

Coronary Artery Disease in Diabetic Patients With Lower-Extremity Arterial Disease: Disease Characteristics and Survival

A report from the Coronary Artery Surgery Study (CASS) registry

JOSHUA I. BARZILAY, MD
RICHARD A. KRONMAL, PHD
VERA BITTNER, MD

ELAINE EAKER, SCD
CAMPBELL EVANS, MSC
ERIC D. FOSTER, MD

OBJECTIVE — Patients who have diabetes and lower-extremity arterial disease (LEAD) are at an increased risk of dying from coronary artery disease (CAD). This study was undertaken to: 1) define the clinical and arteriographic factors associated with LEAD among diabetic patients; 2) determine the long-term survival and predictors of mortality of diabetic patients with LEAD, compared to those without LEAD; and 3) determine if the presence of LEAD is an independent risk factor for mortality among diabetic patients with CAD.

RESEARCH DESIGN AND METHODS — A total of 263 diabetic patients from the Coronary Artery Surgery Study (CASS) registry with LEAD, who were ≥ 50 years of age, and who had arteriographically proven CAD, were identified and followed for a mean of 12.8 years. A total of 1,349 comparably aged diabetic patients from the CASS registry with CAD and no evidence of LEAD were followed for an equivalent period of time.

RESULTS — Compared with diabetic patients without LEAD, diabetic patients with LEAD were characterized by the presence of cerebrovascular disease, a high rate of current smoking, elevated systolic blood pressure, high grades of angina pectoris, and digitalis use. Severity of epicardial CAD and extent of CAD were not independent predictors of the presence of LEAD. On follow-up, diabetic patients with LEAD had significantly higher mortality (mostly cardiovascular) than diabetic patients without LEAD, with a median survival of 8.1 and 10.9 years, respectively. On multivariate analysis, age, the number of significantly narrowed coronary arteries, and the presence of left ventricular dysfunction predicted mortality in both subsets of diabetic patients. Among all the diabetic patients with CAD, the presence of LEAD was an independent risk factor for mortality.

CONCLUSIONS — Diabetic patients with LEAD have a higher mortality rate (mostly cardiovascular) than diabetic patients without LEAD, despite no apparent anatomic differences in the severity and extent of CAD. This suggests that factors associated with the presence of LEAD, other than the anatomy of the coronary circulation, may play a role in determining survival among diabetic patients with LEAD and CAD.

From Department of Medicine (J.I.B.), Division of Endocrinology, Emory University School of Medicine, Atlanta, Georgia; the Coordinating Center for Collaborative Studies in Coronary Artery Surgery (R.A.K.), University of Washington, Seattle, Washington; the Department of Medicine (V.B.), Division of Cardiovascular Disease, University of Alabama at Birmingham, Birmingham, Alabama; the Division of Surveillance and Epidemiology (E.E.), Epidemiology Program Office, Centers for Disease Control, Atlanta, Georgia; the Department of Social Statistics (C.E.), University of Southampton, Southampton, U.K.; and the Division of Cardiothoracic Surgery (E.D.F.), Albany Medical College, Albany, New York.

Address correspondence and reprint requests to Joshua Barzilay, MD, Kaiser Permanente of Georgia, 200 Crescent Center Parkway, Tucker, GA 30084. E-mail joshua.barzilay@kp.org.

Received for publication 18 October 1996 and accepted in revised form 29 May 1997.

Abbreviations: CABG, coronary artery bypass graft; CAD, coronary artery disease; CASS, Coronary Artery Surgery Study; CHF, congestive heart failure; CVA, cerebrovascular accident; IMA, internal mammary artery; LEAD, lower-extremity arterial disease; LV, left ventricular; PTCA, percutaneous transluminal coronary angioplasty; TIA, transient ischemic attack.

Patients with lower-extremity arterial disease (LEAD) have a 10-year reduction in life expectancy and a doubling of mortality, compared with individuals without LEAD (1–4). The primary cause of death is coronary artery disease (CAD), which accounts for more than 50% of mortality (5–11). Diabetic patients in particular are prone to the development of LEAD and concomitant CAD. In the Framingham Study, for example, diabetic patients were found to have a four- to sixfold increased prevalence of LEAD, compared with nondiabetic patients, and a two- to fourfold increased mortality rate, largely due to CAD (12–14). More information regarding the nature of CAD in this setting and its prognosis would therefore be of interest.

