Medical Compared With Surgical Management of Unstable Angina

5-Year Mortality and Morbidity in the Veterans Administration Study

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We evaluated medical in comparison to surgical plus medical (surgical) treatment of unstable angina using a prospective randomized protocol that stratified patients by clinical presentation and by invasive evaluation of left ventricular (LV) function. Clinical presentations were as follows—type 1: progressive or new onset angina relieved by medication; type 2: prolonged bouts of angina poorly or incompletely relieved by medication. Abnormal LV function was arbitrarily defined as ejection fraction less than 0.50 or LV end-diastolic pressure 16 mm Hg or more. Of 468 patients, 237 were assigned to medical and 231 to surgical therapy. There were 374 type 1 and 94 type 2 patients. LV function was normal in 334 and abnormal in 134 patients. Compared with results at 24 months, this 60-month follow-up study showed important differences in survival for patients with three-vessel disease: 75% for medical and 89% for surgical patients (p<0.02). The cumulative 5-year rate of repeat hospitalizations for cardiac reasons was less with surgical patients for either clinical presentation. For type 1, medical patients had a 56% rate, and surgical patients had a 42% rate (p=0.004). For type 2, medical patients had a 62% rate, and surgical patients had a 43% rate (p=0.05). Overall mortality did not differ between the two treatments, and this remained true in type 1 versus type 2 patients and in those with normal versus abnormal LV function. However, regression analysis of medical and surgical groups with ejection fraction as a continuous variable showed that mortality of medical patients depended on ejection fraction (p=0.004), whereas the mortality of surgical patients did not (p=0.76), and survival in the surgical group was higher in the lowest ejection fraction tercile—73% for medical and 86% for surgical patients, p=0.03. We conclude that surgery improves survival in patients with three-vessel disease and leads to fewer subsequent hospitalizations for cardiac reasons. An impaired ejection fraction had an adverse impact on survival of medical patients but not on surgical patients, and mortality in surgical patients was improved compared with medical patients in the lowest ejection fraction tercile. (Circulation 1989;80:1176–1189)

The intermediate and long-term outcome of medical compared with surgical management of patients with unstable angina pectoris has not been fully defined. In 1978, the National Heart, Lung, and Blood Institute (NHLBI) reported

*For the Veterans Administration Cooperative Study Group 28; see Appendix 3.

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a 30-month average follow-up of 288 randomized patients showing superior symptom relief but no overall survival differences between medical and surgical groups.1 Before this report, the Veterans Administration had undertaken a prospective, stratified, and randomized study of unstable angina that culminated in the enrollment of 468 patients during a 6-year period ending June 30, 1982. The first report of end-point data at a minimum follow-up of 24 months substantially confirmed the NHLBI study conclusions on overall medical and surgical survival—a high initial crossover rate to surgery and no difference in the occurrence of nonfatal myocardial infarctions in the medical and surgical cohorts. However, significantly increased survival was shown for surgical patients who had impaired ejection
fractions. A recent interim paper at 36 months of follow-up reported on 134 of these 468 patients with abnormal left ventricular function, which was prospectively defined as an ejection fraction less than 50% or a left ventricular end-diastolic pressure equal to or greater than 16 mm Hg. The cumulative 3-year mortality for surgical patients with left ventricular dysfunction so defined was 6.1%, whereas it was 17.6% for comparable medical patients \( p = 0.039 \). This report once again addresses the outcomes of the entire 468 randomized patient cohort at a mean follow-up of 72 months (minimum of 60 months for all patients). It shows how effective medical and surgical therapies are in the long-term by providing important information on survival and cardiac events for and within each of the treatment cohorts.

**Methods**

Male patients less than 70 years of age admitted for chest pain were screened and offered a coronary arteriogram if they proved to have unstable angina. Their syndrome was stratified by clinical criteria into type 1 or type 2. Type 1 patients had angina pectoris for more than 2 months that had progressed symptomatically because of an increase in the frequency of episodes (doubling of the average number of attacks per day) or in its severity (doubling of the average daily dose of nitrates) or because angina appeared at rest within 8 weeks of the time when the patient was considered for entry. The qualifying symptoms had to have been present within 10 days of the date of entry. Type 1 patients also included those with angina pectoris of 2 months or less in whom pain was produced by less than ordinary activity (New York Heart Association class III) or with angina of recent onset with recurrent chest pain at rest. Electrocardiographic changes, that is, ST segment depression of 1 mm or more or T wave inversion, were sought with the resting chest pain. A positive exercise test was required if a patient did not have ST segment or T wave changes during chest pain at rest.

