Heart Failure

Prognostic Impact of Diabetes Mellitus in Patients With Heart Failure According to the Etiology of Left Ventricular Systolic Dysfunction

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OBJECTIVES We sought to determine the relative impact of diabetes mellitus on prognosis in ischemic compared with nonischemic cardiomyopathy.

BACKGROUND Ischemic myocardium is characterized by increased reliance on aerobic and anaerobic glycolysis. Because glucose utilization by cardiomyocytes is an insulin-mediated process, we hypothesized that diabetes would have a more adverse impact on mortality and progression of heart failure in ischemic compared with nonischemic cardiomyopathy.

METHODS We performed a retrospective analysis of the Studies Of Left Ventricular Dysfunction (SOLVD) Prevention and Treatment trials.

RESULTS In adjusted analyses, diabetes mellitus was strongly associated with an increased risk for all-cause mortality in patients with ischemic cardiomyopathy, (relative risk [RR] 1.37, 95% confidence interval [CI] 1.21 to 1.55; $p < 0.0001$), but not in those with nonischemic cardiomyopathy (RR 0.98, 95% CI 0.76 to 1.32; $p = 0.98$). The increased mortality in patients with ischemic cardiomyopathy compared with nonischemic cardiomyopathy was limited to those with ischemic cardiomyopathy and diabetes mellitus (RR 1.37, 95% CI 1.21 to 1.56; $p < 0.0001$). When patients with ischemic cardiomyopathy and diabetes mellitus were excluded, there was no significant difference in mortality risk between the ischemic and nonischemic cardiomyopathy groups after adjusted analysis (RR 0.99, 95% CI 0.86 to 1.15; $p = 0.99$). Previous surgical revascularization identified patients within the cohort with ischemic cardiomyopathy and diabetes mellitus, with improved prognosis.

CONCLUSIONS The differential impact of diabetes on mortality and heart failure progression according to the etiology of heart failure suggests that diabetes and ischemic heart disease interact to accelerate the progression of myocardial dysfunction. Evaluation of the potential for revascularization may be particularly important in patients with ischemic cardiomyopathy and diabetes mellitus. (J Am Coll Cardiol 2001;38:421–8) © 2001 by the American College of Cardiology

A report from the original Studies Of Left Ventricular Dysfunction (SOLVD) investigators clearly identified diabetes mellitus as an independent predictor of increased mortality in heart failure (1). However, the relative prognostic impact of diabetes mellitus in ischemic compared with nonischemic cardiomyopathy has not been well characterized. Ischemic myocardium is characterized by increased reliance on glucose for both aerobic and anaerobic glycolysis, as well as decreased utilization of free fatty acids for energy metabolism (2,3). The utilization of glucose by cardiomyocytes is an insulin-mediated process (4). We hypothesized, therefore, that diabetes mellitus would have a more deleterious impact on mortality and heart failure progression in ischemic compared with nonischemic cardiomyopathy. In addition, the prevailing opinion is that isch-

emic cardiomyopathy is associated with a more adverse prognosis than nonischemic cardiomyopathy (5). We were interested in determining the implications of the relative prognostic impact of diabetes mellitus according to the etiology of heart failure, based on our understanding of the epidemiology of ischemic and nonischemic cardiomyopathy. To address these hypotheses, we conducted a retrospective analysis of the 6,797 participants in the SOLVD Prevention and Treatment trials.

METHODS

Patient population. The SOLVD Prevention and Treatment trials studied the survival benefit of enalapril in patients with asymptomatic and symptomatic heart failure, respectively. There were 4,228 participants in the Prevention trial, which enrolled patients with asymptomatic left ventricular systolic dysfunction. The SOLVD Treatment trial enrolled 2,569 patients with symptomatic systolic heart failure. The details of the rationale and design of the SOLVD trials have been published (6).

Patients were eligible for either trial if they had a

Abbreviations and Acronyms
NYHA = New York Heart Association
SOLVD = Studies Of Left Ventricular Dysfunction

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documented ejection fraction ≤35%. Participants were randomized to the angiotensin-converting enzyme inhibitor, enalapril, or placebo. Exclusion criteria included active angina pectoris requiring surgical intervention, unstable angina, myocardial infarction within one month, renal failure (defined as a creatinine value >2.0 mg/dl) or severe pulmonary disease.

