

# The Benefits of Treating Hyperlipidemia to Prevent Coronary Heart Disease

## Estimating Changes in Life Expectancy and Morbidity

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**Objective.**—To evaluate the lifetime benefits of reducing total serum cholesterol levels to prevent coronary heart disease (CHD).

**Design.**—We developed a CHD primary prevention computer model to estimate the benefits associated with lifelong risk factor modification. We validated the model by comparing the computer estimates with the observed results of three primary CHD prevention trials.

**Patients.**—Men and women age 35 to 65 years who are free of CHD, with total serum cholesterol levels ranging from 5.2 to 7.8 mmol/L (200 to 300 mg/dL), with or without additional CHD risk factors.

**Interventions.**—Serum cholesterol reduction through dietary modification or diet and medications.

**Main Outcome Measures.**—Changes in life expectancy and the delay of symptomatic CHD.

**Results.**—The computer forecasts for CHD end points closely matched the observed results of the Lipid Research Clinics Trial, the Helsinki Heart Study, and MRFIT. We then applied the computer model to low-risk and high-risk men and women with total serum cholesterol levels between 5.2 and 7.8 mmol/L (200 and 300 mg/dL) and estimated that, after reducing serum cholesterol levels 5% to 33%, the average life expectancy would increase by 0.03 to 3.16 years. We also forecast that the average onset of symptomatic CHD would be delayed among these patient groups by 0.06 to 4.98 years.

**Conclusion.**—We conclude that this computer model accurately estimates the results of clinical trials and can be used to forecast the changes in life expectancy and morbidity (the development of CHD) associated with specific CHD risk reduction interventions. The wide variation surrounding these estimates underscores the need to better define which groups of individuals will gain the most from cholesterol reduction.

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THE PRIMARY prevention of coronary heart disease (CHD) by reducing total serum cholesterol levels has been conclusively demonstrated in a number of randomized controlled clinical trials.<sup>1,2</sup> This has resulted in a growing consensus to implement nationwide screening to detect and treat hypercholesterolemia.<sup>3-6</sup> However, others remain critical of the potential benefits of such a massive primary prevention program.<sup>7,8</sup> Accordingly, the current debate surrounding cholesterol reduction asks not only "Can it reduce CHD events?" but also "How substantial are the long-term benefits?" While the first question is of great importance to medical scientists, the second is equally important to patients, practicing physicians, public health officials, and health funding agencies.

Unfortunately, clinical trials usually last 5 to 10 years. While they may demonstrate that cholesterol reduction works in the short term, they are unable to define the long-term benefits that might accrue over a lifetime of intervention. The costs of extending a randomized trial over the lifetime of all the participants would likely be prohibitive. Nonetheless, clinical and policy decisions must be made despite the limited information at hand.

Patients advised to alter dietary habits or to start taking medication may ask "How much longer will I live as a result of this intervention?" Decreased morbidity or improved quality of life through the delay of symptomatic CHD is also

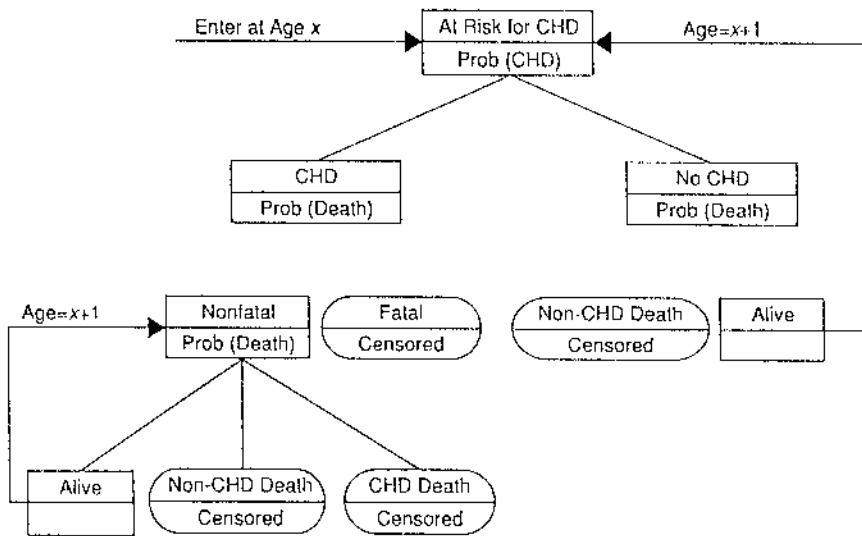


Fig 1.—Overview of coronary heart disease (CHD) model. Persons free of CHD enter the model at age  $x$  years and are at risk (Prob) of CHD events over the following year. Those who develop CHD may suffer a CHD death or a non-CHD death and are removed from the model. At the end of 1 year, all survivors with CHD age 1 year ( $x+1$ ) and remain at risk of CHD or non-CHD death. All persons without CHD remain at risk of non-CHD death, and the survivors after 1 year reenter the model at age  $x+1$ .

an implicit goal of risk factor modification. To date, neither of these important clinical outcomes has been empirically determined.

