Effect of Bypass Surgery on Survival in Patients in Low- and High-risk Subgroups Delineated by the Use of Simple Clinical Variables

Prepared by Katherine Detre, M.D., Dr. P.H., Peter Peduzzi, Ph.D., Marvin Murphy, M.D., Herbert Hultgren, M.D., James Thomsen, M.D., Albert Oberman, M.D., Timothy Takaro, M.D., and the Veterans Administration Cooperative Study Group for Surgery for Coronary Arterial Occlusive Disease

SUMMARY A multivariate risk function was developed on data from 508 medical patients in the Veterans Administration (VA) randomized study of coronary bypass surgery. The variables, in order of importance, were ST-segment depression on resting ECG, history of myocardial infarction, history of hypertension and New York Heart Association functional classification III or IV. These noninvasive variables have been reported to be risk factors in natural-history studies of coronary heart disease (CHD). Applying the risk function to medical and surgical patients of the 1972-1974 cohort yielded a 5-year probability of dying for each patient. Investigation of treatment effects in approximate terciles obtained by collapsing the probability distribution into low-, middle- and high-risk groups showed that surgery was beneficial for patients in the high-risk tercile even after removal of patients with left main coronary artery disease (17% surgical vs 34% medical mortality at 5 years; p < 0.01). This finding was accentuated when patients in the 10 hospitals with the lowest operative mortality (3.3%) were compared. Mortality results in the low-risk tercile favored medical treatment (medical vs surgical mortality 7% vs 17%; p < 0.05).

The risk function predicted mortality well not only for the VA medical group, but also for an independent symptomatic CHD population from the University of Alabama angiography registry. This report further delineates the advantages and limitations of coronary bypass surgery in CHD patients with chronic stable angina.

THE VETERANS ADMINISTRATION (VA) cooperative study of coronary bypass surgery, initiated in 1970, is a randomized clinical trial of surgical vs medical therapy for patients with stable angina. The study population consists of men with objective evidence of arteriosclerotic heart disease demonstrated by an abnormal resting ECG or exercise test who had stable angina for at least 6 months and received medical treatment for at least 3 months. To qualify angiographically, patients had to have a 50% or greater reduction of luminal diameter in one or more major coronary arteries of which the distal portion was suitable for saphenous vein bypass grafting. Reasons for exclusion were occurrence of myocardial infarction (MI) within 6 months before entry into the study or of congestive heart failure within 3 weeks before entry, presence of ventricular aneurysm, persistent hypertension (diastolic blood pressure >100 mm Hg) despite treatment, or myocardial contractility insufficient to provide the patient with a reasonable surgical risk.

During the 78-month observation period, improved survival was reported for surgical patients who had > 50% narrowing of the left main coronary artery. The surgical benefit was greatest in patients with left main disease who had additional right coronary artery disease and impaired left ventricular function. Subsequently, 2-3-year preliminary results showed no significant treatment differences in survival in the remaining patients without left main disease. Although another large-scale randomized study of coronary bypass surgery reported improved survival with surgery in the subgroup with three-vessel disease and no left main disease, a similar subgroup in the VA study did not confirm this finding.

Epidemiologic studies consistently identified certain clinical symptoms and signs as indicators of poor prognosis in coronary heart disease (CHD). These noninvasive clinical risk factors or variables include New York Heart Association (NYHA) functional classification III or IV, history of MI or congestive heart failure, hypertension or diabetes, and electrocardiographic abnormalities.

Because the response to bypass surgery appeared to be associated with presence of selected risk factors, the purpose of the current study was to delineate new subgroups of patients at various levels of risk and to

From the Veterans Administration Cooperative Study Group for Surgery for Coronary Arterial Occlusive Disease.

Supported by the Veterans Administration Cooperative Studies Program, Medical Research Service, Veterans Administration Central Office, and grant NIH-SP-50-HL17-667-05, NHLBI.

Address for correspondence: Katherine M. Detre, M.D., Cooperative Studies Program Coordinating Center, Veterans Administration Medical Center, West Spring Street, West Haven, Connecticut 06516.

Received June 2, 1980; revision accepted October 3, 1980.

Circulation 63, No. 6, 1981.
identify treatment response at each level. Our present report describes the method by which the variables were selected and combined into a multivariate risk function, the validation of the risk function and its use for the comparative evaluation of the treatment effects in high- and low-risk groups.

Methods

Natural History (1970–1974 Medical Cohort)

The characteristics of the patient population of the VA Coronary Bypass Surgery Study have been reported in detail. The clinical course of the 508 patients who were assigned to medical treatment during 1970–1974 provided the natural history for the entire population of the study. During the 6.5-year average follow-up, 145 deaths occurred in this cohort, in which survival status was known for 98.6% of all patients. In the same cohort, 109 patients (21%) crossed over to surgical treatment. Twenty percent of the 109 had left main disease, a subgroup of patients for whom crossover was made optional in 1976.

Risk Function

A multivariate risk function is a weighted combination of selected risk factors resulting in a risk score. To develop such a risk function on our data, we selected risk factors based on four considerations: They were found to be associated with increased mortality in previous epidemiologic studies of the natural history of CHD; they were risk factors in our patients; they were prevalent in our population; and they were measured in most of our patients.