Defining etiology of left ventricular systolic dysfunction.
In each enrolled participant, the SOLVD site investigator determined the most likely etiology of heart failure and indicated it on the baseline form. Choices included "ischemic," "nonischemic" and "other." This was based on the site investigator's opinion after reviewing all of the available information. The subjects did not routinely undergo cardiac catheterization or noninvasive testing to make this determination. For the present analysis, we refined the definition of ischemic etiology to minimize misclassification. The present analysis defined a participant as having an ischemic etiology of heart failure if any of the following were present: 1) classification as ischemic etiology by original SOLVD investigator; 2) previous myocardial infarction; and 3) previous surgical revascularization.

Definition of diabetes. The baseline form, completed for all participants, included information on the presence or absence of a history of diabetes mellitus. Data on the duration of diabetes, severity of diabetes (i.e., glycosylated hemoglobin) and medications used to treat diabetes were not available. For the purposes of the present analysis, we studied the impact of diabetes mellitus by stratifying patients into those with and without a history of diabetes mellitus at baseline.

Definitions of end points. The cause of death was determined by the site investigators after a detailed review of the circumstances of death. Categories included "pump failure," "arrhythmia with antecedent worsening of heart failure" and "arrhythymia with no antecedent worsening of heart failure." For the present analysis, we defined pump failure death to include those deaths, attributed by the original SOLVD investigators, as due to "pump failure," as well as those attributed to "arrhythmia with antecedent worsening of heart failure." Consequently, the definition of "arrhythmic death" in the present analysis was limited to those deaths classified by the original SOLVD investigators as "arrhythmia with no antecedent worsening of heart failure." The definition of death due to myocardial infarction was not standardized, but was based on a detailed review of all information available on each death by the original SOLVD investigators.

Data collection, definitions and statistical analysis.
Baseline data were collected at the time of enrollment in either of the SOLVD trials. Group comparisons of continuous data were done using the Student t test, assuming unequal variances in the comparison groups when appropriate. Group comparisons of categorical data were done using the chi-square test. A p value ≤0.05 was considered statistically significant. Kaplan-Meier survival curves were formally compared by using the log-rank test.

Univariate and multivariate relationships were investigated using a Cox proportional hazards model. Two-sided 95% confidence intervals were constructed around each point estimate of relative risk, and a p value ≤0.05 was considered statistically significant. For multivariate analyses, participants in the Prevention and Treatment trials were combined to increase statistical power. In the adjusted analyses, age and left ventricular ejection fraction were analyzed as continuous variables. The following variables were analyzed as dichotomous variables: gender, SOLVD trial (Treatment vs. Prevention), self-reported race/ethnicity (African-American/black vs. white or other), baseline use of beta-blocker (yes vs. no), aspirin (yes vs. no), New York Heart Association (NYHA) functional class (III or IV vs. I or II) and randomization assignment (enalapril vs. placebo). Statistical analyses were conducted using the Statistical Analysis Software (SAS), version 8.0 (Cary, North Carolina).

RESULTS

Baseline comparisons (Tables 1 and 2). Of the participants with an ischemic etiology of heart failure, those with diabetes mellitus in each trial were older and more of them were African-American, compared with those without a history of diabetes mellitus. In the Treatment trial, the patients with ischemic cardiomyopathy and diabetes mellitus had more advanced heart failure according to NYHA functional class, but a slightly higher mean ejection fraction. Of the participants with a nonischemic etiology of heart failure, those with diabetes in each trial were slightly older than the nondiabetic subjects. In the Prevention trial, the nonischemic diabetic cohort had a greater proportion of women. In the Treatment trial, the nonischemic diabetic cohort had slightly increased baseline creatinine levels and a greater proportion with NYHA functional class III or IV heart failure symptoms, compared with the nonischemic subjects without diabetes. The overall prevalence of surgical revascularization was similar in patients with and without diabetes mellitus among those with ischemic cardiomyopathy in the Prevention trial, but in the Treatment trial, the patients with diabetes mellitus had a slightly lower prevalence of previous surgical revascularization.