Type 2 unstable angina was defined as recurring episodes of prolonged chest pain resistant to or incompletely relieved by nitrates. At least one episode of chest pain at rest lasting 15 minutes or more was required within 10 days of entry in the study. Documentation of ST segment depression or elevation of 1 mm or more or of T-wave inversion during at least one episode of pain was required. Serial electrocardiograms and serum creatine kinase measurements were used to exclude acute myocardial infarction.

**Screening and Informed Consent**

Exclusion was performed hierarchically with the first reason for exclusion tabulated during the screening process (Appendix 1). Written, informed consent was obtained for ventriculography, coronary arteriography, randomization, and subsequent follow-up studies, including repeat arteriography at 1 year. A coronary stenosis was defined as critical if the diameter of a lumen was decreased by 75% or more as determined by inspection of the opacified lumen of the artery in multiple views. The left ventricular ejection fraction was calculated with the area or volume method from a 30° right anterior oblique projection. The principal reasons for exclusion after arteriography included left main stenosis, normal coronary arteries, or coronary arteries without critical stenoses (Appendix 2).

**Randomization, Stratification, and Follow-up**

A date for "operation" was chosen before randomization. The patients were stratified by type of unstable angina and ventricular function. Ventricular function was defined as normal if the left ventricular ejection fraction was 0.50 or higher and if the left ventricular end-diastolic pressure was less than 16 mm Hg. Randomization was performed centrally at the Coordinating Center, West Haven, Connecticut, immediately after the patient was accepted as an operative candidate. The patient was assigned to receive either medical therapy alone or surgical therapy plus medical therapy (hereafter referred to as "surgical therapy"). Therapy was considered to start on the preselected date of operation for medical patients and on the actual date of operation for surgical patients. Follow-up began with the starting date of therapy. Electrocardiograms were obtained on days 1, 2, 3, 5, and 10 of follow-up in all patients. Perioperative myocardial infarctions were defined as Q wave infarctions (see criteria immediately below) occurring on the day of operation or up to and including the 10th postoperative day. Patients were examined quarterly during the first 2 years and semiannually thereafter. At 1 year, all patients were scheduled for a second cardiac catheterization to image the native coronary circulation and any aortocoronary grafts. Left ventricular angiography was also performed.

**Interpretation of Electrocardiograms and Angiograms**

Interpretations of electrocardiograms and angiograms presented here are those of the local investigators. There was agreement between participating investigators and central angiographic review regarding number of major vessels involved on 440 (95%) of 464 baseline cineangiographic films. All electrocardiograms were interpreted centrally with a Hewlett-Packard 5000 ECG Management System and were edited by the same cardiologist. A transmural myocardial infarction was defined by the appearance of Q waves or QS deflections lasting for 0.04 second or longer, with evolutionary ST-T wave changes on the electrocardiogram and at least one of the following: a history compatible with a myocardial infarction or an increase in myocardial (MB) creatine kinase that was 1.5 times normal or higher or twice baseline, with an appropriate rise and fall.
to normal or baseline values. A non-Q wave myocardial infarction was defined by persistent (>24 hours) ST depression or T wave inversion without the appearance of new Q waves and by either an appropriate history or enzyme changes (or both) as described above. A myocardial infarction was defined as fatal if death occurred within 30 days after its onset.

Statistical Analysis and Sample Size

Operative mortality included any death occurring within 30 days after surgery. A corresponding 30-day mortality rate for medically treated patients was defined as the number of deaths occurring within 30 days after the assigned start of therapy. Life table methods were used to calculate cumulative survival and morbidity rates from date of assigned start of therapy. The Mantel-Haenszel statistic was used to evaluate differences between the cumulative curves. The primary analysis was performed according to treatment assigned at randomization, regardless of adherence. Multiple logistic regression analysis was used to study the relation between baseline variables and survival. Analyses involving the effect of baseline ejection fraction took into account assigned treatment, baseline ejection fraction, and the interaction between assigned treatment and baseline ejection fraction. The left ventricular ejection fraction (LVEF) was treated as a continuous independent variable. The logistic curve with the best fit was calculated as mortality = 1/[1 + e^{-(a+bLVEF)}] in which the values of the coefficients a and b were obtained by an iterative process. Maximum likelihood estimates were computed by the Newton-Raphson method. The sample sizes were separately planned for the type 1 and type 2 groups to detect a 50% reduction in the 5-year mortality rate for surgical compared with medical therapy at a power of 0.95. This was based on an assumed medical mortality of 30% at 5 years for type 1 patients and 50% at 5 years for type 2 patients. It was estimated that 400 type 1 and 200 type 2 patients would be needed to achieve this goal. All p values reflect two-sided tests of significance.