Because of these constraints, we did not include risk factors such as congestive heart failure, diabetes, use of digitalis and diuretics, cardiointercostal ratio, peripheral pulses, conduction defects and ventricular premature complexes. The four noninvasive characteristics that met all the above criteria were NYHA functional class III or IV, history of hypertension, history of MI, and ST-segment depression. The presence or absence of the two historical variables was assessed by questioning the patient at the initial baseline examination. The NYHA functional classification III or IV included patients whose physical activity was markedly limited by their coronary disease. Presence and magnitude of ST-segment depression were determined on the basis of a centralized evaluation of all baseline ECGs at the Minnesota ECG laboratory. ST-segment depression was present if any degree of abnormality of the ST-segment existed by the Minnesota codes 4-1 to 4-4. The risk function was developed by applying the Cox-Breslow life-table regression model to the following data of the 1970–1974 medical patients: presence or absence of the four noninvasive predictors, individual survival times and survival status. To avoid any possible effects attributable to late surgery that would have biased the natural history of the medical group, only deaths of medical patients who adhered to the assigned medical treatment were considered in this analysis (117 deaths). Details of the method for developing the risk function are given in appendix A.

The risk function was used to compute a probability of dying in 5 years (Pdeath) for each patient, and these probabilities were arranged in ascending order. Approximate terciles of risk — low, middle and high — were created by dividing the probability distribution into three groups with nearly equal numbers of subjects. The low tercile was expected to have the lowest actual mortality rate and the high tercile the highest.

Thus, selection of the risk factors was made from external sources reported by earlier population studies in the literature and was not based on an internal search of study data. However, because the coefficients or weights for the variables were estimated on the basis of the mortality experience of the medically treated group, we expected that a better relationship would be found between theoretical probabilities and actual mortality experience of the medically treated group than if the weights were also obtained from external sources. Therefore, first we had to establish the general validity of the risk function.

Validation

Two major methods were used to test the validity of the risk function: an external method that used an independent population, and an internal method that used a statistical technique called the jackknife procedure. The latter method is described in appendix B.

From the University of Alabama Medical Center, data on 535 medically treated patients who had coronary angiography from 1973–1975 were obtained. Male patients who had < 50% stenosis in a major coronary artery and all female patients were excluded to approximate more closely the VA population. The risk function developed from the VA medical patients was then applied to this independent population to obtain estimated probabilities of dying and to compare these estimates with the mortality rates that were actually observed.

Treatment Comparison (1972–1974 Medical-Surgical Cohort)

After initial development of angiographic and surgical techniques, a final phase of the VA Coronary Bypass Surgery Study (January 1972 through December 1974) was initiated. In analyses of treatment comparisons, only the experience of patients randomized during the final phase was used. The 1972–1974 cohort consists of 686 patients, 354 of whom were assigned to medical and 332 to surgical treatment. The operative mortality (30-day) rate during this period was 5.8% (18 of 312) for all operations and 5.0% (15 of 297) for operations including saphenous vein bypass grafts only. (Of the 15 patients who had other surgical procedures, 12 had an internal mammary artery graft, one had an internal mammary artery graft only, one had internal thoracic artery implant, and one had the implant procedure only.)
Survival Status

Survival times were calculated from the date of randomization to death or to the date of last contact. For most patients, this date was the time of the most recent clinic visit. For patients who had not been seen in the last 9 months, the survival status was checked through a centralized VA locating system, called BIRLS, within the month before the survival analyses were performed. If no death record was found through BIRLS, the date of the search was used as the date of last contact.

Survival time of nonadherers was calculated in two ways: (1) treatment policy or treatment assigned: from randomization to date of death or date of last clinic visit, ignoring crossover; and (2) the crossover method: from randomization to the date of crossover. Crossover is the date of randomization plus 1 day for patients randomized to surgery but who did not receive surgery, and is the time from randomization to the date of surgery for medically assigned patients who later had surgery. Therefore, deaths that occurred after crossover were counted against the original treatment assignment in method 1, but were not counted as deaths in method 2.

Application of Risk Function to Survival Data

After validation, the risk function was applied to the 1972–1974 cohort of medical and surgical patients (n = 686). This resulted in a calculated PD(1331), or risk score, for each patient. Again, approximate terciles of risk (low, middle and high) were formed so that within each tercile the medical and surgical patients had the same risk scores. In each tercile of risk, comparison of survival experience between the medically and surgically treated patients was determined by the Mantel-Haenszel chi-square method, which was applied to actuarial survival tables. Both survival analyses — treatment policy and crossover method — were carried out for all patients and for patients without left main disease from all 13 participating hospitals. The same analyses were repeated for subjects from 10 hospitals, excluding the three hospitals with the highest operative mortality rates.

Subjects to whom the risk function could not be applied because of missing information were analyzed by treatment as a separate group. Their survival experience on the two treatments was added to that tercile where it would reduce the treatment difference the most. This ensured that any treatment differences obtained were conservative, and that every patient in the study was accounted for in the analyses.

