Survival in Subgroups of Patients with Left Main Coronary Artery Disease
Veterans Administration Cooperative Study of Surgery for Coronary Arterial Occlusive Disease

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SUMMARY This report presents the 42-month survival experience of 91 patients with a significant lesion of the left main coronary artery in the Veterans Administration Cooperative Study of Coronary Bypass Surgery. Survival in surgical patients was significantly better than that in the medical group (p = 0.016), even after adjustments were made for two important differences in baseline characteristics — duration of angina and high risk by angiographic criteria — between the two groups (p = 0.019). Subgroups based on severity of left main stenosis and on left ventricular (LV) function showed significant trends in favor of surgery in patients with more than 75% left main stenosis and in those with abnormal LV function. A similar but nonsignificant trend was seen in the two subgroups with 50–75% stenosis or with normal LV function. The surgical benefits were not significantly different from the categories of the subgroups defined separately by stenosis and LV function. Low-, middle- and high-risk subgroups based on four noninvasive clinical predictors also showed significantly improved survival with surgery in the high-risk group. The low-risk groups showed a slight, nonsignificant disadvantage with surgical treatment. These data support the view that patients with left main disease are not a homogeneous group. High- and low-risk subgroups with different outcomes and responses to treatment can be delineated by angiographic or clinical criteria. For most patients with left main disease, coronary artery bypass grafting offers improved longevity.

INTEREST in the management of patients with coronary artery disease has focused on subgroups of patients defined by arteriographic findings. In the Veterans Administration Cooperative Study, the first subgroup with significantly improved survival when managed surgically and followed for 2–3 years was that of patients with disease of the left main coronary artery.1 Other reports, including the only other randomized controlled study,2 confirmed this finding. Patients with left main disease are not a homogeneous group.3,4 Those with more severe stenosis or with an abnormality of left ventricular (LV) function were reported to have a worse prognosis.4 In coronary heart disease patients without left main disease, a benefit from surgery has also been reported in subgroups based on clinical criteria alone.5 In this report, we examine the effects of bypass surgery on survival and on the incidence of myocardial infarction (MI) in angiographically and clinically defined subgroups of patients with left main coronary artery disease.

Methods

The screening and selection of patients have been described.1,6,7 In brief, during 1972–1974, 686 adult male patients with angina pectoris entered the randomized controlled trial of the effect of the saphenous vein bypass graft operation on long-term survival. Review of all baseline coronary arteriograms revealed 91 patients who had a significant stenosis (at least 50% reduction of the luminal diameter) of the left main coronary artery. The coronary arteriograms were reviewed to confirm the presence of a significant left main lesion and to assess the degree of stenosis. MIs that occurred after randomization were identified in accordance with definitions used by the Coronary Drug Project1 and by Hultgren et al.8 (appendix A). ECGs and autopsy protocols, as well as most left ventriculograms, were reviewed centrally (appendix B).

In the left main subgroup, 43 patients were assigned to medical treatment and 48 to surgical treatment. Twenty-one medical and two surgical patients did not adhere to assigned therapy. * However, most of the crossovers from the medical to the surgical group occurred after 42 months of follow-up, when study clinicians were informed that a significant benefit from surgery had been identified. Therefore, survival comparisons for left main patients have been limited to the first 42 months of follow-up, because beyond that point the cumulative crossover rate increased markedly (fig. 1). Only eight patients (19%) crossed over to surgical treatment during this period.

The difference in the 42-month survival between the two treatment groups was evaluated by the Cox life-table regression model, which permits adjustment for baseline covariates.10 In the analysis, deaths were counted by treatment assignment, which counts all deaths by original treatment assigned, and by a crossover method, which does not count experience after crossover. Results are given only by treatment as-

*The nonadherence rate for the medical group was 11% at the time of our initial report.1

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signed because similar findings were obtained by the crossover method.

Differences in survival between treatment groups were evaluated within the following subgroups: (1) left main stenosis greater than 75% and 50–75%; (2) abnormal* and normal LV function; and (3) noninvasively derived low-, middle- and high-risk terciles, based on combinations of four clinical characteristics (table 1). The clinical patterns in the table describe increasing probability of dying based on a multivariate risk function. The distribution of certain baseline angiographic variables within low, middle and high noninvasive risk terciles was also examined.

