Effect of Completeness of Revascularization on Long-term Outcome of Patients With Three-Vessel Disease Undergoing Coronary Artery Bypass Surgery

A Report From the Coronary Artery Surgery Study (CASS) Registry

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Background. Complete revascularization after coronary artery bypass surgery is a logical goal and improves symptomatic outcome and survival. However, the impact of complete revascularization in patients with three-vessel coronary disease with varying severities of angina and left ventricular dysfunction has not been clearly defined.

Methods and Results. The study was performed as a retrospective analysis of 3,372 nonrandomized surgical patients from the Coronary Artery Surgery Study (CASS) Registry who had three-vessel coronary disease. Group 1 (894 patients) had class I or II angina (Canadian Cardiovascular Society criteria) and group 2 (2,478 patients) had class III or IV angina. In group 1, adjusted cumulative 4-year survivals according to the number of vessels bypassed were 85% (one vessel), 94% (two vessels), 96% (three vessels), and 96% (more than three vessels) (log rank, \( p=0.022 \)). Adjusted event-free survival (death, myocardial infarction, definite angina, or reoperation) was not influenced by the number of vessels bypassed, nor was the anginal status among patients remaining alive after 5 years. In group 2, adjusted cumulative 5-year survivals were 78% (one vessel), 85% (two vessels), 90% (three vessels), and 87% (more than three vessels) (log rank, \( p=0.074 \)). Adjusted event-free survivals after 6 years were 23% (one vessel), 23% (two vessels), 29% (three vessels), and 31% (more than three vessels) (\( p=0.025 \)); at 5 years, those with more complete revascularization were more likely to be asymptomatic or free of severe angina. Among group 2 patients with ejection fractions \(<0.35\), 6-year survival was 69% for those with grafts to three or more vessels versus 45% for those with grafts to two vessels (\( p=0.04 \)). Placing grafts to three or more vessels was independently associated with improved survival and event-free survival in group 2 but not group 1 patients. The case-fatality rates among 529 patients experiencing a myocardial infarction during follow-up was significantly higher for patients with less complete revascularization.

Conclusions. Complete revascularization (grafts to three or more vessels) in patients with three-vessel coronary disease appears to most benefit those with severe angina and left ventricular dysfunction.

(Circulation 1992;86:446–457)

Key Words • revascularization, myocardial • coronary disease • coronary artery bypass

In patients with multivessel disease who undergo coronary artery bypass surgery, the concept of complete myocardial revascularization is logical and appears to result in improved symptomatic outcome and survival compared with incomplete revascularization.1–4 Few studies to date have addressed the impact of complete versus incomplete revascularization in patients with three-vessel coronary disease and left ventricular dysfunction—a subgroup in whom the benefits of complete revascularization may be particularly evident. There are many reasons why patients with three-vessel disease have a variable number of vessels bypassed with varying degrees of the completeness of revascularization achieved, but whether bypassing fewer than three or more than three vessels influences long-term outcome independently of baseline characteristics is unknown. The issue of completeness of revascularization on long-term outcome has now assumed increasing importance with the expanding use of coronary balloon angioplasty as an alternative to coronary artery bypass surgery in patients with multivessel coronary artery disease.

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Received March 5, 1991; revision accepted May 4, 1992.
To examine the influence of completeness of revascularization on long-term outcome after coronary bypass surgery, data were analyzed from a large, prospectively entered, nonrandomized multicenter registry study of patients with three-vessel coronary disease who had coronary surgical revascularization. A major objective was to evaluate the impact of the specific number of bypassed vessels on the late morbidity and mortality in these patients after dividing patients into subgroups based on the severity of their angina and degree of left ventricular dysfunction prior to surgery.

Methods

The details of the Coronary Artery Surgery Study (CASS) design, methods, definitions of terms, quality control, and baseline data have been described previously.\textsuperscript{5}

Coronary Angiographic Analysis

For the purpose of this study, three-vessel disease was defined by the presence of significant coronary artery obstruction of at least 70% stenosis (visually assessed) in each of the three major vessels or their major branches. These were defined in a right-dominant circulation by the right coronary artery, the left anterior descending, and left circumflex arteries. In a left-dominant circulation, the three vessels were defined by the left anterior descending and diagonal artery, the proximal circumflex and marginal branches, and by the distal circumflex and its posterolateral branches. Significant (at least 50%) stenosis of the left main coronary artery was considered as two-vessel disease when the coronary circulation was right-dominant and three-vessel disease when left-dominant.

Hemodynamic and Ventriculographic Analysis

Left ventriculograms were performed in a 30° right anterior oblique projection, and the cardiac silhouette was divided into five segments. Wall motion in each of these five segments was graded from 1 to 6: 1 being normal; 2, moderate hypokinesis; 3, severe hypokinesis; 4, akinesis; 5, dyskinesis; and 6, aneurysmal. A left ventricular wall motion score was obtained by adding the values for each of the five segments, with a combined score of 5 indicating normal ventricular function with higher scores indicating increasing degrees of hypokinesis. Ejection fraction was measured using the techniques available in the individual laboratories.

