PATHOPHYSIOLOGY AND NATURAL HISTORY
CORONARY ARTERY DISEASE

Coronary Artery Surgery Study (CASS): a randomized trial of coronary artery bypass surgery
Survival data

CASS Principal Investigators and their Associates*

ABSTRACT CASS includes a multicenter patient registry and a randomized controlled clinical trial. It is designed to assess the effect of coronary artery bypass surgery on mortality and selected nonfatal end points. From August 1975 to May 1979, 780 patients with stable ischemic heart disease were randomly assigned to receive surgical (n = 390) or nonsurgical (n = 390) treatment and were followed through April 15, 1983. At 5 years, the average annual mortality rate in patients assigned to surgical treatment was 1.1%. The annual mortality rate in those receiving medical therapy was 1.6%. Annual mortality rates in patients with single-, double-, and triple-vessel disease who were in the surgical group were 0.7%, 1.0%, and 1.5%; the corresponding rates in patients in the medical group were 1.4%, 1.2%, and 2.1%. The differences were not statistically significant. Nearly 75% of the patients had entry ejection fractions of at least 0.50. The annual mortality rates in patients in the surgical group in this subgroup with single-, double-, and triple-vessel disease were 0.8%, 0.8%, and 1.2% and corresponding rates in the medical group were 1.1%, 0.6%, and 1.2%. The annual rate of bypass surgery in patients who were initially assigned to receive medical treatment was 4.7%. The excellent survival rates observed both in CASS patients assigned to receive medical and those assigned to receive surgical therapy and the similarity of survival rates in the two groups of patients in this randomized trial lead to the conclusion that patients similar to those enrolled in this trial can safely defer bypass surgery until symptoms worsen to the point that surgical palliation is required.


CORONARY ARTERY DISEASE is a major cause of morbidity and mortality in the United States. In spite of encouraging decreases in age-adjusted mortality during the past decade,1 in 1980 coronary artery disease was the cause of 566,000 deaths.2 Over 683,000 patients were admitted to hospitals in the United States that year with acute myocardial infarction.3 An estimated 5.4 million individuals have been diagnosed as having coronary artery disease as manifest by chronic angina or healed myocardial infarction.†

Medical and surgical therapies for patients with coronary artery disease have changed considerably over the past 20 years. Medical management now includes aggressive modification of risk factors, liberal use of nitrates, administration of β-adrenoceptor-blocking drugs, and more recently use of calcium antagonists. Current modes of medical therapy for coronary artery disease may favorably influence survival in selected patients. For example, results of three recent controlled trials support the premise that long-term administration of β-blocking drugs reduces mortality in survivors of acute myocardial infarction.4,6

Surgical treatment of patients with coronary artery disease has evolved from ineffective procedures such as thoracic sympathectomy, epicardial abrasion, and internal mammary artery ligation to the currently favored procedure, coronary artery bypass grafting with the use of either reversed saphenous vein or internal mammary artery grafts. Experienced surgical teams perform this procedure with low risk to the patient. Numerous reports attest to the fact that complete or partial relief of angina is accomplished in 60% to 90% of patients in the months and years after bypass.7,8 Coronary artery bypass surgery is often the treatment of choice for patients who have poorly controlled angina and coronary arterial anatomy making revascularization possible.9 The marked relief of angina after coronary bypass, the low operative risk, the increas-
ingly widespread availability of experienced surgical teams, and the belief of many physicians that the procedure may reduce long-term mortality have resulted in a rapid increase in the number of bypass procedures performed in the United States, from an estimated 24,000 in 1971 to an estimated 159,000 in 1981. * In 1973 the National Heart, Lung and Blood Institute organized a patient registry and a randomized trial designed to compare results of medical and surgical therapy in patients with coronary artery disease. The goal of the randomized trial is to rigorously evaluate the effect of assigned treatment on total mortality in well-defined subsets of patients with coronary artery disease. In this first end point report from the randomized trial, survival in patients assigned to surgical therapy is compared with survival in patients assigned to receive medical management.

Methods

Details of CASS design, study protocol, procedure for randomization, quality-control measures, and the baseline characteristics of the participating patients have been previously published. 10 CASS consists of a patient registry and a randomized trial. All patients undergoing coronary arteriography for suspected or proven coronary artery disease at 15 clinical sites were asked to participate in the registry and 94% agreed. Patients entering the randomized trial were drawn from the registry at the 11 sites that participated in the trial; four CASS sites participated in the registry only.

All registry patients at the 11 randomizing sites were screened for potential participation in the trial. Patients qualifying on clinical and angiographic grounds were randomly assigned to receive medical or surgical therapy after informed consent had been obtained. Clinical criteria for inclusion included age of 65 years or less, angina that was Canadian Cardiovascular Society class I or II11 with or without a history of myocardial infarction, or well-documented myocardial infarction more than 3 weeks before randomization. Clinical criteria for exclusion were prior coronary bypass surgery, unstable or progressive angina, angina more severe than class II (angina occurring after climbing one flight of stairs or walking two blocks is class II), congestive heart failure (New York Heart Association class III or IV), a coexisting illness that would increase the likelihood of death within 5 years, and a variety of practical exclusions that might limit active participation during follow-up such as geographic inaccessibility, psychological problems, or language barriers. 10

Coronary arteriograms and left ventriculograms were obtained and analyzed according to a common protocol. Left ventriculographic examination was performed in the right anterior oblique projection. Both ejection fraction and subjective assessment of left ventricular wall motion were recorded, as were the severity and morphologic characteristics of all significant coronary lesions. 10 Angiographic requirements for participation in the trial included the presence of significant operable coronary artery disease, defined as either 70% or greater reduction in the internal diameter of the right, left anterior descending, or left circumflex coronary artery, or 50% or greater reduction in the internal diameter of the left main coronary artery. Patients with 70% or greater luminal diameter reduction of the left main coronary artery were excluded, as were those with a recognized ejection fraction of less than 0.35 and those likely to require additional procedures such as valve replacement or resection of a ventricular aneurysm.

