Determinants of Severity of Coronary Artery Disease in Australian Men and Women

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Background  Factors predicting the occurrence of premature coronary artery disease (CAD) may not be quantitatively the same as those predicting CAD severity, particularly in women, in whom there have been few studies.

Methods and Results  To determine factors predictive of severity of CAD and of angina pectoris, we documented atherogenic variables and the extent of CAD at angiography in 594 consecutively studied men and women aged 65 years or less. Severity was assessed from the number of involved major coronary arteries with significant (>50%) luminal obstructions and from a coronary disease severity score. We related severity to quantitative and categorical atherogenic variables and assessed severity of angina (no angina, stable angina, or unstable angina) at the time of study in the same way. There were eight variables independently predictive of severity: in descending order of relative importance, male gender, diabetes, smoking dose, ratio of total cholesterol to high-density lipoprotein cholesterol (TC/HDL-C), lipoprotein(a) [Lp(a)], age, positive family history, and hypertension. These correctly classified 43.3% of patients into no-, one-, two-, and three-vessel disease categories and accounted for 25.8% of variance of severity. Among 246 patients not taking lipid-lowering or \( \beta \)-blockers, these variables (in slightly different order) correctly classified 49.2% of patients and accounted for 36% of the variance. Among men (n=427), seven significant variables correctly classified 39.3% of patients compared with 54.5% in women (n=167). For those not taking the above drugs, these proportions were 49.4% and 65.4%, respectively. Among the quantitative variables, total smoking dose was the most predictive independent variable irrespective of current or ex-smoking habit and was more predictive in women than in men; of the lipid variables, high TC/HDL-C (or low HDL-C) and high Lp(a) were consistently highly predictive for all patients and in the subgroup analyses. Patients with unstable angina had higher coronary severity scores and Lp(a) levels and were more likely to have diabetes, hypertension, or a positive family history.

Conclusions  We conclude that the quantitative variables most relevant to severity of premature CAD and to its prevention in Australian men and women are total amount of lifetime smoking, TC/HDL-C (or HDL-C), and Lp(a) and that patients with unstable versus stable angina usually have more severe disease and higher Lp(a). (Circulation. 1994;89: 1974-1981.)

Key Words  • smoking • lipoprotein(a) • cholesterol • angina

Since World War II, there has been a concentration of effort in developed countries to define factors associated with increased risk of coronary artery disease (CAD) with the aim of implementing effective prevention. As recently reviewed,\(^1\)\(^-\)\(^5\) it is known that increased levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), apolipoprotein (apo) B, lipoprotein(a) [Lp(a)], and possibly triglycerides (TG), as well as low levels of high-density lipoprotein cholesterol (HDL-C) and apo A-I, are associated with increased coronary risk; so are diabetes, hypertension, smoking, and a positive family history of premature CAD. Prospective studies have correlated these factors with coronary events.\(^6\)\(^,\)\(^7\) However, few studies have examined the relation between these variables and the severity of CAD, as documented by its extent anatomically and clinically according to the severity of angina. This is particularly so for studies in women. Although left ventricular function is an important determinant of long-term outcome in patients with CAD, so also is the extent of the anatomic atherosclerotic involvement\(^8\) and the presence of stable versus unstable angina.\(^8\)\(^,\)\(^9\)

In the present study, we aimed to define in Australian men and women with premature CAD the relation between potentially atherogenic variables, both categorical and quantitative, and the extent of major vessel CAD and the severity of angina.

Methods

Patient Population

We studied consecutive patients aged 65 years or less, both men and women, who were referred to the Prince Henry Hospital for coronary angiography over a 1-year period during 1991 and 1992 excluding only patients shown to have significant (>50% luminal obstruction) left main disease because it was difficult to categorize this small proportion of the total (<5%) within the classification system we used (see below). Consent was obtained from each patient for the study, which was approved by the Ethics Committee of the University of New South Wales. A 10-mL venous blood sample was drawn before the angiogram after a 4- to 6-hour fast, and the plasma sample was aliquoted and stored at \(-70^\circ C\) until analysis.