The following study, based on a cohort of the Coronary Artery Surgery Study (CASS) registry, was undertaken to clarify several points regarding CAD in diabetic patients with concomitant LEAD. The first was to describe the anatomic extent of CAD, compared with diabetic patients from CASS without evidence of LEAD, and to define the clinical and arteriographic factors independently associated with the presence of LEAD among diabetic patients. The second was to determine the survival over an average of almost 13 years of follow-up, compared with diabetic patients without LEAD, and to determine the factors predictive of mortality. The last was to determine if the presence of LEAD among diabetic patients with CAD was an independent risk factor for mortality.

RESEARCH DESIGN AND METHODS

The Coronary Artery Surgery Study (CASS) is a multi-institutional research program consisting of a randomized trial of medical and surgical treatments of CAD and a registry of patients undergoing diagnostic coronary arteriography for the presence of suspected coronary artery disease. Details of the design, quality

control, and data entry have been previously described (15). Between 1 July 1974 and 31 May 1979, a total of 24,959 patients (men, $n = 18,894$; women, $n = 6,065$) who underwent cardiac arteriography at 15 cooperating clinical sites were enrolled in the registry. The registry served as a repository for information on all consecutive patients who underwent coronary arteriography for the study and treatment of CAD at the participating sites. The registry was also the source from which candidates for the randomized trial were identified.

Only patients in whom the primary indication for coronary arteriography was suspected or proved CAD were included in the registry. Patients with normal coronary arteries were included in the registry. Patients studied because of the suspicion of CAD who were found to have another form of heart disease were excluded. Those who underwent coronary arteriography for the evaluation of other conditions, such as valvular heart disease, cardiomyopathies, and congenital heart disease, were also excluded even if subsequent evidence showed that CAD was a major clinical problem.

Enrollment in the registry was contingent on obtaining the patient's signed informed consent. Exclusion criteria included: inaccessibility to follow-up, substantial language barrier, referral to a CASS site expressly for surgery with coronary arteriography performed elsewhere, cardiomyopathy not due to ischemic heart disease, idiopathic hypertrophic subaortic stenosis, and significant valvular heart disease. Of the eligible subjects, 4% declined to participate in the study and an additional 2% were not enrolled for a number of reasons, such as medical emergency or unavailability of study personnel. Thus, 94% of eligible patients were enrolled.

Baseline history, physical, and laboratory information were collected from each patient at the time of entry into CASS at the participating clinical sites and were transmitted to the Coordinating Center at the University of Washington. Angina was graded according to the classification of the Canadian Cardiovascular Society (16) with a category added for angina unrelated to exertion. Unstable angina was defined as a change in the pattern of chest pain within 2 months before entry into the study. History of myocardial infarction required that the patient had been informed by the physician of a definite infarct. A history of cerebrovascular accident (CVA) or transient ischemic attack (TIA) required evidence or

history of permanent or transient paralysis, respectively. Clinical variables related to left ventricular failure included a history of congestive heart failure (CHF) and the use of digitalis or diuretics.

More than 80% of the patients having arteriography in the registry for suspicion of CAD had chest pain as the predominant symptom. The rest had CHF, arrhythmia, noncardiac chest pain, fatigue, or were asymptomatic. Of those with angina pectoris, the majority had grades II and III. Unstable angina was present in ~50% of those with definite angina and in 30% of those with probable angina.

Disease of the proximal coronary vessels was defined by the presence on arteriogram of a lesion with at least 70% narrowing of the luminal diameter of the right coronary, left anterior descending coronary, or circumflex coronary artery. For the left main coronary artery, the threshold for disease was 50% obstruction. Left main coronary artery disease was classified as two-vessel disease if the coronary circulation was right-dominant (posterior descending artery arising from the right coronary artery) or as three-vessel disease if the coronary circulation was left-dominant (posterior descending artery originating from the left circumflex artery). As a measure of the extent and severity of CAD, the coronary vasculature was divided into 27 segments, and the total number of segments with narrowing of $\geq 50\%$ was tabulated.

Arteriography revealed that 12% of men and 40% of women in the registry had normal coronary arteries. An additional 9 and 15%, respectively, had mild-to-moderate degrees of angiographic coronary disease. Thus, 79 and 45% of all registry men and women, respectively, had significant CAD (one vessel, two vessel, and three vessel disease: 21, 25, and 34% in men and 17, 14, and 14% in women). Left main artery disease was diagnosed in 9% of men and 4% of women.

Left ventricular cine-angiography was carried out in the 30° right anterior oblique projection. Systolic wall motion of the five left ventricular wall segments (anterobasal, anterolateral, apical, diaphragmatic, and posterobasal) was scored as follows: normal = 1; moderate hypokinesia = 2; severe hypokinesia = 3; akinesia = 4; dyskinesia = 5; and aneurysm = 6. The left ventricular wall motion score (LV score) is the sum of the segmental scores. A score of 5 indicates normal ventricular function. A score of ≥ 15 implies severely disturbed ventricular

function and was encountered in 6% of registry participants; 47% of participants had normal LV wall motion. Ejection fraction was also calculated based on arteriography. An ejection fraction >0.5 occurred in 70.7% of the men and 85.5% of the women, whereas an ejection fraction of <0.3 occurred in 5.9% of the men and 2.6% of the women.