Prognostic impact of diabetes is influenced by etiology of heart failure. Marked differences in the association between diabetes and mortality were demonstrated in partic-

Table 1. Baseline Characteristics of Patients Stratified by Etiology of Heart Failure and Diabetes Status: SOLVD Prevention Trial

	Ischemic Cohort		Nonischemic Cohort	
	Diabetes (n = 575)	No Diabetes (n = 3,086)	Diabetes (n = 72)	No Diabetes (n = 490)
Age (years)	61.6 ± 8.9	59.1 ± 10.1*	60.4 ± 9.5	56.5 ± 12.8†
Ejection fraction (%)	28.7 ± 5.4	28.6 ± 5.5	28.3 ± 5.7	26.9 ± 6.3
Creatinine (mg/dl)	1.15 ± 0.29	1.15 ± 0.26	1.16 ± 0.40	1.14 ± 0.38
CABG	35.0%	34.4%	0%	0%
History of MI	88.4%	93.1%*	0%	0%
History of hypertension	51.3%	33.8%*	63.9%	37.6%*
Atrial fibrillation	2.9%	2.3%	12.5%	14.5%
Gender				
Male	86.8%	90.3%‡	73.6%	83.5%‡
Female	13.2%	9.7%‡	26.4%	16.5%‡
Race				
Black	13.7%	5.9%*	31.9%	24.3%
White	86.3%	94.1%*	68.1%	75.7%
Randomization to enalapril	51.3%	50.1%	43.1%	47.8%

*p ≤ 0.001; †p ≤ 0.01 and >0.001; ‡p ≤ 0.05 and >0.01 for comparisons between diabetics and nondiabetics in each etiology group. Data are presented as the mean value ± SD or percentage of patients.
CABG = coronary artery bypass graft surgery; MI = myocardial infarction; SOLVD = Studies Of Left Ventricular Dysfunction.

ipants stratified by etiology of heart failure. As demonstrated in multivariate analysis (Table 3), diabetes remained independently associated with an increased risk of all-cause mortality, pump failure death and the composite end point (death from any cause or hospital admission for heart failure) in the subjects with ischemic cardiomyopathy; however, there was no association between diabetes and outcomes in the nonischemic cohort. The p value for evidence of interaction between diabetes mellitus and the etiology of heart failure upon the risk for all-cause mortality was highly significant (p = 0.007).

Because diabetes mellitus was not associated with prognosis in nonischemic cardiomyopathy, we combined the diabetic and nondiabetic subjects with nonischemic cardio-

myopathy into a single cohort. Survival was compared in each trial by separating the subjects into three cohorts: 1) patients with ischemic cardiomyopathy and no history of diabetes mellitus; 2) patients with nonischemic cardiomyopathy with or without a history of diabetes mellitus; and 3) patients with ischemic cardiomyopathy and a history of diabetes mellitus. The unadjusted survival curves for these three cohorts in each of the SOLVD trials are demonstrated in Figures 1 and 2. In each trial, the cohort with ischemic cardiomyopathy and diabetes mellitus experienced the greatest mortality. In the Prevention trial, the nonischemic cohort's mortality was higher than that of the patients with ischemic cardiomyopathy without diabetes mellitus. In the Treatment trial, the survival of the patients with ischemic

Table 2. Baseline Characteristics of Patients Stratified by Etiology of Heart Failure and Diabetes Status: SOLVD Treatment Trial

	Ischemic Cohort		Nonischemic Cohort	
	Diabetes (n = 534)	No Diabetes (n = 1,392)	Diabetes (n = 129)	No Diabetes (n = 513)
Age (years)	63.2 ± 8.0	61.5 ± 9.3*	60.1 ± 9.8	57.2 ± 12.0†
Ejection fraction (%)	26.0 ± 6.5	25.0 ± 6.6†	24.6 ± 6.9	23.3 ± 6.9
Creatinine (mg/dl)	1.25 ± 0.35	1.24 ± 0.30	1.30 ± 0.33	1.21 ± 0.31†
CABG	27.5%	33.2%‡	0%	0%
History of MI	86.5%	88.0%	0%	0%
History of hypertension	52.1%	37.2%*	60.5%	41.1%*
Atrial fibrillation	6.4%	5.9%	12.4%	23.2%†
Gender				
Male	78.3%	84.4%†	68.2%	74.7%
Female	21.7%	15.6%†	31.8%	25.3%
Race				
Black	16.7%	8.8%*	28.7%	28.9%
White	83.3%	91.2%*	71.3%	71.1%
Randomization to enalapril	48.3%	49.4%	48.1%	54.2%

*p ≤ 0.001; †p ≤ 0.01 and >0.001; ‡p ≤ 0.05 and >0.01 for comparisons between diabetics and nondiabetics in each etiology group. Data are presented as the mean value ± SD or percentage of patients.
Abbreviations as in Table 1.

