Risk Factors and Angiographic Coronary Artery Disease: A Report from the Coronary Artery Surgery Study (CASS)

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SUMMARY The findings for 14 risk variables were correlated with the results of coronary arteriography in 8807 patients registered in the interinstitutional Coronary Artery Surgery Study (CASS). Discriminant-function analysis revealed that age, sex, cigarette smoking and the level of blood cholesterol best distinguished between the groups with (6688 patients) and without (2119 patients) coronary artery disease. A family history of coronary artery disease and the presence of hypertension or diabetes were of additional, but less, discriminating value. The relative risk for coronary artery disease in patients with the combination of cigarette smoking and an elevated cholesterol level was high (> 4) in females age 55 years or younger and in males age 35 years or younger. Few females age 45 years or younger (seven of 97) had coronary artery disease when both of these risk factors were absent. In spite of these correlations, only limited gains accrued from the use of discriminant-function analysis in correctly allocating patients into disease and nondisease groups. This indicates that, while certain factors are significantly correlated with coronary angiographic findings, their value for predicting the presence of coronary artery disease is limited.

PREVIOUS SURVEYS1-4 of large, asymptomatic populations have established a firm relationship between clinical risk factors and the development of clinical manifestations of coronary artery disease (CAD). Characteristics such as age, sex, cigarette smoking, serum cholesterol level, hypertension and diabetes have identified groups at higher risk for later occurrence of angina, myocardial infarction and cardiac death. However, long-term follow-ups of asymptomatic groups have revealed that many subjects have remained free of manifestations of CAD even when multiple risk factors were present.2,5 The lack of specificity and low sensitivity of some of the clinical end points used in those studies, such as angina and sudden death, may have masked stronger associations between risk factors and CAD. Also, the risk factors may be related more to the clinical manifestations than to the CAD. Werk6 has reviewed problems in the conduct and interpretation of large clinical trials that study risk factors.

Coronary arteriography provides a precise anatomic delineation of the presence or absence of CAD during life and, if a large enough sample is available, allows risk factors to be correlated with the precise diagnosis. Accordingly, the registry data from the interinstitutional Coronary Artery Surgery Study (CASS), sponsored by the National Institutes of Health (NIH), were reviewed to correlate clinical risk factors with arteriographically defined coronary anatomy. This study was designed to determine whether, in patients considered for coronary arteriography, profiles of high and low incidence of CAD can be defined on the basis of risk factor data alone.

Methods

Since October 1974, clinical, laboratory and angiographic data have been collected in a standardized fashion and entered into a registry from consecutive patients undergoing coronary arteriography for clinically suspected CAD at 15 participating clinical centers of CASS. Patients with significant

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valvular disease or nonischemic cardiomyopathy are not included. Information from the initial history, physical examination and routine laboratory tests is coded in a prospective manner. The interpretation of coronary arteriograms is coded on specific forms as defined in the protocol. Twenty-seven separate anatomic segments of the coronary arterial circulation are defined. The degree of coronary arterial narrowing is recorded for each segment as the percentage of reduction in the luminal diameter. Data are entered into a central computer file at the CASS Coordinating Center at the University of Washington from peripheral on-site computer terminals.

The participants in CASS have devoted considerable effort to ensure a high quality of recorded data. Physicians and data technicians from each site meet regularly to review the techniques for patient interview and data collection. An extensive manual of operations outlines the definitions for each variable. At an annual meeting of the data technicians and the coordinating center, the performance and problems in obtaining and reporting data are reviewed. Data are transferred to the coordinating center from participating sites via an “intelligent” terminal (Datapoint 1100, Datapoint Corporation), which is programmed to provide multiple checks of data entered. Several routines for quality control are built into the computer program used at the coordinating center so that inconsistent or unreasonable entries are queried or rejected.

Each site is visited at least yearly by members of the National Heart, Lung and Blood Institute Project office and the coordinating center to discuss and to verify data and review hospital records. Monthly reports of completeness of data collection are reviewed by each principal investigator regularly.

Because of the importance of arteriography to the success of this study, there is enthusiastic cooperation among the participants to achieve a maximal uniform standard of performance. The quality of arteriography at each site is regularly reviewed. State of the art meetings of all participating angiographers are held at least yearly. Selected films are reviewed in an ongoing quality-control program. Some of the design and quality control aspects of CASS have been detailed by Kronmal et al.7 A full report is being prepared for publication (Killip T: Organization, Protocol and Clinical Data Base in the NIH Coronary Artery Surgery Study [CASS]).

