Ten-Year Incidence of Myocardial Infarction and Prognosis After Infarction

Department of Veterans Affairs Cooperative Study of Coronary Artery Bypass Surgery

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Background. The 10-year incidence of myocardial infarction (fatal and nonfatal) and the prognosis after infarction were evaluated in 686 patients with stable angina who were randomly assigned to medical or surgical treatment in the Veterans Administration Cooperative Study of Coronary Artery Bypass Surgery.

Methods and Results. Myocardial infarction was defined by either new Q wave findings or clinical symptoms compatible with myocardial infarction accompanied by serum enzyme elevations with or without electrocardiographic findings. Treatment comparisons were made according to original treatment assignment; 35% of the medical cohort had bypass surgery during the 10-year follow-up period. The overall cumulative infarction rate was somewhat higher in patients assigned to surgery (36%) than in medical patients (31%) (p=0.13) due to perioperative infarctions (13%) and an accelerated infarction rate after the fifth year of follow-up (average, 2.4%/yr in the surgical group versus 1.4%/yr in the medical group). The 10-year cumulative incidence of death or myocardial infarction was also higher in surgical (54%) than in medical (49%) patients (p=0.20). According to the Cox model, the estimated risk of death after infarction was 59% lower in surgical than in medical patients (p<0.0001). The reduction in postinfarction mortality with surgery was most striking in the first month after the event: 99% in the first month (p<0.0001) and 49% subsequently (p<0.0001). The estimated risk of death in the absence of infarction was nearly identical regardless of treatment (p=0.75). Exclusion of perioperative infarctions did not alter the findings.

Conclusions. Although surgery does not reduce the incidence of myocardial infarction overall, it does reduce the risk of mortality after infarction, particularly in the first 30 days after the event (fatal infarctions). (Circulation 1991;83:747–755)

Coronary bypass surgery improves survival and may reduce the incidence of sudden death in certain high-risk subgroups of patients with symptomatic coronary artery disease1–8; however, little information is available on the long-term effect of bypass surgery on the incidence of myocardial infarction. In a previous publication,5 we reported a 5-year incidence of nonfatal Q wave myocardial infarction of 14% with medical therapy and 15% with surgical therapy. The European randomized study2 reported rates of 11% for medical therapy and 15% for surgical therapy in the first 5 years of follow-up. Corresponding rates for the Coronary Artery Surgery Study (CASS) were 11% and 14%, respectively.5

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In this report, we present the 10-year incidence of all myocardial infarctions (fatal and nonfatal) and of death or infarction in all medically and surgically assigned patients. The effect of treatment on prognosis after infarction was also evaluated.

Methods

Patients

As described in previous reports,7,8 the Department of Veterans Affairs Cooperative Study of Coronary Artery Bypass Surgery is a randomized trial of
medical versus medical plus surgical therapy for patients with stable angina pectoris and angiographically proven coronary artery disease. All aspects of the study protocol were approved by the human rights committee at the coordinating center and by the institutional review boards at each participating medical center. Written informed consent was obtained from all study patients before randomization. Between 1972 and 1974, 686 patients who satisfied the following eligibility criteria were enrolled in the study: stable angina for more than 6 months with at least a 3-month trial of medical management; electrocardiographic evidence of prior myocardial infarction or ischemic changes at rest or with exercise; and at least one major coronary artery with a 50% or greater stenosis and a graftable distal segment.

Ten-year follow-up data were complete for both the primary and secondary end points of the study—survival status and incidence of myocardial infarction. No patients were lost to follow-up.

Myocardial Infarction

In the VA study, definite myocardial infarction was defined by either new Q wave findings or clinical symptoms compatible with myocardial infarction accompanied by serum enzyme elevations with or without electrocardiographic findings. Myocardial infarction was classified as suspected when clinical symptoms of infarction were not supported by electrocardiographic changes and serum enzyme elevations. The occurrence of myocardial infarction was ascertained from several sources: regularly scheduled electrocardiograms; hospitalization, follow-up, and operative reports; autopsy protocols; and death summaries. Follow-up visits were scheduled for all patients at 3-month intervals during the first 2 years and semiannually thereafter. Electrocardiograms were obtained at the first 3-month follow-up visit and at all annual clinic visits. The number of scheduled follow-up electrocardiograms that were obtained was 2,407 in the medical group and 2,327 in the surgical group. The corresponding rates per person-year of follow-up were 0.90 in both treatment groups.