Treatment

No patient was required to follow a fixed daily regimen of drugs without regard to symptoms. Investigators were free to use approved antianginal drugs of their choice alone or in combination. Diet, weight reduction, cessation of smoking, systematic exercise, and regulation of work and leisure activities were all considered part of medical treatment. Long-term anticoagulation with warfarin (coumadin) or heparin was not used, but administration of aspirin or dipyridamole alone or together was allowed. Aspirin was not used systematically during the initial hospitalization. Aortocoronary saphenous vein bypass grafting was performed as described by Favaron. One patient received an internal mammary artery graft because a suitable vein was not available for grafting. Initially, cardiopulmonary bypass with moderate hemodilution and mild hypothermia with aortic cross-clamping was used. Later, cold potassium cardioplegia was used and became routine by 1978.

Approval of Protocol

The protocol for the study was approved by the Veterans Administration Cooperative Studies Evaluation Committee, the Human Rights Committee of the West Haven Cooperative Studies Program Coordinating Committee, and the Research and Development Committee and Human Rights Subcommittee of each participating Veterans Administration Medical Center. A Data Monitoring Board of outside experts, which was not involved in the planning or the day-to-day implementation of the study, monitored the results.

Results

Outcome of Randomization

Of the 468 patients randomized, 237 were assigned to medicine and 231 to surgery. There were 374 type 1 patients and 94 type 2 patients; 134 (29%) of all patients had abnormal left ventricular function. There was no significant difference in the distribution of these clinical and functional characteristics between medical and surgical cohorts. Specific prognostically related characteristics including age, prior myocardial infarction, diabetes, hypertension, number of major epicardial vessels involved, and ejection fraction were similarly distributed between the medical and surgical cohorts (Table 1).

Outcomes of Initial Hospitalization and Graft Patency

Outcome of initial hospitalization and graft patency at 1 year have been reported previously. No deaths occurred while the patients awaited surgery. For medical treatment, the mean and median intervals between randomization and the prerandomization start of therapy were 3.6 and 4.0 days, respectively. For surgical treatment, the mean and median intervals between randomization and operation were 9.3 and 5.0 days, respectively. Nine deaths occurred at or within 30 days of surgery, which was an operative mortality of 4.1% (4.3% for type 1; 2.1% for type 2). The average number of grafts placed was 2.7 per patient. Selective contrast arteriography at 1 year was performed in 67% (140 of 209; 115 type 1 and 25 type 2) eligible surgical patients. Of 365 grafts studied, 273 (74.8%) were patent. The patency rate was 75.3% (226 of 300) in type 1 and 72.3% (47 of 65) in type 2 patients. The percentage of type 1 patients with at least one graft patent at the end of 1 year was 92.2, and for type 2 patients, the corresponding percentage was 88.0. The percentages of type 1 and type 2 patients with all grafts patent at the end of 1 year were 54.8 and 52.0, respectively.
TABLE 1. Baseline Characteristics of Randomized Patients

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Type 1</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Medicine</td>
<td>Surgery</td>
<td>Medicine</td>
</tr>
<tr>
<td></td>
<td>(n=237)</td>
<td>(n=231)</td>
<td>(n=190)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>56.3±6.9</td>
<td>55.7±7.1</td>
<td>56.2±6.9</td>
</tr>
<tr>
<td>History of myocardial infarction</td>
<td>42.6</td>
<td>41.7</td>
<td>40.5</td>
</tr>
<tr>
<td>Diabetes</td>
<td>17.9</td>
<td>16.2</td>
<td>17.0</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>129.4±17.7</td>
<td>132.5±21.2</td>
<td>128.9±17.2</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>79.4±10.3</td>
<td>80.7±11.1</td>
<td>79.2±10.3</td>
</tr>
<tr>
<td>Abnormal left ventricular function</td>
<td>28.7</td>
<td>28.6</td>
<td>30.0</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>62.7±12.6</td>
<td>63.5±13.8</td>
<td>62.6±12.5</td>
</tr>
<tr>
<td>Vessels diseased</td>
<td>One</td>
<td>18.6</td>
<td>18.8</td>
</tr>
<tr>
<td></td>
<td>Two</td>
<td>33.1</td>
<td>36.7</td>
</tr>
<tr>
<td></td>
<td>Three</td>
<td>48.3</td>
<td>44.5</td>
</tr>
</tbody>
</table>

Values are mean±SD where applicable.

Adherence to Randomization Assignment

Figure 1A shows the cumulative rate of crossover of patients who failed medical therapy and received bypass surgery. Of the 237 patients originally assigned to medical therapy, 96 (43%) failed treatment and received surgical therapy by 60 months. Fifty of these patients crossed over in the first 6 months after randomization, and another 27 patients crossed over in the subsequent 12 months. Thus, more than three fourths of the patients failing medical treatment occurred within 18 months of randomization. In the first 30 days, the crossover rate was higher among patients with type 2 than among those with type 1 (19.1% vs. 5.8%, \(p<0.01\)) stratification assignment. Thereafter, the clinical presentation (type 1 vs. type 2) did not forecast a different crossover rate (Figure 1B). The operative mortality based on all crossover patients to 5 years was 8.3%, which was eight of 96 patients.