Eligible consenting patients were randomly assigned to groups by means of telephone contact with the CASS coordinating center, during which the CASS Principal Investigator or his or her designate certified the patient’s eligibility, and specified certain features required for stratified randomization. Randomization was stratified by clinical site, number of diseased vessels, and ejection fraction within three different clinical subgroups. Patients with angina and ejection fractions of at least 0.50 were randomized within group A, those with angina and ejection fractions less than 0.50 were randomized within group B, and those free of angina after well-documented myocardial infarction were randomized within group C.

The surgical team at each site operated on patients assigned to receive surgical therapy as soon as the elective surgery schedule would permit. Early postoperative angiographic examination was performed in a sample of patients receiving surgical therapy. A concerted effort was made by CASS investigators to ensure optimal surgical and medical therapy for patients participating in this trial.

The details of medical and surgical management have been published. 10 All patients, including those assigned to the surgical group, received medical therapy. For example, surgically treated patients were advised to modify risk factors, and those who developed recurrent or worsening angina during follow-up were usually given nitrates and β-blocking drugs. Conversely, medically treated patients whose angina worsened during follow-up in spite of aggressive medical therapy were not denied bypass surgery.

Patients were examined at 6 month intervals for the duration of the follow-up period. Details concerning events such as death, hospitalization, new or recurrent cardiovascular symptoms such as angina, dyspnea, and fatigue, and details concerning new or continuing drug therapy were routinely recorded at 6 month intervals. Other data were collected less frequently, including (1) a resting electrocardiogram at 6 month intervals for 2 years and yearly thereafter, (2) maximal treadmill exercise test results at 6, 18, and 60 months, and (3) repeat coronary arteriograms in a small number of patients at 18 months and in all willing patients 60 months after enrollment.

Electrocardiograms were assessed at the CASS central electrocardiographic laboratory. 10 Electrocardiograms demonstrating the interval development of significant new Q waves were independently read by members of a committee of expert electrocardiographers unaware of clinical details; disagreements were adjudicated by the committee as a whole. Perioperative infarction was diagnosed, by means of serial electrocardiograms, when the review committee agreed that a new major Q wave had appeared during the perioperative interval.

The first patient was randomly assigned in August 1975, the last in May 1979. Vital status was known on 779 of the participating patients as of April 15, 1983; one surgically treated patient was lost to follow-up after 4½ years. Thus, all patients have been followed for 46 months, 69% have been followed for 60 months, 40% for 72 months, and 11% for 84 months.

Group differences at baseline were assessed by the chi-square test for discrete variables; the two sample t test is used for continuous variables. 12 The log-rank statistic, computed from all of the follow-up data, was used to assess the statistical significance of the observed differences between survival curves for the medical and surgical groups. 13 This analysis includes all randomly assigned patients. All data on events were included in the calculations according to the original randomization group regardless of subsequent therapy patients may have.
PATHOPHYSIOLOGY AND NATURAL HISTORY—CORONARY ARTERY DISEASE

received. Survival curves for all patients extend to 6 years, while subgroup survival curves include data from 5 years of follow-up. The small numbers of patients followed for longer intervals make estimates beyond these cutoff points quite unstable. The annual mortality and crossover rates discussed below are derived from 5 year follow-up data. For example, in figure 6, A, the 5 year mortality estimate for patients assigned to receive medical treatment is 5% (or 1% annually). In all survival curves, the error bars represent one-half of 97.5% confidence intervals for the cumulative percent survival at each year calculated with the Greenwood standard error.14 The p values cited in each figure are two-sided and uncorrected for multiple comparisons.

Results

Source of patients. The CASS registry includes a total of 24,959 patients who, during the interval from July 1974 to May 31, 1979, underwent coronary arteriographic examination at the 15 participating CASS registry sites because of suspected coronary artery disease. Of this group 23% were enrolled at four CASS sites that did not participate in the randomized study and 10% were studied during a pilot phase before the start of the randomized trial in August 1975. Thus, 16,626 registry patients were screened to determine their eligibility for entry into the randomized trial.

CASS REGISTRY AT RANDOMIZING SITES
N = 16,626

Patients were frequently excluded for more than one reason. Exclusion factors are arbitrarily ordered in figure 1 to form mutually exclusive categories. The first category in this hierarchy includes individuals with normal coronary arteries and those with less than 70% luminal diameter reduction (normal or minimal disease), the next includes those with no operable vessels, and the others those with severe angina, those with severe left main coronary stenosis, those excluded by protocol definition, and finally those meeting protocol requirements. The shaded portion of the figure illustrates the percentage of patients in whom therapeutic assignment to surgery or medicine was generally uncontested. With the exception of the 12.7% eligible for randomization, the percentages in each exclusion category in figure 1 would change with a different hierarchy of exclusions. For example, the 36.5% of patients excluded because of class III or IV angina are patients with at least one diseased vessel and at least one operable vessel. Therefore, this category does not include all CASS registry patients with class III and IV angina. The total number of registry patients with 70% or greater reduction in luminal diameter of the left main coronary artery was 714 of 16,626 or 4.3%, but a value of 1.5% is obtained when the chosen hierarchy of exclusions is used.

During the recruitment period, 2099 (12.7%) CASS registry patients met the criteria for participation in this study; 780 patients, 37% of those eligible, were randomly assigned to receive medical or surgical therapy. Three hundred and ninety patients were assigned to each group and 514 were group A patients, 106 group B patients, and 160 group C patients. As illustrated in figure 1, the remaining 1319 patients were eligible for this study but did not participate because of physician or patient refusal. These randomizable patients have been followed as part of the CASS registry; they have similar baseline characteristics and subsequent mortality. A comparison of randomized and randomizable patients is the subject of a separate report.15

Baseline characteristics. Randomization created balanced treatment groups with respect to important prognostic characteristics, as depicted in tables 1 and 2. The two groups of patients were similar with respect to age, sex, work status, severity of angina, history of myocardial infarction, hypertension, congestive heart failure, and use of medication. The groups were well matched for electrocardiographic, arteriographic, and ventriculographic characteristics. There were no statistically significant differences between patients assigned to receive surgical and those assigned to receive medical therapy with respect to the baseline character-
TABLE 1
Clinical description of medical and surgical groups at entry