All resting electrocardiograms were coded centrally at the Minnesota Electrocardiographic Laboratory, University of Minnesota, Minneapolis, using the Minnesota code and were subsequently overread for serial change by Dr. J. Thomsen of the Veterans Administration Medical Center, Madison, Wis. All reported infarctions were reviewed centrally and classified as definite or suspected, fatal or nonfatal, and perioperative or late. The central review of myocardial infarction was blinded to treatment whenever possible. An infarction was classified as fatal if the patient died within 4 weeks of the event and as nonfatal otherwise; it was classified as perioperative if it occurred within 30 days of operation and as Q wave if a new persistent Q wave of 0.04 second or more appeared on the electrocardiogram. This report analyzes all definite infarctions (fatal and nonfatal) that occurred in the first 10 years of follow-up; suspected infarctions were not analyzed.

Risk Groups

The angiographic subgroups evaluated in this report were defined according to the number of vessels diseased (one, two, or three) and left ventricular function. Left ventricular function was considered impaired if ejection fraction was less than 50% or if a moderate to severe contraction abnormality was present. The combination of three-vessel disease and impaired left ventricular function was classified as high angiographic risk; all other patients were classified as low angiographic risk. Low, middle, and high clinical risk groups were based on a multivariate risk function to predict 5-year survival, with four established clinical risk factors measured at baseline: New York Heart Association classification, history of hypertension, previous myocardial infarction, and ST segment depression on the resting electrocardiogram.

Graft Patency

Of the 332 patients assigned to surgical treatment, 312 had the operation, 289 survived to 1 year, 260 to 5 years, and 202 to 10 years. Graft patency was assessed in 85% of surviving patients at 1 year, in 60% of those who survived 5 years, and in 40% of 10-year survivors. The relation between graft patency, myocardial infarction, and mortality was assessed using the 1-year patency data. Patients were classified into three patency groups: all grafts closed (0% patency), some grafts open (partial patency), and all grafts open (100% patency).

Nonadherence

In the first 10 years of follow-up, 124 of 354 medically assigned patients crossed over to surgery (22 with left main disease at entry); the median time to surgery was about 4 years. An evaluation of the first 75 crossovers without left main disease indicated that the majority (80%) had surgery for progression or persistence of angina; 17% had surgery for unstable angina.

Only 20 of the 332 surgically assigned patients had no operation.

Statistical Methods

The data were analyzed according to original treatment assignment regardless of adherence, that is, by “intent-to-treat.” In the analysis, two end points were evaluated: 1) time to first myocardial infarction and 2) time to first infarction or death. Life-table methods were used to calculate cumulative incidence rates for each end point. For the first end point, patients who died without prior myocardial infarction were counted as lost to follow-up at the time of death. Differences in cumulative incidence rates between medically and surgically assigned patients were tested by the log-rank statistic.

The effect of treatment on mortality in the presence and absence of intervening myocardial infarc-
tion was estimated by the Cox proportional-hazards model.12 This method accounted both for time-to-death and for time-to-infarction bias (i.e., patients being longer at risk of dying because of the earlier occurrence of myocardial infarction in the surgical than in the medical group). This method was also used to adjust for relevant prognostic variables. (See “Appendix” for details.) Results are expressed as the estimated relative risk of dying with surgical compared with medical therapy. Relative risk values less than 1 indicate lower mortality in the surgical group, and values greater than 1 indicate higher mortality with surgical therapy. Relative risk estimates based on crude mortality rates will differ from those based on the Cox model because crude rates do not take into account either time to death or time to infarction. The Cox model was fitted to the data using the BMDP program P2L.13

All analyses, including the analysis of mortality subsequent to infarction, were restricted to the 10-year period from date of randomization and not from infarction. Mortality subsequent to infarction includes fatal infarction, even when infarction and death occurred on the same day.

