Ten-Year Follow-up of Quality of Life in Patients Randomized to Receive Medical Therapy or Coronary Artery Bypass Graft Surgery

The Coronary Artery Surgery Study (CASS)

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Quality of life indexes were assessed in 780 patients 10 years after randomization to medical therapy (n=390) or coronary artery bypass graft surgery (n=390) in the Coronary Artery Surgery Study. At 10 years, mortality was 21.8% in the medical group and 19.2% in the surgical group (p=NS), and 144 (37%) of the medical group had undergone surgery because of increasing chest pain. At study entry, 22% of medical and surgical patients were angina free; at 1 and 5 years after entry, the frequency of asymptomatic patients was 66% and 63% in the surgical group and 30% and 38% in the medical group. However, by 10 years after entry, the proportion of patients free of angina had fallen to 47% in the surgical group and to 42% in the medical group. Activity limitation and use of ß-blockers and long-acting nitrates were less in the surgical than the medical group at 1 and 5 years after entry but little different from the medical group at 10 years after entry. Throughout follow-up, recreational status, employment status, frequency of heart failure, use of other medications, and hospitalization frequency were similar between the two groups. Thus, indexes of quality of life such as angina relief, increased activity, and reduction in use of antianginal medications initially appear superior in patients with stable manifestations of ischemic heart disease assigned to surgery, but by 10 years after entry, these advantages are much less apparent. Although the observed similarities of the medically and surgically assigned groups at 10 years reflect return of symptoms in the surgical group to some extent, a more important explanation is the performance of late surgery in a large proportion of the medically assigned patients, rendering them asymptomatic. (Circulation 1990;82:1647–1658)

Coronary artery bypass graft surgery (CABG) has become established as a powerful therapy for prolonging survival and improving the quality of life of certain subsets of patients with coronary artery disease.1 However, extended follow-up of large cohorts of patients undergoing CABG now suggests that much of the benefit of CABG in prolonging life may be considerably diminished after 10 years.2,3

* A listing of principal and coinvestigators is presented in the Appendix.


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There are only limited data on the long-term effects of CABG compared with medical therapy on quality of life of patients with coronary artery disease.4 The purpose of this study is to present the

See p 1859

10-year follow-up of quality-of-life descriptors in patients randomized to receive medicine or CABG in the Coronary Artery Surgery Study (CASS), a multicenter collaborative trial sponsored by the National Heart, Lung, and Blood Institute.

Methods

Study Design

The CASS was a prospective, randomized study in which 780 patients with 70% or more diameter stenosis of one or more operable coronary arteries were
randomized to receive medical therapy or CABG at 11 participating sites (Appendix) between 1974 and 1979. A comprehensive description of the study design and initial findings were previously reported.\textsuperscript{5-10} Patients were eligible for randomization in CASS only if they fell into one of the three prospectively defined clinical subsets: 1) group A, mild angina (Canadian Heart Association class I or II\textsuperscript{11}) and normal left ventricular function (n=514 patients or 66\% of total); 2) group B, mild angina and moderately impaired left ventricular function (n=106 patients or 14\% of total); or 3) group C, free of angina after myocardial infarction (n=160 patients or 20\% of total). These three clinical subsets were used as strata for block randomization.

After randomization, all patients received medical care by their referring physicians. The CASS Steering Committee provided guidelines for the management of angina pectoris, congestive heart failure, and risk factors.\textsuperscript{5} Patients randomized to receive surgical therapy underwent elective CABG at a mean of 54 days (range, 5-345 days) after assignment. CABG was also performed in some patients initially assigned to medical therapy if the patient and referring physician requested, usually because of the development of unacceptable angina despite optimal medical therapy.

Detailed information on the patients' symptomatology, activity level, employment, and smoking habits was collected at baseline and at 6-month intervals thereafter. Frequency, duration, and reasons for repeated hospitalization were obtained by annual questionnaire. Follow-up data presented in this report were acquired within 6 months of the scheduled follow-up date.

