

# Comparison of Coronary Artery Bypass Grafting Versus Medical Therapy on Long-Term Outcome in Patients With Ischemic Cardiomyopathy (A 25-Year Experience from the Duke Cardiovascular Disease Databank)

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In this observational treatment comparison in a single center over 25 years, we sought to assess long-term outcomes of coronary artery bypass surgery (CABG) or medical therapy in patients with heart failure, coronary artery disease, and left ventricular systolic dysfunction. The benefit of CABG compared with medical therapy alone in these patients is a source of continuing clinical debate. This analysis considered all patients with New York Heart Association class II or greater symptoms, 1 or more epicardial coronary vessels with a  $\geq 75\%$  stenosis, and a left ventricular ejection fraction  $< 40\%$  who underwent an initial cardiac catheterization at Duke University Medical Center from 1969 to 1994. Patients were classified into the medical therapy group ( $n = 1,052$ ) or CABG group ( $n = 339$ ) depending on which therapy they received within 30 days of catheterization. Cardiovascular event and mortality follow-up commenced on

the day of CABG, or at catheterization plus 8 days (the mean time to CABG) for the medical therapy arm. A Cox proportional-hazards model was employed to adjust for differences in baseline characteristics. In the first 30 days from baseline, there was an interaction between treatment strategy and number of diseased vessels. Unadjusted, event-free, and adjusted survival strongly favored CABG over medical therapy after 30 days to  $> 10$  years regardless of the extent of coronary disease ( $p < 0.001$ ). Thus, regardless of the severity of coronary disease, heart failure symptoms, or ventricular dysfunction, CABG provides extended event-free and survival advantage over medical therapy alone in patients with an ischemic cardiomyopathy. ©2002 by Excerpta Medica, Inc.

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**T**he first experience of coronary artery bypass surgery (CABG) in patients with heart failure was associated with high mortality rates. This led to the reluctance to approach these patients for surgical revascularization. The randomized controlled clinical trials comparing CABG with medical therapy excluded patients with significant left ventricular dysfunction or clinical heart failure. Therefore, our knowledge base must depend on large registries and clinical databases that can compare favorably with randomized trials.<sup>1</sup> Because of the continued clinical uncertainty about the benefit of a surgical revascularization strategy in patients with heart failure, we designed this study to assess the long-term outcomes of CABG or medical therapy in patients with left ven-

tricular systolic dysfunction, clinical heart failure, and coronary artery disease.

## METHODS

**Patient population:** The study population comprised a subset of the 54,498 patients who underwent cardiac catheterization between July 1969 and February 1994 at Duke University Medical Center. Patient inclusion stopped in 1994 to allow time for long-term follow-up. Of these patients, the study group included those undergoing their first cardiac catheterization at Duke University in this time period who had  $\geq 75\%$  diameter stenosis in 1 of the 3 major epicardial vessels and an ejection fraction  $< 40\%$  with New York Heart Association class  $\geq II$  symptoms. The study population therefore comprised 1,454 patients with left ventricular systolic dysfunction and clinical heart failure of ischemic etiology.

**Data collection and management:** Pertinent baseline variables from the patients' history, physical examination, laboratory studies, chest x-ray, and 12-lead electrocardiogram were collected prospectively on standard forms as part of the patient care process and stored in the Duke Cardiovascular Disease Databank.