Eleven patients did not undergo surgery after having been assigned to it and were classified as crossover patients to medical therapy.

Survival

The status of each of the 468 randomized patients was determined for the entire 5 years of follow-up. For those surviving patients who were not seen in the clinic at the end of 5 years (8.5%; 40 of 468; 17 medical and 23 surgical), survival status and new hospitalization status were determined from the VA National Patient Treatment Files and the VA Burial Identification and Records Locator Subsystem. The overall survival at 60 months was 81% in the medical group and 84% in the surgical group (\(p=0.45\), Figure 2). When mortality was analyzed according to prerandomization stratification by clinical presentation, there were also no significant differences shown in survival (Figures 3A, 3B). The mortality for type 2 patients treated surgically was 15% compared with 23% for type 2 patients treated medically, but this difference was not statistically significant (\(p=0.29\), Figure 3B).

There was also no difference in 5-year mortality between the two treatment groups when the data were analyzed in terms of normal or abnormal left ventricular function or ejection fraction greater or less than 0.50 (Table 2). The 60-month medical mortality for patients with ejection fraction less than 0.50 was 33% (14 of 42); the 60-month surgical mortality for patients with ejection fraction less than 0.05 was 21% (eight of 39); \(p=0.22\). Thus, the previously reported significant 36-month survival advantage for surgical patients with ejection fractions less than 0.50 was not sustained. Because of the limitations of using left ventricular ejection fraction as a categorical variable,\(^2\) that is, with arbitrary operator cutoff points, we have continued to analyze 5-year mortality using left ventricular ejection fraction as a continuous variable (Figure 4). There was no dependence of mortality on left ventricular ejection fraction in the surgical group; the slope of the line relating mortality to left ventricular ejection fraction is not significantly different from zero (\(p=0.76\)). On the other hand, there is a significant (\(p=0.004\)) dependence of mortality on ejection fraction for patients treated medically. The worse the ejection fraction, the poorer was survival in the medical patients. A similar conclusion is reached when 5-year mortality is related to left ventricular function by dividing the total population into thirds throughout the entire range of ejection fraction (Table 2). In the lowest ejection fraction tercile, cumulative 5-year mortality for patients undergoing surgery was 14% compared with 27% for those patients treated medically (\(p=0.03\)).

When outcomes were analyzed using coronary angiographic characteristics, significant differences emerged for certain patient subgroups. Figure 5A–C is a composite showing cumulative mortality of medical compared with surgical therapy in patients with one-, two-, and three-vessel disease. Surgical therapy led to a significantly lower mortality than
medical therapy (11% vs. 24%, \( p<0.02 \)) when patients had three-vessel disease. The survival advantage for surgical patients became significant only after 36 months after the start of therapy. If three-vessel disease with left ventricular dysfunction is considered, the subgroup diminishes in size \((n=216\) for three-vessel disease; \(n=70\) for three-vessel disease and left ventricular dysfunction), but the survival advantage for surgery increases (29% medical vs. 9% surgical mortality at 60 months; \( p<0.05 \)).

**Nonfatal Myocardial Infarction**

A total of 78 nonfatal myocardial infarctions were documented throughout this 5-year follow-up period for an overall incidence of 16.7%. Of these, 42

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**Figure 1.** Panel A: Plot of cumulative crossover of medical patients to surgical therapy. The first point represents crossover at 1 month; remaining points are at 6-month intervals. Panel B: Plot of cumulative crossover of medical patients subdivided into type 1 or type 2 clinical presentation. (Plot as in Panel A.)
occurred in the medical group and 36 in the surgical group (NS). Classification by prerandomization stratification into type 1 versus type 2 or normal versus abnormal left ventricular function showed similar outcomes in the medical and surgical cohorts (Table 3). Combining all myocardial infarctions and all deaths as significant events also did not show a significant difference between medical and surgical cohorts or any prerandomization grouping.

Perioperative (up to 10 day) myocardial infarction occurred in 27 of 231 patients (11.7%); the rate was 10.3% (19 of 184) in type 1 patients and 17.0% (eight of 47) in type 2 patients; \( p=0.20 \). For medical patients, myocardial infarction in the first 30 days after assigned "start of therapy" occurred in 11 of 237 patients (4.6%); the rate was 2.6% (five of 190) in type 1 patients and 12.8% (six of 47) in type 2 patients (\( p=0.003 \)).

