The effect of medical and surgical treatment on subsequent sudden cardiac death in patients with coronary artery disease: a report from the Coronary Artery Surgery Study


ABSTRACT The effect of medical and surgical treatment on subsequent sudden cardiac death was assessed in 13,476 patients in the Coronary Artery Surgery Study registry who had significant coronary artery disease, operable vessels, and no significant valvular disease. (Patients were assigned to medical or surgical therapy on the basis of clinical judgment and not according to a randomization scheme; therefore, biases associated with unknown variables could not be evaluated.) Sudden cardiac death occurred in 452 patients (3.4%) during a mean follow-up of 4.6 years. Five year survival free of sudden death for medically treated patients was 94 ± 0.3%, and that for surgically treated patients was 98 ± 0.2% (p < .0001). Twelve baseline clinical, electrocardiographic, and angiographic variables were significantly different between patients alive at the last follow-up and those suffering sudden death. Data on these variables were available for 11,508 patients. Sudden death occurred in 257 (4.9%) of 5258 medically treated and 101 (1.6%) of 6250 surgically treated patients. In a high-risk patient subset with three-vessel disease and history of congestive heart failure, 91% of surgically treated patients had not suffered sudden death compared with 69% of medically treated patients. After Cox survival analysis was used to correct for baseline variables, surgical treatment had an independent effect on sudden death (p < .0001). This reduction was most pronounced in high-risk patients.

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SUDDEN CARDIAC DEATH is a major health problem, with approximately 400,000 deaths per year in the United States.1,2 Information on the clinical setting and mechanism has been obtained from autopsy series, coronary care units, and patients resuscitated after out-of-hospital arrest.3–6 Patients at increased risk can be identified by clinical features and angiographic findings.5,6,17–21 Although ventricular arrhythmias are the usual mechanism,16,22,23 the initiating events remain unknown.24–26 In some patients, the arrhythmia may result from ischemia. If ischemia is important, coronary artery bypass grafting (CABG) could potentially play an important role and may reduce the incidence of sudden cardiac death.

Previous studies on the role of CABG for prevention of sudden cardiac death have suggested a benefit from operation but have been limited by small sample size, variable patient selection, or the retrospective nature of the study.23,27,28 The Coronary Artery Surgery Study (CASS) circumvents some of these problems by virtue of the study design, sample size, and prospective entry and follow-up. This study analyzes the CASS registry, characterizes patients at increased risk for sudden cardiac death, and compares the impact of medical therapy alone with that of CABG on the incidence of sudden cardiac death in patients with coronary artery disease (CAD).

Materials and methods

Details of the CASS study, including methods, definition of terms, quality control, and baseline data, have been described.29 From 1975 to 1979, 20,270 patients without prior CABG who were undergoing coronary angiography for evaluation of suspected CAD were enrolled and prospectively studied. Except for 780 patients enrolled at 11 CASS randomizing centers, most of the patients (19,490) received medical or surgical treatment on the basis of patient and physician judgment. This analysis of observational data deals with the CASS registry and is not confined to randomized patients. Biases associated with unknown variables could not be evaluated.
The vital status as of December 1982 was known for 98% of the originally enrolled 20,270 patients: 98.1% of medically and 98.9% of surgically treated patients. The purpose of this study was to evaluate the effect of medical and surgical therapy on sudden cardiac death. We did not analyze the effect of medical and surgical therapy on all causes of death; this is the topic of forthcoming studies. The analysis is restricted to patients with significant CAD and operable vessels but no significant valvular heart disease at the time of initial angiography.

Definitions

Sudden cardiac death. Sudden cardiac death is defined as the sudden occurrence of death within 1 hr after the onset of symptoms and generally before the availability of medical attention. The circumstances under which death occurred were specified whenever possible. Sudden deaths were classified as occurring at home, at work, during recreational activity, in the hospital, or en route to the hospital. Sudden deaths were further classified as witnessed or unwitnessed. The definition of witnessed sudden cardiac death is difficult. A subcommittee of the steering committee of CASS reviewed all deaths of the randomized patients and categorized them as sudden death, nonsudden cardiac death, and noncardiac death. Unwitnessed sudden cardiac death was thought to have occurred when the patient was alive and well when last seen and soon after was discovered to be dead (for example, during sleep). In this study, 23 patients died suddenly within 30 days after cardiac operation; their deaths were considered cases of perioperative mortality and not sudden deaths.