Special provisions were made during the recruitment phase for monitoring the interpretation of coronary arteriograms and the evaluation of ventricular motion. Techniques for measuring these variables were standardized and reviewed repeatedly at meetings of angiographers. Differences among angiographers in interpretation of percentage stenosis and the number of diseased vessels were low for good-quality films and diminished as the study progressed (17). By the end of enrollment, $<3\%$ of the original readings were deemed to be of inadequate quality, a level better than that reported in previous studies.

Assignment of patients to medical or surgical treatment in the registry was not randomized and was done on an individual basis by the treating physician. A number of dominant factors, however, were found to influence the assignment to surgery (18). These included the amount of myocardium believed to be at risk from lesions of the proximal vessels, the severity of angina, the number of operable lesions, changes in activity level, unstable angina, and the presence of left main artery obstruction or stenosis. The presence of LEAD did not influence the decision to operate.

Patient populations

Because the impact of diabetes on the prevalence of LEAD is greatest (in absolute terms) in older individuals (14,19,20), the present study is confined to individuals ≥ 50 years of age, most of whom would have had adult-onset diabetes.

There were a total of 12,538 patients in the CASS registry who were ≥ 50 years of age with at least one coronary segment that was occluded $\geq 50\%$. Of these, 1,612 (12.9%) were diabetic, as ascertained by patient self-report of insulin (19.4%) or oral hypoglycemic agent use (45.7%) or by a history of dietary intervention to control blood glucose (47.9%). Of these diabetic patients, 263 (16.3%) reported having pain in the calf muscles upon ambulation, which subsided with rest, having had prior vascular surgical repair, having been told of vascular disease in the past, or having

absent pedal pulses on examination at the time of entry into the registry.

For the first part of this study, the 263 diabetic patients with evidence of LEAD and the 1,349 diabetic patients without evidence of LEAD were studied. Descriptive clinical and arteriographic features were derived. Factors independently associated with the presence of LEAD were derived by multivariate analysis.

For the second part of this study, survival over an average of almost 13 years of follow-up was calculated for the two groups and compared. Factors predictive of survival were estimated using multivariate analysis. The effects of coronary artery bypass graft (CABG) surgery versus medical therapy on survival were examined also (details of the follow-up time calculations have been previously published [21]).

Follow-up

Clinical follow-up was obtained through 1991 in all patients for a mean of 12.8 years (range, 0 to 15.9 years; one patient dying on the day of surgery). Information was collected primarily by telephone interview, via mailed questionnaire, or through the use of the National Death Index (22). In the event of a patient's death, a detailed report of the circumstances was filed based on hospital records or based on telephone interviews with treating physicians or family members. Of the patients, <2% were lost to follow-up. Deaths were classified as either cardiac or noncardiac. Cardiac deaths included causes directly or indirectly related to heart disease or to sudden unexplained death (occurring within 1 h of the onset of symptoms and generally before the availability of medical care). Noncardiac disease included diseases related to atherosclerosis, but not related to the heart, or to diseases unrelated to atherosclerosis.

Statistical analysis

Comparisons of discrete variables were performed using a χ^2 test, and continuous variables by a two-sample *t* test. All *P* values were two-tailed. Logistic regression analysis was used to determine variables associated with LEAD among all the diabetic patients. Survival curves were calculated by the life-table method and compared by generalized Wilcoxon's test (23). A Cox proportional-hazards model (24) was used to determine independent predictors of mortality using the following variables, which have been found to be predictive of survival in patients with CAD from previous CASS

Table 1—Descriptive features of diabetic patients with CAD, ≥ 50 years of age, with or without concomitant LEAD

Characteristic	Diabetic patients with LEAD	Diabetic patients without LEAD
<i>n</i>	263	1,349
Age (years)	59.1 \pm 5.9	59.2 \pm 5.9
Sex (% male)	77.6	76.7
Race (% white)	97.0	96.5
Systolic blood pressure (mmHg)	138.6 \pm 23.4	134.6 \pm 21.1
Diastolic blood pressure (mmHg)	81.5 \pm 13.8	80.0 \pm 12.0
Cholesterol (mg%)	232.6 \pm 53.7	227.0 \pm 55.7
Family history of CAD (%)	44.1	40.2
Smoking status (%)		
Current	35.4	19.4
Former	45.2	46.8
Never	19.4	33.8
History (%)		
Prior myocardial infarction	45.9	47.2
Systemic hypertension	13.8	11.2
Left ventricular hypertrophy	4.4	4.6
Congestive heart failure	21.3	18.0
Cerebrovascular accident/ transient ischemic attack	14.1	3.8
Angina pectoris (%)		
No angina	7.6	12.6
Class I	1.1	3.4
Class II	16.0	20.8
Class III	38.8	34.7
Class IV	27.8	20.0
Nonexertional	8.7	8.5
Unstable angina (%)	41.8	36.9
Medications (%)		
Diuretics	37.9	34.6
Digitalis	34.7	26.8
Beta-blockers	50.0	49.7

