Eighteen-Year Follow-up in the Veterans Affairs Cooperative Study of Coronary Artery Bypass Surgery for Stable Angina

The VA Coronary Artery Bypass Surgery Cooperative Study Group

Background. The 18-year effect of bypass surgery compared with medical therapy on survival, incidence of myocardial infarction, and relief of angina was evaluated in 686 randomized patients with stable angina in the Veterans Affairs Cooperative Study of Coronary Artery Bypass Surgery.

Methods and Results. The primary treatment comparisons were made according to intent to treat; 44% of the entire medical cohort had bypass surgery during a median follow-up of 16.8 years. Overall 18-year survival rates were 33% for medicine compared with 30% for surgery (p=0.60). Survival rates for high-risk patients without left main disease, which had shown a significant advantage for surgical therapy up to 11 years, were 23% medicine versus 24% surgery for patients with three-vessel disease and impaired left ventricular function (p=0.49) and 22% versus 25% for those with multiple clinical risk factors (p=0.12). For patients with two-vessel disease, who had significantly better survival with medical therapy at 11 years, rates were similar at 18 years in the two treatment groups (34% medicine versus 36% surgery, p=0.09). Cumulative 18-year myocardial infarction rates (fatal plus nonfatal) were 41% in medical and 49% in surgical patients (13% perioperative infarction rate), p=0.15. Nonfatal infarction rates were lower with medical than with surgical therapy (32% versus 44%, p=0.015), but fatal infarction rates were similar (14% medicine versus 13% surgery, p=0.62). The combined rate of myocardial infarction or death was also lower with medical therapy (75% versus 82%, p=0.016). In contrast, surgery reduced mortality after myocardial infarction by 35% at 10 years (p<0.001) but only by 13% at 18 years (p=0.09). The percent of medical and surgical patients who were angina-free was 3% versus 22% (p<0.001) at 1 year and 4% versus 12% (p<0.001) at 5 years compared with rates of 6% versus 5% (p>0.50) at 10 years and 3% versus 4% (p>0.50) at 15 years.

Conclusions. The benefits of coronary artery bypass surgery on survival, symptoms, and postinfarction mortality were transient and lasted fewer than 11 years. The benefits began to diminish after 5 years, when graft closure accelerated. Surgery was effective in reducing mortality only for patients with a poor natural history. Low-risk patients, who had a good prognosis with medical therapy, derived no survival benefit with surgical therapy at any time during the follow-up period. Regardless of risk, surgery also did not reduce the incidence of myocardial infarction or the combined incidence of infarction or death.

(Circulation 1992;86:121-130)

KEY WORDS  •  angina, stable  •  CABG  •  mortality  •  myocardial infarction  •  quality of life

The Department of Veterans Affairs (VA) Cooperative Study of Coronary Artery Bypass Surgery was the first large-scale randomized trial designed to evaluate the effect of bypass surgery compared with medical therapy for patients with stable angina pectoris. The definitive phase of the trial was conducted between 1972 and 1989. In 1975, the VA trial first reported a statistically significant survival benefit with surgical therapy for patients with left main coronary artery disease.1 In a subsequent report after 11 years of follow-up, survival benefit for patients without left main disease was observed only for the small subgroup of patients with multiple clinical and angiographic risk factors.2 Beyond 7 years, however, a gradual loss of survival benefit occurred, presumably because of increasing graft closure. Similarly, surgically treated patients had significantly more relief of angina and better exercise performance during the first 5 years of follow-up,3 but by 10 years, relief of angina and exercise performance were comparable in the two treatment groups. In a recent report, we demonstrated that although coronary artery bypass surgery does not reduce the overall risk of myocardial infarction, it does reduce the risk of mortality after infarction, particularly in the first 30 days after the event.4

In this report, we present the 18-year results of bypass surgery compared with medical therapy on survival and incidence of myocardial infarction; 15-year data are presented for relief of angina. Causes of death in the two treatment groups and the long-term rates of crossover from medical to surgical therapy and of repeat surgery are also reported.

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Received July 3, 1991; revision accepted March 12, 1992.
Patients

The VA Cooperative Study of Coronary Artery Bypass Surgery was a randomized controlled trial of medical versus medical plus surgical therapy for patients with stable angina pectoris and angiographically indicated coronary artery disease. 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; ECG evidence of previous 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. The primary study endpoint was mortality (all causes), and the secondary endpoints were incidence of myocardial infarction and severity of angina. 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.

