDL-C levels increased the proportion of the population for which medication treatment was relatively cost-effective.

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From the Centre for the Analysis of Cost-Effective Care, the Centre for Cardiovascular Risk Assessment, and the Division of Clinical Epidemiology, the Montreal (Quebec) General Hospital (Drs Hamilton and Grover, Mr Racicot, Ms Zowall, and Mr Coupal); and the Departments of Medicine (Drs Hamilton and Grover), Economics (Dr Hamilton), and Epidemiology and Biostatistics (Dr Grover), McGill University, Montreal, Quebec.

Reprint requests to the Centre for the Analysis of Cost-Effective Care, the Montreal General Hospital, 1650 Cedar Ave, Montreal, Quebec, Canada H3G 1A4 (Dr Grover).

DURING the 1980s, consensus guidelines recommended nationwide screening to detect and treat hypercholesterolemia for the primary prevention of coronary heart disease (CHD). Specifically, the guidelines targeted high-risk individuals for dietary intervention and/or drug therapy. Because the consensus guidelines were constructed with little consideration for their cost implications, there soon followed a number of studies evaluating the cost-effectiveness of various drugs in reducing total serum cholesterol.

Some of these studies limited their measure of cost-effectiveness to cost per percentage reduction in serum cholesterol.[1] This restricted the ability to compare the results with a wide range of interventions, which generally report cost-effectiveness in terms of cost per year of life saved. Other studies reported cost-effectiveness in terms of cost per year of life saved, but did not report cost-effectiveness estimates across the range of significant risk factors such as age, sex, and presence or absence of cigarette smoking and high blood pressure.[2,3] Goldman et al[4] estimated the cost-effectiveness of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors for a range of risk factors and found that primary prevention was attractive only for certain subgroups.

While previous cost-effectiveness analyses have accounted for the beneficial effect of drug therapy in reducing total serum cholesterol, these studies have not included the supplemental effect that some drugs can have in increasing high-density lipoprotein cholesterol (HDL-C) levels. This would be expected to further decrease CHD and increase life expectancy. In addition, only one previous study included the impact of expected increases in non-CHD health care expenditures incurred during years of life gained attributable to therapy in their cost-effectiveness calculations.[3] However, these costs were assumed to be constant across age groups.

In this study, we evaluated the lifetime cost-effectiveness of a common HMG-CoA reductase inhibitor (lovastatin) for treatment of high blood cholesterol levels. We added cost data to a validated CHD pre-

vention computer model that estimates the benefits of lifelong risk factor modification. The updated model takes into account the costs of intervention, savings in CHD health care costs attributable to intervention, the additional age-specific non-CHD costs resulting from patients' living longer after intervention, and the beneficial effects of increasing HDL-C attributable to these drugs.

METHODS

Calculation of Cost-effectiveness

We calculated the cost-effectiveness of intervention from a societal perspective and evaluated the net social costs of drug therapy (in 1992-1993 Canadian dollars) against its net effectiveness, measured in terms of additional years of life expectancy. Our estimates are expected values, reflecting the average experience of all persons with elevated levels of cholesterol and not just those who develop CHD.

We calculated cost-effectiveness as the ratio of the net change in medical care costs to the net increase in life expectancy[5] as follows:

$$(\Delta CRx - \Delta CCHD + \Delta CNonCHD)/\Delta LE$$

where ΔCRx is the expected lifetime cost of a given regimen of drug therapy; $\Delta CCHD$, the expected savings in lifetime medical care costs as a result of reducing CHD events; $\Delta CNonCHD$, the expected cost of treating non-CHD diseases during the years of additional life gained by treatment; and ΔLE, the increase in life expectancy that results from adherence to the specified regimen of drug therapy. We discounted all future treatment costs and changes in life expectancy at an annual rate of 5%.

Lifetime Cost of Drug Therapy

We used lovastatin as an example of an HMG-CoA reductase inhibitor because it is the most commonly prescribed drug in this category and there is substantial literature on its clinical effectiveness. The retail cost of lovastatin was estimated at $2.16 per 20-mg pill based on a telephone survey of 12 Montreal-area pharmacies on December 9, 1993. We thus estimated annual drug costs of $789 for a regimen of 20 mg of lovastatin per day.