The statistical methods have been described by DeRouen et al. Briefly, separate treatment effects (surgery vs medicine) were estimated simultaneously for each subgroup category from the Cox life-table regression model. A test of homogeneity was then constructed to determine if the separate treatment effects were the same across subgroup categories. A nonsignificant homogeneity test indicates that differences between treatment effects are due to chance variation, i.e., the treatment effect was constant across subgroup categories. A significant homogeneity test indicates that the effect of treatment was different for each subgroup category.

Results

Baseline comparability of the two groups with respect to 22 historical, electrocardiographic and angiographic characteristics, as well as severity of angina, is shown in table 2. Only one characteristic, duration of angina, was significantly different, being longer in the surgical group. A higher proportion of surgical patients had abnormal LV function (NS).

The distribution of two important angiographic characteristics at entry in each noninvasive risk tercile is shown in table 3. This demonstrates a marginal correlation between invasively and noninvasively derived risk categories, with significantly more severe coronary arterial disease and LV dysfunction distributed in the noninvasively derived high-risk group.

The average interval between randomization and surgery was 35 days. One surgically randomized patient had an acute MI 2 weeks after entry and died 2 years later without surgery. Three medically randomized patients died within 1 month of entry.

In the surgical group, two patients received a single bypass graft, 27 two grafts, and 17 three or more grafts. The 30-day operative mortality was 6.5% (three of 46).

At 42 months there was a significant \( p = 0.016 \) benefit in survival for patients treated surgically (fig. 2). This treatment difference remained significant after adjustment for high angiographic risk and duration of angina \( p = 0.019 \).

Table 4 shows survival and treatment comparisons in the subgroups based on degree of left main stenosis, LV function and clinical risk tercile. A significant beneficial effect on survival was observed for surgical

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*Abnormal LV size or cardiothoracic ratio greater than 0.49, abnormal left ventricular contractility, left ventricular end-diastolic pressure greater than 14 mm Hg or ejection fraction less than 45%.

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**TABLE 1. Clinical Pattern by Treatment Assigned (1972–1974 Left Main Lesion Cohort)**

<table>
<thead>
<tr>
<th>Clinical pattern</th>
<th>Probability of dying*</th>
<th>No. of pts</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low tercile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----</td>
<td>0.067</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>NY---</td>
<td>0.088</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>--HP</td>
<td>0.123</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>-MI</td>
<td>0.148</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Middle tercile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NY-HP</td>
<td>0.159</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>--ST</td>
<td>0.182</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>NYMI---</td>
<td>0.190</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>NY---ST</td>
<td>0.232</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>High tercile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-MIHP</td>
<td>0.261</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>--HPST</td>
<td>0.316</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>NYMIHP</td>
<td>0.329</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>MI-</td>
<td>0.369</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>NY-HPST</td>
<td>0.393</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>NYMI-</td>
<td>0.455</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>-MIHPST</td>
<td>0.582</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>NYMIHPST</td>
<td>0.683</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

One surgical patient has no tercile classification because of missing data.

*Five-year probability of dying predicted from multivariate risk function.

