Fifteen year survival study of patients with obstructive coronary artery disease

William J. Proudfit, M.D., Albert V.G. Bruschke, M.D., Julie P. MacMillan, M.P.H., George W. Williams, Ph.D., and F. Mason Sones Jr., M.D.

ABSTRACT Survival rates were determined for a group of 598 patients in whom severe coronary disease was demonstrated by arteriography; initially they were treated medically and were followed-up for 15 years. Deaths due to noncoronary causes were uncommon (5% of total) in the first 5 year period but were frequent (36%) in the third period. Survival rates were 48%, 28%, 18%, and 9% for patients with single-, double-, triple-, and left main artery disease, respectively. Abnormalities documented by ventriculography were related to survival. In 386 patients who would have been candidates for bypass surgery, survival rates were 58%, 35%, 26%, and 11% for those with single-, double-, triple-, and left main artery disease, respectively. Cardiac survival curves for single-, double-, and triple-artery disease in candidates for surgery and curves constructed on the basis of 3% mortality per artery per year corresponded fairly closely. When an abnormal electrocardiogram (ECG) is considered as a single variable in multivariate analysis, 5 year survival rates of candidates for surgery were influenced by the following in order of importance: abnormal ECG, symptoms at least 5 years in duration, triple-artery disease, double-artery disease, and arteriosclerosis obliterans. A simple prognostic stratification was devised that used only ECGs and duration of symptoms for each subset based on the number of arteries affected.


Because of problems in the study of the natural history of coronary disease, many of which are insurmountable, no completely satisfactory investigation of survival is possible. The present objective is to update studies in a large group of patients proved to have severe coronary disease by arteriography and to examine the association between clinical and invasively obtained variables and survival.

Methods

The methods and terms used in the study have been described. At 15 year follow-up, three of 601 patients who had severe coronary disease were excluded from the series on the basis of the original criteria for selection: two were found to have had poudrage operations less than 1 year after catheterization, and one had had a Vineberg operation at 3 years. One of the three had single-artery disease, and two had involvement of two arteries; two had functional class II angina, and the other had experienced prolonged attacks of pain. Two additional patients had had bypass operations at 85 and 88 months, so these were considered dropouts at those dates instead of 10 year survivors. Fifteen year follow-up was obtained in all of the remaining 598 patients except for one, a criminal who was incarcerated at the time of the previous follow-up.

Several additional methods were required. Arteriosclerosis obliterans was coded if a femoral or posterior tibial pulse was absent or when diminished femoral pulses or femoral bruits were associated with intermittent claudication. Stroke was diagnosed if there was a history of sudden loss of motor function of an extremity or rapid onset of aphasia. For comparison with another report, electrocardiograms (ECGs) were recoded according to the Minnesota criteria for ST segments without knowledge of survival status.

Cardiac survival rates have been reported, although total survival rates (all deaths counted) were studied for some subsets. Total survival is used in the present study, with a few exceptions specifically noted. Patients were considered dropouts for actuarial survival studies at the middle of the year in which coronary operation occurred. For cardiac survival, deaths due to noncardiac causes were considered dropouts in the year of occurrence. Survival rates were calculated by the actuarial method. Equality of survival curves was tested by a nonparametric rank test, the Breslow statistic. Multivariate statistical analyses used the Cox proportional hazards model, permitting a stepwise selection of covariates significantly associated with survival; at each step the removal criterion was $p \geq .15$, and the entry criterion was $p \leq .10$. The test statistic was adjusted for variables that had already been entered in the model. Details of statistical methods will be supplied on request.

Sixty of the original 598 patients had operations for coronary disease during the period of the study.

Results

During the first 5 years, 95% of all deaths were due to coronary disease, but the percentages were 84% and

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64% for the second and third 5 year periods, respectively. Figure 1 shows the total survival curves in relation to the number of arteries narrowed at least 50%. In general the curves for triple-artery disease and involvement of the left main coronary artery are similar; survival rates were best for those with single-artery disease, and the curve for those patients with involvement of two arteries lies between the curves for those with double- and triple-artery disease. Differences in survival rates dependent on the number of arteries affected are significant (p < .001).