Definition of Terms

Status on chest pain, heart failure, activity limitation, employment, recreation, drug therapy, hospitalization, and smoking were defined previously.\textsuperscript{7}

Statistical Analysis

This report is based on data received by the CASS Coordinating Center as of December 4, 1988. Patients were analyzed in the group to which they were randomized regardless of therapy received (an intent-to-treat analysis). Discrete variables at fixed follow-up times were analyzed by the $\chi^2$ test. The number of hospitalizations was compared between groups by assuming a Poisson number proportional to exposure time and comparing the rates (defined as proportional to the number of hospitalizations divided by the total exposure time) to give the $p$ value. Time to an event (for example, CABG) was compared and tested by life-table analysis with the log-rank test.

In several instances, additional comparisons between medical and surgical groups were made, censoring data from patients who failed to follow their original treatment assignment. Data from surgical group patients were also censored at the time of repeated CABG, if it was performed. In these censored analyses only data from the time before surgery were used for medical group patients, and only data from the time after initial CABG were used in the surgical group patients.

Results

Duration and Completeness of Follow-up

At the time of this report, mean duration of follow-up was 11 years (range, 9.0-13.1 years). Follow-up was 99.7\% complete (778 of 780) for obtaining data on vital status. (Two patients were lost to follow-up at 4.6 and 10.5 years, respectively.) For other variables, follow-up was less complete, usually because data were not obtained or were obtained outside the follow-up period. For each variable, the number of patients followed up at each time interval is indicated in the tables and figures. Mortality at 10 years after entry was 21.8\% in the medical group and 19.2\% in the surgical group ($p=\text{NS}$).

Compliance With Randomized Treatment Assignment

Of the 390 patients randomly allocated to medical treatment, 144 (37\%) subsequently underwent CABG during the next 10 years (Figure 1). Of the 390 patients randomly assigned to CABG, 41 (11\%) initially refused, but of these 41, 13 patients subsequently underwent CABG at a mean of 3.6 years after randomization.

Baseline Characteristics

Clinical, electrocardiographic, ventriculographic, and arteriographic descriptors of the medical and surgical groups were similar at entry and have been previously reported.\textsuperscript{5,6}

Functional Status

Chest pain. Although chest pain status was similar at entry in medical and surgical patients (22\% asymptomatic in each group), at 1 and 5 years after entry, a larger proportion of surgical patients had become asymptomatic (66\% versus 30\% at 1 year; 63\% versus 38\% at 5 years). However, by 10 years of follow-up,
the proportion of surgical patients who were asymptomatic had declined (47%), and the proportion of medical patients who were asymptomatic had increased (42%), thus blunting, but not eradicating, the significant difference between chest pain status in the two groups. When medical and surgical groups were compared according to the number of diseased vessels at the time of randomization, the favorable influence on chest pain status seen at 1 year of follow-up was not observed at the 5 and 10 years of follow-up in patients with one-vessel disease or at 10 years of follow-up in patients with two- or three-vessel disease (Figure 2B-D).

Analysis of chest pain status according to clinical subset at entry (group A, B, or C) (Figure 3A and B) again demonstrated the contrast in asymptomatic status between medical and surgical groups at 1 and 5 years of follow-up but showed a less-striking contrast at 10 years. Among the group C patients, who entered the study free of angina after infarction, no significant difference in chest pain status between medically and surgically assigned patients was noted after 1 year of follow-up. In both groups, A-B and C, the proportion of asymptomatic patients in the surgical group declined at each follow-up interval after year 1. In group A-B, the proportion of medical patients without chest pain appeared to increase at each follow-up interval. However, when data for patients who did not adhere to the assigned treatment (medical or surgical) were censored from the analysis, the percentage of asymptomatic patients in the medical group remained more constant during follow-up (Figure 3C and D). Of importance, in these censored analyses, the proportion of patients free of chest pain was greater in the surgical group even at 10 years (groups A-B, no chest pain in 18% medical versus 38% surgical group, p<0.001; group C, no chest pain in 28% medical versus 53% surgical group, p=0.002).

Heart failure. Absence of heart failure symptoms was reported at 1, 5, and 10 years of follow-up in 95%, 89%, and 72% of the medical group and in 94%, 91%, and 75% of the surgical group, respectively (p=NS) (deaths included in the denominator). In the censored analysis, heart failure was absent at 10 years of follow-up in 42% of the medical group and 62% of the surgical group (p<0.0001).