<table>
<thead>
<tr>
<th>Variable</th>
<th>Medical group (n = 390)</th>
<th>Surgical group (n = 390)</th>
<th>Total (n = 780)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>50.9</td>
<td>51.5</td>
<td>51.2</td>
</tr>
<tr>
<td>SD</td>
<td>7.5</td>
<td>7.3</td>
<td>7.4</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>90.0</td>
<td>90.5</td>
<td>90.3</td>
</tr>
<tr>
<td>Female</td>
<td>10.0</td>
<td>9.5</td>
<td>9.7</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>98.7</td>
<td>98.0</td>
<td>98.3</td>
</tr>
<tr>
<td>Work status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full-time</td>
<td>64.1</td>
<td>71.0</td>
<td>67.6</td>
</tr>
<tr>
<td>Part-time</td>
<td>4.6</td>
<td>4.6</td>
<td>4.6</td>
</tr>
<tr>
<td>Retired or quit</td>
<td>22.8</td>
<td>19.5</td>
<td>21.2</td>
</tr>
<tr>
<td>Otherb</td>
<td>8.5</td>
<td>4.9</td>
<td>6.7</td>
</tr>
<tr>
<td>Angina</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No angina</td>
<td>21.5</td>
<td>22.1</td>
<td>21.8</td>
</tr>
<tr>
<td>Class I</td>
<td>12.1</td>
<td>16.9</td>
<td>14.5</td>
</tr>
<tr>
<td>Class II</td>
<td>62.3</td>
<td>55.6</td>
<td>59.0</td>
</tr>
<tr>
<td>Class III and IV</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Nonexertional</td>
<td>4.1</td>
<td>5.4</td>
<td>4.7</td>
</tr>
<tr>
<td>History</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior MI</td>
<td>62.6</td>
<td>57.2</td>
<td>59.9</td>
</tr>
<tr>
<td>Hypertension</td>
<td>29.4</td>
<td>32.7</td>
<td>31.1</td>
</tr>
<tr>
<td>Congestive failure</td>
<td>2.3</td>
<td>3.9</td>
<td>3.1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>8.1</td>
<td>9.3</td>
<td>8.7</td>
</tr>
<tr>
<td>Stroke</td>
<td>2.1</td>
<td>2.1</td>
<td>2.1</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>9.3</td>
<td>7.3</td>
<td>8.3</td>
</tr>
<tr>
<td>Cigarette use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present smoker</td>
<td>40.8</td>
<td>38.7</td>
<td>39.7</td>
</tr>
<tr>
<td>Former smoker</td>
<td>43.6</td>
<td>44.4</td>
<td>44.0</td>
</tr>
<tr>
<td>Never smoked</td>
<td>15.6</td>
<td>16.9</td>
<td>16.3</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present smoker</td>
<td>54.9</td>
<td>56.2</td>
<td>55.5</td>
</tr>
<tr>
<td>Former smoker</td>
<td>44.6</td>
<td>47.3</td>
<td>46.0</td>
</tr>
<tr>
<td>Never smoked</td>
<td>42.6</td>
<td>44.1</td>
<td>43.3</td>
</tr>
<tr>
<td>Antithrombotics</td>
<td>9.0</td>
<td>9.7</td>
<td>9.4</td>
</tr>
</tbody>
</table>

aValues, except those for age, are percentages.
bUnemployed, temporary sick leave, disabled secondary to a noncardiac illness.

The percentages of patients with single-, double-, and triple-vessel disease, applying the definition of at least 70% luminal reduction, was 27%, 40%, and 33%, respectively. In all CASS analyses this 70% definition is used, but in two other large randomized stud-

ies16-23 a definition of 50% luminal diameter reduction was used. Applying the 50% definition to the randomly assigned patients in this study changes the percentages to 18%, 32%, and 50% for single-, double-, and triple-vessel disease, respectively.

Compliance to therapeutic assignment. Of 390 subjects randomly allocated to operative treatment, two died before their scheduled date of surgery; 41 (11%) initially refused surgery and thus "crossed" to medical therapy. During the follow-up interval, 10 of these patients subsequently had bypass surgery so that only 31 (8%) noncompliant surgical group patients remained. The likelihood of a patient refusing surgery is inversely related to the angiographically determined severity of coronary disease. Thus, 15% of patients with single-vessel disease assigned to receive surgical therapy declined operation, whereas only 3% of those with triple-vessel disease refused operation (p = .02).

TABLE 2
Electrocardiographic, ventriculographic, and arteriographic description of patients in medical and surgical groups at entry

<table>
<thead>
<tr>
<th>Variable</th>
<th>Medical group (n = 390)</th>
<th>Surgical group (n = 390)</th>
<th>Total (n = 780)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q Wave MI</td>
<td>29.4</td>
<td>29.0</td>
<td>29.2</td>
</tr>
<tr>
<td>ST depression</td>
<td>11.2</td>
<td>8.5</td>
<td>9.8</td>
</tr>
<tr>
<td>T wave inversion</td>
<td>38.4</td>
<td>36.7</td>
<td>37.6</td>
</tr>
<tr>
<td>Normal ECG</td>
<td>30.8</td>
<td>27.1</td>
<td>28.9</td>
</tr>
<tr>
<td>One-vessel diseaseb</td>
<td>27.4</td>
<td>27.4</td>
<td>27.4</td>
</tr>
<tr>
<td>Two-vessel diseaseb</td>
<td>38.0</td>
<td>41.0</td>
<td>39.5</td>
</tr>
<tr>
<td>Three-vessel diseaseb</td>
<td>34.6</td>
<td>31.5</td>
<td>33.1</td>
</tr>
<tr>
<td>Left anterior descending artery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70% or greater lesion in one or more segments</td>
<td>71.3</td>
<td>72.1</td>
<td>71.7</td>
</tr>
<tr>
<td>70% or greater lesion in a proximal segment</td>
<td>30.3</td>
<td>32.8</td>
<td>31.5</td>
</tr>
<tr>
<td>Left ventricular scorec</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>39.0</td>
<td>39.1</td>
<td>39.1</td>
</tr>
<tr>
<td>6-10</td>
<td>43.9</td>
<td>41.9</td>
<td>42.9</td>
</tr>
<tr>
<td>11-15</td>
<td>15.3</td>
<td>17.5</td>
<td>16.4</td>
</tr>
<tr>
<td>16-20</td>
<td>1.8</td>
<td>1.5</td>
<td>1.7</td>
</tr>
<tr>
<td>Left ventricular ejection fraction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 50</td>
<td>21.0</td>
<td>20.0</td>
<td>20.5</td>
</tr>
<tr>
<td>≥ 50</td>
<td>72.8</td>
<td>74.6</td>
<td>73.7</td>
</tr>
<tr>
<td>Not measuredd</td>
<td>6.2</td>
<td>5.4</td>
<td>5.8</td>
</tr>
</tbody>
</table>