To estimate the increased life expectancy associated with CHD risk factor modification among patients free of symptomatic disease, we have developed a computer model based on the Framingham Heart Study, Canadian Life Tables, and Canada Health Survey Data. Incorporating a life-table approach, this model estimates the average increased life expectancy associated with modifying one or more CHD risk factors. It also forecasts changes in one measure of morbidity: years of life free of symptoms of CHD, including angina, coronary insufficiency, and myocardial infarction.

We have validated this model by comparing the computer estimates with the published results of three major clinical trials. Given the model's accuracy, we then forecasted the expected benefits of reducing different levels of total serum cholesterol among men and women of different ages at high and low risk for CHD. The results of these analyses underscore the tremendous variation surrounding the estimated benefits of cholesterol intervention.

## METHODS

### Primary Coronary Events

The primary CHD model calculates the annual probability of dying from CHD or other (non-CHD) causes and the annual risk of specific CHD events

for an individual free of CHD at entry into the model (Fig 1). The annual probability of each specific CHD event (total CHD, CHD death, and myocardial infarction) was based on Framingham multivariate logistic regression models published in 1987.<sup>12</sup> These models estimate, for men or women, the probability of a CHD event during an 8-year period as a function of age, diastolic blood pressure (DBP), total serum cholesterol level (CHL), the presence of left ventricular hypertrophy (LVH), the presence of glucose intolerance (GLU), and the presence of cigarette smoking (CIG), as defined in the Framingham Heart Study. To determine the annual probability of a CHD event, the calculated 8-year probability was divided by eight. We therefore assumed that the distribution of events between years 1 and 8 was essentially uniform, so that one eighth of the 8-year probability approximated the annual probability. This simplifying assumption was made after inspecting the published probability estimates for developing CHD over 2, 4, 6, and 8 years.<sup>13</sup> Dividing each probability estimate by the years of follow-up demonstrated similar annual CHD risk estimates over 2 to 8 years of follow-up.

The annual probability of CHD events was then adjusted for the level of high-density lipoprotein (HDL) cholesterol using a gender-specific HDL modifier ( $HDL_{mod}$ ) for men or women. This adjustment was calculated by fitting an exponential curve to the HDL multipliers published by the Framingham

Study,<sup>14</sup> so that:

$$HDL_{mod} = \exp(1.80 - 0.040 \times HDL)$$

for men, and

$$HDL_{mod} = \exp(2.42 - 0.044 \times HDL)$$

for women.

Therefore, in our model, the annual probability of all CHD events is calculated as:

$$(1/8) \times \{[\exp(RISK)]/[1 + \exp(RISK)]\} \times (HDL_{mod}),$$

where RISK is a function of gender-specific Framingham Study  $\beta$  coefficients, so that, for men:

$$\begin{aligned} RISK = & (0.29 \times AGE) - (0.0015 \times AGE^2) \\ & + (0.02 \times CHL) + (0.02 \times DBP) \\ & + (0.44 \times CIG) + (0.62 \times LVH) \\ & + (0.28 \times GLU) \\ & - (0.00027 \times CHL \times AGE) \\ & - 17.01. \end{aligned}$$

Specific end points included the risk of myocardial infarction, uncomplicated angina pectoris or coronary insufficiency, CHD death, all CHD events, and non-fatal CHD (all CHD events minus CHD deaths).

Cholesterol reduction occasionally increased risks among the elderly (age >74 years) due to a negative coefficient for the age-cholesterol interaction. We assumed that this effect represented a modeling phenomenon, not a clinical one, because the Framingham model was based on individuals age 35 through 74 years at entry. Therefore, we computed the age-specific annual CHD risk until age 74 years and then fixed all subsequent yearly risks at that level so that the association between serum cholesterol level and CHD risk might approach zero but was never negative.