Table 3. Prognostic Impact of Diabetes According to Etiology of Heart Failure: Adjusted Analyses of the SOLVD Prevention and Treatment Trials Combined

	Ischemic Etiology*		Nonischemic Etiology†	
	RR (95% CI)	p Value	RR (95% CI)	p Value
ACM	1.37 (1.21–1.55)	<0.0001	0.98 (0.76–1.32)	0.99
Pump failure	1.44 (1.18–1.76)	0.0003	0.91 (0.70–1.50)	0.91
Arrhythmia	1.25 (0.97–1.61)	0.09	0.99 (0.53–1.87)	0.99
MI	1.21 (0.85–1.72)	0.29	1.09 (0.38–3.13)	0.86
ACM or hospital admission for CHF	1.51 (1.36–1.68)	<0.0001	1.17 (0.94–1.46)	0.16

*Adjusted for age, ejection fraction, New York Heart Association functional class, baseline creatinine value, gender, race (black vs. non-black), baseline use of beta-blocker or aspirin, coronary artery bypass graft surgery (CABG) and randomization to enalapril or placebo. †Adjusted for same covariates, except CABG.

ACM = all-cause mortality; CHF = congestive heart failure; CI = confidence interval; MI = myocardial infarction; RR = relative risk; SOLVD = Studies Of Left Ventricular Dysfunction.

cardiomyopathy without diabetes mellitus was indistinguishable from that of the patients with nonischemic cardiomyopathy.

Results of adjusted analyses (Table 4). After adjusting for potential confounders, the cohort consisting of patients with ischemic cardiomyopathy and diabetes mellitus demonstrated an increased risk of all-cause mortality, compared with the cohort with ischemic cardiomyopathy without diabetes mellitus and the cohort of nonischemic cardiomyopathy. The increased risk in the ischemic diabetic cohort, compared with the ischemic nondiabetic cohort, was related to an increased risk of pump failure death and a trend toward an increased risk of arrhythmic deaths, but no significant increase in the risk of death attributed to fatal myocardial infarction. The increased risk of all-cause mortality in the ischemic diabetic cohort, compared with the nonischemic cohort, was related to an increased risk for each mode of cardiovascular death. There was no significant difference in mortality risk when comparing the cohort with ischemic cardiomyopathy without diabetes mellitus with the cohort with nonischemic cardiomyopathy.