Results

Risk Function

The risk function is given by the following equation:

\[
PD(1331) = 1 - \frac{0.8053 \exp(0.2757(x_1 - 1.57) + 0.6374(x_2 - 1.29) + 0.831(x_3 - 1.61) + 1.0579(x_4 - 1.27))}{1 + \exp(0.2757(x_1 - 1.57) + 0.6374(x_2 - 1.29) + 0.831(x_3 - 1.61) + 1.0579(x_4 - 1.27))}
\]

where \(x_1 = NYHA \) class III or IV, \(x_2 = \) history of hypertension, \(x_3 = \) history of MI, \(x_4 = ST\)-segment depression on resting ECG by Minnesota code, and 0.8053 = the probability of surviving longer than 5 years when all variables are equal to the mean values found in this population (i.e., \(\bar{x}_1 = 1.57, \bar{x}_2 = 1.29, \bar{x}_3 = 1.61, \bar{x}_4 = 1.27\)). The mean values represent the prevalence of the risk factors at baseline. The absence of a risk factor was coded as 1 and the presence as 2, so the mean of 1.57 indicates that 57% of the medical patients had been in NYHA class III or IV. Similarly, 29% had a history of hypertension, 61% had a history of MI and 27% had some ST-segment depression.

The predicted PD(1331) was determined for the 494 medical patients who had complete information on the four noninvasive variables and on survival. Thus, a patient who, for example, was in NYHA class II (\(x_1 = 1\)), no history of hypertension or MI (\(x_2, x_3 = 1\)) and had ST depression (\(x_4 = 2\)) would have a PD(1331) of

\[
\frac{1 - 0.8053 \exp(0.2757(1 - 1.57) + 0.6374(1 - 1.29) + 0.831(1 - 1.61) + 1.0579(1 - 1.27))}{1 + \exp(0.2757(1 - 1.57) + 0.6374(1 - 1.29) + 0.831(1 - 1.61) + 1.0579(1 - 1.27))} = 0.18
\]

and would belong to a group of patients whose predicted mortality in 5 years was 18%. Each patient was assigned to one of 16 possible categories or probability groups derived from these four dichotomous variables. The range of the PD(1331) for the 16 categories in our medical patients was 0.067–0.683, while the range of the actual 5-year cumulative mortality rate was 0.043–0.600. The regression of observed on predicted mortality yielded a slope (b ± sE(b)) of 0.829 ± 0.155, which means that with each unit change in PD there is, on the average, a 0.829 change in the observed mortality rate, almost a one-to-one relationship.

Validation

The risk function was next applied to the independent population from the arteriography registry of the University of Alabama Medical Center. Of the 535 medically treated male patients whose survival status was known, only 12 had to be excluded because of missing information on one or more of the four noninvasive variables. Although NYHA functional class was not recorded for the Alabama patients, a comparable variable that measured dyspnea on exertion was used as a substitute.

The average follow-up period for the Alabama patients was 3 years, so the VA risk function was adjusted to predict 3-year instead of 5-year mortality. This was accomplished by taking the underlying PD at 3 years (0.8617) for the VA population. There was good agreement between predicted and observed mortality. The slope of the fitted regression line (b ± sE(b)) was 0.728 ± 0.144. This result indicates that the VA risk function is predictive of mortality in an independent symptomatic CHD population. The slight reduction of the slope was expected, because the fit in an independent population is generally not as good as that obtained when the risk function is applied back to the data from which it was developed.

Treatment Comparison

Comparison of survival between medical and surgical treatment groups was made within each tercile of...
TABLE 1. Five-year Cumulative Survival Rates* in Noninvasive Risk Groups—1972-1974 Cohort

<table>
<thead>
<tr>
<th>Noninvasive risk group</th>
<th>Left main included</th>
<th></th>
<th>M-H x² at 5 yrs†</th>
<th></th>
<th>Left main excluded</th>
<th></th>
<th>M-H x² at 5 yrs†</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Medical</td>
<td>Surgical</td>
<td></td>
<td></td>
<td>Medical</td>
<td>Surgical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n = 686</td>
<td>n = 138</td>
<td>n = 131</td>
<td></td>
<td></td>
<td>n = 123</td>
<td>n = 113</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>0.93</td>
<td>0.83</td>
<td>6.59$</td>
<td></td>
<td>0.93</td>
<td>0.83</td>
<td>5.77$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(0.92)</td>
<td>(0.81)</td>
<td>(7.64)$</td>
<td></td>
<td>(0.93)</td>
<td>(0.82)</td>
<td>(7.15)$</td>
<td></td>
</tr>
<tr>
<td>Middle</td>
<td>0.77</td>
<td>0.82</td>
<td>0.34</td>
<td></td>
<td>0.82</td>
<td>0.81</td>
<td>0.20</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(0.76)</td>
<td>(0.83)</td>
<td>(1.12)</td>
<td></td>
<td>(0.79)</td>
<td>(0.81)</td>
<td>(0.07)</td>
<td></td>
</tr>
<tr>
<td>n = 113</td>
<td>n = 105</td>
<td></td>
<td></td>
<td></td>
<td>n = 97</td>
<td>n = 87</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High†</td>
<td>0.62</td>
<td>0.83</td>
<td>13.7**</td>
<td></td>
<td>0.66</td>
<td>0.83</td>
<td>7.22$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(0.62)</td>
<td>(0.82)</td>
<td>(12.6)**</td>
<td></td>
<td>(0.64)</td>
<td>(0.82)</td>
<td>(7.59)$</td>
<td></td>
</tr>
</tbody>
</table>