Activity limitation. Activity limitation status was similar at baseline in medical and surgical groups (18% of surgical group was free of limitations versus 15% of medical group), but at 1 and 5 years after entry, more surgical patients were free of activity limitations (60% versus 31% at 1 year; 49% versus 29% at 5 years), which is a trend that had almost completely disappeared at 10 years (34% versus 28%) (Figure 4). The censored analysis (Figure 4B) demonstrates that, even at 10 years, more (noncensored) patients initially assigned to surgical than to medical therapy were free of activity limitation (30% versus 13%, p<0.001).

Employment. Although slightly more surgically assigned patients were employed at baseline (76% versus 69%, p=0.03), this difference disappeared during follow-up, and the proportion of patients who were employed in both groups progressively diminished at 1, 5, and 10 years after entry (surgical group: 68%, 56%, 34%; medical group: 66%, 50%, 32%) (Figure 5). Again, the censored analysis showed important trends in favor of surgical management with 29% of the surgical group and 17% of the medical group employed 10 years after entry (p<0.001).

Recreation. Recreational status did not differ between the assigned groups at baseline or at any follow-up interval. Recreational activity level was moderate-strenuous in 21% of the medical group at baseline and in 30%, 29%, and 25% at 1, 5, and 10 years after entry, respectively. In the surgical group, recreational activity level was moderate-strenuous in 25%, 38%, 32%, and 26%, respectively, at these intervals. In the censored analysis, at 10 years after entry, moderate or strenuous recreational activity was reported in 13% of the medical group and in 22% of the surgical group (p=0.003).

Treatments

β-Blockers and nitrates. Although equal proportions of medically and surgically assigned patients were taking β-blockers and nitrates, respectively, at entry, the use of each of these drugs decreased 1 year after entry in the surgical group, then increased slowly during the remainder of the 10-year follow-up period (Figure 6). In the medical group, there was increased use of β-blockers and nitrates during the first 2 years after entry, then an apparent decline in the usage of both agents. However, when patients who did not adhere to assigned therapy are excluded from the analysis (Figure 6 C,D), the decline in use of these antianginal drugs by the medical group is less obvious.

Miscellaneous drug therapy. Nitroglycerin, like long-acting nitrates, was used more commonly in medical patients at 1 and 5 years but not at 10 years after entry (Table 1). Otherwise, there were only minimal intergroup differences in the use of medication. Calcium-channel blockers were used by approximately one fourth of each group at the 10-year follow-up. Longitudinal trends in drug use in both groups revealed an almost 10-fold increase in antiplatelet therapy, a twofold to threefold increase in the use of hypoglycemics, a twofold increase in the use of lipid-lowering agents, a lesser increase in diuretic and digitalis use, and a decline in the use of tranquilizers.

Hospitalizations. Of the 780 randomized patients, hospitalization one or more times occurred in 85.6% (334 of 390) of the medical group and 97.7% (381 of 390) of the surgical group (p<0.0001). The cumulative number of hospitalizations was greater for patients assigned to surgery, primarily owing to readmission for the protocol-assigned CABG (Figure 7).
FIGURE 2. Bar graphs of chest pain status. All study patients (panel A); those with one-vessel disease (panel B); those with two-vessel disease (panel C); those with three-vessel disease (panel D). M, medical assignment; S, surgical assignment.
Figure 3. Bar graphs of chest pain status. Groups A and B (panel A); group C (panel B); group A and B (censored analysis) (panel C); group C (censored analysis) (panel D). In the censored analyses, data from medical group patients were removed from the strata at the time of coronary artery bypass graft surgery, data from surgical group patients were included only after they actually underwent surgery, and data from surgical group patients were censored when repeated surgery was performed. Statistical comparisons are provided only for the noncensored analyses shown on panels A,B. M, medical assignment; S, surgical assignment.
Figure 4. Bar graphs of activity limitation. All patients (panel A); censored analysis (panel B). Included within the moderate-severe category are patients for whom amount of activity limitation was uncertain because activities had been limited on physician's advice. Statistical comparisons are provided only for the noncensored analyses. M, medical assignment; S, surgical assignment.