Lipoprotein Analysis

TC, HDL-C, and TG levels were measured by the hospital's clinical chemistry department using standard enzymatic methods. The LDL-C levels were calculated using the Friedewald formula. We measured levels of apo A-I, apo B, and Lp(a) using ELISA methods developed in our laboratory.\(^10\)\(^-\)\(^12\) The

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interassay and intra-assay coefficients of variations were 5.1% and 8.2% for the apo A-I assay, 4.0% and 6.6% for the apo B assay, and 3.5% and 5.2% for Lp(a), respectively.

Patient Histories

We recorded for each patient the presence or absence (yes/no) of a history of hypertension requiring treatment, of diabetes, of angina pectoris, and of myocardial infarction. Patients were also classified according to whether they were receiving β-adrenergic-blocking or lipid-lowering drugs. The presence or absence of a positive family history of premature CAD was also recorded. Patients with a positive family history were those who had one or more first-degree relatives with documented CAD before the age of 65 years. The presence and severity of angina pectoris were recorded according to whether each patient was experiencing no angina, stable angina, or unstable angina at the time of cardiac catheterization. All those classified as having unstable angina had an increase in pain frequency as well as rest pain.

We documented the smoking history of each patient. For those who had been or were smoking, we determined the accumulated smoking dose according to Weintraub et al.,\textsuperscript{13} including the duration of the smoking history. The life-long smoking dose was calculated by multiplying the mean number of cigarettes smoked daily and the number of years of smoking (pack-years; ie, smoking one pack of 20 cigarettes each day for 1 year).\textsuperscript{13,14} The patient was considered to be a current daily smoker if she or he had regularly smoked at least 5 cigarettes per day for at least the previous 3 months or had stopped smoking for less than 1 year.\textsuperscript{14} Because the number of pack-years is an approximate value, we recorded the smoking dose semiquantitatively; we classified as light smokers those who had smoked 10 or fewer pack-years, as medium smokers those whose "smoking dose" was between 10 and 20 pack-years, and as heavy smokers those with more than 20 pack-years of smoking. Patients who had stopped smoking for at least 1 year were classified as ex-smokers. Thus, smokers were classified as non-smokers, light current or ex-smokers, medium current or ex-smokers, or heavy current or ex-smokers.

Documentation of CAD Severity

The severity of CAD was determined in two ways. The angiograms were assessed by two cardiologists who were unaware that the patients were to be included in the study, and each angiogram was classified as revealing either no coronary lesions with more than 50% luminal stenosis or as having one, two, or three major epicardial coronary arteries with more than 50% luminal obstructions. In a second approach, we used the Green Lane coronary scoring system,\textsuperscript{15} which provides a numerical value for lesion severity and takes account of the amount of myocardium supplied by an affected vessel; the maximal score is 15.

Statistical Analysis

The levels of lipoproteins and apolipoproteins are presented as mean±SD, and the differences among subgroups of patients were compared by ANOVA for all four patient subgroups (no-, one-, two-, or three-vessel disease) or by Student's t test for comparisons between two subgroups. Because the levels of TG and Lp(a) were skewed, we logarithmically (log 10) transformed these levels before the statistical analysis. Pearson χ² analysis was used for categorical variables among subgroups of patients.

To identify the variables important for distinguishing differing CAD severity among patients and to explore approaches to predicting severity, we used discriminant analysis to assess relations between the severity of CAD determined by the number of diseased vessels (>50% obstruction) and lipoprotein and apolipoprotein levels, age, smoking dose, and patient history. In this statistical model,\textsuperscript{16} the Wilks' lambda is used to evaluate the relative importance of each individual independent variable in predicting the dependent variable, ie, CAD severity. The value for Wilks' lambda is the proportion of unexplained variance of CAD severity attributable to an independent factor.

The necessary assumptions were checked before the discriminant analysis was conducted. After levels of TG and Lp(a) were logarithmically transformed, all continuous independent variables had multivariate normal distributions in each of the four patient subgroups. The covariance matrices of all four patient groups were also not different as tested by Box's M test. In the analysis, independent variables are entered into the model, one at each step in descending order of minimizing the sum of unexplained variance. This model enables us to predict CAD severity from the identified independent risk factors and to assess the validity of predictions by comparing them with the actual CAD severity determined at angiography. We assessed this from the percentage of patients correctly predicted to have either no-, one-, two-, or three-vessel disease. We also used multiple least-squares linear regression analysis to explore relations between the continuous (Green Lane) coronary severity scores and lipid variables, with the categorical factors being controlled separately. All statistical analyses were executed with the spss statistical software package.