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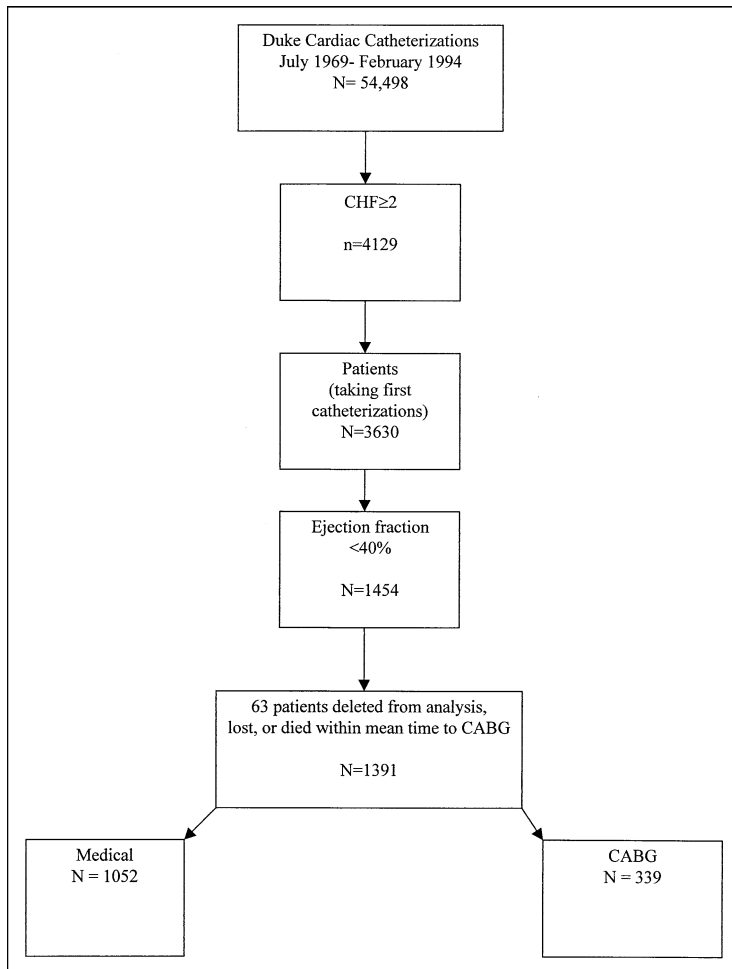


FIGURE 1. Patient selection. CHF = congestive heart failure.

Results of the cardiac catheterization and procedural details of the CABG procedures were also collected prospectively. Definitions of important prognostic variables have been published.<sup>2,3</sup>

**Cardiac catheterization:** Significant coronary stenosis was defined as at least 1 major coronary artery or branch narrowed  $\geq 75\%$  in diameter. Arterial lesions were graded by visual consensus of at least 2 experienced observers on an ordinal scale of 0, 10%, 25%, 50%, 75%, 95%, or 100% luminal stenosis. Coronary artery disease was classified as 1-, 2-, or 3-vessel disease. Left ventriculography was performed using multiple oblique and angulated projections. Biplane ventriculography was conducted in 96% of patients. Ejection fraction was calculated using the modified area-length method.<sup>4</sup> Mitral regurgitation was visually quantified on an ordinal scale from 0 to 4.

**Coronary revascularization and medical therapy:** Standard cardiac surgical and anesthesia techniques used at Duke during the period of the study have been described.<sup>3</sup> Over the duration of the study, operative techniques improved significantly. Anesthesia techniques have improved, with increased specialization, newer drugs, better understanding of the physiology of extracorporeal perfusion, and the introduction of

intraoperative transesophageal echocardiography. Surgery has improved through better myocardial preservation (cardioplegia, cardiopulmonary bypass hypothermia, and topical myocardial cooling), better surgical technique, and increasing use of left internal mammary grafts by 1985. Medical therapy became more aggressive over the study period with the greater use of low-dose  $\beta$  blockers, angiotensin-converting enzyme inhibitors, aspirin, and lipid-lowering agents.

**Follow-up procedures and outcome ascertainment:** The ascertainment of clinical events was conducted by research associates who contacted patients at 6 months and 1 year after presentation, and then annually. Follow-up began on the date of revascularization for CABG patients and the date of catheterization plus the mean time to CABG (8 days) for medical patients. The day of catheterization plus the mean time to CABG was chosen as the beginning of the follow-up period for the medical group in an attempt to equalize the 2 arms by removing early deaths from the medical arm. Without this definition, patients who died within a few days of the catheterization but who may have been scheduled to undergo revascularization would have become part of the medical therapy arm, unfairly penalizing that treatment strategy. To address this problem, the 63 medical patients who died or were lost to follow-up before the mean time to bypass surgery (8 days) in this population were deleted from the analysis. This left a

final analysis population of 1,391 patients: 1,052 patients classified as treated medically and 339 as treated with CABG (Figure 1).