Although the survival rate was high at 5 years for patients with single-artery disease, there was a distinct change in the survival curves at 4 years. The change in slope was more striking for patients with lesions of the circumflex and right coronary arteries than that for patients in whom the anterior descending artery was involved. Cardiac survival rates of subsets were also studied because the relatively low mortality in single-artery disease makes deaths due to noncardiac reasons more important statistically. Cardiac survival rates were 90%, 73%, and 66% for those with right coronary artery disease (n = 91) at 5, 10, and 15 years; cardiac survival rates were 80%, 70%, and 64% for those with circumflex disease (n = 31) and 81%, 56%, and 46% for those in the subset in which the anterior descending artery was involved (n = 74). Comparative survival rates for those with circumflex artery disease were limited by the small sample size, but survival rates were higher for the 91 patients with right coronary artery disease than for the 74 who had anterior descending artery involvement (p < .05). Most patients (79%) who had severe obstruction of one artery had either mild (n = 70) or moderate (n = 84) narrowing of one or both of the other coronary arteries. Cardiac survival rates were higher for patients who had lesions causing mild obstruction (93% vs 78% at 5 years, and 67% vs 47% at 15 years; p = .04).

Survival rates for patients with three degrees of involvement of single arteries (50 to 89%, 90 to 99%, and total occlusion) showed a trend toward higher mortality with increasing degrees of obstruction. All subsets of patients were grouped together and cardiac survival rates were calculated, but no statistically significant difference in the subsets based on severity of obstruction could be demonstrated. Similar studies of double- and triple-artery disease showed no consistent associations with survival rates, which were related more to the number of arteries severely narrowed than to the severity of arterial narrowing. In patients with double-artery disease, the combination of lesions of the anterior descending and circumflex arteries showed a trend toward lower survival rates, but only 39 patients were in this subset. In patients having left dominant circulation, 5 and 15 year survival rates were 69% and 46% for the 13 who had lesions of the anterior descending artery, 60% and 20% for the five with circumflex involvement, and 40% and 20% for the 10 who had both types of lesions. Because of the small sample size, a test of equivalence of the survival curves would have low power.

Division of the patients who had left main coronary artery disease into subsets characterized by the number of other arteries affected was not productive, perhaps because of the small numbers of patients. No significant difference was found at 5 years for single-, double-, or triple-artery disease for the 10, 23, and eight patients in these subsets, respectively, and the three patients who had no severe involvement of other arteries all died within 6 years. Three of the 23 who had severe disease in two other arteries survived 15 years, but all other patients in whom the left main artery was involved died. Differences in survival rates based on severity of obstruction of at least 50% of the left main coronary artery were not significant statistically. Two patients had total occlusion and died at 48 and 71 months. Seven had at least 90% narrowing of a patent artery: four died in the first year, one in the tenth year, one was living at 187 months, and one had bypass operation at 145 months. Thirty-five patients had less than 90% obstruction: seven died within 1 year, 17 within 5 years, 10 between 5 and 10 years, five between 10 and 15 years, and one at 200 months; one was living at 193 months, and one had bypass operation at 111 months. The numbers of patients in subsets were small.
Influence of minor lesions of the left main artery was studied. For patients with involvement of the other three arteries, survival rates at 5 years were 50% for those without lesions of the left main artery ($n = 106$), 44% for those with mild (<30%) lesions of the left main artery ($n = 23$), and 10% for those with moderate (30% to <50%) lesions of the left main artery ($n = 10$). Survival rates at 15 years were 20%, 12%, and 10% for the same subsets, respectively. Survival rates at 5 years were lower for patients with moderate lesions of the left main artery than for those with mild narrowing (nine of 10 died vs 13 of 23), but the difference is not significant statistically, perhaps because the subsets are too small to detect a difference. Mild-to-moderate narrowing of the left main artery did not affect survival rates of patients with single- or double-artery disease.

Total survival rates were related to ventriculographic findings and are shown in figure 2. A normal ventriculogram was associated with the best prognosis, and localized impairment of left ventricular contractility had a mildly adverse effect. Ventricular aneurysm and moderate or severe impairment of left ventricular contractility were ominous signs, with diffuse impairment being more serious, especially in the early years of follow-up. The influence of the number of arteries narrowed and the presence or absence of localized impairment of contractility on prognosis is shown in figure 3. No significant difference in the subsets determined by ventriculography was found for disease of two arteries, but there was a significant difference in the single- and triple-artery subsets (both $p = .03$).

![FIGURE 3](image)

**FIGURE 3.** Survival rate for patients with single- and triple-artery disease with normal ventricles and localized impairment of ventricular contractility. The two curves for double-artery disease did not differ significantly.