The study was approved by the Ethics Committee of the University of New South Wales.

Results

Relation Between the Number of Significantly Diseased (>50%) Vessels and Independent Risk Factors

Five hundred ninety-four patients were entered into the study — 427 men and 167 women, of whom 358 men and 91 women had at least one major coronary artery with a significant obstruction (>50%). There were no significant differences in age, body mass index (BMI), or lipid levels between the men and women except for TG and ratio of TC to HDL-C, which were higher in men (P<.01 and P<.0001, respectively), and for HDL-C, which was lower in men (P<.0001). The patient data in relation to age, BMI, and lipid variables for each of the four severity subgroups are shown in Table 1. There are no significant differences in age, BMI, and apo A-I among patients with different numbers of diseased vessels, and although there are increases in the levels of TC, LDL-C, apo B, and ratio of apo B to apo A-I with the increase in number of diseased vessels, the differences are also not statistically significant. By using ANOVA, there are significant differences in the ratio of TC to HDL-C (F=10.46, P=.0001), HDL-C (F=8.73, P=.0001), log-TG (F=6.29, P=.0001), and log-Lp(a) (F=5.486, P=.001) for patients with different numbers of diseased vessels. However, except for Lp(a) levels, these differences are mainly between patients with significant disease and those without significant disease and not between patients with one-, two-, or three-diseased vessels. Lp(a) levels are higher in patients with two or three diseased vessels than in those with only one diseased vessel (P=.004) or no significant vessel disease (P=.001).

The relations between patients with diabetes, hypertension, or positive family history of premature CAD and number of significantly diseased vessels were assessed by Pearson χ² analysis, as shown in Table 2. There are significant associations between diabetes and CAD severity (χ²=29.28, P=.0001), hypertension and severity (χ²=14.92, P=.0019), and positive family his-
tory and the severity ($\chi^2 = 10.23, P = .0167$). From Table 2, it is clear that the percentage of diabetic patients with no significantly diseased vessels (4.4%) is much lower than the average (24.4%), whereas the percentage of diabetic patients with three-vessel disease (44.1%) is much higher than the average (21.4%).

As shown in Table 3, there is a very strong positive relation between lifetime cigarette consumption and CAD severity ($\chi^2 = 66.97, P = .000001$). When we subgrouped patients according to current and past smoking habit by linking together current light, medium, and heavy smokers into a single group and ignoring total lifetime cigarette consumption, as illustrated in Table 3, there was no statistically significant difference in CAD severity between ex-smokers and current smokers ($\chi^2 = 4.38, P = .222$).

We documented patients receiving lipid-lowering and $\beta$-adrenergic–blocking agents to explore the confounding effects of drug administration. Only 90 patients were taking lipid-lowering drugs, but 310 were receiving $\beta$-adrenergic–blocking agents. As expected, the 90 patients taking lipid-lowering drugs had lower LDL-C levels ($P < .001$), lower ratios of apo B to apo A-I ($P < .001$), and lower ratios of TC to LDL-C ($P < .01$) but slightly higher TG ($P < .05$) than patients not taking them. The 310 patients receiving $\beta$-adrenergic–blocking drugs had a lower LDL-C (1.06±0.3 versus 1.13±0.36, $P < .01$) and higher log-TG (0.33±0.21 versus 0.28±0.22, $P < .01$). Apo A-I was also lower in the $\beta$-blocker users (1.19±0.37 versus 1.26±0.43, $P < .05$).

**Determinants of CAD Severity**

We used discriminant analysis to evaluate possible interactive effects among risk factors, their independent associations with severity, and their relative importance in predicting severity. The number of significantly diseased vessels was the dependent variable. When all 594 patients were included in the analysis, eight indepen-

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**Table 1. Quantitative Variables Measured in Patients Aged 65 Years or Less in Relation to the Number of Vessels With Significant (More Than 50%) Luminal Obstructions**

