A Benchmark for Evaluating Innovative Treatment of Left Main Coronary Disease

Joseph F. Sabik, III, MD; Eugene H. Blackstone, MD; Michael Firstenberg, MD; Bruce W. Lytle, MD

Background—Left main trunk stenosis (≥50%) has traditionally been treated with coronary artery bypass grafting. Improvements in coronary stents have led some to advocate percutaneous coronary intervention. To provide a benchmark of outcomes against which percutaneous coronary intervention may be compared, we (1) assessed survival and freedom from coronary re-intervention after coronary artery bypass grafting in these patients and (2) identified their risk factors.

Methods and Results—From 1971 to 1998, the first 1000 primary coronary artery bypass grafting patients (n=26 927) were followed every 5 years. Of these, 3803 had left main trunk stenosis ≥50%. A multivariable, nonproportional hazards, time-related analysis was performed to model survival and freedom from coronary re-intervention (percutaneous coronary intervention or reoperation) and to identify their risk factors. Survival at 30 days, 1, 5, 10, 15, and 20 years was 97.6%, 93.6%, 83%, 64%, 44%, and 28%, respectively, and freedom from coronary re-intervention was 99.7%, 98.9%, 96.6%, 89%, 76%, and 61%, respectively. Worse left ventricular function (P<0.0001), diabetes (P<0.0001), hypertension (P<0.001), peripheral arterial disease (P=0.0002), smoking (P<0.0001), and elevated triglycerides (P=0.01) decreased survival, and younger age (P<0.0001), elevated triglycerides (P=0.005), and incomplete revascularization (P=0.003) increased coronary re-intervention. Internal thoracic artery grafting of the left anterior descending improved survival and decreased coronary re-intervention.

Conclusions—This study provides a 20-year outcome benchmark for surgical treatment of left main trunk disease. It indicates that simple comparisons of new treatments are inadequate without risk adjustment. Risk factor adjustment should be used when comparing coronary artery bypass grafting with current and future treatment innovations and when selecting the best treatment strategy for individual patients. (Circulation. 2007;116[suppl I]:I-232–I-239.)

Key Words: coronary disease ♦ surgery ♦ revascularization ♦ angioplasty ♦ risk factors

Ever since the randomized studies of the 1970s and 1980s that compared medical therapy with surgical revascularization for patients with chronic stable angina and coronary artery disease, important left main trunk stenosis has been treated with coronary artery bypass grafting (CABG). With recent advances in percutaneous catheter–based therapies of coronary artery disease, such as drug-eluting stents and periprocedural antiplatelet drugs, advocates have suggested that percutaneous therapy of left main trunk stenosis may be as effective as surgical revascularization.1,2 To provide a benchmark of surgical revascularization outcomes against which percutaneous coronary intervention (PCI) and future innovations may be compared, we determined long-term survival and freedom from coronary re-intervention after CABG in patients with important left main trunk stenosis, and identified patient and operative factors associated with long-term mortality and likelihood of subsequent coronary intervention.

Patients and Methods

Patients
From 1971 to 1998, 48 758 patients underwent primary isolated CABG at Cleveland Clinic. The first 1000 consecutive patients of each year (elective, urgent, or emergent) were actively followed every 5 years (n=26 927). A total of 3803 had left main trunk stenosis ≥50%, and they comprise the study population (Table 1). Patient, operative, and follow-up variables were obtained from the Cardiovascular Information Registry, which has been approved for use in research by the Institutional Review Board, with patient consent waived.

Mean follow-up for survival was 8.2±6.7 years, with 2294 patients followed ≥5 years, 1288±10 years, 622±15 years, and 237±20 years. Mean follow-up for re-intervention was 7.5±6.0 years, with 2239 patients followed ≥5 years, 1162±10 years, 440±15 years, and 130±20 years. One hundred and three (2.7%) were lost to follow-up. Total follow-up was 30 200 patient-years for survival and 27 618 patient-years for re-intervention.

