Changes in Cholesterol and Triglyceride as Predictors of Ischemic Heart Disease in Men

ROBERT J. GLYNN, PH.D., BERNARD ROSNER, PH.D., AND JEREMIAH E. SILBERT, M.D.

SUMMARY We examined the relation of longitudinal changes in cholesterol and triglyceride to the subsequent development of heart disease. The data were from 1437 participants of the Normative Aging Study, a prospective study of men from the Boston area who were free of ischemic heart disease on two examinations approximately 5 years apart. Forty-four had symptoms or ECG findings of ischemic heart disease after their second but before their third examination, a period of 3–5 years. The risk of heart disease was studied using a multiple logistic risk model that took into account smoking and other risk factors. Changes in cholesterol and triglyceride levels between Exams 1 and 2, when corrected for regression to the mean, were better predictors of heart disease incurred between Exams 2 and 3 than initial levels of cholesterol, triglyceride or systolic blood pressure. When two age groups (28–52 years and 53–85 years) were considered, changes were important predictors in each age group. These findings suggest the importance of monitoring lipid changes over time.

PROSPECTIVE epidemiologic studies have helped to identify the importance of lipid levels as predictors of ischemic heart disease.1–6 Generally, these studies have focused on the relation between a single measurement of lipid levels, usually at entry into the study, and the subsequent development of heart disease. However, even when no intervention is made to lower them, cholesterol or triglyceride levels fluctuate substantially over the course of a few years. The association between these changes and the subsequent development of heart disease is unknown. A person’s risk of heart disease may be significantly altered by changes in lipid levels.

To relate a change in lipid levels to subsequent heart disease requires a design that follows subjects for a fixed period of time during which they remain free of heart disease and then considers the incidence of heart disease during a subsequent time period. To accomplish this, we used data from the Normative Aging Study, a longitudinal study of men from the Greater Boston area. Changes in serum cholesterol, triglyceride and systolic blood pressure between Exams 1 and 2 were related to ischemic heart disease developed between Exams 2 and 3. Multiple logistic regression analysis was used to compare the predictive power of changes in lipid levels and systolic blood pressure with that of initial levels.

Changes in lipids and blood pressure were studied by a new method, called “residual change,”7,8 because men with high lipid or blood pressure levels at Exam 1 tended to have lower levels at Exam 2, and those with low levels at Exam 1 tended to have higher levels at Exam 2. This phenomenon, regression to the mean, is analogous to that observed by Galton, who developed the idea of regression to explain the tendency for tall men to father shorter sons and short men taller sons.8,9 Thus, “raw change” (Exam 2 level minus Exam 1 level) was rejected as a measure of change because it would depend on Exam 1 level. Residual change is independent of initial level. It is intuitively the difference between an individual’s observed and his predicted Exam 2 levels, with the predicted level based on his age group and Exam 1 level. Residual change has been discussed and used extensively in psychometry,10,11 but has only recently been introduced in epidemiologic work.

Materials and Methods

Population

The Normative Aging Study was established by the Veterans Administration in 1963. Six thousand male volunteers from the Greater Boston area were screened for acceptance into the study according to laboratory, clinical, radiologic and electrocardiographic criteria. Volunteers who had a history of such chronic conditions as heart disease, diabetes, cancer, peptic ulcer, gout, and recurrent asthma, bronchitis and sinusitis were not admitted to the study. Volunteers who had a systolic blood pressure greater than 140 mm Hg or a diastolic blood pressure greater than 90 mm Hg were also excluded. Acceptable conditions included childhood diseases (such as rheumatic fever or kidney infection) that had not precluded military service, as well as hepatitis, malaria, jaundice or anemia, if no sequelae were present and functions were intact. Hyperlipidemia was not a screening criterion.

Two thousand two hundred eighty men, ages 21–81 years (mean 42 years), were accepted into the Normative Aging Study. The social and demographic characteristics of the study population have been described.12 The participants were enrolled and received their first medical examination between 1963 and 1970. Subsequently, men younger than age 53 years reported for examinations every 5 years; after age 53 years, they reported every 3 years.