### All-Cause Mortality and Noncardiac Events

The annual mean age- and sex-specific probability of all-cause death ( $Prob(ACD_{ann})$ ) was based on 1986 Canadian Life Tables published by Statistics Canada.<sup>15</sup> These tables present the age-specific annual probability of dying from all causes for men and women in Canada starting at birth and terminating at age 102 years. This mean annual probability was adjusted for the relative risks (RRs) associated with cigarette smoking (yes or no), glucose intolerance (yes or no), and the level of DBP using logistic regression ( $\beta$  coefficients published by the Framingham Study,<sup>16</sup> which identified these risk factors as being significantly associated with all-cause mortality. The age- and sex-specific distribution of these risk factors was based on Canada Health Survey data.<sup>17</sup> We used absolute rather than standardized  $\beta$  coefficients to make the

results independent of any potential differences in risk factor distribution between the Framingham and Canada Health Survey samples. The estimates of the RRs, based on  $\beta$  coefficients, were then corrected for the fact that, in the logistic regression model, the probability associated with the mean value of the risk factor distribution is lower than the mean of individual probabilities calculated from the same distribution. In the case of DBP, the approximate correction proposed by Berwick et al<sup>18</sup> for continuous risk factors was used, resulting in:

$$RR_{cor}(DBP) = \exp \left\{ \beta(DBP - DBP_{CAN}) - [(\beta_{st})^2/2] \right\},$$

where  $DBP_{CAN}$  indicates the mean DBP reported by the Canada Health Survey and  $\beta_{st}$  is the standardized  $\beta$  coefficient for DBP.<sup>18</sup> For a binary risk factor (CIG or GLU) with the reported prevalence  $p_{CAN}$ , the uncorrected relative risk associated with level  $x$  (where  $x = 1$  or  $0$ , denoting the presence or absence of a risk factor, respectively) was calculated as:

$$RR(x) = \exp [\beta(x - p_{CAN})].$$

Accordingly, the following exact formula was obtained and used for computing the corrected RR for a specific patient group in which the prevalence of this factor equals  $\pi$ :

$$RR_{cor}(\pi) = \frac{\pi RR(1) + (1 - \pi) RR(0)}{p_{CAN} RR(1) + (1 - p_{CAN}) RR(0)},$$

In a group of patients homogeneous with respect to a given binary risk factor,  $\pi$  is set to 0 or 1 and the above formulas still hold. Finally, based on these results and the demonstrated independence of risk factors, the probability of all-cause mortality associated with a given risk profile was computed as:

$$\text{Prob [ACD(DBP, CIG, GLU)]} = \text{Prob (ACD}_{crude}) \times RR_{cor}(DBP) \times RR_{cor}(CIG) \times RR_{cor}(GLU).$$

The probability of non-CHD death was calculated as the difference between all-cause mortality and CHD mortality. As non-CHD mortality was assumed to be independent of lipid levels and left ventricular hypertrophy, we did not include specific CHD risk profile levels in this calculation of CHD risk but rather used population-based estimates from Framingham Study and Canada Health Survey data.

These elements were integrated into a primary CHD life-table model. Each year, a number of individuals are predicted to die of CHD or other causes and are removed from the group at risk. Individuals who suffer nonfatal CHD

events were moved from the primary to the secondary CHD model.

### Secondary Coronary Events

In the secondary CHD model, the risk of dying during the 12 months following a nonfatal myocardial infarction (MI) was estimated from Framingham data.<sup>19</sup> The risk of other secondary CHD events was based on the annual risk of primary CHD events after adjustment for the presence of CHD. This adjustment was also based on Framingham data.<sup>19</sup> For example, for men age 35 through 64 years,

$$\text{Prob [CHD}_{death}(MI)] = 4.44 \times \text{Prob [CHD}_{death}(\text{No MI})].$$

### CHD Model

The above submodels were then integrated into a CHD model in which all individuals entering the model were assumed to be free of CHD at time 0 (Fig 1). Each year a number of individuals were predicted to die of CHD or other (non-CHD) causes. The risk of nonfatal CHD events, such as myocardial infarction or angina pectoris/coronary insufficiency, was also computed, and these individuals then moved from the primary CHD model to the secondary CHD model. At the end of 1 year, the number of remaining individuals at risk for primary CHD was calculated as the difference between those at the beginning of the year and those who had died and/or developed CHD. The annual cumulative mortality differences among survivors (with and without intervention) over the total life expectancy represented the total years of life saved following intervention. Dividing the total years of life saved by the original number of individuals at risk at time 0 resulted in the average years of life saved per individual.

To calculate years of life free of CHD, we used a similar procedure, and the outcome of interest included the development of CHD (angina, coronary insufficiency, or myocardial infarction) or death.