All values of $p$ are two-tailed and uncorrected for multiple comparisons.

**Results**

**Patient Characteristics**

The clinical, angiographic, ventriculographic, and electrocardiographic descriptors of the medically and surgically assigned groups were similar at entry.7 Briefly, overall mean age was 51 years, 60% of patients had a history of prior myocardial infarction, 85% had multivessel disease (30% double, 55% triple), 54% had impaired left ventricular function, and 30% were considered high risk angiographically (three-vessel disease with impaired left ventricular function).

**Crude Infarction Rates**

During the 10-year follow-up period, 99 (28%) of the 354 medically assigned patients and 110 (33%) of the 332 surgically assigned patients had at least one fatal or nonfatal myocardial infarction (Table 1). Nonfatal infarction occurred in 20% of medical patients and in 29% of surgical patients, two to four times more frequently than did fatal infarctions.

A total of 117 myocardial infarctions occurred in 99 of the medically assigned patients. Of these, 33 (28%) were fatal (Table 2). In the surgically assigned group, 141 infarctions occurred in 110 patients, and 25 (18%) were fatal. Of the 117 infarctions in the medical group, 84 (72%) were Q wave; 93 (66%) of 141 infarctions in the surgical group were Q wave. As expected, the percent of Q wave events that were fatal (27%) was about two times higher than the rate for non-Q wave events (14%). Nevertheless, the percent of total events that were fatal was about 30% lower in the surgical group, irrespective of the type of infarction.

A total of 47 infarctions occurred in 39 of the 124 medical crossovers, 16 before and 31 after surgery. Only two patients had an infarction both before and after surgery. Perioperative infarction occurred in 16 crossover patients (13%), and operative death occurred in five patients (4%), of whom four had a fatal infarction. Among the 312 surgically assigned and operated patients, 133 infarctions occurred in 103 patients. The numbers of perioperative infarctions and operative deaths were 41 (13%) and 18 (6%), respectively. Seven of the 18 operative deaths sustained a fatal infarction.

**Cumulative Infarction Rates**

Figure 1, top panel shows the 10-year cumulative incidence of total (left graph) and nonfatal (right graph) infarction according to treatment assignment. At 10 years, the overall cumulative infarction rate was 31% in medically assigned patients and 36% in surgically assigned patients ($p=0.13$), slightly higher than the crude rates shown in Table 1. The sharp early increase in the surgical curve reflected the high perioperative infarction rate (13%). Although cumulative infarction rates converged at 5 years (24%), the

<table>
<thead>
<tr>
<th>Type of MI</th>
<th>Medicine (N=354)</th>
<th>Surgery (N=332)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$n$</td>
<td>$%$</td>
</tr>
<tr>
<td>Any MI (Q wave or non-Q wave)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal</td>
<td>33</td>
<td>9.3</td>
</tr>
<tr>
<td>Nonfatal</td>
<td>72</td>
<td>20.3</td>
</tr>
<tr>
<td>Total</td>
<td>99</td>
<td>28.0</td>
</tr>
<tr>
<td>Q wave MI*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal</td>
<td>27</td>
<td>7.6</td>
</tr>
<tr>
<td>Nonfatal</td>
<td>52</td>
<td>14.7</td>
</tr>
<tr>
<td>Total</td>
<td>76</td>
<td>21.5</td>
</tr>
</tbody>
</table>

MI, myocardial infarction; $N$, total number of patients in treatment group; $n$, number of patients with MI; $\%$, percent of all randomized patients in the treatment group.

Numbers and percents for fatal and nonfatal infarctions include the few patients who had both events.

