Relative Impact of Targeted Versus Populationwide Cholesterol Interventions on the Incidence of Coronary Heart Disease

Projections of the Coronary Heart Disease Policy Model

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We used the Coronary Heart Disease Policy Model, a state-transition computer simulation, to assess the absolute and relative effects of two different national cholesterol interventions: a targeted program to identify and treat all individuals with elevated serum cholesterol levels (≥250 mg/dl) versus a populationwide program to reduce everyone’s serum cholesterol level. Based on the assumptions inherent in our model, which uses the Framingham Heart Study coefficients, we estimate the targeted program would reduce projected coronary heart disease absolute incidence by 8–10% in men ages 35–54 years and by 1–4% in men ages 55–74 years. Our model suggests that similar reductions in coronary heart disease incidence could be achieved by a 10 mg/dl populationwide reduction in serum cholesterol levels. In women, the targeted program would yield greater relative and absolute benefits and would be equivalent to a ∼23 mg/dl populationwide reduction in serum cholesterol. We conclude that it would be inadvisable to rely solely on targeted cholesterol reduction programs to reduce national coronary heart disease. (Circulation 1989;80:254–260)

As documented by reports from the National Heart, Lung, and Blood Institute and the Food and Drug Administration, physicians are becoming more aggressive in recommending dietary and drug treatment of hypercholesterolemia1 and US adults are increasingly likely to make dietary changes to lower their blood cholesterol levels.2 In a 1986 survey of 1,277 practicing physicians, the respondents tended to recommend dietary therapy at a median blood cholesterol level of about 250 mg/dl and drug therapy at a median level of about 310 mg/dl.1 More recently, the National Cholesterol Education Program defined a high serum cholesterol level as 240 mg/dl or higher and recommended that a lipoprotein analysis be performed in such cases. When the low density lipoprotein cholesterol level is 130 mg/dl or higher, specific interventions were suggested.3

The data to support the importance of serum cholesterol in the development of coronary heart disease and the value of lowering it to reduce coronary heart disease incidence are impressive.4–11 The Framingham risk model has proven to be remarkably applicable to other populational risk studies,7,8,12 and the results of interventional trials have been remarkably similar to what would be predicted based on the Framingham model.6

In the past, various analyses have been performed to estimate the effects of cholesterol reduction on the short-term coronary heart disease incidence or mortality rates of certain segments of the US population13–15 or the effect of cholesterol reduction on an individual’s life expectancy.16 However, such analyses do not focus on the nationwide cumulative effect of such programs in the steady state.

We have recently reported on a state-transition, computer-simulation model that uses the Framingham risk data to estimate the annual incidence of coronary heart disease among US adults 35–84 years old for the next 25 years.17 This model serves as an ideal mechanism to evaluate the long-term national effects of various programs to lower serum cholesterol levels.

Methods

The Coronary Heart Disease Policy Model17 is a state-transition, computer-simulation model consist-
TABLE 1. Actual Framingham Heart Study $\beta$-Coefficients for Cholesterol Versus Smoothed Coefficients Used in the Coronary Heart Disease Policy Model

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Framingham coefficients (SEM)</th>
<th>Smoothed coefficients</th>
<th>Framingham coefficients (SEM)</th>
<th>Smoothed coefficients</th>
</tr>
</thead>
<tbody>
<tr>
<td>35–44</td>
<td>0.011 (0.003)</td>
<td></td>
<td>0.023 (0.005)</td>
<td>0.01309</td>
</tr>
<tr>
<td>45–54</td>
<td>0.009 (0.002)</td>
<td>0.00815</td>
<td>0.005 (0.002)</td>
<td>0.01025</td>
</tr>
<tr>
<td>55–64</td>
<td>0.005 (0.001)</td>
<td>0.00588</td>
<td>0.007 (0.001)</td>
<td>0.00741</td>
</tr>
<tr>
<td>65–74</td>
<td>0.003 (0.002)</td>
<td>0.00360</td>
<td>0.007 (0.002)</td>
<td>0.00457</td>
</tr>
<tr>
<td>75–84</td>
<td>0.003 (0.003)</td>
<td>0.00133</td>
<td>0.000 (0.003)</td>
<td>0.00172</td>
</tr>
<tr>
<td>85–94</td>
<td>0.002 (0.007)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The overall projected effects of intervention programs to lower serum cholesterol levels are minimally different depending on whether the actual or smoothed coefficients are used (see “Results”).