Survival in revascularized diabetics with ischemic cardiomyopathy. The baseline characteristics of subjects with and without a history of coronary artery bypass graft surgery were compared in the diabetic and nondiabetic cohorts (Tables 5 and 6). The subjects without surgical revascularization were more likely to be female and African-American in the diabetic and nondiabetic cohorts. Of the patients with
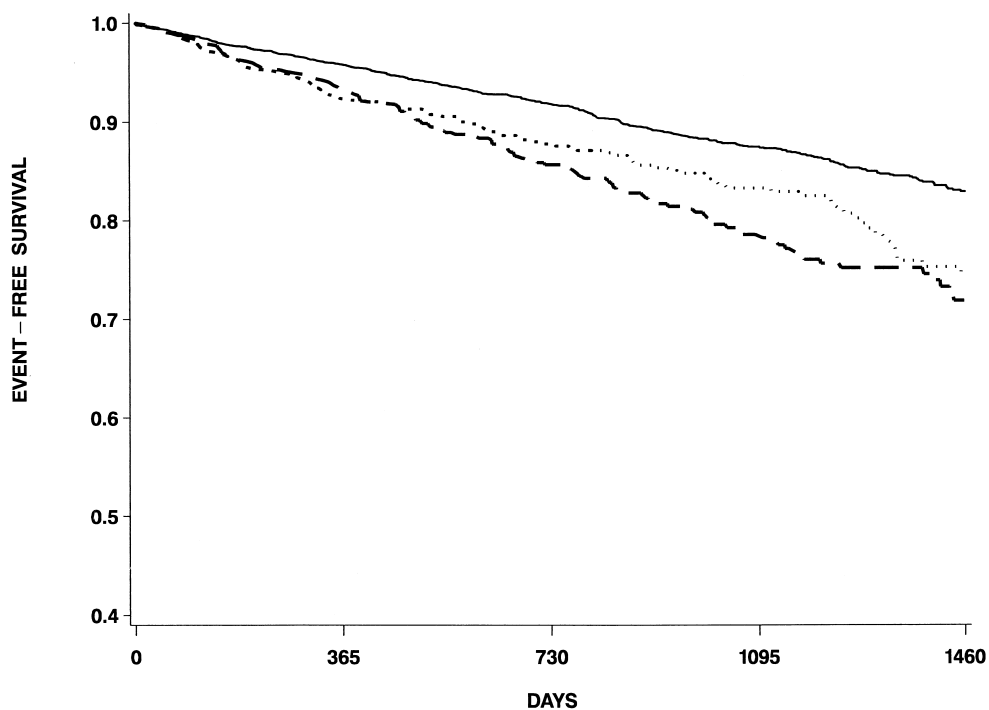
Figure 1. Survival free from all-cause mortality in the three cohorts in the Studies Of Left Ventricular Dysfunction (SOLVD) Prevention trial. The patients with ischemic cardiomyopathy and diabetes (n = 575; **dashed line**) had increased mortality compared with the patients with ischemic cardiomyopathy and no diabetes (n = 3,086; **solid line**) (p < 0.0001 by log-rank), but not significantly greater than that of the patients with nonischemic cardiomyopathy (n = 562; **dotted line**) (p = 0.21 by log-rank). The cohort with ischemic cardiomyopathy without diabetes (n = 3,086; **solid line**) demonstrated significantly lower mortality compared with the nonischemic cohort (p = 0.007 by log-rank) and the ischemic cohort with diabetes.
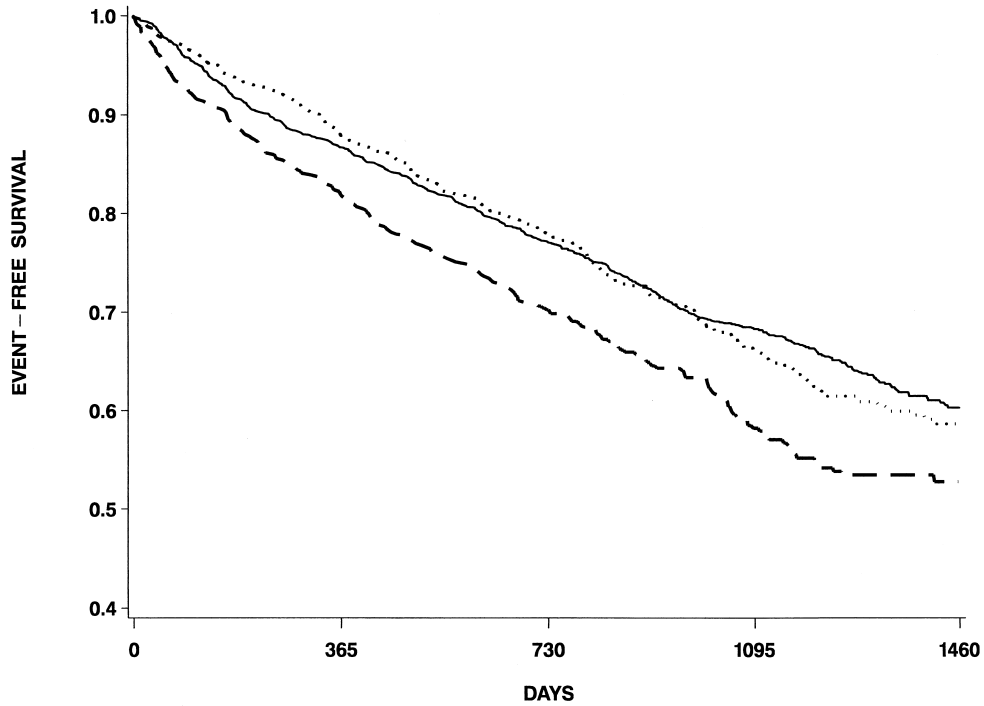
Figure 2. Survival free from all-cause mortality in the three cohorts in the Studies Of Left Ventricular Dysfunction (SOLVD) Treatment trial. The patients with ischemic cardiomyopathy and diabetes (n = 534; **dashed line**) had increased mortality compared with the patients with ischemic cardiomyopathy without diabetes (n = 1,392; **solid line**) and patients with nonischemic cardiomyopathy (n = 642; **dotted line**) (p < 0.0001 log-rank for both comparisons.) There was no significant difference in survival between the patients with ischemic cardiomyopathy without diabetes and the patients with nonischemic cardiomyopathy.