We estimated that treatment with lovastatin in the first year would also require on average four physician visits ($25.20 per visit), four blood test sample collections ($4.81 per sample), four lipid profiles ($19.26 per profile), and four biochemical profiles (sequential multiple analyzer computer profiles, $5.82 per profile). The estimated costs of physician visits were based on an average of negotiated reimbursement fees for these services in Ontario and Quebec in 1992.[6-8] The cost of laboratory tests was based on the average of fully allocated hospital unit laboratory costs at the Montreal General Hospital and laboratory reimbursements in Ontario. Following the first year of treatment, individuals were assumed to continue (until death) on a regimen of 20 mg of lovastatin per day and to require two physician visits, two blood test sample collections, two lipid profiles, and two sequential multiple analyzer computer profiles per year at the same unit prices specified in year 1. The sum of these costs was estimated to be $1009 in the initial year, and $899 per year thereafter.

Table 1.—Serum Cholesterol Levels by Age and Sex*

Age, y	90th Percentile Total Serum Cholesterol, mmol/L (mg/dL)		Mean HDL-C, mmol/L (mg/dL)	
	Men	Women	Men	Women
25-34	6.6 (254)	6.3 (243)	1.2 (45.0)	1.4 (52.5)
35-44	7.1 (275)	6.7 (260)	1.1 (44.2)	1.4 (52.7)
45-54	7.3 (283)	7.5 (290)	1.1 (44.1)	1.4 (55.1)
55-64	7.4 (288)	8.1 (314)	1.2 (46.0)	1.4 (55.9)
65-74	7.2 (279)	8.0 (309)	1.2 (45.7)	1.4 (53.2)

*Derived from the second National Health and Nutrition Examination Survey.[9] HDL-C indicates high-density lipoprotein cholesterol.

Intervention Group and Predicted Lipid Modification

Our intervention group consisted of men and women aged 30 to 70 years who were free of CHD, had total serum cholesterol levels equal to the 90th percentile of the US distribution in their age and sex group, and had HDL-C levels equal to the mean of the US distribution in their age and sex group. Information on these lipid levels was derived from the second US National Health and Nutrition Examination Survey[9] (Table 1). For each age and sex group, we also contrasted the effects of lovastatin therapy for high-risk individuals (ie, smokers with diastolic blood pressure of 100 mm Hg) vs low-risk persons (ie, nonsmokers with diastolic blood pressure of 80 mm Hg).

We used results from the Expanded Clinical Evaluation of Lovastatin (EXCEL) study to predict the effects of a regimen of 20 mg of lovastatin per day on lipid levels.[10] The EXCEL study enrolled patients with moderate hypercholesterolemia (mean cholesterol, 6.67 mmol/L [258 mg/dL]; HDL-C, 1.16 mmol/L [45 mg/dL]) and found that after a 48-week treatment period with 20 mg of lovastatin per day, patients' total serum cholesterol declined an average of 17% and HDL-C increased an average of 7%. We assumed that the effectiveness of lovastatin is the same as that observed in EXCEL and that the benefits do not wane over time.

The CHD Prevention Model

Estimates of increased life expectancy due to cholesterol modification were derived using the CHD prevention model.[11] The CHD prevention model calculates the annual probability of dying from CHD or other causes and the annual risk of CHD events (with and without intervention) for an individual free of symptomatic CHD at entry into the model. The annual risk of developing a specific CHD end point was based on data published by the Framingham Heart Study[12] and is a function of a patient's age, sex, diastolic blood pressure, total serum cholesterol level, HDL-C level, the presence of left ventricular hypertrophy (yes or no), the presence of glucose intolerance (yes or no), and smoking status (yes or no). The risk of all-cause death was based on the 1986 Canadian Life Tables published by Statistics Canada[13] after adjustment for the level of diastolic blood pressure and the presence of cigarette smoking and diabetes. Non-CHD death was calculated as the difference between all-cause mortality and CHD mortality.

The risk of secondary CHD events was based on the logistic equations for primary events after adjustment for the presence of CHD.[14] The increased risk of dying during the 12 months following a nonfatal myocardial infarction was also estimated from Framingham data.