A myocardial jeopardy score was implemented to relate the degree of functional impairment in specific segments of myocardium supplied by vessels with significant coronary narrowing. No myocardial jeopardy (0) was defined by wall motion scores $\geq 4$ (as defined above) in both anterior and inferior wall segments supplied by vessels with $\geq 70\%$ lesions. Inferior jeopardy (1) was defined when a vessel with a $\geq 70\%$ stenosis supplied an inferior wall with a wall motion score of $< 4$ in the presence of an anterior wall motion score of $\geq 4$ with a $\geq 70\%$ lesion of the left anterior descending artery (i.e., the inferior wall but not the anterior wall was considered viable and in jeopardy) and vice versa for anterior jeopardy (2). Myocardial jeopardy in both regions (3) was present when both the anterior and inferior walls each had wall motion scores of $< 4$.

Patient Population

Selected for analysis from the CASS Registry were 3,372 patients with three-vessel disease who underwent isolated coronary bypass surgery between July 1974 and June 1979 and had not had coronary bypass surgery previously. Excluded were patients who did not have angina as their primary symptom or who underwent additional cardiac surgical procedures such as cardiac valve replacement.

The severity of angina was graded from I to IV according to the Canadian Cardiovascular Society criteria: 894 patients had class I or II (group 1: mild angina) and 2,478 patients had class III or IV (group 2: severe angina).

Surgical Techniques and Definitions

Anesthetic and surgical techniques varied among the participating institutions. An average of 3.2 distal anastomoses were performed per patient. Saphenous vein grafts were generally used, although 16% of patients received an internal mammary artery graft alone or in combination with saphenous veins.

The extent of revascularization was defined by the number of the three major vessels (or their major branches) receiving a bypass graft. For example, in the situation in which grafts were placed to the left anterior descending and circumflex vessels and/or their branches but not to the right coronary artery, this was categorized as two vessels bypassed. If all three major vessels were bypassed, but in addition, separate or sequential grafts were placed to one or more of their major branches, this was categorized as more than three vessels grafted. Among these 3,372 patients, 67 (2.0%) had one, 1,065 patients (31.6%) had two, 1,276 patients (37.8%) had three, and 964 patients (28.6%) had more than three vessels bypassed. Grafts were placed by the artery involved to the left anterior descending coronary artery in 98%, to the right coronary artery in 83%, and to the circumflex artery in 86% of patients. It should be emphasized that neither the surgical assessment of the state of the vessels and grafts at the time of surgery nor the specific reasons for nonrevascularization of vessels was recorded in the CASS data base. Operative mortality was defined as death within 30 days after the day of surgery or before hospital discharge.

Follow-up

Annual clinical follow-up was obtained in all patients, primarily by a mailed questionnaire or by telephone interview, for a mean period of 4.9 years (maximum of 8.1 years). In the event of subsequent coronary events or death, additional information from the referring physician and institution was recorded.

Statistical Analysis

Univariate analysis of discrete variables was performed by means of the Pearson $\chi^2$ test, and continuous variables were analyzed using the two-sample $t$ test. The importance of revascularization variables was examined using a Cox proportional hazards model with a conservative approach. First, a stepwise step-up model was constructed using 56 preoperative variables as possible predictors (based on patient history and physical examination, angiographic, anatomic, and hemodynamic
findings) but omitting the number of vessels bypassed. After these models were constructed, revascularization variables were then entered into the model to determine their significance as predictive variables. The possible predictive revascularization variables included the specific vessels bypassed and the number of vessels bypassed: 1) one versus more than one, 2) two versus one and three or more, and 3) three or more versus less than three. Adjustments were not made for multiple comparisons in these models because of the expected high correlation among the revascularization variables. However, a conservative approach would involve multiplying each probability value obtained by three.

The survival curves were calculated with the life-table method and compared by the log rank statistic. Because there were a number of baseline imbalances among patients with different numbers of vessels bypassed, it was appropriate to adjust the graphical presentations to take this into account: Stepwise Cox models (vide supra), omitting the number of vessels bypassed but using other baseline variables, were used to develop a linear adjustment index (the index was the linear function used in the Cox model). The cases were then divided into quartiles of estimated risk; the graphs presented are the directly adjusted time-to-end point curves. The log rank statistic was obtained by summing the observed and expected numbers of events and covariance matrices for the four strata.

### Results

#### Baseline Characteristics

Detailed preoperative characteristics of the 3,372 patients are summarized in Table 1. There were several important differences between those who had one, two, three, or more than three vessels bypassed. In particular, there were important differences in patients with one vessel bypassed versus the remainder of the population in variables reflecting left ventricular function (history of cardiac failure, left ventricular end-diastolic pressure, and ejection fraction). Anterior myocardial jeopardy indicating significant left anterior descending coronary artery obstruction with a viable anterior wall was also more common in this group.

