Risk of Incident Heart Failure in Patients With Diabetes and Asymptomatic Left Ventricular Systolic Dysfunction

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OBJECTIVE

Although diabetes is well known to be common in prevalent heart failure (HF) and portends a poor prognosis, the role of diabetes in the development of incident HF is less well understood. We studied the role of diabetes in the transition from asymptomatic left ventricular systolic dysfunction (ALVSD) to overt HF in the prevention arm of the Studies of Left Ventricular Dysfunction (SOLVD-P).

RESEARCH DESIGN AND METHODS

We examined the development of symptomatic HF, HF hospitalization, and cardiovascular death according to diabetes status at baseline in patients in SOLVD-P. These outcomes were analyzed by using cumulative incidence curves and Cox regression models adjusted for age, sex, and other prognostic factors, including randomized treatment, HF severity, and comorbidity.

RESULTS

Of the 4,223 eligible participants, 647 (15%) had diabetes at baseline. Patients with diabetes were older and had a higher average weight, systolic blood pressure, and heart rate. During the median follow-up of 36 months, 861 of the 3,576 patients without diabetes (24%) developed HF compared with 214 of the 647 patients with diabetes (33%). In unadjusted analyses, patients with diabetes had a higher risk of development of HF (hazard ratio 1.53 [95% CI 1.32–1.78]; $P < 0.001$), HF hospitalization (2.04 [1.65–2.52]; $P < 0.0001$), and the composite outcome of development of HF or cardiovascular death (1.48 [1.30–1.69]; $P < 0.001$). The effect of enalapril on outcomes was not modified by diabetes status.

CONCLUSIONS

In patients with ALVSD, diabetes is associated with an increased risk of developing HF. Development of HF is associated with an increased risk of death irrespective of diabetes status.

Heart failure (HF) and type 2 diabetes are two modern epidemics, and many patients have both conditions. Their coexistence places individuals at very high risk of adverse cardiovascular outcomes, underscoring the importance of understanding the interactions between the two conditions (1–6). Patients with diabetes have a higher incidence of cardiovascular disease, including a two- to fourfold higher risk of HF, than people without diabetes (7–11). However, we do not fully understand the link between diabetes and the development of HF. For example, we still do not know

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whether diabetes causes HF directly or whether the higher risk of HF simply reflects the greater frequency of hypertension and myocardial infarction in patients with diabetes. If diabetes does directly promote the development of HF, it should also accelerate the development of HF in patients with preexisting subclinical cardiac damage. To test this hypothesis, we examined the progression from asymptomatic left ventricular systolic dysfunction (ALVSD) to overt HF in patients with and without diabetes in the prevention arm of the Studies of Left Ventricular Dysfunction (SOLVD-P).

RESEARCH DESIGN AND METHODS

Study Population

We used the public use copy of the SOLVD-P database obtained from the National Heart, Lung, and Blood Institute, which sponsored the trial. SOLVD-P studied the effect of enalapril on the development of HF and on mortality in patients with ALVSD (12–14). Patients were eligible if they had a documented left ventricular ejection fraction (LVEF) $\leq$35%, had little or no limitation of exercise tolerance as a result of dyspnea or fatigue, and were not receiving diuretics, digoxin, or vasodilators for the treatment of HF (but could receive these for other indications, e.g., hypertension, atrial fibrillation). According to the SOLVD protocol, participants had to exhibit no symptoms or signs of overt HF during a 3-week run-in period. During this period, patients received open-label enalapril for 2–7 days followed by open-label placebo for 14–17 days, after which they were randomly assigned 1:1 to double-blind enalapril or placebo.

Definition of Diabetes

At baseline, investigators reported whether patients did or did not have a history of diabetes. Data on the duration of diabetes, glycated hemoglobin, and treatments for diabetes were not collected. In the current analyzes, we stratified patients by history of diabetes at baseline.

Outcomes

Patients were seen 2 and 6 weeks after randomization, at 4 months, and then every 4 months until the end of study. The development of HF was a prespecified end point defined by the onset of symptoms and/or signs of congestive heart failure (i.e., shortness of breath on exertion or at rest, evidence of fluid retention, e.g., peripheral edema, pulmonary congestion, jugular venous distension), which in the opinion of the site investigator, was sufficiently severe to warrant pharmacologic treatment. Hospital admission for HF and death as a result of HF were additional prespecified HF end points (which were potentially overlapping, nonmutually exclusive events). In the current analyses, we examined the following outcomes: *1*) development of HF, *2*) HF hospitalization, *3*) death from cardiovascular causes, and *4*) death from any cause according to diabetes status at baseline (and in the case of all-cause death, also after development of HF).