The submodels were then integrated into the CHD prevention model in which all individuals entering the model are assumed to be free of CHD at time 0. Each year, a number of individuals are predicted to die of CHD or other (non-CHD) causes. The risk of nonfatal CHD events, such as myocardial infarction, angina pectoris, or coronary insufficiency, is also computed, and these individuals are then moved from the primary coronary model to the secondary coronary model. At the end of each year, the number of remaining individuals at risk for primary CHD is calculated as those at the beginning of the year minus those who had died and/

or developed CHD. This model has been validated by accurately predicting the results of clinical trials.[15]

The model has also been updated to allow for the progression of CHD in individuals who experience a primary nonfatal CHD event. For example, the model now allows for the probability of experiencing a myocardial infarction following the development of angina or coronary insufficiency, the recurrence of infarction, or progression to congestive heart failure following an initial or recurrent myocardial infarction. Prediction of primary events in the computer model remains the same. The updated model was validated against data from three prospective clinical trials, with changes in predicted total mortality rates of less than 6% compared with the earlier model.

By specifying an individual's initial and expected lipid levels after intervention and holding all other risk factors constant, the CHD prevention model can be used to predict the benefits of cholesterol modification. The annual cumulative mortality difference among survivors (with and without intervention) over the total life expectancy represents the total years of life saved following intervention. Dividing total years of life saved by the original number of individuals at risk at time 0 results in the average years of life saved per individual. All individuals were assumed to be free of left ventricular hypertrophy and glucose intolerance. We also assumed that the reduction in CHD risk resulting from lipid modification occurred after a 2-year lag, based on the results of clinical trials.

Savings in Medical Care Costs Attributable to CHD Events Prevented

For each individual, the probability of experiencing an event in each year was then multiplied by the corresponding cost of treatment (based on Canadian data) to obtain annual expected expenditures of coronary care with and without intervention. Follow-up medical costs were also assigned to years following the development of CHD. The cumulative difference in discounted lifetime treatment costs of coronary events with and without intervention thus represents the savings in medical care costs attributable to CHD events prevented.

Treatment costs were assigned to each of the following acute, nonsurgical manifestations of CHD: sudden death, fatal myocardial infarction, nonfatal myocardial infarction (with and without complications), angina or coronary insufficiency, congestive heart failure, arrhythmia for patients younger than 70 years (with and without complications), and arrhythmia for patients aged 70 years and older. Treatment costs for each medical event included the costs of hospitalization, physicians' fees, and outpatient and emergency services when applicable.

Hospital costs for each medical event were estimated by multiplying the average length of stay in hospital for each diagnosis[16] by the average cost per inpatient day in Canada ($434 in 1992) and the diagnosis related group (DRG) cost weight per day for each particular diagnosis. The average cost per inpatient day in Canada was derived by multiplying the reported Canadian average total hospital costs per patient-day in 1989 ($463) by the proportion of that cost related to inpatient care (80.1%),[17] adjusted to 1992 levels using the hospital implicit price index (1.17).

The average length of stay and the DRG cost weight per day for each diagnosis were derived from Hospital Medical Records Institute of Canada (HMRI) data. The DRG cost weights were developed by HMRI to adjust figures on daily inpatient costs for the systematic differences in resource utilization across diagnoses. HMRI derived the case weights based on the cost per case of each diagnosis as reported in New York State cost data.

Costs of physician services for emergency, inpatient, and outpatient care were based on reasonable estimates of the resources that would be required. For example, patients with a nonfatal myocardial infarction without complications were assumed to require one cardiologist consultation, one general practitioner assessment on admission, and daily cardiologist and general practitioner visits while in the hospital.

Hospital emergency services were calculated, including transportation costs and costs per hour of emergency hospital care, based on fully allocated unit costs at the Montreal General Hospital. When appropriate, outpatient care for each coronary-related procedure was also calculated.