Assumptions of the Model

The demographic-epidemiologic submodel was initially constructed with the US population for 1980 by age and sex\cite{18} and the estimated proportion of persons with no history of coronary heart disease.\cite{19} The distributions of smoking status, diastolic blood pressure, relative weight, and serum cholesterol were taken from the Second Health and Nutrition Examination Survey,\cite{20} and the four risk-factor distributions were, for simplicity purposes, assumed to be independent, conditionally on age range and sex.

The number of US residents who enter the model in each subsequent year after 1981 by turning 35 years of age was estimated from projections of the US Bureau of the Census.\cite{21,22} Risk factor changes with age were estimated based on population cross-sectional data.\cite{20}

For each of the 540 cells, relative risk coefficients were based on data from the Framingham Heart Study.\cite{23} The age- and sex-specific coefficients that were used for all risk factors in the demographic-epidemiologic submodel were obtained from the Framingham Heart Study's 30-year follow-up. These raw coefficients were smoothed by age for each sex by means of a weighted least-squares regression of the Framingham coefficients on the midpoint of each 10-year age interval, where the weights used are the inverse of the coefficient's SEMs. For men, each of our smoothed cholesterol estimates (Table 1) was within one SEM of the age- and sex-specific Framingham estimates. For women, the smoothing process yielded age trends that more closely resembled the Framingham trends in men. Overall, noncardiac disease mortality was based on US Vital Statistics.\cite{24} Incidence rates for ages 35–74 were based on the Framingham Heart Study,\cite{25} with a secular adjustment for the decline in coronary heart disease incidence since the beginning of the Framingham Heart Study\cite{26} and with extrapolation to ages 75–84 and linear interpolation to smooth the age-specific annual rates.\cite{17}
Framingham cholesterol coefficients were used instead of our smoothed estimates. In addition, projections were made under the assumption that our smoothed Framingham cholesterol coefficients might be inaccurate. All runs were performed through the year 2015 to assess the long-term effects of the various programs.

Results

Under our baseline projections, in which cohort-specific risk factor profiles change with age as they have historically, the age-adjusted coronary heart disease incidence rate among US men 35–84 years old would be lower in 2015 than in 1990 (Table 2). This is because the younger cohorts of men have a more favorable risk factor profile than the older cohorts. For example, in men 55–74 years old in 2015, the mean cholesterol level is projected to be about 4 mg/dl lower than in men 55–74 years old in 1990, based on the current cohort-specific cholesterol levels. However, because of major increases in the population, the absolute annual number of new cases of coronary heart disease is projected to increase by 37%.

Effect of a Targeted Program in 1990 to Reduce all Cholesterol Levels Above 250 mg/dl to 250 mg/dl

A targeted cholesterol intervention program, which would identify all persons with cholesterol levels of more than 250 mg/dl and reduce them to 250 mg/dl beginning in 1990, is projected to lower coronary heart disease incidence rates and absolute incidence in 2015 by about 8–10% in men 35–54 years old and by about 4–6% in men 55–64 years old (Table 3A). In men 65–84 years old, however, coronary heart disease incidence rates are predicted to decline only slightly, and the absolute incidence

| Table 2. Baseline Projections in US Men and Women 35–84 Years Old: No Changes in Cohort-Specific Risk Factor Profiles |
|---|---|---|
| | 1990 | 2015 | Change (%) |
| Age-adjusted annual incidence per 100 persons | | | |
| Men | 0.91 | 0.89 | -2 |
| Women | 0.60 | 0.60 | . . . |
| Absolute annual incidence of coronary heart disease | 763,211 | 1,044,218 | +37 |

Interventions

Risk factor interventions, such as reductions in cholesterol, are simulated by using interactive features of the Coronary Heart Disease Policy Model. These risk factor changes can be made in a given year, and the impact on coronary heart disease incidence can be estimated through the year 2015.