Statistical Analyses

Baseline characteristics were described by use of proportions for categorical variables and means $\pm$ SD for continuous variables. Baseline differences between patients with and without diabetes were tested using χ^2 test for categorical variables and ANOVA for continuous variables. We estimated Kaplan-Meier curves for all-cause mortality and cumulative incidence curves for all other outcomes with death or death from noncardiovascular causes as a competing risk using the Aalen-Johansen method (15). Log-rank and Gray tests were used to analyze unadjusted differences. Event rates for each outcome of interest are presented per 1,000 person-years (PY) of follow-up. Cox proportional hazards regression models were used to compare risks between patients with and without history of diabetes for all outcomes of interest and the effect of enalapril on these outcomes according to diabetes status at baseline. The adjusted Cox regression models included information on age, sex, treatment effect, race, New York Heart Association (NYHA) class, smoking status, LVEF, systolic blood pressure, heart rate, creatinine level, angina at baseline and history of myocardial infarction, chronic obstructive pulmonary disease (COPD), stroke, atrial fibrillation, and hypertension. Sex, age, and treatment effect were tested for interactions with diabetes status in relation to all outcomes and, unless stated otherwise, found to be absent. Interactions between atrial fibrillation and heart rate as well as angina at baseline and history of myocardial infarction in relation to all outcomes were tested and found to be absent. The assumption of linearity was tested for age, LVEF, heart rate, systolic blood pressure, and creatinine level. Log [$-$log(survival)] curves were used to evaluate the proportional hazards assumption. Furthermore, analyses with blood pressure, creatinine level, and myocardial infarction as time-dependent covariates were carried out. The rate of total HF hospitalizations was compared using negative binomial regression with log duration of follow-up as the offset (16). Analyses were performed with Stata 14 and R version 3.3.2 statistical software.

RESULTS

Baseline Characteristics

A total of 4,223 (99.9%) patients had information about history of diabetes recorded. Of these, 647 (15%) had a diagnosis of diabetes. Patients with diabetes were older (mean age 61 years vs. 58 years in patients without diabetes); were more likely to be female (15% vs. 11%); had a higher weight (mean 85 vs. 81 kg), systolic blood pressure (130 vs. 125 mmHg), and heart rate (78 vs. 74 beats/min); and were of different racial composition (76% white and 16% black vs. 88% white and 8% blacks) (Table 1). History of hypertension and treatment with diuretics were also more common among patients with diabetes than among those without.

Clinical Outcomes According to Diabetes Status

During the median follow-up of 36 months (quartiles 1–3 26–47 months), 861 of the 3,576 patients without diabetes (24.1%) developed HF; among the 647 patients with diabetes, 214 (33.1%) developed HF (as assessed by time to first occurrence of either symptoms/signs or HF hospitalization; the components of this composite are shown in Supplementary Table 1). A median time to development of HF could not be calculated in patients without diabetes, but the time taken for 25% of these patients to develop HF was 1,178 days compared with 602 days in those with diabetes. As well as a higher risk of developing HF (Fig. 1*A*), patients with diabetes had a higher risk of HF hospitalization (Fig. 1*B*) and of the composite end point of development of HF or cardiovascular death (Fig. 1*C*) than patients without diabetes. Patients with diabetes were at greater risk of death from any cause than those without diabetes (Fig. 1*D*).