Costs of surgical inpatient care for patients experiencing CHD events also included probability-weighted costs of the following coronary procedures: coronary artery bypass grafting (with and without catheterization), angioplasty, coronary catheterization, pacemaker insertion, and pacemaker replacement. Unit costs for surgical procedures were calculated as mentioned herein. The probability of undergoing each surgical procedure was based on the relative annual incidence of surgical procedures in Canada compared with the number of admissions for acute myocardial infarction.[18]

Finally, outpatient care costs for survivors of coronary events are included in the model, with separate cost estimates for the first year of the event vs subsequent years. These costs include the costs of general practitioner visits, specialist consultations, diagnostic tests, and drugs, based on reasonable estimates of the use of these services.

Additional Non-CHD Costs Attributable to Increased Life Expectancy

Counterbalanced against the savings in medical care costs attributable to the prevention of CHD-related mortality and morbidity are higher costs of care for non-CHD diseases during a patient's additional years of expected life. We computed sex-specific annual non-CHD health care costs for each 10-year age group (from age 25 through 34 years to age 75 years or more) and multiplied these figures by the additional years of life gained for patients undergoing treatment to obtain an estimate of lifetime non-CHD costs attributable to lipid therapy.

Non-CHD health care costs per capita include physician, hospital, and drug costs. We relied on information from a number of federal and provincial data sources to obtain estimates of the non-CHD costs related to each expenditure category. For each expenditure category, non-CHD costs per capita were computed by deriving an estimate of total expenditures by all persons in each age and sex category, subtracting the portion of these costs attributable to CHD, and dividing this difference by the total population in the particular age and sex group.

Population estimates by age and sex were obtained from Statistics Canada.[19] Estimates of aggregate hospital expenditures were derived by multiplying the average cost per inpatient day by the aggregate number of inpatient days reported for each age and sex group in 1992.[20] Aggregate physician expenditures were obtained by multiplying the average of per capita physician costs by age and sex (indexed to 1992 prices) in British Columbia,[21] Saskatchewan (Patrick Melia, Medical Care Insurance Branch of Saskatchewan Health, Regina, Saskatchewan, written communication, October 1993), and Quebec[22] by Canadian population figures. Aggregate drug expenditures were obtained by multiplying the average of per capita annual drug expenditures by age and sex in Ontario and Saskatchewan in 1987[23] by the 1992 hospital implicit price index and Canadian population figures.

Hospital costs related to CHD events were estimated by multiplying the number of medical and surgical hospital admissions for patients with acute myocardial infarction and other ischemic heart

disease by their average length of stay in hospital and average costs per inpatient day. CHD related physician payments in Canada were derived by multiplying the ratio of age- and sex-specific CHD-related physician payments (*ICD-9*[24] codes 402, 410-414, 426-428) to total physician payments in Saskatchewan by our estimates of aggregate Canadian physician expenditures by age and sex described herein. Aggregate CHD-related drug expenditures were derived by multiplying an estimate of average CHD-related drug expenditures for persons with CHD by the estimated number of persons with CHD in each age and sex group. The CHD-related drug expenditures for CHD patients were estimated by multiplying unit prices for all CHD-related drugs, including antihypertensives, vasodilators, anti-arrhythmics, β-blockers, digitalis, calcium channel blockers, angiotensin-converting enzyme inhibitors, cholesterol reducers, aspirin, and anticoagulants, by the proportion of CHD patients reporting use of these drugs as derived from previously published Canadian studies.[25,26] The number of persons with CHD was estimated by multiplying age- and sex-specific figures on prevalence of CHD in Canada[27] by the population in each demographic category.

Finally, we checked our calculations by using our age- and sex-specific figures for CHD and non-CHD costs to compute population-weighted sums of annual expenditures for hospital, physician, and drug expenditures. These figures were then compared with Canadian national accounting data. In each case, we found our weighted sum underestimated aggregate expenditures. Thus, per capita non-CHD costs for hospital, physician, and drug expenditures were adjusted upward according to the estimated underprediction in each particular expenditure category.

RESULTS

Lifetime Cost of Lipid Therapy

Table 2 presents estimates of the undiscounted lifetime costs of lovastatin therapy. These costs varied substantially by age at initiation of therapy. The undiscounted lifetime cost of 20 mg of lovastatin per day for high-risk men (smokers with diastolic blood pressure of 100 mm Hg) ranged from $34 399 at age 30 years to $8033 at age 70 years. Lifetime costs of therapy were slightly greater for high-risk women, reflecting their longer life expectancy. They ranged from $40 201 if therapy is initiated at age 30 years to $11 167 if therapy is initiated at age 70 years. Lifetime costs of therapy for low-risk individuals were approximately $4000 to $6600 greater than high-risk persons in each age group because of their longer life expectancy.