*Includes seven medical and 10 surgical patients who had both a Q wave and a non-Q wave infarction.
Figure 1. Graphs showing cumulative incidence of total myocardial infarction (MI) (graphs on the left) and of nonfatal MI (graphs on the right) according to treatment assigned and type of MI. M, medical treatment; S, surgical treatment. The top panel displays total infarctions, the middle panel displays Q wave infarctions, and the lower panel displays non-Q wave infarctions. Numbers on curves are infarction rates at 1, 5, and 10 years in the respective treatment groups. Numbers at risk at baseline, 5 years, and 10 years are indicated at bottom of figure.
rates diverged thereafter, when the infarction rate accelerated in the surgical group and reached a plateau in the medical group. The average annual infarction rate during this latter time period was 2.4% for the surgically assigned patients versus 1.4% for the medically assigned patients. For nonfatal infarction, trends were similar, but the treatment difference was significant (p=0.01). The middle and bottom panels of Figure 1 display similar trends for Q wave and non-Q wave infarction, respectively.

The cumulative incidence of death or infarction at 10 years was 49% in the medical and 54% in the surgical group (p=0.20) (Figure 2). The sharp early increase in the surgical curve reflected the combined effect of perioperative infarction (13%) and operative mortality (6%). The medical and surgical curves converged at about 4 years and then remained similar up to 10 years. Late acceleration of the combined event rate was observed in the surgical group.

### Risk of Dying in Patients With and Without Infarction

Crude 10-year mortality rates according to treatment and infarction are given in Table 3. Overall mortality rates were 40% for the medical group and 36% for the surgical group (p=0.20). Mortality rates in patients without myocardial infarction were comparable in the two treatment groups: 32% for surgical patients and 29% for medical patients. In contrast, for patients who sustained an infarction, subsequent mortality was about one third lower in the surgical than in the medical group: 44% versus 67%. When only nonfatal infarctions were considered, the mortality rates subsequent to infarction were 35% in the surgical and 54% in the medical

### Table 2. Number and Percent of Myocardial Infarctions According to Treatment Assigned in the First 10 Years of Follow-up

<table>
<thead>
<tr>
<th>Type of MI</th>
<th>Medicine (N=354)</th>
<th>Surgery (N=332)</th>
<th>Combined total (N=686)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Any MI (Q wave or non-Q wave)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal</td>
<td>33</td>
<td>28.2</td>
<td>25</td>
</tr>
<tr>
<td>Nonfatal</td>
<td>84</td>
<td>71.8</td>
<td>116</td>
</tr>
<tr>
<td>Total</td>
<td>117</td>
<td>100.0</td>
<td>141</td>
</tr>
<tr>
<td>Q wave MI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal</td>
<td>27</td>
<td>32.1</td>
<td>20</td>
</tr>
<tr>
<td>Nonfatal</td>
<td>57</td>
<td>67.9</td>
<td>73</td>
</tr>
<tr>
<td>Total</td>
<td>84</td>
<td>100.0</td>
<td>93</td>
</tr>
</tbody>
</table>

MI, myocardial infarction; N, total number of patients in each treatment group or combined total; n, number of MIs; %, percent of total MIs.
patients. The association between nonfatal myocardial infarction and subsequent mortality was highly significant only in the medical group. Mortality was 54% in patients with nonfatal infarction and 29% for those without infarction \((p<0.001)\). Corresponding rates for surgical patients were 35% and 32%, respectively. In addition, the proportion of all patients with infarction whose initial event was fatal was 27% in the medical group compared with 14% in the surgical group. Thus, with surgery, infarctions tended to be nonfatal and more benign in terms of subsequent mortality.

Table 4 displays the estimated relative risks of dying in the surgical compared with the medical treatment group by the Cox model. In the absence of infarction, the risk of dying was similar in both treatment groups \((\text{relative risk}=1.06, p=0.75)\). However, for those who sustained an infarction, the relative risk of dying after the initial event was 0.41 \((p<0.0001)\), indicating a nearly 60% reduction in mortality in the surgical group. This reduction in mortality was greater during the first month after infarction \((99\%, p<0.0001)\) than in those who survived longer than 1 month \((49\%, p<0.0001)\). Reduction in mortality was also greater for Q wave \((67\%, p<0.0001)\) compared with non-Q wave infarction \((45\%, p=0.11)\), but the difference was not significant \((p=0.26)\). Findings were similar when patients with left main disease were excluded from analysis (not shown).