From the mass of baseline data recorded, 14 variables were selected for study (table 1). Three variables relate to age and sex, three describe cigarette-smoking experience, five refer to the clinical history (appendix 1), two are clinical measurements and one is a laboratory test.

Methods for the measurement of serum cholesterol level varied among institutions and we did not attempt to standardize results from individual laboratories. Fasting blood glucose, triglyceride levels and packed cell volume were not included in the final analysis because they were not required data for CASS. Blood pressure recorded at patient entry into the study was not analyzed because it was variably influenced by concomitant treatments. Characteristics considered to be manifestations of disease (such as symptoms, ECG changes and findings on chest roentgenogram), rather than precursors, also were excluded from the discriminant analysis.

Stepwise linear discriminant function analysis, using program BMDP-77,8 was used to identify variables that were helpful in predicting the presence or absence of CAD. In an effort to minimize the effect of nonlinear interactions between variables that were considered to be important in the analysis, discriminant analyses were repeated in more homogeneous subsets.

In all, 13,540 patients were entered into the CASS registry between August 1975 and August 1977. Patient exclusions from the study group were 125 patients with a missing baseline form, 724 with previous coronary artery surgery, and 3884 with incomplete data for one or more of the 14 variables tested (in most instances the cholesterol value was missing). The remaining 8807 made up the study group.

From analysis of the arteriograms, the patients were divided into two groups: those with disease and those without disease. The disease group included 6688 patients with one or more coronary artery segments showing stenosis of 50% or more. The 2119 patients without disease either had no angiographic evidence of CAD (1702 patients) or had evidence of minimal disease only; that is, less than 50% narrowing (417 patients).

Results

Distribution of age and sex was different in the two groups. Subjects with disease had a mean age of 53.3 years and 84% were males, whereas those without disease had a mean age of 49.1 years and 51% were males. Because of these differences and the subsequent determination that the risk associated with cigarette smoking and serum cholesterol level differed with both age and sex, discriminant analyses were performed in

<table>
<thead>
<tr>
<th>Table 1. Risk Variables in Angiographic Coronary Artery Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Age (years) on entry into study</td>
</tr>
<tr>
<td>2. Age (years) at initial symptoms (INICAD)</td>
</tr>
<tr>
<td>3. Sex</td>
</tr>
<tr>
<td>4. Presently a cigarette smoker (CGPRES)*</td>
</tr>
<tr>
<td>5. Formerly a cigarette smoker (CGFORM)</td>
</tr>
<tr>
<td>6. Ever been a cigarette smoker (CIGNEV)</td>
</tr>
<tr>
<td>7. Hypertension (HYPTEN)†</td>
</tr>
<tr>
<td>8. Diabetes mellitus (DIABET)</td>
</tr>
<tr>
<td>9. Cerebrovascular disease (CERBVR)</td>
</tr>
<tr>
<td>10. Peripheral arterial disease (PERART)</td>
</tr>
<tr>
<td>11. Family history (FAMHIST)</td>
</tr>
<tr>
<td>12. Weight (kg)</td>
</tr>
<tr>
<td>13. Height (cm)</td>
</tr>
<tr>
<td>14. Plasma cholesterol (CHOLE) (mg/dl)</td>
</tr>
</tbody>
</table>

*For variables 4–11, 0 = no and 1 = yes.
†See appendix 1 for definitions of variables 7–11.
nine age–sex subgroups (tables 2 and 3). The mean weight and height of the subjects without disease were significantly greater than those of subjects with disease (tables 2 and 3). Discriminant analysis revealed that the combination of the history of cigarette smoking (especially CIGNEV*) and the level of blood cholesterol on entry into the study was the most powerful factor in distinguishing between the groups with and without CAD. Other variables, such as FAMHST, HYPEN, and DIABET* were of some help in some patient subsets (appendix 2) but had less predictive value.

The variables that entered early (which most often were CHOLES, CIGNEV and AGE) were the most helpful in discriminating. The negative coefficients of CHOLES and CIGNEV indicate that high cholesterol levels and high values for CIGNEV (that is, the patient had at some time been a smoker) increase the chance of classification into the disease group. Conversely, for variables with positive coefficients, a low value for the variable increases the chance of classification into the disease group.