Follow-up

The original study protocol specified that all patients would be followed for 5 years from the date of entry. Follow-up was subsequently extended to 10 years and later to a minimum of 15 years. Follow-up was completed on December 31, 1989. At that time, all patients had been followed for 15 years, 87% for 16 years, 73% for 17 years, and 63% for 18 years. Median follow-up was 16.8 years, and only one patient was lost to follow-up.

All study patients returned for annual clinic visits through 1984; thereafter, follow-up was accomplished centrally by an annual telephone interview or mail questionnaire from the coordinating center.

Risk Groups

Patients were classified angiographically into low- or high-risk subgroups according to the number of vessels diseased and left ventricular function. Left ventricular function was considered impaired if the ejection fraction was less than 50% or if a moderate to severe contraction abnormality was present. The presence or absence of left ventricular function impairment was determined according to central reading of the baseline left ventriculograms. The repeatability of the central laboratory was established before the review. Ejection fraction was measured in 584 patients and estimated as normal or abnormal in 102 patients. Patients who had three-vessel disease and impaired left ventricular function were classified as high angiographic risk; all other patients were of low angiographic risk. Low-, middle-, and high-clinical-risk groups were based on a multivariate risk function to predict 5-year survival using four established clinical risk factors measured at baseline: New York Heart Association classification III or IV, history of hypertension, history of myocardial infarction, and ST segment depression on the resting ECG. Patients in the low-clinical-risk subgroup included those with no or only one risk factor except for ST depression. The high-risk subgroup consisted of patients with combination of two or three of the strongest predictors (ST depression, a history of myocardial infarction, and a history of hypertension), i.e., those with multiple clinical risk factors.

Myocardial Infarction

In this study, 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 ECG findings. All resting ECGs during the clinical follow-up phase of the trial were coded centrally at the Minnesota Electrocardiographic Laboratory using the Minnesota code and subsequently overread serially by one of the study cardiologists.

Every reported infarction was 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 suspected when clinical symptoms of infarction were not supported by ECG changes or serum enzyme elevations; as fatal if the patient died within 4 weeks of the event and as nonfatal otherwise; as perioperative if the infarction occurred within 30 days of operation; and as Q wave if a new persistent Q wave of $\geq 0.04$ second appeared on the ECG. This report analyzes only definite myocardial infarctions.

Angina

Severity of angina was measured by a reproducible angina score based on specific items recorded on a physician-administered angina questionnaire. The score consisted of a severity score and a medication score. The severity score (range, 0–9) measured the frequency of angina, presence of rest angina, and type of activity producing angina. The medication score (range, 0–9) assessed the use of nitroglycerin, long-acting nitrates, and $\beta$-blockers. Initially, the medication score included only the use of propranolol but was later modified to include newer $\beta$-blockers. The combined score (0–18) represented an overall index of angina. Patients were classified into four severity groups on the basis of the magnitude of their angina score: no angina (score, 0), mild angina (scores, 1–7), moderate angina (scores, 8–11), and severe angina (scores, 12–18). To account for patients with missing data, survivors without scores and patients who died were also classified in separate categories.

The angina questionnaire was not implemented until 1973; thus, only about one half of the patients had a baseline angina score. However, the baseline risk characteristics of patients with scores were comparable to those of patients without scores at entry. Follow-up scores were obtained in 88% of 1-year survivors, 93% of 5-year survivors, 74% of 10-year survivors, and 77% of 15-year survivors.

Nonadherence

Of the 354 medically assigned patients, 154 eventually had bypass surgery, and 24 of these patients also had a second operation. Operative mortality was 4.6% for the initial operation and 12.5% for repeat surgery. The cumulative rate of crossover from medical to surgical therapy was 62% at 18 years (Figure 1); median time to crossover was 5 years.
FIGURE 1. Graph showing cumulative rates of crossover from medical (M) to surgical (S) therapy and cumulative repeat surgery rates for surgically assigned patients who had surgery calculated from date of randomization. Numbers of patients at risk are given at bottom of figure. Crossover and repeat surgery rates are indicated on each curve at 5, 7, 11, 15, and 18 years.

Only 20 of the 332 surgically assigned patients did not have the bypass surgery. Of the 312 patients who had surgery, 67 (21%) have had repeat surgery. Operative mortality was 5.8% for the initial surgery and 11.9% for the second surgery. The cumulative rate of repeat surgery was 41% at 18 years (Figure 1); median time to repeat surgery was 9.7 years.

