Estimating the Benefits of Modifying Risk Factors of Cardiovascular Disease

A Comparison of Primary vs Secondary Prevention

Steven A. Grover, MD, MPA, FRCPC; Steve Paquet, MSc; Carey Levinton, BSc; Louis Coupal, MSc; Hanna Zowall, MA

Objectives: To compare the potential years of life saved (YOLS) associated with risk factor modification in the primary and secondary prevention of cardiovascular disease (CVD).

Methods: The CVD life expectancy model estimates the risk of death due to coronary disease, stroke, and other causes based on the levels of independent risk factors (such as age, blood pressure, and blood lipid levels) found in the cohort of the Lipid Research Clinics. The model was validated by comparing its predictions with the observed fatal outcomes of 9 randomized clinical trials. We then estimated the YOLS associated with treating hyperlipidemia or hypertension among hypothetical patient groups with and without CVD at baseline. We defined high-risk patients as those with 3 risk factors (hyperlipidemia, cigarette smoking, and hypertension) and low-risk patients as those with isolated hypertension or hyperlipidemia.

Results: The fatal events predicted by the model were consistent with the clinical trial results. Among men and women with hyperlipidemia without CVD, the forecasted benefits of lipid therapy were substantially greater among high-risk groups vs low-risk groups (4.74-0.78 YOLS vs 2.50-0.25 YOLS, respectively). Among those with CVD, the forecasted benefits of treatment were similar for both high-risk and low-risk groups (4.65-0.65 YOLS vs 3.84-0.58 YOLS, respectively). The results for hypertension therapy also demonstrated greater benefits for high-risk vs low-risk patients undergoing primary prevention therapy (1.34-0.29 YOLS vs 0.85-0.13 YOLS, respectively), and the forecasted benefits in secondary prevention were similar (1.26-0.23 YOLS vs 1.00-0.23 YOLS, respectively).

Conclusions: The clinical approach to risk factor modification in primary prevention should be different from that in secondary prevention. The forecasted benefits of therapy among patients without CVD are greatest in the presence of other risk factors. Among those with CVD, the benefits of therapy are equivalent, thereby obviating the need to target high-risk patients.

Arch Intern Med. 1998;158:655-662

From the Centre for the Analysis of Cost-Effective Care (Dr Grover, Mr Paquet, Mr Levinton, Mr Coupal, and Ms Zowall) and the Divisions of General Internal Medicine (Dr Grover) and Clinical Epidemiology (Dr Grover, Mr Paquet, Mr Levinton, Mr Coupal, and Ms Zowall), Montreal General Hospital; the Departments of Medicine and Epidemiology and Biostatistics (Dr Grover), McGill University, Montreal, Quebec.

RECENT CLINICAL trials evaluating the effects of modifying blood lipid levels in subjects with cardiovascular disease (CVD) have demonstrated substantial benefits in terms of reducing the risks of recurrent disease and extending overall survival. The Scandinavian Simvastatin Survival Study[1] (4S) demonstrated mean changes in levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol of –25%, –35% and +8%, respectively, after lipid lowering treatment. During a median follow-up of 5.4 years, a 35% reduction in deaths due to coronary events and nonfatal myocardial infarctions was discovered between the intervention and control groups. In the Cholesterol and Recurrent Events (CARE) trial,[2] subjects with more modest levels of hyperlipidemia were also shown to benefit from modification of lipid levels. In this study, mean changes in levels of total cholesterol, LDL cholesterol, and HDL cholesterol of –20%, –28%, and +5%, respectively, resulted in a 24% reduction in deaths due to coronary events and nonfatal myocardial infarctions.

Although the 4S[1] and CARE[2] study were designed to evaluate the impact of use of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) on coronary events, both studies also reported reductions in the rates of stroke in the treatment groups. In a post hoc analysis, 4S showed a 30% reduction in the rates of fatal and nonfatal cerebrovascular events in the simvastatin group vs the placebo group. The CARE study also reported a 31% lower stroke rate in the pravastatin group vs the placebo group. This potential beneficial effect of lipid lowering

SUBJECTS AND METHODS

The CVD life expectancy model estimates the benefits of CVD risk factor modification for both primary and secondary prevention. For given levels of CVD risk factors, this Markov model describes the yearly transitions to 3 causes of death: coronary disease, stroke, and other. The yearly probabilities associated with these transitions are estimated using multivariate logistic regression coefficients derived from data from the Lipid Research Clinics (LRC) program prevalence and follow-up studies.[16-18]

LRC COHORT

The LRC prevalence studies were conducted from 1972 to 1976 in 10 clinics in North America to determine the prevalence of dyslipoproteinemias and related factors.[16-18] A 15% random sample of participants plus all patients with abnormal lipid values determined primarily by sex- and age-specific threshold levels of plasma cholesterol and triglycerides were invited to return for a second visit (visit 2).[19] The group with abnormal lipid values was not included in the determination of the logistic coefficients used in the current CVD model. Among the 15% random sample, we also excluded patients who (1) were taking digitalis or antiarrhythmic or lipid-altering medications; (2) were pregnant; (3) had been fasting for less than 12 hours prior to lipid testing; or (4) had their blood sample frozen prior to analysis.

All men and women aged 30 years and older at visit 2 were followed up prospectively to provide data on subsequent mortality. Telephone or mail contact began annually in July 1977, and subjects were followed up through June 1987, for an average follow-up of 12.2 years. Specific causes of mortality were ascertained by review of death certificates and hospital records, and the vital status of 99% of the subjects was established at least once during the follow-up period. Details of laboratory and quality control procedures have been described elsewhere.[16,19]

The clinical characteristics of the cohort used in the model are found in **Table 1**. At baseline, subjects were classified as having CVD if they had a diagnosis or symptoms of coronary heart disease, cerebrovascular disease, or peripheral vascular disease. The clinical criteria for these 3 diagnoses have been previously described.[20]

ESTIMATING FATAL OUTCOMES

We developed 3 multivariate models to predict the risk of death due to coronary disease, stroke, or other causes. A selection of variables from the LRC follow-up data found to be univariately associated with each of the fatal end points were entered in a forward stepwise logistic regression model. The following variables were entered into each model: age; sex; blood pressure (systolic, diastolic, and mean); body mass index (calculated as the weight in kilograms divided by the square of the height in meters); smoking status; alcohol consumption status; use of medication to reduce blood pressure; and presence of CVD, diabetes, or left ventricular hypertrophy. Measurement of cholesterol levels included total, HDL, LDL, non-HDL, and triglycerides. Glucose intolerance was defined as taking medication for diabetes or having a plasma glucose level greater than 6.7 mmol/L (120 mg/dL). Cigarette smoking was defined as presently smoking cigarettes. Mean blood pressure was calculated as ⅔ the diastolic blood pressure plus ⅓ the systolic blood pressure.