diabetes mellitus, those without surgical revascularization did not differ from those with surgical revascularization with regard to mean ejection fraction, severity of heart failure, as assessed by NYHA functional class, measures of vascular disease (pulse pressure and history of stroke) and baseline renal function, as assessed by the creatinine value. The unadjusted incidence of all-cause mortality (Table 7) in these groups demonstrates that previous surgical revascularization identifies a subgroup within the ischemic cardiomyopathy/diabetes mellitus cohort with improved survival, and the absolute magnitude of the unadjusted mortality reduc-

tion associated with previous surgical revascularization is greater in the patients with diabetes mellitus.

DISCUSSION

Major findings. The original SOLVD investigators identified diabetes as a strong independent predictor of mortality in patients with heart failure (1). The present analysis extends these findings and adds to our understanding of the impact of diabetes in patients with heart failure. Several of these findings deserve emphasis. First, the prognostic impact of diabetes mellitus in systolic heart failure appears to

Table 4. Adjusted Analyses of Cohort Survival

Cause of Death	RR (95% CI) p Value				
	ACM	Pump Failure	SCD	MI	Death or Hospital Admission for CHF
Group 2 vs. group 1*	0.99 (0.86–1.15) 0.99	1.22 (0.99–1.50) 0.07	0.81 (0.61–1.08) 0.16	0.40 (0.25–0.66) 0.0003	1.15 (1.02–1.29) 0.022
Group 3 vs. group 1†	1.37 (1.21–1.56) <0.0001	1.45 (1.19–1.77) 0.0002	1.25 (0.97–1.62) 0.09	1.20 (0.84–1.70) 0.29	1.51 (1.36–1.68) <0.0001
Group 3 vs. group 2*	1.45 (1.22–1.72) <0.0001	1.29 (1.01–1.65) 0.04	1.54 (1.08–2.19) 0.02	3.16 (1.78–5.61) <0.0001	1.37 (1.19–1.57) <0.0001

*Adjusted for age, ejection fraction, New York Heart Association functional class, SOLVD trial (Treatment vs. Prevention trial), gender, race, baseline use of beta-blocker or aspirin and randomization to enalapril or placebo. †Adjusted for the same variables as just listed, plus surgical revascularization. Group 1 (reference group): ischemic nondiabetic cohort (n = 4,478); Group 2: nonischemic cohort with and without diabetes (n = 1,204); and Group 3: ischemic diabetic cohort (n = 1,109).

SCD = sudden cardiac death; other abbreviations as in Table 3.

Table 5. Baseline Characteristics of Patients Stratified by Coronary Artery Bypass Graft Surgery and Diabetes Status: SOLVD Prevention Trial

	Ischemic Diabetic Cohort		Ischemic Nondiabetic Cohort	
	CABG (n = 201)	No CABG (n = 374)	CABG (n = 1,061)	No CABG (n = 2,025)
Age (years)	61.9 ± 8.2	61.4 ± 9.2	60.3 ± 9.1	58.5 ± 10.6*
Ejection fraction (%)	28.8 ± 4.8	28.6 ± 5.8	28.9 ± 5.3	28.3 ± 5.6†
Creatinine (mg/dl)	1.15 ± 0.24	1.16 ± 0.31	1.17 ± 0.26	1.14 ± 0.25‡
History of CVA	9.0%	7.2%	6.2%	5.3%
History of hypertension	46.3%	54.0%	36.6%	32.3%‡
Atrial fibrillation	2.5%	3.2%	2.5%	2.2%
Pulse pressure (mm Hg)	40.2 ± 6.8	39.2 ± 7.4	37.2 ± 6.9	36.8 ± 6.9
Gender				
Male	91%	85%‡	95%	88%*
Female	9%	15%‡	5%	12%*
Race				
Black	7%	17%*	4%	7%*
White	93%	83%*	96%	93%*
NYHA functional class				
II	35%	37%	32%	33%
I	65%	63%	68%	67%