Adjustment for known baseline risk factors—left main disease, angiographic risk, and clinical risk—tended to magnify the beneficial effect of surgery, particularly for those patients with non–Q wave infarctions.

To determine whether the above results could possibly be attributed to the perceived better prognosis of perioperative infarction in surgical patients, the analyses were repeated excluding all perioperative infarctions. The findings (Table 4) were similar.

**Graft Patency**

The relation between graft patency at 1 year, myocardial infarction, and 10-year mortality is presented in Table 5 for 247 surgically assigned patients. Overall, infarction \((p=0.16)\) and mortality rates \((p=0.06)\) decreased with increasing graft patency. Infarction rates were 45%, 30%, and 29%, whereas mortality rates were 32%, 35%, and 22% for patients with 0%, partial, and 100% patency, respectively.

### Table 3. Ten-Year Crude Mortality Rates in Patients With and Without Myocardial Infarction According to Treatment Assigned

<table>
<thead>
<tr>
<th></th>
<th>Medicine (N=354)</th>
<th>Surgery (N=332)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Deaths/patients</td>
<td>%</td>
</tr>
<tr>
<td>Total mortality</td>
<td>141/354</td>
<td>39.8</td>
</tr>
<tr>
<td>Without MI</td>
<td>75/255</td>
<td>29.4</td>
</tr>
<tr>
<td>With MI</td>
<td>66/99</td>
<td>66.7</td>
</tr>
<tr>
<td>≤30 days*</td>
<td>27/99</td>
<td>27.3</td>
</tr>
<tr>
<td>Survived &gt;30 days†</td>
<td>39/72</td>
<td>54.2</td>
</tr>
</tbody>
</table>

MI, myocardial infarction. Mortality rates are 10 years from date of randomization for all patients.

*30-day time period after the initial infarction, that is, the fatal time period.

†Patients with nonfatal infarction.

### Table 4. Unadjusted and Adjusted Estimates of the Relative Risk of Dying With Surgery Compared With Medicine According to the Cox Model for Patients With and Without Myocardial Infarction by Treatment Assigned

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Relative risk</td>
<td>95% CI</td>
</tr>
<tr>
<td>Without MI</td>
<td>1.06</td>
<td>(0.76–1.46)</td>
</tr>
<tr>
<td>With MI</td>
<td>0.41</td>
<td>(0.28–0.60)</td>
</tr>
<tr>
<td>≤30 days after MI*</td>
<td>0.007</td>
<td>(0.002–0.025)</td>
</tr>
<tr>
<td>&gt;30 days after MI</td>
<td>0.51</td>
<td>(0.35–0.75)</td>
</tr>
<tr>
<td>Q wave</td>
<td>0.33</td>
<td>(0.22–0.51)</td>
</tr>
<tr>
<td>Non–Q wave</td>
<td>0.55</td>
<td>(0.26–1.16)</td>
</tr>
<tr>
<td>Nonperioperative MI</td>
<td>0.42</td>
<td>(0.27–0.64)</td>
</tr>
<tr>
<td>≤30 days after MI*</td>
<td>0.009</td>
<td>(0.002–0.037)</td>
</tr>
<tr>
<td>&gt;30 days after MI</td>
<td>0.49</td>
<td>(0.32–0.77)</td>
</tr>
<tr>
<td>Q wave</td>
<td>0.42</td>
<td>(0.25–0.68)</td>
</tr>
<tr>
<td>Non–Q wave</td>
<td>0.46</td>
<td>(0.20–1.06)</td>
</tr>
</tbody>
</table>

CI, confidence interval; MI, myocardial infarction.

Estimates are adjusted for left main disease and angiographic and clinical risk at baseline.

*30-day period after infarction, that is, the fatal time period.
patients who died without patent grafts, 60% sustained a prior infarction compared with 33% and 36% in the groups with some or all grafts patent.