Table 1—Baseline characteristics of patients with and without diabetes

	No diabetes	Diabetes	*P* value
Patients, *n* (%)	3,576 (85)	647 (15)	
Age (years), mean ± SD	58 ± 11	61 ± 9	<0.0001
Male sex, *n* (%)	3,195 (89)	552 (85)	0.003
Race, *n* (%)			<0.0001
White	3,160 (88)	494 (76)	
Black	301 (8)	102 (16)	
Other	112 (3)	50 (8)	
Enalapril treatment, *n* (%)	1,781 (50)	326 (50)	
NYHA class, *n* (%)			0.38
I	2,403 (67)	417 (64)	
II	1,169 (33)	229 (35)	
III	4 (0.1)	1 (0.2)	
Weight (kg), mean ± SD	81 ± 14	85 ± 15	<0.0001
Current smoker, *n* (%)	865 (24)	129 (20)	0.16
LVEF	0.28 ± 0.06	0.29 ± 0.05	0.11
Blood pressure (mmHg), mean ± SD			
Systolic	125 ± 16	130 ± 17	<0.0001
Diastolic	78 ± 10	78 ± 10	0.52
Heart rate (beats/min), mean ± SD	74 ± 12	78 ± 13	<0.0001
Sodium (mmol/L), mean ± SD	140 ± 3	139 ± 3	<0.0001
Potassium (mmol/L), mean ± SD	4.3 ± 0.4	4.4 ± 0.4	0.22
Creatinine (μmol/L), mean ± SD	101 ± 23	102 ± 26	0.41
Medical history, *n* (%)			
Myocardial infarction	2,873 (80)	508 (79)	0.31
Atrial fibrillation	373 (10)	75 (12)	0.38
COPD	180 (5)	46 (7)	0.03
Stroke	200 (6)	49 (8)	0.05
Hypertension	1,226 (34)	341 (53)	<0.0001
Angina pectoris*	1,186 (33)	245 (38)	0.05
Drug therapy, *n* (%)			
Diuretics	560 (16)	145 (22)	<0.0001
Digoxin	446 (12)	82 (13)	0.89
β-Blockers	848 (24)	167 (26)	0.25
Antiplatelet agents	1,921 (54)	371 (57)	0.08
Anticoagulant agents	444 (12)	54 (8)	0.003
Antiarrhythmic drugs	569 (16)	68 (11)	0.0004
Calcium-channel blockers	1,216 (34)	259 (40)	0.02

*At baseline.

The risk of these outcomes remained elevated in patients with diabetes when examined in adjusted Cox regression analyses (Table 2).

An incident myocardial infarction after randomization and before development of HF occurred in 5.9% of patients without diabetes compared with 5.6% among those with diabetes. In analyses including myocardial infarction as a time-dependent covariate, the risk of development of HF remained significantly higher in patients with diabetes than in those without (adjusted hazard ratio 1.30 [95% CI 1.11–1.52]; $P = 0.001$). Similarly, inclusion of systolic blood pressure or creatinine level as time-dependent covariates did not weaken the association between diabetes and development of HF (1.32 [1.12–1.54]; $P = 0.001$ vs. 1.29 [1.10–1.50]; $P = 0.002$, respectively).

The total number of HF hospitalizations (taking into account repeat admissions) according to diabetes status is shown in Supplementary Table 2. The crude rate of HF hospitalizations was 110 per 1,000 PY for patients with diabetes and 55 per 1,000 PY among patients without diabetes; this yielded an adjusted incidence rate ratio of 1.93 (95% CI 1.44–2.59; $P < 0.0001$).

Other Predictors of Incident HF

Older age, black race, NYHA class II (vs. I), lower LVEF, higher heart rate and creatinine level, and history of COPD were all associated with development of HF (Supplementary Fig. 1), HF hospitalization, and the composite end point of HF hospitalization and cardiovascular death (data not shown). Diabetes remained an independent predictor of all outcomes examined, even when these other predictive variables were taken into account (Table 2 and Supplementary Fig. 1).

Survival Overall and After an HF Event

In patients who did not develop HF, the risk of death over ≤4 years of follow-up was 14% (12–16%) in those without diabetes at baseline and 22% (16–27%) in those with diabetes (Fig. 2). In patients who developed HF, the risk of death was 29% (25–33%) in those without diabetes at baseline and 37% (29–45%) in those with diabetes. With a focus on the period after development of HF, the risk of death was 33% (28–37%) in patients without diabetes and 42% (33–50%) in patients with diabetes ($P = 0.0004$); the respective mortality rates were 128 (111–147) and 181 (143–230) per 1,000 PY. The high mortality rate after development of HF was similar whether the first manifestation of HF was development of symptoms/signs or admission to the hospital (Supplementary Fig. 2). A median time to death after development of HF could not be calculated, but in those without diabetes, the time taken for death to occur in 25% of patients was 862 days compared with 478 days in patients with diabetes.

In adjusted analyses, patients who developed HF had a significantly higher risk of subsequent death than patients who did not develop HF (Table 2). However, the relative risk of death in patients who developed HF (vs. those who did not) was similar in participants with and without diabetes.

Effect of Enalapril According to Diabetes Status

The effect of enalapril on the outcomes analyzed was not modified by diabetes status as shown in Supplementary Table 3. Enalapril significantly reduced the occurrence of development of HF, HF hospitalization, and the combined end point of development of HF or cardiovascular death in patients with and without diabetes. Enalapril did not reduce the risk of death from cardiovascular or all causes, overall, or in patients with or without diabetes.