aValues are percentages.
bLuminal diameter reduction of at least 70%.
cFive ventricular segments viewed in the right anterior oblique projection. Grading scale: Normal = 1, moderate hypokinesis = 2, severe hypokinesis = 3, akinesis = 4, dyskinesis = 5, aneurysmal = 6. Total score attained by adding values of each segment. Maximum observed score was 20.
dTechnically uninterpretable ventriculograms.
Patients assigned to surgical therapy who accepted this assignment from the outset had bypass surgery a mean of 54 days after randomization (range 5 to 345 days). During the follow-up period 10 patients who were assigned to the surgical group but did not comply initially had surgery a mean 934 days after randomization.

Of 390 patients assigned to receive medical therapy, 23.5% (4.7% per year) had bypass surgery by 5 years and thus "crossed" to surgical therapy. In most instances crossover was due to the development of worsening angina in spite of vigorous medical therapy. The estimated annual rate of crossover from the medical group to surgical therapy is directly related to the extent of coronary disease noted at entry. The annual crossover rates for those in the medical group who had single-, double- and triple-vessel disease were 2.0%, 4.2%, and 7.6%, respectively. The observed differences in annual crossover rates among these subgroups of patients are unlikely to have arisen by chance (p < .001). Cumulative time to surgery in patients assigned to receive surgical therapy and in those assigned to these medical subgroups is shown in figure 2.

Surgical therapy. In patients randomly assigned to undergo surgery, operative mortality, defined as death occurring in the hospital or within 30 days of surgery, was 1.4% (five of 357 patients). One operative death occurred at each of three CASS sites; there were two operative deaths at another site. There were no operative deaths at the seven other CASS randomizing sites. The operative mortality in those patients initially assigned to medical therapy but subsequently undergoing surgery was 2.0% (two of 100 patients). Perioperative myocardial infarction in the patients assigned to surgical therapy occurred in 23 of 357 or 6.4%. Operative mortality and perioperative myocardial infarction rates are for all patients followed over the entire follow-up interval, which ended April 15, 1983.

A total of 954 distal anastomoses were constructed in 357 patients in the surgical group, an average of 2.7 per patient. In patients with single-, double-, and triple-vessel disease the average number of distal anastomoses was 1.7, 2.7, and 3.4, respectively. Graft patency in 129 patients was assessed within 60 days of surgery and the results have been published. A total of 334 distal anastomoses were evaluated in the 129 patients; 90% of the grafts were open, 97% of patients had at least one open graft, and in 81% of patients all grafts were patent.

Medical therapy. A standard protocol for medical treatment was developed by CASS investigators and shared with physicians involved in the care of all of the randomly assigned patients. This included efforts to modify risk factors as well as the use of nitrates and β-blocking drugs. β-blocking drugs were used with equal frequency in both groups at entry, but were subsequently given more frequently to patients assigned to medical therapy. The percentages of patients in the medical group given β-blocking drugs at 12, 36, and 60 months were 63%, 65%, and 64%; the corresponding percentages for those in the surgical group were 22%, 28%, and 34%. These differences are statistically significant (p < .001). Approximately 25% of patients in both groups who smoked cigarettes when they entered the trial reported at follow-up contacts that they had quit. There was no difference between the two groups with respect to the proportion who smoked during the follow-up period. The severity of angina, use of medication, rates of recurrent nonfatal myocardial infarction and hospitalization, as well as other indices of quality of life are topics of separate reports. 24, 25

Mortality. There were no significant differences among survival rates for the two treatment groups (figure 3) or for any of the subgroups (figures 4 through 7). A total of 65 deaths occurred during the entire follow-up interval through April 15, 1983. Thirty-six patients in the medical group and 29 in the surgical group died.

Patients assigned to medical therapy experienced an estimated annual mortality of 1.6%. For patients with single-vessel disease treated medically, annual mortality was 1.4%; in patients with double-vessel disease the rate was 1.2% and in patients with triple-vessel disease, 2.1%. In patients assigned to medical treatment who had moderately impaired ventricular function (ejection fraction less than 0.50) the annual mortality rate was 3.3%.

The estimated annual mortality rate in patients assigned to surgical therapy was 1.1%. In patients with single-, double-, and triple-vessel disease, annual mortality rates were 0.7%, 1.0%, and 1.5%, respectively. In the surgically assigned patients with ejection frac-

Vol. 68, No. 5, November 1983
tions less than 0.50 there was an annual mortality rate of 1.7%.

There were no statistically significant differences among survival curves for medical and surgical groups when patients were grouped according to presence of single-, double-, or triple-vessel disease (figure 4), by clinical subgroup (figure 5), ejection fraction, or by a combination of number of diseased vessels and ejection fraction (figures 6 and 7). There was no statistically significant difference between patients with left anterior descending coronary artery lesions at baseline between medical and surgical groups.

The mortality in patients in the medical group was increased in the presence of impaired ventricular function (ejection fraction of less than 0.50) when compared with that in those with ejection fractions of at least 0.50 (p < .0001); the survival curve for patients in the surgical group who had impaired ventricular function and that for those with normal ventricular function (ejection fraction of at least 0.50) were not significantly different (p = .30).

A number of additional subgroups were formed based on patient characteristics at entry into the study and differences in mortality among the subgroups were examined. Variables used in the formation of the group included presence or absence of myocardial infarction, degree of myocardial jeopardy, history of hypertension, presence or absence of ST depression on a resting electrocardiogram, and history of peripheral vascular disease. No statistically significant differences between the patients in the medical and surgical groups were observed in these subgroups.