We used a 10-year follow-up for death due to both coronary disease and stroke to maximize the numbers of events available for each risk function. For other deaths, a 5-year follow-up was used because it produced a more robust risk function despite fewer outcomes.

Independent risk factors associated with each end point are presented in **Table 2**. For example, the risk factors associated with death due to coronary disease included cigarette smoking, female vs male sex, mean blood pressure, the presence of CVD, age, the presence of glucose intolerance, and the natural log of the LDL/HDL cholesterol ratio. The log transformation was used to normalize the skewed distribution of the LDL/HDL cholesterol ratio.

Risk factors for death due to stroke included cigarette smoking, mean blood pressure, the presence of CVD, age, glucose intolerance, and the natural log of the LDL/HDL cholesterol ratio. For other deaths, risk factors in the final model were cigarette smoking, sex, and the square of age. All risk factors were statistically significant ($P<.05$) with the exception of the variable sex for the outcome of other deaths. Although it was not significant, we included this variable in the model because it reduced the risk for women as expected.

The annual probability of each fatal outcome could then be calculated for a cohort of subjects with specified levels of risk factors. For example, the 1-year probability of death due to coronary disease based on a 10-year risk function is calculated as 1/10 the 10-year risk, which is a function of the level of risk factors for death due to coronary disease.

For all simulations, the proportion of subjects developing nonfatal CVD and surviving was calculated

therapy in reversing the progression of carotid atherosclerosis and its impact on cerebrovascular events had been previously suggested by some earlier research, but the results were modest and inconsistent.[3-5] Given the conflicting results of prior epidemiological studies and stroke prevention trials,[6-10] neither 4S[1] nor CARE[2] were designed to demonstrate this unanticipated result.

Clinicians, patients, and health care payers are now faced with the reality of treating hyperlipidemia and hypertension among patients with CVD. This secondary prevention will require lifelong therapy based on the results of short-term clinical trials. Disease simulation models will therefore be required to estimate the long-term benefits of therapy for specific groups of patients. To fully evaluate the benefits, both cerebrovascular and coronary events must be considered. For modification of lipid levels, previous models focusing only on coronary disease may also underestimate the impact on stroke given the recent trial results.[11-15]

We have developed a CVD life expectancy model to estimate the benefits of risk factor modification in the primary and secondary prevention of CVD, including

annually. The probabilities of developing coronary insufficiency, a nonfatal myocardial infarction, a transient ischemic attack, or a nonfatal stroke were estimated by the ratios of nonfatal to fatal events predicted by the results of the LRC Primary Prevention Trial,[21] Framingham Heart Study,[22] or the 4S.[1]

ESTIMATING LIFE EXPECTANCY

To estimate life expectancy, a cohort of subjects (n=1000) with or without CVD is entered into the model at age *x* (30-74 years) with specified levels of risk factors. In the year after entry into the model, subjects either die of coronary disease, cerebrovascular disease, or other causes or survive.

Survivors may have developed nonfatal coronary or cerebrovascular disease or remain disease free. Surviving subjects age 1 year and reenter the model for the following year. This process continues until all subjects die or reach 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 experienced by the cohort and dividing by the subjects at risk at entry into the model (n=1000).

When comparing treatments having a differential impact on risk factors and hence survival, the benefits associated with one treatment over the other are the years of life saved (YOLS) due to the better treatment minus the worse or no treatment. This value is computed as

$$\text{YOLS} = \text{LE}_{\text{Better}} - \text{LE}_{\text{Worse}},$$

where LE indicates life expectancy.

MODEL VALIDATION

The accuracy of the model to forecast the benefits of treating hypertension or hyperlipidemia was assessed using the results of primary prevention lipid trials including the LRC Coronary Primary Prevention Trial,[21] the Helsinki Heart Study,[23] and the West of Scotland Coronary Prevention Study[24]; secondary prevention lipid trials including the Program on the Surgical Control of the Hyperlipidemias,[25] the 4S,[1] and the CARE[2] trials; and hypertension trials including the Systolic Hypertension in the Elderly Program,[26] the Metoprolol Atherosclerosis Prevention in Hypertensives,[27] and the Multiple Risk Factor Intervention Trial.[28] Each of these trials was selected as risk factor levels at baseline and after interventions could be obtained from published reports.

For lipid trials, a 1-year delay was assumed to occur before the observed reductions in lipid levels translated into a full decrease in risk as predicted by the multivariate risk function. This is consistent with delays in benefits observed in randomized placebo-controlled clinical trials of lipid-lowering treatments. We also assumed a 1-year period would be required for the benefits of hypertension therapy to occur. In addition, we assumed that only 50% of the predicted benefits of blood pressure reduction would be actually realized based on a meta-analysis of hypertension trials by Collins and coworkers.[29] When LDL cholesterol levels were not reported in the results of clinical trials, deaths due to coronary disease and stroke were predicted with a model developed using the natural log of the total/HDL cholesterol ratio instead of the natural log of the LDL/HDL cholesterol ratio.