Values are unadjusted for differences between groups.

studies: number of diseased epicardial vessels, number of coronary occlusions, LV score, presence or absence of valvular heart disease, left main coronary artery disease, smoking, hypertension, systolic and diastolic blood pressure, sex, age, history of previous myocardial infarction, and congestive heart failure. In addition, a treatment variable (surgical versus medical) was added.

RESULTS

Clinical and arteriographic variables

Baseline clinical variables for the diabetic patients with and without evidence of LEAD are shown in Table 1. These variables are descriptive and unadjusted for the many differences between the groups. Diabetic subjects with LEAD had a higher

prevalence of current smoking, prior CVA/TIA, higher grades of stable or unstable angina pectoris, higher systolic blood pressure, and digitalis use, compared with diabetic patients without evidence of LEAD. They did not differ from them with respect to age, sex, race, diastolic blood pressure, total cholesterol, family history of CAD, history of hypertension, CHF, diuretic or beta-blocker use, or hypoglycemic agent use.

Arteriographically, diabetic patients with LEAD had a high prevalence of multivessel epicardial disease that was slightly greater (unadjusted for other factors) than that found in diabetic patients without LEAD (Table 2). The diabetic patients with LEAD also had a high total number of coronary segments with at least 50% narrowing. There was, however, no difference when

Table 2—Angiographic features of diabetic patients with CAD, ≥ 50 years of age, with or without concomitant LEAD

Characteristic	Diabetic patients with LEAD	Diabetic patients without LEAD
n	263	1,349
Number of significantly narrowed coronary arteries (%)		
0	3.8	3.9
1	12.2	20.0
2	28.1	25.7
3	55.9	50.4
Number of coronary segments with $\geq 50\%$ diameter narrowing (%)		
1	4.9	8.8
2–5	48.7	50.7
6–10	42.2	36.7
11+	4.2	3.8
Degree of left main coronary artery stenosis (%)		
<30%	80.2	83.7
30–49%	6.5	4.2
50–69%	6.5	5.2
70–100%	6.8	6.9
Ejection fraction (mean \pm SD)	56.2 \pm 17.8	56.2 \pm 16.8
LV score (%)		
5	27.6	30.5
6–10	37.4	37.2
11–15	24.1	22.8
16+	10.9	9.5

Values are unadjusted for differences between groups.

compared with diabetic patients without LEAD. Likewise, there was no difference between the two groups with regard to the degree of left main coronary artery stenosis, ejection fraction, or LV score.

Factors independently associated with the presence of LEAD among the diabetic patients are listed in Table 3. Cerebrovascular disease, current smoking, elevated systolic blood pressure, high degrees of angina pectoris, and digitalis use were significantly associated with the presence of LEAD. The degree of epicardial coronary disease, the diffuseness of CAD lesions, and indexes of left ventricular dysfunction (ejection fraction and LV score) were not independently associated with the presence of LEAD.

Comparison of survival rates

On follow-up, diabetic patients with LEAD had higher mortality rates than diabetic patients without LEAD: by 37.4% at 5 years (32.7% mortality for those with LEAD vs. 23.8% for those without LEAD), by 29.9% at 10 years (59.1 vs. 45.5%), and

by 3.8% at 15 years (77.1 vs. 74.3%) ($P = 0.0012$, Wilcoxon's test for equality of survival curves; Fig. 1). Median survival for diabetic patients with LEAD was 8.1 years, compared with 10.9 years for those without LEAD. Cardiac disease accounted for 72.8 and 75.3% of all deaths, respectively, of which 12.5 and 7.3%, respectively, were sudden deaths.

Factors independently predicting mortality are shown in Table 4. For all the diabetic patients, age, multivessel epicardial coronary disease, poor myocardial contractility (the presence of CHF or ventricular wall motion abnormalities), and raised systolic blood pressure or history of hypertension were significantly related to mortality. The type of treatment for CAD was also of significance, with those undergoing CABG surgery having a 33% reduction in mortality, compared with those treated medically. The presence of LEAD was an independent risk factor for mortality, increasing mortality risk by 21%. Sex and smoking were not predictive factors in this model. When each of the diabetic subgroups was analyzed

separately, the same pattern of predictive factors was found to be significant for those with or without evidence of LEAD.