Self-administered questionnaires were the predominant follow-up tools. Telephone contact was reserved for patients who did not return questionnaires. Survival status was complete for 97% of patients. Patient survival status was confirmed by the National Death Index and maintained by the National Center for Health Statistics.<sup>5</sup> The primary end point for the study was all-cause mortality. The combined secondary end point was time to a major event (death, myocardial infarction, or any revascularization procedure).

**Data analysis:** DESCRIPTIVE STATISTICS: Baseline characteristics were summarized in terms of the median and the 25th and 75th percentiles for continuous measures and percentages for discrete measures. Kaplan-Meier survival estimates<sup>6</sup> were used to describe patterns of all-cause mortality by treatment group. Because of a significant interaction between treatment and number of diseased vessels within the first 30 days from baseline (date of treatment), curves and estimates are presented by treatment for 1-, 2-, and 3-vessel disease for the first 30 days. Estimates for

>30 days from baseline (conditional on surviving at least 30 days) are presented by treatment.

Because this was not a randomized trial, patients were designated as CABG patients if they underwent surgery within 30 days of their initial catheterization. In this manner, we assumed an intention to treat with CABG based on the diagnostic catheterization. This, of course, implies that if a patient was not treated with CABG within 30 days of diagnosis, then the physician's intention was to treat the patient with medical therapy. For CABG patients, the days until the event was calculated beginning at the date of the surgery. For patients in the medical arm, the timing began at the date of catheterization plus 8 days. If medical patients were subsequently crossed over to the CABG arm (i.e., they underwent CABG >30 days after catheterization), they remained in the medical treatment arm. All analyses are based on this implied intention-to-treat basis.

**ADJUSTED SURVIVAL ANALYSIS:** Because these 2 treatment strategies were not randomly assigned, we expected important prognostic characteristics to be unequally distributed between the 2 groups, creating differences in survival due simply to differences in baseline prognostic factors rather than the treatment itself. To control for these differences, we used an established Cox proportional-hazards model of long-term survival developed from a larger population of Duke patients treated for coronary artery disease between 1984 to 1990.<sup>2</sup> This model produced a set of key baseline and diagnostic factors that were predictive of survival: age, sex, acuity of presentation, congestive heart failure, chest pain, extracardiac vascular disease, comorbidity (renal insufficiency, chronic obstructive lung disease, cancer excluding skin, liver disease), year of catheterization, coronary disease severity, left ventricular ejection fraction, mitral insufficiency, and a propensity score (to adjust for factors favoring CABG over medical therapy). Disease severity was then estimated for all patients in our study using the baseline medical risk, or hazard score, from the model of the larger population. This hazard score was calculated by first multiplying each factor with its corresponding Cox regression coefficient and then summing these products. After adjustment for disease severity, the treatment effect could be better evaluated.

Some potentially important characteristics of our study population were criteria for exclusion from the larger population from which the baseline hazard score was originally formulated.<sup>2</sup> These variables (presence of significant [ $\geq 75\%$ ] left main narrowing, mitral regurgitation of grade 3 or 4, and previous CABG) were included in the adjusted survival models in addition to the hazard score. Year of catheterization was also included, because the population with congestive heart failure spanned a longer time period than the larger population. Thus, all adjusted treatment effects were calculated using Cox proportional-hazards models that included baseline medical hazard, presence of left main disease, presence of mitral insufficiency, previous CABG, year of catheterization,

and finally, the intended treatment (medical vs CABG).

Because early procedural mortality creates a pattern of crossing survival curves, the proportional-hazards assumptions of the Cox model are violated. To account for this in making treatment comparisons, hazard ratios for treatment are presented for 2 different time intervals. These intervals are baseline to 30 days and >30 days from baseline (conditional on surviving 30 days). Two separate Cox proportional-hazards models were used to obtain these hazard ratios. To obtain hazard ratios for survival in the first 30 days from baseline, a Cox model was developed on the population-truncating survival in the first 30 days. Hazard ratios for survival >30 days from baseline (conditional on surviving 30 days) were obtained by developing a Cox model on the subset of the population surviving at least 30 days from baseline.