#### Surgery

The operative mortality was 1.8% in group 1 and 3.5% in group 2, but there was no significant difference in operative mortality according to the number of vessels bypassed. Ninety-eight percent of patients received a graft to the left anterior descending coronary artery. In only 30 patients was a significant (≥70%) stenosis of the proximal segment of this vessel left

### Table 1. Baseline Characteristics of 3,372 CASS Surgical Patients With Three-Vessel Disease Who Had One or More Vessels Bypassed

<table>
<thead>
<tr>
<th>Variable</th>
<th>1 (n=67)</th>
<th>2 (n=1,065)</th>
<th>3 (n=1,276)</th>
<th>&gt;3 (n=964)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of vessels bypassed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>58 (86.6)</td>
<td>921 (86.5)</td>
<td>1,104 (86.5)</td>
<td>857 (88.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Age (years)</td>
<td>54±9</td>
<td>56±9</td>
<td>56±8</td>
<td>57±8</td>
<td>NS</td>
</tr>
<tr>
<td>One or more associated medical diseases*</td>
<td>29 (43.3)</td>
<td>612 (57.5)</td>
<td>709 (55.6)</td>
<td>550 (57.1)</td>
<td>NS</td>
</tr>
<tr>
<td>History of myocardial infarction</td>
<td>41 (61.2)</td>
<td>639 (60.1)</td>
<td>695 (54.6)</td>
<td>540 (56.0)</td>
<td>0.0463</td>
</tr>
<tr>
<td>History of congestive cardiac failure</td>
<td>13 (20.0)</td>
<td>101 (9.7)</td>
<td>119 (9.5)</td>
<td>81 (8.5)</td>
<td>0.0243</td>
</tr>
<tr>
<td>Moderate-to-severe functional impairment caused by heart failure</td>
<td>1 (1.5)</td>
<td>39 (3.7)</td>
<td>48 (3.8)</td>
<td>28 (2.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>32 (47.8)</td>
<td>440 (41.3)</td>
<td>562 (44.0)</td>
<td>412 (42.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Angiographic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal vessel involvement</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>9 (13.4)</td>
<td>128 (12.0)</td>
<td>114 (8.9)</td>
<td>106 (11.0)</td>
<td></td>
</tr>
<tr>
<td>One</td>
<td>15 (22.4)</td>
<td>293 (27.5)</td>
<td>344 (27.0)</td>
<td>245 (25.4)</td>
<td></td>
</tr>
<tr>
<td>Two</td>
<td>18 (26.9)</td>
<td>307 (28.8)</td>
<td>490 (38.4)</td>
<td>348 (36.1)</td>
<td></td>
</tr>
<tr>
<td>Three</td>
<td>25 (37.3)</td>
<td>337 (31.6)</td>
<td>328 (25.7)</td>
<td>265 (27.5)</td>
<td></td>
</tr>
<tr>
<td>Myocardial jeopardy†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0= None</td>
<td>16 (24.2)</td>
<td>126 (11.9)</td>
<td>143 (11.3)</td>
<td>104 (10.8)</td>
<td></td>
</tr>
<tr>
<td>1= Inferior wall</td>
<td>8 (12.1)</td>
<td>152 (14.4)</td>
<td>193 (15.2)</td>
<td>151 (15.7)</td>
<td></td>
</tr>
<tr>
<td>2=Anterior wall</td>
<td>24 (36.4)</td>
<td>277 (26.2)</td>
<td>225 (17.7)</td>
<td>188 (19.6)</td>
<td></td>
</tr>
<tr>
<td>3=Both</td>
<td>18 (27.2)</td>
<td>502 (47.5)</td>
<td>708 (55.8)</td>
<td>517 (53.9)</td>
<td></td>
</tr>
<tr>
<td>Left ventricular wall motion score†</td>
<td>9.5±4.0</td>
<td>8.6±3.5</td>
<td>8.5±3.7</td>
<td>8.3±3.3</td>
<td>0.0672</td>
</tr>
<tr>
<td>Hemodynamic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ventricular end-diastolic pressure (mm Hg)</td>
<td>15±8</td>
<td>14±7</td>
<td>14±7</td>
<td>13±7</td>
<td>0.0394</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>56±17</td>
<td>57±14</td>
<td>59±15</td>
<td>58±14</td>
<td>0.0431</td>
</tr>
</tbody>
</table>

CASS, Coronary Artery Surgery Study.
All continuous data are given as mean±1 SD.
* Diseases include hypertension, diabetes, cerebrovascular, peripheral arterial, valvular heart disease, chronic pulmonary, thrombophlebitis, and hepatic.
† See “Methods.”
unbypassed (two of 35 patients with one vessel bypassed, 28 of 601 patients with two vessels bypassed, but none with three or more vessels bypassed).

**Late Outcome After Surgery**

*Group 1: Mild angina.* With the use of the Cox proportional hazards model, the independent predictors of late survival and event-free survival were determined (Table 2). Survival was independently related to baseline patient characteristics such as the number of associated medical diseases, age, and impairment of left ventricular function. In addition, the presence of a bypass graft to only one major vessel was an independent predictor of mortality (relative risk almost four-fold). Event-free survival was not independently influenced by revascularization status but rather by the number of associated diseases, absence of a proximal left anterior descending stenosis, and employment status.