CONCLUSIONS— In this study of consecutively enrolled patients with suspected CAD, we found that of those patients ≥ 50 years of age with arteriographically documented CAD, 12.9% had diabetes, of whom 16.3% had evidence of LEAD by history or physical examination. Thus, 2.1% of this cohort had both diabetes and LEAD. As the proportion of elderly individuals in the population increases and the number of individuals with adult-onset diabetes grows, it is reasonable to assume that more such patients will come to medical attention and the need for knowledge regarding their disease and treatment will grow.

The diabetic patients with LEAD in this study were found to have high degrees of angina pectoris, smoking, and evidence of cerebrovascular disease, compared with diabetic patients without evidence of LEAD. They were also found to have a high prevalence of multivessel epicardial CAD and a high number of lesions throughout the coronary vasculature. On multivariate analysis, however, the severity and extent of CAD were not found to be independently associated with the presence of LEAD. It was further found that the survival of diabetic patients with LEAD was worse than that of the diabetic patients without LEAD (the majority dying of CAD), even though the risk factors predicting mortality were very similar. This suggests that factors associated with the presence of LEAD, other than the anatomy of the coronary circulation and those factors measured here, may have played a role in determining survival. What these factors were is uncertain. One possibility is impaired coronary vasoregulatory control due to autonomic neuropathy (25) or to the deposition of advanced glycosylation endproducts secondary to prolonged duration of diabetes (26). Adult-onset diabetic patients with LEAD are known to have a longer duration of diabetes than diabetic patients without LEAD (27). It is also known that diabetic cardiovascular autonomic neuropathy is associated with sudden death, most probably from arrhythmias (25). Unfortunately, no information is available in the CASS registry to substantiate this supposition. It would, however, help explain the high proportion of sudden deaths occurring among the diabetic patients with LEAD.

Table 3—Factors independently associated (logistic regression analysis) with the presence of LEAD in a cohort of diabetic patients with CAD

Variable	Odds ratio (95% CI)	P value
CVA/TIA (yes vs. no)	1.96 (1.55–2.48)	<0.001
Smoking status		<0.001
Nonsmoker	1.00 (reference)	
Former smoker	0.97 (0.80–1.17)	
Current smoker	1.92 (1.56–2.36)	
Systolic blood pressure (per 5 mmHg change)	1.05 (1.02–1.08)	0.003
Angina pectoris		0.004
No angina	1.00 (reference)	
Class I	0.39 (0.14–1.07)	
Class II	1.04 (0.72–1.50)	
Class III	1.44 (1.06–1.95)	
Class IV	1.72 (1.24–2.40)	
Unrelated to exertion	1.29 (0.83–2.03)	
Digitalis use (yes vs. no)	1.23 (1.16–1.43)	0.005

It should also be noted that even though there were differences in survival between the diabetic patients with or without LEAD in the first 10 years of follow-up, the overall long-term prognosis for both groups of subjects was poor. Only ~25% of the entire diabetic cohort was alive at 15 years, thereby emphasizing the poor prognosis associated with CAD in diabetic patients in the era of CASS. To our knowledge, this is one of the few studies in which such long-term outcomes for diabetic patients with CAD have been reported.

They are similar to the results reported by Smith et al. (28) from the Duke University Surgery Registry, which tracked diabetic patients for 19 years.

Limitations

Several limitations of this study should be noted. First, the results regarding the efficacy of surgical therapy, compared with medical therapy for CAD, were not based on randomized data. They are therefore open to question and should be interpreted with caution. Ideally, comparisons of outcomes

between surgical and medical management of CAD are best done through randomized trials. The cost of such trials, however, is high and patients belonging to narrowly defined subgroups such as ours may not always be available in large enough numbers.

Second, the diagnosis of LEAD was ascertained in part by patient self-report of leg pain provoked by ambulation, being told of having vascular disease in the past, or by examination at the time of entry into the study. Such methods are imprecise and, when compared with more accurate tests (such as echo-doppler or angiography), lead to a high degree of misclassification (especially in diabetic patients [4,29–31]) and to the exclusion of patients who are asymptomatic. As such, some of the patients in this study may actually not have had LEAD, whereas others with true illness were inadvertently excluded. While this is true, the clinical characteristics associated with the present cohort (such as current smoking, elevated systolic blood pressure, and increased prevalence of CVA/TIA) are similar to those described in other studies of patients with LEAD who were diagnosed by more accurate means (32,33).