Of 598 patients, 386 would have been candidates for bypass surgery by 1975 criteria. Total survival rates by number of arteries severely narrowed are shown in figure 4. Cardiac survival rates compared with survival rates calculated on the basis of fixed mortality of 3%, 6%, 9%, and 12% per year are shown in table 1 (constant hazard function). Correspondence of the observed and the hypothetical figures is fairly close except for the lower observed mortality for single-artery disease in the first 5 years and the lower observed mortality in the tenth to fifteenth year for patients who had disease of three arteries. All the survival figures are higher for candidates for surgery than that for the whole group because of exclusion of patients who had...
Pathophysiology and Natural History—Coronary Artery Disease

**TABLE 1**
Cardiac survival rates of candidates for surgery compared with fixed rates

<table>
<thead>
<tr>
<th>Artery</th>
<th>Fixed rate mortality/yr (%)</th>
<th>Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td>5 yr</td>
</tr>
<tr>
<td>One</td>
<td>3</td>
<td>92</td>
</tr>
<tr>
<td>Two</td>
<td>6</td>
<td>69</td>
</tr>
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<td>Three</td>
<td>9</td>
<td>58</td>
</tr>
<tr>
<td>LMA</td>
<td>12</td>
<td>56</td>
</tr>
</tbody>
</table>

LMA = left main coronary artery.
Survival at 6 years: 85% for one artery.

Serious impairment of left ventricular function from the surgical group (p < .001).

Survival rates were lower for candidates for surgery who had moderate narrowing of the artery or arteries not severely affected than for those whose narrowing was mild for both single- and double-artery disease, but the differences were not significant statistically. Patients who had severe narrowing of two main arteries (without left main artery obstruction) were divided into groups according to the three possible combinations of double-artery disease. No prognostic difference was found.

Severity of obstruction in single-, double-, and triple-artery disease was analyzed for candidates for surgery in a manner similar to that for the whole group (table 2). The results were also similar, with the number of arteries affected generally more important prognostically than the severity of obstruction.

The influence of localized impairment of left ventricular contractility is shown for candidates for surgery in figure 5. The survival rate was 30% at 15 years for those with local impairment compared with 43% for patients who had normal ventricles (p = .03).

**TABLE 2**
Degree of obstruction, number of arteries, and survival rate in candidates for surgery

<table>
<thead>
<tr>
<th>Maximal lesion 50%–89%</th>
<th>Maximal lesion 90%–100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of arteries</td>
<td>No. of patients</td>
</tr>
<tr>
<td>1</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>10</td>
</tr>
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</tbody>
</table>

Survival rates were poor for patients who had diffuse impairment of contractility or ventricular aneurysm (with 15 year survival rates of 21% and 16%, respectively), and overall differences in survival rates based on ventriculographic findings were significant (p = .0013). Anterior impairment of left ventricular contractility in candidates for surgery (n = 51) was similar prognostically to inferior impairment in candidates for surgery (n = 32) at all intervals (15 year survival rates of 28% and 31%, respectively).

Patients in various subsets characterized by presence or absence of collateral circulation showed 10 year survival rates that were higher for those not having visible collaterals. The exception was the subset for single-artery disease in which those patients who had collateral circulation had a higher survival rate. Extension of the study to 15 years showed that this higher survival rate had persisted, but the difference was not significant statistically. An attempt was made to analyze survival rates in patients with double-artery disease to determine the influence of jeopardy of the
collaterals by the presence of disease of at least 50% narrowing proximal to the origin of the collateral vessels from the supplying artery in the absence of myocardial infarction. Because of the small sample size, a test of significance would not be able to detect a difference in the two survival curves.

Candidates for surgery who had end-diastolic pressures greater than 20 mm Hg had lower survival rates than those whose pressure was 20 mm Hg or lower (p = .03). Survival rates were not affected significantly by elevations to 16 to 20 mm Hg.

Table 3 shows the relationship of total actuarial survival rates to certain clinical variables. Analyses based on cardiac survival rates yielded similar results. The survival rate was higher for patients less than 50 years old than for the older age group. Disease of a single artery was slightly more common (34% vs 31%) and lesions of the left main artery were less prevalent (6% vs 9%) in the younger group, but the survival rate was higher for younger patients in each subset of single-, double-, and triple-artery disease compared with that of the older group. There was no sex difference in survival rates. Those whose symptoms were more than 5 years in duration had lower survival rates than those whose symptoms were of shorter duration. There was a trend toward a higher survival rate for patients whose symptoms were less than 1 year in duration compared with those who had symptoms for 1 to 5 years. In subsets of patients classified by the number of arteries affected, the survival rate was lower for those having symptoms for longer than 5 years than for patients having shorter histories. Those whose angina pectoris was severe had a lower survival rate than those with milder angina when functional classes I and II are compared with classes III and IV. Congestive heart failure was an adverse factor as was evidence of arteriosclerosis obliterans. Deaths occurred in 41 of 46 eligible patients (including two patients who underwent operation and were considered dropouts) with arteriosclerosis obliterans, and 38 of the deaths were cardiac related. The number of patients with a history of stroke was too small (n = 10) for meaningful analysis. Family history of coronary disease did not affect prognosis. Heavy smoking appeared to have an adverse effect, but with lesser use of cigarettes, risk of smoking was not statistically significant. Although combined systolic and diastolic hypertension influenced prognosis, systolic hypertension alone did not.