Study End Points
End points of the study were all-cause mortality and first coronary re-intervention (either PCI or reoperative CABG) for recurrent
TABLE 1. Baseline Patient Characteristics (n=3803)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%) or Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demography</td>
<td></td>
</tr>
<tr>
<td>Age (years, mean±SD)</td>
<td>62±10</td>
</tr>
<tr>
<td>Male</td>
<td>3081 (81)</td>
</tr>
<tr>
<td>Noncardiac comorbidity</td>
<td></td>
</tr>
<tr>
<td>Diabetes (medically treated)</td>
<td>573 (16)</td>
</tr>
<tr>
<td>History of smoking</td>
<td>1810 (51)</td>
</tr>
<tr>
<td>Laboratory values (mean±SD)</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>239±55</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>150±43</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>38±11</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>181±111</td>
</tr>
<tr>
<td>Blood urea nitrogen (mg/dL)</td>
<td>19.4±10.5</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.3±0.6</td>
</tr>
<tr>
<td>Symptoms and clinical status</td>
<td></td>
</tr>
<tr>
<td>NYHA class</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>635 (17)</td>
</tr>
<tr>
<td>II</td>
<td>1404 (37)</td>
</tr>
<tr>
<td>III</td>
<td>394 (10)</td>
</tr>
<tr>
<td>IV</td>
<td>1368 (36)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (0.05)</td>
</tr>
<tr>
<td>Emergency operation</td>
<td>175/3696* (4.7)</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>3 (0.08)</td>
</tr>
<tr>
<td>On IABP</td>
<td>13 (0.34)</td>
</tr>
<tr>
<td>On ECMO</td>
<td>1 (0.03)</td>
</tr>
<tr>
<td>On LVAD</td>
<td>2 (0.05)</td>
</tr>
<tr>
<td>Cardiac comorbidity</td>
<td></td>
</tr>
<tr>
<td>Left ventricular dysfunction</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1811 (50)</td>
</tr>
<tr>
<td>Mild</td>
<td>640 (26)</td>
</tr>
<tr>
<td>Moderate</td>
<td>572 (16)</td>
</tr>
<tr>
<td>Severe</td>
<td>275 (8)</td>
</tr>
<tr>
<td>Unknown</td>
<td>205 (5)</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>1822 (48)</td>
</tr>
<tr>
<td>MI within 72 hours</td>
<td>25 (0.66)</td>
</tr>
<tr>
<td>Coronary artery disease (≥50% stenosis)</td>
<td></td>
</tr>
<tr>
<td>LMT</td>
<td>3803 (100)</td>
</tr>
<tr>
<td>LAD</td>
<td>3115 (82)</td>
</tr>
<tr>
<td>LCx</td>
<td>2746 (72)</td>
</tr>
<tr>
<td>RCA</td>
<td>3110 (82)</td>
</tr>
<tr>
<td>No. of diseased systems (≥50% stenosis)</td>
<td></td>
</tr>
<tr>
<td>0 (LMT stenosis only)</td>
<td>143 (4)</td>
</tr>
<tr>
<td>1</td>
<td>483 (13)</td>
</tr>
<tr>
<td>2</td>
<td>1043 (27)</td>
</tr>
<tr>
<td>3</td>
<td>2143 (56)</td>
</tr>
<tr>
<td>Operative procedure</td>
<td></td>
</tr>
<tr>
<td>Intra-aortic balloon pump</td>
<td>89 (2)</td>
</tr>
<tr>
<td>Incomplete revascularization</td>
<td>812 (21)</td>
</tr>
<tr>
<td>Single ITA grafting</td>
<td>1921 (51)</td>
</tr>
<tr>
<td>Bilateral ITA grafting</td>
<td>335 (8)</td>
</tr>
<tr>
<td>ITA graft to</td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>2086 (55)</td>
</tr>
<tr>
<td>LCx</td>
<td>361 (10)</td>
</tr>
<tr>
<td>RCA</td>
<td>57 (2)</td>
</tr>
</tbody>
</table>

*Data available.

ECMO indicates extracorporeal membrane oxygenation; HDL, high-density lipoprotein; IABP, intra-aortic balloon pump; ITA, internal thoracic artery; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; LDL, low-density lipoprotein; LMT, left main trunk; NYHA, New York Heart Association; RCA, right coronary artery; and SD, standard deviation.

myocardial ischemia. Noncoronary heart reoperations or combined CABG and noncoronary procedures, such as valve, aortic, or ventricular aneurysm surgery, were ignored (n=37).