10 hospitals

| n = 591                | n = 120           | n = 113 |    | n = 106           | n = 100 |    |
| Low                    | 0.93              | 0.84 | 4.62$         |    | 0.93              | 0.83 | 4.98$          |    |
|                        | (0.92)            | (0.83) | (4.81)$       |    | (0.93)            | (0.82) | (5.36)$        |    |
| n = 84                 | n = 84            |    |               |    | n = 75            | n = 73 |    |
| Middle                 | 0.74              | 0.84 | 1.46          |    | 0.78              | 0.82 | 0.11           |    |
|                        | (0.73)            | (0.84) | (2.41)        |    | (0.76)            | (0.83) | (0.60)         |    |
| n = 100                | n = 90            |    |               |    | n = 85            | n = 72 |    |
| High†                  | 0.61              | 0.89 | 21.6**        |    | 0.64              | 0.90 | 14.6**         |    |
|                        | (0.61)            | (0.87) | (18.8)**      |    | (0.63)            | (0.88) | (13.9)**       |    |

*The open numbers represent survival rates by crossover method; numbers in parentheses represent survival rates by treatment assigned (treatment policy).
†Mantel-Haenszel chi-square.
‡Patients whose probability of dying could not be calculated because of missing data are counted in the high-risk group.
§p < 0.05.
¶p < 0.01.
**p < 0.0005.

risk created by application of the risk function to the 1972-1974 cohort. The results of these survival analyses are displayed in table 1 for all patients with and without left main coronary artery disease. Death from all causes was the end point used in the analyses. Survival results indicate an advantage for the surgical treatment group in the high-risk tercile. The advantage is highly significant (p < 0.0005) for all patients and is still significant (< 0.01) after removal of the left-main subgroup. Conversely, for the low-risk tercile, the medical survival was significantly better for all patients and for the subgroup without left main disease (p < 0.05). The significant differences in the high- and low-risk terciles remained unchanged after adjustment was made for most important angiographic risk variables, such as number of diseased vessels and status of ventricular function.

Table 1 also displays results of an identical analysis using data from those 10 hospitals where the 30-day operative mortality rate was 3.3%. This permitted comparison of the treatment effect in a group where the operative mortality was diminished and thus the surgical mortality more closely reflected late surgical deaths. The results of these analyses accentuate the survival differences in the high-risk group. Again, low-risk patients in the 10 hospitals, as in all hospitals, had significantly better survival on medical therapy. Thirty-day and operative mortalities are given in table 2 for all medical and surgical risk subgroups for all 13 hospitals and for the 10 hospitals for patients without left main disease.

Among the six patients without left main disease in the 1972-1974 medical and surgical cohort for whom the PD could not be calculated because of incomplete data, both medical patients survived and three of the

TABLE 2. Thirty-day Mortality* in Noninvasive Risk Groups—1972-1974 cohort

<table>
<thead>
<tr>
<th>Noninvasive risk group</th>
<th>All hospitals</th>
<th>10 hospitals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Med %</td>
<td>Surg %</td>
</tr>
<tr>
<td>Low</td>
<td>0</td>
<td>5.3</td>
</tr>
<tr>
<td>Middle</td>
<td>0</td>
<td>5.9</td>
</tr>
<tr>
<td>High</td>
<td>0</td>
<td>4.6</td>
</tr>
</tbody>
</table>

*Medical deaths within 30 days from date of entry and surgical deaths within 30 days after operation. Patients with left main disease are excluded. Patients whose probability of dying could not be calculated are included in the high tercile.
Figure 1. Cumulative survival rates in each risk tercile for all 1972–1974 patients without left main disease. Patients with missing data were included in the high-risk tercile and survival rates were determined by the crossover method. The Mantel-Haenszel chi-square statistic was used to compare survival rates in the two treatment groups at 5 years. Results are shown separately for all hospitals and for the 10 hospitals with low operative mortality rates.

Four surgical patients died. In the survival analyses (table 1), these patients were included in the high-risk tercile — the surgical because their survival was poorer than that of the average surgical patient in the high-risk group, and the medical because their survival was better than that of the average high-risk medical patient.

Figure 1 shows cumulative survival curves by treatment for each tercile of risk for all hospitals and for the 10 hospitals. The differences between the survival
### Table 3. Clinical Patterns and Probabilities—1972–1974 Cohort*