## RESULTS

**Baseline characteristics:** Table 1 lists baseline clinical characteristics of the 1,411 patients. Many of the baseline characteristics were similar in both groups. The median age in the medically treated group was 62 years, and 25% of the patients were aged >68, versus a median age of 63 in the CABG group, with 25% of the patients aged >68. Other important baseline clinical characteristics that were similar included the percentage of women, smoking history, hypertension, diabetes mellitus, hyperlipidemia, peripheral vascular disease, and cerebral vascular disease. In addition, the heart failure class was similarly distributed in the 2 groups, although a history of myocardial infarction was higher in the CABG group (88% vs 77%).

**Angiographic characteristics:** Table 1 also lists angiographic characteristics of patients treated with medical therapy versus CABG. The severity of diseased vessels was greater in the CABG group, as reflected by greater multivessel disease (87% vs 76%), a greater percentage of left main disease (18% vs 6%), and a greater percentage of proximal left anterior descending disease (48% vs 38%). In contrast, the degree of left ventricular dysfunction was greater in the medically treated group, with a median ejection fraction of 26% in the medically treated group, versus 29% in the surgically treated group. Furthermore, the degree of advanced mitral regurgitation (3+ or 4+) was 15% in the medically treated group versus 11% in the CABG group.

**Survival and event-free survival estimates by disease status:** The unadjusted survival analysis for the overall study cohort revealed a significant interaction between number of diseased vessels and treatment strategy within the first 30 days. For example, in patients with 1-vessel disease there was a survival benefit of medicine over CABG ( $p = 0.002$ ). For 2-vessel disease there was no significant difference between the medicine and CABG ( $p = 0.83$ ) treatment strategies. For 3-vessel disease there was a trend toward survival benefit of medicine over CABG ( $p = 0.05$ ). Event-free survival during the first 30 days favored medicine

TABLE 1 Baseline Characteristics		
	Medical Therapy (n = 1,068)	Bypass Surgery (n = 343)
Age (yrs)	62 (54, 68)	63 (56, 68)
Men	72%	73%
Cigarette smokers	68%	68%
Systemic hypertension	55%	56%
Diabetes mellitus	32%	34%
Hyperlipidemia	31%	25%
Previous myocardial infarction	77%	88%
Peripheral vascular disease	16%	14%
Cerebrovascular disease	12%	12%
S3 gallop	38%	36%
NYHA heart failure class		
II	34%	32%
III	36%	31%
IV	30%	37%
Angina pectoris	69%	69%
Unstable	46%	36%
Progressive	32%	37%
Stable	22%	27%
Number of narrowed coronary arteries		
1	24%	13%
2	25%	20%
3	51%	67%
Proximal LAD disease	38%	48%
Left main disease	6%	18%
Left ventricular ejection fraction	26% (20, 32)	29% (22, 34)
Mitral regurgitation $\geq$ +3	15%	11%

Values are expressed as medians (25th and 75th percentiles) for continuous measures, percentages for categorical measures.  
NYHA = New York Heart Association; LAD = left anterior descending.

TABLE 2 Selected Studies of CABG in Patient Cohorts With Left Ventricular Dysfunction and Heart Failure				
Study	No.	EF	Follow-up (mo)	Survival (%)
Spencer 1971 <sup>7</sup>	C 40	NR	10	C 63
Mundth 1971 <sup>8</sup>	C 40	NR	15	C 76
Solignac 1974 <sup>9</sup>	C 11	<30	36	C 36
Zubiate 1977 <sup>10</sup>	C 140	<20	NR	C >5yrs = 59
Tyras 1984 <sup>11</sup>	C 196	<40	51.6	C 5yrs = 76.2
Louie 1991 <sup>12</sup>	C 19	23	12.1	C 3yrs = 72
Magovern 1993 <sup>13</sup>	C 27	31	20	C 89
Dreyfus 1994 <sup>14</sup>	46	23	18	C 1 yr = 86.5, 2 yrs = 86.5

C = patients who underwent CABG; EF = ejection fraction; M = patients given medical therapy; NR = not reported.

over CABG for all degrees of diseased vessels ( $p < 0.001$ ).

From 30 days onward, conditional on surviving 30 days, the survival advantage favored CABG over medicine for all degrees of coronary disease severity ( $p < 0.001$ ). In addition, event-free survival favored bypass surgery over medicine in these patients ( $p < 0.001$ ).