Graft Patency
All surgically assigned patients who had surgery were offered restudy of their vein grafts at 1, 5, and 10 years after surgery to assess patency of the grafts, regardless of whether symptoms were present. Graft patency was evaluated in 247 (85%) of 289 1-year survivors, in 157 (60%) of 260 5-year survivors, and in 80 (40%) of 202 10-year survivors. Sixty-six (33%) of the 10-year survivors had graft studies at 1, 5, and 10 years. Cumulative patency rates were calculated both for all patients with studies and for the 66 patients with all three graft studies.

Cause of Death
Cause of death was established by a central review of all death summaries and autopsy reports. Sudden death was defined as any cardiac death that occurred within 24 hours of symptoms of the terminal event. Sufficient information was available to determine the cause of death for all but 58 (13%) of the 434 patients who died.

Statistical Methods
The primary analysis was by “intent to treat,” i.e., all patients assigned to medical therapy compared with all patients assigned to surgical therapy. Thus, “medicine” and “surgery” in this report always imply the random assignment to these treatments unless stated otherwise. Crossovers from medical to surgical therapy were counted in the medical group, and surgically assigned patients who did not have surgery were counted in the surgical group. In addition to the primary analysis by intent to treat, analysis was done by the censored method, which censors nonadherers at the time of treatment change. Results of the censored analysis are given in the “Appendix.”

Time-to-event data for death and first myocardial infarction were analyzed by life table methods. For the analyses of nonfatal infarction, patients who died without previous myocardial infarction were counted as lost to follow-up at the time of death. Differences in cumulative event rates between medically and surgically assigned patients were tested by the log-rank statistic.

The effect of treatment on 10-year and 18-year mortality was examined in patients with and without myocardial infarction. Crude mortality ratios for surgery relative to medicine were calculated, and the $\chi^2$ statistic was used to test whether the ratio was different from 1. Ratios less than 1 indicated a reduction in mortality with surgical therapy, and those greater than 1 indicated an increase. The percent reduction or increase in mortality was obtained by subtracting the ratio from 1. In an earlier report, Cox proportional hazards model was used to estimate the effect of treatment on 10-year mortality in patients with and without infarction. Because the proportional hazards assumption was not valid after 10 years, the Cox model was not used to estimate treatment effects in this report.

Analysis of survival and infarction was done in all patients and in angiographic and clinical subgroups of patients specified in the original study protocol. Although patients were retrospectively stratified into subgroups, the plans for analysis were specified prospectively and not after inspection of the data.

Differences in mean angina scores between the two treatment groups were tested by the $t$ statistic. The $\chi^2$ statistic was used to test for differences in the distribution of no angina, mild angina, moderate angina, and severe angina between the two treatment groups.

All probability values reported are two-tailed and uncorrected for multiple comparisons. In the survival figures, only values of $p<0.05$ are reported at 5, 7, 11, 15, and 18 years, respectively.

Results
Survival
The 18-year cumulative survival rates according to intent to treat were 33% for medically assigned patients and 30% for surgically assigned patients ($p=0.60$; Figure 2). A significant survival advantage with surgical therapy was found only at 7 years (77% surgery versus 70% medicine, $p=0.043$). After 7 years, the mortality rate accelerated in the surgical group, and by 11 years, the survival rates were identical in both treatment groups (58%). Average annual mortality rates for the first 7 years were 3.3% surgical and 4.3% medical. Average annual rates between 7 and 11 years were higher in the surgical group: 4.8% surgical versus 3% medical. After 11 years, mortality rates remained somewhat higher in surgical patients: 4% per year surgical versus 3.6% per year medical. For both treatment
groups, the primary cause of death was cardiac in about 70% of cases (Table 1). Myocardial infarction accounted for 30% of all deaths; 18% were sudden, and 8% were operative.

Cumulative survival rates for angiographic and clinical subgroups of patients are summarized in Table 2 and Figures 3–5. For the 91 patients who had left main disease, survival was superior with surgical therapy for the entire period of follow-up; however, treatment differences were significant only up to 7 years (53% medicine versus 79% surgery, p=0.007). As in all patients, the mortality rate accelerated in the surgical group after year 7 of follow-up. Average annual mortality rates up to 7 years were 3% surgery compared with 6.7% with medical treatment and 4.9% versus 2.6% thereafter. In the left main subgroup, all but two of the 43 patients assigned to medical therapy either died (19 patients) or crossed over to surgical therapy (22 patients) in the first 8 years of follow-up. The cumulative crossover rate was nearly 80% at 8 years. Consequently, treatment comparisons after 8 years were solely comparisons of early versus delayed surgery.