*p ≤ 0.001; †p ≤ 0.01 and >0.001; ‡p ≤ 0.05 and >0.01. Data are presented as the mean value ± SD or percentage of patients. CVA = cerebrovascular accident; NYHA = New York Heart Association; other abbreviations as in Table 1.

be determined by the etiology of left ventricular systolic dysfunction. Specifically, diabetes mellitus was strongly associated with an increased risk of mortality in subjects with ischemic cardiomyopathy, but there was no association between diabetes mellitus and mortality risk in those with nonischemic cardiomyopathy. Second, the prevailing opinion is that ischemic cardiomyopathy is associated with an adverse prognosis, compared with nonischemic cardiomyopathy (5). Our data suggest that the adverse prognosis associated with ischemic cardiomyopathy is limited to patients with diabetes mellitus. In fact, once these patients are

excluded, the adjusted mortality risk is essentially identical in patients with ischemic and nonischemic cardiomyopathy. Third, it appears that previous surgical revascularization is associated with a reduction in the adverse prognostic impact of diabetes in patients with ischemic cardiomyopathy and diabetes mellitus.

Impact of diabetes on modes of death in ischemic cardiomyopathy. An interesting finding was the spectrum of risk associated with the various modes of death in the patients with ischemic cardiomyopathy stratified according to diabetes mellitus. Diabetes mellitus is associated with

Table 6. Baseline Characteristics of Patients Stratified by Coronary Artery Bypass Graft Surgery and Diabetes Status: SOLVD Treatment Trial

	Ischemic Diabetic Cohort		Ischemic Nondiabetic Cohort	
	CABG (n = 147)	No CABG (n = 387)	CABG (n = 462)	No CABG (n = 930)
Age (years)	62.8 ± 8.0	63.3 ± 8.0	61.4 ± 9.0	61.5 ± 9.4
Ejection fraction (%)	27.2 ± 5.7	25.6 ± 6.7†	25.7 ± 6.4	24.7 ± 6.7†
Creatinine (mg/dl)	1.29 ± 0.38	1.24 ± 0.33	1.25 ± 0.29	1.23 ± 0.30
History of CVA	8.2%	10.6%	9.7%	7.3%
History of hypertension	48.3%	53.5%	36.4%	37.6%
Atrial fibrillation	5.4%	6.7%	5.8%	5.9%
Pulse pressure (mm Hg)	39.8 ± 8.5	39.5 ± 7.9	38.1 ± 8.2	37.5 ± 7.7
Gender				
Male	83%	76%	89%	82%*
Female	17%	24%	11%	18%*
Race				
Black	11%	19%‡	5%	10%†
White	89%	81%‡	95%	90%†
NYHA functional class				
IV	4%	2%	1%	1%
III	35%	38%	27%	28%
II	57%	54%	58%	58%
I	4%	6%	14%	13%

*p ≤ 0.001; †p ≤ 0.01 and >0.001; ‡p ≤ 0.05 and >0.01. Data are presented as the mean value ± SD or percentage of patients. Abbreviations as in Tables 1 and 5.

Table 7. Incidence of Death and Modes of Death According to Surgical Revascularization Status in Diabetic and Nondiabetic Patients

	Prevention Trial			
	No Diabetes		Diabetes	
	CABG	No CABG	CABG	No CABG
ACM	4.1%	4.9%	5.4%	9.3%*
Pump failure	1.5%	1.2%	2.2%	2.6%
Arrhythmia	0.9%	1.9%*	1.1%	2.7%‡
MI	0.9%	0.8%	0.7%	1.3%
Death or hospital admission for CHF	6.1%	7.0%	9.4%	13.4%‡

	Treatment Trial			
	No Diabetes		Diabetes	
	CABG	No CABG	CABG	No CABG
ACM	10.9%	13.9%‡	12.5%	19.5%†
Pump failure	5.2%	6.1%	5.7%	9.9%‡
Arrhythmia	2.4%	3.7%‡	2.6%	4.4%
MI	1.8%	1.8%	1.3%	2.3%
Death or hospital admission for CHF	16.0%	18.3%	19.5%	26.6%†

*p ≤ 0.05 and p > 0.01 by log-rank; †Log-rank p ≤ 0.01 and p > 0.001 by log-rank; ‡p ≤ 0.001 by log-rank. Data are presented as the percentage of patients.
Abbreviations as in Table 3.