<table>
<thead>
<tr>
<th>Probability of dying</th>
<th>Clinical pattern†</th>
<th>No. of pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low tercile</td>
<td>-</td>
<td>0.067230</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>0.087612</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>0.123349</td>
</tr>
<tr>
<td></td>
<td>UNK</td>
<td>0.147773</td>
</tr>
<tr>
<td>Middle tercile</td>
<td>NH</td>
<td>0.159230</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>0.181650</td>
</tr>
<tr>
<td></td>
<td>N-M</td>
<td>0.189953</td>
</tr>
<tr>
<td></td>
<td>N-S</td>
<td>0.232106</td>
</tr>
<tr>
<td>High tercile</td>
<td>NM</td>
<td>0.261005</td>
</tr>
<tr>
<td></td>
<td>N-H</td>
<td>0.315585</td>
</tr>
<tr>
<td></td>
<td>NHM</td>
<td>0.328661</td>
</tr>
<tr>
<td></td>
<td>MS</td>
<td>0.369083</td>
</tr>
<tr>
<td></td>
<td>N-HM</td>
<td>0.393206</td>
</tr>
<tr>
<td></td>
<td>N-MS</td>
<td>0.454904</td>
</tr>
<tr>
<td></td>
<td>-MS</td>
<td>0.581537</td>
</tr>
<tr>
<td></td>
<td>N-HMS</td>
<td>0.682660</td>
</tr>
<tr>
<td></td>
<td>UNK</td>
<td>6</td>
</tr>
</tbody>
</table>

*Patients with left main disease are excluded.

Abbreviations: N = New York Heart Association class III or IV; H = history of hypertension; M = history of myocardial infarction; S = ST-segment depression on resting ECG; UNK = pattern unknown because of missing data.

The curves of the medical and surgical groups are clearly a function of the risk groups.

### Clinical Patterns of the Risk Terciles

After the terciles were created with the sole intent to achieve groups of equal number without overlapping probabilities, we examined what clinical interpretation, if any, could be attached to the terciles. Patterns of presence or absence of the four variables are shown in Table 3 for the 595 patients without left main disease. The 16 patterns correspond to the increasing risk of dying so that the group that had none of the risk factors had the lowest PD, and the group with M1 alone had the highest PD of all the groups in the low-risk tercile. The same principle holds true for all terciles. As a result, the high-risk tercile includes patients with all four and with any combination of three characteristics present, as well as those with any two characteristics, provided that NYHA was not one of them. Most subjects who had ST-segment depression (80%) were in the high-risk tercile. The low-risk tercile had patients with none or only one risk characteristic, except patients with ST depression alone, who became part of the middle-risk group.

Table 4 gives the average predicted PD and observed cumulative mortality rates by treatment in both groups of hospitals. The average PD's within each tercile are similar for both treatments. In the medical groups, the mean PD's correspond with the observed cumulative mortality rates. In contrast to the mortality experience in the medically managed groups, which was highly dependent on the risk factors, the mortality in the surgically managed patients varied only within the narrow range of 0.105–0.195, and was independent of the risk factors and of the PD's to a remarkable degree.

### Noninvasive vs Invasive Risk Factors

It seemed logical to examine whether the risk function of noninvasive variables assigns patients to the same high-, middle- and low-risk groups as do the well-known invasive risk factors, such as number of diseased vessels and abnormal left ventricular function. In the following analyses, the relationship between the two methods of risk classification was explored in the patients without left main disease.

Table 5 shows that the percentage of medical patients with three diseased vessels is nearly the same in the low-, middle- and high-risk groups of the noninvasive classification, 48%, 49% and 52%. Similarly, the percentage of high-risk patients is similar in patients with one, two or three diseased vessels, 36%, 27% and 33%. Accordingly, the chi-square of 3.8 indicates that the noninvasive risk status is independent of the number of diseased vessels.

The same results hold true when the 89 deaths are cross-classified by vessel disease and risk tercile. The percentage of deaths in patients with three-vessel disease is about the same in each tercile (Table 5), 60%, 63% and 64% for low, middle and high risk, respectively. Conversely, the proportion of deaths in the high-risk tercile for one-, two- and three-vessel disease is also nearly the same, 50%, 52% and 54%. Thus, the chi-square of 0.459 reflects the independence of the two risk measures — the noninvasive risk tercile and
the number of diseased vessels — in classifying mortality.

By adding the status of the left ventricular function to the number of diseased vessels, six invasive risk groups were formed. Risk groups 1–3 are those with one-, two- and three-vessel disease and normal left ventricular function, and groups 4–6 are those with one-, two- and three-vessel disease with abnormal left ventricular function. (Group 6, for example, would include patients with three-vessel disease and abnormal left ventricular function.) Table 6 gives the cross-classification of these risk categories against the noninvasive terciles for patients without left main disease. The percentage of patients of high angiographic risk (risk group 6) in the low, middle and high noninvasive terciles are 37%, 44% and 49%, respectively (table 6). Conversely, the percentage of high-risk patients by the noninvasive measure who are in the angiographic low (groups 1–4), middle (group 5), and high (group 6) groups are 26%, 30% and 36%. The slight trend in the increasing percentages implies a relationship, though not significant, between the invasive and noninvasive classifications of risk that was not present when angiographic risk was based only on number of diseased vessels (table 5). Similar trends were observed when death was cross-classified in the same manner (table 6).

The mortality rates among patients who are classified as high risk by both invasive and noninvasive methods differ markedly from those in patients who are classified as low risk on both. Table 7, obtained from table 6, gives the actual mortality rates. The mortality rate in risk group 6 is 29% and the rate in the noninvasive high-risk tercile is 35%, but mortality in the high-risk group by both classifications is 45%. Thus, the two risk dimensions together delineate an even higher, though smaller, risk group.