ESTIMATING THE BENEFITS OF TREATMENTS FOR HYPERLIPIDEMIA OR HYPERTENSION

We conservatively assumed that the benefits of all interventions stopped at age 75 years. The benefits of modification of lipid levels and hypertension intervention for men and women aged 40, 50, 60, and 70 years with and without CVD were then calculated using the model. We further classified subjects as being at low and high risk based on the hypothetical presence of other risk factors. For the lipid simulations, we defined low-risk subjects as those who did not smoke cigarettes and had a blood pressure of 120/80 mm Hg, and high-risk subjects were defined as those who smoked cigarettes and had a blood pressure of 160/100 mm Hg, consistent with earlier analyses.[11] For hypertension intervention simulations, low-risk subjects were defined as those who did not smoke with an LDL/HDL cholesterol ratio of 3.50 (LDL cholesterol, 3.85 mmol/L [149 mg/dL] and HDL cholesterol, 1.1 mmol/L [43 mg/dL]) and high-risk subjects were defined as those who smoked with an LDL/HDL cholesterol ratio of 4.90 (LDL cholesterol, 4.90 mmol/L [189 mg/dL] and HDL cholesterol, 1.0 mmol/L [39 mg/dL]).

The impact of intervention on lipid levels was assumed to be a 35% decrease in LDL cholesterol levels and an 8% increase in HDL cholesterol levels, similar to the results of the 4S.[1] These simulations were performed for subjects with a baseline LDL cholesterol level of 5.46 mmol/L [211 mg/dL] and an HDL cholesterol level of 1.1 mmol/L [43 mg/dL]. The hypertension intervention simulations assumed reductions of 10 mm Hg in systolic blood pressure and 7 mm Hg in diastolic blood pressure from a baseline blood pressure of 160/100 mm Hg, which approximated the results of the 3 previously cited hypertension trials.[26-28]

coronary disease and stroke. In this study, we present the model, validate the accuracy of the model predictions, and compare the benefits of treating hyperlipidemia and hypertension in primary and secondary prevention.

RESULTS

MODEL VALIDATION

The model demonstrated reasonable accuracy at predicting mortality from coronary disease in primary and secondary prevention lipid trials, hypertension trials, and the Multiple Risk Factor Intervention Trial[28] (**Figure 1**). First, the model correctly forecasted the increased incidence of deaths due to coronary disease among the secondary prevention lipid trials (Program on the Surgical Control of the Hyperlipidemias,[25] CARE,[2] and 4S[1]) vs the primary prevention trials (LRC,[21] West of Scotland Coronary Prevention Group,[24] and the Helsinki Heart Study[23]). Second, the deaths due to coronary disease in the hypertension trials (Metoprolol Atherosclerosis Prevention in Hypertensives[27] and Systolic Hypertension in the El-

Table 1. Patient Characteristics in the Lipid Research Clinics Cohort

Risk Factors*	Values
Mean ± SE age, y	47.1±0.17
Mean ± SE cholesterol level, mmol/L (mg/dL)	
Total	5.32±0.01 (205±0.4)
LDL	3.49±0.01 (135±0.4)
HDL	1.36±0.01 (53±0.4)
Total/HDL cholesterol ratio	4.28±0.03
LDL/HDL cholesterol ratio	2.84±0.02
Mean ± SE triglyceride level, mmol/L (mg/dL)	1.40±0.01 (124±0.9)
Mean ± SE blood pressure, mm Hg	
Systolic	124±0.27
Diastolic	79±0.16
Mean†	94±0.18
Mean ± SE body mass index, kg/m²‡	25.49±0.06
White race, %	95
Male sex, %	52
Cardiovascular disease at entry, %	4.9
Family history of CHD, %	23
Glucose intolerance, %	3.4
Definite left ventricular hypertrophy, %	0.4
Cigarette smokers, %	33.4
Taking blood pressure medication, %	7.5

**LDL indicates low-density lipoprotein; HDL, high-density lipoprotein; and CHD, coronary heart disease.*
†Mean blood pressure equals ⅔ distolic + ⅓ systolic.
‡Body mass index is calculated as the weight in kilograms divided by the square of the height in meters.

derly Program[26]) and Multiple Risk Factor Intervention Trial[28] were also predicted by the model. Third, the predicted results in both the intervention and control groups of the 9 randomized trials correlate strongly with those that were actually observed (R^2=0.96; 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 and HDL cholesterol levels, mean blood pressure, and smoking habits across different therapeutic interventions and different patient populations.

Similar results were obtained for the model forecasting death due to stroke (R^2=0.68; P=.004) and total deaths (R^2=0.92; P<.001). Finally, the forecasted absolute reduction in fatal events predicted by the model approximated the results actually observed between the intervention and control arms of each clinical trial (**Table 3**). For instance, the net impact of modifying lipid levels in the LRC study[21] resulted in a net reduction of 4.73 fatal coronary events per 1000 (between the cholestyramine and diet vs diet only groups) vs 6.37 that were actually observed. For death due to stroke, the model forecasted a reduction of less than 1 event per 1000 compared with zero, which was actually observed. Finally, in terms of total mortality, the model predicted a reduction of 4.72 events per 1000 vs 1.69, which was actually observed. Among 9 randomized clinical trials, the predicted benefits of intervention fell within the 95% confidence interval of the observed results for 25 (96%) of 26 outcomes. These results confirm the ability of the model to accurately capture the net impact of risk factor modification in terms of cardiovascular mortality and total mortality.

Table 2. Odds Ratio for Independent Risk Factors Included in the Final Models*

Risk Factors	CHD Death	Stroke Death	Other Deaths
Cigarette smoking	1.907†	3.674†	2.508‡
Sex	0.446‡	. . .	0.909
Mean blood pressure	1.033§	1.055‡	. . .
Cardiovascular disease	3.722§	4.171‡	. . .
Age	1.080§	1.135§	. . .
Age²	. . .	. . .	1.001§
Glucose intolerance	3.309§	7.089§	. . .
Natural log LDL/HDL (per unit)	5.066§	3.740†	. . .

**CHD indicates coronary heart disease; LDL, low-density lipoprotein; HDL, high-density lipoprotein; and ellipses, not applicable.*
†P<.05.
‡P<.005.
§P<.001.