An effect of patient exclusion due to incomplete data (for example, cholesterol level) was considered. Therefore, similar analyses were performed on patient data from one site where information was essentially complete for all variables. The resulting discriminant functions were not substantially different.

For each of the nine subsets, the discriminant function obtained (appendix 2) was tested for its ability to correctly allocate patients into either the disease group or the no-disease group. In the youngest group of males, application of the discriminant function improved the percentage correctly allocated from 50.1% to 70.3% (table 4). With increasing age, the incidence of disease increased and the additional value of the discriminant function score decreased.

The discriminant function results suggested age- and sex-dependent effects for some of the risk factors. To investigate this, relative risks* for cigarette smoking and high cholesterol values were calculated both singly and in combination (table 5). The relative risks were higher in the younger age groups and in females.
TABLE 3. Mean (=sd) Values for Females in No-disease (ND) and Disease (D) Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Females &lt;45 years ND</th>
<th>Females &lt;45 years D</th>
<th>Females 46-55 years ND</th>
<th>Females 46-55 years D</th>
<th>Females 56-65 years ND</th>
<th>Females 56-65 years D</th>
<th>Females &gt;65 years ND</th>
<th>Females &gt;65 years D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>40.0 ± 4.5</td>
<td>40.2 ± 4.2</td>
<td>50.8 ± 5.3</td>
<td>51.1 ± 2.8</td>
<td>59.6 ± 2.9</td>
<td>60.3 ± 2.7</td>
<td>69.2 ± 3.0</td>
<td>69.2 ± 2.9</td>
</tr>
<tr>
<td>INICAD</td>
<td>38.0 ± 5.4</td>
<td>38.4 ± 5.3</td>
<td>47.8 ± 4.8</td>
<td>48.3 ± 2.9</td>
<td>55.2 ± 7.3</td>
<td>56.3 ± 5.9</td>
<td>65.0 ± 8.6</td>
<td>64.1 ± 5.6</td>
</tr>
<tr>
<td>CGPRES</td>
<td>0.37 ± 0.48</td>
<td>0.59 ± 0.49</td>
<td>0.27 ± 0.45</td>
<td>0.47 ± 0.50</td>
<td>0.14 ± 0.45</td>
<td>0.28 ± 0.45</td>
<td>0.07 ± 0.25</td>
<td>0.14 ± 0.35</td>
</tr>
<tr>
<td>CGFORM</td>
<td>0.19 ± 0.39</td>
<td>0.25 ± 0.41</td>
<td>0.21 ± 0.47</td>
<td>0.33 ± 0.43</td>
<td>0.25 ± 0.43</td>
<td>0.35 ± 0.48</td>
<td>0.18 ± 0.30</td>
<td>0.29 ± 0.46</td>
</tr>
<tr>
<td>CIGNEV</td>
<td>0.56 ± 0.50</td>
<td>0.84 ± 0.50</td>
<td>0.48 ± 0.50</td>
<td>0.81 ± 0.50</td>
<td>0.39 ± 0.49</td>
<td>0.62 ± 0.49</td>
<td>0.24 ± 0.44</td>
<td>0.43 ± 0.50</td>
</tr>
<tr>
<td>HYPHEN</td>
<td>0.26 ± 0.44</td>
<td>0.30 ± 0.46</td>
<td>0.36 ± 0.50</td>
<td>0.48 ± 0.50</td>
<td>0.35 ± 0.48</td>
<td>0.53 ± 0.50</td>
<td>0.49 ± 0.51</td>
<td>0.53 ± 0.50</td>
</tr>
<tr>
<td>DIABET</td>
<td>0.07 ± 0.11</td>
<td>0.08 ± 0.19</td>
<td>0.07 ± 0.17</td>
<td>0.15 ± 0.16</td>
<td>0.08 ± 0.16</td>
<td>0.15 ± 0.20</td>
<td>0.18 ± 0.07</td>
<td>0.17 ± 0.05</td>
</tr>
<tr>
<td>CEREBRV</td>
<td>0.17 ± 0.38</td>
<td>0.10 ± 0.31</td>
<td>0.19 ± 0.39</td>
<td>0.18 ± 0.38</td>
<td>0.19 ± 0.39</td>
<td>0.16 ± 0.37</td>
<td>0.37 ± 0.37</td>
<td>0.38 ± 0.35</td>
</tr>
<tr>
<td>PERART</td>
<td>0.58 ± 0.49</td>
<td>0.56 ± 0.50</td>
<td>0.52 ± 0.49</td>
<td>0.61 ± 0.50</td>
<td>0.47 ± 0.49</td>
<td>0.51 ± 0.50</td>
<td>0.31 ± 0.37</td>
<td>0.37 ± 0.35</td>
</tr>
<tr>
<td>FAMHST</td>
<td>66.9 ± 15.6</td>
<td>64.2 ± 13.8</td>
<td>66.7 ± 12.6</td>
<td>65.3 ± 12.3</td>
<td>63.5 ± 10.9</td>
<td>65.3 ± 14.5</td>
<td>62.9 ± 9.6</td>
<td>62.4 ± 10.5</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>162.2 ± 6.8</td>
<td>161.3 ± 6.6</td>
<td>162.1 ± 6.3</td>
<td>160.1 ± 6.2</td>
<td>160.5 ± 6.2</td>
<td>160.3 ± 6.9</td>
<td>161.0 ± 7.0</td>
<td>159.0 ± 6.1</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>214 ± 47</td>
<td>235 ± 47</td>
<td>225 ± 47</td>
<td>249 ± 47</td>
<td>232 ± 47</td>
<td>252 ± 47</td>
<td>248 ± 47</td>
<td>256 ± 47</td>
</tr>
</tbody>
</table>