Coronary artery disease. Significant CAD was defined as 70% or more luminal diameter narrowing of the right coronary artery or of the left anterior descending or circumflex coronary arteries or their major branches or as 50% or more stenosis of the left main coronary artery. In a patient with a dominant right or balanced coronary artery system, significant stenosis of the left main coronary artery was coded as two-vessel disease; in a patient with a dominant left coronary artery, significant stenosis of the left main coronary artery was coded as three-vessel disease.

Operable vessel. The term “operable vessel” is a measure of anatomic suitability for CABG. In a patient with significant CAD, an operable vessel is one with 50% or more stenosis but a normal-sized distal vessel.

Left ventricular function. Left ventricular function was quantitated by use of monoplane left ventricular angiography. Ejection fraction was calculated by the area-length method. The left ventricle was divided on the right anterior oblique projection into five segments, each of which was coded for wall motion as normal, hypokinetic, akinetic, or dyskinetic. The following scoring system was used for the left ventricle: 5, normal left ventricle; 6 to 9, mild left ventricular hypokinesis; 10 to 12, moderate left ventricular regional wall motion abnormalities; and greater than 12, severe left ventricular dysfunction.

Myocardial jeopardy index. This index was derived to identify myocardium at risk for the development of ischemia. It is used to evaluate the importance of a specific stenosis supplying an area of myocardium. Anterior myocardial jeopardy was present when a significant stenosis of the left main coronary artery or the left anterior descending artery occurred in conjunction with “viable myocardium” (that is, normal or only hypokinetic anterior left ventricular wall segments). Inferior jeopardy was present when a significant stenosis of the proximal or mid right coronary artery (or left main coronary artery or proximal circumflex artery in a left dominant system) occurred in conjunction with normal or only hypokinetic inferior wall segments.

Congestive heart failure (CHF) score. CHF was graded from 0 (no CHF) to 4 (severe CHF). This score is a count of four items: a history of CHF, the presence of pulmonary rales at baseline, the use of digitalis, and the use of diuretics at baseline. Functional impairment due to CHF was assessed with a score ranging from 0 (no CHF) to 5 (symptoms of severe CHF).

Statistical analysis. Statistical comparisons between groups were performed by use of t test analysis for continuous variables and \( \chi^2 \) analysis for discrete variables. Differences in the rates of sudden death between medically and surgically treated patients were tested by the log-rank test on the basis of the entire follow-up experience.\(^\text{32-34} \) Patients who died from other causes were included in the group at risk for sudden death up to the time of death.

Medically treated patients were those who did not undergo operation or those who underwent operation late in the study period. Surgically treated patients were those who had CABG during hospitalization at their enrolling institution, when 95% of patients have surgery. The number of days after enrollment within which 95% of the operations were performed was determined for each hospital (average time, 4 months). At each hospital, patients who had an operation during this period, or within 90 days if this period was less than 90 days, were excluded from the medical group. Survival time was counted from the average days to operation for the hospital where the patient was enrolled.\(^\text{35} \) (Eleven medically treated patients had sudden death within 30 days after this point; these patients were excluded.) Patients who died before this cutoff were excluded from the analysis. This type of analysis removes the unfair bias of early deaths attributed to medical therapy in patients who may have been assigned to undergo operation.

Cox regression analysis of the time to sudden cardiac death was used to adjust the comparison of medically and surgically treated patients for covariates. For the medically treated patients alone, five variables were selected by stepwise analysis of the time to sudden death from a group of 36 potential covariates (table 1). These variables and the coefficients estimated by the Cox analysis were used to construct a linear index of risk. The index was used to separate patients into quartiles ranging from low to high risk (see Appendix). Medically and surgically treated patients were compared within quartiles.