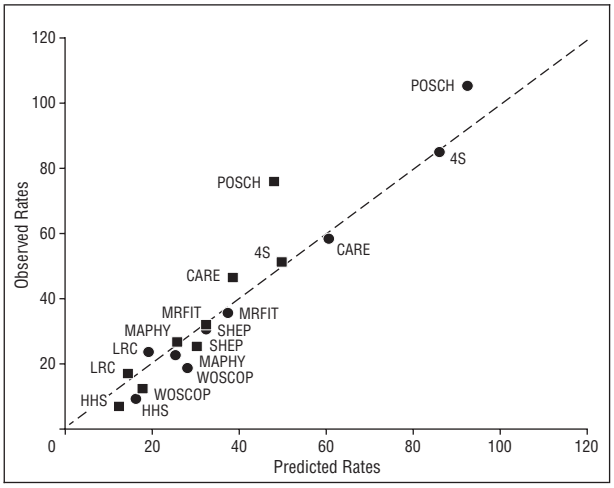

Figure 1. *The forecasted rates of death caused by coronary heart disease (per 1000) using the cardiovascular life expectancy model vs the rates observed in prevention trials. POSCH indicates Program on the Surgical Control of the Hyperlipidemias[25]; 4S, Scandinavian Simvastatin Survival Study[1]; CARE, Cholesterol and Recurrent Events Trial[2]; MRFIT, Multiple Risk Factor Intervention Trial[28]; SHEP, Systolic Hypertension in the Elderly Program[26]; MAPHY, Metoprolol Atherosclerosis Prevention in Hypertensives[27]; LRC, Lipid Research Clinics Coronary Primary Prevention Trial[21]; WOSCOP, West of Scotland Coronary Prevention Study[24]; HHS, Helsinki Heart Study[23]; squares, the active intervention arm of each study (except for the MAPHY metoprolol group); and circles, the placebo or usual care groups (except for the MAPHY diuretics group).*

FORECASTING THE BENEFITS OF TREATING HYPERLIPIDEMIA

We forecasted the YOLS for low-risk men with hyperlipidemia who are free of disease and using therapy with 3-hydroxy-3-methylglutaryl coenzyme A, which ranged from 2.50 YOLS for those aged 40 years to 0.43 YOLS for those aged 70 years (**Figure 2**, A). For high-risk patients (smokers with hypertension), the forecasted benefits were approximately 2-fold greater, ranging from 4.74 YOLS for those aged 40 years to 0.78 YOLS for those aged 70 years. Among women free of disease, the forecasted benefits of therapy were less than those predicted for men, reflecting the lower absolute risk of CVD among women with all other things being equal (Figure 2, C). Nonetheless, the forecasted benefits of treating high-risk women

Table 3. Predicted Differences in Outcomes vs Observed Trial Results (Deaths per 1000)

	Differences in Deaths Between Study Groups*					
	CHD		Stroke		Total	
Study	Predicted	Observed (95% CI)	Predicted	Observed (95% CI)	Predicted	Observed (95% CI)
LRC[21]	4.73	6.37 (–3.05, 15.78)	0.16	0.00 (–2.06, 2.06)	4.72	1.69 (–10.75, 14.14)
HHS[23]	3.77	2.53 (–3.46, 8.52)	0.17	–0.95 (–4.48, 2.57)	4.03	–1.25 (–10.60, 8.10)
WOSCOP[24]	10.20	6.11 (–0.15, 12.37)	. . .	. . .	10.38	8.89 (–0.46, 18.25)
POSCH[25]	44.21	29.51 (–11.74, 70.76)	2.61	2.42 (–8.06, 12.91)	46.16	32.29 (–15.97, 80.55)
4S[1]	36.06	35.04 (19.88, 50.21)	4.07†	–0.91 (–5.84, 4.03)	40.40	33.24 (15.27, 51.16)
CARE[2]	20.94	11.27 (–2.68, 25.23}	2.06	–2.38 (–7.75, 2.98)	22.80	8.05 (–9.88, 25.98)
SHEP[26]	1.95	5.84 (–15.34, 7.17)	1.48	1.68 (–8.91, 0.32)	2.56	12.00 (–25.69, 4.33)
MAPHY[27]	–0.43	–4.09 (–3.95, 15.64)	–0.04	–4.30 (–2.79, 6.14)	–0.53	–10.68 (–5.20, 29.21)
MRFIT[28]	4.88	3.67 (–2.67, 10.03)	0.54	0.46 (–1.69, 2.61)	5.20	6.25 (–3.30, 15.79)

**Refers to differences between treatment and control arms except for MAPHY (metoprolol vs diuretics) and MRFIT (special intervention vs usual care). CHD indicates coronary heart disease; CI, confidence interval; LRC, Lipid Research Clinics; HHS, Helsinki Heart Study; WOSCOP, West of Scotland Coronary Prevention Study; POSCH, Program on the Surgical Control of the Hyperlipidemias; 4S, Scandinavian Simvastatin Survival Study; CARE, Cholesterol and Recurrent Events trial; SHEP, Systolic Hypertension in the Elderly Program; MAPHY, Metoprolol Atherosclerosis Prevention in Hypertensives; MRFIT, Multiple Risk Factor Intervention Trial; and ellipses, data not reported.*

†All the predictions (except stroke death for 4S) of the cardiovascular disease life expectancy model fall within the 95% CIs observed in each clinical study.

(3.76-0.80 YOLS) were approximately 3-fold greater than those predicted for low-risk women (1.12-0.25 YOLS), further emphasizing the importance of selecting high-risk men and women for therapy to lower lipid levels in the primary prevention of CVD (Figure 2, A and C).

Among low-risk subjects with CVD, the forecasted benefits of therapy to lower lipid levels were generally greater than those predicted for subjects without CVD (Figure 2, B and D). Although men were predicted to benefit more than women, the sex differences surrounding secondary prevention were not as striking as those estimated for primary prevention. For instance, among those with CVD, we forecasted 3.84 YOLS for a 40-year-old man without other risk factors compared with 2.58 YOLS for a woman of the same age. Accordingly, the benefits for a man are approximately 50% greater than for a woman with all other things being equal. In the absence of CVD, forecasted benefits for a 40-year-old man were 2.50 YOLS vs 1.12 YOLS for a woman of the same age; a more than 2-fold difference.

For high-risk men and women with CVD, the benefits of therapy were essentially the same (4.65-0.65 YOLS vs 4.39-0.75 YOLS, respectively). Moreover, the forecasted benefits of treating high-risk patients with CVD were only slightly greater than those forecasted for low-risk patients. Among high-risk and low-risk men, there was essentially no difference in the forecasted benefits of treatment. The benefits of treating high-risk women were greater than those predicted for low-risk women, but the difference was substantially smaller than that predicted for women without CVD.