Abbreviations: NY = New York Heart Association class III or IV; HP = history of hypertension; MI = history of myocardial infarction; ST = ST depression on resting ECG; -- = absence of factor.
Table 2. Percent Distribution of Baseline Variables by Treatment Assigned (1972–1974 Left Main Lesion Cohort)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Medical (n = 43)</th>
<th>Surgical (n = 48)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(%)</td>
<td>(%)</td>
</tr>
<tr>
<td>Historical factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA class III-IV</td>
<td>60.5</td>
<td>62.5</td>
</tr>
<tr>
<td>Hx of MI</td>
<td>51.2</td>
<td>54.2</td>
</tr>
<tr>
<td>Duration of angina &gt; 1 year</td>
<td>55.8</td>
<td>79.2*</td>
</tr>
<tr>
<td>Hx of hypertension</td>
<td>30.2</td>
<td>27.1</td>
</tr>
<tr>
<td>Hx of CHF</td>
<td>7.0</td>
<td>10.4</td>
</tr>
<tr>
<td>Risk tercile†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>34.9</td>
<td>38.3</td>
</tr>
<tr>
<td>Mid</td>
<td>27.9</td>
<td>25.5</td>
</tr>
<tr>
<td>High</td>
<td>37.2</td>
<td>36.2</td>
</tr>
<tr>
<td>Angina questionnaire</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digitalis/diuretics</td>
<td>24.0</td>
<td>25.9</td>
</tr>
<tr>
<td>NTG once or more/day</td>
<td>53.8</td>
<td>55.6</td>
</tr>
<tr>
<td>Propranolol</td>
<td>44.0</td>
<td>48.1</td>
</tr>
<tr>
<td>Angina 4 episodes or more/day</td>
<td>32.0</td>
<td>25.9</td>
</tr>
<tr>
<td>Angina during sedentary activity</td>
<td>56.0</td>
<td>55.6</td>
</tr>
<tr>
<td>ECG factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any ECG abnormality</td>
<td>86.0</td>
<td>78.7</td>
</tr>
<tr>
<td>Evidence of MI</td>
<td>58.1</td>
<td>55.3</td>
</tr>
<tr>
<td>ST-segment depression</td>
<td>34.9</td>
<td>36.2</td>
</tr>
<tr>
<td>Angiographic factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal LV function</td>
<td>67.4</td>
<td>80.9</td>
</tr>
<tr>
<td>Abnormal LV contractility</td>
<td>55.8</td>
<td>72.3</td>
</tr>
<tr>
<td>3-vessel disease</td>
<td>93.0</td>
<td>81.3</td>
</tr>
<tr>
<td>High/low risk‡</td>
<td>60.5</td>
<td>68.1</td>
</tr>
<tr>
<td>LML &gt; 75%</td>
<td>48.8</td>
<td>47.9</td>
</tr>
<tr>
<td>Ejection fraction &lt; 50%§</td>
<td>27.8</td>
<td>17.0</td>
</tr>
</tbody>
</table>

*p < 0.02.
†Risk tercile based on four noninvasive variables: NYHA class III or IV, history of hypertension, history of MI, presence of ST-segment depression on resting ECG.
‡Angiographic high risk — three-vessel disease and abnormal LV function; low risk — one-, two-, or three-vessel disease and normal LV function; one- and two-vessel disease and abnormal LV function.
§Sixty-five ejection fractions were determined centrally and 25 were determined by the investigators.

Abbreviations: NYHA = New York Heart Association; Hx = history; MI = myocardial infarction; NTG = nitroglycerin; LV = left ventricular; LML = left main lesion.

Figure 2. Cumulative survival rates, by treatment assigned for patients with left main coronary artery disease, 1972–1974 cohort. M = medical; S = surgical.

Patients with stenoses greater than 75%. Although the difference in survival between treatment groups was not significant in the subgroup with 50–75% stenosis, the benefit was still in favor of surgery. The homogeneity test was not significant, indicating that the surgical benefits for the two stenosis subgroups were not sufficiently different. Further, a nonsignificant difference of 7% in favor of surgery was seen in 23 patients with normal LV function, while a significant difference of 27% in the same direction was observed in the 67 patients with abnormal LV function. However, the difference in survival between the two LV function subgroups was again not significant (homogeneity

Table 3. Distribution of Angiographic Variables by Tercile*

<table>
<thead>
<tr>
<th>Risk tercile</th>
<th>Low (n = 33)</th>
<th>Middle (n = 24)</th>
<th>High (n = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiographic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>risk group†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>17</td>
<td>53.1%</td>
<td>6</td>
</tr>
<tr>
<td>High</td>
<td>15</td>
<td>46.9%</td>
<td>18</td>
</tr>
<tr>
<td>Ejection fraction (%)§</td>
<td>32</td>
<td>65.6±11.7</td>
<td>24</td>
</tr>
</tbody>
</table>

*One patient was excluded because his risk tercile was unknown and one patient in the low tercile has unknown angiographic risk and ejection fraction.
†See table 2 for definitions of low- and high-risk groups.
‡Values are mean ± sd.