The subjects for the current study were the 1437 men who, by March 1, 1979, had two complete medi-
cal examinations, were free from ischemic heart disease at Exam 2 and either had a third examination or died of ischemic heart disease before their scheduled third examination. The other 843 Normative Aging Study participants were excluded for the following reasons: 419 men had not yet reported for their third examination; 280 men dropped out of the study or were lost to follow-up; 27 men had ischemic heart disease at Exam 2; 38 men died before Exam 2 or before Exam 3 of causes other than heart disease; and 79 men had missing data for height, weight or smoking status at Exam 1 or total cholesterol or systolic blood pressure at Exam 1 or 2.

The 1437 men included in this study compared at Exam 1 to the 843 excluded men as follows. The included men were older than the excluded men (mean age 43.5 ± 9.2 vs 40.2 ± 9.6 years) (± sd). However, the distributions of lipid levels of the two groups were almost identical. The mean total cholesterol level of the included group was 203.7 ± 44.1 mg/dl compared with 204.7 ± 46.5 mg/dl for the excluded group; the mean serum triglyceride level for the included men was 135.6 ± 58.7 mg/dl compared with 135.1 ± 59.0 mg/dl for the excluded men. The distributions of body mass index and systolic blood pressure levels were also very similar for both groups; however, the percentage of cigarette smokers was lower in the included group (35.8% vs 44.4%, χ² = 15.38, p < 0.001). Similar results were obtained when the data were analyzed within specific age groups (< 40 years, 40–52 years, and ≥ 53 years). The age difference between groups is partly attributable to the shorter interval between examinations for older men, which makes it more likely that younger men have not yet reported for their third examination. Austin et al. reported that smokers are less likely than nonsmokers to continue to participate in longitudinal studies.

Physical Examination and Ischemic Heart Disease Diagnosis

The medical examinations included medical history, physical examination, ECG and standard blood and urine tests. Serum cholesterol was measured by the colorimetric method of Sperry. The fasting serum triglyceride level, not evaluated at the beginning of the study, was measured beginning in 1965 by the method of Van Handel and Ko. All lipid determinations were performed in the clinical laboratory of the Veterans Administration Outpatient Clinic. Quality control was maintained by running with each 10 samples two aqueous standards as well as samples from the Massachusetts Society of Pathologists regional quality control pools levels 1 and 2. When standards differed by more than 2 standard deviations from the expected value, analyses were repeated.

A diagnosis of ischemic heart disease at the third examination was based on one or more of the following conditions:

1. Myocardial infarction diagnosed at Exam 3 according to the criteria of the Framingham Heart Study. Myocardial infarction was diagnosed only when documented by the occurrence of unequivocal electrocardiographic changes indicating the evolution of an infarction, including ST-segment elevation in the electrocardiographic tracing associated with terminal inversion of T waves and the loss of initial QRS potentials (i.e., development of "pathologic" Q waves lasting 0.04 second or longer), followed by serial changes indicating reversion toward normal.

2. Angina pectoris diagnosed at Exam 3 when the patient had recurrent symptoms of chest discomfort lasting up to 15 minutes, distinctly related to exertion or excitement and relieved by rest or nitroglycerin, and also complained that the discomfort radiated into the arms or neck. The diagnosis was rejected when another explanation was possible or the discomfort also occurred as often at rest.

3. Death between Exam 2 and the scheduled Exam 3 with the primary cause of death being ischemic heart disease determined by death certificate (ICDA code 410 or 412). The concordance of death certificate codes with hospital record diagnoses was shown in a recent study to be 87% for myocardial infarction (ICDA 410) and 65% for ischemic heart disease (ICDA 412).

Of the 1437 men in this study, all free of ischemic heart disease at Exam 2, 44 developed ischemic heart disease between Exams 2 and 3. Of these, 24 had myocardial infarctions (11 of them also had angina), 16 had angina without a diagnosis of myocardial infarction, and four died of ischemic heart disease between Exams 2 and 3.