Table 2.—Lifetime Cost of Lovastatin Therapy at 20 mg/d* (Undiscounted Canadian Dollars)

	Age, y				
	30	40	50	60	70
Low-risk†					
Men	40 967	32 917	25 170	18 228	12 009
Women	46 102	37 975	30 059	22 393	15 242
High-risk‡					
Men	34 399	26 428	19 123	13 058	8033
Women	40 201	32 187	24 571	17 462	11 167

*Lifetime costs are based on Canadian data sources (see "Methods").
†Nonsmokers with diastolic blood pressure of 80 mm Hg.
‡Smokers with diastolic blood pressure of 100 mm Hg.

Table 3.—Change in Life Expectancy Attributable to Lifelong Lovastatin Therapy at 20 mg/d* (Undiscounted Years)

	Age, y				
	30	40	50	60	70
Low-risk†					
Men	1.36	1.44	1.09	0.60	0.23
Women	0.92	0.99	0.94	0.73	0.42
High-risk‡					
Men	2.03	2.04	1.43	0.70	0.23
Women	1.03	1.10	1.02	0.75	0.37

*Lifetime expectancy figures are computed including the beneficial effect of lovastatin on high-density lipoprotein cholesterol.
†Nonsmokers with diastolic blood pressure of 80 mm Hg.
‡Smokers with diastolic blood pressure of 100 mm Hg.

Change in Life Expectancy Attributable to Lifelong Lipid Therapy

Table 3 contains estimated changes in life expectancy (undiscounted) attributable to lifelong therapy for all individuals. High-risk men who start therapy at ages 30, 50, or 70 years could expect to gain 2.03, 1.43, or 0.23 years of life, respectively. High-risk women 30, 50, or 70 years of age at initiation of therapy could expect to gain 1.03, 1.02, or 0.37 years of life, respectively. Relative to high-risk individuals, undiscounted life expectancy gains were substantially lower for younger low-risk persons (33% lower for low- vs high-risk men at age 30 years), but this disparity disappeared when therapy was initiated at older ages. This is attributable to the persistent high mortality rates for elderly hypertensive smokers when only lipids are treated.

Cost-effectiveness of Lovastatin and the Impact of Non-CHD Costs

The costs and benefits of all cost-effectiveness ratios were discounted at 5%. Estimates of the cost-effectiveness of lifelong therapy with 20 mg of lovastatin per day are presented in Table 4. The cost-effectiveness ratios are presented with and without non-CHD costs incurred during years of life gained after therapy for the treatment group. All cost-effectiveness ratios in Table 4 are calculated including the beneficial effects of lovastatin on HDL-C.

A comparison of the cost-effectiveness calculations with or without non-CHD costs reveals that the differential between the two figures tends to increase with age. At age 30 years, the cost per year of life saved is 5.0% greater when including non-CHD costs for low-risk men ($76 749 vs $73 121) and 3.1% greater for low-risk women ($155 891 vs $151 132). For intervention at age 70 years, the cost per year of life saved including non-CHD costs is 11.8% greater for low-risk men ($75 625 vs $67 634) and 17.1% greater for low-risk women ($55 579 vs $47 445). Non-CHD costs display a similar impact on cost-effectiveness ratios across age groups for high-risk persons. Non-CHD costs have their most sizable effect on 60-year-old high-risk men, increasing the cost-effectiveness ratio by 23.1% ($27 872 vs $22 642).

The increasing effect with age of non-CHD costs on the cost-effectiveness calculations is attributable to the fact that additional non-CHD costs are only accrued at the end of life, during the years of life gained because of the intervention. If lipid treatment begins at age 30 years, additional non-CHD costs are not incurred until well into the future and are thus heavily discounted. Conversely, if lipid treatment begins at age 70 years, the non-CHD costs are incurred more rapidly, and thus have a larger, more immediate impact on the net costs of therapy.