These simulations suggest that among patients with hyperlipidemia and CVD, the presence of other risk factors has little impact on the forecasted benefits of modifying the blood lipid levels. While targeting high-risk patients in primary prevention is essential, it may be irrelevant in secondary prevention once symptomatic disease is apparent.

FORECASTING THE BENEFITS OF TREATING HYPERTENSION

The forecasted benefits of treating hypertension among patients with and without CVD are consistent with those described for hyperlipidemia. In primary prevention, high-risk men will benefit more than those at low risk (1.19-0.29 YOLS vs 0.85-0.17 YOLS, respectively) (**Figure 3**, A). In secondary prevention, the presence of symptomatic CVD also negates the importance of identifying other cardiovascular risk factors when selecting which patients to treat for hypertension because the benefits of therapy for high- vs low-risk men are similar (1.08-0.23 YOLS vs 1.00-0.23 YOLS) (Figure 3, B). Similar results were found for women (Figure 3, C and D).

COMMENT

We have developed and validated a CVD life expectancy model that forecasts the benefits of risk factor modification in primary and secondary prevention. Predicted outcomes include deaths due to coronary disease, stroke, and other causes. Accordingly, the benefits of treating modifiable risk factors, such as hyperlipidemia, hypertension, or cigarette smoking, can be compared in terms of their impact on mortality due to coronary or cerebrovascular disease and other causes.

This model builds on more than a decade of previous work assessing the impact of risk factors on coronary disease or stroke.[11-15] Accordingly, the methods and results of this model are similar to those that have been published. However, this model differs in a number of important respects. Although previous modeling usually has been based on the data from the Framingham study,[10] we have used data from LRC[16-19] because subjects in this cohort included those with and without CVD at baseline. Nonetheless, the independent risk factors presented in Table 2 are consistent with previously published results.[10] Moreover, previous analyses[20] have dem-

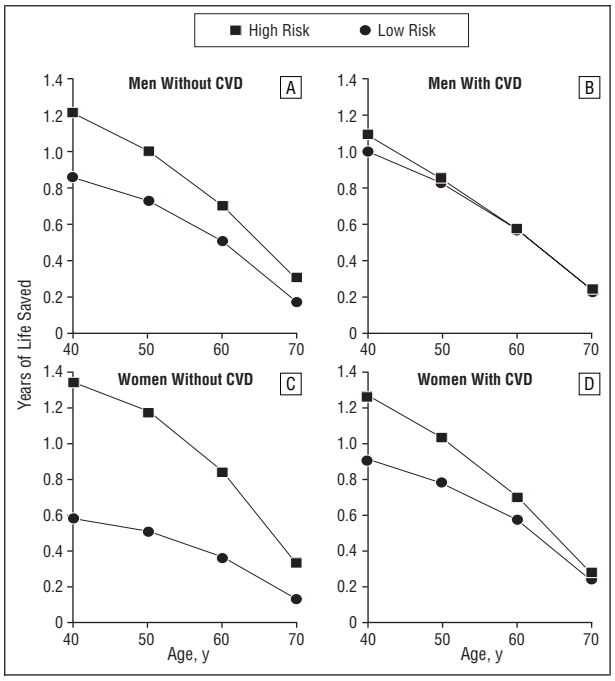

Figure 2. *Forecasted years of life saved following treatment of hypertension in subjects with cardiovascular disease (CVD). High-risk subjects are those who smoke cigarettes and have a low-density lipoprotein (LDL) cholesterol level of 4.9 mmol/L (189 mg/dL) and high-density lipoprotein (HDL) cholesterol level of 1.0 mmol/L (39 mg/dL) (LDL/HDL=4.9). Low-risk subjects are those who do not smoke cigarettes and have an LDL cholesterol level of 3.85 mmol/L (149 mg/dL) and an HDL cholesterol level of 1.1 mmol/L (43 mg/dL) (LDL/HDL=3.5) with blood pressure of 120/80 mm Hg or lower.*

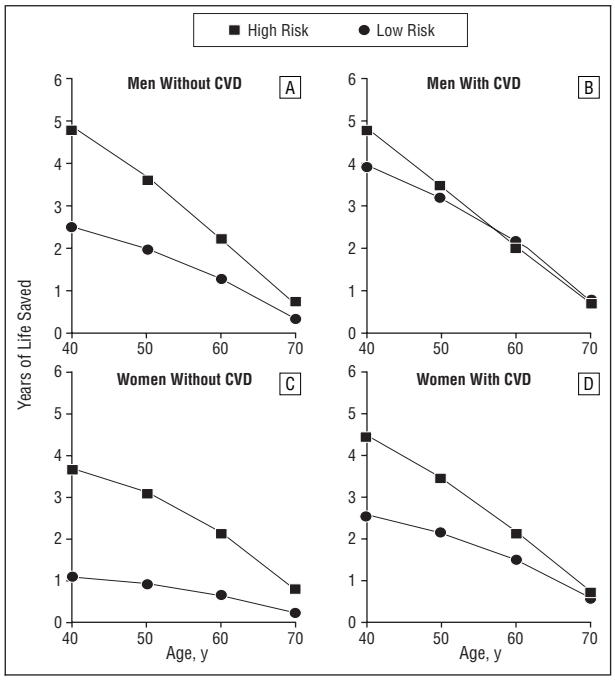

Figure 3. *Forecasted years of life saved following lipid level modification in subjects with cardiovascular disease (CVD). High-risk subjects are those who smoke cigarettes and have a blood pressure of at least 160/100 mm Hg. Low-risk subjects are those who do not smoke cigarettes and have a blood pressure of 120/80 mm Hg or lower.*

onstrated that the multivariate equations from the Framingham Heart Study are strongly predictive for deaths due to coronary disease in the LRC cohort.