For the current analyses, the demographic-epidemiologic submodel was run using baseline assumptions through the year 2015. Then, the model was rerun using the scenario in which all cholesterol levels of more than 250 mg/dl were reduced to 250 mg/dl beginning in 1990. In this scenario, it was assumed that all such cholesterol levels would remain 250 mg/dl in subsequent years and that cholesterol levels of entering 35-year-olds would also be reduced to 250 mg/dl if they otherwise would have been higher. To determine the populationwide reduction in cholesterol levels that would be required to achieve results similar to those of the targeted programs, multiple runs were performed with various populationwide cholesterol reductions ranging from 5 to 25 mg/dl.

Sensitivity analyses were performed to determine the effect of a delayed response to cholesterol reduction on eventual incidence rates and to determine how incidence rates might vary if the actual
TABLE 4. Percent of all Cases of New Onset Coronary Heart Disease That Are Predicted to Occur in Persons With Cholesterol Levels of More Than 250 mg/dl*

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Men (%)</th>
<th>Women (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>35-54</td>
<td>36</td>
<td>56</td>
</tr>
<tr>
<td>55-64</td>
<td>30</td>
<td>57</td>
</tr>
<tr>
<td>65-74</td>
<td>27</td>
<td>50</td>
</tr>
<tr>
<td>75-84</td>
<td>24</td>
<td>39</td>
</tr>
<tr>
<td>Overall</td>
<td>30</td>
<td>50</td>
</tr>
</tbody>
</table>

*Based on projected population distribution in the year 2015.

of coronary heart disease to be essentially unchanged. This targeted program is expected to have a greater effect in younger than in older men because a higher proportion of the new cases of coronary heart disease in younger men occur in men with high cholesterol levels (Table 4). Incidence rates are projected to fall more than absolute incidence in men more than 55 years old because a targeted program "enriches" the older age groups with men who have survived to that age with cholesterol levels of 250 mg/dl and who are still prone to develop coronary heart disease. Overall, in the year 2015, the targeted program is predicted to reduce annual coronary heart disease incidence by 4%, to reduce coronary heart disease prevalence by more than 310,000 cases (about 5%), and to increase the absolute number of men who are alive without coronary heart disease by about 500,000 (0.8%).

Among women of all age ranges, a targeted program to identify and treat all cholesterol levels of more than 250 mg/dl and to lower them to 250 mg/dl is predicted to result in a 16–18% reduction in coronary heart disease incidence (Table 3B). Thus, in women, the percent change in incidence is projected to be about 2.5-fold more than in men. The projected impact of the targeted program is relatively greater in women than in men because coronary heart disease in women is more concentrated in persons with high cholesterol levels than it is in men (Table 4). In women, the targeted program is projected to reduce coronary heart disease prevalence by more than 420,000 cases and to result in about 630,000 more women alive without coronary heart disease in the year 2015 than if risk factor interventions were not undertaken, for an increase of almost 1% in the number of women alive without coronary heart disease. Of note is that the targeted program actually yields a greater absolute reduction in coronary heart disease incidence and prevalence in women than in men.

Comparison of Populationwide Programs to Targeted Programs

In populationwide simulations (see "Methods"), a 10 mg/dl populationwide reduction in cholesterol levels in men, which is about a 5% reduction, would result in essentially the same predicted reductions in coronary heart disease incidence and prevalence and increase in the number of men alive without coronary heart disease as could be achieved by the target-250 program. In women, a 23 mg/dl populationwide reduction in cholesterol would be required to achieve benefits equivalent to the targeted program.

Sensitivity Analyses

If reductions in cholesterol levels that were achieved in 1990 did not have an effect on coronary heart disease incidence for another 3 years, the coronary heart disease incidence rates in 2015 would be virtually identical to what would be achieved by 2015 if the cholesterol reductions had an immediate benefit. Even with a 3-year delay in effects, the benefits of cholesterol reduction programs by the year 2015 for reducing the prevalence of coronary heart disease and for increasing the number of persons alive without coronary heart disease would be about 97% of the benefits that would be achieved if the program had an immediate onset of reduction in heart disease incidence. Thus, our projections are minimally affected by assumptions about the delay between the onset of cholesterol reduction and its impact on coronary heart disease incidence.