Data Analysis

When a clinical variable is assessed at two times, there are two reasons to expect regression to the mean: measurement variation and biologic variation. These may be illustrated by the example of total cholesterol. To the extent that a person has a "true" cholesterol level at a given time (the cholesterol level varies both diurnally and seasonally), if a single measure of that level yields a high score (for the population), then it is more likely that the measure has erred above the "true" level than below. A second measure, even one taken several years later, will more likely be lower. Biologic causes tending to normalize cholesterol levels over time may be attributed to homeostatic mechanisms which have been described elsewhere. Thus, it might be expected that extreme cholesterol values at Exam 1 will more likely be closer to normal at Exam 2. To consider changes that may be pathologic in risk factors such as cholesterol, it is necessary to control for or remove the effects of regression to the mean. The regression to the mean effect is especially pronounced in lipid measures, which exhibit high variation over time. The method described below to obtain residual change scores is the simplest direct method of removing the regression to the mean component from change.

Residual changes between Exams 1 and 2 were measured for cholesterol, triglyceride (log), and systolic blood pressure by the following technique. Men were
The residual years, 40–52 into computed 53–85 years, 40–52 cholesterol, component change is defined as the difference between the observed Exam 2 level and the Exam 2 level predicted by the regression line from the observed Exam 1 level.

The method is illustrated in figure 1. For men ages 40–52 years, the regression line of Exam 2 on Exam 1 cholesterol levels was \( Y_2 = 144 + 0.39Y_1 \). Thus, if a 45-year-old participant’s cholesterol was 150 mg/dl at Exam 1 and 180 mg/dl at Exam 2, his predicted Exam 2 cholesterol would be 144 ± 0.39 (150) = 202.5 mg/dl and the residual cholesterol change therefore would be 180 – 202.5 = –22.5 mg/dl. Similarly, if his Exam 1 and 2 cholesterol levels were 250 mg/dl and 280 mg/dl, respectively, then his predicted Exam 2 cholesterol would be 241.5 mg/dl and the residual cholesterol change would be 38.5 mg/dl. Thus, the same raw changes in cholesterol level result in very different residual changes, as residual change accounts for the tendency for levels to move toward the mean. Residual change may also be thought of as the component of change remaining after the regression component of change is removed. Also removed with the regression component are any changes between mean levels at Exams 1 and 2 that might be due to aging or the Exam 1 selection criteria. For example, the mean serum cholesterol level of the population under consideration increased from 203.7 mg/dl at Exam 1 to 224.1 mg/dl at Exam 2.

A logistic model was used to relate the development of ischemic heart disease between Exams 2 and 3 to residual changes between Exams 1 and 2 in total cholesterol, systolic blood pressure and triglyceride. Exam 1 levels of cholesterol, triglyceride and systolic blood pressure as well as body mass index and cigarette smoking were also considered as risk factors. Changes in body mass index and cigarette smoking were not assessed, as these risk factors were not measured at Exam 2. To normalize distributions, natural logarithm transforms were made on triglyceride (the transformed variable was denoted triglyceride [log]) and the number of packs of cigarettes per day. All logistic regressions were determined by the maximum likelihood method using the BMDPLR program.

Associations were first computed for each risk factor individually. Because there were only 44 cases, separate models were not initially computed for each age group; rather, the protective effect of being younger than 40 years and the increased risk of being older than 52 years old were estimated by including two indicator age variables in each model. Stepwise logistic regression was used to obtain the best multivariate model. Because triglycerides have been measured in the Normative Aging Study only since 1965, two models were fitted: The first used the 1086 participants who had Exam 1 and 2 triglyceride measurements and considered all the above-mentioned risk factors; the second used all 1437 participants, including the 351 that did not have two triglyceride measurements, and considered all risk factors except Exam 1 triglyceride (log) and residual triglyceride (log) change. In each model, as in the univariate case, the effect of age was controlled by two indicator variables. Risk factors were entered into the model in a stepwise fashion with the variable entered on a given step that most improved the prediction. The stepwise process ended when no variables improved the model at a significance level of \( p = 0.10 \). Finally, because of the potential effect of aging and the varying lengths of time between examinations for men younger and older than 53 years, separate models were fitted in the age groups under 52 years and 53 years or older. The hypothesis of no association between a risk factor and heart disease was tested at each step by a likelihood ratio test.

