The relation between high density lipoprotein cholesterol (HDL-C) and the development of myocardial infarction was examined in 2425 subjects, aged 50 to 79 years, who were enrolled in the Framingham Study from 1969 to 1971. After 12 years of follow-up, men in the bottom three quartiles of HDL-C (∼52 mg/dl) experienced a 60% to 70% excess of myocardial infarction as compared to men whose HDL-C levels were higher (p<0.05). The effect of HDL-C was especially strong in women. In separate comparisons to the 4th quartile of HDL-C (∼67 mg/dl), the risk of myocardial infarction increased from a fourfold excess in the adjacent 3rd quartile (56 to 66 mg/dl, p<0.01) to a nearly sixfold excess in the 1st quartile (∼46 mg/dl, p<0.001). These results persisted after adjusting for age and other risk factors. In addition, a significant effect of HDL-C remained in subjects who had the lowest concentrations of total cholesterol (∼192 mg/dl in men and 211 mg/dl in women) in which 29% had levels of HDL-C (∼36 mg/dl in men and 46 mg/dl in women) that were associated with a marked elevation in the incidence of myocardial infarction. We conclude that screening for total cholesterol alone in men and women aged 50 and older may not adequately identify the coronary candidate. In addition, selective screening of HDL-C only for individuals with high concentrations of total cholesterol can leave the false impression that low total cholesterol is uniformly associated with a healthy risk profile.

Methods

Since 1948, the Framingham Study has biennially followed 5209 men and women for the development of cardiovascular disease. Sampling methods, response rates, follow-up, and examination procedures have been described elsewhere.11,12 From 1969 to 1971, fasting levels of HDL-C were first determined among study participants after heparin-manganese chloride precipitation of fresh plasma, following a modified protocol adopted by the Lipid Research Clinics.13 For this report, subjects were followed for 12 years from the time of HDL-C measurement for the development of myocardial infarction. All subjects were free of coronary heart disease (including myocardial infarction, angina pectoris, and coronary insufficiency) at the time the follow-up began. Further details on the definition of coronary heart disease are given elsewhere.14,15

In the course of follow-up, the diagnosis of myocardial infarction was based on electrocardiogram (ECG) and enzyme criteria. The ECG criteria included ST segment elevation associated with terminal inversion of T waves and the loss of initial QRS potential (pathologic Q waves of 0.04 second or greater), followed by serial changes indicating reversion toward normal. A stable ECG pattern, including pathologic Q waves, or a loss of initial QRS potential in those leads in which this would not be expected, was used as evidence for an old or remote myocardial infarction. An interim myocardial infarction (between clinic exams) was noted when changes from a previous tracing...
showed development of an unexplained loss of R wave potential or the appearance of pathologic Q waves.

The enzyme criteria for the diagnosis of myocardial infarction were based on hospital reports showing abnormal concentrations of SGOT of at least 50 units/l, LDH of at least 200 units/l, CPK greater than 100 IU/ml, or positive CPK-MB isoenzyme, along with a history of prolonged ischemic pain. When available, autopsy reports were also used to provide evidence of myocardial infarction.

To illustrate the effects of HDL-C, 12-year, age-adjusted incidence rates of myocardial infarction were calculated by quartiles of HDL-C. For men, the 1st through 4th quartiles consisted of the following ranges of HDL-C, respectively: 12 to 36, 37 to 44, 45 to 52, and 53 to 129 mg/dl. For women, corresponding quartiles were as follows: 23 to 46, 47 to 55, 56 to 66, and 67 to 139 mg/dl.

For purposes of detecting an independent effect of HDL-C on myocardial infarction, control of potential confounding risk factors was necessary. Important risk factors measured at the beginning of follow-up included total cholesterol, systolic blood pressure, body mass index [weight divided by height squared (kg/m²)], diabetes, current cigarette use, and the receipt of postmenopausal estrogen replacement therapy in women.

To help illustrate the relation between the additional risk factors and concentrations of HDL-C, mean levels of each risk factor were compared across quartiles of HDL-C. Adjustments were made for age by using analysis of covariance and logistic regression models. Techniques used to measure the risk factors have been reported elsewhere.

To estimate the independent effect of HDL-C, proportional hazards models were used to follow subjects over 12 years for the development of a myocardial infarction. Relative risks of myocardial infarction were estimated comparing the 1st through 3rd quartiles of HDL-C to the 4th quartile. Estimates of relative risk were based on the corresponding regression coefficient associated with each of the lower three quartiles compared separately to the 4th quartile. Comparisons were adjusted for age alone and also for age and the preceding covariates.