Table 4.—Cost-effectiveness (Canadian Dollars per Year of Life Saved) of Cholesterol Reduction Using Lovastatin at 20 mg/d (Discounted)*

	Without Non-CHD Costs Age, y					With Non-CHD Costs Age, y				
	30	40	50	60	70	30	40	50	60	70
Low-risk†										
Men	73 121	42 504	35 526	41 945	67 634	76 749	46 571	40 436	48 214	75 625
Women	151 132	86 551	56 191	44 525	47 445	155 891	91 655	61 898	51 293	55 579
High-risk‡										
Men	33 257	19 415	17 231	22 642	42 458	35 785	22 297	20 882	27 872	50 079
Women	101 868	57 689	37 453	30 540	35 166	105 708	61 891	42 313	36 627	43 127

*All costs and benefits in the cost-effectiveness ratios are discounted at an annual rate of 5%. Cost estimates are based on Canadian data sources. CHD indicates coronary heart disease.
†Nonsmokers with diastolic blood pressure of 80 mm Hg.
‡Smokers with diastolic blood pressure of 100 mm Hg.

Cost-effectiveness and the Beneficial Effects of HDL-C

In Table 5, we compare cost-effectiveness ratios including and excluding the beneficial effects of lovastatin on HDL-C. All cost-effectiveness calculations in Table 5 are performed including non-CHD costs. The cost-effectiveness ratios including the beneficial effects of HDL-C are on average 40% lower than cost-effectiveness ratios that exclude HDL-C effects. For low-risk men at age 50 years, the costs per year of life saved are 34% lower when the HDL-C effect is included ($40 436 vs $61 077). The cost-effectiveness ratio is 41% lower when the HDL-C effect is included for 50-year-old low-risk women ($61 898 vs $105 111). Similar effects of including HDL-C in the cost-effectiveness calculations are obtained for high-risk persons. This effect of considering HDL-C on cost-effectiveness ratios increases with age, reflecting the strong and persistent impact of HDL-C on CHD risk at all ages, while the impact of total cholesterol on CHD risk declines with age.[11]

Using the cost per year of life saved of renal dialysis as an example of a commonly accepted cost-effective treatment ($40 000 to $45 000 per year of life saved in 1992 dollars),[28,29] we can evaluate the cost-effectiveness of treatment with HMG-CoA reductase inhibitors for specific subgroups. Based on our cost-effectiveness results, which incorporate the beneficial effect of increased HDL-C, lovastatin appears to be relatively cost-effective for high-risk men of all ages ($20 882 to $50 079) and high-risk women aged 50 to 70 years ($36 627 to $43 127). In addition, treatment with lovastatin appears to be relatively cost-effective for low-risk men aged 40 to 60 years ($46 571 to $48 214).

COMMENT

We used a CHD prevention computer model to estimate the cost-effectiveness of HMG-CoA reductase inhibitors in the treatment of high cholesterol levels. Clearly, the validity of these estimates is of paramount concern. The CHD prevention model we used is comparable with other recently published models in that the estimated benefits of smoking cessation, cholesterol reduction, and blood pressure reduction for men are similar between models.[15] Moreover, the CHD prevention model has been validated by accurately predicting the results of three primary prevention clinical trials.[11]

The benefits of lipid modification that are derived from the model are based on observational data from the Framingham Study, which finds a negative correlation between HDL-C and CHD risk in a community population. However, there has never been a long-term clinical trial specifically aimed at determining the relative CHD risk reduction associated with only raising HDL-C. Nevertheless, data from the Helsinki Heart Study[30] indicate that increases in HDL-C resulting from treatment with gemfibrozil are at least as important as reductions in cholesterol and low-density lipoprotein in reducing subsequent incidence of CHD. Moreover, the CHD prevention computer model accurately predicts the reduction in cardiac events resulting from gemfibrozil treatment that were observed in this trial. The computer model predicts a difference of 12.9 cardiac events (per 1000 people) between the gemfibrozil and placebo groups, while the observed difference was 14.1 cardiac events.[11]

We find that non-CHD costs add as little as 3% to the cost-effectiveness ratios for patients beginning treatment at age 30 years, but up to 23% for those starting at age 70 years. It has been argued that these general future medical costs should not be included when determining the cost-effectiveness of an intervention for a particular disease because these costs are not relevant to deciding whether or not the treatment in question is a good investment.[31] However, given that cholesterol-lowering drugs have the potential of being prescribed to a large portion of the population, it is important to determine the magnitude of non-CHD costs relative to direct CHD costs because they appear to be significant for specific treatment groups.