Significantly different from no-disease group (two-sample, one-sided t test):
* p < 0.05, p < 0.01;
† p < 0.005;
‡ p < 0.0025;
§ p < 0.001.
¶ Values are coded as in table 1.

The presence of one or both risk factors had the greatest relative effect in the young female subjects (figs. 1 and 2). However, although absolute risks were higher in the older patients, a history of cigarette smoking or a high plasma cholesterol level had less relative effect in the older age groups.

The group without disease resembled the general population with regard to smoking habits and mean cholesterol level, while the disease group did not (table 6).

Discussion

In this group of patients undergoing coronary arteriography, certain risk factors (for example, age, sex, cigarette smoking and serum cholesterol level) were correlated significantly with the finding of obstructive CAD. In some subsets, family history, diabetes and hypertension also had significant predictive value. These findings support other studies relating the presence of these factors to the development of clinical manifestations of CAD.14-8

The large data base available permitted multivariate analyses in nine subsets of patients, thus reducing the possibility that nonlinear interactions of other variables with age and sex might obscure important results. An important finding was not only that increasing age and male sex were powerful risk factors for CAD, but also that their presence overwhelmed or "washed out" the effect of other risk factors; that is, in the oldest group of males, other risk factors had only a weak effect. Conversely, in the absence of these two most important risk factors, that is, in females 45 years old or less, other risk factors such as cigarette smoking and serum cholesterol level had considerable importance. A recent angiographic study by Waters et al.,9 corroborates our findings in these young women.

The age dependence of these effects has been previously noted in studies relating risk factors to clinical end points.10-13 It also has been observed in studies relating serum cholesterol level to presence and extent of disease.14,15 The small number of patients in previous angiographic studies generally has not allowed application of the multivariate analytic techniques used here. However, univariate analyses have shown a relationship between total cholesterol, low-density lipoprotein cholesterol, and triglyceride levels and the presence of CAD.8,14-24 In one other study28 in which multivariate analyses were performed, the combination of risk factors of age,
TABLE 4. Results of Discriminant Function Analysis for Coronary Artery Disease