Variables and Definitions

Values of patient characteristics and operative techniques used in the multivariable analyses were obtained at primary CABG. Left ventricular function was graded as normal (ejection fraction [EF]=60%), mild dysfunction (EF 40% to 59%), moderate dysfunction (EF 25% to 39%), and severe dysfunction (EF <25%).

A coronary artery system was considered importantly stenotic if it contained a ≥50%-diameter obstruction. Incomplete revascularization was defined as failure to graft any system containing ≥50% stenosis, or both left anterior descending coronary artery (LAD) and circumflex systems for ≥50% left main trunk stenosis. Experience was expressed as the continuous interval from January 1, 1971, to date of operation. This variable is used to account for patient factors, operative techniques, and medical therapies that may have changed over time and affected survival, but could not be included in our analysis.

Statistical Methods

Analysis

Distributions of time from primary CABG to either death or first coronary reintervention were estimated parametrically using multiphase hazard methodology. This involved determining the number of hazard phases, appropriate form of equation for each phase, and parameters characterizing distribution of times to either death or first coronary reintervention. (For additional details, see http://www.clevelandclinic.org/heartcenter/hazard.)

To identify which patient characteristics and operative techniques (see Appendix) were associated with death and coronary reintervention, multivariable analyses were performed in the hazard-function domain. Bootstrap aggregation (bagging) using the median rule was used for variable selection, including linearizing transformations of continuous and ordinal variables. Interactions among statistically significant variables were also sought by bagging. The probability-value criterion for retention of variables was 0.05.

Presentation

Categorical variables are summarized as frequencies and percentages and continuous variables as means and standard deviations. Asymmetric confidence limits are equivalent to ±1 SE (68%).

Statement of Responsibility

The authors had full access to the data and take full responsibility for their integrity. All authors have read and agree to the manuscript as written.

Results

Mortality

Non-Risk-Adjusted Survival

A total of 98 patients (2.6%, confidence limits 2.3% to 2.9%) died in-hospital, and hospital mortality was consistent across time (Figure 1), despite an important increase in patient risk factors (supplemental Figure 1, available online at http://circ.ahajournals.org). An additional 1491 patients died after hospital discharge. Non–risk-adjusted survival was 97.6%, 93.6%, 83%, 64%, 44%, and 28% at 1 month, 1, 5, 10, 15, and 20 years, respectively (Figure 2A). A 2-phase hazard model was identified, consisting of a short, rapidly declining early phase followed by a long, slow-rising late phase that began ∼1 year after CABG (Figure 2B); 201 patients died during the early phase and 1388 during the late phase.
Risk Factors for Death
Multivariable analysis identified 5 general categories of factors associated with likelihood of dying: patient demography, noncardiac comorbidity, cardiac comorbidity, primary operative procedure, and experience (Table 2). Because the early hazard phase was small and late hazard phase large, factors influencing the late phase had a greater impact on likelihood of death.

Patient Demography
Older (P<0.0001) and larger (P<0.0001) patients had decreased long-term survival.

Noncardiac Comorbidity
History of smoking (P<0.001), peripheral arterial disease (P=0.0002), hypertension (P=0.001), insulin-treated diabetes (P<0.0001), and elevated serum creatinine (P<0.0001) and triglycerides (P=0.02) were associated with decreased survival.
Cardiac Comorbidity
Worse left ventricular function ($P<0.0001$), previous myocardial infarction ($P=0.0002$), and inferior left ventricular wall motion abnormality ($P=0.02$) were associated with decreased long-term survival. Preoperative atrial fibrillation ($P=0.009$) also decreased survival.

Operative Procedure
Internal thoracic artery (ITA) grafting of the LAD, diagonal, or LAD and diagonal coronary arteries ($P=0.003$) improved late survival. We did not demonstrate a further improvement in survival with bilateral ITA grafting. Use of ITA grafting increased from about 20% during the 1970s to about 80% thereafter (supplemental Figure 2).

Experience
Because prevalence of patient risk factors increased with time, but early mortality remained the same, patients operated on later in the series had better risk-adjusted survival ($P<0.0001$). In addition, the apparent worse long-term survival of patients operated on in recent decades (Figure 3A) was accounted for completely by change in prevalence of patient risk factors (Figure 3B).