We have also integrated deaths due to both coronary disease and stroke so that the impact of treating hypertension, hyperlipidemia, or cigarette smoking can be better compared across the 2 major causes of death due to CVD. This model is also the first to be validated on both primary and secondary prevention clinical trials, which is an essential step before completing simulations to estimate the effectiveness and cost-effectiveness of therapy.[30,31] Accordingly, it can be used to compare the predicted benefits of risk factor modification before and after the development of symptomatic CVD.

Despite the validation of short-term clinical trials, the simulations presented in this study should be accepted with caution because they represent long-term forecasts, which have no comparable results from clinical studies. For instance, we have conservatively assumed that all the benefits forecasted by the model stop at age 75 years. This recognizes that randomized clinical trials in subjects older than 75 years have not been completed, and one can only speculate on the potential benefits of risk factor modification among these patients. It should also be noted that models previously published by our group and others[10,32,33] have included interaction terms between age and other risk factors to capture the declining impact of these factors among the elderly. Although such interaction terms were evaluated in the current model, they either were not statistically significant or entered the model at the expense of other important risk factors we were not prepared to exclude. In fact, we suspect that many of the modifiable risk factors decline in importance with advancing age. However, the present model, based on the limited number of events documented in the LRC[17,18] cohort, possesses insufficient power to include relatively weak but potentially important age interaction terms.

The results of our simulations for the primary prevention of CVD are similar to those previously reported for coronary disease alone.[33-35] When comparing the forecasted changes in life expectancy, high-risk patients generally benefit more than low-risk patients, the young more than the elderly, and men more than women. The actual estimates published herein are also similar to previously published estimates of primary prevention using coronary risk models based on data from the Framingham Heart Study. For instance, Tsevat et al[35] estimated that reducing the risk of coronary disease through the control of hypertension (diastolic blood pressure, <94 mm Hg) would increase life expectancy by 1.0 to 1.2 years for men and 0.6 to 1.2 years for women aged 35 years. Using somewhat similar assumptions, we estimate that after a reduction in the risk of coronary disease and stroke, life expectancy will be increased 0.85 to 1.19 years for men and 0.59 to 1.34 years for women aged 40 years.

When forecasting the benefits of modification of lipid levels, the CVD life expectancy model focuses on changes in the LDL/HDL cholesterol ratio. In a previously published model based on data from the Framingham Heart Study, Hamilton et al[11] estimated that a 17% reduction in total cholesterol levels and a 7% increase in HDL cholesterol levels after use of lovastatin, 20 mg, would re-

sult in an increased life expectancy for adults aged 30 to 70 years of 0.23 to 2.03 years for men and 0.37 to 1.10 years for women free of disease. This earlier model focused only on the reduction of risk of coronary disease. If the impact of blood lipid levels on the risk of stroke is ignored, the current model estimates range from 0.39 to 3.96 years for men and 0.21 to 2.62 years for women when more intensive therapy with simvastatin is considered (total cholesterol and LDL cholesterol levels reduced 25% and 35%, respectively, and HDL cholesterol levels increased 8%).

Moreover, this model can be used to estimate the recently recognized impact of modification of lipid levels on the risk of stroke, which may be particularly relevant for the use of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors in both primary and secondary prevention.[36] Including the lipid impact on the risk of stroke with simvastatin therapy, we estimate changes in life expectancy between 0.43 to 4.74 years for men and 0.25 to 3.76 years for women.

The CVD life expectancy model confirms the importance of targeting high-risk patients for primary prevention of CVD. In the absence of symptomatic CVD, the impact of treating hyperlipidemia or hypertension will be greatest for those with other risk factors. Low-risk patients may never develop the disease despite the presence of hypertension or hyperlipidemia; therefore, the benefits of long-term therapy will be less, on average, for low-risk patients.

With increasing age, the benefits of therapy decline even if the relative risk associated with a risk factor remains stable across all age groups. This reflects the attenuated life expectancy of the elderly, therefore reducing the benefits of therapy. An elderly patient who has not yet developed symptomatic CVD may benefit little from risk factor modification even in the presence of 1 or more risk factors. While we do not advocate denying treatment or stopping treatment among older patients, this observation must be incorporated into the decision making between patients and physicians when a specific risk factor is diagnosed for primary prevention.[30,37,38]

Among patients with CVD, it is essential to identify all the modifiable risk factors that might be responsible for the development of disease. However, the results of these simulations suggest that the potential benefits of treating hyperlipidemia or hypertension are relatively consistent among patients with CVD regardless of the other risk factors present. The benefits are also generally greater among those with CVD than those without CVD, further underscoring the importance of risk factor management among those with symptomatic disease. This is particularly relevant among the elderly where the forecasted benefits of treatment are substantially greater among those with disease, thereby expanding the therapeutic window for intervention.

The primary and secondary prevention of CVD represents a potentially enormous effort for health care providers and a significant economic burden for health care payers. However, the increase in the forcasted life expectancy with interventions to treat hyperlipidemia or hypertension may be substantial, particularly when the combined benefits on fatal cerebrovascular and coronary events are considered together. Increasingly constrained health care resources demand that cost-effective risk factor modification be targeted toward those patients who are most likely to benefit substantially.[30] Accordingly, these results suggest that we must recognize the unique objectives of primary and secondary prevention interventions as well as the different anticipated benefits of the patients who will receive them.

Accepted for publication July 31, 1997.

Supported by grants from the Dairy Farmers of Canada, Montreal, Quebec, and Merck Frosst Canada Inc, Montreal. Dr Grover is a senior research scientist (chercheur-bousier) supported by the Fonds de la Recherche en Santé du Quebec, Montreal.

We acknowledge the generous assistance of David J. Gordon, MD, National Heart, Lung, and Blood Institute, Bethesda, Md, for helping us secure the LRC data tapes. Although the LRC data tapes are presented in this article, the LRC investigators took no part in the analyses and the interpretations presented herein. We also thank Nadine Bouchard for her excellent secretarial support.

Corresponding author: Steven A. Grover, MD, MPA, FRCPC, Centre for the Analysis of Cost-Effective Care, The Montreal General Hospital, 1650 Cedar Ave, Montreal, Quebec, Canada H3G 1A4.