When actual Framingham cholesterol coefficients were used in our projections instead of the smoothed coefficients, there were some variations in specific age ranges, but the overall impact of each of the cholesterol reduction programs was within about 1% of our baseline results, and all comparisons of targeted versus populationwide programs were nearly identical to what we found the smoothed coefficients. When the coefficients that relate cholesterol levels to coronary heart disease incidence were varied by 1 SD above or below our smooth Framingham Heart Study’s estimated coefficients, the absolute impact of each of the cholesterol reduction programs varied substantially. For example, if the true coefficient for cholesterol as a predictor of the annual risk of developing coronary heart disease is 1 SD below our smoothed Framingham coefficients, the impact of both targeted and populationwide cholesterol reduction programs would be only about 67% as great in men and 48% as great in women because reductions in cholesterol would have less effect on coronary risk. Conversely, if the coefficients are really 1 SD higher than our smoothed Framingham coefficients, the impact of cholesterol reduction programs would be about 1.4-fold higher in men and about 1.8-fold higher in women. However, even these changes in the coefficients for cholesterol would not affect the relative comparison between targeted versus populationwide programs, and the target-250 program would still be the equivalent of about a 10 mg/dl populationwide cholesterol reduction in men and about a 23 mg/dl populationwide reduction in women.

Of course, more aggressive targeted programs would have greater impact. For example, if all persons with cholesterol levels of more than 250 mg/dl had them lowered to 240 mg/dl, the equiva-
lent populationwide reduction in serum cholesterol would be about 12.5 mg/dl in men and about 27.5 mg/dl in women. If serum cholesterol was reduced to 250 mg/dl in persons who started at more than 300 mg/dl but to 230 mg/dl in all persons who started at 250–299 mg/dl, the equivalent populationwide program would require a ~14 mg/dl reduction in all men and a ~28 mg/dl reduction in all women.

Discussion

Our approach to the assessment of potential policies for cholesterol reduction is fundamentally different from most previous approaches. We have not tried to assess the benefit for the individual,16 and we have not focused on any limited age or sex group. Most important, we have looked far enough into the future to allow for an estimation of the effects of various programs during the steady state. Thus, our estimates demonstrate how risk factor reduction programs tend to delay rather than to prevent the onset of coronary heart disease.

Our two programs are, of course, hypothetical. It is unlikely that either could ever be 100% effective, and there is no reason why one must be chosen exclusively of any component of the other.

In our model, risk factors are considered independently of each other. To the extent that serum cholesterol levels are modestly correlated with weight and blood pressure, the benefits of cholesterol reduction might be even greater if these other risk factors changed concomitantly. The effect of such relations on the comparison of the targeted versus the populationwide program are speculative. To the extent that the risk factors are aggregated, the targeted program could be somewhat more favorable. However, if a targeted program requires medications that do not affect weight or blood pressure and the populationwide program includes weight loss as well as cholesterol reduction, the latter may be more favorable.

Our model was created before the National Cholesterol Education Program chose 240 mg/dl as its target cholesterol level. However, our sensitivity analyses indicate that our message would be minimally affected by such modest changes in target levels.

Although targeted cholesterol reduction programs have the superficial advantage of allowing potential therapy to be directed to the highest risk individuals, there is no single cut off to distinguish an elevated from a “normal” serum cholesterol level. Thus, about 70% of new coronary heart disease cases in men and about 50% of new cases in women may be in persons with cholesterol levels of less than 250 mg/dl. The high absolute numbers of new cases of coronary heart disease among persons without “elevated” serum cholesterol levels is because there are far more at-risk individuals with cholesterol levels less than 250 mg/dl than with levels above this cut off.

It should be noted that for younger age ranges, each 1% reduction in serum cholesterol yielded about a 2% reduction in the incidence of coronary heart disease, consistent with what has been found in the types of persons who have been included in randomized trials.6 However, at higher ages, the cholesterol coefficients are smaller,23 and the population is enriched with persons whose coronary disease has been delayed, thus reducing our estimate of the percent impact of cholesterol reduction programs in these age ranges.