TABLE 3
Clinical variables in 598 patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Subset</th>
<th>No. of patients</th>
<th>Survival (%)</th>
<th>Level of significance (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&lt;50 yr</td>
<td>306</td>
<td>92 74 56 38</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td>≥50 yr</td>
<td>292</td>
<td>82 56 38 24</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>M</td>
<td>534</td>
<td>88 64 44 30</td>
<td></td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>64</td>
<td>92 64 40 32</td>
<td></td>
</tr>
<tr>
<td>Duration of</td>
<td>&lt;5 yr</td>
<td>420</td>
<td>89 70 47 34</td>
<td></td>
</tr>
<tr>
<td>history of pain</td>
<td>≥5 yr</td>
<td>174</td>
<td>84 44 35 23</td>
<td>&lt;.0001</td>
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<td>Functional class</td>
<td>I</td>
<td>12</td>
<td>92 67 58 58</td>
<td></td>
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<tr>
<td>angina</td>
<td>II</td>
<td>189</td>
<td>92 67 46 36</td>
<td></td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>137</td>
<td>83 56 37 22</td>
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<td></td>
<td>IV</td>
<td>41</td>
<td>73 49 37 28</td>
<td></td>
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<td>Congestive failure</td>
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<td></td>
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<tr>
<td></td>
<td>Present</td>
<td>37</td>
<td>51 22 5 3</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>ASO</td>
<td>Absent</td>
<td>550</td>
<td>89 66 45 32</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>48</td>
<td>85 44 20 13</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Smoking</td>
<td>None</td>
<td>175</td>
<td>92 70 49 37</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥2 packs</td>
<td>78</td>
<td>85 60 38 23</td>
<td>.03</td>
</tr>
<tr>
<td>Blood pressureA</td>
<td>Normal</td>
<td>412</td>
<td>88 67 47 33</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>77</td>
<td>90 51 22 14</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>None</td>
<td>561</td>
<td>89 65 44 32</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clinical</td>
<td>22</td>
<td>73 41 23 14</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>≤250 mg/dl</td>
<td>234</td>
<td>86 65 41 27</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>&gt;250 mg/dl</td>
<td>364</td>
<td>89 63 44 33</td>
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</tbody>
</table>

ASO = arteriosclerosis obliterans.

*A Blood pressure: high = systolic ≥150 mm Hg and diastolic ≥100 mm Hg.

Other subjects mentioned in text.
Only six patients had diastolic pressures of 100 mm Hg or more without systolic hypertension; two were drop-outs from surgery, and the other four were dead within 15 years. Clinical diabetes was a prognostic factor; a trend toward a lower survival rate in the 26 who had an abnormal glucose tolerance test did not reach statistical significance. Cholesterol levels were not related to survival rates (p = .41).

Similar analyses for most variables are shown in table 4 for the 386 candidates for surgery. The results resemble those of the whole group except that statistical significance was not meaningful for several comparisons because of the small numbers of patients. The survival rate was higher for the candidates for surgery (p < .001).

Patients whose ECGs were normal had higher survival rates than those whose records showed any abnormality (p = .0001). Table 5 shows the survival rate for patients in various subsets as determined by ECGs. Repolarization abnormalities not explained by associated transmural myocardial infarction or intraventricular conduction defects were coded under each of these categories, which accounts for the greater number of patients in the subsets when compared with the total patients. The survival rate was low when the ECG showed evidence of left ventricular hypertrophy or an intraventricular conduction defect. The results for candidates for surgery were similar. Radiologic evidence of cardiac enlargement was associated with a relatively low survival rate (p < .0001), but the survival rate was not significantly lower in candidates for surgery who had cardiac enlargement.

Division of candidates for surgery into subsets defined by the "simple clinical variables" used by the Veterans Administration group is shown in table 6. Patients who had lesions of the left main artery that caused greater than 50% narrowing were excluded in both studies. Because intraventricular conduction defects cause ST segment depression and are of ominous prognostic significance independent of other findings, 20 patients with intraventricular conduction block were excluded from our analysis. The percentages of patients in the subsets vary considerably in the two series. No satisfactory prognostic stratification was derived, although patients with single variables tended to have lower mortality than those with multiple variables. The mortality was low in the subset with no clinical variables; mortality in that group was similar to that of candidates for surgery who had normal ECGs. The differences in mortality between the fifth and fifteenth year were similar in most subsets. Recalculations that used only mortality due to cardiac reasons yielded no additional information.