In addition, the effect of HDL-C within each quartile of total cholesterol was examined. For men, the 1st through 4th quartiles consisted of the following ranges of total cholesterol concentrations, respectively: 116 to 192, 193 to 215, 216 to 244, and 245 to 376 mg/dl. For women, corresponding quartiles were as follows: 124 to 192, 193 to 216, 217 to 237, 238 to 266, and 267 to 412 mg/dl.

The fit of the proportional hazards model was examined by observing changes in the proportionality assumption with time and with risk factor level. The results indicated that use of such models was appropriate. All tests of significance were two-sided.

**Results**

Of the 5209 participants in the original Framingham cohort, fasting levels of HDL-C were first determined in 2788 subjects during biennial examinations received from 1969 to 1971. Among this group, 1007 men and 1418 women were free of coronary heart disease and constituted the subjects for this study. At the beginning of follow-up, subjects were aged 50 to 79 years.

Table 1 gives the age-adjusted, 12-year incidence of myocardial infarction by quartile of HDL-C. For both sexes, the highest rate of myocardial infarction occurred among subjects whose HDL-C was in the lowest quartile (15.3/100 for men and 10.6/100 for women). These rates were significantly greater (p<0.05) than the rates experienced by those whose HDL-C fell in the highest quartile (9.4/100 for men and 1.4/100 for women).

For men, the rates of myocardial infarction in the 2nd and 3rd quartiles of HDL-C were similar (14.8/100 and 14.9/100, respectively). For women, the rate of myocardial infarction declined significantly with each increase in HDL-C quartile (p<0.01).

Table 2 provides the age-adjusted mean levels of the selected risk factors. For women, total cholesterol increased with each increase in HDL-C quartile. In each sex group, subjects in the lowest quartile of HDL-C had significantly lower levels of total cholesterol as compared to those in the highest quartile (p<0.05).

For women, systolic blood pressure decreased with increased HDL-C. Women in the lowest quartile of HDL-C had significantly higher blood pressures than those in the top quartile (p<0.05). No such association was seen in men.

Body mass index was the risk factor most strongly related to HDL-C. Compared to subjects in each of the bottom three quartiles of HDL-C, those in the highest quartile were significantly leaner (p<0.01).

In both sexes, diabetes was also more common in those in the lowest quartile of HDL-C as compared to the other quartiles. Compared to women in the top quartile, it was significantly more frequent in the lowest quartile, as was the use of cigarettes (p<0.05). Past or current use of postmenopausal estrogens by women was also significantly less frequent in the 1st and 2nd HDL-C quartiles as compared to the top quartile (p<0.01).

Table 3 provides estimates of the relative risk of myocardial infarction comparing each of the 1st through 3rd quartiles of HDL-C to the 4th quartile.

**Table 1. Age-adjusted 12-Year Incidence (Rate/100) of Myocardial Infarction by Quartile of High Density Lipoprotein Cholesterol**

<table>
<thead>
<tr>
<th>HDL-C quartile (mg/dl)</th>
<th>Number at risk</th>
<th>Number of events</th>
<th>Age-adjusted rate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st (12 to 36)</td>
<td>239</td>
<td>36</td>
<td>15.3*</td>
</tr>
<tr>
<td>2nd (37 to 44)</td>
<td>275</td>
<td>41</td>
<td>14.8</td>
</tr>
<tr>
<td>3rd (45 to 52)</td>
<td>231</td>
<td>34</td>
<td>14.9</td>
</tr>
<tr>
<td>4th (53 to 129)</td>
<td>262</td>
<td>25</td>
<td>9.4</td>
</tr>
<tr>
<td>Total</td>
<td>1007</td>
<td>136</td>
<td>13.5</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st (23 to 46)</td>
<td>356</td>
<td>38</td>
<td>10.8†</td>
</tr>
<tr>
<td>2nd (47 to 55)</td>
<td>354</td>
<td>26</td>
<td>7.4†</td>
</tr>
<tr>
<td>3rd (56 to 66)</td>
<td>353</td>
<td>23</td>
<td>6.5†</td>
</tr>
<tr>
<td>4th (67 to 139)</td>
<td>355</td>
<td>5</td>
<td>1.4</td>
</tr>
<tr>
<td>Total</td>
<td>1418</td>
<td>92</td>
<td>6.5</td>
</tr>
</tbody>
</table>

Significant excess of events compared to the 4th quartile:

*p<0.05, †p<0.01, ‡p<0.001.
er significant, although a significant excess in the 2nd quartile emerged. When comparing the incidence of myocardial infarction among men in the combined bottom three quartiles of HDL-C (< 52 mg/dl), men in the top quartile were at significantly lower risk (p < 0.05).