Discussion

Patients with coronary artery disease vary widely with respect to severity of symptoms, extent and distribution of coronary artery lesions, ventricular function, and prognosis. For example, recent CASS registry estimates of annual mortality in patients managed nonoperatively range from 1.3% in those with single-vessel disease and well-preserved ventricular function to 12.5% in those with triple-vessel disease and impaired ventricular function. This CASS registry study included patients with coronary disease of a wide range of severity. Noninvasive descriptors appear to add independent prognostic information. Given the large reported range of annual mortality rates in subgroups of patients treated medically, a treatment strategy of immediate surgery may be advantageous in some patients but not in others.

CASS, which incorporates both a registry and a randomized trial, is designed to permit observational data analysis across the entire spectrum of patients undergoing diagnostic coronary arteriography (CASS registry) as well as a more rigorous comparison of mortality in well-defined subgroups randomly assigned to medical or surgical therapy (CASS randomized trial). This methodologic approach delineates the population from which trial participants are drawn, which in turn permits more confidence in applying trial findings to the general population of patients undergoing coronary arteriography.

In 71% of the 16,626 registry patients undergoing coronary arteriography at CASS randomizing sites during the recruitment period, assignment to medical or surgical therapy would not have been a point of contention. As illustrated in figure 1, 28% of these patients had either normal coronary arteriograms or no lesion causing 70% or greater luminal diameter reduction and no left main lesion causing 50% or greater luminal diameter reduction. An additional 4.9% had no operable vessels. Thus, 33% of CASS registry patients were not candidates for surgery and were therefore excluded from participation in the trial.

Class III or IV angina was present in 36.5% of registry patients; patients with left main coronary lesions causing at least 70% luminal diameter reduction made up an additional 1.5%. Coronary artery bypass surgery results in either complete relief or partial improvement in symptoms of chest pain in a majority of patients with severe angina; patients with severe angina were therefore excluded from the randomized trial. Bypass surgery improves longevity in patients with severe left main artery lesions, so randomization of these patients would not have been ethical. Thus, 38%
of registry patients were excluded from this study because surgical therapy was known to be effective for relieving symptoms or prolonging life.

The remaining 29% or 4780 patients in the CASS registry (unshaded portion of figure 1) had clinical and anatomic features that make the choice of treatment difficult: symptoms were not severe, coronary anatomy was surgically approachable, and the effect surgery would have on longevity was not known. Of this group of 4780 patients, 56% were excluded by the CASS protocol for a variety of scientific and practical reasons including prior coronary bypass surgery, severe congestive heart failure, age over 65, or inaccessibility due to geographic, language, or psychologic barriers. The findings of the CASS randomized trial are most clearly applicable to the remaining 2099 patients, 12.7% of all patients undergoing diagnostic coronary arteriography during the trial recruitment interval and 44% of patients for whom the best therapeutic choice is a matter of the physician's judgment and patient preference rather than generally accepted practice.

Execution of the CASS protocol was successful. Patients randomly assigned to medical or surgical therapy had similar clinical and anatomic features (tables 1

Vol. 68, No. 5, November 1983

FIGURE 4. Five-year cumulative survival in groups with single-, double-, and triple-vessel disease, with disease being defined as at least 70% luminal diameter reduction.

FIGURE 5. Five-year cumulative survival in clinical subgroups. A. Patients with mild-to-moderate angina and with ejection fractions of at least 0.50. B. Patients with mild-to-moderate angina and ejection fractions of less than 0.50. C. Angina-free survivors of well-documented acute myocardial infarction.
and 2). Vital status was known on all patients but one lost to follow-up after 4½ years. Compliance to therapeutic assignment was influenced by the development of worsening angina in those assigned medical therapy and by reconsideration in a small proportion of those assigned to surgery. Crossover rates were similar to those observed in both the European and Veterans Administration trials.

For all analyses reported in this article patients were considered to belong to the group to which they were initially assigned (intention to treat) regardless of subsequent therapy they received. In clinical trials as in

**FIGURE 6.** Five-year cumulative survival rates for patients with ejection fractions of at least 0.50 (A) and patients with ejection fractions of at least 0.50 and single- (B), double- (C), and triple- (D) vessel disease. Luminal diameter reduction of at least 70% was required for diagnosis of vessel disease.

**FIGURE 7.** Five-year cumulative survival rates for patients with ejection fractions of less than 0.50 (A) and patients with ejection fractions of less than 0.50 and single- (B), double- (C), and triple- (D) vessel disease. Vessel disease was diagnosed as described in figure 6.
the practice of medicine some patients do not comply with therapeutic assignment, raising the question of whether a more appropriate analysis might be comparison of outcome in groups created by treatment received rather than treatment assigned. However, analysis by treatment received violates the process of randomization; groups created in this post hoc fashion are quite likely to be unbalanced for both known and, more importantly, unrecognized prognostically important characteristics. An unbiased comparison of outcome is difficult, if not impossible, when analysis is by treatment received. Analyses of CASS mortality data by treatment received and by means of censoring at the time of crossover do not change the results. These analyses are not reported since they are of dubious scientific merit in the context of a randomized trial.

Analysis by assigned treatment influences the hypotheses that can be tested because of the slow, steady rate of crossover to surgical therapy in the medical group. Given the observed degree of noncompliance to treatment assignment, CASS cannot definitively test the true contrast in outcome between medical and surgical therapy, since it is impossible from a practical standpoint to restrict therapy during follow-up. Patients assigned to the medical group who developed worsening angina during the course of the study were not denied the opportunity to seek improvement by bypass surgery and surgically treated patients with worsening angina were treated medically as well. However, the CASS tests the practical hypothesis that a strategy of prompt elective surgery results in a different mortality rate than a strategy of deferred surgery contingent upon worsening symptoms.

Patients undergoing coronary artery bypass grafting as part of the CASS in the period from 1975 to 1979 enjoyed excellent results. The operative mortality of 1.4% is similar to the currently reported surgical risk. The number of grafts fashioned and bypass patency rates are similar to those reported in other recent series. The incidence of perioperative myocardial infarction, determined according to a vigorously applied algorithm, was 6.4%. This rate is difficult to compare with the reports of others because of wide variability in the criteria used to diagnose this complication, but it is within the range of rates reported in studies relying on electrocardiographic Q wave criteria.