CONCLUSIONS

To our knowledge, the SOLVD-P trial remains the only detailed source of

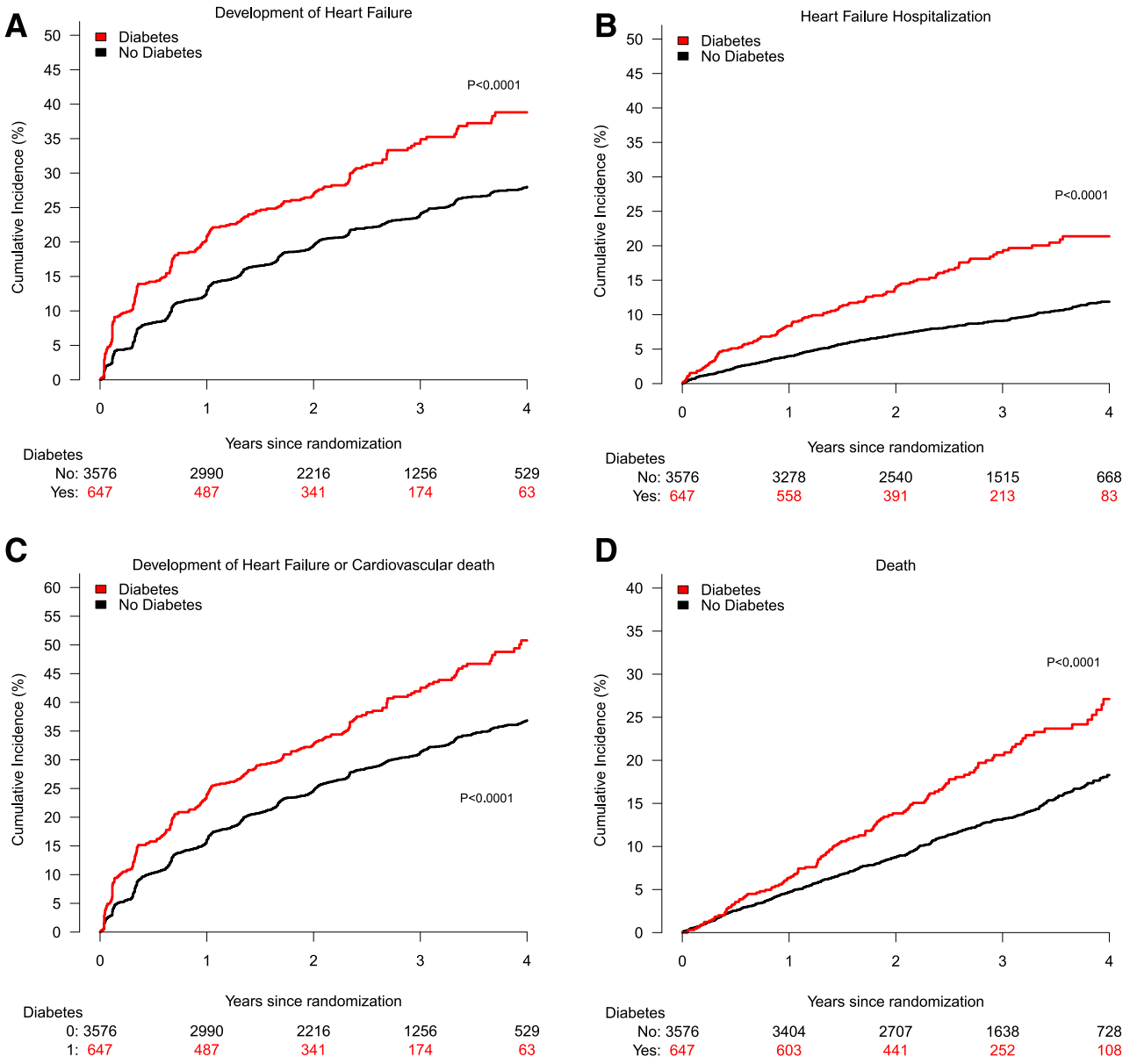

Figure 1—*A* and *B*: Cumulative incidence of development of HF and HF hospitalization, with death as competing risk among patients with and without diabetes. *C*: Risk of developing HF, HF hospitalization, or cardiovascular death, with noncardiovascular death as competing risk, among patients with and without diabetes. *D*: Risk of death among patients with and without diabetes.