Interactions
Four interactions between variables muted the individual effects of the 2 variables on survival. Three of these muted negative effects: older age and inferior left ventricular wall motion abnormality ($P=0.004$; ie, less than an additive impact on survival), older age and insulin-treated diabetes ($P=0.003$), and a history of smoking and insulin-treated diabetes ($P=0.0001$). An interaction that muted the positive effect of a variable on survival was older age and ITA grafting of the diagonal coronary artery ($P=0.02$; ie, grafting was less effective in older patients than younger ones).

Reintervention
Non–Risk-Adjusted Freedom From Reintervention
A total of 419 patients underwent coronary reintervention, percutaneous in 146 and reoperation in 273. Non–risk-adjusted freedom from reintervention was 99.7%, 98.9%, 96.6%, 89%, 76%, and 61% at 1 month, 1, 5, 10, 15, and 20 years, respectively (Figure 4A). A 2-phase hazard model was identified, consisting of a short, rapidly declining early phase followed by a long, slow-rising late phase that began ≈1 1/2 years after CABG (Figure 4B). Thirty-eight patients underwent reintervention during the early phase and 381 during the late phase.

Risk Factors for Reintervention
As with mortality, multivariable analysis identified 5 general categories of factors associated with likelihood of undergoing coronary reintervention: patient demography, noncardiac comorbidity, cardiac comorbidity, primary operative procedure, and experience (Table 3). Because the early hazard phase was small and late phase large, factors influencing the late phase had a greater impact on likelihood of reintervention.

Patient Demography
Older patients were less likely than younger ones to undergo coronary reintervention ($P<0.0001$).

Noncardiac Comorbidity
History of smoking ($P=0.007$) was associated with lower likelihood of coronary reintervention. Increased hematocrit ($P=0.02$) and serum triglycerides ($P=0.005$) were associated with increased likelihood of reintervention.

Cardiac Comorbidity
Isolated stenosis of the left main trunk ($P=0.002$) and coronary artery codominance ($P=0.01$) both decreased the likelihood of coronary reintervention, as did a previous myocardial infarction ($P=0.04$) and inferior left ventricular wall motion abnormality ($P=0.005$). The more symptomatic a patient at primary operation, the greater was the risk of reintervention ($P=0.02$).
Operative Procedure
ITA grafting reduced the risk of coronary reintervention. Saphenous vein grafts to the LAD (P=0.001) and incomplete revascularization of the right coronary artery (P=0.003) increased the likelihood of reintervention. Patients operated on later in the series were less likely to undergo reintervention (P<0.0001).

Risk Prediction
Using the multivariable models for mortality and coronary reintervention (Tables 2 and 3), predictions can be generated for patient-specific values for risk factors. This is illustrated by simulating a high- and low-risk patient. The simulated high-risk patient has many of the risk factors associated with likelihood of reintervention or death, whereas the low-risk patient has few (Figure 5A and 5B).

Discussion
Background
Ever since the randomized studies comparing CABG with medical therapy in the 1970s and 1980s, surgical revascularization has been the standard of care for treating patients with important left main trunk stenosis. These studies found that 3-year mortality in patients undergoing CABG was less than one third (9% versus 31%) that of medically treated patients, and there was a 2-fold increase (13.3 versus 6.6 years) in median survival.6–9 Because of these findings, the consensus panel of The American College of Cardiology/American Heart Association 2004 Guideline Update for Coronary Artery Bypass Graft Surgery recommended that “CABG should be performed in patients...with significant left main coronary artery stenosis,” whether they are asymptomatic or have mild, stable, or unstable angina/non–ST-segment-elevation myocardial infarction.10