The 22 covariates eligible for inclusion in the Cox

**TABLE 4**
Clinical variables in 386 candidates for surgery

<table>
<thead>
<tr>
<th>Variable</th>
<th>Subset</th>
<th>No. of patients</th>
<th>Survival (%)</th>
<th>Level of significance (p value)</th>
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<td></td>
<td></td>
<td></td>
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<td>5 yr</td>
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<td>Age</td>
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<td></td>
<td>≥50 yr</td>
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<td>64</td>
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<td>M</td>
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<td>95</td>
<td>78</td>
</tr>
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<td>Duration of</td>
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<td>77</td>
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<td>IV</td>
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<td>79</td>
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<tr>
<td>ASO</td>
<td>Absent</td>
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<td>Present</td>
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<td>97</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td>≥2 packs</td>
<td>39</td>
<td>87</td>
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<tr>
<td>Blood pressure</td>
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<td>High</td>
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<td>86</td>
<td>55</td>
</tr>
<tr>
<td>Diabetes</td>
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<td>323</td>
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<tr>
<td></td>
<td>Clinical</td>
<td>10</td>
<td>80</td>
<td>40</td>
</tr>
</tbody>
</table>

Abbreviations as in table 3.

*p = .12; if left main artery cases are excluded p = .05.

Number of patients too small for meaningful calculation.

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model were the demographic, clinical, ECG, and invasively obtained variables that were found to be significant in earlier analyses of the data. For the first set of analyses, candidates for surgery without severe lesions of the left main artery were used. Table 7 shows the results in order of selection for 5, 10, and 15 year survival. Double- and triple-artery disease are among the top three variables for each survival period. Long duration of symptoms was most significant for 5 year survival. Certain variables such as arteriosclerosis obliterans, clinical diabetes, two ECG abnormalities (intraventricular conduction defects and left ventricular hypertrophy), and severe abnormalities as determined by ventriculography (severe diffuse impairment of contractility and ventricular aneurysm) are relatively infrequent but ominous manifestations. For example, all patients who had ECG evidence of left ventricular hypertrophy died. Multivariate analysis was repeated without these variables and we used only patients whose symptoms were less than 5 years in duration, the latter representing the majority of patients studied arteriographically in present practice. Triple-artery disease was the most important variable for 5 year survival, followed by hypertension, myocardial infarction (as determined by an ECG), and repolarization abnormalities (p = .04, .05, and .08, respectively). Because each of the abnormal ECG variables coded was either insignificant or too infrequent to be studied separately in the model, all ECG abnormalities were pooled as a single variable and analysis of candidates for surgery, excluding those with left main artery disease, was performed. An abnormal ECG replaced long duration of history as the most important variable. Finally, a similar analysis was done on the entire study group, including those not considered candidates for surgery, and the results are shown in table 8. Severe diffuse impairment of contractility of the left ventricle was the most significant variable followed closely by an abnormal ECG and then disease of three arteries.

A prognostic stratification that used only duration of history and the ECG is shown in table 9. The subsets were not different statistically (p = .23) in single-artery disease but were different for double- and triple-artery disease (p = .001 and .002, respectively). This would suggest an interaction of three variables: duration of symptoms, ECG, and number of arteries affected.

Discussion

One of the many difficulties encountered in survival studies of patients with coronary disease is that of dropouts. Patient selection is an intentional dropout process that makes no two studies strictly comparable. Compliance with therapeutic advice is another prob-
TABLE 6
Actuarial mortality with Veterans Administration simple clinical variables

<table>
<thead>
<tr>
<th>Variables</th>
<th>Cleveland Clinic Foundation</th>
<th>Veteran’s Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of patients</td>
<td>Dead (%)</td>
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<tr>
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<tr>
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<tr>
<td>NY-HH-ST</td>
<td>16</td>
<td>40</td>
</tr>
<tr>
<td>NY-MI-ST</td>
<td>21</td>
<td>38</td>
</tr>
<tr>
<td>HH-MI-ST</td>
<td>11</td>
<td>39</td>
</tr>
<tr>
<td>NY-HH-MI-ST</td>
<td>5</td>
<td>40</td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>6</td>
</tr>
</tbody>
</table>

NY = New York Heart functional class III or IV; HH = hypertension or history of hypertension; MI = history of myocardial infarction; ST = ST segment depression.