Discussion

In this report, we examined the 10-year incidence of myocardial infarction in patients assigned to bypass surgery versus medical treatment. The surgical group had more total infarctions, more nonfatal and more Q wave events due to postoperative complications, and a late increase that was assumed to result from graft failure. Similar trends for higher infarction rates in the surgical group were reported at 5 years for both the European Coronary Surgery Study in 1985 and CASS in 1984. In the European study, the 5-year incidence of total nonfatal infarction was 15% in the surgical and 11% in the medical group, yet the total mortality in that study was in reverse: 11% surgical and 20% medical (p=0.022). The group concluded, therefore, that "bypass surgery does not protect the myocardium from infarction but prevents fatal outcome." Similarly, the VA study also observed a lower overall 10-year mortality with surgical therapy (36% versus 40%, p=NS). However, the 10-year incidence of infarction was in reverse: 36% in the surgical and 31% in the medical group for total infarction and 32% versus 23% (p=0.011) for nonfatal infarction.

To explore why the higher incidence of myocardial infarction in the surgical group was not paralleled by a concomitant increase in fatal outcomes, we examined the effect of treatment on 10-year survival in patients with and without interim myocardial infarction. We found that, whereas survival after infarction was significantly improved in the surgical group, no beneficial effect was seen in patients without infarction. The overall reduction in postinfarction mortality was approximately 60% and was highest (99%) during the first 30 days after the event. The lower postinfarction mortality in the surgical group occurred despite the fact that surgical patients were at risk of dying for a longer time than the medical patients, because their median time to the initial infarction was earlier (6 versus 27 months). The striking reduction of postinfarction mortality could not be explained by the perceived benign nature of perioperative infarction in the surgical group, since the protection persisted when perioperative infarctions were excluded from the analysis.

We speculate that, whereas the occurrence of infarction itself may be independent of revascularization and depends more on intravascular events such as plaque rupture and thrombosis, the consequences of infarction may be significantly altered by successful revascularization. The protective effect of patent grafts on myocardial reserve may become clinically apparent only after an insult by occluded blood supply. This phenomenon may be similar to the case argued by Epstein et al that fatal coronary consequences due to occlusion tend to occur more frequently when collaterals have no chance to enlarge and mature, as with hemodynamically insignificant lesions. Conversely, when collaterals or grafts are functional, they do exert a protective effect.

Bypass surgery could modify the effect of infarction on survival in other ways. In an earlier report, we demonstrated that patent grafts protected left ventricular ejection fraction from the adverse effects of myocardial infarction. Crean et al reported that infarct size tended to be smaller in patients with previous bypass surgery and that the location of the lesions causing the infarction were in the smaller nonproximal vessels. Infarct size and location could not be determined in our present report.

Our main conclusion that, by whatever mechanism, the prognosis after myocardial infarction improves in the surgical group is different from that of Wiseman et al, who found prior bypass surgery to be a marker for higher mortality after myocardial infarction. This variation could be due to the difference in study designs. Wiseman et al followed two groups of myocardial infarction cases, those who had prior bypass surgery and those who did not. Although members of both groups were approximately 55 years old at recruitment, the postbypass group had surgery an average of 66 months earlier. Such patients with a longer history of disease may have a worse prognosis. In addition, the similarity in the calculated extent of vessel disease at entry was based on the inclusion of grafts in the operated group. It is known that disease progression in older grafts is more rapid and that this could explain the increased incidence of cardiac events during the 34 months of follow-up after infarction. In the present report, the median duration between operation and myocardial infarction was 6 months. Different age of the grafts at the time of infarction is likely to exert either a beneficial or a deleterious effect on survival.

There are several potential sources of bias in this report: 1) bias in the ascertainment of myocardial infarction, 2) imbalances in baseline risk factors, 3) time-to-infarction or length sampling bias, and 4)
crossovers. Every effort was made to ascertain the occurrence of all myocardial infarctions in study patients. Multiple data sources were used, including serial electrocardiograms and hospitalization, follow-up, operative, autopsy, and death reports. There was no difference between treatment groups in the ascertainment of infarction occurrence from scheduled electrocardiograms. Despite these efforts, some infarctions may have been missed, particularly in those patients who died under circumstances in which information on the cause of death was unavailable or incomplete. However, there was no evidence that the completeness of mortality data differed between the two treatment groups. Similarly, adjustment for prognostic risk factors—left main disease, angiographic risk, and clinical risk—did not markedly alter the treatment comparisons.