From a public policy perspective, our primary analysis and all of our sensitivity analyses suggest that relatively small populationwide reductions in serum cholesterol levels would be more efficacious in men than extremely ambitious, and 100% successful, targeted programs. Although men are at higher risk for coronary heart disease than women, an elevated serum cholesterol level is actually a more important public health problem in women, because a greater percentage of new cases of coronary heart disease in women occur in the setting of a high cholesterol level. Furthermore, the targeted program actually has a greater absolute impact in women than in men. Thus, for reducing coronary heart disease incidence in women, targeted programs are relatively more attractive than populationwide programs.

Data on the ability of populationwide programs to reduce serum cholesterol levels are limited. In the North Karelia, Finland, study, a comprehensive community-based program of education using local community action, social support, and environmental modifications resulted in a 4% reduction in mean serum cholesterol levels in men and 1% in women at the end of 5 years compared with the changes that were found in a control region;27 after 10 years, there was still a 3% reduction in men and 1% reduction in women.28 This reduction in serum cholesterol and in other risk factors was thought to be related, in part, to more active participation by physicians and nurses in cardiovascular disease control.29 The changes in serum cholesterol levels reflected alterations in health behavior throughout the population without any consistent relation to the individual’s preprogram risk factor status.30 Although this was not a typical randomized control trial and although the intervention program also lowered smoking rates and blood pressure levels, it was interesting that the subsequent decline in coronary disease mortality in the North Karelia area was significantly greater than the declines in other counties of Finland.31 In the Stanford Three Community Study, a 2-year mass media cardiovascular health education program in two communities in California resulted in about a 3% greater reduction in serum cholesterol levels compared with a control community.32

The 3–4% net reduction in serum cholesterol levels found in the Finland and California experiences would translate into about a 7 mg/dl reduction.
Even without organized mass interventions, serum cholesterol levels in US men declined by an average of ~4 mg/dl from 1960–1962 to 1970–1974,13,33 and an additional 3.3 mg/dl reduction was found from 1973–1974 to 1980–1982 in Minnesota.44 If a further reduction in cholesterol levels based on new populationwide mass interventions could be added to the general trend toward reduced serum cholesterol levels in the United States over recent years,13,33 then a 10 mg/dl reduction in the average serum cholesterol level of US men appears to be a practical goal. However, a 23 mg/dl populationwide reduction in women would be almost double what might be expected even by the sum of ongoing national trends and the effects of any new populationwide mass educational intervention.

Although the mass screening programs that would be required as a prelude to a targeted intervention program can be accomplished at relatively low cost per person,35 the subsequent treatment with medications would be substantially more costly.36 Compared with hypertension, where the targeted approach has been adopted, for hyperlipidemia the measurement of serum levels is more expensive and inconvenient, there is no clear agreement about the level of abnormality that requires intervention, and treatment regimens may be less effective and more difficult to implement.37

Unfortunately, it is not possible to validate future projections until the actual events occur. It is likely that other changes will occur in the next 25 years to alter any projections that can be made now. We are also limited by our reliance on total cholesterol levels rather than fractionated values. Nevertheless, our analyses demonstrate what would happen given the assumptions on which our model is based, and our model could be used to make projections under any other sets of assumptions that any other analysts would like to consider.

Our analyses emphasize the distinction between populational versus individual prevention strategies.38–40 Our data in men also suggest that relatively modest populationwide cholesterol reductions that are likely to be achievable based on the national trends and on the Finland and Stanford experiences,27,28,31 without concomitant blood pressure reductions, would be equivalent to very ambitious targeted programs.

Our analyses should not suggest that a nation must choose between a purely populationwide program versus a purely targeted program. Nevertheless, we believe that reliance solely on targeted programs would be ill advised.

References


KEY WORDS • coronary heart disease • cholesterol • clinical trials
Relative impact of targeted versus populationwide cholesterol interventions on the incidence of coronary heart disease. Projections of the Coronary Heart Disease Policy Model.
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Circulation. 1989;80:254-260
doi: 10.1161/01.CIR.80.2.254

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1989 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

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