more diffuse and severe coronary artery disease and increased mortality from acute coronary syndromes and myocardial infarction (7–9). Therefore, the increased mortality in the patients with ischemic cardiomyopathy and diabetes mellitus might be expected. However, the increased risk of all-cause mortality in the subjects with ischemic cardiomyopathy and a history of diabetes mellitus, compared with those without a history of diabetes mellitus, was related to an increased risk of progression of heart failure, as suggested by the increased risk of pump failure death and the composite end point of death from any cause or hospital admission for heart failure. The risk of myocardial infarction did not reach statistical significance. There was a trend toward an increased risk of arrhythmic death in the patients with ischemic cardiomyopathy and diabetes, compared with those without diabetes mellitus. However, we know from a recent autopsy study that recurrent myocardial infarction accounts for many deaths in patients with ischemic cardiomyopathy (10). The trend toward greater arrhythmic death in the subjects with diabetes and ischemic cardiomyopathy, compared with those without diabetes mellitus, may suggest, based on published data (10), that many of the deaths attributed to a fatal arrhythmia may indeed have resulted from a myocardial infarction. Finally, nonfatal infarctions may have been more common in the subjects with diabetes mellitus and ischemic cardiomyopathy and resulted in acceleration of left ventricular dysfunction.

Impact of surgical revascularization. Previous surgical revascularization identified a subgroup within the diabetic cohort with ischemic cardiomyopathy with substantially lower mortality. The adverse prognosis in the nonrevascularized diabetic patients with systolic dysfunction may reflect the influence of selection bias in the determination of which diabetics with ischemic cardiomyopathy were offered surgical revascularization. Interestingly, the baseline characteristics of the diabetics with and without surgical revascularization did not identify obvious differences in comorbidities or measures of the severity of heart failure between the groups that might be expected to detract from their candidacy for surgical revascularization. However, it should be emphasized that surgical revascularization was not a randomized treatment, and we had little data on the completeness of revascularization in each subject. These patients were highly selected in an era when surgical revascularization was often not performed on the basis of a low ejection fraction, and the presence of diabetes may have created a selection bias explaining these results.

Potential explanations for the interaction between diabetes and etiology of heart failure. The differential impact of diabetes on mortality according to the etiology of heart failure suggests that diabetes mellitus and ischemic heart disease interact to accelerate the progression of myocardial dysfunction. As mentioned already, this may be partly explained by an increased risk of nonfatal myocardial infarctions, incomplete revascularization in those who had surgical revascularization or comorbidities resulting from diabetes. However, as hypothesis-generating, these data suggest that there may be additional mechanisms for a deleterious synergy between these two disease processes. For example, ischemic cardiomyopathy is characterized by a shift in myocardial substrate utilization from free fatty acids to increased reliance on glucose and glycolysis (2,3,11,12). This has been demonstrated in animal models mimicking the chronic decrease in coronary blood flow that is thought to characterize hibernating myocardium (2,3). Glucose uptake into cardiomyocytes requires insulin (4) and has been demonstrated to be impaired in an animal model of type II diabetes (13). In the presence of the greater reliance on glycolysis and decreased reliance of free fatty acid metabolism that occurs in chronic coronary artery disease, the impaired myocardial glucose uptake characteristic of diabetes may be particularly deleterious (2,3). In addition, the cumulative oxidative stress of chronic ischemia may be additive to the oxidative stress superimposed by diabetes. This oxidative stress results in myocardial subcellular remodeling, leading to abnormal intracellular calcium homeostasis (14).

Study limitations. The limitations of this retrospective study must be emphasized. The determination of the exact etiology of heart failure was not based on routine cardiac catheterization, and it is likely that there was some misclassification. Surgical revascularization was not randomized, but was determined by history at the time of randomization, and we did not have data on the severity of coronary disease or other factors that may have excluded some of the

ischemic diabetic patients from receiving surgical revascularization. Classification of the causes of death in heart failure is imprecise and subject to misclassification. Therefore, the data relating each cohort's relative risk according to the mode of death should be interpreted with caution.

Conclusions. The differential impact of diabetes on mortality and heart failure progression, based on the etiology of heart failure, suggests that diabetes and ischemic heart disease interact to accelerate the progression of myocardial dysfunction. Evaluation of the potential for revascularization may be particularly important in patients with coronary artery disease who have both diabetes and heart failure.

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