<table>
<thead>
<tr>
<th>No. of Significantly Diseased Vessels*</th>
<th>None</th>
<th>One</th>
<th>Two</th>
<th>Three</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>145</td>
<td>188</td>
<td>134</td>
<td>127</td>
<td>594</td>
</tr>
<tr>
<td>Age, y</td>
<td>53.8 (8.8)</td>
<td>53.9 (8.0)</td>
<td>55.2 (7.3)</td>
<td>56.0 (7.6)</td>
<td>55.6 (8.0)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.0 (4.6)</td>
<td>26.6 (3.8)</td>
<td>26.5 (3.4)</td>
<td>27.0 (3.9)</td>
<td>26.8 (3.9)</td>
</tr>
<tr>
<td>TC, mmol/L</td>
<td>5.57 (1.11)</td>
<td>5.68 (1.03)</td>
<td>5.80 (1.04)</td>
<td>5.79 (1.07)</td>
<td>5.71 (1.06)</td>
</tr>
<tr>
<td>TG, mmol/L</td>
<td>1.98 (0.96)</td>
<td>2.44 (1.77)</td>
<td>2.28 (1.07)</td>
<td>2.64 (1.71)</td>
<td>2.34 (1.46)</td>
</tr>
<tr>
<td>Log-TG</td>
<td>0.25 (0.21)</td>
<td>0.32 (0.23)</td>
<td>0.32 (0.19)</td>
<td>0.36 (0.23)</td>
<td>0.31 (0.22)</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>1.21 (0.39)</td>
<td>1.06 (0.31)</td>
<td>1.07 (0.30)</td>
<td>1.03 (0.29)</td>
<td>1.08 (0.33)</td>
</tr>
<tr>
<td>LDL-C, mmol/L</td>
<td>3.47 (1.03)</td>
<td>3.53 (1.00)</td>
<td>3.71 (0.99)</td>
<td>3.57 (1.07)</td>
<td>3.57 (1.02)</td>
</tr>
<tr>
<td>Apo A-I, g/L</td>
<td>1.25 (0.38)</td>
<td>1.20 (0.39)</td>
<td>1.21 (0.42)</td>
<td>1.25 (0.40)</td>
<td>1.22 (0.40)</td>
</tr>
<tr>
<td>Log Apo B, g/L</td>
<td>1.29 (0.42)</td>
<td>1.29 (0.49)</td>
<td>1.33 (0.55)</td>
<td>1.40 (0.56)</td>
<td>1.32 (0.50)</td>
</tr>
<tr>
<td>Lp(a), mg/L</td>
<td>176 (1-1745)</td>
<td>183 (1-1750)</td>
<td>321 (1-1880)</td>
<td>346 (1-1800)</td>
<td>232 (1-1800)</td>
</tr>
<tr>
<td>Log Lp(a)</td>
<td>1.17 (0.58)</td>
<td>1.24 (0.60)</td>
<td>1.43 (0.53)</td>
<td>1.36 (0.63)</td>
<td>1.29 (0.60)</td>
</tr>
<tr>
<td>TC/HDL-C</td>
<td>4.94 (1.59)</td>
<td>5.74 (1.78)</td>
<td>5.76 (1.55)</td>
<td>6.04 (1.89)</td>
<td>5.63 (1.75)</td>
</tr>
<tr>
<td>Apo B/apo A-I</td>
<td>1.10 (0.41)</td>
<td>1.17 (0.82)</td>
<td>1.16 (0.59)</td>
<td>1.23 (0.67)</td>
<td>1.17 (0.65)</td>
</tr>
</tbody>
</table>

Table 1. Quantitative Variables Measured in Patients Aged 65 Years or Less in Relation to the Number of Vessels With Significant (More Than 50%) Luminal Obstructions

**Table 2. Relations Between the Number of Significantly Diseased Vessels and History of Diabetes or Hypertension or Family History of Premature Coronary Artery Disease**