In the logistic model, an overall measure of the magnitude of association between a given risk factor and disease is the standardized odds ratio. If \( R_0 \) is the predicted heart disease risk of a person with a specified level of a risk factor and \( R_t \) is the predicted risk of a person 1 standard deviation higher on that risk factor but with the same values for all other predictors in the model, the standardized odds ratio is \( [R_t/(1 - R_t)]/[R_0/(1 - R_0)] \). Under the logistic model, the standardized odds ratio is independent of the level of the referent, and if risk is small, it approximates the relative risk.

**Results**

The 5-year incidences of ischemic heart disease for men ages 28–39 years and 40–52 years and the 3-year incidences for men ages 53–85 years are shown by risk factor categories in table 1. For each risk factor except cigarette smoking, a subject was categorized according to whether he was at least 1 standard deviation below the mean, between 1 standard deviation below and 1 standard deviation above the mean, or at least 1 standard deviation above the mean. Incidences by categories of Exam 1 triglyceride (log) and residual

![Figure 1. Regression of Exam 2 on Exam 1 cholesterol levels.](image-url)
triglyceride (log) change were based on 1086 men, while for all other risk factors there were 1437 men at risk. In each age group the heart disease incidence for those 1 standard deviation (44.4 mg/dl) below the mean in residual cholesterol change was one-third or less the incidence of those 1 standard deviation above the mean. A similar result holds for residual triglyceride (log) change and body mass index.

Table 2 shows logistic regression results that relate risk factors individually, controlling only for age, to the development of heart disease. The coefficients themselves are not directly comparable because they depend on units of measurement. The standardized odds ratio gives a standardized measure of the magnitude of the relation between a risk factor and heart disease. It was greatest for residual cholesterol change and residual triglyceride (log) change. P values, derived from likelihood ratio tests, indicate a significant association between heart disease and residual cholesterol change, residual triglyceride (log) change, Exam
1 triglyceride (log), residual systolic blood pressure change, body mass index and cigarette smoking.

Multivariate relations between risk factors and ischemic heart disease obtained by stepwise logistic regression are summarized in tables 3, 4, 5 and 6. The data in table 3 are from the 1086 men in whom triglyceride was measured at Exams 1 and 2. Two indicator variables were used to estimate the effects of age: residual triglyceride (log) change had the strongest association with ischemic heart disease. After this risk factor was entered, residual cholesterol change was no longer a significant independent predictor (p > 0.10). However, in this subpopulation, cigarette smoking and Exam 1 triglyceride (log) were independent predictors.

Multivariate results for all 1437 participants, including the 351 men who did not have two triglyceride measures, are shown in table 4. In this analysis, Exam 1 triglyceride (log) and residual triglyceride (log) change were not considered. Residual cholesterol change was the best predictor for this population, and body mass index and cigarette smoking showed additional independent associations with the incidence of heart disease.

Tables 5 and 6 summarize risk relations in the age groups 28–52 years and 53–85 years. Among men in whom triglyceride was measured twice (table 5), residual triglyceride (log) change was a strong independent predictor in each age group. Also, in both age groups, residual triglyceride (log) change was more predictive than residual cholesterol change, and residual cholesterol change was not predictive after controlling for residual triglyceride (log) change. Among older men, Exam 1 triglyceride (log) was most predictive and Exam 1 cholesterol had some independent predictive relation with the incidence of heart disease, after controlling for Exam 1 triglyceride (log) and residual triglyceride (log) change.

When all 1437 participants were included and triglyceride was not considered (table 6), residual cholesterol change was an independent predictor for both age groups, but its associated risk was stronger among the young. As in the reduced population with two triglyceride measures, an initial level, in this case Exam 1 cholesterol, was most predictive for older men. However, initial cholesterol was not predictive among the young.

**Discussion**

The present findings indicate the importance of changes in risk factors as predictors of ischemic heart disease. Residual changes in cholesterol, triglyceride and systolic blood pressure were considerably better predictors of subsequent heart disease than the respective Exam 1 levels. When all risk factors were considered together, residual triglyceride (log) change was the best predictor for the subpopulation that had two triglyceride measurements; residual cholesterol change predicted best for the entire population when triglyceride was not considered. When separate age groups were considered, both residual cholesterol and triglyceride changes were strong predictors in each age group.