In patients with mild angina, the cumulative 6-year survival (adjusted for preoperative baseline imbalances) was similar for those with two, three, or more than three bypassed vessels (Figure 1A). At 6 years, the adjusted cumulative survival with two grafts was 89%, with three was 92%, and with more than three was 88%. In comparison, among patients who had only a single vessel bypassed, the adjusted cumulative survival after 4 years was significantly lower than the other three groups (85%, \( p = 0.022 \)), although it should be emphasized that there were only 11 patients who underwent bypass of a single vessel. The number of vessels bypassed failed to significantly influence event-free survival, that is, freedom from death, myocardial infarction, reoperation, or development of definite angina (Figure 1B). When patients with three and more than three bypassed vessels were combined and compared with those with two bypassed vessels, there were no significant differences noted in either survival or event-free survival.

Among patients with preoperative mild angina remaining alive after 5 years of follow-up, the majority were asymptomatic. No significant difference was observed in their functional status according to the number of vessels bypassed (Figure 2).

*Group 2: Severe angina.* Multivariate analysis revealed that survival was improved to a significant degree (by approximately 25%) when three or more vessels had been bypassed versus fewer than three vessels (Table 3). In addition to a number of baseline functional and angiographic variables, bypassing three or more vessels also significantly improved event-free survival to a small degree in this patient population.

The adjusted cumulative survival among patients with severe angina was lower for patients with only a single vessel bypassed compared with patients with two or more bypassed vessels (Figure 3A). The adjusted 5-year survival with one bypassed vessel was 78%, worse than the 6-year adjusted survivals of 81%, 86%, and 86% among patients with two, three, and more than three bypassed vessels, respectively (\( p = 0.074 \)). Adjusted event-free survival was influenced to a small but statistically significant degree by the number of vessels bypassed with poorer outcome observed in those patients with fewer bypassed vessels (Figure 3B). Thus, at 6 years, 31% of patients with more than three bypassed vessels remained free of events compared with 29% with three, 23% with two, and 23% with only one (\( p = 0.025 \)).

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**Table 2. Multivariate Analysis of Long-term Mortality and Combined Cardiac Events of Death, Myocardial Infarction, Reoperation, or Definite Angina in Patients With Mild Angina in Whom One or More Vessels Were Bypassed**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate p value</th>
<th>Multivariate normal test statistic (( p ))</th>
<th>Relative risk (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ventricular wall motion score*</td>
<td>&lt;0.0001</td>
<td>4.33 (&lt;0.0001)</td>
<td>1.153 (1.081, 1.230)</td>
</tr>
<tr>
<td>Number of associated medical diseases†</td>
<td>&lt;0.0001</td>
<td>3.27 (0.0011)</td>
<td>1.563 (1.196, 2.043)</td>
</tr>
<tr>
<td>Age</td>
<td>&lt;0.0001</td>
<td>2.04 (0.0411)</td>
<td>1.297 (1.011, 1.664)</td>
</tr>
<tr>
<td>Congestive heart failure score‡</td>
<td>0.0010</td>
<td>2.59 (0.0097)</td>
<td>1.040 (1.010, 1.071)</td>
</tr>
<tr>
<td>Number of operable vessels</td>
<td>0.0360</td>
<td>2.39 (0.0168)</td>
<td>1.710 (1.102, 2.653)</td>
</tr>
<tr>
<td>Revascularization variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Only one vessel bypassed</td>
<td>0.0007</td>
<td>2.47 (0.0134)</td>
<td>3.852 (1.323, 11.209)</td>
</tr>
<tr>
<td>Combined cardiac events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of associated medical diseases</td>
<td>&lt;0.0001</td>
<td>4.24 (&lt;0.0001)</td>
<td>1.273 (1.139, 1.424)</td>
</tr>
<tr>
<td>Proximal left anterior descending stenosis</td>
<td>0.0015</td>
<td>-3.07 (0.0022)</td>
<td>0.996 (0.994, 0.999)</td>
</tr>
<tr>
<td>Employment status</td>
<td>0.0090</td>
<td>2.52 (0.0118)</td>
<td>1.095 (1.020, 1.175)</td>
</tr>
<tr>
<td>Revascularization variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cox proportional hazards model used.
*See “Methods.”
†Diseases include hypertension, diabetes, cerebrovascular, peripheral arterial, valvular heart disease, chronic pulmonary, thrombophlebitis, and hepatic.
‡Based on a score representing the number of positive responses to history of cardiac failure, use of diuretics, presence of pulmonary rates, and an S3 gallop on the admission physical examination (possible scores, 0–5).
Figure 1. Graphs show adjusted cumulative 6-year survival (panel A) and event-free survival (death, myocardial infarction, reoperation, and definite angina) (panel B) in group 1 patients with preoperative mild angina, comparing patients with varying degrees of revascularization as defined by the number of vessels bypassed.

Figure 4 shows the functional status of surviving patients in group 2 after 5 years of follow-up, revealing that patients with more than one bypassed vessel were more likely to be free of angina and less likely to have severe angina than those patients with one bypassed vessel \((p=0.0072)\). It is also apparent that there is a close relation between the number of vessels bypassed and symptomatic status at follow-up.