<table>
<thead>
<tr>
<th>No. of Significantly Diseased Vessels</th>
<th>None</th>
<th>One</th>
<th>Two</th>
<th>Three</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nondiabetic</td>
<td>142  (27.0%)</td>
<td>169 (32.1%)</td>
<td>118 (22.4%)</td>
<td>97 (18.4%)</td>
<td>526</td>
</tr>
<tr>
<td>Diabetic</td>
<td>3    (4.4%)</td>
<td>19 (27.9%)</td>
<td>16 (23.5%)</td>
<td>30 (44.1%)</td>
<td>68</td>
</tr>
<tr>
<td>Nonhypertensive</td>
<td>106  (28.0%)</td>
<td>126 (33.3%)</td>
<td>80 (21.2%)</td>
<td>66 (17.5%)</td>
<td>378</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>39   (18.1%)</td>
<td>62 (28.7%)</td>
<td>54 (25.0%)</td>
<td>61 (28.2%)</td>
<td>216</td>
</tr>
<tr>
<td>Negative family history</td>
<td>96   (29.3%)</td>
<td>101 (30.8%)</td>
<td>65 (19.8%)</td>
<td>66 (20.1%)</td>
<td>328</td>
</tr>
<tr>
<td>Positive family history</td>
<td>49   (18.4%)</td>
<td>67 (32.7%)</td>
<td>69 (25.9%)</td>
<td>61 (22.9%)</td>
<td>266</td>
</tr>
<tr>
<td>Total</td>
<td>145  (24.2%)</td>
<td>188 (31.6%)</td>
<td>134 (22.6%)</td>
<td>127 (21.4%)</td>
<td>594</td>
</tr>
</tbody>
</table>

Table 2. Relations Between the Number of Significantly Diseased Vessels and History of Diabetes or Hypertension or Family History of Premature Coronary Artery Disease
TABLE 3. Relation Between Number of Significantly Diseased Vessels and 'Smoking Dose' and Current Versus Ex-Smokers

<table>
<thead>
<tr>
<th>Smoking dose, pack-years</th>
<th>None</th>
<th>One</th>
<th>Two</th>
<th>Three</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>78 (43.3%)</td>
<td>54 (30%)</td>
<td>24 (13.3%)</td>
<td>24 (13.3%)</td>
<td>180 (100%)</td>
</tr>
<tr>
<td>&lt;10</td>
<td>15 (22.1%)</td>
<td>17 (25%)</td>
<td>16 (23.5%)</td>
<td>20 (29.4%)</td>
<td>68 (100%)</td>
</tr>
<tr>
<td>10-20</td>
<td>3 (11.5%)</td>
<td>8 (30%)</td>
<td>7 (26.9%)</td>
<td>8 (30.8%)</td>
<td>26 (100%)</td>
</tr>
<tr>
<td>&gt;20</td>
<td>49 (15.3%)</td>
<td>109 (34.1%)</td>
<td>87 (27.2%)</td>
<td>75 (23.4%)</td>
<td>320 (100%)</td>
</tr>
<tr>
<td>Total (Pearson $\chi^2=66.97$, $P=0.00001$)</td>
<td>145 (24.2%)</td>
<td>188 (31.6%)</td>
<td>134 (22.6%)</td>
<td>127 (21.4%)</td>
<td>594 (100%)</td>
</tr>
</tbody>
</table>

Smoking status

| Ex-smokers | 26 (21.8%) | 35 (29.4%) | 32 (26.9%) | 26 (21.8%) | 119 (100%) |
| Current smokers | 41 (13.9%) | 99 (33.6%) | 78 (26.4%) | 77 (26.1%) | 295 (100%) |
| Total (Pearson $\chi^2=4.38$, $P=0.222$) | 67 (16.2%) | 134 (32.4%) | 110 (26.6%) | 103 (24.9%) | 414 (100%) |

dent variables were significantly associated with CAD severity. In descending order of relative importance, these variables are male gender, diabetes, smoking dose, ratio of TC to HDL-C, Lp(a), age, positive family history, and hypertension. As shown in Table 4, these eight variables correctly classified 43.3% of patients. This is significantly different ($P<0.0001$) from the 25% expected from the null hypothesis, i.e., an even distribution among the four subgroups (no-, one-, two-, and three-vessel disease). The minimized Wilks’ lambda is .742, i.e., 25.8% of the variance of CAD severity can be explained by these eight variables. Their relative contributions are male gender, 8.3%; diabetes, 4.6%; smoking dose, 3.4%; ratio of TC to HDL-C, 2.5%; Lp(a), 2.2%; age, 1.9%; positive family history, 1.6%; and hypertension, 1.2%. In contrast, BMI, TC, TG, LDL-C, apo A-I, apo B, and ratio of apo B to apo A-I were not significant predictors. Although HDL-C alone is also predictive (negatively) of severity (2.2%, $P<0.01$), it loses its significance when ratio of TC to HDL-C is included in the model.