Although the hypothesis that variations in serum lipid levels are related to heart disease is not new, few
TABLE 5. Multiple Logistic Coefficients of Risk Factors for Ischemic Heart Disease by Age (Men with Exam 1 and 2 Triglyceride Measures)

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Logistic coeff</th>
<th>SD of risk factor</th>
<th>Standard odds ratio</th>
<th>Two-sided p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ages 28–52 years (734 men, 16 with ischemic heart disease)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Log (1 + cig. packs/day)</td>
<td>1.407</td>
<td>0.384</td>
<td>1.72</td>
<td>0.016</td>
</tr>
<tr>
<td>Residual triglyceride (log) change</td>
<td>1.122</td>
<td>0.403</td>
<td>1.57</td>
<td>0.054</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.143</td>
<td>2.872</td>
<td>1.51</td>
<td>0.084</td>
</tr>
<tr>
<td>Constant</td>
<td>-8.234</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ages 53–85 years (352 men, 18 with ischemic heart disease)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exam 1 triglyceride (log)</td>
<td>1.520</td>
<td>0.368</td>
<td>1.75</td>
<td>0.001</td>
</tr>
<tr>
<td>Residual triglyceride (log) change</td>
<td>1.494</td>
<td>0.371</td>
<td>1.71</td>
<td>0.032</td>
</tr>
<tr>
<td>Exam 1 cholesterol</td>
<td>0.009</td>
<td>45.89</td>
<td>1.51</td>
<td>0.084</td>
</tr>
<tr>
<td>Constant</td>
<td>-12.547</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: See table 2.

data are available on long-term serial correlations of lipids. Elveback et al.2 studied the variability of serum cholesterol and triglyceride in 10 children over 1 week, and concluded that a single determination of whole serum triglyceride carried limited significance in children because, within the week, the level can change by a factor of two. Shekelle et al.28 presented data from 1900 male adult employees of the Western Electric Company in Chicago, ages 40–55 years, who had two examinations 1 year apart. The correlation of serum cholesterol levels between the two exams for the 1556 participants who reported no systematic change in diet between exams was 0.653. This correlation might be expected to be lower if men who changed diets between exams were included. Correlations of serum cholesterol levels between Exams 1 and 2 for the 1437 men in the present study, with 3–5 years between examinations were 0.302 for men younger than 40 years old, 0.360 for men 40–52 years old, and 0.295 for men age 53 years and older. Correlations of triglyceride (log) levels in this population were comparable: 0.379 for men younger than age 40 years, 0.297 for men ages 40–52 years old, and 0.378 for men age 53 years and older.

The standard deviations in the residual changes are of interest because they describe the extent to which the levels fluctuate. The standard deviations in the residual changes in lipids and systolic blood pressure were greater than the standard deviations of the corresponding Exam 1 levels (table 2). This is possible because the standard deviations of the Exam 2 levels (cholesterol 47.38, triglyceride [log] 0.418, systolic blood pressure 14.35) were greater than the corresponding Exam 1 level standard deviations. These differences between Exam 1 and 2 standard deviations were statistically significant according to Pitman's test for correlated variances,29 and they remained significant when men developing heart disease between Exams 1 and 2 were included. The increased variance in systolic blood pressure is not surprising, as the distribution of this variable at Exam 1 was truncated by selection, and James19 showed that the variance of a variable truncated at initial assessment are higher at a subsequent assessment. The variance of lipid measures

TABLE 6. Multiple Logistic Coefficients of Risk Factors for Ischemic Heart Disease by Age