Both medically and surgically treated patients were included in a second stepwise Cox analysis using the same 36 covariates. The effect of operation on the time to sudden cardiac death was assessed by adding a variable for operation at the final step and testing that its coefficient was significantly different from zero. The relative risk of sudden death for patients undergoing CABG was estimated by \( \exp (b) \), where \( b \) is the coefficient estimated by the Cox analysis for the therapy covariate.\(^\text{32} \)

Results

Comparison of patients suffering sudden cardiac death with those alive at follow-up. There were 13,476 patients

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Scoring</th>
<th>Coefficient</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional impairment due to CHF</td>
<td>0–4</td>
<td>.4012</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Number of diseased vessels</td>
<td>0–3</td>
<td>.7341</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>LV score</td>
<td>5–30</td>
<td>.0843</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>% LM stenosis</td>
<td>0–100</td>
<td>.0088</td>
<td>.002</td>
</tr>
<tr>
<td>QRS duration</td>
<td>0–20</td>
<td>.0875</td>
<td>.002</td>
</tr>
</tbody>
</table>

\( \text{LM} = \) left main coronary artery; \( \text{LV} = \) left ventricular.

\(^\text{a}\)Constant, \(-3.0544\).
with significant CAD, operable vessels, and no significant valvular heart disease. Subsequent sudden cardiac death occurred in 452 of these patients (3.4%). In 313 patients (70%), the deaths were witnessed. The 452 deaths account for 26% of the 1725 deaths that occurred in the 13,476 patients during a mean follow-up of 4.6 years (figure 1). In addition to the 452 patients who suffered sudden cardiac death, 978 patients died of cardiac causes but not suddenly, and 295 patients died of noncardiac causes.

Selected baseline characteristics of the 452 patients with subsequent sudden cardiac death and the patients alive at the most recent follow-up are compared in table 2. The 12 baseline variables that were significantly different between patients alive at most recent follow-up and those suffering sudden cardiac death fell into three groups: (1) Clinical variables — impairment due to left ventricular failure (p < .0001), antiarrhythmic therapy (p = .005), symptoms of a cardiac arrhythmia (p = .009), concurrent illnesses (including diabetes mellitus, cerebrovascular or peripheral vascular disease, hypertension, or chronic pulmonary disease) (p = .024), unstable angina (p = .035), and male sex (p = .049). (2) Resting electrocardiographic variables — QRS duration (p < .0001), ventricular premature beats on the resting electrocardiogram (p = .005), any arrhythmia on the resting electrocardiogram (p = .009), and ST segment depression (p = .012). (3) Angiographic variables — abnormal left ventricular score with more severe regional wall motion abnormalities (p < .0001) and a greater number of vessels involved (p < .0001).

Effect of operation on sudden cardiac death. Of the 13,476 patients, 7216 (54%) underwent CABG; 6260 (46%) were treated medically. In most patients, allocation to the surgically or medically treated group was at the discretion of the primary physician and not by random assignment. During follow-up, sudden cardiac death occurred in 452 (3.4%) of the 13,476 patients. The surgically treated group had a significant reduction in incidence of sudden cardiac death. Subsequent sudden cardiac death occurred in 323 (5.2%) of the 6260 medically treated patients and in 129 (1.8%) of the 7216 surgically treated patients (table 3). The 5 year survival free of sudden death for medically treated patients was 94 ± 0.3%, and that for surgically treated patients was 98 ± 0.2% (p < .0001).

In addition to the reduction in sudden cardiac death in the surgically treated patients, there was also a reduction in nonsudden cardiac death (table 3). The 5 year incidence of nonsudden cardiac death was 9.6% for medically treated patients and 5.3% for surgically treated patients (p < .0001). The relative risk of sudden death within 5 years in the medically treated group compared with that in the surgically treated group (medical mortality divided by surgical mortality) was 2.94. There was also an increased relative risk of nonsudden cardiac death within 5 years, but it was of less magnitude — 1.91. The relative risk of noncardiac death within 5 years in the medically treated group compared with that in the surgically treated group was 0.88.

The effect of CABG on sudden cardiac death was analyzed in patients with witnessed and those with unwitnessed sudden cardiac death to determine whether there was a differential effect in these two groups. For witnessed sudden death, the 5 year survival free of sudden death was 99 ± 0.1% for surgically treated patients and 96 ± 0.3% for medically treated patients. Results were similar for patients suffering unwitnessed death, in whom the 5 year survival free of nonsudden death was 99 ± 0.1% for surgically treated patients and 98 ± 0.2% for medically treated patients.