**Adjusted survival analysis:** In the adjusted survival analysis, a similar interaction was seen between the number of diseased vessels and treatment strategy within the first 30 days from baseline. For 1-vessel disease the survival benefit of medicine over CABG was significant ( $p = 0.01$ ). For 2-vessel disease there was no significant difference between medicine and CABG ( $p = 0.36$ ). For 3-vessel disease there was a trend for survival benefit of medicine over CABG ( $p = 0.03$ ).

In the follow-up period  $>30$  days from baseline (conditional on surviving 30 days), the survival status of these patients strongly favored bypass surgery over medicine ( $p < 0.001$ ). A treatment interaction with the number of diseased vessels was not found.

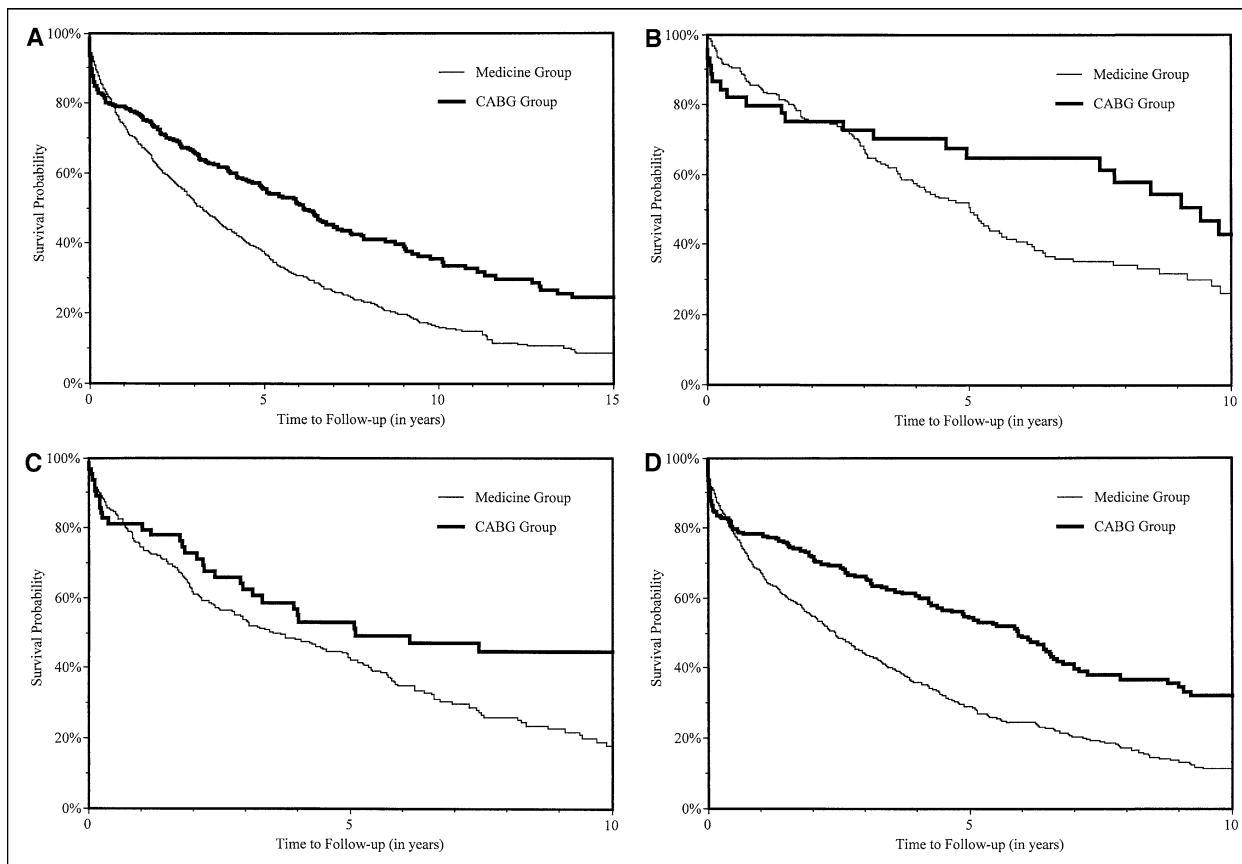
An adjusted Cox proportional-hazards ratio for CABG/medical therapy, ignoring the treatment interaction within the first 30 days and the violation of the proportional-hazards assumptions of the Cox model, was 0.50 (95% confidence interval 0.42 to 0.60).