New Hospitalizations

There were 74 new hospitalizations in the medical cohort and 52 in the surgical cohort in the first 6 months after randomization. In semiannual intervals thereafter, hospitalizations reported as percentage of patients initially at risk were nearly equal in each group. Thus, in the remaining 54 months of the 60-month follow-up, there were 101 hospitalizations in the medical group and 103 in the surgical group (\( p=0.06 \)).

When hospitalization for cardiac reasons (primarily recurrent angina) were evaluated, there was an important difference between medical and surgical groups. Hospitalization was twice as frequent in the medical cohort in the first 6 months after randomization (22% vs. 11%), and the difference in cumulative occurrence increased slightly, thereafter being 32% versus 19% at 1 year and 57% versus 43% at 5 years in each cohort (\( p=0.001 \)). This remained true when patients were subdivided by type 1 and type 2 presentation (Figures 6A and 6B).

Drug Therapy

Drug therapy was tracked for use of nitrates and \( \beta \)-blockers from the inception of the study. Calcium channel blockers were not FDA approved when the study began and were not subsequently reported. Table 4 shows the distribution of medical and surgical patients reporting use of nitrates and \( \beta \)-blockers at 1, 3, and 5 years. The percentage of surgical patients taking nitrates was significantly less than medical patients taking nitrates at each of these points. Although the percentage of surgical patients taking \( \beta \)-blockers was also significantly less than the percentage of medical patients taking \( \beta \)-blockers at 1 and 3 years, this difference was not significant at 5 years.

Discussion

The findings reported here add substantially to our previous report\(^2\) of survival outcome in this study group at 24 months of follow-up after randomization. In that earlier report, a survival difference between medical and surgical cohorts was not shown either for the overall groups or for patients with one-, two-, or three-vessel disease as determined by baseline angiography. As is evident from Figure 5C, an important divergence in mortality occurred between 24 and 36 months in the three-vessel dis-
ease subgroups. By 60 months, the mortality in the medical group was 24%, whereas in the surgical group, it was 11% ($p=0.014$). This observation indicates that the full impact of a surgical procedure on survival of patients with three-vessel disease is not necessarily detected by follow-up periods as short as 2 years. This outcome is consistent with similar observations made in the Coronary Artery Surgery Study (CASS) and VA trials evaluating coronary bypass surgery for patients with stable angina. The NIH study of unstable angina was terminated after a mean follow-up of 30 months, thus precluding such observations in the only comparable multicenter trial of unstable angina to date. The survival advantage at 5 years for patients with three-vessel disease who received surgical therapy
was independent of left ventricular function, which is an important difference from the CASS and prior VA coronary surgical trials of stable angina pectoris but which is consistent with the European Coronary Surgery Study.14

Another important variable relating to 5-year mortality is abnormal left ventricular function. This was the focus of our interim 36-month report3 that addressed survival in the 134 of these 468 patients with left ventricular dysfunction, which was defined

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**TABLE 2. Mortality Rate by Ejection Fraction**

<table>
<thead>
<tr>
<th>Therapy (mo)</th>
<th>Medical (%)</th>
<th>Surgical (%)</th>
<th>Medical and Surgical (%)</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ejection fraction of 30–49 (n=42)</td>
<td>12±5</td>
<td>3±3</td>
<td>9</td>
<td>0.11</td>
</tr>
<tr>
<td>36</td>
<td>24±7</td>
<td>8±4</td>
<td>16</td>
<td>0.05</td>
</tr>
<tr>
<td>60</td>
<td>33±7</td>
<td>21±6</td>
<td>12</td>
<td>0.22</td>
</tr>
</tbody>
</table>

| Ejection fraction of ≥50 (n=191) | 6±2        | 9±2          | 5±2                      | 1       | 0.71|
| 36                   | 6±2        | 9±2          | 5±2                      | 1       | 0.78|
| 60                   | 15±3       | 14±3         | 1                        | 0.82    |

<table>
<thead>
<tr>
<th>Ejection fraction percentile</th>
<th>Medical (%)</th>
<th>Surgical (%)</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowest tercile</td>
<td>30–58</td>
<td>27±5</td>
<td>14±4</td>
</tr>
<tr>
<td>Middle tercile</td>
<td>59–69</td>
<td>19±4</td>
<td>16±4</td>
</tr>
<tr>
<td>Highest tercile</td>
<td>70–93</td>
<td>9±3</td>
<td>17±4</td>
</tr>
</tbody>
</table>

Values are mortality rate±SEM where applicable.

Ejection fraction could not be determined in four patients in each treatment group; all were reported to have normal left ventricular function.

$p$ value is for logrank test.