Recommended medical therapy is outlined in the CASS protocol. Patients were referred to the participating CASS sites from a large number of practicing physicians. After entry into the randomized trial, patients were returned to the care of their personal physicians. The recommended outline of medical treatment was forwarded to these physicians. No attempt was made to further standardize medical therapy; the responsible physician was free to choose optimal therapy according to his or her best judgment. At each follow-up visit, symptoms and therapy were carefully reviewed and recorded.

The survival of CASS patients assigned to medical therapy is excellent. When the CASS was initially designed, review of available published data suggested that the annual medical mortality rate in patients with proven coronary artery disease would be approximately 4%. Calculations have been published estimating the statistical power of CASS to detect clinically important differences in survival for an assumed annual medical mortality of 2% and 4%.

The annual mortality in patients assigned to medical therapy is 1.6%, a figure considerably lower than that estimated during trial design and lower than the annual medical mortality of 3.3% noted in the European Collaborative Study and than the 4.3% reported in the Veterans Administration Study. The excellent long-term results in CASS patients assigned to medical therapy reduces the power of the experiment to detect a reduction in mortality afforded by prompt elective coronary artery bypass. Thus, if medical mortality for these patients is in truth 1.6% a year, a 50% reduction in mortality would be discerned with the present sample size with a probability .65. A 30% reduction would be detected with a probability .26. Indeed, a sample size of over 4600 would have been required to detect a 30% reduction in mortality with 90% surety given the observed CASS medical mortality rate. The clinical significance of the observed nonsignificant reduction in estimated mortality for the individual patient is quite small (1.1% vs 1.6% annual risk). The difference in the annual mortality rates for patients with good ventricular function at entry is even smaller (0.8% vs 1.0%).

Only 160 patients with ejection fractions of less than 0.50 participated in the present study. As shown in figure 7, the survival curves reveal a statistically non-significant advantage for the patients assigned to surgical therapy, especially in those with three-vessel disease. Because of the small sample size, a large improvement in survival due to immediate surgical intervention cannot be excluded as a possibility. For example, if medical mortality in this subset of patients is 3.3% a year, a sample size of 650 would be required to discern a surgically induced 50% reduction in 5 year mortality in this subgroup with 90% surety. A 30% reduction would require a sample size of over 2000.

Analysis of data from the 1319 patients qualifying

Vol. 68, No. 5, November 1983 947
for randomization but declining to participate (the randomizable group for whom therapy was chosen in consultation with the personal physician rather than by random assignment) reveals an outcome in those treated medically similar to that reported in the randomly assigned patients who received medical therapy. Patients who agreed to be randomly assigned to treatment did not differ in long-term survival when compared with those who declined randomization.15

In contrast to the European Collaborative Study, the CASS does not show a significant decrease in survival rates for patients with three-vessel disease and ejection fractions greater than 0.50, or in patients with two- or three-vessel disease involving the left anterior descending coronary artery. The subgroup in this study in which a trend in favor of surgery (those with three-vessel disease with ejection fractions less than 0.50) was revealed was not included in the European Study. The reasons for the apparent differences between results of the two studies may lie in variations in referral patterns, the medical therapy used in the two studies, the exclusion of patients with single- vessel disease in the European study and, perhaps most importantly, the inclusion of patients with more severe angina in the European trial. The excellent survival rate observed in CASS medical patients is the major difference between the results of the two studies.

Neither the Veterans Administration Study nor the CASS shows a significant overall difference in outcome when medical and surgical therapy are compared. Since the Veterans Administration Study was initiated, changes have been made in the process of selection of patients for coronary arteriography and in surgical technique (with a lowering of operative mortality) and there have been improvements with respect to graft patency and perioperative infarction rate, as well as more effective application of medical therapy, including administration of nitrates and \( \beta \)-blocking drugs. These secular changes make close comparison difficult. In contrast to the Veterans Administration Study, CASS included patients with less impairment of ventricular performance at entry. The small CASS subgroup with impaired ventricular performance more closely resembles patients included in the Veterans Administration trial. An analysis of CASS subgroups of patients with prior myocardial infarction, ST segment depression apparent on the resting electrocardiogram, and history of hypertension does not reveal statistically significant survival differences between patients assigned to receive medical and those assigned to receive surgical therapy.

CASS trial results are most applicable to patients with mild-to-moderate angina and to angina-free survivors of myocardial infarction with surgically approachable coronary artery disease. CASS registry data reveal that 12.7% of all patients undergoing diagnostic coronary arteriography at the 11 CASS sites from August 1975 to May 1979 meet these criteria. More importantly, this subset includes 44% of those patients (unshaded area of figure 1) for whom the therapeutic choice between surgery and medical management is a matter of judgment rather than widely accepted practice. In these patients a treatment strategy of prompt elective coronary artery bypass surgery does not result in improved survival when compared with a strategy of medical management unless worsening symptoms make surgery necessary. In patients with unimpaired ventricular performance on entry into the study (ejection fraction of at least 0.50), the survival curves are indistinguishable. In those with impaired ventricular performance, a statistically nonsignificant trend in favor of surgery is evident, and may represent a true survival advantage for patients assigned to surgical therapy. Insufficient numbers of patients in this subgroup prevent rigorous testing of this hypothesis, but further follow-up of CASS randomly assigned patients is planned and may clarify this trend.

In patients similar to those enrolled in the CASS trial, a strategy of medical management until worsening symptoms require surgical palliation does not carry a mortality penalty. Furthermore, deferring surgery does decrease immediate health care costs and preserve both veins and mediastinum if surgery is required later. Thus, the decision to proceed with bypass surgery in these patients can be reduced to a question of whether the current level of symptoms is acceptable to the patient. These findings have important implications for both cardiologists and cardiac surgeons in their diagnostic and therapeutic efforts.