For women, the inverse association between HDL-C and myocardial infarction was much clearer. Without exception, lower concentrations of HDL-C were significantly associated with an increased relative risk of myocardial infarction. After adjusting for age and the other risk factors, those in the bottom 25% of HDL-C values experienced nearly six times the rate of coronary events as compared to those in the top 25% (p < 0.001). Women in the middle two quartiles of HDL-C also experienced an excess of coronary events as compared to the highest quartile. For those in the 3rd quartile of HDL-C, there was a nearly fivefold excess (p < 0.01), and in the adjacent 2nd quartile of moderately high levels of HDL-C, a fourfold excess was experienced (p < 0.01).

Table 4 gives the 12-year, age-adjusted incidence of myocardial infarction by quartile of HDL-C within each quartile of total cholesterol. In both sexes, the effect of low HDL-C levels persisted in subjects who had the lowest concentrations of total cholesterol. For men whose total cholesterol fell below the 25th percentile, the 12-year incidence of myocardial infarction declined significantly (p < 0.01) from 17.1/100 in the 1st quartile of HDL-C to 2.2/100 in the 4th quartile. For women, a similar and significant (p < 0.05) decline from 9.4/100 in the 1st HDL-C quartile to 1.3/100 in the top quartile was observed.

The effect of HDL-C appeared to diminish in men with total cholesterol concentrations exceeding 192 mg/dl. Although not significant, those in the top quartile of HDL-C usually experienced the lowest rates of myocardial infarction. In contrast, the effect of HDL-C in women remained graded and strong for the entire distribution of total cholesterol values (p < 0.05). In addition, the effect of HDL-C was
not significantly altered in the presence of high or low concentrations of total cholesterol.

Discussion

The focus of this report is on individuals aged 50 and older, where findings demonstrate that HDL-C is inversely related to the development of myocardial infarction, particularly in women. In addition, the data provide further evidence of an effect of low levels of HDL-C on the development of hard or definite coronary events, comprising 53% of all coronary heart disease observed in the Framingham sample.

Inclusion of coronary deaths without a documented myocardial infarction (occurring in 37 of 1007 men and 23 of 1418 women) failed to alter considerably the magnitude of these findings. Including such events increased the relative risk calculations in Table 3 only slightly for men. Nevertheless, the excess risk of either myocardial infarction or death from coronary heart disease in each of the bottom HDL-C quartiles significantly exceeded the rate in the top quartile in separate comparisons (p<0.05). In women, the corresponding relative risks remained significant, but were lower than those displayed in Table 3, increasing from a threefold excess of events in the 3rd quartile of HDL-C (p<0.01) to a fivefold excess in the 1st quartile (p<0.001). In both men and women, however, most of the coronary deaths that occurred without a documented myocardial infarction occurred suddenly (45 of 60 within 1 hour of symptom onset) and may have involved other risk factors unique to sudden death.

The effect of including other coronary endpoints, such as angina pectoris and coronary insufficiency, has been described elsewhere in a recent publication. In that report, the effect of HDL-C as a continuous variable was examined. In the current report, while choosing to consider a more objective coronary manifestation, we examined disease incidence across ranges of HDL-C. Doing so eliminates the need to assume a strict linear relationship involving HDL-C and enables detection of an excess of event rates in categories of HDL-C that may not be obvious from constrained parametric models. The additional stratification of total cholesterol into quartiles also permits the detection of an interaction effect with HDL-C, which appears to be absent.

Unfortunately, the data and analyses remain limited, as it is difficult to determine how much myocardial disease could be prevented by increasing HDL-C levels in a population of men and women aged 50 and older. It seems possible that some disease could be prevented, based on the hypothesis that HDL-C can remove cholesterol from arterial walls. Other mechanisms or metabolic derangements may also exist, however. Clearly, such mechanisms are complicated, since low concentrations of HDL-C often appear with additional atherosclerotic traits, especially hypertriglyceridemia and obesity. Additional traits may also include hyperinsulinemia, clotting abnormalities, sex hormone imbalances, and other risk factors not routinely measured at all Framingham examinations.