The effect of CABG on reduction in sudden cardiac death was dependent on the patient subset analyzed. In patients at low risk for the development of sudden cardiac death (for example, one- or two-vessel disease and no CHF), although there was a statistically significant difference, actual differences in incidence of sudden death at 5 years of follow-up between the medically and surgically treated groups (figure 2, A and B) were too small to be of clinical help. Among the patients with three-vessel disease and no CHF there was both a statistically significant and a clinical difference: 98% of patients treated surgically had not suffered sudden cardiac death, whereas 92% of the patients treated medically had not suffered sudden cardiac death (figure 2, C). The biggest effect of CABG, however, was noted in patients with two- or three-vessel disease and a history of CHF (figure 3, A and B). In
patients with three-vessel disease and a history of CHF, 91% of the patients treated surgically were alive, whereas 69% of the patients treated medically were alive.

Cox survival analysis. Data on all variables (see Appendix) were available for 6250 surgically treated patients and 5258 medically treated patients. These 11,508 patients were analyzed to assess the incidence of sudden cardiac death and the effect of CABG on sudden cardiac death. Patients were separated into quartiles based on the risk of sudden cardiac death as determined by Cox survival analysis. In each quartile, cumulative survival curves were then computed for medically and surgically treated patients (figure 4). The difference in the incidence of sudden cardiac death between the medically and surgically treated patients increased with the risk quartile. In the lowest-risk quartile, the incidence of sudden cardiac death at 5 years of follow-up was similar for the medically (1%) and surgically (0%) treated patients (p = .08). In the