REFERENCES

1. Pedersen TR, Kjekshus J, Berg K, et al, for the Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet.* 1994;344:1383-1389.
2. Sacks FM, Pfeffer MA, Moye LA, et al, for the Cholesterol and Recurrent Events Trial Investigators. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med.* 1996; 335:1001-1009.
3. Crouse JR III, Byington RP, Bond MG, et al. Pravastatin, lipids, and artherosclerosis in the carotid arteries (PLAC-II). *Am J Cardiol.* 1995;75:455-459.
4. Blankenhorn DH, Selzer RH, Crawford DW, et al. Beneficial effects of colestipol-niacin therapy on the common carotid artery: two- and four-year reduction of intima-media thickness measured by ultrasound. *Circulation.* 1993;88:20-28.
5. Furberg CD, Byington RP, Crouse JR, et al. Pravastatin, lipids and major coronary events. *Am J Cardiol.* 1994;73:1133-1134.
6. Welin LZ, Svärdsudd K, Wilhelmsen L, Larsson B, Tibblin G. Analysis of risk factors for stroke in a cohort of men born in 1913. *N Engl J Med.* 1987;317:521-526.
7. Hebert PR, Gaziano M, Hennekens CH. An overview of trials of cholesterol lowering and risk of stroke. *Arch Intern Med.* 1995;155:50-55.
8. Atkins D, Psaty BM, Koepsell TD, Longstreth WT Jr, Larson EB. Cholesterol reduction and the risk for stroke in men: a meta-analysis of randomized, controlled trials. *Ann Intern Med.* 1993;119:136-145.
9. Iso H, Jacobs DR Jr, Wentworth D, Neaton JD, Cohen JD, for the MRFIT Research Group. Serum cholesterol levels and six-year mortality from stroke in 350 977 men screened for the multiple risk factor intervention trial. *N Engl J Med.* 1989;320:904-910.
10. Anderson KM, Odell PM, Wilson PWF, Kannel WB. Cardiovascular disease risk profiles. *Am Heart J.* 1990;121:293-298.
11. Hamilton VH, Racicot FE, Zowall H, Coupal L, Grover SA. The cost-effectiveness of HMG-CoA reductase inhibitors to prevent coronary heart disease: estimating the benefits of increasing HDL-C. *JAMA.* 1995;273:1032-1038.
12. Goldman L, Weinstein MC, Goldman PA, Williams LW. Cost-effectiveness of HMG-CoA reductase inhibition for primary and secondary prevention of coronary heart disease. *JAMA.* 1991;265:1145-1151.
13. Hay JW, Wittels EH, Gotto AM Jr. An economic evaluation of lovastatin for cholesterol lowering and coronary artery disease reduction. *Am J Cardiol.* 1991;67: 789-796.

14. Kinosian BP, Eisenberg JM. Cutting into cholesterol: cost-effective alternatives for treating hypercholesterolemia. *JAMA.* 1988;259:2249-2254.
15. Oster G, Epstein AM. Cost-effectiveness of antihyperlipidemic therapy in the prevention of coronary heart disease: the case of cholestyramine. *JAMA.* 1987;258: 2381-2387.
16. Central Patient Registry and Coordinating Centre for the Lipid Research Clinics. *Reference Manual for the Lipid Research Clinics Prevalence Study.* Vols 1 and 2. Chapel Hill: University of North Carolina; 1974.
17. The Lipid Research Clinics Program Epidemiology Committee. Plasma lipid distributions in selected North American populations: the Lipid Research Clinics Prevalence Study. *Circulation.* 1979;60:427-439.
18. Heiss G, Tamir I, Davis CE, et al. Lipoprotein-cholesterol distributions in selected North American populations: the Lipid Research Clinics Program Prevalence Study. *Circulation.* 1980;61:302-315.
19. Lipid Research Clinics Program. *Manual of Laboratory Operations: Lipid and Lipoprotein Analysis.* Vol 1. Bethesda, Md: National Heart, Lung, and Blood Institute, National Institutes of Health; 1974. US Dept of Health, Education and Welfare publication NIH 75-628.
20. Grover SA, Coupal L, Hu X-P. Identifying adults at increased risk of coronary disease: how well do the current cholesterol guidelines work? *JAMA.* 1995;274: 801-806.
21. Lipid Research Clinics Program. The Lipid Research Clinics Coronary Primary Prevention Trial results, II: the relationship of reduction in incidence of coronary heart disease to cholesterol lowering. *JAMA.* 1984;251:365-374.
22. Kannel WB, Wolf PA, Garrison RJ. Survival following initial cardiovascular events: 30-year follow-up. In: *The Framingham Study: An Epidemiological Investigation of Cardiovascular Disease.* Bethesda, Md: National Heart, Lung, and Blood Institute; 1988:§35. Publication NIH 88-2969.
23. Manninen V, Elo O, Frick H, et al. Lipid alterations and decline in the incidence of coronary heart disease in the Helsinki Heart Study. *JAMA.* 1988;260:641-651.
24. Shepherd J, Cobbe SM, Ford I, et al, for the West of Scotland Coronary Prevention Study Group. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med.* 1995;333:1301-1307.
25. Buchwald H, Varco RL, Matts JP, et al, and the POSCH Group. Effect of partial ileal bypass surgery on mortality and morbidity from coronary heart disease in patients with hypercholesterolemia. *N Engl J Med.* 1990;323:946-955.
26. SHEP Cooperative Research Group. Prevention of stroke antihypertensive drug treatment in older persons with isolated systolic hypertension. *JAMA.* 1991;265: 255-264.
27. Wikstrand J, Warnold I, Olsson G, Tuomilheto J, Elmfeldt D, Berglund G. Primary prevention with metoprolol in patients with hypertension. *JAMA.* 1988; 259:1976-1982.
28. The Multiple Risk Factor Intervention Trial Research Group. Mortality rates after 10.5 years for participants in the Multiple Risk Factor Intervention Trial: findings related to a priori hypothesis of the trial. *JAMA.* 1990;263:1795-1801.
29. Collins R, Peto R, MacMahon S, et al. Blood pressure, stroke, and coronary heart disease, part 2: short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. *Lancet.* 1990;335:827-838.
30. 27th Bethesda Conference. Matching the intensity of risk factor management with the hazard for coronary disease events. *J Am Coll Cardiol.* 1996;27:964-1057.
31. Goldman L, Gordon DJ, Rifkind BM, et al. Cost and health implications of cholesterol lowering. *Circulation.* 1992;85:1960-1968.
32. Abbott RD, McGee D, Kannel WB, Wolf PA, Garrison RJ. The probability of developing certain cardiovascular disease in eight years at specified values of some characteristics. In: *The Framingham Study: An Epidemiological Investigation of Cardiovascular Disease.* Bethesda, Md: US Dept of Health, Education and Welfare; 1987:§37. Publication NIH 87-2284.
33. Grover SA, Abrahamowicz M, Joseph L, Brewer C, Coupal L, Suissa S. The benefits of treating hyperlipidemia to prevent coronary heart disease: estimating changes in life expectancy and morbidity. *JAMA.* 1992;267:816-822.
34. Taylor WC, Pass TM, Shepard DS, Komaroff AL. Cholesterol reduction and life expectancy: a model incorporating multiple risk factors. *Ann Intern Med.* 1987; 106:605-614.
35. Tsevat J, Weinstein MC, Williams LW, Tosteson AN, Goldman L. Expected gains in life expectancy from various coronary heart disease risk factor modifications. *Circulation.* 1991;83:1194-1201.
36. Crouse JR III, Byington RP, Furberg CD. Reductase inhibitor monotherapy prevents stroke. *Circulation.* 1996;94(suppl):I-540.
37. Garber AM, Littenberg B, Sox HC, Wagner JL, Gluck M. Costs and health consequences of cholesterol screening for asymptomatic older Americans. *Arch Intern Med.* 1991;151:1089-1095.
38. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Summary of the second report of the national cholesterol education program expert panel on detection, evaluation, and treatment of high blood cholesterol in adults. *JAMA.* 1993;269:3015.