## DISCUSSION

Although a number of observational series<sup>7-14</sup> have reported patient outcomes with coronary artery bypass grafting in patients with heart failure (Table 2), this study is the first large observational treatment comparison of the 25-year survival experience for CABG versus medical therapy in patients with coronary disease and clinical heart failure. The first major finding of this analysis is that regardless of the extent of coronary disease, CABG carries a significant long-term unadjusted and adjusted survival advantage (Figures 2 and 3) and event-free survival advantage (Figure 4) over medical therapy beyond 30 days in patients with coronary artery disease, an ejection fraction of  $<40\%$ , and New York Heart Association class II to IV heart failure. Second, there appears to be an interaction between follow-up time, disease severity, and treatment strategy so that the advantage of CABG was not seen within the first 30 days; in fact, medical therapy conferred an

advantage over bypass surgery during that period, particularly in patients with 1- and 3-vessel disease. This increased risk within the first 30 days from baseline is most likely explained by the well-known early procedural risk incurred by CABG. Beyond 30 days, however, the relation was quite strongly in favor of CABG as the preferred treatment strategy with respect to survival. Third, the treatment strategy, as a determinant of survival beyond 30 days, conferred independent information on the likelihood of mortality in this patient population.

The combination of severe coronary artery disease and advanced left ventricular function carries a dismal outlook with medical therapy. Some studies have assessed the 5-year survival rate of patients with heart failure caused by ischemic cardiomyopathy to be as low as 59%.<sup>15</sup> Despite this extremely poor overall



**FIGURE 2.** Unadjusted survival curves for CABG versus medical therapy. **A**, overall; **B**, 1-vessel disease; **C**, 2-vessel disease; **D**, 3-vessel disease.

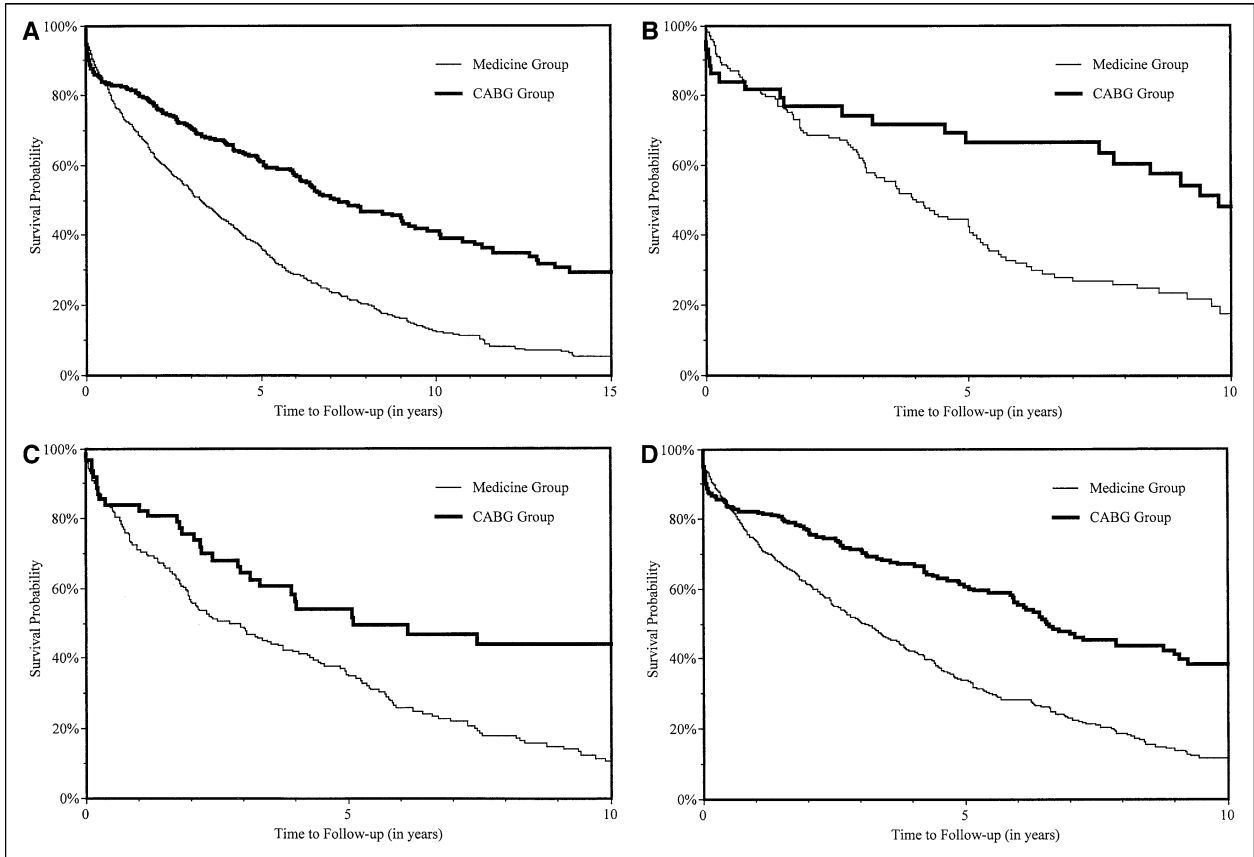
prognosis, cardiologists have traditionally been reluctant to refer these patients for CABG. Similarly, surgeons have been reluctant to accept such patients given the increased operative risk, although this reluctance has decreased over time. The concerns raised by physicians are that the increased operative risk in this setting may not offset the potential benefits with limited chance of improving prognosis.