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Medical</th>
<th>Surgical</th>
<th>Difference$</th>
<th>Treatment\textsuperscript{+} effect</th>
<th>Homogeneity\textsuperscript{‡} $p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>91</td>
<td>0.65</td>
<td>0.88</td>
<td>0.23</td>
<td>0.016</td>
<td></td>
</tr>
<tr>
<td>Stenosis 50–75%</td>
<td>47</td>
<td>0.82</td>
<td>0.92</td>
<td>0.10</td>
<td>0.089</td>
<td>0.47</td>
</tr>
<tr>
<td>&gt; 75%</td>
<td>44</td>
<td>0.48</td>
<td>0.83</td>
<td>0.35</td>
<td>0.036</td>
<td></td>
</tr>
<tr>
<td>LV function</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>23</td>
<td>0.71</td>
<td>0.78</td>
<td>0.07</td>
<td>0.10</td>
<td>0.27</td>
</tr>
<tr>
<td>Abnormal</td>
<td>67</td>
<td>0.62</td>
<td>0.89</td>
<td>0.27</td>
<td>0.012</td>
<td></td>
</tr>
<tr>
<td>Tercile\textsuperscript{*}</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>33</td>
<td>0.93</td>
<td>0.83</td>
<td>-0.10</td>
<td>&gt;0.50</td>
<td>0.035</td>
</tr>
<tr>
<td>Middle</td>
<td>24</td>
<td>0.58</td>
<td>0.92</td>
<td>0.34</td>
<td>0.073</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>33</td>
<td>0.44</td>
<td>0.88</td>
<td>0.44</td>
<td>0.004</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{*}Missing data on one patient for each factor.
\textsuperscript{+}Test of overall difference in survival between treatment groups within a subgroup category.
\textsuperscript{‡}Test of equality of treatment effects across subgroup categories.
\textsuperscript{§}Surgical minus medical.

$p = 0.27)$, presumably because of the lack of power in the small samples.

In the high-risk tercile (n = 33), there is a significant survival benefit from surgery (88% vs 44%, $p = 0.004$), while in the middle-risk subgroup (n = 24), the surgical benefit is only marginally significant (92% vs 58%, $p = 0.073$). The low-risk tercile shows a slight nonsignificant disadvantage from surgery (83% vs 93%) (fig. 3). However, it would be difficult to find any subgroup of patients with left main disease whose survival rate is better than the 93% observed in this small medical group (n = 15). The test of the homogeneity of the treatment differences across the terciles was significant ($p = 0.035$).

Fifty of 43 operated patients (93%) who survived 1 year had angiography approximately 1 year after surgery to visualize the vein grafts. Three patients died during the first postoperative year of follow-up. Table 5 shows graft patency rates by risk tercile in the 40 patients who had a 1-year study. Seventy-two of 94 grafts placed were patent (77%), a higher rate than reported for the earlier 1970–1974 cohort.\textsuperscript{1}

None of the 12 patients in the low-risk tercile who had vein graft studies 1 year postoperatively (which provided the data for the 1-year graft patency rate of 64% for this tercile) died. None of the three patients in this subgroup who died had postoperative vein graft study, two because they died within the first year and one because he had no graft angiography.

Table 6 is a summary of the number of MIs by treatment assigned. Twenty-eight percent of the medical and 31% of the surgical group had at least one MI. There were 15 MIs in the medical and 19 MIs in the surgical group. Including both definite and suspected MIs, the fatality rates due to MI were 18.6% in the medical group and 6.3% in the surgical group ($p =$

\textbf{FIGURE 3. Cumulative survival rates in risk terciles by treatment assigned.} M = medical; S = surgical.
0.071). If one excludes suspected fatal MIs, the fatality rates for the medical and surgical groups were not different. There were eight definite perioperative MIs among 46 surgically randomized and operated patients (17%), including two that were fatal (4.3%). There were two surgical nonadherers and eight medical crossovers; similar results were obtained when the analysis was repeated for adherers only. One surgical patient had a preoperative MI. There were no perioperative MIs in the medical crossover group and only one nonfatal MI after surgery in this group. One of the two surgical nonadherers had a nonfatal MI.

In the medical group, the number of MIs was about the same for each tercile, but six of the eight fatal MIs were in the high-risk tercile. Eleven of 19 total MIs and two of three fatal MIs for surgical patients were in the low tercile. Because of the small numbers, treatment comparisons between terciles were not made for MI.