### Discussion

The four noninvasive clinical variables used in the current study were among the eight best predictors used in a risk function of 20 variables described in a report of the Coronary Drug Project (CDP). All CDP patients had at least one MI, so history of MI was not applicable; however, the number of previous infarcts was found to be a risk indicator. Oberman and Baldone tested 21 noninvasive risk indicators and found significant correlation between mortality and five clinical variables: ST depression, history of MI, heart size, ventricular conduction defects and anti-hypertensive medication. ST-segment depression has

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Noninvasive risk tercile</td>
<td>Invasive risk group*</td>
<td>%</td>
<td>Medial, left main excluded</td>
</tr>
<tr>
<td>1-4</td>
<td>5</td>
<td>6</td>
<td>Total</td>
</tr>
<tr>
<td>Medical, left main excluded</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>58</td>
<td>47</td>
<td>61</td>
</tr>
<tr>
<td>Middle</td>
<td>35</td>
<td>34</td>
<td>55</td>
</tr>
<tr>
<td>High</td>
<td>33</td>
<td>35</td>
<td>65</td>
</tr>
<tr>
<td>Total</td>
<td>126</td>
<td>116</td>
<td>181</td>
</tr>
<tr>
<td>% noninvasive high risk</td>
<td>26</td>
<td>30</td>
<td>36</td>
</tr>
<tr>
<td>Adherer deaths†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>3</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Middle</td>
<td>6</td>
<td>5</td>
<td>16</td>
</tr>
<tr>
<td>High</td>
<td>5</td>
<td>13</td>
<td>29</td>
</tr>
<tr>
<td>Total</td>
<td>14</td>
<td>22</td>
<td>53</td>
</tr>
<tr>
<td>% noninvasive high risk</td>
<td>36</td>
<td>59</td>
<td>55</td>
</tr>
</tbody>
</table>

*Invasive risk groups 1–4 include patients with one, two or three diseased vessels with normal left ventricular function (LVF) and those with one-vessel disease and abnormal LVF; groups 5 and 6 include patients with abnormal LVF and two or three diseased vessels, respectively.

†Deaths after crossover are excluded.

| Table 7. Mortality Rates of Medical Patients (1970–1974) Classified by Both Noninvasive and Angiographic Risk* |
|---------------------------------|--------|--------|--------|
| Noninvasive risk tercile | Invasive risk group | % | Low | Middle | High | Total |
| 1-4 | 5 | 6 | Total | | | |
| Medical, left main excluded | | | | | | |
| Low | 0.06 | 0.09 | 0.13 | 0.09 |
| Middle | 0.17 | 0.15 | 0.29 | 0.22 |
| High | 0.15 | 0.37 | 0.45 | 0.35 |
| Total | 0.11 | 0.19 | 0.29 | 0.21 |

*As noted in table 6, patients with left main disease are excluded and mortality is based on adherer deaths.

---

*Number of vessels with ≥ 50 reduction in luminal diameter.
†Deaths after crossover are excluded.
been uniformly found to be the most potent risk indicator in all secondary natural history studies of CHD. Together with hypertension, it was first identified by Frank in 1968. When used in combination with angiographic variables, ST depression remained an independent, strong risk factor.14,17

One may question the value of clinical variables obtained by history alone without more specific criteria. In our study, careful review of the initial history data recorded at baseline revealed that 86% of the patients with a history of MI had mentioned the actual date when the infarct occurred. However, baseline electrocardiographic evidence to document the Q-QS abnormality was present in only 53%. The possibility of reversion of the Q-QS abnormality with time after MI and the fact that a subendocardial infarct is not manifested electrocardiographically by Q-QS abnormality may account for this discrepancy. Therefore, the historical variable may be far more sensitive in detecting previous MI's than objective ECG data measured at one point in time. A similar review of the baseline data on hypertension showed that only 52% of all patients with a history of hypertension had a diastolic blood pressure > 90 mm Hg at entry. Presumably, the same explanation could apply here. However, there may be overreporting for this variable because data on drug usage for high blood pressure, which would have strengthened the validity of history of hypertension, were not collected at baseline. The NYHA classification variable used in our patients was based on the old criteria as specified in the study protocol.9 The ST-segment depression variable used the same criteria defined in the CDP study.7 All four variables were independently predictive of mortality.

We attempted to increase the power of our risk score by expanding the historical variables on hypertension and MI to include actual recorded values of blood pressure and electrocardiographic evidence of MI at baseline. However, the advantage was minimal.

One might well ask why these four clinical risk factors identify a high-risk group. We may conjecture that hypertension and MI can lead to a variable degree of myocardial hypertrophy. Hypertension is an established cause of increased myocardial mass, and it is recognized that an increase in left ventricular mass usually occurs after MI in patients with CHD.18 Amelioration of ischemia in these patients may then be a very important part of the surgical treatment that produces a favorable result.

No strong evidence was found in our study population that those patients who scored high by the noninvasive risk measure (high P50) would also be of high risk invasively (three-vessel disease and abnormal left ventricular function), and vice versa. This lack of significant association may be partly explained by the exclusion of patients with left main disease from the analysis. When the patients who have left main coronary artery disease are included, the relationship between the two classifications of risk is slightly strengthened. However, the relationship between invasive and noninvasive risk groups needs to be further explored in data from other CHD study populations.