Correction

Spelling Error in Figure. In the article titled "Homocyst(e)ine and Coronary Artery Disease," published in the November 10, 1997, issue of the ARCHIVES (*Arch Intern Med.* 1997;157:2299-2308), "Cystine" in Figure 1 on page 2300 should read "Cysteine."

REFERENCES

1. Schappert SM. *National Ambulatory Medical Care Survey: 1991 Summary.* 13th ed. Atlanta, Ga: Centers for Disease Control and Prevention; 1995.
2. Irwin RS, Corrao WM, Pratter MR. Chronic persistent cough in the adult: the spectrum and frequency of causes and successful outcome of specific therapy. *Am Rev Respir Dis.* 1981;123:413-417.
3. Holinger LD. Chronic cough in infants and children. *Laryngoscope.* 1986;96: 316-322.
4. Irwin RS, Curley FJ, French CL. Chronic cough: the spectrum and frequency of causes, key components of the diagnostic evaluation, and outcome of specific therapy. *Am Rev Respir Dis.* 1990;141:640-647.
5. Poe RH, Harder RV, Israel RH, Kallay MC. Chronic persistent cough: experience in diagnosis and outcome using an anatomic diagnostic protocol. *Chest.* 1989; 95:723-728.
6. Irwin RS, Pratter MR, Holland PS, Corwin RW, Hughes JP. Postnasal drip causes cough and is associated with reversible upper airway obstruction. *Chest.* 1984; 85:346-352.
7. Irwin RS, Zawacki JK, Curley FJ, French CL, Hoffman PJ. Chronic cough as the sole presenting manifestation of gastroesophageal reflux. *Am Rev Respir Dis.* 1989;140:1294-1300.
8. Medical Research Council. Committee report on the aetiology of chronic bronchitis. *Lancet.* 1965;1:775-778.
9. Fraser RG, Pare JAP, Pare PD, Fraser RS, Genereux GP. Diseases of the airways. In: *Diagnosis of Diseases of the Chest.* 3rd ed. Philadelphia, Pa: WB Saunders Co; 1990:1969-2275.
10. Smyrnios NA, Irwin RS, Curley FJ. Chronic cough with a history of excessive sputum production: the spectrum and frequency of causes, key components of the diagnostic evaluation, and outcome of specific therapy. *Chest.* 1995;108: 991-997.
11. Pratter MR, Bartter TC, Akers S, Dubois J. An algorithmic approach to chronic cough. *Ann Intern Med.* 1993;119:977-983.
12. Hoffstein V. Persistent cough in nonsmokers. *Can Respir J.* 1994;1:40-47.
13. O'Connell F, Thomas VE, Pride NB, Fuller RW. Capsaicin cough sensitivity decreases with successful treatment of chronic cough. *Am J Respir Crit Care Med.* 1994;150:374-380.
14. Puolijoki H, Lahdensuo A. Causes of prolonged cough in patients referred to a chest clinic. *Ann Med.* 1989;21:425-427.
15. French CL, Irwin RS, Curley FJ, Krikorian CJ. The impact of chronic cough on quality of life. *Arch Intern Med.* In press.
16. Irwin RS, French CL, Curley FJ, Zawacki JK, Bennet FM. Chronic cough due to gastroesophageal reflux: clinical, diagnostic, and pathogenetic aspects. *Chest.* 1993;104:1511-1517.
17. Mold JW, Reed LE, Davis AB, Allen ML, Decktor DL, Robinson M. Prevalence of gastroesophageal reflux in elderly patients in a primary care setting. *Am J Gastroenterol.* 1991;86:965-970.
18. Richter JE, Castell DO. Gastroesophageal reflux: pathogenesis, diagnosis, and therapy. *Ann Intern Med.* 1982;97:93-103.
19. Burr ML, Charles TJ, Roy K, Seaton A. Asthma in the elderly: an epidemiologic survey. *BMJ.* 1979;1:1041-1044.
20. Burrows B, Barbee RA, Cline MG, Knudson RJ, Lebowitz MD. Characteristics of asthma among elderly adults in a sample of the general population. *Chest.* 1991; 100:935-942.

Correction

Error in Figure Legends. In the original investigation titled "Estimating the Benefits of Modifying Risk Factors of Cardiovascular Disease," published in the March 23 issue of the ARCHIVES (1998;158:655-662), the legends for Figure 2 and Figure 3 were accidentally reversed during processing for publication. The journal apologizes for the error.