Patients with left main artery lesions are excluded.

symptoms are of increasing severity, a condition associated with an ominous prognosis; thus, the remaining medical patients would be expected to have a relatively better prognosis. Most nonrandomized studies have excluded patients who had early operation, although the term “early” has various definitions.2,10-19 However, the Coronary Artery Surgery Study (CASS) report includes such patients until the date of operation so that the denominator is relatively large in calculation for actuarial tables of the proportion dying each year.20 Although this method may be acceptable statistically, it creates a favorable survival bias if results are compared with those of studies in which early operation is a criterion for exclusion, particularly when the majority of patients are dropouts due to operation, as in the CASS report. In a few instances, candidates for surgery have been studied in particular; this subset is selected from the medical group and would be expected to have a different prognosis.1,15,16,21

A more nebulous factor in evaluation of studies initiated 5 to 20 years ago is that there have been advances in medical therapy over these years. Because there has been no controlled prognostic study of medical therapy of patients with chronic coronary disease, the effect is speculative, but it could be a problem in any long-term study.

Although patients selected for coronary arteriography tend to be free from prognostically serious noncardiac disease, the incidence of deaths due to such disease becomes a problem in long-term follow-up of a group whose average age may be 50 years at the time of study.

TABLE 7
Cox regression analysis: covariables significantly associated with survival rates of candidates for surgery

<table>
<thead>
<tr>
<th>Step</th>
<th>Variable</th>
<th>5 year ( \chi^2 )</th>
<th>p value</th>
<th>10 year ( \chi^2 )</th>
<th>p value</th>
<th>15 year ( \chi^2 )</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Symptoms ( \geq 60 ) mo</td>
<td>22.2</td>
<td>&lt;.001</td>
<td>17.6</td>
<td>&lt;.001</td>
<td>12.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>2</td>
<td>3-artery disease</td>
<td>6.8</td>
<td>.009</td>
<td>9.9</td>
<td>.002</td>
<td>10.8</td>
<td>.001</td>
</tr>
<tr>
<td>3</td>
<td>2-artery disease</td>
<td>10.9</td>
<td>.001</td>
<td>8.8</td>
<td>.003</td>
<td>8.0</td>
<td>.005</td>
</tr>
<tr>
<td>4</td>
<td>ASO</td>
<td>5.0</td>
<td>.02</td>
<td>5.0</td>
<td>.03</td>
<td>7.5</td>
<td>.006</td>
</tr>
<tr>
<td>5</td>
<td>LVH</td>
<td>3.1</td>
<td>.08</td>
<td>5.2</td>
<td>.02</td>
<td>5.7</td>
<td>.02</td>
</tr>
<tr>
<td>6</td>
<td>MI</td>
<td>3.6</td>
<td>.06</td>
<td>5.3</td>
<td>.02</td>
<td>5.1</td>
<td>.02</td>
</tr>
<tr>
<td>7</td>
<td>ST or T</td>
<td>6.9</td>
<td>.009</td>
<td>5.5</td>
<td>.02</td>
<td>4.0</td>
<td>.05</td>
</tr>
<tr>
<td>8</td>
<td>VCD</td>
<td>5.6</td>
<td>.02</td>
<td>2.8</td>
<td>.09</td>
<td>3.7</td>
<td>.06</td>
</tr>
<tr>
<td>9</td>
<td>Enlarged heart</td>
<td>3.8</td>
<td>.05</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ECG groupings are mutually exclusive.

\( ^{\text{a}} \)Patients with left main artery disease are excluded.

\( ^{\text{b}} \)If abnormal ECG is counted as a single variable, \( \chi^2 = 27.8 \) for ECG and 19.4 for symptoms \( \geq 60 \) months.

\( ^{\text{c}} \)All with LVH died before 15 years, producing a singularity in the Cox regression analysis, making analysis including LVH impossible to perform for 15 year survival.

ASO = arteriosclerosis obliterans; LVH = left ventricular hypertrophy (ECG); MI = myocardial infarction (ECG); ST or T = repolarization abnormalities; VCD = intraventricular conduction defect; EDP = end-diastolic pressure of the left ventricle.

Vol. 68, No. 5, November 1983 993
No 15 year study of patients investigated by arteriography is available for comparison. The longest follow-up is the Johns Hopkins report by Platia et al.\textsuperscript{21} In that study 78 patients who were catheterized between 1960 and 1967 and had at least 70% narrowing of one or more coronary arteries were considered candidates for surgery as determined in 1978. Ventriculograms were not available, but patients were excluded who had cardiac enlargement on x-ray, end-diastolic pressure exceeding 20 mm Hg, or congestive heart failure. One 70% lesion was required but 50% narrowing was considered significant. Follow-up was for a mean period of 9.9 years. One of 10 patients who had severe lesions of a single artery died — he was one of the seven who had lesions of the anterior descending artery. The survival rate was about 76% for those with double-artery disease (n = 27) and about 45% for those with triple-artery disease (n = 41). Only 10 of the 78 patients had less than 70% narrowing of the anterior descending artery and none died. For comparison, cardiac survival rates at 10 years for candidates for surgery in the present study were 77%, 55%, and 35% for 111, 149, and 92 patients who had severe disease of one, two, and three arteries, respectively; no statistically significant difference was found between those having and not having lesions of the anterior descending artery. Differences in survival rates between the Johns Hopkins series and the present study population may be due partly to differences in the mean ages of patients (about 42 vs 49.9 years), categorization of left ventricular function, and the size of the study groups.