Lastly, CASS patients were recruited in the mid-to-late 1970s, at a time that would not reflect the many changes in medical and surgical management of CAD of the current era. In particular, percutaneous transluminal coronary angioplasties (PTCAs) were not available and internal mammary artery (IMA) bypasses were rarely performed dur-

Table 4—Multivariate analysis (Cox proportional hazards regression) of factors independently predicting mortality in diabetic patients, ≥50 years of age, with or without concomitant LEAD

	All diabetic patients	Diabetic patients with LEAD	Diabetic patients without LEAD
Age (per year)	1.04 (1.02–1.05)	1.03 (1.002–1.06)	1.04 (1.03–1.05)
Number of coronary occlusions (per one segment change, range 1–27)	1.05 (1.02–1.08)	—	1.06 (1.02–1.09)
Number of significantly narrowed coronary arteries			
0	1.0	1.0	1.0
1	1.58 (0.92–2.71)	2.69 (0.60–12.11)	1.38 (0.77–2.45)
2	1.98 (1.16–3.39)	4.03 (0.95–17.04)	1.72 (0.97–3.06)
3	2.36 (1.36–4.09)	6.90 (1.64–28.97)	1.89 (1.05–3.41)
Degree of left main coronary stenosis (%)	1.003 (1.001–1.005)	—	1.004 (1.001–1.007)
CHF (yes vs. no)	1.76 (1.49–2.07)	1.87 (1.25–2.80)	1.69 (1.41–2.02)
LV wall motion score (per one unit change, range 5–30)	1.09 (1.07–1.10)	1.06 (1.02–1.10)	1.09 (1.07–1.11)
LEAD (yes vs. no)	1.21 (1.02–1.44)	—	—
Hypertension (yes vs. no)	1.19 (1.04–1.36)	—	1.29 (1.11–1.49)
Systolic blood pressure (per 5 mmHg change)	1.02 (1.01–1.04)	1.04 (1.01–1.07)	—
Therapy (surgical vs. medical)	0.67 (0.58–0.78)	0.77 (0.55–1.07)	0.65 (0.56–0.76)
Valvular heart disease (yes vs. no)	—	2.67 (1.05–6.81)	—

Data are hazard ratios (95% CI).

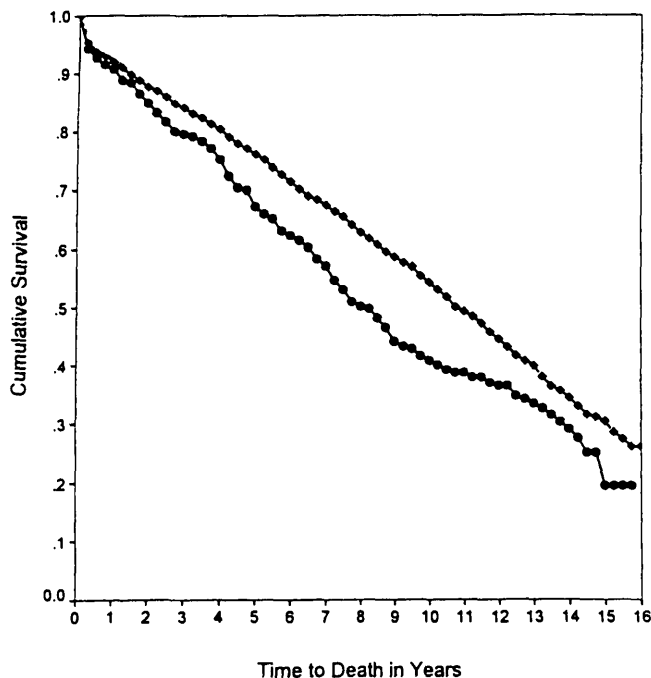


Figure 1—Cumulative survival rates for diabetic patients with CAD, with (●) or without (◆) concomitant LEAD. All patients were ≥ 50 years of age and members of the CASS registry.

ing the study period. Also, newer medications, such as ACE inhibitors, were not available during the early follow-up phase of this study. Given these changes, it is possible that the survival rates of the diabetic patients with or without LEAD may have changed considerably and, hence, that our results are no longer relevant to the current era. While these arguments are true, several arguments, we believe, still make our overall conclusions timely. First, despite the generally wide application of angioplasties in diabetic patients, restenosis rates remain high and their long-term efficacy has not been demonstrated (34). The recently reported Bypass Angioplasty Revascularization Investigation, for example, which compared PTCA with CABG surgery outcomes for CAD in patients from the late 1980s and early 1990s, showed decreased survival with PTCA in diabetic patients (35). Five-year survival rates for the diabetic patients treated by CABG in that study (80.6%) were only somewhat better than those of the diabetic patients without LEAD in our study (76.2%) who were treated either surgically or medically (though considerably better than the diabetic patients with LEAD [67.3%]). Second, despite the efficacy of IMA bypasses in improving survival after CABG surgery, their efficacy in improving long-term survival in diabetic patients has not been demonstrated. In the Duke Uni-