Causes of death were examined in detail for the 42 months of follow-up. There were 21 deaths, 15 among the medical adherers, none in the eight medical crossovers and six in the surgical group. The cause of death in all but two of the 21 cases was proved by autopsy or was clinically judged to be cardiac. There were only two noncardiac deaths, both in the medical group. One noncardiac death was due to suicide and the other to fibroliposarcoma. Specific cardiac causes of death in the remaining medical patients were acute MI in seven (proved by autopsy in two); probable cardiac arrhythmia resulting in sudden death but without evidence of acute MI in four (with autopsy in one case, showing severe coronary atherosclerosis); and probable cardiac death with neither MI nor sudden death in the remaining two patients. Four of the six cardiac deaths in the surgical group were attributed to acute MI, documented by autopsy in three. Two of these were perioperative and one was a late fatal MI in a patient who refused surgery. An additional perioperative death was caused by a technical problem (dehiscence of the internal mammary artery–coronary artery anastomosis). The sixth death occurred in an unoperated patient 2 years after randomization and was attributed to congestive cardiac failure.

The incidence of sudden death (within 24 hours of onset of symptoms of the terminal event) was 14% (six of 43) in the medical and 0% in the surgical group (p = 0.007).

**Discussion**

The initial report on the subgroup of patients with left main disease included the years 1970 and 1971, designated a "learning period," before adequate experience with angiographic and surgical techniques had been obtained in many cooperating institutions. To increase the probability of obtaining a comprehensive and valid comparison of treatment methods, the years 1972–1974 were prospectively designated as the definitive years of the study. The results noted in the earlier report were the same as those reported here. They constituted the first indication of the beneficial effects of bypass surgery in a randomized controlled trial of patients who had significant disease of the left main coronary artery.

In the earlier report, we demonstrated the effect of abnormal LV function and presence of right coronary artery disease on both natural history and treatment. For patients who had the above risk factors the prognosis was very poor and the benefit due to surgery was great. In patients without these risk factors, the treatment effect was more modest. Lee et al. suggested that the distribution of baseline risk factors could have accounted for the favorable

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**Table 5. Patency Rates by Tercile in Patients with Left Main Lesions: 1972–1974**

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of vessels grafted</th>
<th>No. of grafts patent</th>
<th>Patency rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tercile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>28</td>
<td>18</td>
<td>64.3%</td>
</tr>
<tr>
<td>Middle</td>
<td>27</td>
<td>22</td>
<td>81.5%</td>
</tr>
<tr>
<td>High</td>
<td>38</td>
<td>32</td>
<td>84.2%</td>
</tr>
<tr>
<td>Total</td>
<td>93</td>
<td>72</td>
<td>77.4%</td>
</tr>
</tbody>
</table>

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**Table 6. Distribution of Definite and Suspected Myocardial Infarction within 42 Months of Entry by Treatment Assigned**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Medical (n = 43)</th>
<th>Surgical (n = 48)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(No. of pts) (%)</td>
<td>(No. of pts) (%)</td>
</tr>
<tr>
<td>No. of MIs/pt</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>31 (36) 72.1 (83.7)</td>
<td>32 (34) 66.7 (70.8)</td>
</tr>
<tr>
<td>1</td>
<td>10 (6) 23.3 (14.0)</td>
<td>15 (13) 31.3 (27.1)</td>
</tr>
<tr>
<td>2</td>
<td>1 (0) 2.3 (0.0)</td>
<td>0 (0) 0.0 (0.0)</td>
</tr>
<tr>
<td>3</td>
<td>1 (1) 2.3 (2.3)</td>
<td>0 (1) 0.0 (2.1)</td>
</tr>
<tr>
<td>4</td>
<td>1 (0) 2.1 (0.0)</td>
<td></td>
</tr>
<tr>
<td>No. of MIs</td>
<td>15 (9)</td>
<td></td>
</tr>
<tr>
<td>No. of perioperative MIs*</td>
<td>2 (2) 25.0 (25.0)</td>
<td>9 (8) 19.6 (17.4)</td>
</tr>
<tr>
<td>No. of fatal MIs</td>
<td>8 (3) 18.6 (7.0)</td>
<td>3 (3) 6.3 (6.3)</td>
</tr>
</tbody>
</table>

*Numbers in parentheses refer to definite MIs (see appendix).
*Perioperative MI rates were calculated for eight medical and 46 surgical patients.
Abbreviations: MI = myocardial infarction.
surgical outcome in the left main subgroup. We have shown, however, that the findings remain significant even after adjustment for risk factors. The European Study Group confirmed the Veterans Administration left main findings, as have most recent observational studies.