**Cumulative Survival Stratified According to Preoperative Ejection Fraction**

Cumulative survival was also analyzed after stratifying patients by ejection fraction after excluding the 67 patients with only one graft, as they represented too small a number on which to perform subgroup analyses. Additionally, to compare enough patients in each ejection fraction subgroup, patients with three and more than three bypassed vessels were combined and compared with those with two bypassed vessels. Combining the patients with three and more than three bypassed vessels appeared to be justified, as the differences in probability of survival over 6 years between these two subgroups were not statistically significant at any level of ejection fraction \((<0.35, 0.35-0.49, \text{ or } \geq 0.50)\) in either group 1 or group 2. Of the 3,305 patients analyzed, 2,476 patients had ventriculograms from which ejection fractions were calculated before surgery.

**Group 1: Mild angina.** Figure 5 shows the cumulative survivals for patients with mild angina stratified according to initial ejection fraction. After 6 years, no significant differences in survival between those with two bypassed vessels and for those with three or more were observed for any of the three strata.

**Group 2: Severe angina.** In contrast to patients with preoperative mild angina, those with severe angina who had initial ejection fractions <0.35 and had three or more vessels bypassed had longer survival than those with similar ejection fractions but grafts to only two vessels. Six-year cumulative survival was 69% versus 45%, respectively \((p=0.04)\) (Figure 6A). No significant difference was observed among patients with higher ejection fractions (Figures 6B and 6C).

**Sudden Cardiac Death and Myocardial Infarction**

No overall influence on the adjusted cumulative incidence of sudden cardiac death or myocardial infarction was observed between patients with bypasses to one, two, three, or more than three vessels after 6 years (Figure 7). During follow-up, late myocardial infarction occurred in 529 patients, of which 71 (13.4%) were fatal. The case-fatality rate was significantly higher among patients who had only one or two vessels bypassed compared with those with three or more than three (Table 4).

**Discussion**

Coronary artery bypass surgery has been demonstrated in observational and randomized trials to improve survival in patients with stable angina who have significant left main coronary artery obstruction compared with medical treatment. In randomized trials, surgery has also been shown to improve the survival of patients who have three-vessel coronary disease with severe angina as well as mild angina, particularly those with left ventricular dysfunction. Two large coronary surgery registry studies have also provided information about surgical versus medical survival.
CASS Registry indicated that surgical therapy results in improved survival compared with medical therapy with two- or three-vessel disease in patients with moderate or severe angina.\textsuperscript{13,14} The Duke University Registry also indicated improvement in survival for patients treated surgically with left main, two-, or three-vessel disease, particularly in those with left ventricular dysfunction.\textsuperscript{15,16}

Although the concept of complete myocardial revascularization with coronary artery surgery is logical and has been strongly advocated, this is not always possible in patients with multivessel disease. This usually reflects the interaction between baseline clinical and anatomical characteristics such as left ventricular function, previous myocardial infarction, degree of distal disease, and caliber of diseased vessels. It is therefore important to consider whether or not incomplete myocardial revascularization compromises the long-term results of coronary bypass surgery compared with complete revascularization independently of differences in preoperative characteristics.

**Present Study**

The results of the present study demonstrate that, for patients undergoing surgical revascularization who had mild angina preoperatively (group 1), bypassing at least two vessels conferred significant benefit over bypassing a single vessel in terms of overall long-term survival. However, the number of patients who received only a single graft was very small in this group, and it is difficult to reach any firm conclusion about this group of patients. No difference was observed in cumulative survival among those with bypasses to two versus three or more than three vessels, even after stratification for ejection fraction; neither was there any apparent influence of revascularization status on event-free survival (death, myocardial infarction, reoperation, and definite angina).

Among patients with severe preoperative angina (group 2), a reduction in late survival and event-free survival was observed in patients with only a single vessel bypassed. However, major baseline differences in this population were probably partly responsible for this observation, as it was not found to be an independent risk factor after multivariate analysis. On the other hand, more complete revascularization (i.e., bypassing three or more vessels versus one or two) was associated with improved survival and event-free survival independently of any baseline differences. After 5 years, patients with