versity Surgery Registry (36), for example, which was carried out in the 1980s and in which 67% of the diabetic patients had IMA grafting, the 5-year survival rate for the diabetic patients was $\sim 80\%$, similar to the 76.2% survival of diabetic patients without LEAD in this study of those treated surgically or medically. At 8 years of follow-up, overall survival among the Duke diabetic patients was $\sim 65\%$, similar to the diabetic patients in CASS without LEAD (63.0%) (though better than the survival in the diabetic patients with LEAD [57.3%]). Whether IMA grafting will provide better long-term survival beyond this period of time, compared with our results, is unknown. Our results, therefore, seem to parallel the results of this more recent study and do not appear to be invalidated by the elapsed time from the inception of CASS. Lastly, our study offers the advantage of prolonged follow-up.

References

1. Jelles R, Gaardsting O, Hougaard Jensen K, Baekgaard N, Tonnesen KH, Schroeder T: Fate in intermittent claudication: outcome and risk factors. *Br Med J* 293:1137–1140, 1986
2. Dormandy J, Mahir M, Ascady G, Belsano F, De Leeuw P, Blombery P, Bousser MG, Clement D, Coffman J, Deutshinoff A: Fate of the patient with chronic leg ischaemia. *J*

Cardiovasc Surg 30:50–57, 1989

3. McDaniel MD, Cronenwett JL: Basic data related to the natural history of intermittent claudication. *Ann Vasc Surg* 3:273–277, 1989
4. Criqui MH, Langer RN, Fronck A, Feigelson HS, Klauber MR, McCann TJ, Browner D: Mortality over a period of 10 years in patients with peripheral arterial disease. *N Engl J Med* 326:381–386, 1992
5. Hertzner NR: Fatal myocardial infarction following lower extremity revascularization. Two hundred seventy-three patients followed six to eleven postoperative years. *Ann Surg* 198:667–673, 1980
6. Crawford ES, Bomberger RA, Glaeser DH, Saleh SA, Russell WL: Aortoiliac occlusive disease: factors influencing survival and function following reconstructive operation over a twenty-five year period. *Surgery* 90:1055–1067, 1981
7. Jamieson WRE, Janusz MT, Miyagishima RT, Gerein AN: Influence of ischemic heart disease on early and late mortality after surgery for peripheral occlusive vascular disease. *Circulation* 66 (Suppl. 1):192–197, 1982
8. Cutler BS: Prevention of cardiac complications in peripheral vascular surgery. *Surg Clin North Am* 66:281–292, 1986
9. McCann RL, Clements FM: Silent myocardial ischemia in patients undergoing peripheral vascular surgery: incidence and association with perioperative cardiac morbidity and mortality. *J Vasc Surg* 9:583–587, 1989
10. Zellner JL, Elliott BM, Robinson JG, Hendrix GH, Spicer KM: Preoperative evaluation of cardiac risk using dobutamine thallium imaging in vascular surgery. *Ann Vasc Surg* 4:238–243, 1990
11. Gersh BJ, Rihal CS, Rooke TW, Ballard DJ: Evaluation and management of patients with both peripheral vascular and coronary artery disease. *J Am Coll Cardiol* 18:203–214, 1991
12. Gordon T, Kannel WB: Predisposition to atherosclerosis in the head, heart, and legs: the Framingham Study. *JAMA* 221:661–666, 1972
13. Kannel WB, McGee DL: Diabetes and cardiovascular disease: the Framingham study. *JAMA* 241:2035–2038, 1979
14. Kannel WB, McGee DL: Update on some epidemiologic features of intermittent claudication: the Framingham Study. *J Am Geriatr Soc* 33:13–18, 1985
15. Principal Investigators of CASS and Their Associates: National Heart, Lung, and Blood Institute Coronary Artery Surgery Study. *Circulation* 63 (Suppl. 1):11–181, 1981
16. Campeau I: Grading of angina pectoris. *Circulation* 54:522–523, 1975
17. Fisher LD, Judkins MP, Lesperance J, Cameron A, Swaye P, Ryan T, Maynard C,