The heterogeneity of patients with left main lesions has been pointed out by several observers, but disputed by others, insofar as the need for surgical management is concerned. Conley et al., in their study of the natural history of the disease, found that medically treated patients with left main lesions less than 70% had survival rates similar to those of patients with three-vessel disease without left main lesions. A poorer prognosis was associated not only with lesions of 70% or greater, but also with certain noninvasive risk factors, including a history of congestive failure, the presence of rest pain, cardiomegaly, ST-segment depression on the resting ECG, and an abnormal left ventricular contraction pattern.

Campeau et al. compared the survival of subsets of medically and surgically treated patients in a nonrandomized retrospective study and found significantly improved survival after surgery in patients with left main stenoses greater than 50% and associated stenoses greater than 70% of the right coronary artery. However, survival remained significantly higher in operated than in unoperated patients whether luminal diameter of the left main artery was reduced to 50-60% or to more than 70%. They also found a significant benefit for surgery in two left main subgroups: LV ejection fraction of 45% or greater and LV end-diastolic pressure less than 20 mm Hg. No significant treatment differences were observed for the more severe categories of ejection fraction or LV end-diastolic pressure.

In the randomized controlled study by the European group, significantly improved survival at 3 years was reported in operated patients with left main stenosis greater than 50% and LV ejection fraction greater than 50%. In that study, no subgroup analyses were reported, probably because only 59 patients had left main disease.

The Veterans Administration results show a significant benefit for surgery in three subgroups of patients with left main disease: stenosis greater than 75%, abnormal LV function, and high noninvasive risk. Despite the lack of statistical significance in the subgroups with normal LV function and lesser left main stenosis, surgery had a beneficial effect in these subgroups also.

Similarly, patients in both the noninvasive high- and middle-risk terciles have improved survival with surgical treatment. Medical patients in the noninvasive low-risk tercile had a 93% 42-month survival, which might be difficult to improve upon by any form of treatment. Indeed, the treatment comparison shows that for this subgroup, surgery may be detrimental. The small, nonsignificant survival disadvantage for surgery in the low-risk tercile indicates that some patients with left main disease have a favorable prognosis when treated medically. This result agrees with our finding in the larger group of patients without left main disease.

Table 3 indicates that there is a marginal relationship between noninvasively derived prognostic risk factors and those identified by invasive or angiographic techniques. Thus, severity of anatomic disease and of physiologic dysfunction can be predicted to some extent by classifying patients in accordance with noninvasive criteria. This relationship may be part of the explanation for the clearcut differences in prognosis of the natural history of the disease in the control group when they are divided into the three noninvasive risk terciles.

Chaitman and associates reported the heterogeneity of patients with left main lesions in a study of 1172 nonrandomized operated cases by identifying several factors that delineate patients at high and low operative risk. For example, while overall operative mortality was 4.2%, patients in the high-risk group, delineated by left coronary artery dominance, had an operative mortality of 12%. In our study, overall operative mortality was 6.5% (three of 46), but for patients with left coronary artery dominance, mortality was 14% (one of seven).

Perioperative MI rates after aortocoronary bypass surgery have varied from 4% to 27%, depending on methods of detection and diagnostic criteria used, selection of patients, and anesthetic, surgical and myocardial preservation techniques. For patients with left main lesions, MI rates of 3%, 14% and 15% have been reported, using more stringent diagnostic criteria than ours. In accordance with the definitions in appendix A, the rate of perioperative MI in this study was 19.6%.

In our patients who underwent the operation between 1972 and 1974, bypass surgery did not appear to alter the incidence of MI significantly. Fatal MIs, both definite and suspected, were fewer among surgically randomized patients (6% vs 18.6%), but when the analysis was limited to definite MI, the rates were almost identical (6% vs 7%). Sudden death was not seen after surgery during the observation period, in contrast to a 14% incidence in medically randomized patients (p = 0.007). With the improvements in anesthetic and myocardial preservation techniques introduced after the close of this study, the reported incidence of perioperative MI for patients with coronary bypass surgery is considerably lower than that reported here.