Figure 5. Bar graph of employment status. All patients (panel A); censored analysis (panel B). Statistical comparisons are provided only for the noncensored analyses. M, medical assignment; S, surgical assignment.
Figure 6. Plot of use of β-receptor blockers and long-acting nitrates. Noncensored analyses (panels A and B); censored analyses (panels C and D). Statistical comparisons are provided only for the noncensored analyses.
TABLE 1. Miscellaneous Drug Use (Percentage on Drug and Alive at Follow-up)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Baseline</th>
<th>Medical (n=390)</th>
<th>Surgical (n=390)</th>
<th>Yr 1</th>
<th>Medical (n=383)</th>
<th>Surgical (n=377)</th>
<th>Yr 5</th>
<th>Medical (n=358)</th>
<th>Surgical (n=370)</th>
<th>Yr 10</th>
<th>Medical (n=254)</th>
<th>Surgical (n=259)</th>
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<tr>
<td>Nitroglycerin*</td>
<td>54.9</td>
<td>56.2</td>
<td>49.3</td>
<td>13.5*</td>
<td>39.4</td>
<td>20.0*</td>
<td>29.1</td>
<td>26.3</td>
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<td>Calcium-channel blocker</td>
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<td>Diuretic</td>
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<td>17.2</td>
<td>20.4</td>
<td>17.0</td>
<td>25.4</td>
<td>28.6</td>
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<td>Digitalis</td>
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<td>Tranquilizer</td>
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<td>16.5</td>
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<tr>
<td>Antiplatelet</td>
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<td>31.3†</td>
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<td>Hypoglycemic</td>
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<td>8.4</td>
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<tr>
<td>Antiarrhythmic</td>
<td>9.0</td>
<td>9.7</td>
<td>14.1</td>
<td>10.1</td>
<td>14.2</td>
<td>11.4</td>
<td>8.7</td>
<td>10.8</td>
<td></td>
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</table>

*In the censored analysis, use of nitroglycerin in the medical and surgical groups, respectively, was 45.3% and 8.4% at 1 year, 29.6% and 15.3% at 5 years, and 19.0% and 20.2% at 10 years.

Frequency of calcium channel blocker usage was uniformly recorded only at year 10 (n=251 medical and n=256 surgical patients).

*p<0.0001; †p<0.05.

The total number of days hospitalized per 1,000 patient-days of exposure was 6.7 in the medical group and 9.7 in the surgical group (p<0.0001). If rehospitalizations for protocol CABG are excluded, the total number of days hospitalized per 1,000 patient-days of exposure is 6.7 in the medical group and 6.1 in the surgical group (p<0.0001). Excluded from these analyses are hospitalizations (245 medical and 209 surgical) for coronary arteriography performed on patients at approximately 18 and 60 months after entry as part of the study protocol.

Of the 1,256 total hospitalizations in the medical group, 748 (60%) were for cardiac reasons. Of the 1,487 total hospitalizations in the surgical group, 980 (66%) were for cardiac reasons (p<0.0001). Other than CABG, the major reasons for hospitalization were remarkably similar between medically and surgically assigned patients (Figure 8).

Other revascularization procedures. Percutaneous transluminal coronary angiography was performed in nine medical and 10 surgical group patients during the 10-year follow-up. An initial CABG was performed in 144 (37%) of the 390 medically assigned patients during the 10-year follow-up, and repeated CABG was performed in 15 patients (3.8%). An initial CABG was performed in 360 (92%) of the surgically assigned

**FIGURE 7.** Plot of total number of rehospitalizations including those for protocol-mandated coronary artery bypass graft surgery. Excluded are scheduled hospitalizations for coronary arteriography performed as part of the study protocol at 18 and 60 months after entry.
patients, a single repeated CABG in 32 (8.2%), two repeated CABGs in two (0.5%), and three repeated CABGs in one patient (0.3%) (Table 2).