information on the natural history of ALVSD and, in particular, on the progression of ALVSD to symptomatic HF. As such, this data set also provides a unique opportunity to investigate whether diabetes accelerates the progression of ALVSD to symptomatic HF, which is exactly what we found. Patients with diabetes were 1.5–2.0 times as likely to develop HF or to be hospitalized for HF. The occurrence of HF in patients with diabetes led to a similar relative ramping up in risk of subsequent death as the development of HF did in individuals without diabetes; patients who developed HF were two to three times more likely to die than those who did not develop HF, irrespective of baseline diabetes status. The rate of death after development of HF was higher in patients with diabetes than in those without. Despite their shorter life expectancy, patients with diabetes also had more cumulative HF hospitalizations (taking into account repeat admissions), with double the rate of admissions (110 vs. 55) per 1,000 PY of follow-up.

One of the great conundrums in this field has been the question of whether diabetes per se promotes the development of HF or whether the relationship between diabetes and HF is due to comorbidities such as myocardial infarction and hypertension (17–19). SOLVD-P helps to address this problem. Most patients in SOLVD-P had a history of myocardial infarction at baseline (with a similar proportion in those with and without diabetes), and the occurrence of further myocardial infarction was systematically documented during follow-up in the trial. Few patients (<6%) who developed HF had a myocardial infarction reported after randomization but before the development of HF, and the accounting for these in a time-dependent covariate analysis did not weaken the relationship between diabetes and development of HF.

Table 2—Event rates and HRs for all outcomes according to diabetes status

	Events, *n*	Crude rate per 1,000 PY	Unadjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)*	*P* value
HF development						
Diabetes	214	157 (138–180)	1.53 (1.32–1.78)	<0.0001	1.30 (1.11–1.52)	0.001
No diabetes	861	99 (93–106)	1.00 (ref.)		1.00 (ref.)	
HF hospitalization						
Diabetes	114	73 (61–88)	2.04(1.65–2.52)	<0.0001	1.75 (1.40–2.19)	<0.0001
No Diabetes	342	35 (32–39)	1.00 (ref.)		1.00 (ref.)	
HF development or CV death						
Diabetes	267	196 (174–221)	1.48 (1.30–1.69)	<0.0001	1.29 (1.12–1.49)	<0.0001
No diabetes	1,120	129 (122–137)	1.00 (ref.)		1.00 (ref.)	
CV death						
Diabetes	113	65 (54–78)	1.53 (1.25–1.89)	<0.0001	1.42 (1.14–1.76)	0.001
No diabetes	440	43 (39–47)	1.00 (ref.)		1.00 (ref.)	
All-cause mortality						
Diabetes	132	76 (64–90)	1.56 (1.29–1.89)	<0.0001	1.43 (1.17–1.74)	0.001
No diabetes	505	49 (45–53)	1.00 (ref.)		1.00 (ref.)	
All-cause mortality in relation to development of HF						
HF and diabetes	68	115 (91–146)	2.95 (2.27–3.85)	<0.0001	2.47 (1.87–3.27)	<0.0001
HF and no diabetes	204	79 (69–90)	2.01 (1.68–2.40)	<0.0001	1.63 (1.35–1.96)	<0.0001
No HF and diabetes	64	56 (44–71)	1.44 (1.10–1.89)	0.008	1.29 (0.98–1.71)	0.07
No HF and no diabetes	301	39 (35–44)	1.00 (ref.)		1.00 (ref.)	

CV, cardiovascular; HR, hazard ratio; ref., reference. *Adjusted for age, sex, treatment effect, race, NYHA class, smoking status, LVEF, systolic blood pressure, heart rate, creatinine level, angina at baseline, and history of myocardial infarction, COPD, stroke, atrial fibrillation, and hypertension.

This finding indicates that diabetes can accelerate the risk of developing HF without the occurrence of clinically recognized myocardial infarction. Patients might have experienced silent myocardial infarction, though, which may be more common in those with diabetes (20). Silent myocardial infarction, however, was not collected in SOLVD-P, although when it has been looked for, silent myocardial infarction was uncommon compared with recognized infarction and is unlikely to explain the excess risk of HF.

Apparently counterintuitively, we found that a history of myocardial infarction was associated with a lower likelihood of all outcomes. However, four out of five patients in the study had a history of myocardial infarction, and this finding may reflect the play of chance in the small subgroup without myocardial infarction. The alternative underlying cause of ALVSD in the patients without a history of myocardial infarction may have carried a particularly poor prognosis.