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**TABLE 3. Multivariate Analysis of Long-term Mortality and Combined Cardiac Events of Death, Myocardial Infarction, Reoperation, or Definite Angina in Patients With Severe Angina in Whom One or More Vessels Were Bypassed**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate ( p ) value</th>
<th>Multivariate normal test statistic (( p ))</th>
<th>Relative risk (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mortality</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congestive heart failure score</td>
<td>&lt;0.0001</td>
<td>4.38 (&lt;0.0001)</td>
<td>1.29 (1.149, 1.438)</td>
</tr>
<tr>
<td>Left ventricular wall motion score</td>
<td>&lt;0.0001</td>
<td>5.88 (&lt;0.0001)</td>
<td>1.10 (1.063, 1.130)</td>
</tr>
<tr>
<td>Number of associated medical diseases</td>
<td>&lt;0.0001</td>
<td>5.86 (&lt;0.0001)</td>
<td>1.39 (1.247, 1.557)</td>
</tr>
<tr>
<td>Age</td>
<td>&lt;0.0001</td>
<td>3.27 (0.0011)</td>
<td>1.03 (1.010, 1.041)</td>
</tr>
<tr>
<td>Number of proximal vessels diseased</td>
<td>0.0007</td>
<td>2.51 (0.0119)</td>
<td>1.17 (1.035, 1.322)</td>
</tr>
<tr>
<td>Left ventricular end-diastolic pressure</td>
<td>&lt;0.0001</td>
<td>2.25 (0.0245)</td>
<td>1.02 (1.002, 1.032)</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>0.0023</td>
<td>2.29 (0.220)</td>
<td>1.32 (1.040, 1.663)</td>
</tr>
<tr>
<td><strong>Revascularization variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Three or more vessels bypassed</td>
<td>0.0195</td>
<td>-2.48 (0.0132)</td>
<td>0.745 (0.591, 0.940)</td>
</tr>
<tr>
<td><strong>Combined cardiac events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of associated medical diseases</td>
<td>&lt;0.0001</td>
<td>4.21 (&lt;0.0001)</td>
<td>1.128 (1.066, 1.192)</td>
</tr>
<tr>
<td>Height at baseline</td>
<td>&lt;0.0001</td>
<td>-3.76 (0.0002)</td>
<td>0.989 (0.983, 0.995)</td>
</tr>
<tr>
<td>Limitation of activities at baseline</td>
<td>0.0001</td>
<td>2.15 (0.0313)</td>
<td>1.050 (1.004, 1.097)</td>
</tr>
<tr>
<td>Number of proximal vessels diseased</td>
<td>0.0120</td>
<td>-2.74 (0.0062)</td>
<td>0.927 (0.878, 0.979)</td>
</tr>
<tr>
<td>Recreational activity (strenuous through to sedentary)</td>
<td>0.0001</td>
<td>2.39 (0.0170)</td>
<td>1.093 (1.016, 1.175)</td>
</tr>
<tr>
<td>Presence of rales</td>
<td>0.0017</td>
<td>2.58 (0.0109)</td>
<td>1.426 (1.089, 1.867)</td>
</tr>
<tr>
<td>Collateral vessels on angiogram</td>
<td>0.0311</td>
<td>-2.77 (0.0055)</td>
<td>0.847 (0.753, 0.952)</td>
</tr>
<tr>
<td>Myocardial jeopardy score*</td>
<td>0.0091</td>
<td>-2.09 (0.0396)</td>
<td>0.948 (0.902, 0.997)</td>
</tr>
<tr>
<td>Age</td>
<td>0.3101</td>
<td>-2.82 (0.0048)</td>
<td>0.991 (0.984, 0.997)</td>
</tr>
<tr>
<td>Canadian Cardiovascular Society Class</td>
<td>0.0037</td>
<td>2.53 (0.0114)</td>
<td>1.149 (1.032, 1.280)</td>
</tr>
<tr>
<td>Employment status</td>
<td>0.0002</td>
<td>2.43 (0.0151)</td>
<td>1.050 (1.010, 1.092)</td>
</tr>
<tr>
<td>Number of segments with &gt;50% stenosis</td>
<td>0.1201</td>
<td>2.17 (0.0298)</td>
<td>1.026 (1.003, 1.050)</td>
</tr>
<tr>
<td><strong>Revascularization status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Three or more vessels bypassed</td>
<td>0.0012</td>
<td>-2.62 (0.0088)</td>
<td>0.866 (0.777, 0.964)</td>
</tr>
</tbody>
</table>

Cox proportional hazards model used.

* Diseases include hypertension, diabetes, cerebrovascular, peripheral arterial, valvular heart disease, chronic pulmonary, thrombophlebitis, and hepatic.
more complete revascularization were also more likely to be asymptomatic or to have less severe angina than those with incomplete revascularization. Subset analysis revealed significant survival benefit in those patients with significant left ventricular dysfunction (i.e., ejection fraction <0.35) with three or more vessels bypassed compared with those with two.

It should be emphasized that, in addition to the revascularization variables discussed above, a number of important preoperative functional and angiographic variables were also independently predictive of survival and event-free survival. The presence of congestive heart failure, extensive regional wall motion abnormalities, the number of associated medical diseases, and the patient’s age were particularly important predictors of long-term outcome.

When the cumulative incidence of sudden cardiac death and myocardial infarction were examined together, no major differences were found among patients in whom two, three, or more than three vessels had been bypassed. Patients in whom only a single vessel had been bypassed fared a little worse, but this did not reach statistical significance. An important finding, however, was that patients with fewer vessels bypassed had a greater likelihood of fatal myocardial infarction compared with those with more complete revascularization.

**Previous Studies**

A number of nonrandomized studies have emphasized that incomplete myocardial revascularization after coronary artery bypass surgery results in poorer symptomatic outcome and survival compared with complete revascularization. Completeness of revascularization was defined in these studies as either bypassing all significant lesions (with varying definitions of “significant”) or revascularizing all ischemic myocardial segments. Only three series specifically examined patients with three-vessel disease, whereas the others analyzed patients with one-, two-, and three-vessel disease as a composite group.