Randomized controlled trials of surgical procedures have been criticized when the number of patients who did not adhere to the assigned therapy becomes large. This problem is compounded when, during the course of the trial, a significant difference in outcome between surgical and nonsurgical treatment groups is identified. Ethical considerations require that these findings be made known to participants and to patients in the study, so that they may be offered the therapy that is proving to be more effective. When this happens, the value of the controlled trial is compromised because the randomization is impaired. To assure the validity
of the study, outcome comparisons between treatment groups were limited to 42 months of follow-up. This restriction avoids the problem of making too many assumptions and attempts to adjust for known discrepancies in the analysis of the data.

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References
Appendix A

Definition of Myocardial Infarction

A. Definite acute MI was diagnosed if one of the following criteria was met:
1. New abnormal Q wave findings not present on patient’s last ECG;
2. Clinical symptoms compatible with MI in conjunction with serum enzyme elevation and newly developed persistent (1–3 months) nonspecific ECG findings such as ST-segment changes, T-wave changes ventricular or atioventricular conduction defects, or arrhythmias;
3. Clinical symptoms compatible with MI with serum enzyme elevations without ECG findings.

B. Definite acute MI was classified as fatal if
1. death occurred within 4 weeks of acute MI and no autopsy was done;
2. myocardial necrosis was identified at autopsy either grossly or microscopically;
3. death occurred within 8 hours of acute MI, characterized clinically by typical chest pain and accompanied by either of the following:
   (a) confirmatory ECG or enzymatic findings or
   (b) autopsy evidence of coronary occlusive disease or myocardial necrosis.

C. Definite MI was nonfatal if none of the criteria for fatal MI was present.

D. Suspected MI was diagnosed when clinical symptoms compatible with MI were reported accompanied by either of the following:
1. new nonspecific ECG findings, such as ST-T changes, and borderline serum enzyme elevations or enzyme studies not done;
2. no new ECG findings or ECG not done and borderline serum enzyme studies not done.

E. Suspected MI was classified as fatal when
1. death occurred within 4 weeks of the clinically suspected MI and no autopsy was done;
2. death occurred within hours of the clinically suspected acute MI and autopsy yielded no evidence of myocardial necrosis.

F. Postoperative MIs were classified as definite or suspected using specific criteria.*

1. Definite postoperative MI:
   (a) new persistent Q wave of 0.04 second or longer on ECG; or
   (b) new QS deflections on ECG associated with characteristic evolutionary changes in ST segment and T-waves; or
   (c) ECG evidence of acute ischemic injury accompanied by abnormal serum enzyme levels (CPK > 200, LDH > 900, SGOT > 90). (Ischemic injury changes on ECG include: flat ST-segment depression > 2 mm on left ventricular leads persisting > 48 hours; deep T-wave inversions persisting for 48 hours; ventricular arrhythmias such as ventricular tachycardia or fibrillation; absence of new significant Q waves or QS deflections.)

2. Suspected postoperative MI was diagnosed if only ECG or enzymatic criteria (1c), but not both, were present.

Appendix B

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-Investigators: Andrew A. Gage, M.D. Physician: Italo Besseghini, M.D.

Cleveland, Ohio — Co-Investigators: Berian Davies, M.D., Julie Clayman, M.D. Past Co-Investigator: Cathel A. Macleod, M.D. Past Physicians: Robert C. Bahler, 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., Kenneth Piters, M.D. Past Co-Investigators: Harold W. March, M.D., Nolan Resnick, M.D., Jack C. Kern, M.D., Joan Orlando, M.D., Michael B. Pine, M.D.

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

Minneapolis, Minnesota — Co-Investigators: Gordon L. Pierpont, M.D., Yoshiho 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; Past Cardiological Co-Chairman: David Littmann, M.D.

Cooperative Studies Program Coordinating Center


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; Consultant: 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), Bethesda, Maryland.

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ECG Reading Center
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LV Angiogram Analysis Lab
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