Because the cost of lovastatin constitutes the largest component of intervention costs, we assessed the sensitivity of our results to 10% variations in the cost of this drug. These variations in drug costs result in similar changes in cost per year of life saved (8% to 9%). Thus, our estimates of cost-effectiveness are sensitive to changes in the cost of medication.

We also recalculated our results using discount rates other than 5%. When costs and benefits were discounted at a 3% annual rate, costs per year of life saved declined by approximately 30% for the youngest patients and 10% for the oldest. The larger decline in the cost-effectiveness ratios for younger individuals reflects their larger relative gain in life expectancy resulting from application of the lower discount rate to future life years saved. Conversely, a 7% annual rate increases cost per year of life saved by about 30% for the youngest individuals and by about 10% for the oldest. Thus, our results are also sensitive to choice of discount rate.

Although our analysis is based on the unit prices of medical inputs and medical practice patterns in Canada, our conclusions are generalizable to medical practice in the United States. Our primary conclusion is that accounting for the increasing HDL-C effect of HMG-CoA reductase inhibitors substantially improves the cost-effectiveness of these drugs relative to prior estimates that fail to consider the HDL-C effect. Current differences in the absolute costs of treating CHD in Canada and the United States will not undermine this conclusion. In addition, our predicted annual costs of intervention ($1009 Canadian in year 1 and $899 per year thereafter) are similar to the $715 US annual costs (or $994 Canadian at an exchange rate of 1.39) estimated by Goldman et al[4] in an analysis of the cost-effectiveness of lovastatin based on 1989 US cost data. However, although previous studies in-

Table 5.—Cost-effectiveness (Canadian Dollars per Year of Life Saved) of Cholesterol Reduction Using Lovastatin at 20 mg/d (Discounted)*

	Without HDL-C Effect, Age, y					With HDL-C Effect, Age, y				
	30	40	50	60	70	30	40	50	60	70
Low-risk†										
Men	106 261	65 101	61 077	88 994	208 905	76 749	46 571	40 436	48 214	75 625
Women	257 170	151 758	105 111	94 684	121 155	155 891	91 655	61 898	51 293	55 579
High-risk‡										
Men	47 875	30 201	30 366	48 533	123 561	35 785	22 297	20 882	27 872	50 079
Women	169 779	100 239	70 694	66 874	94 618	105 708	61 891	42 313	36 627	43 127

*All costs and benefits in the cost-effectiveness ratios are discounted at an annual rate of 5%. Cost estimates are based on Canadian data sources. HDL-C indicates high-density lipoprotein cholesterol.
†Nonsmokers with diastolic blood pressure of 80 mm Hg.
‡Smokers with diastolic blood pressure of 100 mm Hg.

dicate that risk of CHD mortality is the same in these two countries, care for cardiac patients is more aggressive in the United States.[25,32] Thus, because the cost savings from avoiding treatment of CHD events will be greater, the cost per year of life saved resulting from intervention in the United States may be even lower.

Therapy with HMG-CoA reductase inhibitors is relatively cost-effective compared with other lipid therapies once the HDL-C effect is considered. For instance, the HDL-C–adjusted cost-effectiveness ratios for high-risk men aged 30 to 70 years ($20 882 to $50 079) compare favorably with cost-effectiveness ratios estimated by Kinosian and Eisenberg[2] for cholestyramine resin ($65 100 per year of life saved) and colestipol hydrochloride ($63 900 per year of life saved) for men aged 48 years with initial cholesterol greater than 6.85 mmol/L (>265 mg/dL) and 38% smoking prevalence.[2] Oster and Epstein[3] found that cholestyramine was relatively cost-effective only for the youngest high-risk men in their study ($39 000 to $45 300 per year of life saved for men aged 35 to 49 years with smoking, hypertension, and diabetes as risk factors). In contrast, the HDL-C–adjusted results imply that lovastatin is relatively cost-effective for high-risk men of all ages ($20 882 to $50 079 per year of life saved), as well as for low-risk men between the ages of 40 and 60 years ($40 436 to $48 214 per year of life saved).