**FIGURE 4. Plot of mortality for medical and surgical patients using ejection fraction as a continuous variable. Curves computed by logistic regression analysis based on 5-year mortality of medical and surgical patients by assigned treatment. For reference, mean observed percent mortality for medical patients (○) and surgical patients (●) are illustrated for ejection fraction intervals 0.30–0.49, 0.50–0.69, and ≥0.70.**
FIGURE 5. Plot of cumulative mortality for medical and surgical patients classified by one-vessel disease (Panel A), two-vessel disease (Panel B), three-vessel disease (Panel C). Format as in Figure 3.
TABLE 3. Effect of Therapy on 5-Year Cumulative Incidence of Nonfatal Myocardial Infarction

<table>
<thead>
<tr>
<th>Type</th>
<th>Medicine</th>
<th>n</th>
<th>Myocardial infarction</th>
<th>%</th>
<th>SEM</th>
<th>Surgery</th>
<th>n</th>
<th>Myocardial infarction</th>
<th>%</th>
<th>SEM</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>Normal LV function</td>
<td>190</td>
<td>35</td>
<td>18.4</td>
<td>2.8</td>
<td>184</td>
<td>26</td>
<td>14.1</td>
<td>2.6</td>
<td>0.26</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Abnormal LV function</td>
<td>133</td>
<td>27</td>
<td>20.3</td>
<td>3.5</td>
<td>134</td>
<td>21</td>
<td>15.7</td>
<td>3.1</td>
<td>0.32</td>
<td></td>
</tr>
<tr>
<td>Type 2</td>
<td>Normal LV function</td>
<td>57</td>
<td>8</td>
<td>14.0</td>
<td>4.6</td>
<td>50</td>
<td>5</td>
<td>10.0</td>
<td>4.2</td>
<td>0.52</td>
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<tr>
<td></td>
<td>Abnormal LV function</td>
<td>47</td>
<td>7</td>
<td>14.9</td>
<td>5.2</td>
<td>47</td>
<td>10</td>
<td>21.3</td>
<td>6.0</td>
<td>0.42</td>
<td></td>
</tr>
<tr>
<td>LV function</td>
<td>Normal</td>
<td>11</td>
<td>3</td>
<td>27.3</td>
<td>13.4</td>
<td>16</td>
<td>5</td>
<td>31.3</td>
<td>11.6</td>
<td>0.82</td>
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<tr>
<td></td>
<td>Abnormal</td>
<td>169</td>
<td>31</td>
<td>18.3</td>
<td>3.0</td>
<td>165</td>
<td>26</td>
<td>15.8</td>
<td>2.8</td>
<td>0.53</td>
<td></td>
</tr>
<tr>
<td></td>
<td>All patients</td>
<td>237</td>
<td>42</td>
<td>17.7</td>
<td>2.5</td>
<td>231</td>
<td>36</td>
<td>15.6</td>
<td>2.4</td>
<td>0.54</td>
<td></td>
</tr>
</tbody>
</table>

Five additional medical patients and three additional surgical patients had a myocardial infarction between date of randomization and start of therapy.

as a resting ejection fraction of less than 50% or a left ventricular end-diastolic pressure greater than 16 mm Hg. In that report, further classification by number of vessels diseased in these patients with left ventricular dysfunction did not show a statistically significant survival advantage for either medical or surgical treatment at 36 months. Seventy of these 134 patients had three-vessel disease, and the 36-month survival was 92% for these patients assigned to surgery and 82% for those assigned to medicine (p=0.13). Of considerable interest, analysis of survival at 5 years in this cohort with left ventricular dysfunction now shows only a trend favoring survival with surgical therapy, which no longer achieves statistical significance (p=0.09).

Our previous report emphasizes the strong tendency in clinical medicine to characterize left ventricular dysfunction categorically using arbitrarily assigned operator cutoff numbers to subdivide patient groups. Thus, when the value of <0.50 was used to define abnormal ejection fraction, there was not a consistent survival advantage to surgically assigned patients with abnormal ejection fractions at 3 and 5 years (Table 2). More specifically, at 36 months, surgical mortality was 16% lower than medical mortality (24% for medical vs. 8% for surgical; p=0.05). Between 36 and 60 months, there were five surgical deaths and four medical deaths, which resulted at 60 months in a surgical morality that was 12% lower than that of medical mortality (33% for medical vs. 21% for surgical; p=0.22). However, when left ventricular ejection fraction was considered as a continuous (rather than dichotomous) variable, curves of medical versus surgical mortality by logistic multiple regression analysis show an important survival advantage for surgery, which is consistent with our initial report at 2 years. This observation was supported using a percentile subdivision of the patient population. Patients in the lowest ejection fraction tercile also had a significant survival advantage at 5 years when treated surgically (Table 2).