<table>
<thead>
<tr>
<th>TABLE 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparison of baseline characteristics of 452 patients who suffered sudden cardiac death and those of the 11,751 patients alive at follow-up</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Alive (n = 5217)</th>
<th>Dead (n = 323)</th>
<th>Alive (n = 6534)</th>
<th>Dead (n = 129)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>4382 (84)</td>
<td>287 (89)</td>
<td>5548 (85)</td>
<td>116 (90)</td>
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<tr>
<td>Prior myocardial infarction</td>
<td>3245 (62)</td>
<td>247 (76)</td>
<td>3496 (54)</td>
<td>99 (77)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1704 (33)</td>
<td>113 (36)</td>
<td>2259 (35)</td>
<td>54 (43)</td>
</tr>
<tr>
<td>History of cardiac arrest</td>
<td>291 (6)</td>
<td>28 (9)</td>
<td>287 (4)</td>
<td>18 (14)</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>1076 (21)</td>
<td>81 (25)</td>
<td>2724 (42)</td>
<td>53 (41)</td>
</tr>
<tr>
<td>Canadian heart class III or IV angina</td>
<td>1556 (30)</td>
<td>133 (41)</td>
<td>3923 (60)</td>
<td>72 (56)</td>
</tr>
<tr>
<td>CHF score ≥3</td>
<td>218 (4)</td>
<td>94 (29)</td>
<td>221 (3)</td>
<td>19 (15)</td>
</tr>
<tr>
<td>Moderate-to-severe left ventricular impairment</td>
<td>204 (4)</td>
<td>78 (24)</td>
<td>177 (3)</td>
<td>22 (17)</td>
</tr>
<tr>
<td>Drugs at baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiarrhythmics</td>
<td>535 (10)</td>
<td>66 (20)</td>
<td>548 (8)</td>
<td>32 (25)</td>
</tr>
<tr>
<td>Nitrates</td>
<td>2583 (50)</td>
<td>166 (51)</td>
<td>3983 (61)</td>
<td>70 (54)</td>
</tr>
<tr>
<td>β-Adrenergic blockers</td>
<td>2399 (46)</td>
<td>116 (36)</td>
<td>3920 (60)</td>
<td>61 (47)</td>
</tr>
<tr>
<td>Digitalis</td>
<td>787 (15)</td>
<td>128 (40)</td>
<td>876 (13)</td>
<td>38 (29)</td>
</tr>
<tr>
<td>Baseline electrocardiographic abnormalities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST segment depression</td>
<td>481 (9)</td>
<td>65 (20)</td>
<td>1001 (15)</td>
<td>35 (27)</td>
</tr>
<tr>
<td>QRS duration</td>
<td>380 (7)</td>
<td>55 (17)</td>
<td>526 (8)</td>
<td>22 (17)</td>
</tr>
<tr>
<td>Any arrhythmia on baseline electrocardiogram</td>
<td>594 (11)</td>
<td>63 (20)</td>
<td>754 (12)</td>
<td>27 (21)</td>
</tr>
<tr>
<td>CAD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One vessel</td>
<td>2173 (42)</td>
<td>42 (13)</td>
<td>1141 (17)</td>
<td>9 (7)</td>
</tr>
<tr>
<td>Two vessel</td>
<td>1716 (33)</td>
<td>99 (31)</td>
<td>2133 (33)</td>
<td>30 (23)</td>
</tr>
<tr>
<td>Three vessel</td>
<td>1299 (25)</td>
<td>181 (56)</td>
<td>3257 (50)</td>
<td>90 (70)</td>
</tr>
<tr>
<td>Left main coronary artery stenosed ≥50%</td>
<td>194 (4)</td>
<td>40 (12)</td>
<td>993 (15)</td>
<td>31 (24)</td>
</tr>
<tr>
<td>Proximal left anterior descending artery stenosed ≥70%</td>
<td>1363 (26)</td>
<td>137 (42)</td>
<td>3032 (46)</td>
<td>73 (57)</td>
</tr>
<tr>
<td>Proximal right coronary artery stenosed ≥70%</td>
<td>1569 (30)</td>
<td>150 (47)</td>
<td>2704 (42)</td>
<td>74 (57)</td>
</tr>
<tr>
<td>Proximal circumflex artery stenosed ≥70%</td>
<td>715 (14)</td>
<td>92 (28)</td>
<td>1604 (25)</td>
<td>39 (30)</td>
</tr>
<tr>
<td>Ventricular function</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate or severe cardiomegaly on chest roentgenogram</td>
<td>192 (4)</td>
<td>60 (19)</td>
<td>190 (3)</td>
<td>16 (12)</td>
</tr>
<tr>
<td>Ejection fraction &lt;0.50</td>
<td>1169 (22)</td>
<td>157 (49)</td>
<td>1137 (17)</td>
<td>58 (45)</td>
</tr>
<tr>
<td>Left ventricular wall score ≥10</td>
<td>1708 (33)</td>
<td>224 (69)</td>
<td>1781 (28)</td>
<td>77 (60)</td>
</tr>
<tr>
<td>Myocardial jeopardy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior</td>
<td>1311 (25)</td>
<td>54 (17)</td>
<td>2073 (32)</td>
<td>27 (21)</td>
</tr>
<tr>
<td>Inferior</td>
<td>1082 (21)</td>
<td>59 (18)</td>
<td>1117 (17)</td>
<td>31 (24)</td>
</tr>
<tr>
<td>Both</td>
<td>625 (12)</td>
<td>45 (14)</td>
<td>2122 (33)</td>
<td>25 (19)</td>
</tr>
<tr>
<td>Proximal vessel CAD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One vessel</td>
<td>2036 (39)</td>
<td>94 (29)</td>
<td>2389 (37)</td>
<td>43 (33)</td>
</tr>
<tr>
<td>Two vessel</td>
<td>619 (12)</td>
<td>91 (28)</td>
<td>1705 (26)</td>
<td>30 (23)</td>
</tr>
<tr>
<td>Three vessel</td>
<td>181 (3)</td>
<td>45 (14)</td>
<td>878 (13)</td>
<td>35 (27)</td>
</tr>
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</table>
TABLE 3
Comparison of incidences of sudden cardiac, nonsudden cardiac, and noncardiac death in 13,476 medically and surgically treated patients

<table>
<thead>
<tr>
<th>Group</th>
<th>Medical</th>
<th>Surgical</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Sudden death</td>
<td>323</td>
<td>5.2</td>
<td>129</td>
</tr>
<tr>
<td>Nonsudden cardiac death</td>
<td>598</td>
<td>9.6</td>
<td>380</td>
</tr>
<tr>
<td>Noncardiac death</td>
<td>122</td>
<td>1.9</td>
<td>173</td>
</tr>
<tr>
<td>Alive at last follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5 yr</td>
<td>2,709</td>
<td>43.3</td>
<td>3,054</td>
</tr>
<tr>
<td>&gt;5 yr</td>
<td>2,508</td>
<td>40.1</td>
<td>3,480</td>
</tr>
<tr>
<td>Total</td>
<td>6,260</td>
<td></td>
<td>7,216</td>
</tr>
</tbody>
</table>

highest-risk quartile, the incidence of sudden cardiac death was 16% for medically treated patients and 5% for surgically treated patients (p < .0001).