Recent improvements in PCI technology have led some to suggest that percutaneous intervention may be as effective as surgical revascularization in treating patients with left main trunk stenosis.1,2 Indeed, observational studies have demonstrated similar hospital mortality and early survival in such patients treated with either CABG or PCI. For example, at 1 year, Chiefflo and colleagues reported similar hospital mortality and better 1-year outcomes in 50 percutaneously treated patients versus 123 surgically revascularized ones.1 Although these studies were nonrandomized, they suggest
efficiency, and heart failure of grade 3 or higher are risk factors. Ellis and colleagues reported that older age, renal insufficiency, and coronary codominance, internal thoracic artery grafting of left anterior descending at primary CABG. Low-risk patient: 40-year-old male, normal left ventricular function, no comorbidities, internal thoracic artery grafting at primary CABG. Low-risk patient: 60-year-old male, mild angina at primary CABG, previous myocardial infarction, smoker, normal triglycerides, isolated left main trunk stenosis, coronary codominance, internal thoracic artery grafting of left anterior descending at primary CABG. Low-risk patient: 40-year-old male, normal left ventricular function, no comorbidities, internal thoracic artery grafting at primary CABG. B, Predicted freedom from coronary reintervention after primary isolated CABG for left main trunk stenosis: high- and low-risk patients. Solid lines represent parametric estimates enclosed within dashed 68% confidence limits (±1 SE). A, Predicted survival. High-risk patient: 70-year-old male, atrial fibrillation, severe left ventricular dysfunction, previous myocardial infarction, inferior left ventricular wall motion abnormality, smoker, hypertension, peripheral arterial disease, insulin-treated diabetes, elevated triglycerides, renal insufficiency, no internal thoracic artery grafting at primary CABG. Low-risk patient: 40-year-old male, normal left ventricular function, no comorbidities, internal thoracic artery grafting of left anterior descending at primary CABG. B, Predicted freedom from coronary reintervention after primary isolated CABG for left main trunk stenosis. In the Unprotected Left Main Trunk Intervention Multi-Center Assessment Registry, 1-year mortality was 40% in high-risk patients, but only 3.5% in low-risk patients. Lesion location (left main ostium, body, or distal/bifurcation) has also been shown to be an important factor in predicting outcomes after PCI. To better understand outcomes after surgical revascularization for left main trunk stenosis, we determined 20-year survival and freedom from coronary reintervention in such patients. To understand what patient and operative factors influence mortality and need or bias for coronary reintervention, we used parametric multivariable analysis. We chose this methodology in part because risk (hazard) varies with time after interventions, and different risk factors influence early versus late events (nonproportional hazards). In addition, this method can be used to generate risk predictions for individual patients based on their particular risk factors. Individual survival and reintervention predictions can be useful in informing patients of their expected long-term outcomes after surgery, as well as in identifying “surgical high-risk” patients who may benefit from PCI or other less invasive innovations.

**Principal Findings**

**Survival**

Survival after CABG was lower in our study cohort than reported for the general population of CABG patients. Sergeant and colleagues reported overall survival of a general population of patients undergoing CABG to be 97%, 92%, 81%, and 66%, at 1, 5, 10, and 15 years, respectively, almost 10% better at 5 years and >20% better at 15 years than what we observed in this study. Left main trunk stenosis has been demonstrated to be a risk factor for early mortality after coronary surgery, and the magnitude of its detrimental effect on long-term survival is demonstrated in the current study.

Both patient and operative factors influenced late mortality. Patient comorbidities, such as obesity, hypertension, insulin-treated diabetes, renal insufficiency, vascular disease, and greater left ventricular dysfunction, decreased late survival, whereas operative factors, such as ITA grafting of the LAD, improved it. These comorbidities are all known to negatively influence survival of the general population, and they therefore would be expected to negatively affect survival of patients after CABG. The benefit of ITA grafting versus saphenous vein grafting in prolonging survival after surgical revascularization is well documented.

**Reintervention**

Unadjusted overall freedom from coronary reintervention was similar in this series of patients to that reported in our

that in some patients with left main trunk stenosis, PCI may be as effective as surgical revascularization. They also suggest that a method to identify which patients derive greater benefit from one or the other therapy would be useful.

The importance of risk stratification in estimating outcomes of patients after either surgical or percutaneous therapy for left main trunk disease is beginning to be understood. Ellis and colleagues reported that older age, renal insufficiency, and heart failure of grade 3 or higher are risk factors for hospital death after CABG in patients with left main trunk stenosis. They estimated that 2% to 3% of patients are at high (>20%) risk and an additional 7% at moderate (6%) risk. Hospital death was uncommon (<2%) in the remaining patients. Similarly, poorer 3-year survival (40%) was found in patients with more than one of the following characteristics: renal dysfunction, advanced age, or chronic obstructive pulmonary disease. The importance of risk stratification has also been demonstrated for percutaneous therapy of left main trunk stenosis. In the Unprotected Left Main Trunk Intervention
previous study of a general population of CABG patients.19 This is not surprising, considering that left main trunk stenosis was not identified in that study as a factor influencing need or bias for reintervention.