If survival is related to the number of arteries severely narrowed, the relationship should be most evident in cardiac survival rates of candidates for surgery, because of the exclusion of those patients who had severe impairment of left ventricular function, which was considered to be a contraindication to operation when candidacy for operation was coded in 1975. A fairly good association was found between actual survival curves and those calculated on the basis of 3% mortality per artery severely narrowed per year. At 5 years, the survival rate was higher for single-artery disease than the 3% curve, but by the sixth year the difference was only 2%. Change in the slope of survival curves for single-artery disease have been reported.\textsuperscript{14, 22} The flattening near the end of the 15 year survival curve for patients with triple-artery disease may mean that the 25 patients who were not operated on and who survived to enter the third 5 year period had disease that was nonprogressive or only slowly progressive. In general, prognosis correlated better with the number of arteries severely obstructed than with the severity of narrowing. It is likely that death usually is due to progression of disease. Both increase in the number of arteries narrowed and in the severity of narrowing have been demonstrated arteriographically.\textsuperscript{23, 24}

Extension of the follow-up to 15 years showed persistence of the disparity between rates for patients who had normal ventricles and rates for those who had localized impairment of left ventricular contractility. Curves for patients with severe diffuse impairment and left ventricular aneurysm flattened out after 10 years, but the survivors were few. As in the case of triple-artery disease, the possibility that the disease has “burned out” in most of the 10 year survivors cannot be excluded.

Elevation of the end-diastolic pressure to greater than 20 mm Hg was a significant prognostic factor. However, this measurement has serious limitations,
and considerable elevation of pressure is usually reflected in ventriculographic findings.

The same clinical factors affecting survival rates at 10 years were operative at the 15 year follow-up.\(^1\) However, two additional clinical findings were studied in relation to survival: arteriosclerosis obliterans and stroke. Both had been coded originally but had not been related to survival previously. Arteriosclerosis obliterans was an adverse factor. Harris et al.\(^{25}\) found the history of peripheral vascular disease to be an adverse prognostic factor in coronary disease. Stroke was not shown to affect prognosis significantly, probably because of the small number of patients selected for catheterization.

Recently, a subset of the patients from the Johns Hopkins study was studied in a way that makes possible comparison with other reports of clinical variables in relation to long-term survival.\(^{21}\) Findings from 78 patients who would have been candidates for bypass grafting had it been available were analyzed. Survival rates were found not to be related to the functional class of angina. The 10 year survival rates were about 78% for those with normal resting ECGs compared with approximately 42% for those with abnormal ECGs. History of myocardial infarction was an adverse factor. In the present study the functional class of angina was associated with prognosis, with survival rates being low in patients with severe symptoms. The survival rate of candidates for surgery who had abnormal ECGs was similar to that of the report from Johns Hopkins but was lower (63% at 10 years) than that in the Hopkins’ experience for those who had normal records. Differences in the size of the groups studied, our use of ventriculographic criteria in determining candidacy for surgery, the mean age of the patients, and perhaps the duration of symptoms may account for variations in survival rate between the two studies.

The Veterans Administration group reported the prognostic significance of four “simple clinical variables” independent of invasive studies.\(^{26}\) Combinations of the four variables revealed no clear prognostic stratification in the present study, although patients with no variable or single variables had lower mortalities than those with multiple factors.

Multivariate analysis of prognostic factors has been reported by four groups.\(^{11}\)\(^{25}\)\(^{27}\)\(^{28}\) Oberman et al.\(^{11}\) reported a discriminant function analysis on 210 patients not undergoing surgery who had at least 50% narrowing of one or more coronary arteries. Ventriculograms were not available, and candidacy for surgery was not considered. Heart size, anterior descending artery involvement, dyspnea and orthopnea, heart rate, and left main artery disease were the important prognostic indicators. It was believed that 18% of the patients had congestive heart failure, and 79% had a cardiac area by x-ray greater than “an optimal dividing point.” Advanced disease in these patients as compared with that of our candidates for surgery may account for some of the differences in prognostic variables.