A second Cox survival analysis was done to assess the individual effect of CABG or medical therapy on outcome. For both medically and surgically treated patients, nine baseline variables were significant at the p < .01 level in the stepwise analysis. These included functional impairment due to CHF (p < .0001), left ventricular wall motion score (p < .0001), number of diseased vessels (p < .0001), QRS duration (p < .0001), antiarrhythmic therapy (p = .005), myocardial jeopardy index (p = .006), any arrhythmia on the electrocardiogram (p = .009), ventricular ectopy on the resting electrocardiogram (p = .006), and ST segment depression on the electrocardiogram (p = .01). Three other variables — unstable angina, associated noncardiac illnesses, and male sex — were statistically significant at the p < .05 level. Even in the presence of these factors, surgical therapy had an independent effect on sudden cardiac death (p < .0001). The relative risk of dying for the medically treated group compared with the surgically treated group was 3.31 (95% confidence interval, 2.35 to 4.65).

Discussion

Sudden cardiac death usually occurs in patients with latent or manifest CAD. In the large, prospectively followed patient population of this study, we confirmed that certain clinical, electrocardiographic, and angiographic features are associated with an increased incidence of sudden cardiac death. These factors, which include severe and extensive CAD, impaired

FIGURE 2. Percent of patients without sudden cardiac death in surgically treated group (A) compared with that in medically treated group (●). None of the patients had a history of CHF. A, Patients with one-vessel disease. B, Patients with two-vessel disease. C, Patients with three-vessel disease. The actual numbers of patients are given for each survival curve.

FIGURE 3. Percent of patients without sudden cardiac death in surgically treated group (A) compared with that in medically treated group (●). All of the patients had a history of CHF. A, Patients with two-vessel disease. B, Patients with three-vessel disease. The actual numbers of patients are given for each survival curve.
left ventricular function, and ST segment depression and ventricular ectopy on the resting electrocardiogram, have been described in autopsy series of patients with acute infarction and in patients resuscitated after cardiac arrest.6-10, 13, 15, 17, 18, 35 Although the overall incidence of sudden cardiac death in this patient population was low (3.4%), a particularly high-risk quartile of patients could be identified. In this group, the incidence of sudden cardiac death in the medically treated patients was 16% during the 5 year follow-up. In this high-risk quartile, unmeasured variables (for example, ambulatory monitoring, electrophysiologic evaluation, functional testing, and specific details about antiarrhythmic drug therapy, including drug dosage and drug levels) that were not routinely obtained in patients in CASS may have been of significant additional value. The extent to which these variables could further help to identify a smaller group of very high-risk patients within this population is unknown.

A more important finding in this patient population was that CABG is associated with a significantly decreased incidence of sudden cardiac death. Although there was a decreased incidence of all cardiac deaths in surgically treated patients, the reduction was most striking for sudden cardiac death. For the entire group of patients, the relative risk of dying suddenly in the medical group compared with the surgical group was 2.94. The relative risk of nonsudden cardiac death was less at 1.91 in the medically compared with the surgically treated group.

It must be remembered that this is an analysis of observational data, and biases associated with unknown variables could not be evaluated. There could, therefore, be other reasons for differences in survival independent of CABG or medical therapy. In the specific subsets of symptomatic high-risk patients with a history of CHF and operable two- or three-vessel disease, CABG was associated with an independent beneficial effect. In these patients, the relative risk of dying for the medically treated group compared with the surgically treated group was 3.31 (95% confidence interval, 2.35 to 4.65). According to previous studies, the greatest overall benefit from CABG for survival is demonstrated in the patients at highest risk.31, 36-39 Our data indicate that a reduction in sudden cardiac death contributes to the benefit of CABG. This has important implications for patients at very high risk, such as those with three-vessel disease and a history of CHF, in whom medical therapy is associated with a 31% incidence of sudden cardiac death during 5 years whereas surgical therapy is associated with a 9% incidence. For the large group of patients with CAD, however, the incidence of sudden cardiac death is still relatively low. This may reflect the fact that patients with sudden death as their initial presentation of CAD never survived the episode and therefore were never enrolled in the CASS study.