- Bourassa M, Kennedy JW, Gosselin A, Kemp H, Faxon D, Wexler L, Davis KD: Reproducibility of coronary arteriographic reading in the Coronary Artery Surgery Study (CASS). *Cathet Cardiovasc Diagn* 8:565-575, 1982
18. Alderman EL, Fisher L, Maynard C, Mock MD, Ringqvist I, Bourassa MG, Kaiser GC, Gillespie MJ: Determinants of coronary surgery in a consecutive patient series from geographically dispersed medical centers: the Coronary Artery Surgery Study. *Circulation* 66 (Suppl 1):16-115, 1982
 19. Hertzner NR, Young JR, Beven EG, O'Hara PJ, Graor RA, Ruschhaupt WF, Maljovec LC: Late results of coronary bypass in patients presenting with lower extremity ischemia: the Cleveland Clinic Study. *Ann Vasc Surg* 1:411-420, 1986
 20. Arous EJ, Baum PL, Cutler BS: The ischemic exercise test in patients with peripheral vascular disease: implications for management. *Arch Surg* 119:780-783, 1984
 21. Barzilay JI, Kronmal RA, Bittner V, Eaker E, Evans C, Foster ED: Coronary artery disease and coronary artery bypass grafting in diabetic patients aged ≥ 65 years (report from the Coronary Artery Surgery Study [CASS] registry). *Am J Cardiol* 74:334-339, 1994
 22. Davis KB, Fisher L, Gillespie MJ, Pettinger M: A test of the National Death Index using the Coronary Artery Surgery Study (CASS). *Control Clin Trials* 6:179-191, 1985
 23. Gehan EA: A generalized Wilcoxon test for comparing arbitrarily simply-censored samples. *Biometrika* 52:203-223, 1965
 24. Cox DR: Regression models and life-tables. *JR Stat Soc* 34:187-202, 1972
 25. Ewing DJ, Clarke BF: Diabetic autonomic neuropathy: present insights and future prospects. *Diabetes Care* 9:648-665, 1986
 26. Bucala R, Tracey KJ, Cerami A: Advanced glycosylation products quench nitric oxide and mediate defective endothelium: dependent vasodilatation in experimental diabetes. *J Clin Invest* 87:432-438, 1991
 27. West KM, Ahuja MMS, Bennett PH, Czyzyk A, De Acosta OM, Fuller JH, Grab B, Grabauskas V, Jarrett RJ, Kosaka K, Keen H, Krolewski AS, Milki E, Schliack V, Teuscher A, Watkins PJ, Stober JA: The role of circulating glucose and triglyceride concentrations and their interactions with other "risk factors" as determinants of arterial disease in nine diabetic population samples from the WHO multinational study. *Diabetes Care* 6:361-369, 1983
 28. Smith LR, Harrell FE, Rankin JS, Califf RM, Pryor DB, Muhlbaier LH, Lee KL, Mark DB, Jones RH, Oldham HN: Determinants of early versus late cardiac death in patients undergoing coronary artery bypass graft surgery. *Circulation* 84 (Suppl. III):III245-III253, 1991
 29. Criqui MH, Fronek A, Klauber MR, Barrett-Connor E, Gabriel S: The sensitivity, specificity, and predictive value of traditional clinical evaluation of peripheral arterial disease: results from noninvasive testing in a defined population. *Circulation* 71:516-522, 1985
 30. Marinelli MR, Beach KW, Glass MJ, Primozich JF, Strandness DE: Noninvasive testing versus clinical evaluation of arterial disease: a prospective study. *JAMA* 241:2031-2034, 1979
 31. Orchard TJ, Strandness DE: Assessment of peripheral vascular disease in diabetics. *Circulation* 88:819-828, 1993
 32. Fowkes FG, Housley E, Riemersma RA, Macintyre CC, Cawood EH, Prescott RJ, Ruckley CV: Smoking, lipids, glucose intolerance, and blood pressure as risk factors for peripheral atherosclerosis compared with ischemic heart disease in the Edinburgh Artery Study. *Am J Epidemiol* 135:331-340, 1992
 33. Beach KW, Strandness E: Arteriosclerosis obliterans and associated risk factors in insulin-dependent and non-insulin-dependent diabetes. *Diabetes* 29:882-888, 1980
 34. Carozza JP, Kuntz RE, Fishman RF, Baim DS: Restenosis after arterial injury caused by coronary stenting in patients with diabetes mellitus. *Ann Intern Med* 118:344-349, 1993
 35. The Bypass Angioplasty Revascularization Investigation (BARI) Investigators: Comparison of coronary bypass surgery with angioplasty in patients with multivessel disease. *N Engl J Med* 335:217-225, 1996
 36. Morris JJ, Smith LR, Jones RH, Glower DD, Morris PB, Muhlbaier LH, Reves JG, Rankin JS: Influence of diabetes and mammary artery grafting on survival after coronary bypass. *Circulation* 84 (Suppl. III):III275-III284, 1991