### Model Validation

The accuracy of this computer model was evaluated using data from three CHD primary prevention clinical trials. They included the Helsinki Heart Study<sup>20</sup> and the Lipid Research Clinics Coronary Primary Prevention Trial.<sup>12</sup> The Multiple Risk Factor Intervention Trial (MRFIT), for which the interventions included smoking cessation, cholesterol reduction, and the control of hypertension, was also evaluated.<sup>22,23</sup>

The risk profiles of subjects following randomization were obtained from published reports that included summary

statistics for age, sex, total serum cholesterol level, HDL cholesterol level, and DBP and the prevalence of cigarette smokers, left ventricular hypertrophy, and glucose intolerance (Table 1). When multiple measures at different visits were available for the preintervention or postintervention states, we averaged the results to summarize the experience of cohorts in each trial.

For MRFIT, smoking cessation rates were published as reported by patients themselves or adjusted using the serum thiocyanate level as a more objective measure.<sup>22</sup> For our analysis, we calculated postintervention smoking rates as the average of the reported smoking prevalence (RSP) over six annual visits corrected for the thiocyanate-adjusted quit rate at 12 months:

$$RSP \times [(1 - \text{Thiocyanate-Adjusted Quit Rate}) / (1 - \text{Reported Quit Rate})],$$

eg, for the special intervention group after intervention (for which RSP = 0.342),<sup>22</sup>

$$CSP = 0.342 \times [(1 - 0.31) / (1 - 0.43)] = 41.4\%,$$

where CSP indicates corrected smoking prevalence.

### Life Expectancy and Lipid Modification

To estimate the lifetime benefits associated with reducing the total serum cholesterol level, the computer model was applied to a range of patient profiles. This analysis focused on low-risk men or women age 35, 45, 55, or 65 years whose only risk factor for CHD was hypercholesterolemia, as well as on high-risk individuals with hypercholesterolemia and hypertension who smoked cigarettes.

To estimate the potential benefits of treating hypercholesterolemia, varying levels at baseline were considered, including 5.7, 6.2, and 7.8 mmol/L (220, 240, and 300 mg/dL). The expected reduction in total serum cholesterol level was assumed to be 5% for dietary intervention, based on the observed reductions of 4.9% and 5% published by the Lipid Research Clinics Trial<sup>1</sup> and MRFIT.<sup>22</sup> A reduction to 5.2 mmol/L for treatment with diet and medication was based on the current recommendations of various expert panels.<sup>24</sup>

### Statistical Analyses

In comparing the results of the clinical trials with those generated by the computer model, 95% confidence intervals (CIs) (using the exact method) were computed for all results of the clinical trials to account for the limited precision of these estimates.

Table 1.—Average Patient Profiles From Clinical Trials\*

	MRFIT		Helsinki Heart Study		Lipid Research Clinics Trial	
	UC	SI	Placebo	Gemfibrozil	Placebo	Cholestyramine
	Baseline Levels					
Age, y	46	46	47.4	47.2	46	48
Sex	M	M	M	M	M	M
Total cholesterol, mmol/L	6.57	6.57	7.31	7.31	7.78	7.78
HDL cholesterol, mmol/L	1.12	1.12	1.24	1.23	1.20	1.19
Diastolic blood pressure, mm Hg	95.1	95.1	91.0	91.5	80.0	80.0
Smokers, %	61.3	61.6	35.8	36.5	37.0	38.0
Left ventricular hypertrophy, %†	0	0	0	0	0	0
Diabetes, %‡	0	0	2.9	2.4	0	0
	Intervention Levels					
Total cholesterol, mmol/L	6.31	6.13	7.05	6.36	7.37	6.61
HDL cholesterol, mmol/L	1.14	1.13	1.22	1.34	1.20	1.23
Diastolic blood pressure, mm Hg	85.9	82.1	91.0	91.5	76.5	76.0
Smokers, %	51.0‡	41.4‡	32.3	33.0	30.5	31.5

\*MRFIT indicates Multiple Risk Factor Intervention Trial; UC, usual care; SI, special intervention; and HDL, high-density lipoprotein.

†A value of 0 indicates that this factor was not present among participants in the study.

‡Thiocyanate-adjusted smoking rates (see the "Methods" section).