CASS

Clinical centers

University of Alabama in Birmingham: Birmingham, Principal Investigators: William J. Rogers, M.D., Richard O. Russell, Jr., M.D. (former); Associate Investigators: Albert Oberman, M.D., Nicholas T. Kououchouos, M.D.; Data Technicians: Rosa Kimerling, Mary Lynn Mandy, Glenda Barnes, R.N. (former), Marlene Means (former), Phyllis Newsom (former); Others: Benigno Soto, M.D., P. Nath, M.D., Sanford P. Bishop, Ph.D., Sammy Scalisi, Helen Boerner, Martha Armstrong, Victoria Talley, Jeanne Arnold (former), Matt Beavers (former), Jim Kitts, P.A. (former), Toni Price (former), Marian Oberman (former), Suzanne Bearman (former), Myrna Goldstein (former), Sharon Stein (former), Morty Roach (former), Steve Williams (former), William Brodie, R.N. (former).

Albany Medical College of Union University, Albany, Principal Investigators: Eric D. Foster, M.D., Julio A. Sosa, M.D.; Associate Investigators: Joseph T. Doyle, M.D., Martin F.
McKneally, M.D., Joseph B. McIlIFF, M.D., Harry Odabashian, M.D. (former), Thomas M. Oldner, M.D.; Study Coordinator: Joyce A. Carpenter; Data Technicians: Sally Abele, Stephen Cameron, William Olewien, Frank Strickler.

Boston University Medical Center and Evans Memorial Department of Clinical Research, Boston, Principal Investigator: Thomas J. Ryan, M.D.; Associate Investigators: Robert L. Berger, M.D., David P. Faxon, M.D., David C. Heuter, M.D. (former), Mirle A. Kellett, M.D., John R. McCormick, M.D., Edgar C. Schick, M.D., Donald A. Weiner, M.D., Laura F. Wexler, M.D.; Project Managers: Carolyn H. McCabe, B.S., Sandra Pfund, R.N. (former); Data Technicians: Sally S. Cutler, B.S., Patricia DeAngelis, R.N. (former), Patricia Hollum (former), Mary-Grace Lett; Financial Manager: Wanda McGovern, B.A.

Loma Linda University School of Medicine, Loma Linda, Principal Investigators: C. Joan Coggin, M.D., Melvin P. Judkins, M.D., Ellsworth E. Wareham, M.D.; Associate Investigators: Winston A. Mitchell, M.D. (former), Patrick M. Moliney, M.D.; Data Technicians: Isla Andersen, Carol Mason, Pat Meyer; Project Coordinator: Eileen Judkins, R.N.


Massachusetts General Hospital, Boston, Principal Investigators: J. Warren Harthorne, M.D., W. Gerald Austen, M.D., Eldred Mundtn, M.D. (former); Associate Investigators: Robert E. Dinsmore, M.D., Stephen Miller, M.D., Frederick Levine, M.D. (former), Dimitrios Linos, M.D. (former), John McDermott, M.D. (former), Frederick Poulin, M.D. (former), Sayed Quadri, M.D. (former), Vincent DiCola, M.D.; Data Technicians: Emily Gminter, Lucy Matson, May Beth Connor (former), Jane Porter (former), Mary Ferraro (former), Stephen Gottlieb (former), Margaret Fleury (former), Elizabeth Chantrrell (former), Margaret Brungarber (former), Patricia A. Galvin (former), Sandra Rossi (former), Andrea Freeman (former), Carol McGlinchey (former), David Bindman (former).


Miami Heart Institute, Miami Beach, Principal Investigator: Arthur J. Gosselin, M.D.; Associate Investigators: Paul S. Swayne, M.D., Ernest Traad, M.D., Parry B. Larsen, M.D. (former); Data Technicians: Hazel J. Yon, Rose P. Callen, Marilyn Baram (former), Evelyn Ananias (former), Maria Walz (former), Debrah Fiore-Bradley (former), Donna Dobbs (former); Secretaries: Alexis Benjamin (former), Beth Hendel (former), Rosita Mila (former), Claudette Broomfield (former), Maria Canet (former).

Institut de Cardiologie de Montreal, Montreal, Principal Investigator: Martial G. Bourassa, M.D.; Associate Investigators: Claude Goulet, M.D., Jacques Lesperance, M.D., Bernard R. Chaitman, M.D. (former), Claude M. Grondin, M.D., B. Charles Solymoss, M.D., Yves Castonguay, M.D., Lucien Campeau, M.D.; Research Associate: Margot Methé, R.N.; Data Technicians: Micheline Labbe, Claudette Faille, Celine Guilbeault, Manon Bellemare (former), Diane Tourville (former).

New York University Medical Center, New York, Principal Investigators: Ephraim Glassman, M.D., Michael Schloss, M.D.; Associate Investigator: Wayne Isom, M.D.; Data Technicians: Deborah Walzer, Carolyn Mungo, Ruth Gonzalez.

St. Louis University School of Medicine, St. Louis, Principal Investigators: George C. Kaiser, M.D. (Director), J. Gerard Mudd, M.D.; Associate Investigators: Naseer Ahmad, M.D., Henrick B. Barme, M.D., John E. Codd, M.D., David M. Harshman, M.D., John P. Merjavy, M.D., D. Glenn Pennington, M.D., Dennis H. Tyras, M.D., Robert D. Wiens, M.D., Vallee L. Willman, M.D., Hillel Laks, M.D. (former), Alexander Mark, M.D. (former); Data Technicians: Polly Porter Fogarty, Project Administrator, Jean LoPiccolo, Assistant Project Administrator, Karen Kelley, Marceca Freeman, Esther Muller, Rex Tannahill, Judi Willenbrink, Kristine Allen (former), James Bertram (former), Douglas Clermont (former), Claudia Day (former), Barbara Fineberg (former), Kelly Fitzgerald (former), Dorothy Hoffman (former), Mary McCarthy (former), Susan Neill (former), Pat Otto (former), George Schroeder (former), Diane Waack (former), Marc Zelenka (former).