To explore possible sex differences, we conducted the discriminant analysis in male and female patient subgroups separately. Among 427 male patients, the significant variables in descending order are Lp(a), diabetes, ratio of TC to HDL-C, age, smoking dose, positive family history of premature CAD, and BMI. They explain 17.3% of the variance of CAD severity (minimized Wilks’ lambda, .827) and correctly predict 39.3% of cases (Table 4). Among the 167 female patients, the

TABLE 4. Coronary Artery Disease Severity (Number of Significantly Diseased Vessels) Predicted in a Discriminate Model by Independent Risk Factors

<table>
<thead>
<tr>
<th>Observed Group Membership</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>Predicted group membership among 594 patients*</td>
</tr>
<tr>
<td>None</td>
</tr>
<tr>
<td>One</td>
</tr>
<tr>
<td>Two</td>
</tr>
<tr>
<td>Three</td>
</tr>
<tr>
<td>Predicted group membership among 427 male patients†</td>
</tr>
<tr>
<td>None</td>
</tr>
<tr>
<td>One</td>
</tr>
<tr>
<td>Two</td>
</tr>
<tr>
<td>Three</td>
</tr>
<tr>
<td>Predicted group membership among 167 female patients‡</td>
</tr>
<tr>
<td>None</td>
</tr>
<tr>
<td>One</td>
</tr>
<tr>
<td>Two</td>
</tr>
<tr>
<td>Three</td>
</tr>
</tbody>
</table>

*Overall percent of "grouped" cases correctly classified=43.3%.
†Overall percent of "grouped" cases correctly classified=39.3%.
‡Overall percent of "grouped" cases correctly classified=54.5%.
significant variables in descending order are smoking dose, diabetes, TG, hypertension, positive family history, ratio of TC to HDL-C, and Lp(a). They can explain 37.3% of CAD severity variance (minimized Wilks’ lambda, .628) and correctly classify 54.5% of patients (Table 5).

When the analysis was confined to the 246 patients not taking lipid-lowering or β-adrenergic-blocking drugs, these independent variables are slightly more predictive—from 43.3% to 49.2% (Table 5). The relative importance is changed so that the order is diabetes (12%), smoking dose (6.6%), age (4.4%), male gender (4%), hypertension (3%), log-Lp(a) (3%), ratio of TC to HDL (2%), and positive family history (1%). Together, they explain 36% of the CAD severity variance in these patients.

When this subgroup analysis was further restricted to those male and female patients not taking lipid-lowering or β-blocking drugs, the variables are more predictive of severity in both male and female subgroups. Correctly classified cases were 49.4% for male (Table 5) and 65.4% for female (Table 5) patients. The order of relative importance for male patients is diabetes, Lp(a), age, ratio of TC to HDL-C, positive family history, smoking dose, and hypertension. They explain 35.7% of the variance in CAD severity. For female patients, the order is the same, and 56.9% of the variance in CAD severity is explained.

Although the number of disease vessels and Green Lane coronary scores quantitate different aspects of CAD severity, in our study these two variables were highly correlated (r=.821, P<.00001). Multiple least-squares linear regression analysis confirmed that smoking dose, ratio of TC to HDL-C, Lp(a), age, and TG are significantly associated with the score (multiple R = .27, P=.0001). These associations and their order of relative importance, as judged by their partial correlation coefficients, among all 594 patients were not different than those for the subgroup of 246 patients not receiving lipid-lowering or β-adrenergic-blocking drugs. The same patterns of associations were found among subgroups of patients without diabetes or without hypertension. Among female patients, TG was a more powerful predictor of the coronary score than ratio of TC to HDL-C and Lp(a), as we also found in the discriminant analysis. In the 252 patients who had a negative family history of coronary disease, low HDL-C was the only variable that correlated with the coronary score (r=.222, P=.007), whereas in the 242 patients with a positive family history, Lp(a) level was the only variable that correlated (r=.206, P=.011).