Many studies have defined completeness of revascularization at late follow-up angiography by the absence of occluded grafts and absence of residual or new lesions that had not been bypassed. Such studies may provide important information but are unlikely to influence a surgeon’s decision whether or not to strive for complete revascularization at the time of surgery. Graft attrition and progression of native vessel disease are two very important processes that will affect long-term prognosis, but how they influence outcome among patients with complete versus incomplete revascularization is unknown. In addition, when multiple grafts and anastomoses are used, there is the potential for accelerated atherosclerotic disease in bypassed native vessels that were only moderately diseased in addition to the problems of early closure of grafts used to bypass small and diffusely diseased vessels.

The relation between completeness of myocardial revascularization and long-term outcome in patients with three-vessel disease is not clear. Lawrie and associates have demonstrated that survival is dramatically worse in patients with poor ventricular function if one or more unbypassed lesions are present. In their study, advanced age, residual disease (particularly of the left
FIGURE 5. Graphs show cumulative 6-year survival in group 1 patients, comparing complete revascularization (three or more bypassed vessels) and incomplete revascularization (two bypassed vessels) and stratified according to preoperative left ventricular ejection fraction (EF). Survival is shown for those with ejection fractions <0.35 in panel A, ejection fractions between 0.35 and 0.49 in panel B, and ejection fractions ≥0.50 in panel C.

FIGURE 6. Graphs show cumulative 6-year survival in group 2 patients, comparing complete revascularization (three or more bypassed vessels) and incomplete revascularization (two bypassed vessels) and stratified according to preoperative left ventricular ejection fraction (EF). Survival is shown for those with ejection fractions of <0.35 in panel A, ejection fractions between 0.35 and 0.49 in panel B, and ejection fractions ≥0.50 in panel C.

anterior descending and circumflex coronary arteries), and poor left ventricular function were found to be the most important predictors of late mortality among all patients, and it was concluded that more than three grafts would be unlikely to improve survival in patients who had good left ventricular function. These conclusions appear to be supported, in part, by the present study, which revealed that bypassing three or more vessels resulted in improved survival only in those with severe angina, particularly when left ventricular function was impaired.

In contrast, another study has shown that long-term survival was primarily related to completeness of revascularization rather than to left ventricular function. However, analysis of this study reveals that significant differences existed between those patients with complete versus incomplete revascularization with respect to ventricular function, with the latter patients having more abnormal wall motion and lower ejection fractions. Their data, therefore, do not refute the adverse impact of left ventricular dysfunction on late outcome independent of the extent of revascularization, although our own data would infer that the major benefit of complete revascularization is among patients with left ventricular dysfunction and severe ischemia. Tiras and colleagues also observed that among patients with multivessel disease, late survival was improved in patients with normal preoperative left ventricular function or with complete revascularization, although the interaction between these two variables was not analyzed.
Importance of Bypassing the Left Anterior Descending Coronary Artery

The significant influence of residual disease of the left anterior descending coronary artery on survival has been demonstrated in previous surgical studies. In one study, it was concluded that the first two or three grafts were associated with the greatest improvement in survival, with residual lesions in the left anterior descending or left circumflex coronary arteries being the most important predictors of mortality. It should be emphasized that 98% of patients in this current series received a graft to the left anterior descending coronary artery, and so the overall influence of this on late outcome could not be determined. Therefore, our data regarding completeness of revascularization should not be applied to patients undergoing a similar degree of revascularization in the absence of a graft to the left anterior descending coronary artery.

Comparison With Coronary Balloon Angioplasty

Coronary angioplasty has been increasingly used in patients with multivessel disease, but the studies reported to date addressing the issue of revascularization status have generally categorized two- and three-vessel disease as a single entity. Whereas most surgical series of multivessel disease comprise a majority of three-vessel disease, the reverse applies to coronary angioplasty series in which about two thirds of multivessel disease patients have two-vessel disease. At present, complete revascularization among patients with three-vessel disease undergoing coronary balloon angioplasty is achieved in only 16 to 25% of cases. Reeder and associates have demonstrated that long-term outcome in patients with multivessel disease appears to be determined more by baseline characteristics than completeness of revascularization defined by angioplasty criteria; these observations have also been confirmed by other investigators. Dilatation of only the "culprit lesion" appears to be a feasible strategy in patients with unstable angina and multivessel disease, but the patient populations have been very small and follow-up very short compared with most surgical series.

Completeness of myocardial revascularization has thus become an important and controversial issue for patients with multivessel disease undergoing myocardial revascularization with coronary balloon angioplasty as an alternative to coronary artery bypass surgery. Crucial to the determination of the choice of either procedure will be the results of ongoing randomized trials such as the National Heart, Lung, and Blood Institute-sponsored Bypass Angioplasty Revascularization Investigation study.