## RESULTS

### Model Validation

The computer model accurately forecasted the results observed in the Helsinki Heart Study, Lipid Research Clinics Trial, and MRFIT over 5, 7.4, and 10.5 years, respectively (Table 2). For example, following 10.5 years of observation in MRFIT, fatal CHD ischemic events numbered 31.4 per 1000 (95% CI, 27.4 to 35.9 per 1000) in the special intervention group and 35.1 per 1000 (95% CI, 30.8 to 39.8 per 1000) in the usual care group, corresponding to computer estimates of 26.7 and 32.6 per 1000, respectively. Annual CHD event rates (available only for MRFIT and the Helsinki Heart Study) forecasted by the model fell within the 95% CI of the observed results in 25 (96%) of 26 instances. The computer model was further evaluated by comparing all-cause mortality; in MRFIT, 12 (75%) of the 16 forecasted annual mortality rates fell within the 95% CI of the observed results. The estimated cumulative event rates also closely matched those observed in the clinical trials (not available for the Lipid Research Clinics Trial) (Fig 2).

We also estimated the lifetime benefits of treatment based on the risk factor modification observed over the short-term follow-up of these clinical trials. Among those using cholestyramine in the Lipid Research Clinics Trial, the net benefits of treatment compared with diet alone would average 0.70 years of life saved for each individual. Among those using gemfibrozil in the Helsinki Heart Study, the lifetime benefits of treatment would average 1.06 years of life saved. In MRFIT, the net benefits for the special intervention group compared with the usual care group following reductions in total serum cholesterol

Table 2.—Validation of Computer-Estimated CHD Events Against the Observed Results of Clinical Trials\*

Clinical Trial	Mean Follow-up, y	Measure	Events per 1000		
			Computer Estimate	Observed Result	(95% Confidence Interval)
MRFIT	10.5	CHD deaths			
		SI group	26.7	31.4	(27.4 to 35.9)
		UC group	32.6	35.1	(30.8 to 39.8)
		Total deaths			
Lipid Research Clinics Trial	7.4	CHD deaths			
		Cholestyramine	15.9	15.7	(11.1 to 22.4)
		Placebo	20.7	20.0	(14.6 to 27.4)
		Total deaths			
Helsinki Heart Study	5	Cardiac events			
		Gemfibrozil	30.9	27.3	(21.1 to 35.3)
		Placebo	43.8	41.4	(33.6 to 51.0)
		Nonfatal myocardial infarctions			
		Gemfibrozil	20.9	21.9	(16.5 to 29.3)
		Placebo	29.3	35.0	(27.9 to 43.9)
		CHD deaths			
		Gemfibrozil	10.0	6.8	(4.1 to 11.4)
		Placebo	14.6	9.4	(6.0 to 14.6)
		Total deaths			
Gemfibrozil	27.7	21.9	(16.5 to 29.3)		
Placebo	32.2	20.7	(15.4 to 27.9)		

\*CHD indicates coronary heart disease; MRFIT, Multiple Risk Factor Intervention Trial; SI, special intervention; and UC, usual care.

level, smoking cessation, and blood pressure reduction would average 1.14 years of life saved per individual.

### Forecasted Changes in Life Expectancy and Morbidity

The forecasted lifetime benefits of cholesterol reduction varied greatly depending on the baseline level, the presence or absence of other risk factors, and the age and sex of the individual. Among 35-year-old men without other risk factors for CHD (low risk), reducing the serum cholesterol level from 7.8 to 5.2

mmol/L (300 to 200 mg/dL) with diet and medication resulted in an average increased life expectancy of 1.64 years (Table 3). The average increased life expectancy among 35-year-old low-risk women was 0.98 years. The estimated benefits decreased with advancing age, so that the increased life expectancy for those age 65 years was 0.31 for men and 0.41 for women.

Among low-risk individuals, the average increased life expectancy associated with dietary intervention alone was usually small, ranging from 0.03 years

for 65-year-old men with a baseline serum cholesterol level of 5.7 mmol/L to 0.32 years for 35-year-old men with a baseline serum cholesterol level of 7.8 mmol/L. This modest benefit was due primarily to the small reduction in total serum cholesterol level we assumed would occur, on average, with isolated dietary intervention.<sup>1,22</sup>

Among low-risk individuals the additional years of life free of symptomatic CHD were approximately twofold greater than the forecasted changes in life expectancy. Similar patterns across age and sex were observed. The maximum benefit was forecasted among 35-year-old men and women with a cholesterol level of 7.8 mmol/L who received dietary intervention and medication. The computer model estimated that the onset of symptomatic CHD would be delayed 4.05 years in men and 2.14 years in women. Older men and women would receive less benefit, as would those with lower levels of baseline cholesterol. The benefits of dietary intervention alone were again modest, with a maximum delay of 0.75 years predicted for 35-year-old men with cholesterol levels of 7.8 mmol/L.