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Logistic coeff</th>
<th>SD of risk factor</th>
<th>Standard odds ratio</th>
<th>Two-sided p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ages 28–52 years (1021 men, 25 with ischemic heart disease)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Residual cholesterol change</td>
<td>0.014</td>
<td>43.59</td>
<td>1.84</td>
<td>0.0004</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.182</td>
<td>2.921</td>
<td>1.70</td>
<td>0.008</td>
</tr>
<tr>
<td>Log (1 + cig. packs/day)</td>
<td>1.247</td>
<td>0.406</td>
<td>1.66</td>
<td>0.007</td>
</tr>
<tr>
<td>Constant</td>
<td>-9.238</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ages 53–85 years (416 men, 19 with ischemic heart disease)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exam 1 cholesterol</td>
<td>0.010</td>
<td>44.78</td>
<td>1.56</td>
<td>0.039</td>
</tr>
<tr>
<td>Residual cholesterol change</td>
<td>0.008</td>
<td>46.48</td>
<td>1.45</td>
<td>0.077</td>
</tr>
<tr>
<td>Constant</td>
<td>-5.342</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: See table 2.
may have increased due to aging, selection, or their modest correlation with blood pressure.

Factors that might affect the results of this study include sampling bias, laboratory bias and losses to follow-up. The study population consisted of initially healthy male volunteers. This sampling technique limits the generalizability of the results. The residual change technique, by its use of average predicted values, compensates for many patterns of laboratory bias. However, there are hypothetical patterns of bias for which it does not compensate. For example, if the reliability of the Exam 2 measurements was greater than that of the Exam 1 measurements, spuriously significant residual change levels might result. The men who participated throughout the study were older at the initial examination than the men lost to follow-up. But there were no significant differences in baseline lipid and blood pressure levels between the two groups.

In contrast to the present study, other prospective heart disease studies found that initial levels of serum cholesterol and systolic blood pressure were strongly related to the incidence of heart disease. However, the present study had important design differences that may account for the different findings. The Normative Aging Study population was screened for health and the screening criteria included blood pressure. Additionally, no men were considered unless they were free of ischemic heart disease at Exam 2. Thus, the predictive power of Exam 1 levels was evaluated after a minimum of 3–5 years. This was done to test how long a single measurement would maintain its predictive power. Indeed, if all heart disease cases between Exams 1 and 3 are considered, then Exam 1 cholesterol is a very significant predictor and predicts better than Exam 1 systolic blood pressure, body mass index or cigarette smoking.

Longitudinal blood pressure data from the Manitoba Follow-up Study, based on a 26-year observation period, showed that systolic blood pressure after entry was more strongly associated with ischemic heart disease incidence than was entry blood pressure. The Manitoba investigators found that the systolic blood pressure measurement closest to the event was the most predictive. Together with the Normative Aging Study data, this implies the importance of considering intermittent measures when relating risk factors to heart disease in a prospective study.

Kahn and Dawber reported the relation between multiple measures of cholesterol and the development of coronary heart disease in the Framingham population. They placed subjects at risk at each biennial examination and thus to some extent incorporated the change in cholesterol levels. Among Framingham men, the cholesterol measure closest to the event was more predictive of coronary heart disease death than was the initial cholesterol level, but later cholesterol measures did not improve prediction in other diagnostic categories of heart disease. Kahn and Dawber also considered other functions of sequential cholesterol measures as predictors of heart disease, but not residual change. They reached no definitive conclusion about the value of multiple cholesterol measures in a longitudinal study.

No attempt was made to alter lipid levels among Normative Aging Study volunteers. Nevertheless, residual cholesterol changes between Exams 1 and 2 ranged from −142 to 238 mg% (so 44.44 mg%), and residual triglyceride (log) change had a similar wide range. Some of this change could be explained by measurement error or normal seasonal changes. However, there was clearly an additional component to change, which was strongly related to the incidence of heart disease. With respect to the current controversy regarding the efficacy of restricting dietary cholesterol, our study does not provide information as to whether changes induced by drug or dietary regimens would have the same relationship with heart disease.

References

11. Cronbach LG, Furby L: How should we measure "change" — or should we? Psych Bull 74: 68, 1970
Changes in cholesterol and triglyceride as predictors of ischemic heart disease in men.
R J Glynn, B Rosner and J E Silbert

Circulation. 1982;66:724-731
doi: 10.1161/01.CIR.66.4.724

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1982 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/66/4/724

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/