One question that commonly arises regarding clinical trials is just how representative randomized study subjects are in relation to the “average” patient with the same clinical problem. This issue may never be answered fully, but it is of interest to note the similarity between clinical, angiographic, and early outcome characteristics of the 468 patients randomized in this study and those of the 288 randomized in the NHLBI study (Table 5). By protocol design, the VA study randomized only male veterans; nevertheless, in the NHLBI study male patients were predominant, and these constituted 82% of the medical group and 86% of the surgical group. The comparability of patients surviving at 1 and 2 years in both cohorts of each study is striking. Of particular note is the greater than 90% medical survival in each study at 2 years in the medical cohorts. Before the NHLBI report, there was a considerably less optimistic prognosis for medical therapy. Medical therapy for all anginal syndromes has improved substantially in recent years. More aggressive use of β-blockade, nitrates, aspirin in the cardiac care unit, and widespread therapy with calcium channel blocking agents have now all been adopted by the consensus of practicing physicians and cardiologists. Yet, all of these advances have come after the 1978 NHLBI report. The “better than expected” survival of medical patients in these and other clinical trials (VA coronary surgery study, CASS) compared with prior observational studies suggests that the selection process for entry into clinical trials itself has an important influence on outcomes.

One of the important limitations of this study is the departure of outcomes of medically treated patients from outcomes anticipated during the planning process. The actual 5-year cumulative medical mortality was 17% in type 1 patients and 23% in type 2 patients. The projected mortalities for these cohorts during the planning process was 30% and 50%, respectively (see “Methods”). This leads to the possibility of a β error (real differences not
observed statistically because of same size) of 30% for type 1 patients and 66% for type 2 patients. The large possibility of β error for type 2 patients stems from an observed mortality less than half of anticipated and an accession rate that also was less than half of anticipated. Further observation of mortality in this study is ongoing to a 10-year follow-up, and based on current event rates, it is anticipated to increase the power to over 90% for type 1 patients but only 55% for type 2 patients.

Another difficult issue in medical-surgical trials is the impact of nonadherence to assigned therapy ("crossovers") particularly because many patients originally assigned to medicine received surgical therapy during the follow-up period. The NHLBI study experienced a cumulative crossover rate of
31% by 24 months; in this study, there was a 34% crossover at 24 months and a 43% crossover by 60 months (Figure 1A). Evaluation of outcomes by treatment assigned ("intention to treat") has long been advocated and recently reaffirmed as the standard of assessment for all clinical trials. Intention to treat analysis preserves randomization, averts investigator bias in selecting patients for crossover, and makes no assumptions of outcomes had crossover failed to occur.

Surgical intervention had neither a beneficial nor an adverse effect on overall nonfatal myocardial infarction incidence (Table 3). These observations regarding the incidence of nonfatal myocardial infarction extend the findings of our prior report at 24 months (12% infarctions in medical and surgical groups) and the NHLBI study at 30 months (11% late infarction in the medical group and 13% in the surgical group). However, surgery had a significantly beneficial impact on the need for repeated hospitalization for cardiac reasons (Figure 6). Most of these hospitalizations were for recurrent chest pain, and most of the benefit was realized in the first 2 years after randomization. These findings are consistent with earlier studies showing fewer symptoms after surgery.

A recent report from Oregon presented 5- and 10-year actuarially predicted survival rates of 92% and 83% based on 1,282 patients with unstable angina who had coronary bypass between 1970 and 1982 in one medical center. After all patients assigned to surgical therapy had been observed for 5 years in our study, the overall survival was 84%. These studies are not strictly comparable for numerous reasons involving both protocol design and population characteristics. The Oregon study was not a randomized trial. Patients were accessed by different criteria; for instance, the Oregon study included patients with angina shortly after an acute myocardial infarction, which was a population not addressed in our VA study. Certain risk factors were more prevalent in the VA population, for example, 8% versus 17% diabetes and 64% versus 90% smokers in the Oregon and VA populations, respectively. Nevertheless, the Oregon report indicates that in some centers and populations the outlook for surgically treated patients with unstable angina may be even better than reported here.

Therapy for acute coronary syndromes has evolved considerably in the decade since this trial was undertaken. Significant advances include use of internal mammary artery grafts, coronary angioplasty, antiplatelet agents to maintain graft patency, aspirin to abort unstable angina, and more widespread use of calcium channel blocking agents and intravenous nitrates. Thrombolysis has taken a firm foothold in early treatment of acute myocardial infarction and is being explored as a treatment for unstable angina. These interventions offer great promise for unstable angina patients. However, whether taken singly or in combination, it is not established that any of these modalities will improve the survival of patients with reduced ejection fraction or with three-vessel disease who develop unstable angina. Until further trials are forthcoming, our data indicate that coronary bypass surgery should be recommended for patients with unstable angina and reduced ejection fraction or three-vessel coronary artery disease suitable for surgical revascularization because it offers improved 5-year survival and a lower requirement for repeat cardiac hospitalization. Surgical therapy also offers the advantage of less dependence on antianginal medication.
**Appendix 1. Outcome of Screening Before Entry**