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>% correctly allocated using random distribution*</th>
<th>% correctly allocated using discriminant function</th>
<th>Gain in % correctly allocated†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤35</td>
<td>50.1</td>
<td>70.3</td>
<td>20.2</td>
</tr>
<tr>
<td>36-45</td>
<td>62.5</td>
<td>75.9</td>
<td>13.4</td>
</tr>
<tr>
<td>46-55</td>
<td>74.5</td>
<td>85.1</td>
<td>10.6</td>
</tr>
<tr>
<td>56-65</td>
<td>83.6</td>
<td>90.4</td>
<td>6.8</td>
</tr>
<tr>
<td>≥66†</td>
<td>90.5</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Females</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤45</td>
<td>54.5</td>
<td>66.8</td>
<td>12.3</td>
</tr>
<tr>
<td>46-55</td>
<td>51.6</td>
<td>71.4</td>
<td>19.8</td>
</tr>
<tr>
<td>56-65</td>
<td>52.4</td>
<td>69.9</td>
<td>17.5</td>
</tr>
<tr>
<td>≥66</td>
<td>64.6</td>
<td>77.2</td>
<td>12.6</td>
</tr>
</tbody>
</table>

*The percentage correctly allocated when patients were randomly assigned to disease (D) or no-disease (ND) groups according to proportion in each group.
†The percentage correctly allocated using discriminant function minus the percentage correctly allocated using random allocation in each group.
†No variable significantly discriminated in this group (see appendix 2).

TABLE 5. Relative Risks and Their 95% Confidence Intervals in Patients With Coronary Artery Disease

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤35</td>
<td>2.73  (1.32-5.63)</td>
<td>2.50  (0.68-9.24)</td>
</tr>
<tr>
<td>36-45</td>
<td>1.39  (0.98-1.97)</td>
<td>3.23  (1.87-5.58)</td>
</tr>
<tr>
<td>46-55</td>
<td>1.18  (0.99-1.41)</td>
<td>2.60  (1.95-3.46)</td>
</tr>
<tr>
<td>≥56</td>
<td>1.04  (0.92-1.19)</td>
<td>1.34  (1.15-1.56)</td>
</tr>
</tbody>
</table>

Smokers vs nonsmokers

High vs low cholesterol

Both

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤35</td>
<td>7.12  (2.80-18.08)</td>
<td>∞†</td>
</tr>
<tr>
<td>36-45</td>
<td>1.77  (1.22-2.57)</td>
<td>5.85  (2.65-12.92)</td>
</tr>
<tr>
<td>46-55</td>
<td>1.37  (1.13-1.66)</td>
<td>4.12  (2.83-6.00)</td>
</tr>
<tr>
<td>≥56</td>
<td>1.09  (0.96-1.24)</td>
<td>1.67  (1.36-2.05)</td>
</tr>
</tbody>
</table>

*Smokers with high cholesterol vs nonsmokers with low cholesterol.
†Zero disease of 12 patients with neither risk factor vs seven diseased of nine patients with both risk factors (p < 0.01, Fisher’s exact test).

cholesterol and cigarette smoking was best correlated with an angiographic occlusion score.

The relative risk associated with both cigarette smoking and an elevated cholesterol level was much greater in the younger patients. For females age 55 years or younger and males age 35 years or younger with this combination of factors, the risk of having CAD was more than four times greater than in those with neither factor present. This is further emphasized by the observation that nine of every 10 patients less than 45 years of age who have CAD had been smokers at some time.

Community studies, such as the Framingham study, have not noted such a striking risk for cigarette smoking and cholesterol level in young adults. Reliance on clinical end points (such as uncomplicated angina pectoris) may have obscured a stronger relationship. Others have shown that a high proportion of young women with the clinical diagnosis of angina pectoris fail to show evidence of CAD at arteriography. This observation may at least partially explain the apparently better prognosis for women with uncomplicated angina pectoris in the Framingham study.

Although risk factors are clearly associated with
both the manifestations of CAD and angiographically demonstrated CAD, the factors are not accurate predictors of finding the disease at arteriography. A small gain in the percentage correctly allocated to disease and no-disease groups was achieved using the results of discriminant-function analysis. However, such a small gain is of limited clinical value. Our results do not support the conclusion of Salel et al.\textsuperscript{29} that risk factors may be used in a practical clinical manner to forecast the presence of CAD in individual patients.

In the subset of females age 45 years or younger, who are nonsmokers with cholesterol levels less than 250 mg/dl, the findings for risk variables helped predict the absence of disease. In spite of an overall 76\% incidence of CAD in the study population, this select subgroup manifested only a 7\% (seven of 97) incidence of CAD. Of the seven affected patients, five had hypertension or type IV hyperlipidemia (or both). Clearly, in young women without risk factors, the clinician should be especially cautious before making the clinical diagnosis of obstructive CAD.