The most meaningful test of the validity of the noninvasive risk function was its applicability to an independent symptomatic CHD population. The VA noninvasive risk function predicted mortality remarkably well in the population from the University of Alabama arteriography registry.

The noninvasive risk terciles have more than statistical interest; the risk groups can be interpreted clinically. Our low-risk medical group without left main disease included all patients with none or only one of the noninvasive risk factors, with the exception of ST depression. This low-risk group, which included approximately one-third of all patients, had a good prognosis on the whole, with a 5-year cumulative mortality rate of 7%. However, the high-risk group, again without left main disease and composed mainly of patients with combinations of the three strongest predictors (ST depression, history of MI and history of hypertension), had a poor prognosis, with a 5-year cumulative mortality rate of 35%.

The prognosis for operated patients, however, remained about the same in each risk tercile, with 5-year cumulative mortality rates of 11–20%. This finding is in agreement with the observation of Kriklin et al.19 and Anderson et al.20 that the bypass operation seems to partially eradicate the effect of the risk factors, thus making the risk groups homogeneous with uniform survival. The 5-year mortality in the operated group was about 15% in all risk groups, so it follows that where the medical survival rate was very poor, as it was in the high-risk tercile, there was a significant benefit from surgery. It is equally true that when the medical prognosis was very good, as it was in the low-risk tercile, there was a significant disadvantage after operation. Even if, in the analysis, hospital mortality were to be totally eliminated and we assumed no impact from that on the late mortality experience (an unrealistic assumption that should not be made), according to our data the prognosis of the low-risk surgical patients after the operation would be no better than that of the medical patients. Both the high- and low-risk findings remained significant after exclusion of patients with left main disease.

In conclusion, our results, using clinical rather than angiographic definitions, further delineate the advantages and limitations of coronary bypass surgery. For subgroups of CHD patients who have poor prognosis defined either by clinical variables, as in the current work, or by angiographic studies reported earlier,1 surgical treatment apparently improves the survival rate.

On the other hand, subgroups that have significant coronary disease but few additional clinical or anatomic risk factors do not live longer and may actually be at a disadvantage after surgery. For this subgroup of CHD patients, survival with medical treatment alone may be sufficiently favorable that surgical intervention, even with improved surgical techniques, need not be considered. No matter how successful the surgical procedure may be, it would be difficult to demonstrate a significant improvement in survival beyond that already observed in the medical low-risk
group unless sample sizes and follow-up periods were extended beyond reasonable limits.

Acknowledgment
We are deeply indebted to our advisor and friend, the late Professor Jerry Cornfield, who followed our work with enthusiasm and healthy skepticism. Because of the latter, 2 years ago we sent an early version of the manuscript to Drs. Oberman, Rosati, Hammermeister and Stammel, and Professors Canner and Meier for criticism. Their comments were very much appreciated.
We thank our Operations Committee for their encouragement, and Terri Hatch and her staff for their dedication throughout the data analysis and preparation of the report.

References

Appendix A
Risk Function
From the Cox model, estimates of the weights for each risk factor (regression coefficients: $\beta_1, \ldots, \beta_n$) and an estimate of the underlying probability of surviving to time $t$ [$F(t)$] were obtained. These estimates were used in the risk function

$$P_D(t) = 1 - F(t)$$

which expresses the probability of dying (PD) within t years. In the VA study a probability of dying within 5 years was computed for each patient by substituting in the formula the observed values for variables $x_1$ to $x_n$ and the mean values of the four baseline risk factors (X1, . . . , X4). A probability could not be estimated for 14 patients because of missing data on one or more of the nonvariable variables.

Appendix B
Jackknife Procedure
The jackknife procedure19 is a statistical technique for internal validation of the nonvariable risk function. This procedure was applied to the 1970–1974 medical cohort using the “leave-one-out” method. By this method, estimates of the weights (regression coefficients) were obtained by the Cox-Breslow procedure after leaving out one patient from the analysis. The resulting risk function was then applied to the excluded patient’s data to obtain his independent predicted probability of dying. This process was repeated until probabilities of dying were estimated for all patients. A separate risk function was developed for each patient, excluding his data, so the resulting jackknife probabilities can be considered independent.

The jackknife probabilities were ordered from lowest to highest and the range (0.063 - 0.707) was divided into six intervals of an approximately equal width of 0.1, except for the last interval (0 - 0.099, 0.100 - 0.199, . . . , 0.499). For the patients in each interval the life table 5-year cumulative mortality rate and the average of the predicted jackknife probabilities of dying were computed. The relationship between observed and predicted mortality was reasonably good. The slope ± standard error of the fitted regression line was 0.772 ± 0.197, somewhat less than the slope of 0.829 attained by the method of resubstitution described in appendix A.

Appendix C
VA Cooperative Study of Surgery
For Coronary Arterial Occlusive Disease:
Participating VA Medical Centers
Buffalo, New York — Co-Investigators: David C. Dean, M.D., Joginder Bhayana, M.D.; Past Co-Investigator: Andrew A. Gage, M.D.; Physician: Italo Bessoqheghi, M.D.
Cleveland, Ohio — Co-Investigators: Marian Davies, M.D., Julie Clayman, M.D.; Past Co-Investigator: Cathal A. Macleod, M.D.; Past Physicians: Robert C. Babler, M.D., Daniel van Heeckeren, M.D.