<table>
<thead>
<tr>
<th>Outcome of screening</th>
<th>Patients (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients screened</td>
<td>3,159</td>
</tr>
<tr>
<td>Patients screened but excluded</td>
<td>2,433</td>
</tr>
<tr>
<td>Patients included</td>
<td>726 (23%)</td>
</tr>
</tbody>
</table>

**Reason for exclusion**

- Acute myocardial infarction: 609
- Character of pain did not qualify: 615
- Onset or change in angina 8 weeks or more before this hospitalization: 53
- Pain of unstable angina not present within 10 days of admission: 17
- Exercise tolerance test performed and found to be negative: 105
- Acute infarction less than 3 months before date of screening: 130
- Previous operation for angina pectoris: 190
- Current participation in another study of unstable angina or another clinical trial: 19
- Question of likelihood of cooperation: 73
- Refusal of consent: 344
- Death before randomization: 6
- Other*: 272

*Reasons included concomitant cardiac and noncardiac disease, requests for surgery, objections of attending physician, and noncompliance with previously recommended medical regimen.

**Appendix 2. Exclusion of Patients After Arteriographic Examination**

<table>
<thead>
<tr>
<th>Reason for exclusion</th>
<th>Patients (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesion in left main artery</td>
<td>90</td>
</tr>
<tr>
<td>Normal coronary arteries</td>
<td>51</td>
</tr>
<tr>
<td>Coronary artery disease without critical stenoses</td>
<td>38</td>
</tr>
<tr>
<td>Distal diffuse coronary artery disease</td>
<td>15</td>
</tr>
<tr>
<td>Left ventricular aneurysm</td>
<td>10</td>
</tr>
<tr>
<td>Ejection fraction less than 0.30</td>
<td>8</td>
</tr>
<tr>
<td>Patient's refusal or ineligibility</td>
<td>8</td>
</tr>
<tr>
<td>Complication of coronary arteriography</td>
<td>4</td>
</tr>
<tr>
<td>(myocardial infarction, cerebrovascular accident, death*)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>31</td>
</tr>
<tr>
<td>Patients examined but excluded</td>
<td>255</td>
</tr>
<tr>
<td>Patients examined</td>
<td>726</td>
</tr>
<tr>
<td>Patients included</td>
<td>471† (65%)</td>
</tr>
</tbody>
</table>

*Death within 24 hours of arteriography.
†Three of these 471 patients were found to have a left ventricular ejection fraction less than 0.30 after the central committee reviewed the arteriograms. These patients were observed but not included in the analyses. Thus, 468 patients constituted the study population.

**Appendix 3. Participants in Veterans Administration Cooperative Study**

**Participating Hospitals and Investigators**


**Executive Committee**

Robert J. Luchi, MD, Medical Co-Chairman, Houston, TX; Stewart M. Scott, MD, Surgical Co-Chairman, Asheville, NC; Alfred Parisi, MD, West Roxbury, MA; Edward A. Stemmer, MD, Long Beach, CA; Andrew Wechsler, MD, Durham, NC; and Robert H. Deupree, PhD, Biostatistician, West Haven, CT.

**Data Monitoring Committee**

John A. Waldhausen, MD, Chairman, Hershey, PA; Lawrence W. Shaw, Biostatistician, Gainesville, FL; John Michael Criley, MD, Torrance, CA; Paul Ebert, MD, Chicago, IL; and Richard O. Russell Jr., MD, Birmingham, AL.

**Human Rights Subcommittee**

Edward R. Ryan, PhD, Chairman, West Haven, CT; Jack H. Evans, New Haven, CT; Richard C. Feldman, New Haven, CT; Barbara A. Kathe, RSM, PhD, New Hartford, CT; Mary Joan Cook, RSM, PhD, W. Hartford, CT; William Field, MD, New Haven, CT; formerly, Hugh L. Dwyer, MD, Woodbridge, CT; James M. Solomon, MD, Guilford, CT; Sarah McCue Horwitz, PhD, Hamden, CT; Willis Pritchett, RPh, New Haven, CT; and Frank Votto, Cheshire, CT.

**Cooperative Studies Program Central Administration (Washington, DC)**

Daniel Deykin, MD, Chief.

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**Programmers**

Katherine Newvine; formerly, Margaret Lee, Gary Johnson, Cynthia Johnson, Joanne Kelly, and Mary Ann O'Brien.
References

Key Words • angina • surgery • ejection fraction
Medical compared with surgical management of unstable angina. 5-year mortality and morbidity in the Veterans Administration Study.
A F Parisi, S Khuri, R H Deupree, G V Sharma, S M Scott and R J Luchi

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