For the 595 patients without left main disease, overall survival trends (not shown) were similar to those for all 686 randomized patients, but no significant treatment differences were found at any time during follow-up. There were also no significant treatment differences for patients with one-vessel or three-vessel disease. However, for patients with two-vessel disease, there was a consistent trend for poorer survival with surgical therapy over the entire period of follow-up. Survival rates at 11 years were 56% surgery and 70% medicine (p=0.038). Corresponding rates at 18 years were 30% and 34%, respectively (p=0.09).

Cumulative survival rates according to angiographic and clinical risk groups are presented in Figures 3 and 4, respectively. By either method of classification, low-risk patients had better survival with medical therapy during the entire follow-up period, but the treatment differences were not significant. In contrast, survival was uniformly superior with surgical therapy for patients in both the angiographic and clinical high-risk subgroups. Treatment differences were significant up to 11 years, after which they rapidly diminished and became nonsignificant by 15 years.

In this trial, the prognosis of medically assigned patients was highly dependent upon their baseline risk status (Figure 5). High-risk patients with left main disease or with multiple angiographic or clinical risk factors had a uniformly poorer survival than low-risk patients. In contrast, the prognosis of surgically assigned patients was generally independent of baseline risk status, particularly in the first 5–7 years of follow-up. Thus, surgery was initially beneficial in those high-risk subgroups of patients who had a poor prognosis with medical therapy.

Myocardial Infarction

Cumulative 18-year probabilities of remaining free of any myocardial infarction and of nonfatal and fatal infarction are displayed in Figure 6 for all patients and in Table 2 for angiographic and clinical subgroups of patients. The overall 18-year event-free rate was consistently but not significantly higher in medical (59%) than in surgical patients (51%). Perioperative infarction occurred in 13% of surgically assigned patients who had surgery and in 11% of medical crossovers. The infarction rate in the surgical group was initially higher

Table 1. Eighteen-Year Cause of Death by Treatment Assigned

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Medicine</th>
<th></th>
<th>Surgery</th>
<th></th>
<th>Total</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>50</td>
<td>23</td>
<td>41</td>
<td>19</td>
<td>91</td>
<td>21</td>
</tr>
<tr>
<td>Sudden death</td>
<td>39</td>
<td>18</td>
<td>39</td>
<td>18</td>
<td>78</td>
<td>18</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>9</td>
<td>4</td>
<td>13</td>
<td>6</td>
<td>21</td>
<td>5</td>
</tr>
<tr>
<td>Operative (CABG)</td>
<td>10</td>
<td>5</td>
<td>24</td>
<td>11</td>
<td>34</td>
<td>8</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>7</td>
<td>3</td>
<td>11</td>
<td>5</td>
<td>18</td>
<td>4</td>
</tr>
<tr>
<td>Other cardiac</td>
<td>51</td>
<td>24</td>
<td>45</td>
<td>21</td>
<td>96</td>
<td>22</td>
</tr>
<tr>
<td>Noncardiac</td>
<td>38</td>
<td>18</td>
<td>39</td>
<td>18</td>
<td>77</td>
<td>18</td>
</tr>
<tr>
<td>Unclassifiable</td>
<td>29</td>
<td>13</td>
<td>29</td>
<td>13</td>
<td>58</td>
<td>13</td>
</tr>
<tr>
<td>Total</td>
<td>217</td>
<td>434</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CABG, coronary artery bypass graft surgery.
TABLE 2. Eighteen-Year Cumulative Probabilities of Being Alive, of Remaining Free of Any, of Nonfatal, and of Fatal Myocardial Infarction, and of Being Alive Without Infarction