Similar to survival, both patient and operative factors influenced the likelihood of undergoing coronary reintervention. Some patient comorbidities, such as history of smoking, myocardial infarction, and older age, decreased the likelihood of coronary reintervention. One explanation for this is that these comorbidities increase the risk associated with reintervention and therefore may bias treatment away from reintervention. Other patient factors, such as higher triglycerides, higher hematocrit, and symptom status, increased the likelihood of reintervention. Elevated triglycerides are a risk factor for arteriosclerosis and may increase the need for reintervention by accelerating arteriosclerosis in both coronary arteries and bypass grafts. Higher hematocrits are present in healthy patients, and they may be markers of patients who likely survive a long time after CABG and thus are more likely to undergo reintervention. Patients who were more symptomatic at their primary revascularization were more likely to undergo coronary reintervention. These patients may have a lower ischemia symptom threshold and therefore are more likely to present with recurrent angina leading to reintervention. ITA grafting of the LAD decreased the likelihood of coronary reintervention. Because of their resistance to arteriosclerosis, ITA grafts are more likely to remain patent than saphenous vein grafts.20 They therefore should be more effective in preventing recurrent myocardial ischemia than saphenous vein grafts. However, another reason ITA grafting may be associated with reduced coronary reintervention is that surgeons may be reluctant to reintervene in patients with patent ITA grafts, either for fear of damaging them or because they believe that as long as the ITA remains patent, the patient is protected against ischemic events.

Incomplete revascularization of the right coronary artery was associated with increased likelihood of coronary reintervention. These patients are more likely to continue to have ischemia after surgical revascularization and require reintervention to relieve their symptoms.

Risk Prediction
There was a wide range in expected long-term outcomes for patients with left main trunk stenosis after surgical revascularization, as illustrated in Figure 5 by the large differences in survival and freedom from reintervention in simulated high- and low-risk patients. Interestingly, as observed by us and other investigators as well,14 patient comorbidities had opposite effects on survival and freedom from reintervention. Thus, multiple comorbidities resulted in decreased predicted survival but greater predicted freedom from reintervention. This may be attributable to bias against reintervening on high-risk patients. ITA grafting was beneficial for both survival and freedom from reintervention.

Strengths and Limitations
Three decades of patients who underwent coronary revascularization were included in this study. The applicability of the findings from such a long study period may be questioned, because patient case mix may change and advances in surgical and medical therapy of coronary disease may negate the findings. However, these concerns do not appear to be important in this study. Although case mix and surgical therapy changed with time, and unadjusted long-term survival decreased with later date of surgery, adjusted long-term survival was similar for all 3 decades of patients (see supplemental Appendix). Also, this long period of study enabled us to evaluate the effect on mortality and reintervention of different surgical techniques that were common in one period of the study but not another, or that required passage of time to reveal their advantages or disadvantages.

The analysis of reintervention may be biased, because this is a study of the clinical practice of coronary reintervention after primary surgery, not of the actual need for coronary reintervention. Because many factors go into the decision to proceed with coronary reintervention, including patient comorbidities, amount of ischemic myocardium, operative risk of reintervention, and benefits of the procedure, our findings on its occurrence and risk factors may be biased.

Values of patient factors used in this analysis were obtained at the time of primary coronary surgery. We were unable to determine how postoperative changes in these patient factors, such as hypertension and hyperlipidemia control, influenced survival and coronary reintervention.

Implications
Coronary artery bypass grafting for left main trunk disease is a proven therapy, and this study provides a 20-year outcome benchmark for current and future alternatives. It indicates that simple observational comparisons are treacherous, because risk factors, particularly those representing noncardiac morbidity, influence outcomes. It also suggests that a composite end point of death or reintervention may be suboptimal, because risk factors for these may exert opposing influence. We have also identified a cohort of patients with multiple risk factors that have high operative risk and poor late survival; these patients may benefit most from PCI and may constitute the ideal target population for a randomized trial. Finally, the present study emphasizes the wide spectrum of outcomes according to risk factors. This strongly suggests that a quantitative method for individual patients’ risk assessment would be beneficial in clinical decision-making and advising patients, as originally suggested in the first guidelines for coronary artery bypass surgery.21

Appendix

Variables Considered in Analyses

Demography
Sex, age (years), height (cm), weight (kg), body surface area (m²), body mass index (kg·m⁻²).