Risk factor management. Because follow-up was conducted by mail or telephone after year 5 of entry into the study, data on cardiac risk factors, other than smoking status, are not available at 10 years. The percentage of patients who smoked was similar at baseline and throughout follow-up in medical and surgical patients. A sharp decline in the prevalence of smoking was noted 1 year after entry; afterward, a lesser, gradual decline continued in smoking prevalence (Figure 9). The interrelations of smoking cessation, mortality, and quality of life in these patients have been reported in abstract form.12

Discussion
This study demonstrates that in the CASS randomized patients, improvements in indexes of quality of life observed in surgically assigned patients during the first 5 years after entry appear to be greatly attenuated by 10 years after entry. At 5-year follow-up, the CASS surgical group had significantly less chest pain, had fewer activity limitations, required less therapy with nitrates and \( \beta \)-blockers, had longer duration of treadmill exercise, and had less evidence of exercise-induced ischemia than the counterpart medical group.7 These observations were consistent with the 5-year follow-up reports of the two other major randomized trials of medical and CABG therapy in stable coronary artery disease, the Veterans Administration Cooperative Study of Coronary Artery Surgery13 and the European Coronary Surgery Study,14 and numerous nonrandomized studies that, in sum, suggested a 25–40% greater likelihood that a patient would be angina free at follow-up if CABG rather than medicine were the initial treatment.15

| Table 2. Initial and Subsequent Coronary Revascularization Procedures After Randomization to Medical Therapy or Coronary Artery Bypass Graft Surgical Therapy |
|---------------------------------|----------------|----------------|-------------|----------------|----------------|----------------|------------|
|                                | Medical (n=390) | Surgical (n=390) |             |               |               |               |           |
|                                | n=% Mean Median | n=% Mean Median | p         |               |               |               |           |
| PTCA                           |               |               |           |               |               |               |           |
| Initial                        | 144 36.9 3 7.5 | 360 92.3 0.3 | 0.512     |               |               |               |           |
| 1st repeated                   | 15 3.8 7.5 | 35 8.9 6.6 | 0.512     |               |               |               |           |
| 2nd repeated                   | 0 0.8 9.0 | 3 0.8 9.0 | NA         |               |               |               |           |
| 3rd repeated                   | 0 0.3 10.0 | 1 0.3 9.6 | NA         |               |               |               |           |

*Categories listed for repeated CABG are mutually exclusive.

PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass graft surgery.
In contrast, as demonstrated in the present report, there was little, if any, difference in freedom from angina and activity limitation 10 years after entry between the medical and surgical groups; furthermore, the earlier-observed marked differences in use of β-blockers and nitrates had narrowed considerably. Ten years after entry, surgical patients had become more symptomatic, whereas a significant proportion of medical patients had become less symptomatic. Our findings are consistent with a recent report from the Veterans Administration Cooperative Study of Coronary Artery Surgery in which the benefits of surgery in the relief of angina and improvement of exercise performance were superior to medical therapy at 5 years, but not at 10 years, after randomization.

There are two major potential explanations for these findings. First, there is probably a declining benefit from surgery over time in the surgical group, which is related to progression of native coronary artery disease and occurrence of graft stenoses, as suggested by the decline in the proportion of asymptomatic surgical group patients over time (Figures 2, 3). Second, and more important, there is a major impact of late CABG that was performed in a substantial proportion of the medically assigned patients. By 10 years after entry, 37% of the CASS randomized medical group (as well as 35% of the Veterans trial medical group) had received CABG, considerably blunting the distinction between the therapies for the two randomized groups (Figure 1). Because CABG was often performed on patients in the medical group with refractory severe angina and because the primary analysis was by “intention to treat,” in which all patients were grouped by initial treatment assignment rather than treatment actually received, the performance of CABG in “medical” patients transformed the status of many from symptomatic to asymptomatic. This phenomenon is evident in the “censored analyses” (Figures 3C and D, 4B, 5B, and 6C and D) in which patients who failed to follow assigned therapy are excluded. It is also evident that, even though the difference in symptomatology between medical and surgical groups was diminishing at 10 years, most indexes of quality of life favored the patients initially assigned to CABG during the 10 years of follow-up.

Percutaneous transluminal angioplasty, which may also have tended to blunt the distinction between the two groups, was used in only a small proportion (2.3% medical and 2.6% surgical) and was performed relatively late during the 10-year follow-up (at 8.2 years after entry in the medical group and 8.0 years after entry in the surgical group, p=NS, Table 2).