St. Luke’s–Roosevelt Hospital Center, New York, Principal Investigator: Harvey G. Kemp, M.D.; Associate Investigators: Airlie Cameron, M.D., George E. Green, M.D., John E. Hutchinson III, M.D., Haroutune A. Melkijian, M.D.; Data Technicians: Lillian Agosto, Carlos Coronado, Patricia Grieshammer, Petronella Marshall, Joanne Oh, Amy Patton, Rosalie Sinkler, Synthia Vega-Piontek, Monica Wachtner, Susan Walsh, Paula Zakos, Patricia Zorena.

Stanford University Medical Center, Stanford, Principal Investigator: Edwin L. Alderman, M.D.; Coinvestigators: James Silverman, M.D., Edward B. Stinson, M.D.; Associate Investigators: Francis Koch, M.D., Paul Cipriano, M.D. (former); Data Technicians: Adriana Krauss, Geeta Charjee, Candace Rabiroff, Anne Schwarzkopf, Sandra Avery (former); Staff Assistant: Susan Groechel.

The Medical College of Wisconsin, Veterans Administration Medical Center, Milwaukee, Principal Investigators: Harold R. Brooks, M.D., Felix E. Tristani, M.D., Lawrence Bonchek, M.D. (former), Michael Keelan, Jr., M.D. (former); Associate Investigators: Virinderjit S. Bamrah, M.D., Robert J. Flemma, M.D., C. Vincent Hughes, Jr., M.D., Donald Tresch, M.D. (former); Data Technicians: Ronald Mack, Patricia Ryan, Marlene Bednarz (former).

Yale University School of Medicine, New Haven, Principal Investigator: Lawrence S. Cohen, M.D.; Associate Investigators: Alexander S. Geha, M.D., Graeme L. Hammond, M.D., Rene A. Langou, M.D., Richard Shaw, M.D. (former), Steven Wolfson, M.D. (former); Data Technicians: Caroline Jacobs, R.N. (former), Abby Miller, B.A., Barbara Nemier.

Central electrocardiographic laboratory

University of Alabama in Birmingham, Birmingham, Principal Investigator: L. Thomas Sheffield, M.D.; Associate Director: David Roitman, M.D.; Coinvestigator: Santosh Kansal, M.D.; Data Management Supervisor: Carol Troxell, B.S.; Administrative Assistant: Myrnie Driskill, B.S.; Data Processing Coordinator: Monika Whitcomb; Clerical Supervisor: Evonne Lawrence; Secretary: Juanita Brasher; Clerk/Stenographer: Sherry Tew; Coding Clerks: Shirley Decker, Jo Ann Kelley, Paula Stanton, Jeanne Arnold.

Coordinating center

University of Washington, Seattle, Principal Investigators: Lloyd D. Fisher, Ph.D., Richard A. Kronmal, Ph.D. (former);
CASS INVESTIGATORS

Associate Investigators: Kathryn B. Davis, Ph.D., Mary Jo Gillespie, M.S. (Deputy Director), J. Ward Kennedy, M.D., Richard A. Kronmal, Ph.D.; System Programming and Data Processing: Lois Danks, Brian LeVerson, Erik Lundberg, Ruth McBride (Supervisor), Rita Mines, Thomas Ormond, Shimon Benami (former), Mary Ann Betts (former), Harvey Friedman (former), Susan Harada (former), Kelly Landreth (former), Robert Mauritsen (former), Thomas Rawson (former); Analysis and Scientific Programming: Marion Atherman, Richard Ells, James Ferguson, David Fray, Cheryl Look, Stephen Luk, Charles Maynard (Supervisor), Mary Pettinger, John Wilson, Elisabeth Cardis (former), Leland DePriest (former), William Halteman (former), Robert Jones (former), Paul Littwin (former), Paula Roberson (former), Bruce Schaalje (former), Andrew Seth (former), Dalice Sim (former), Vicki Stover-Hertzberg (former), Ronald Thomas (former), Terrence Tong (former), William Vollmer (former), Homer Warner (former), Barbara Williams (former), Kathryn Long; Program Staff: Joan Pitell (Supervisor), Jean Savage, Denise Borer (former), Cynthia Bush (former), Margaret Ellwood (former), Janice Halteman (former), Andrea Jarvela (former), Donna King (former), Rhonda Moon (former), Carol Murray (former), Patricia Thornhill (former).

National Heart, Lung and Blood Institute

National Institutes of Health, Bethesda, Current Staff of the Program Office: Eugene R. Passamani, M.D., Peter L. Frommer, M.D., Suzanne Mullin, R.N., M.P.H., Kent Bailey, Ph.D., Barbara Packard, M.D., Ph.D., Betty Nordan; Previous Staff: Per T. Berje, M.D., David L. Demets, Ph.D., John B. Hanks, M.D., David M. McCarthy, M.D., Michael B. Mock, M.D., Alan L. Pinkerson, M.D., Robert A. Poirier, M.D., Ivar Ringqvist, M.D., Patrick M. Sullivan, Hans Wedel, Ph.D.; Central Pathology Laboratory: William C. Roberts, M.D., Bruce F. Waller, M.D.; Policy Advisory and Data Monitoring Board: Lloyd D. Fisher, Ph.D., Ralph Frankowski, Ph.D., William T. Friedewald, M.D., L. Julian Haywood, M.D., Thomas Killip, M.D., Francis Klocke, M.D. (Chairman). Curtis L. Meintert, Ph.D., Richard S. Ross, M.D., David Sabiston, M.D., Harmon Smith, Ph.D., Jeremiah Stamler, M.D., John Vasko, M.D., James H. Ware, Ph.D. (Chairman); Steering Committee: Thomas Killip, M.D., Henry Ford Hospital, Detroit.

References
15. CASS Principal Investigators and their associates: Coronary Artery Surgery Study (CASS). A randomized trial of coronary artery bypass surgery. Comparability of entry characteristics and survival in randomized patients and non-randomized patients meeting randomization criteria. (submitted for publication).
24. CASS Principal Investigators and their associates: Coronary Artery Surgery Study (CASS), a randomized trial of coronary artery bypass surgery. Myocardial infarction results. (submitted for publication).
Coronary artery surgery study (CASS): a randomized trial of coronary artery bypass surgery. Survival data.

Circulation. 1983;68:939-950
doi: 10.1161/01.CIR.68.5.939

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1983 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/68/5/939

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/