It seems apparent, however, that elevated levels of HDL-C are protective against coronary heart disease. Based on the Framingham data, optimal HDL-C levels exceeded 52 mg/dl for men and 66 mg/dl in women. Whether these levels apply to individuals younger than 50 needs further study.

Unfortunately, there are no data that indicate whether therapies for specifically raising HDL-C will reduce the risk of coronary heart disease. Additional studies should focus on the benefits of weight reduction, dieting, and physical activity to increase HDL-C per se and reduce coronary risk.

Successful attempts at increasing HDL-C may have their most noticeable effects in women aged 50 and older, where the association between HDL-C and myocardial infarction was particularly strong in the Framingham data. Among those in the Framingham sample, 75% had HDL-C levels of less than 67 mg/dl, placing them at four to six times the risk of developing a myocardial infarction compared to women with greater HDL-C levels. In addition, the relative health advantage of women, as compared to men, in terms of lower rates of coronary heart disease, begins to disappear when levels of HDL-C are at 46 mg/dl or less.

The association between HDL-C and myocardial infarction also persisted for low levels of total cholesterol in both men and women. This might be unexpected given the hypothesis that HDL-C is protective due to reverse cholesterol transport. Nevertheless, defects in catabolism of very low density lipoprotein (VLDL) cholesterol may result in reduced fasting HDL-C and low density lipoprotein (LDL) cholesterol through the precursor-product relationship among lipoproteins. As a result, levels of VLDL cholesterol (and remnant particles) could become elevated and possibly contribute to atherosclerosis. This may be a reasonable explanation in the postprandial state, since control of fasting LDL and VLDL cholesterol in the Framingham data failed to explain or diminish the independent association between HDL-C and myocardial infarction. Furthermore, within low and high ranges of the less dense lipoprotein particles, in addition to triglyceride, the effect of low HDL-C levels remained, as it did across levels of total cholesterol. Additionally, based on the predictive strength of these various lipid fractions, HDL-C appears to be the most important measure of coronary risk in the Framingham sample.

Subjects who had low levels of HDL-C also comprised a considerable proportion of those who had low concentrations of total cholesterol (≤192 mg/dl in men and 211 mg/dl in women). Of those whose total cholesterol fell in the 1st quartile, approximately 29% (71/247 men and 104/359 women) had levels of HDL-C (<36 mg/dl in men and 46 mg/dl in women) that were associated with a marked elevation in the incidence of myocardial infarction.

In addition, among the latter group who went on to have a myocardial infarction (12 men and 10 women), most were free of other cardiovascular risk factors. For both men and women, 80% were normotensive and 90% were nonobese (<30 kg/m²). None of the subjects had levels of LDL or VLDL cholesterol that exceeded the sex-specific 90th percentile for the entire Framingham sample. Only 9% had triglyceride concentrations above the 90th percentile. Among the ten women with a myocardial infarction, 80% were nondiabetic and 56% were nonsmokers. The only possible risk factors in men that could be used in place of...
HDL-C as markers of high coronary risk included diabetes and cigarette smoking. Nevertheless, nondiabetics and nonsmokers comprised a large proportion of the 12 men who had a myocardial infarction (50% and 33%, respectively). As a result, there appears to be no clear way to predict for men or women which subjects with low levels of total cholesterol are at high risk of coronary heart disease and should have HDL-C concentrations measured.

We conclude, therefore, that if cholesterol screening is to occur in men and women aged 50 and older, a screening for total cholesterol alone may not adequately identify the coronary candidate. Such attempts at screening for total cholesterol, while potentially beneficial for some, can incorrectly classify a substantial proportion of the general population, unless HDL-C determinations are also made. In addition, selective screening of HDL-C only for individuals with elevated concentrations of total cholesterol can leave the false impression that low total cholesterol is uniformly associated with a healthy risk profile. Whether these conclusions apply to younger individuals needs further study.

References

14. Sortie P. Coronary candidate. Such attempts at screening for total cholesterol, while potentially beneficial for some, can incorrectly classify a substantial proportion of the general population, unless HDL-C determinations are also made. In addition, selective screening of HDL-C only for individuals with elevated concentrations of total cholesterol can leave the false impression that low total cholesterol is uniformly associated with a healthy risk profile. Whether these conclusions apply to younger individuals needs further study.

Index Terms: HDL cholesterol • cholesterol screening • myocardial infarction • Framingham Study