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Alive M/S</th>
<th>Without MI M/S</th>
<th>Without nonfatal MI M/S</th>
<th>Without fatal MI M/S</th>
<th>Alive without MI M/S</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>686</td>
<td>0.33 0.30</td>
<td>0.59 0.51</td>
<td>0.68* 0.56*</td>
<td>0.86 0.87</td>
<td>0.25* 0.18*</td>
</tr>
<tr>
<td>Left main</td>
<td>91</td>
<td>0.24 0.25</td>
<td>0.46 0.52</td>
<td>0.56 0.55</td>
<td>0.79 0.85</td>
<td>0.15 0.16</td>
</tr>
<tr>
<td>Non-left main</td>
<td>595</td>
<td>0.34 0.31</td>
<td>0.60 0.51</td>
<td>0.69* 0.56*</td>
<td>0.87 0.87</td>
<td>0.26* 0.17*</td>
</tr>
<tr>
<td>One-vessel</td>
<td>97</td>
<td>0.41 0.54</td>
<td>0.75 0.41</td>
<td>0.77 0.42</td>
<td>0.98 0.93</td>
<td>0.36 0.25</td>
</tr>
<tr>
<td>Two-vessel</td>
<td>213</td>
<td>0.34 0.30</td>
<td>0.60 0.45</td>
<td>0.66 0.54</td>
<td>0.87 0.83</td>
<td>0.28† 0.20†</td>
</tr>
<tr>
<td>Three-vessel</td>
<td>291</td>
<td>0.32 0.25</td>
<td>0.55 0.61</td>
<td>0.68 0.66</td>
<td>0.82 0.87</td>
<td>0.23 0.16</td>
</tr>
<tr>
<td>Low ang. risk</td>
<td>421</td>
<td>0.39 0.34</td>
<td>0.62 0.49</td>
<td>0.69 0.54</td>
<td>0.88 0.86</td>
<td>0.31† 0.18†</td>
</tr>
<tr>
<td>High ang. risk</td>
<td>168</td>
<td>0.21 0.24</td>
<td>0.54 0.58</td>
<td>0.67 0.63</td>
<td>0.82 0.91</td>
<td>0.15 0.16</td>
</tr>
<tr>
<td>Low clinical</td>
<td>236</td>
<td>0.39 0.40</td>
<td>0.72† 0.46†</td>
<td>0.77† 0.50†</td>
<td>0.94 0.89</td>
<td>0.29† 0.22†</td>
</tr>
<tr>
<td>Mid clinical</td>
<td>175</td>
<td>0.37 0.27</td>
<td>0.55 0.56</td>
<td>0.63 0.60</td>
<td>0.85 0.84</td>
<td>0.28 0.14</td>
</tr>
<tr>
<td>High clinical</td>
<td>177</td>
<td>0.22 0.25</td>
<td>0.48 0.53</td>
<td>0.63 0.59</td>
<td>0.76 0.88</td>
<td>0.19 0.19</td>
</tr>
</tbody>
</table>

MI, myocardial infarction; M, medical; S, surgical; ang., angiographic.
*p<0.05.
†p<0.01.

because of perioperative events but converged with that of the medical group at 5 years; thereafter, infarction in the surgical group accelerated to nearly twice the rate in the medical group. The trend for myocardial infarction or death was also similar (not shown); however, the probability of being alive without myocardial infarction was significantly higher at 18 years in medical (25%) than in surgical patients (18%), p=0.016.

The probability of remaining free of nonfatal infarction was significantly higher in the medical group (68% versus 56%, p=0.015), whereas the probability of remaining free of fatal infarction was comparable in both treatment groups (86% medical versus 87% surgical, p=0.62). Trends for angiographic and clinical subgroups of patients were similar to those for all patients.

In a recent report,4 we demonstrated that surgery reduced postinfarction mortality during the first 10 years of follow-up. Table 3 summarizes crude mortality ratios for surgery relative to medicine at 10 and 18 years of follow-up for patients with and without myocardial

![Figure 3](https://circ.ahajournals.org/)

**Figure 3.** Graphs showing cumulative survival rates by intent to treat for patients without left main coronary artery disease according to angiographic risk. Numbers of patients at risk are given at bottom of figure. Survival was significantly better with surgery (S) only for high-risk patients at 5, 7, and 11 years. For low-risk patients, survival was better with medical (M) therapy, but none of the differences were significant.
infarction. Significant reductions in postinfarction mortality were observed with surgical therapy at 10 years in all patients (35% reduction, \( p < 0.001 \)) and in the angiographic (55% reduction, \( p < 0.001 \)) and clinical high-risk subgroups (31% reduction, \( p < 0.05 \)). Corresponding reductions at 18 years were 13%, 8%, and 9%, respectively, and were not significantly different from zero.