Most large multicenter trials of CABG have purposely excluded patients with advanced left ventricular dysfunction. The randomized Coronary Artery Surgery Study (CASS) did not include patients with ejection fractions  $<35\%$ ,<sup>16</sup> and the European Coronary Surgery Study excluded patients with ejection fractions  $<50\%$ .<sup>17</sup> Recent recognition of the importance of stunned and hibernating myocardium has heightened interest in the possible partial reversal of ventricular dysfunction by improved coronary perfusion.<sup>18,19</sup>

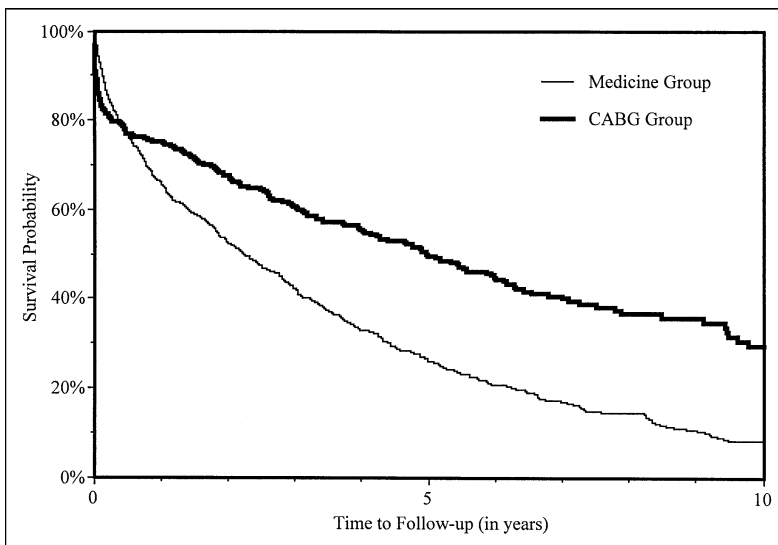
Furthermore, although cardiac transplantation remains a cornerstone of therapy for patients with significant coronary artery disease and decreased left ventricular function who meet appropriate criteria, the availability of donor organs is limiting.<sup>20</sup> Although the 1-year survival rate for heart transplantation is approximately 90%, and most patients are satisfied with their lifestyle, the procedure is not without its disadvantages. Opportunistic infection, hypertension, compli-

cations of steroid therapy, and the potential for chronic graft coronary disease are problems that increase with time. Because of these and other problems,  $>50\%$  of heart transplant patients do not survive beyond 9 years.<sup>21</sup> In addition, recent pharmacologic approaches have shown an attenuated effect on survival in patients with heart failure secondary to ischemic etiology.<sup>22,23</sup> Thus, strategies such as CABG to complement pharmacologic treatment in patients with clinical heart failure and coronary disease need to be explored further as suitable options.