Similar calculations were completed for high-risk individuals who were also hypertensive (DBP, 100 mm Hg) and cigarette smokers (Table 4). The overall benefits of cholesterol reduction tended to be greater among high-risk individuals than among those at low risk. Estimates of years of life saved ranged from 0.05 to 3.16 years, while years free of CHD ranged from 0.06 to 4.98 years. Trends across age groups, sex, and the intensity of intervention were similar to those described for low-risk individuals.

#### COMMENT

This computer model accurately forecasted the results of short-term clinical trials. Accordingly, in the absence of long-term clinical trials, we have used this model to estimate the lifetime benefits of cholesterol reduction in terms of life expectancy and years free of CHD.

Our analyses demonstrate that there is wide variation surrounding the average benefits of cholesterol reduction for men and women at different ages. Following lifetime treatment with drugs and/or diet, the increased life expectancy would range from 0.03 to 1.64 years for low-risk individuals. The delay in CHD development would be approximately twice as large, 0.06 to 4.05 years.

The results of this model are comparable with those of other published models.<sup>24-29</sup> Taylor et al<sup>24</sup> estimated that a lifelong program of dietary modification would result in a 6.7% decline in total serum cholesterol level and an increased

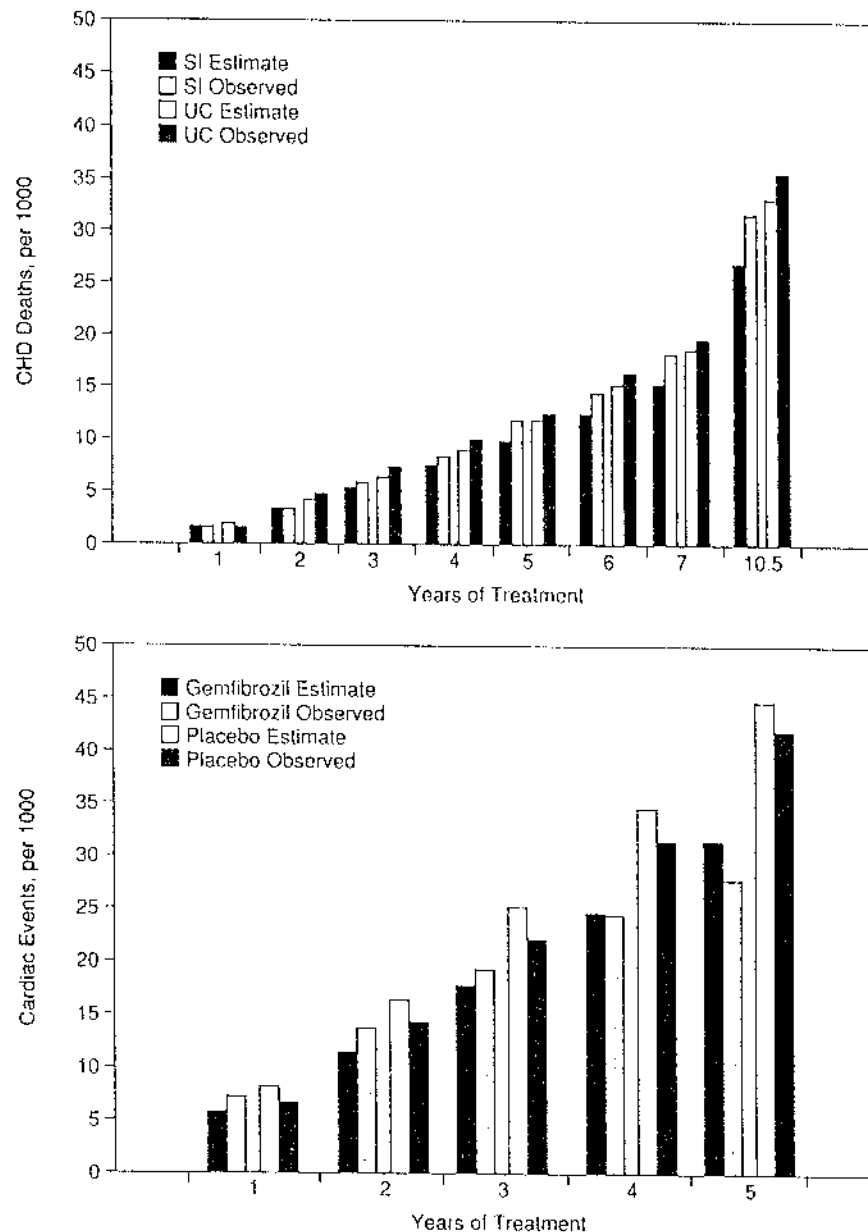


Fig 2.—Estimated results of the coronary heart disease (CHD) model compared with the observed results of clinical trials. Top, CHD deaths in the MRFIT Study, comparing the estimated results for the special intervention (SI) and usual care (UC) groups with the observed results. Bottom, Estimated cardiac events (including cardiac death and fatal and nonfatal myocardial infarction) for the gemfibrozil and placebo groups in the Helsinki Heart Study compared with the observed results.