The Duke group studied 1214 patients and eliminated those (779) who had early operation during the period from November 1969 to January 1978.\(^{25}\) Late operation was done in 127. Criteria for selection included chest pain, and an estimated 75% narrowing of at least one artery was required. Candidacy for surgery was not considered. Thirteen prognostic factors were significant, given here in order of statistical significance: lesions of the left main artery, history of peripheral vascular disease, class IV congestive heart failure, arteriovenous oxygen difference, number of arteries affected, abnormal left ventricular contractility, ventricular premature contractions, intraventricular conduction defect, end-diastolic pressure, anterior left ventricular asynchrony, progressive chest pain, nocturnal pain, and left bundle branch block. It is difficult to directly compare this report with others because candidacy for surgery was a selection factor in other reports except for that of Oberman et al.\(^{11}\) Peripheral vascular disease and intraventricular conduction defects were adverse factors in the Duke study and in the present report. Progressive chest pain and nocturnal pain were not helpful prognostically in the present study.

In the Johns Hopkins study of 78 candidates for surgery, the following factors were considered in order of statistical significance: 70% or greater narrowing in the proximal anterior descending artery combined with a lesion of the right coronary artery, positive stress test, previous myocardial infarction, and at least 70% narrowing in the distal anterior descending artery combined with a lesion of the circumflex artery.\(^{21}\) In the present study combinations of arteries affected were not of much prognostic significance and previous myocardial infarction had only a modest effect. Modern stress tests were not done.

Hammermeister et al.\(^{28}\) have reported the results for 318 patients who did not have early operation, representing 40% of patients who might have been followed from the 1969–1974 entry period. Deaths within 1 month of catheterization were excluded. Forty-nine had late operations. All patients were considered to have at least one graftable artery and had at least 50% narrowing of one or more major arteries. Ejection fraction, age, number of arteries narrowed at least 70%, and ventricular arrhythmias were important prognostic.
variables. In the present series, patients with severe
generalized impairment of left ventricular contractility
(and thus, low ejection fractions) were not considered
candidates for surgery. Age was a univariate prognost-
tic factor but was not a significant multivariate variable
for 5 year survival. Ventricular premature contractions
in the ECG in a patient at rest were included as ventricu-
lar arrhythmias in the Hammermeister study. Our
permanent records show only short strips of ECG leads
taken on two-channel machines, so the frequency of
ventricular premature contractions would be underesti-
mated greatly. For this reason this arrhythmia was not
studied.

Multivariate analysis was carried out for the whole
group, as well as for candidates for surgery, excluding
those with left main artery disease. Previous reports of
multivariate analysis differed in results, and the pres-
tent study is still different. Some variables are known to
be associated with an ominous prognosis, although
found in only a minority of patients. Examples are
severe left main artery disease and marked impairment
of left ventricular function (either diffuse contractile
abnormalities or ventricular aneurysm). The clinician
may want to have a prognostic estimation in the ab-
sence of these abnormalities. Various ECG abnormali-
ties were of prognostic significance, so another analy-
sis was done that considered all ECG abnormalities as
a single variable. Abnormal ECG, long history, triple-
artery disease, double-artery disease, and arterioscle-
rosis obliterans were the significant variables.

Problems with multivariate analysis in clinical re-
search have been reviewed by Feinstein.29 Unfor-
nately, the technique is of limited use to many clini-
cians, partly due to lack of familiarity. An alternative
method of analysis is prognostic stratification by a few
carefully chosen variables.29 Duration of history (5
year dividing point) and ECG (normal or abnormal)
were selected, and survival rates were calculated for
single-, double- and triple-artery disease in candidates
for surgery. This simple method separated prognostic
groups except for subsets of patients with single-artery
disease. Prognostic stratification is used by clinicians,
often unconsciously.

Changes in medical therapy and indications for
coronary arteriography alter the patient population at
baseline. In our experience patients were referred ear-
lier in the course of their disease in a manner that was
characteristic 15 years ago. Angioplasty has been in-
troduced as an alternative to bypass surgery, especially
for patients with single-artery disease. The surgeon is
seeing fewer patients with single-artery disease but
more with severe impairment of left ventricular func-
tion because of the low operative risk in these patients
with ominous prognoses. If candidacy for surgery
were determined today, the prognosis of the whole
group of candidates might be worse than for patients
coded in 1975, as in this study; patients may be seen
earlier but sicker patients are being accepted for oper-
ation.

Survival is dependent on the reserves of patent ar-
teries and contractile myocardium. When the latter is
severely restricted, modest progression of arterial dis-
eease is critical. When it is considered that progression
may be short-term or long-term and is difficult to pre-
dict, it is fortunate that survival is closely associated
with simple clinical and invasively obtained variables.

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script.

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