Independent Variables Associated
With Severity of Angina

As expected, a high proportion of patients with angina, particularly those with unstable angina, were receiving β-adrenergic–blocking drugs (χ²=31.22, P=.0001), and lipid-lowering drug therapy was more frequently used in these patients, although to a lesser extent (χ²=9.32, P=.01). Both hypertension (χ²=12.22, P=.002) and heavy smoking (χ²=41.40, P=.00004) were more prevalent in patients with unstable angina (n=60) than in those with stable angina (n=480) or without angina (n=54). Patients who had a positive family history of CAD or a history of diabetes also tended to be more likely to have unstable angina. The patients with unstable angina had higher coronary scores than those with stable angina (7.79±3.73 versus 6.24±4.4, P<.05) and a higher
log-Lp(a) level (1.46±0.59 versus 1.28±0.59, \( P < .05 \)). Patients without angina had much lower coronary scores (1.87±3.3) and a lower log-Lp(a) level (1.26±0.59).

Discussion

The findings of the present study relate to a representative group of consecutively investigated patients determined by cardiologists to require angiography. Thus, the variables associated with disease severity and the strength of associations we found may differ from patterns in the general population. For example, there may be a bias toward angiography in patients with atypical chest pain and a low likelihood of disease if the patient is also a long-term cigarette smoker. This would inflate the perceived extent of smoking in patients without disease or with only mild disease, and the actual relation between cigarette smoking and CAD severity in the general population may be stronger than seen in our data. The same bias could occur in patients with a positive family history of premature CAD and atypical chest pain and lead to our data underestimating the association between severity and a positive family history. On the other hand, the incidence of significant CAD will be much lower in the general population than in our patient group, and the relation between risk factors and severity of disease will be less than noted here. Despite these considerations, the results of a recently reported World Health Organization Monica Project (relating to a large general population aged 35 to 69 years in an adjacent region, from which some of our patients were referred) are consistent with ours in relation to the three risk factors assessed in that study. In patients without a previous CAD history, smoking was a stronger predictor of first acute myocardial infarction or fatal heart attack than hypertension or cholesterol.\(^{17}\)

A further problem is the confounding effect of lipid-lowering drug use in 90 patients and \( \beta \)-adrenergic blockers in 310 patients. The former would attenuate relations between lipids and disease severity, and the latter could enhance the effects of elevated TG and low HDL-C. Therefore, it was reassuring to find associations of the same distribution and order of magnitude in patients not receiving these drugs as those for the entire patient population and improved predictive power (\( \sim 10\% \)), even though the sample size was greatly reduced. Nevertheless, confining the analysis to patients not taking these drugs decreases the spectrum of patients for whom disease severity is being assessed, and a degree of epidemiological bias remains. Despite these inherent limitations, the study defines strong correlations with disease severity that could be relevant to secondary rather than to primary mechanisms of atherogenesis and to prevention. Discriminant function is an appropriate and robust method for assessing relations between risk factors and severity in this study, in which the independent variables are both continuous and binary, and there is an approximately even number of patients in each of the four subgroups in the analysis. Coronary angiography remains the only investigation permitting accurate premortem quantitation of CAD severity.

The results of the study emphasize the multifactorial nature of CAD severity risk. Of the variables we identified as being independently associated with severity, the most predictive variable—smoking dose—could correctly classify only 30% of cases (25% would be expected by chance). Combining all the independent variables, on the other hand, enabled from 43% to 65% of all cases to be correctly classified as having either no-, one-, two-, or three-vessel disease. But even after combining all these phenotypic factors, there remains a 35% to 60% chance of an incorrect prediction, so there are opportunities for refinements and definition of other risk factors such as hyperhomocysteinemia.\(^{18}\)

Predictors of CAD Severity in Men and Women

An important aim of the present study was to compare factors associated with severity in men and women, and some differences did emerge. It is known that women in the general population in the age group of our study have higher HDL-C and apo A-I levels than men of the same age.\(^{19,20}\) This is also true for our coronary population. Although diabetes, smoking dose, ratio of TC to HDL-C (or HDL-C), Lp(a), hypertension, and a positive family history were significant predictors in both sexes, Lp(a) was more important in men and smoking dose was more important in women. TG was predictive in women but not in men, in whom TG was actually higher. Also, the combined effect of all independent variables was more predictive in women than in men. We have no explanation for these differences. However, the more powerful association of lifetime smoking dose with severity in women than in men was also seen in the large Australian population study of the occurrence of CAD\(^{17}\) (referred to above). Additional explanation for our finding comes from the unequal distribution of heavy smokers in our study population—60% of men and 39% of women—which would tend to diminish the calculated smoking effect in men.