**Relief of Angina**

Mean angina scores at entry and at 1, 5, 10, and 15 years are displayed in Figure 7. According to intent to treat (Figure 7, left panel), the mean score at entry was slightly higher in the surgical group. At 1 year, the surgical score decreased sharply to about one half of the medical score (\( p < 0.0001 \)), and at 5 years it remained about 25% lower than the medical score (\( p < 0.0001 \)). However, by 10 years the scores were similar in the two treatment groups and remained similar at 15 years. When medical crossovers whose angina was also relieved by surgery were censored from the analysis at the time of treatment change (Figure 7, right panel), the medical and surgical scores did not converge at 10 years as in the intent-to-treat analysis. Instead, the treatment difference was marginally significant at 10 years (\( p = 0.051 \)) but became nonsignificant by 15 years (\( p = 0.44 \)). Because of the sparse data, trends in angiographic and clinical subgroups were difficult to interpret but were generally similar to those shown for all patients in Figure 7.

As with the angina score data, the percent of patients who were angina-free was significantly higher with surgical therapy only during the first 5 years of follow-up. Rates for medicine and surgery were 3% versus 22% at 1 year (\( p < 0.001 \)), 4% versus 12% at 5 years (\( p < 0.001 \)), 6% versus 5% at 10 years, and 3% versus 4% at 15 years.

**Cumulative Graft Patency Rates**

Table 4 gives cumulative patency rates at 1, 5, and 10 years for all patients evaluated at any time point and for the small subgroup of 66 patients with all three studies. At 1, 5, and 10 years, graft patency rates were 71%, 64%, and 50% for all patients evaluated versus 74%,

![Figure 4](image-url)

**Figure 4.** Graphs showing cumulative survival rates by intent to treat for patients without left main coronary artery disease according to clinical risk. Numbers of patients at risk are given at bottom of figure. Low-risk patients had significantly better survival with medical (M) therapy up to 5 years; in high-risk patients, survival was significantly greater with surgical (S) therapy at 5, 7, and 11 years.

![Figure 5](image-url)

**Figure 5.** Graphs showing cumulative survival rates for low- and high-risk patients assigned to medical therapy (left panel) and assigned to surgical therapy (right panel). LMD, left main disease; ANG, angiographic.
70%, and 55% for the subgroup with complete data. The annual rate of graft closure for all patients was approximately 2% between 1 and 5 years and 3% between 5 and 10 years. The corresponding rates in the 10-year survivors with all three studies were 1% and 3%, respectively.

Discussion

After 18 years of follow-up in the VA trial, no significant differences were observed in survival either overall or in any subgroup, in relief of angina, or in postinfarction mortality between patients assigned to medical or surgical therapy. The early survival benefits reported with surgery in high-risk patients with left main disease, with multiple clinical or angiographic risk factors, or with myocardial infarction were no longer evident after 11 years. Severity of angina, which had become comparable in the two treatment groups at 10 years, remained comparable thereafter. In contrast, medically assigned patients continued to have significantly lower rates of nonfatal infarction and of infarction or death at 18 years. Survival was also better with medical therapy for low-risk patients throughout the entire period of follow-up, but the treatment differences were never significant except for those with two-vessel disease, and then only at 11 years.

Bypass surgery was effective in reducing mortality only in patients with a poor natural history. As shown in Figure 5, the prognosis of medically assigned patients depended on their baseline risk status, whereas the prognosis of surgically assigned patients was relatively independent of risk. Thus, when natural history was poor, as in patients with left main disease, in those with multiple risk factors, and in those with myocardial infarction, surgery was effective. However, with longer follow-up and increasing graft closure, these early favorable effects diminished. The initial benefit in survival with surgery seen in high-risk patients was never manifested in low-risk patients, who had fewer infarctions and a generally good prognosis. They derived no surgical benefit, in part because of operative mortality.

In this trial, surgery did not improve survival by preventing myocardial infarction. However, it did improve survival after myocardial infarction. We speculate that the benefits of surgery in these patients resulted from patent grafts. Grafts in surgical patients functioned as collaterals, and when grafts remained patent, patients were more likely to survive the insult of myocardial infarction.4 This was similar to the hypothesis of Epstein et al11 that fatal events due to coronary occlusion were more frequent when collaterals failed to enlarge and mature. Patents grafts also protected left ventricular function from the adverse effects of myocardial infarction.12 In surgical patients, progression to complete occlusion (usually proximal) was greater in
grafted than in ungrafted native arteries, particularly when grafts remained patent.13 Thus, when grafts to occluded arteries closed, the myocardium was placed in jeopardy and was less likely to survive the injury of infarction. Consequently, when the rate of myocardial infarction and graft closure both accelerated, the mortality rate in the surgical group increased, and the early surgical benefit deteriorated.