In focusing our analysis on HMG-CoA reductase inhibitors, we have not considered those lipid modifiers that have the greatest potential to increase HDL-C, such as niacin and fibrates. Our analysis demonstrates that accounting for even a modest increase in HDL-C substantially lowers the cost-effectiveness ratios for lovastatin. The same would hold true for other lipid modifiers, particularly those with greater HDL-C effects.

Our estimates of the cost-effectiveness of lovastatin tend to display a U-shaped pattern in relation to age. For each sex and risk group, the cost-effectiveness ratios are higher at age 30 years and age 70 years than they are at age 50 years. This result is in contrast to Goldman et al[4] who found that use of lovastatin for the primary prevention of CHD leads to cost-effectiveness ratios that decline steadily from ages 35 through 44 years to ages 65 through 74 years. The discrepancy arises from the addition of a negative cholesterol-age interaction term in our CHD Prevention Model based on multivariate Framingham data.[11] While the model used by Goldman et al[4] assumes that the risk reduction associated with decreasing cholesterol is constant with age, our model calculates that the benefits of cholesterol reduction decline as individuals age.[12] For instance, when comparing our non–HDL-C–adjusted estimates of the cost-effectiveness of lovastatin for high-risk men with individuals in the study by Goldman et al[4] (cholesterol between 6.47 and 7.73 mmol/L [250 and 299 mg/dL], diastolic blood pressure 95 to 104 mm Hg, smoker, and weight <110% of ideal), we obtain a cost-effectiveness ratio of $30 201 at age 40 years vs the estimate from Goldman et al[4] of $220 000 at age 35 to 44 years, and a ratio of $123 561 at age 70 years vs the estimate from Goldman et al[4] of $57 000 at age 65 to 74 years. At age 60 years, the costs per year of life saved are comparable across the two studies ($48 533 in our study vs $53 000 in Goldman et al[4]).

Even with inclusion of the HDL-C effect, the cost per year of life saved with lovastatin is greater than calculated for some other primary interventions to reduce CHD. For instance, brief advice and counseling by a physician during a routine office visit about quitting smoking costs from $705 to $988 for men per year of life saved and from $1204 to $2058 for women per year of life saved, depending on a patient's age.[33] In addition, the cost per year of life saved for the antihypertensive drug propranolol hydrochloride in the primary prevention of CHD for persons aged 35 through 64 years in the US population is estimated to be $10 900.[34]

However, compared with generally accepted medical therapies such as renal dialysis, treatment with lovastatin appears to be relatively cost-effective for high-risk men of all ages, high-risk women aged 50 to 70 years , and low-risk men aged 40 to 60 years. These results support recent recommendations by Hulley et al[35] that cholesterol screening and treatment is not cost-effective for low-risk men younger than 35 years and low-risk women younger than 45 years.

On the other hand, Hulley and Newman[36] recommend that screening and treatment of hypercholesterolemia are inappropriate for most elderly women and for persons of both sexes in their late 70s. This recommendation is based on findings that the association between total or HDL-C and CHD events is attenuated for older persons[37-40] and may even disappear for persons older than 70 years.[41] As the results in Table 3 indicate, we estimate a decline in the benefits of lipid modification for older individuals. However, intervention for high-risk individuals in this age group remains relatively cost-effective because the lifetime costs of intervention are also lower for this age group.

As the costs of health care continue to rise, clinicians and policymakers will increasingly look toward preventive interventions as a means of improving health and restraining health care costs. Computer simulations of primary interventions to reduce CHD will assist in applying resources in a cost-effective manner, providing these analyses are rigorous and validated. Our present results demonstrate that using HMG-CoA reductase inhibitors may be relatively cost-effective for specific groups of North American adults. Further analyses should consider the possible adverse consequences of treatment, the indirect savings associated with work-related productivity gains, and the quality of life benefits associated with delaying the morbidity of CHD.

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