Little Rock, Arkansas — Co-Investigators: Marvin L. Murphy, M.D., Raymond C. Read, M.D.

Long Beach, California — Co-Investigators: Edward A. Stemmer, M.D., Michael B. Pine, M.D.; Past Co-Investigators: Harold W. March, M.D., Nolan Resnick, M.D., Jack C. Kern, M.D., Joan Orlando, M.D.

Madison, Wisconsin — Co-Investigators: James Thomsen, M.D., Peter Kosolcharoen, M.D., George Kroncke, M.D.; Past Co-Investigator: Donald Kahn, M.D.

Minneapolis, Minnesota — Co-Investigators: Gordon L. Pierpont, M.D., Yoshio Sako, M.D.; Past Co-Investigators: James A. Fischer, M.D., James P. Lillehei, M.D., Kyuhyun Wang, M.D., Carl S. Alexander, M.D.


West Roxbury, Massachusetts — Co-Investigators: Alfred Parisi, M.D., Ernest M. Barsamian, M.D.; Past Co-Investigators: Robert L. Morse, M.D., David Littmann, M.D.

Study Co-Chairmen

Herbert N. Hultgren, M.D., Cardiological Co-Chairman; Timothy Takaro, M.D., Surgical Co-Chairman; David Littmann, M.D., Past Cardiological Co-Chairman.

Cooperative Studies Program Coordinating Center

Yick-Kwong Chan, Ph.D., Director; Katherine M. Detre, M.D., Dr. P.H., VA Medical Center, West Haven, Connecticut (1973–); Peter Peduzzi, Ph.D., VA Medical Center, West Haven, Connecticut (1976–); Elizabeth C. Wright, M.P.H. (1968–1973), Past Statistician.

Executive Committee

Herbert N. Hultgren, M.D., VA Medical Center, Palo Alto, California; Timothy Takaro, M.D., VA Medical Center, Asheville, North Carolina; Marvin Murphy, M.D., VA Medical Center, Little Rock, Arkansas; George Kroncke, M.D., VA Medical Center, Madison, Wisconsin; Katherine M. Detre, M.D., Dr. P.H., VA Medical Center, West Haven, Connecticut; Peter Peduzzi, Ph.D., VA Medical Center, West Haven, Connecticut; Prof. Byron Brown, Stanford University, Palo Alto, California; Past Member: Yoshio Sako, M.D., VA Medical Center, Minneapolis, Minnesota; Past Consultant: Prof. Jerome Cornfield (deceased), George Washington University, Bethesda, Maryland.

Operations Committee

Noble O. Fowler, M.D. (Chairman), Cincinnati, Ohio; Jay L. Ankeney, M.D., Cleveland, Ohio; W. Sterling Edwards, M.D., Albuquerque, New Mexico; J. O’Neal Humphries, M.D., Columbia, South Carolina; William W. Glenn, M.D., New Haven, Connecticut; Ralph F. Frankowski, Ph.D., Houston, Texas; Paul N. Yu, M.D., Rochester, New York; Consultant: Lawrence W. Shaw, A.M., George Washington University, Bethesda, Maryland; Past Members: Charles K. Friedberg, M.D. (deceased) New York, New York; John W. Kirkin, M.D., Birmingham, Alabama; J. Willis Hurst, M.D., Atlanta, Georgia; William R. Best, M.D., Hines, Illinois; James J. Morris, Jr., M.D., Durham, North Carolina; J. David Bristow, M.D., Portland, Oregon; Past Surgical Consultant: David C. Sabiston, Jr., M.D., Durham, North Carolina.

VA Central Office Coordinator

James A. Hagans, M.D., Ph.D.; Past Coordinator: Lawrence W. Shaw, A.M. Past Surgical Coordinators: Mark W. Wolcott, M.D., Francis C. Jackson, M.D.

Cooperative Lipid Studies Laboratory

Steven H. Quarfordt, M.D., VA Medical Center, Durham, North Carolina.

Radiologic Consultant

Martin J. Lipton, M.D., University of California, San Francisco, California.

Pathology Consultants

Johanna van der Bel-Kahn, M.D., Cincinnati, Ohio, William C. Roberts, M.D., National Institutes of Health, Bethesda, Maryland.

Consultant in Arteriographic Interpretation

Goffredo G. Gensini, M.D., Syracuse, New York; Former Consultants: Lawrence S. C. Griffith, M.D., C. Richard Conti, M.D., Richard S. Ross, M.D.

ECG Reading Center

Ronald Primea, M.D., University of Minnesota, Minneapolis, Minnesota.

Left Ventricular Angiogram Analysis Laboratory

Karl Hammermeister, M.D., VA Medical Center, Seattle, Washington.
Effect of bypass surgery on survival in patients in low- and high-risk subgroups delineated by the use of simple clinical variables.

K Detre, P Peduzzi, M Murphy, H Hultgren, J Thomsen, A Oberman and T Takaro

*Circulation*. 1981;63:1329-1338
doi: 10.1161/01.CIR.63.6.1329

*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1981 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/63/6/1329

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

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

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