The analysis of observational data in this large series of prospectively studied patients does not replace a randomized trial. Some important information was not routinely available, including details of the antiarrhythmic drugs used, the drug levels obtained, and Holter monitoring. In addition, statistical techniques can consider only measured variables; other unmeasured characteristics may contribute to the outcome. Although we are mindful of this fact, surgical treatment seems to reduce the incidence of sudden cardiac death independently in patients with symptomatic multivessel disease and diminished left ventricular function.

Another finding of this analysis is broader in scope and deals with the mechanism of sudden cardiac death, which is most commonly secondary to a ventricular arrhythmia.16, 21, 22 Patients with structural heart disease probably have an underlying chronic vulnerability.
to electrical instability.\textsuperscript{25, 26, 40} In addition, an acute event is required to initiate the arrhythmia.

The underlying pathologic abnormalities that result in ventricular dysfunction with fibrosis and dilatation provide the potential electrophysiologic substrate for the chronic predisposition to electrical instability. The acute event may be ischemic.\textsuperscript{7, 41-44} In patients with moderate CAD and normal left ventricular function, arrhythmias associated with transient additional ischemia may be well tolerated. In patients with severe CAD and left ventricular dysfunction, transient additional ischemia may be poorly tolerated and could result in ventricular ectopy or a lethal ventricular arrhythmia.

Relief or reduction of ischemia by CABG may have been the underlying reason for the decrease in sudden cardiac death in our surgically treated patients. In these patients, a reasonable hypothesis is that the relief of ischemia by CABG may have reduced or eliminated the acute precipitating or triggering event and thereby decreased the incidence of sudden cardiac death.

The role of operation in the prevention of sudden cardiac death remains to be determined. The incidence of sudden cardiac death in the large population of patients with CAD is low. Efforts must continue to identify patients at significantly increased risk. In patients at very high risk for sudden cardiac death (for example, those with out-of-hospital cardiac arrest), surgical therapy may offer considerable promise. In other subsets (for example, patients with three-vessel disease and left ventricular impairment), surgical intervention may also be considered in an effort to decrease the incidence of subsequent sudden cardiac death.

Appendix

Baseline variables included in the Cox stepwise survival analyses of sudden cardiac death were sex; history of hypertension, diabetes, myocardial infarction, or cardiac arrest; symptoms of rhythm disturbance; angina; unstable angina; severity of angina; use of antiarrhythmic drugs, \( \beta \)-adrenergic blockers, digitalis, or diuretics; right or left coronary dominance; percentage of stenosis of the left main coronary artery or of the proximal left anterior descending artery; electrocardiographic evidence of premature ventricular contraction or of infarction; QRS duration; electrocardiographic evidence of any abnormality or of arrhythmia; Q waves; T wave abnormality; ST depression; ST elevation; left ventricular score\textsuperscript{29, 31}; presence of aneurysm; number of diseased vessels; amount of myocardium at jeopardy; number of operable vessels; age; history of CHF; impairment due to CHF; CHF score; number of noncardiac illnesses; and occupation.

The variables selected by use of data from medically treated patients only are given in table 1. The risk index was obtained by multiplying each covariate by its coefficient, and the resulting five numbers were summed. The constant 3.0554 was subtracted to normalize the equation so that an average patient in this population had a risk index equal to zero. The quartiles of risk were determined by the cutpoints 0.55, 0.18, and 0.78.

The fit of the Cox model was tested by restricting the data set to a randomly selected two-thirds of the total population. A stepwise Cox survival analysis was used on this subset to construct a linear index of risk on the basis of the selected covariates. The remaining one-third of the population was separated into quintiles on the basis of the derived risk index, and the Cox model estimate of the survival curve during 7 years was estimated for each quintile. In each quintile, the estimate was calculated by use of the average value of the model covariates in that quintile. The Cox model estimate in each quintile was within a 95% confidence band for the corresponding life table estimate.\textsuperscript{34} This was evidence that the Cox proportional-hazards model is an appropriate model for the observed data.

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