The VA trial was originally designed to evaluate the 5-year effect of bypass surgery compared with medical therapy. Patient follow-up was initially extended to 10 years and ultimately to 15 years to evaluate long-term trends. One of the interesting findings of this trial was that patients could be followed for many years with minimal losses to follow-up. In fact, during the last 5 years of the study, annual follow-up was accomplished by telephone interview or mail questionnaire from the coordinating center.7 During this centralized follow-up phase of the trial, an average of 93% of surviving patients were contacted annually for follow-up data, and survival status was known for all but one patient.

There have been only two other long-term, large-scale multicenter trials of coronary artery bypass surgery for stable angina: the European Coronary Surgery Study14 and the National Heart, Lung, and Blood Institute's Coronary Artery Surgery Study (CASS).15,16 Although the patient populations differed, all three trials reported that surgery was most beneficial in improving the survival of high-risk patients. In CASS, high-risk patients were defined as those with three-vessel disease and an ejection fraction less than 50%, similar to the VA's angiographic high-risk group. In the European study, high-risk patients were identified by the following risk factors: advanced age, an abnormal resting ECG, a markedly positive exercise test, peripheral arterial disease, proximal disease of the left anterior descending coronary artery, and a history of hypertension. The VA and European studies observed an attenuation of the surgical benefit with extended follow-up, a phenomenon that was not observed in CASS. Findings regarding the effects of surgery on quality of life and incidence of infarction were generally similar in all three trials. Rates

![Graphs showing mean angina scores at baseline and at 1, 5, 10, and 15 years by intent to treat (left panel) and by censoring nonadherers at the time of treatment change (right panel).](http://circ.ahajournals.org/)

**FIGURE 7.** Graphs showing mean angina scores at baseline and at 1, 5, 10, and 15 years by intent to treat (left panel) and by censoring nonadherers at the time of treatment change (right panel). Numbers of patients evaluated are given at bottom of figure (M, medical; S, surgical). According to intent to treat, angina scores were significantly lower with surgical therapy at 1 and 5 years. Results were similar by the censored method, except that at 10 years the difference in favor of surgery was marginally significant.

### Table 4. Cumulative Patency Rates at 1, 5, and 10 Years

<table>
<thead>
<tr>
<th>Interval (years)</th>
<th>Patients evaluated (n)</th>
<th>Grafts open at beginning of interval (n)</th>
<th>Grafts open at end of interval (n)</th>
<th>Patency rate</th>
<th>Cumulative rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>All data</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>247</td>
<td>503</td>
<td>357</td>
<td>0.710</td>
<td>0.710</td>
</tr>
<tr>
<td>1–5</td>
<td>146</td>
<td>221</td>
<td>198</td>
<td>0.896</td>
<td>0.636</td>
</tr>
<tr>
<td>5–10</td>
<td>67</td>
<td>94</td>
<td>74</td>
<td>0.787</td>
<td>0.501</td>
</tr>
<tr>
<td>Patients with 1+5+10-year studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>66</td>
<td>135</td>
<td>100</td>
<td>0.741</td>
<td>0.741</td>
</tr>
<tr>
<td>1–5</td>
<td>66</td>
<td>100</td>
<td>94</td>
<td>0.940</td>
<td>0.697</td>
</tr>
<tr>
<td>5–10</td>
<td>66</td>
<td>94</td>
<td>74</td>
<td>0.787</td>
<td>0.548</td>
</tr>
</tbody>
</table>
of crossover from medical to surgical therapy were also similar and approached 40% at 10 years. A more detailed comparison of the 10–12-year findings among these three trials is given in Reference 15.

Since the initiation of the VA trial, significant improvements have occurred in both medical and surgical therapies for coronary artery disease, and increased emphasis has been focused on lifestyle changes. Although treatment offered 15–20 years ago is no longer current, the VA and other trials have had a direct impact on the selection of patients for surgery and on the role of bypass surgery for treatment of patients with chronic stable angina. Whether the results of these trials remain directly applicable to current therapy given the improvements in medical and surgical treatment over the past decade is debatable. One would have to conduct another long-term trial to evaluate properly the new approaches to medical and surgical therapy. Nevertheless, the findings of the VA, CASS, and European randomized trials provided the most unbiased data on the relative effectiveness of bypass surgery and have been used recently by the American College of Cardiology/American Heart Association task force to set guidelines and indications for coronary artery bypass graft surgery. Perhaps the most lasting achievement of these studies was the demonstration that long-term controlled clinical trials of emerging new surgical therapies were feasible and, more importantly, that they provided the most unbiased method of evaluating treatment efficacy, a method superior to that of uncontrolled studies.