In contrast to studies using clinical manifestations for diagnosis of CAD,\textsuperscript{30} however, the present analysis, based on anatomic proof of CAD, revealed that patients with angiographic abnormalities were shorter and weighed less than those with no disease. The reason for this finding is not clear, although a number of explanations could be advanced. Obesity may not be a risk factor for disease, but may increase the likelihood that disease will produce symptoms. Obese patients with symptomatic CAD might have reduced their weight before arteriography or not have been selected for arteriography because they had suffered myocardial infarction or had died.

The data presented herein are subject to certain criticisms. First, although the data on risks were coded prospectively, they were collected only a day or two before arteriography. The patient's clinical history and laboratory values (for example, serum cholesterol level), therefore, might not truly reflect the conditions existing during the development of CAD. Estimates made at this time, however, would accurately represent data available to the physician evaluating the likelihood of CAD in symptomatic patients. Second, the measurements of serum cholesterol level among the participating institutions were not standardized. We repeated the discriminant-function analyses on data obtained from one of the larger participating institutions where measurement techniques were uniform and data essentially complete.

\begin{table}
\centering
\caption{Comparisons of Cholesterol Levels and Smoking Habits of Disease and No-disease Groups}
\begin{tabular}{|c|c|c|c|}
\hline
Age (years) & General & No disease & Disease \\
& population & & Smoking habits (% who have smoked)\textsuperscript{*} \\
& & & \\
\hline
Males & & & \\
\leq 24 & 51 & 53.3 (n = 15) & 66.7 (n = 3) \\
25-44 & 76 & 76.7 (n = 404) & 90.5 (n = 870) \\
45-64 & 77 & 70.6 (n = 630) & 83.1 (n = 4,203) \\
\geq 65 & 63 & 73.3 (n = 30) & 69.8 (n = 563) \\
\hline
Females & & & \\
\leq 24 & 38 & 33.3 (n = 3) & No cases \\
25-44 & 54 & 56.5 (n = 223) & 85.8 (n = 113) \\
45-64 & 47 & 45.2 (n = 752) & 70.6 (n = 744) \\
\geq 65 & 19 & 26.2 (n = 61) & 46.9 (n = 192) \\
\hline
Cholesterol level (mg/dl)\textsuperscript{+} & & & \\
Males & & & \\
\leq 24 & — & 168 (n = 15) & 419 (n = 3) \\
25-34 & 201 & 210 (n = 108) & 248 (n = 105) \\
35-44 & 221 & 218 (n = 296) & 240 (n = 765) \\
45-54 & 229 & 216 (n = 403) & 238 (n = 2,123) \\
\geq 55 & 229 & 214 (n = 257) & 228 (n = 2,643) \\
\hline
Females & & & \\
\leq 24 & — & 214 (n = 4) & — \\
25-34 & 194 & 200 (n = 20) & 250 (n = 14) \\
35-44 & 207 & 213 (n = 203) & 229 (n = 99) \\
45-54 & 232 & 225 (n = 435) & 249 (n = 296) \\
\geq 55 & 245 & 233 (n = 378) & 252 (n = 640) \\
\hline
\end{tabular}
\end{table}


\textsuperscript{+}Data from the Health and Nutrition Examination Survey. Advance data from Vital and Health Statistics of NCHS. USD HEW #5. February 22, 1977.
on all patients, but did not find any enhancement of the predictive value for serum cholesterol levels. Third, the possible influence of medical therapy on the blood levels of cholesterol at the time of coronary arteriography must also be considered. At the time of entry into the study, 4.6% of patients in the disease group and 2.4% of patients in the no-disease group were receiving lipid-lowering agents. Of the 5860 patients with cholesterol levels lower than 250 mg/dl, only 3.3% were receiving lipid-lowering agents. These observations make it unlikely that therapy at the time of arteriography was an important complicating factor. Fourth, potentially important risk factors such as plasma triglycerides, plasma high-density lipoprotein, estrogen, progestin use, and duration of natural or surgical menopause have not been assessed because these data were not collected. Finally, the results are derived from a selected group — patients selected for arteriography because of symptoms. The group without anatomic evidence of CAD resembles the general population in incidence of smoking and level of blood cholesterol, while the group with proved CAD does not.