One of the problems in evaluating the effect of treatment in the presence and absence of myocardial infarction is accounting for the time-to-infarction bias. Standard life-table methods that calculate cumulative incidence rates from date of infarction for those with an event and from date of randomization for those without an event cannot be used because time to infarction is ignored. For example, in our study, surgical patients had their infarctions earlier and consequently had a longer follow-up period after the infarction before experiencing an untoward event—recurrent myocardial infarction or death. An approach to analyzing such data is to consider myocardial infarction and the interaction between infarction and treatment as time-dependent covariates in the standard proportional-hazards model, that is, the Cox model. This time-related model assumes that the treatment effect is constant over time. In our study, there was no strong evidence that this assumption was violated during the first 10 years of follow-up. However, with extended follow-up and accelerated surgical mortality, we expect that the proportional-hazards model may no longer be appropriate, and a time-varying hazard model may be required.

Crossovers pose another problem in evaluating the "true" effect of medical versus surgical therapy. Bypass surgery may have aborted some infarctions in patients who received surgery for unstable angina, thereby reducing the overall medical infarction rate. However, examination of the initial 75 crossovers without left main disease revealed that only 17% had surgery for unstable angina. Conversely, surgery may have induced some of the perioperative infarctions that occurred in 13% of the crossovers. Thus, it is difficult to assess the effect of crossovers on the overall medical infarction rate.

In a randomized trial, the intent-to-treat method is the only unbiased method of analysis, even in the presence of crossovers. Analyses that try to account for crossover lose the protection of randomization by introducing uncontrolled bias. For example, censoring all crossovers from the analysis at the time of treatment change is biased, but it can provide some insight into the effect of crossovers on the treatment comparisons. For example, in the VA study, an analysis censoring crossovers yielded results quite similar to those by the intent-to-treat method (not shown). Thus, it is unlikely that the reduction in postinfarction mortality with surgical treatment was influenced by the experience of the medical crossovers.

In summary, the 10-year incidence of myocardial infarction and of death or infarction combined was somewhat higher with surgical than with medical treatment strategy. Both perioperative complications and late acceleration of event rates were contributing factors. Although bypass surgery did not reduce the incidence of infarction, it did significantly reduce the risk of mortality after infarction, especially in the first 30 days.

Appendix

The Cox regression model included treatment (0=medicine, 1=surgery) as a fixed covariate and two time-dependent covariates, one for myocardial infarction and the other for the interaction of treatment and infarction. The infarction variable was assigned a value of 0 up to the time of the first infarction and a value of 1 thereafter. The interaction variable was coded similarly, but the value of 1 was assigned at time of infarction only for surgical patients with infarction. The time-dependent covariates were assigned a value of 0 for all patients without infarction. The risk of death with surgical compared with medical treatment in the absence of infarction was calculated as the exponential of the estimated regression coefficient for treatment. The relative risk of dying after infarction was the exponential of the sum of the regression coefficients for treatment and the interaction term. The significance of each relative risk was tested by the statistic, ln(relative risk)/SE[ln(relative risk)], which has an approximately standard normal distribution. One hundred (1−α) percent confidence intervals were calculated as the relative risk±SE[ln(relative risk)] where Z_{0.975} is the hundredth (1−α/2) percentile of the standard normal distribution. The likelihood ratio statistic was used to test differences among estimates of relative risk, that is, interaction. The proportional-hazards assumption was tested by including time-by-treatment interaction terms in the regression model. Evaluation by this method showed that the proportional-hazards model provided an adequate fit to the data.

Acknowledgments

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**KEY WORDS** • angina • coronary artery disease • Q wave • myocardial infarction • long-term outcome • surgery
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