Other indexes of quality of life that showed little difference between medical and surgical groups both at 5 and 10 years of follow-up were employment status and hospitalization frequency. The frequency of employment in CASS randomized patients diminished steadily throughout follow-up as the study population aged. Failure of CABG to return patients to the work force has been previously described; return to work after CABG is more likely in those who are working immediately before surgery and who have good postoperative ejection fraction and physical activity tolerance, and it is least likely in patients with advanced age, other medical problems, and significant disability compensation. Employment status, therefore, may not precisely reflect the impact of CABG on quality of life. On the other hand, late CABG in the medical group may have favorably affected the proportion of medically assigned patients who returned to work (Figure 5B).
The CASS data reported here represent the first report of 10-year cumulative hospitalization frequencies for patients randomized to medical and surgical therapy for coronary artery disease. In a nonrandomized series, Hamilton et al. observed that surgically treated patients had a 26% reduction in cardiovascular hospitalizations compared with medically treated patients. Subsequently, 5 years of follow-up from the Veterans Administration and CASS trials demonstrated no significant difference in hospitalization frequency between the two groups, provided the initial rehospitalization for protocol-assigned CABG was excluded; such an exclusion is reasonable because CABG, when performed, is more often performed now without requiring rehospitalization, although the direction of the initial hospitalization is increased. In the present report, extension of CASS follow-up to 10 years continues to demonstrate little difference in duration or reasons for hospitalization between medical and surgical groups. Even though angina was initially somewhat less common in surgical patients as described above, the most common reason for rehospitalization in both groups was chest pain (Figure 8). Myocardial infarction, subjectively assessed as "history of heart attack," occurred at a frequency of approximately 2.0% yr, which is remarkably similar to the frequency of objectively documented nonfatal myocardial infarction at 5 years after entry in the Veterans Administration trial (2.9%/yr) and at 5 years after entry in CASS (2.5%/yr).

Limitations of Study

Important limitations to this study include the fact that many of the quality-of-life descriptors are subject to patient, interviewer, or physician bias (for example, angina and activity status) because therapy was obviously not administered in a blinded manner. Reasons for hospitalization are especially subject to bias because during the last 5 years of follow-up, they were assessed by interview and questionnaire rather than by retrieval and review of hospital records. Furthermore, many noncardiac factors, such as advancing age, orthopedic disabilities, and other noncardiac illnesses, may have affected quality-of-life indexes such as activity and employment status. Last, CASS, which recruited patients from 1974 to 1979, cannot assess the significance of newer therapies such as calcium-channel blockers or percutaneous transluminal coronary angioplasty.

Clinical Implications

Extended follow-up of the CASS randomized patients shows relatively little advantage 10 years after an initial surgical approach with regard to long-term relief of angina; activity limitation; use of antianginal medications; frequency of employment; and frequency, duration, and reasons for hospitalization. In patients similar to those randomized in CASS, medical therapy can be initially used in those with normal left ventricular function with the expectation that 1) survival will not be compromised provided CABG is offered when anginal symptoms worsen; 2) CABG will subsequently be required in 35–40% of such patients during the next 10 years; and 3) quality-of-life measures, though initially somewhat inferior to surgical therapy during the first 5 years of follow-up, will be quite similar at 10 years of follow-up, owing primarily to the selective performance of "late" CABG in appropriate patients. Assessment of the role and effectiveness of newer revascularization therapy (percutaneous transluminal coronary angioplasty) in comparison to traditional medical therapy or CABG awaits the results from ongoing comparative trials.

Appendix

Cooperating Clinical Sites


Central Electrocardiographic Laboratory, University of Alabama: L. Thomas Sheffield, MD*, David Roitman, MD, and Carol Troxell, BS.

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Coordinating Center, University of Washington: Kathryn Davis, PhD*, Lloyd Fisher, PhD, Mary Jo Gillespie, MS, J. Ward Kennedy, MD, and Richard Kronmal, PhD.

Chairman of the Steering Committee: Thomas Killip, MD, Beth Israel Medical Center.

National Heart, Lung, and Blood Institute: George Sopko, MD, Rachel Solomon, MHS, Thomas Robertson, MD, Eugene R. Passamani, MD, and Peter Frommer, MD.

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*Principal investigator.
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