Symptoms
New York Heart Association functional class (I, II, III, IV), emergency operation.

Left Ventricular Function
Left ventricular function (normal; mild, moderate, and severe dysfunction), previous myocardial infarction, segmental left ventricular wall motion abnormalities (septal, anterior, inferior, lateral, apical, basilar, none).
Cardiac Comorbidity
Family history of coronary artery disease, atrial fibrillation, complete heart block.

Noncardiac Comorbidity
History of cigarette smoking, peripheral arterial disease, carotid stenosis, hypertension, diabetes (diet-controlled, oral- and insulin-treated), renal insufficiency.

Preoperative Laboratory Values
Total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides, creatinine, blood urea nitrogen, hematocrit.

Coronary Artery Anatomy and Stenosis
Dominance (left, right, codominant), number of coronary artery systems with stenosis ≥50% (one, two, three), left main trunk stenosis (any, ≥50% stenosis, ≥70% stenosis), left anterior descending stenosis (any, ≥50% stenosis, ≥70% stenosis), circumflex stenosis (any, ≥50% stenosis, ≥70% stenosis), right coronary artery stenosis (any, ≥50% stenosis, ≥70% stenosis).

Procedure
Complete revascularization; incomplete revascularization of left anterior descending, circumflex, or right coronary artery system; any internal thoracic artery grafting; internal thoracic artery graft to left anterior descending, circumflex, or right coronary artery; any saphenous vein grafting; saphenous vein graft to left anterior descending, circumflex, or right coronary artery.

Experience
Date of operation (expressed as interval in years from January 1, 1971, to date of operation).

Postoperative Management
Intra-aortic balloon pump.

Disclosures
None.

References
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Appendix: Applicability of Past Data to Contemporary Patients

The purpose of this e-appendix is to demonstrate applicability to present-day patients of findings we obtained from studying 3 decades of patients with left main trunk stenosis who underwent surgical revascularization. The value of observations obtained over a long period is often questioned because patient risk factors change with time and advances occur in surgical and medical therapy. To assess whether these concerns are germane to the findings of this study, we determined the time trends in patient risk factors, surgical therapy (use of internal thoracic arteries [ITA] for revascularization), and survival.

As expected, the prevalence of risk factors increased with later date of operation (e-Figures 1A-D). Thus, patient age at operation, number of women, and patients with medically treated diabetes and worse left ventricular function all increased with time. Advances in surgical therapy over time occurred as well. ITA use increased with later date of operation: In the first decade of the study, ITA use was only about 20%, and in the last two decades, about 80% (e-Figure 2). The increase in risk factors and improvements in surgical therapy (ITA use) would be expected to affect long-term survival oppositely. We observed that unadjusted survival decreased with increasing decade of surgery, suggesting that increasing patient risk factors had a greater effect on survival than did improvements in surgical and medically therapy (manuscript Figure 3A).

In the paper, both patient risk factors and operative factors (ITA use) were included in a multivariable time-related analysis that was used to develop a survival prediction model. To account for patient factors, operative techniques, and medical therapies that may have changed over time and affected survival, but could not be included in our analysis, we used date of operation as a surrogate for them. Although it was statistically associated with mortality (later date of operation decreased long-term mortality), its effect was small and of no clinical importance. When the model was used to predict adjusted survival for a similar patient operated
on in 1970s, 1980s, and 1990s, outcomes were similar for all 3 decades (manuscript Figure 3B). This finding has two important implications. First, it suggests that patient and operative factors influencing survival have been included in our model. Second, risk-adjusted survival after coronary artery bypass grafting for left main disease has not changed over the last 3 decades.
e-Figures 1A–D: Time trends of characteristics of patients with left main trunk stenosis underlying coronary artery bypass grafting (CABG). Closed circles are yearly percentages (mean for age), and solid lines represent trend lines.

1A: Mean age of patients by year of operation.
1B: Percentage of women by year of operation.
1C: Percentage of patients with pharmacologically treated diabetes mellitus by year of operation.
1D: Percentage of patients with moderate or severe left ventricular dysfunction by year of operation.
**e-Figure 2**: Percentage of patients receiving internal thoracic artery grafting by year of operation.