**Appendix**

In addition to the primary analysis by intent-to-treat, analysis by the censored method was performed to provide an assessment of the influence of nonadherers on the treatment comparisons. This method censors all crossovers at the time of treatment change, which was the date of bypass operation for medically assigned patients who had surgery. For surgically assigned patients who did not have surgery, the time of treatment change was arbitrarily set at 1 day after randomization. The survival results by this method are summarized in Figure 8 for all randomized patients and in Table 5 for key angiographic and clinical subgroups of patients. Because this method of analysis is potentially biased, it does not yield valid probability values, and none are reported in Figure 8 or Table 5. Nevertheless, the findings by this method were very similar to those by intent to treat. If we assume that selection for surgery and survival are independent, an assumption that is difficult to verify, the censored results indicate that nonadherence had no significant impact on the treatment comparisons.

**References**


**Table 5. Cumulative Survival Rates by the Censored Method**

<table>
<thead>
<tr>
<th>Group</th>
<th>7 Years</th>
<th></th>
<th>11 Years</th>
<th></th>
<th>15 Years</th>
<th></th>
<th>18 Years</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>S</td>
<td>M</td>
<td>S</td>
<td>M</td>
<td>S</td>
<td>M</td>
<td>S</td>
</tr>
<tr>
<td>All patients</td>
<td>0.70</td>
<td>0.78</td>
<td>0.57</td>
<td>0.58</td>
<td>0.45</td>
<td>0.40</td>
<td>0.26</td>
<td>0.29</td>
</tr>
<tr>
<td>Left main</td>
<td>0.59</td>
<td>0.87</td>
<td>0.41</td>
<td>0.59</td>
<td>0.21</td>
<td>0.39</td>
<td>0.21</td>
<td>0.26</td>
</tr>
<tr>
<td>Non–left main</td>
<td>0.73</td>
<td>0.77</td>
<td>0.59</td>
<td>0.58</td>
<td>0.47</td>
<td>0.41</td>
<td>0.26</td>
<td>0.30</td>
</tr>
<tr>
<td>One-vessel disease</td>
<td>0.85</td>
<td>0.87</td>
<td>0.71</td>
<td>0.69</td>
<td>0.55</td>
<td>0.58</td>
<td>0.36</td>
<td>0.51</td>
</tr>
<tr>
<td>Two-vessel disease</td>
<td>0.83</td>
<td>0.72</td>
<td>0.70</td>
<td>0.54</td>
<td>0.52</td>
<td>0.35</td>
<td>0.36</td>
<td>0.29</td>
</tr>
<tr>
<td>Three-vessel disease</td>
<td>0.63</td>
<td>0.76</td>
<td>0.49</td>
<td>0.57</td>
<td>0.44</td>
<td>0.38</td>
<td>0.37</td>
<td>0.30*</td>
</tr>
<tr>
<td>Low ang. risk</td>
<td>0.84</td>
<td>0.77</td>
<td>0.70</td>
<td>0.60</td>
<td>0.56</td>
<td>0.44</td>
<td>0.41</td>
<td>0.32</td>
</tr>
<tr>
<td>High ang. risk</td>
<td>0.51</td>
<td>0.77</td>
<td>0.38</td>
<td>0.53</td>
<td>0.32</td>
<td>0.32</td>
<td>0.24*</td>
<td>0.25*</td>
</tr>
<tr>
<td>Low clinical risk</td>
<td>0.88</td>
<td>0.82</td>
<td>0.72</td>
<td>0.64</td>
<td>0.58</td>
<td>0.49</td>
<td>0.42*</td>
<td>0.39*</td>
</tr>
<tr>
<td>Mid clinical risk</td>
<td>0.73</td>
<td>0.78</td>
<td>0.64</td>
<td>0.59</td>
<td>0.48</td>
<td>0.40</td>
<td>0.33</td>
<td>0.25</td>
</tr>
<tr>
<td>High clinical risk</td>
<td>0.53</td>
<td>0.73</td>
<td>0.37</td>
<td>0.52</td>
<td>0.33</td>
<td>0.32</td>
<td>0.26</td>
<td>0.26</td>
</tr>
</tbody>
</table>

M, medical; S, surgical; ang., angiographic.

*The 18-year medical survival rate was zero in these subgroups because the only patient at risk in the last year of the study died. Hence, the 17-year rates in both treatment groups are reported because they are more stable.


_Circulation_. 1992;86:121-130
doi: 10.1161/01.CIR.86.1.121

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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