Study Limitations

It should be emphasized that this study was not a randomized study comparing complete versus incomplete coronary revascularization among surgical patients and as such is subject to the limitations of any retrospective analysis. The reasons for incomplete revascularization were not recorded in the CASS records, and so these remain undefined in this study. The reasons were probably numerous and most likely related to surgical and anatomical factors; the importance of these in any possible patient selection bias can only be speculative.

As with most such studies, our definition of three-vessel disease was purely anatomical, based on angiographic criteria. Graft patency was not systematically
studied in the CASS Registry and thus, whether patients who were completely revascularized remained so during the follow-up period is unknown. However, among 546 patients from the CASS randomized study and registry, approximately 90% of all grafts were found to be patent within 60 days of surgery. It is likely that the patency rates in these registry data do not differ much from this.

The use of the internal mammary artery graft in the present series was relatively low (16%) compared with its use today. Survival may have been improved with greater use of the internal mammary artery, particularly because the majority of patients in the present series had the left anterior descending coronary artery bypassed, but whether this would have influenced survival differently among completely versus incompletely revascularized patients is not known.

Ejection fractions were omitted from the multivariate analyses because of the large overlap with the left ventricular wall motion score and the fact that some CASS patients had no ejection fractions computed during that time; however, the results were very similar when a separate analysis was performed that included ejection fraction.

Conclusions

Whereas complete revascularization with coronary artery bypass surgery remains a desirable goal, this is not always possible, but excellent results can still be achieved in some patients. These data suggest that 1) for patients with mild angina, complete revascularization confers no significant benefit on long-term survival or event-free survival; 2) for patients with severe angina, complete revascularization with three or more bypassed vessels is associated with improved long-term survival and event-free survival, although the differences are small for the latter; 3) survival benefit for patients with severe angina is particularly apparent in those with left ventricular dysfunction; 4) more than three grafts to the three major vessels confers no additional discernible benefit over three grafts in terms of survival or event-free survival for any patient subgroup; 5) in patients with late myocardial infarction, complete revascularization appears to reduce the risk of fatal outcome; 6) the influence of the completeness of revascularization on late outcome cannot be evaluated as a single entity without accounting for important baseline variables such as the severity of myocardial ischemia and left ventricular function.

These findings do not, however, suggest that complete revascularization should not be attempted in patients in whom it can be achieved but emphasize that bypassing the three major coronary arteries is particularly necessary in patients with severe ischemia and left ventricular dysfunction. These findings have major implications for patient selection criteria for coronary artery bypass surgery and possibly for coronary angioplasty among patients with three-vessel coronary disease.

Acknowledgments

We wish to thank Peter B. Berger, MD, for critically reviewing the manuscript.

Appendix

Cooperating Clinical Sites

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Loma Linda University, Loma Linda, Calif.: Joan Coggin, MD*.

Marshfield Medical Foundation, Inc., and Marshfield Clinic, Marshfield, Wis.: William Myers, MD*; Richard D. Sautter, MD*; John N. Brownell, MD; Dieter M. Voss, and Robert D. Carlson, MD.

Massachusetts General Hospital, Boston, Mass.: J. Warren Harthorne, MD*; W. Gerald Austen, MD*; Robert Dinsmore, MD; Frederick Levine, MD; and John McDermott, MD.

Mayo Clinic and Mayo Foundation, Rochester, Minn.: Robert L. Frye, MD*; Bernard Gersh, MD; David R. Holmes, MD; Michael B. Mock, MD; Hartzell Schaff, MD; and Ronald E. Vlietstra, MD.

Miami Heart Institute, Miami Beach, Fla.: Arthur J. Gosselin, MD*; Parry B. Larsen, MD; and Paul Swaye, MD.

Montreal Heart Institute, Montreal, Quebec, Canada: Martial G. Bourassa, MD*; Claude Goulet, MD; and Jacques Lesperance, MD.

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St. Louis University, St. Louis, Mo.: George Kaiser, MD*; J. Gerard Mudd, MD*; Robert D. Wiens, MD; Hendrick B. Barner, MD; John E. Codd, MD; Denis H. Teras, MD; Vallee L. Willman, MD; and Bernard R. Chaitman, MD.

St. Luke's Hospital Center, New York, N.Y.: Harvey G. Kemp Jr., MD,* and Airlie Cameron, MD.

Stanford University, Stanford, Calif.: Edwin Alderman, MD*; Francis H. Koch, MD; Paul R. Cipriano, MD; James F. Silverman, MD; and Edward B. Stinson, MD.

Medical College of Wisconsin, Milwaukee, Wis.: Felix Tristani, MD*; Harold L. Brooks, MD*; and Robert J. FleimMa, MD.

Yale University, New Haven, Conn.: Lawrence S. Cohen, MD*; Rene Langou, MD; Alexander S. Geha, MD; Graeme L. Hammond, MD; and Richard K. Shaw, MD.

Central Electrocardiographic Laboratory

University of Alabama, Birmingham: L. Thomas Sheffield, MD*; David Roitman, MD; and Carol Troxell, BS.

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*Principal investigator.
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Circulation. 1992;86:446-457
doi: 10.1161/01.CIR.86.2.446

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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