life expectancy of 3 days to 3 months for low-risk men and women age 20 to 60 years.<sup>24</sup> Assuming a 5% reduction in total serum cholesterol level after dietary intervention, we calculated an increased life expectancy of 11 days (0.03 years) to 4 months (0.32 years) for low-risk men and women age 35 to 65 years.

Our results are also similar to those of a recent analysis by Tsevat et al,<sup>29</sup> where changes in life expectancy for 35-year-olds were estimated after cholesterol reduction. Reducing serum cholesterol levels ranging from 5.2 to 6.2 mmol/L

(200 to 239 mg/dL) to 5.2 mmol/L (200 mg/dL) increased life expectancy 0.5 years for men and 0.4 years for women, while reductions of levels ranging from 6.2 to 7.7 mmol/L (240 to 299 mg/dL) to 5.2 mmol/L (200 mg/dL) increased life expectancy 1.7 years for men and 1.5 years for women. We estimate that, after lowering serum cholesterol levels from 5.7 to 5.2 mmol/L (220 to 200 mg/dL), "low-risk" men and women age 35 years would have an increased life expectancy of 0.23 and 0.15 years, respectively. For baseline cholesterol levels of

Table 3.—Estimated Benefits of Cholesterol Reduction Among Low-Risk\* Individuals

Pretreatment Cholesterol Level, mmol/L	Intervention	Gender	Years of Life Saved by Age (y) at Intervention				Years Free of CHD by Age (y) at Intervention			
			35	45	55	65	35	45	55	65
			5.7	Diet only	M	0.14	0.11	0.07	0.03	0.36
		F	0.08	0.08	0.06	0.04	0.21	0.19	0.14	0.09
	Medication and diet	M	0.23	0.19	0.12	0.05	0.62	0.48	0.28	0.11
		F	0.15	0.14	0.11	0.07	0.36	0.32	0.25	0.15
6.2	Diet only	M	0.17	0.14	0.08	0.03	0.44	0.33	0.19	0.07
		F	0.10	0.09	0.07	0.05	0.24	0.21	0.16	0.10
	Medication and diet	M	0.50	0.41	0.25	0.10	1.31	1.01	0.57	0.21
		F	0.31	0.28	0.23	0.15	0.74	0.66	0.51	0.31
7.8	Diet only	M	0.32	0.25	0.14	0.06	0.75	0.53	0.27	0.09
		F	0.19	0.16	0.12	0.07	0.37	0.32	0.23	0.14
	Medication and diet	M	1.64	1.30	0.78	0.31	4.05	2.98	1.63	0.58
		F	0.98	0.87	0.67	0.41	2.14	1.89	1.42	0.84

\*As defined by the absence of other coronary heart disease (CHD) risk factors and a diastolic blood pressure of 80 mm Hg.

Table 4.—Estimated Benefits of Cholesterol Reduction Among High-Risk\* Individuals

Pretreatment Cholesterol Level, mmol/L	Intervention	Gender	Years of Life Saved by Age (y) at Intervention				Years Free of CHD† by Age (y) at Intervention			
			35	45	55	65	35	45	55	65
			5.7	Diet only	M	0.27	0.22	0.13	0.05	0.47
		F	0.11	0.10	0.08	0.05	0.21	0.18	0.13	0.07
	Medication and diet	M	0.47	0.38	0.23	0.10	0.81	0.59	0.31	0.10
		F	0.18	0.17	0.13	0.08	0.36	0.32	0.23	0.13
6.2	Diet only	M	0.34	0.27	0.16	0.06	0.55	0.39	0.20	0.06
		F	0.13	0.12	0.09	0.05	0.24	0.21	0.15	0.08
	Medication and diet	M	1.00	0.80	0.48	0.19	1.69	1.21	0.62	0.20
		F	0.39	0.35	0.27	0.16	0.75	0.65	0.47	0.26
7.8	Diet only	M	0.60	0.44	0.24	0.09	0.86	0.56	0.26	0.08
		F	0.24	0.20	0.14	0.07	0.37	0.31	0.21	0.11
	Medication and diet	M	3.16	2.44	1.40	0.54	4.98	3.40	1.68	0.53
		F	1.25	1.09	0.80	0.46	2.15	1.85	1.31	0.71

\*As defined by the presence of cigarette smoking and a diastolic blood pressure of 100 mm Hg.  
†CHD indicates coronary heart disease.