Smoking and CAD Severity

The relation between lifetime smoking history and severity of CAD and angina irrespective of current smoking habit is the finding in this study that is most relevant to the population approach to coronary prevention. Although it has been clearly demonstrated that within 1 or 2 years of stopping smoking the risk of subsequent coronary events declines,\(^{21-23}\) the present study clearly shows that total smoking dose is the variable most predictive of the extent of the structural change, rather than current or ex-smoking status. Our result is also in accordance with the findings of Weintraub et al\(^{13}\) in their evaluation of male patients at angiography. However, that investigation did not assess the strength of the association in relation to the contributions of other variables.

Ambrose et al\(^{24}\) showed in a longitudinal study of coronary patients that less-severe (<50%) luminal obstructions may frequently be the culprit lesions for later myocardial infarction and total coronary occlusion. Smoking cessation may diminish the likelihood of such events by reducing the propensity for platelets to aggregate\(^{24}\) and therefore the likelihood of unstable angina or acute myocardial infarction and explain the associated improved coronary event rate. Nevertheless, it is logical to expect long-term structural change as a consequence of total cigarette consumption by thrombogenic mechanisms, and perhaps by lowering HDL-C,\(^{25,26}\) and for these changes to occur progressively over many years. The present data provide a powerful argument for di-
recting antismoking programs toward the young, 30% of whom smoke regularly in Australia.27

Lipids and CAD Severity

Of all the lipid variables we measured, whether they were analyzed in relation to CAD severity in all patients or in the various subgroups of patients investigated, high ratio of TC to HDL-C (or low HDL-C) and high Lp(a) were consistently highly significant predictors of severity. TC, LDL-C, apo B, apo A-I, and ratio of apo B to apo A-I were much less predictive. This suggests that factors predicting the occurrence of CAD may not necessarily be of the same importance as those associated with CAD severity. In general, ratio of TC to HDL-C could be substituted for HDL-C and had slightly more predictive power than low HDL-C.

Circulating levels of Lp(a) are more closely genetically regulated than any of the other lipid variables we measured.28 When we assessed the quantitative variables and CAD severity using the coronary score in linear regression analyses in patients with and without a family history of premature CAD, the Lp(a) level was the only significant factor associated with the coronary score (r=.206, P=.011) in the former and the HDL-C level was the only factor associated (negatively) with the coronary score in the latter (r=-.222, P=.007). The finding of Durrington et al29 that Lp(a) levels could be substituted for a positive family history of premature CAD in male subjects after myocardial infarction is consistent with the present data, which suggest that Lp(a) is an important mediator of the family history contribution to coronary risk and to severity of CAD.

The contribution of high Lp(a) levels to the severity of disease also emerged from findings in patients with unstable angina. These patients had higher coronary scores and higher Lp(a) levels than those with stable angina. They also were more likely to have a positive family history of CAD or a history of hypertension or diabetes. Thus, as a group, they clearly had more-severe disease. Because platelet aggregation and thrombus formation associated with plaque rupture appear to be the usual mechanisms mediating a change from stable to unstable angina,9 the likelihood of elevated Lp(a) reducing the efficacy of thrombolysis30 may be of particular importance in this relatively acute situation.

In summary, this study of severity of CAD in men and women aged 65 years or less identifies a hierarchy of factors different in some respects from that known to be associated with the occurrence of CAD. It also substantiates an association with severity for other factors known to be predictive of increased cardiovascular risk (eg, diabetes, hypertension, male gender, and age). Of particular importance for preventive medicine is the clear association between severity and total smoking dose irrespective of current smoking habit and of its relatively greater importance in women. The study also defines an overriding importance of HDL-C, expressed as ratio of TC to HDL-C or as HDL-C, and of Lp(a) in the severity of CAD. At present, it is difficult to lower elevated Lp(a) except through the use of estrogens in postmenopausal women1,2 and high-dose nicotinic acid.33 However, dietary change, weight reduction in the obese, exercise, and, when indicated, statins, fibric acid derivatives, nicotinic acid, and lipid-lowering resins, used appropriately, all have a potential for improving ratio of TC to HDL-C and HDL-C levels. Also, recent studies indicate that these measures may stabilize progression of CAD and, in some instances, induce regression.34-36

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References


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