**Adjusted survival and event-free survival:** In our study, after an initial increased risk in the first 30 days with the surgical strategy, the survival advantage becomes apparent and remains clinically important throughout the duration of follow-up (Table 3). This analysis does not reveal a loss of effect with the bypass strategy seen in randomized trials because of accelerated graft disease at 7 to 10 years.<sup>24</sup> This reflects the powerful impact that left ventricular dysfunction and clinical symptoms of heart failure have on prognosis. The adjusted survival data suggest that patients with graftable disease and an expected survival of at least 30 days would benefit from the surgical strategy. The overall adjusted analysis ignoring the violation of proportional hazards suggests that all patients meeting the entry criteria for the study would



**FIGURE 3.** Adjusted survival curves for CABG versus medical therapy. *A*, overall; *B*, 1-vessel disease; *C*, 2-vessel disease; *D*, 3-vessel disease.



**FIGURE 4.** Event-free survival curves for CABG versus medical therapy.

have improved long-term survival regardless of their left ventricular ejection fraction, heart failure functional class, coronary artery disease severity, or anginal status (Figure 5). Additionally, event-free survival favored the CABG strategy for long-term success. Patients with heart failure who survive a myocardial infarction still face higher rates of morbidity and mor-

tality.<sup>25</sup> Thus, the finding that event-free survival also favors surgery is also encouraging.

**Treatment strategy and survival time interaction:** There was an important interaction between treatment strategy and survival time. Patients undergoing CABG had an increased early risk of dying. This reflects, almost in its entirety, the perioperative risk of surgery in these high-risk patients. Most of the risk of dying was concentrated in the first 30 days. Over time, the relation demonstrates a survival advantage for all degrees of disease severity with the revascularization strategy. Given this increase in short-term risk, patients with end-stage heart failure having advanced symptoms resistant to aggressive medical measures, and who are not likely to survive several months,

may not be suitable candidates for the surgical strategy.

Although this nonrandom comparison suggests an advantage of CABG over medical therapy, the limitations of a single-site investigation and unadjusted covariates such as graftability of vessels and improvement in medical therapy make a randomized compar-

TABLE 3 Adjusted Cox Proportional-hazards Survival Estimates*		
	Medical Therapy	CABG
1-yr survival	74%	83%
5-yr survival	37%	61%
10-yr survival	13%	42%

\*p < 0.0001, for all comparisons. Weighted average of 1-, 2-, and 3-vessel disease used to calculate the 1-, 5-, and 10-year survival estimates.

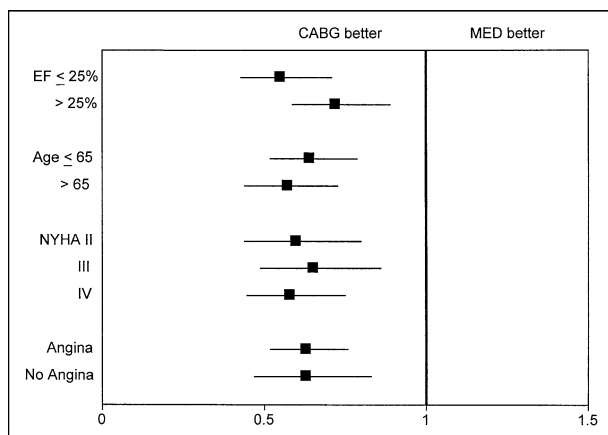


FIGURE 5. Hazard ratios (95% confidence interval) for mortality in subgroups defined by baseline characteristics. EF = ejection fraction; MED = medical; NYHA = New York Heart Association.

ison necessary before changing treatment guidelines. The randomized comparison of CABG and medical therapy versus medical therapy alone, the Surgical Treatment for Ischemic Heart (STICH) failure trial, is now ongoing.

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