6.2 or 7.8 mmol/L (240 or 300 mg/dL), the increased life expectancy after lowering levels to 5.2 mmol/L (200 mg/dL) would be 0.50 or 1.64 years, respectively, for men and 0.31 or 0.98 years, respectively, for women. Although our results are slightly smaller than those reported by Tsevat et al, our estimates are for "low-risk" individuals while Tsevat et al used risk profiles for US men and women. In addition, whereas Tsevat et al used univariate coefficients, we use multivariate logistic coefficients that estimate the effect of each risk factor after adjustment for all others.

As with any computer model, one must view these predictions with caution. Although this model has been validated using clinical trials that focused on middle-aged men, it is unclear how accurately it will perform with other patient groups, such as women, the very young, and the very old. As there are ongoing clinical trials including these patients, it will eventually be possible to validate this model among these groups as well. It must also be recognized that this model assumes that there is no in-

creased risk of non-CHD death (cancer, violence, etc) associated with risk factor modification and therefore calculates the maximum benefits of intervention. However, a number of studies have suggested that the benefits of serum cholesterol reduction may be attenuated by an increased risk of death from non-CHD causes for reasons that remain unclear.<sup>20</sup>

The final results of our study suggest that the benefits of cholesterol reduction would be greatest for young men with very high levels of total serum cholesterol who are aggressively treated with dietary modification and drug therapy. Those with additional risk factors would receive the most benefit. These benefits are based on an expected reduction of total serum cholesterol from 7.8 mmol/L to 5.2 mmol/L, corresponding to a 33% reduction that has been demonstrated in some clinical trials.<sup>21,22</sup> The concomitant elevations in HDL cholesterol associated with some drugs would increase the estimated long-term benefits of treatment.<sup>20</sup>

The 5% reduction we ascribed to dietary intervention approximated from

the Lipid Research Clinics Trial and MRFIT would result in 0.03 to 0.60 years of life saved and 0.06 to 0.86 years free of CHD. However, more intensive dietary intervention could further reduce total serum cholesterol levels, and this would be associated with greater benefits.<sup>23</sup> For instance, if more intensive dieting reduced the total serum cholesterol level by 10% (while maintaining the HDL cholesterol level), this would result in 0.06 to 1.15 years of life saved and 0.11 to 1.69 years free of CHD.

This model suggests decreasing benefits associated with cholesterol modification initiated later in life. This is consistent with the observation that the association between total serum cholesterol level and CHD declines with increasing age.<sup>12</sup> Moreover, competing risks from other fatal diseases, such as cancer, will reduce the benefits of intervention among older individuals. Also, the benefits for women are, in most cases, lower than those estimated for men with similar profiles.

This variation across age and sex is particularly important given the current

recommendations for cholesterol screening and treatment. As total serum cholesterol levels are highest among postmenopausal women, the current strategy to screen all asymptomatic adults would identify over 40% of these women to have a "high cholesterol" level, over 6.2 mmol/L (240 mg/dL).<sup>7,34</sup> However, it is among women age 55 years and over that the estimated benefits of treatment would be among the smallest, ranging from 0.04 to 0.80 additional years of life and 0.07 to 1.31 years free of CHD. Clearly a nationwide cholesterol screening and treatment program must take into consideration not only serum lipid levels and the presence of other risk factors but also the expected benefits of

intervention.

We conclude that the next phase of the cholesterol debate must focus on the benefits of lifelong treatment in terms of not only life expectancy but also quality of life. Given the serious morbidity resulting from the symptoms and treatment of CHD, the potential benefits of delaying the development of CHD should not be completely overshadowed by the estimated changes in life expectancy.

Risk factor handbooks, calculators, and algorithms can provide a basic determination of overall risk status and identify which risk factors should be targeted in specific patients.<sup>35,36</sup> Computer simulations can provide more detailed analysis and a framework for public pol-

icy. These analyses provide the tools to incorporate research data into present-day clinical decision making. To overlook the full potential of these data is a waste of our past investment in health care research and will limit the future impact and efficiency of our best prevention programs.

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