Although providing the best weighted combination of variables for distinguishing between groups with and without arteriographic disease, the linear discriminant function may not accurately represent the strength of these variables as causal factors. For example, if a single factor, such as cigarette smoking, were eventually to be associated with CAD in all patients, a single arteriogram obtained at some moment in the smoking patient's life might or might not uncover the disease because the time of onset and rate of progression will vary. Furthermore, a risk factor with a very strong causal influence may also lead to complications of CAD, such as myocardial infarction or death, and thus, affected patients would not be selected for arteriography. However, the existence of a correlation between risk factors and the presence of CAD does not necessarily imply a cause-and-effect relationship. For example, an elevated cholesterol level might be caused by some unobserved, third factor that also causes CAD.

In conclusion, the large number of carefully evaluated patients undergoing coronary arteriography in CASS has permitted a critical review of the relationship between risk factors and CAD. While a significant relationship between certain factors and angiographic CAD has been demonstrated, information on risk factors was of limited value in predicting which individual patient would be shown to have anatomic proved CAD.

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*Denotes principal investigator.
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APPENDIX 1. Definitions for Clinical History Variables

Hypertension:
The patient has been told that he has hypertension (or high blood pressure) and either has received medication for it or has a written medical history of treated hypertension (or has both).

Diabetes mellitus:
The patient has been told that he has diabetes and has been treated for diabetes by diet or medication (or both) or the patient has a written medical history of treated diabetes mellitus.

Cerebrovascular disease:
The patient had a stroke that resulted in transient or permanent abnormalities in vision, speech or motor functions, or the patient has a written medical history of a cerebrovascular accident or transient ischemic attacks, with abnormalities in vision, speech or motor function that usually return to normal.

Peripheral arterial disease:
The patient has been told by a physician that he has extremely poor blood circulation in his legs and has cramping pain in exercise in the buttocks, thighs or calves, which is relieved by rest and reproduced by the same exercise. This condition is considered present if noted in the written medical history when the patient has claudication in the lower extremities or absent pulses in the lower extremities on physical examination.

Family history:
Patient had direct blood relative (parents, siblings, aunts, uncles) with symptoms of coronary artery disease before the age of 55 years. Included are those with angina pectoris, myocardial infarction and sudden, abrupt death without other obvious cause.

APPENDIX 2. The Actual Discriminant Functions Used in the Nine Subsets*

<table>
<thead>
<tr>
<th>Sex and age (years)</th>
<th>Functions†</th>
</tr>
</thead>
</table>
| Males ≤ 35         | 5.61738 − 0.01529 CHOLE — 1.18230 CIGNEV — 0.94046 CGFORM + 0.00320 WEIGHT − 0.10660 AGE │
| Males 36–45        | 4.64973 − 0.00942 CHOLE — 1.09891 CIGNEV — 0.11893 AGE + 0.00182 WEIGHT − 0.29976 FAMHST │
| Males 46–55        | 4.17309 − 0.00890 CHOLE − 1.12813 CIGNEV — 0.11747 AGE + 0.04582 INICAD − 0.29456 FAMHST │
| Males 56–65        | 6.15033 − 0.15959 AGE − 0.00631 CHOLE − 0.66391 CIGNEV + 0.04918 INICAD + 0.36181 HYPTEN │
| Males ≥ 66         | No variables significantly discriminated │
| Females ≤ 45       | 3.44090 − 1.40545 CIGNEV − 0.00818 CHOLE │
| Females 46–55      | –4.38366 − 1.67637 CIGNEV − 0.00776 CHOLE − 1.00853 DIABET + 0.04949 HEIGHT − 0.46863 HYPTEN │
| Females 56–65      | 9.62533 − 1.46465 CIGNEV − 0.83345 HYPTEN − 0.00806 CHOLE − 0.11795 AGE − 0.70789 DIABET + 0.47091 CGFORM │
| Females ≥ 66       | −10.04334 − 0.86324 CIGNEV + 0.05703 HEIGHT† │

*The variables are listed in the order in which they entered the function.
†All variables added significantly to the discriminant function at p < 0.001, except those indicated †(p < 0.05).
Risk factors and angiographic coronary artery disease: a report from the coronary artery surgery study (CASS).
R E Vlietstra, R L Frye, R A Kronmal, D A Sim, F E Tristani and T Killip, 3rd

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