Patients with diabetes did have a higher systolic blood pressure at baseline than those without diabetes, but in the multivariable adjusted analysis, blood pressure or history of hypertension were not independent predictors of any HF outcome. Furthermore, including systolic blood pressure as a time-varying covariate did not attenuate the higher risk of development of HF development in patients with diabetes compared with those without diabetes. Thus, among patients with ALVSD, higher systolic blood pressure does not seem to be a predictor of adverse outcomes. Although this finding is different from that in patients with hypertension and cardiovascular disease more generally, it is the pattern found in patients with HF and reduced LVEF, where higher systolic pressure is associated with better outcomes (and lower pressure with worse outcomes). Patients with systolic dysfunction generally do not have substantially elevated blood pressure.

In the multivariable analysis, diabetes emerged as a significant predictor of developing HF. Other significant predictors were high heart rate, low LVEF, black race, higher creatinine level, age, and NYHA class, and a history of COPD. This

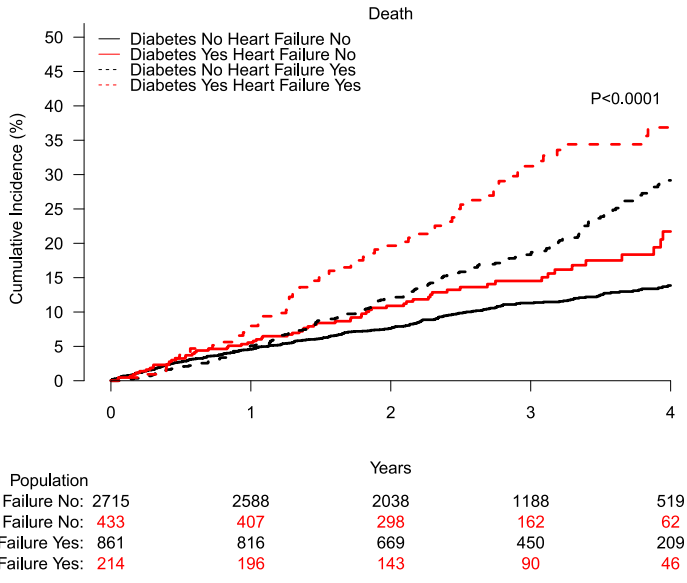

Figure 2—Risk of death according to diabetes status and development of HF.

analysis points to other aspects of diabetes that may be critical to the development of HF. For example, renal dysfunction is a common consequence of diabetes and may contribute to the enhanced risk of HF (although baseline creatinine level was similar in patients with and without diabetes) (21,22). Of note, heart rate was higher in patients with diabetes despite a similar prevalence of atrial fibrillation and similar use of β-blockers and digoxin in those with and without diabetes. Autonomic neuropathy might also contribute to the HF risk related to diabetes, and this finding is of interest in light of the benefit of heart rate–lowering therapy in patients with HF and reduced LVEF (23,24).

We found that enalapril was as effective in reducing the development of HF in patients with diabetes as in those without diabetes. However, the current findings also draw attention to the importance of understanding the cardiovascular effects of treatments for diabetes in these patients, treatments that might attenuate (or accentuate) the risk of developing HF. Such treatments, however, were not recorded in SOLVD-P, although when this trial was conducted, relatively few choices were available (largely sulfonylureas and insulin). Sulfonylureas and insulin both have been associated with an increased risk of HF versus other treatments in observational studies, although no increase with insulin in a large randomized placebo-controlled trial was observed (25–27). The significance of this question has been highlighted in other diabetes trials. Two trials with dipeptidyl peptidase 4 inhibitors raised concerns that the agents studied might increase the risk of developing HF, whereas two others with SGLT2 inhibitors have shown the opposite (28–31). In none of these trials was the HF phenotype described.

The strengths of this study include the unique population of patients with ALVSD and detailed information on demographics, comorbidities, and clinical measurements. This study also has several limitations. It was a retrospective analysis; thus, we do not have data on type and duration of diabetes, glycated hemoglobin, and medication used to treat diabetes. We do not know about possible undiagnosed diabetes at baseline and the development of diabetes during follow-up, although both are likely to have diluted rather than exaggerated the risks reported. An immortal time bias was introduced in analyses of risk of death in patients developing HF (i.e., patients had to be alive until the development of HF). Thus, the true risk of death associated with the development of HF might be even higher than the reported results.

In conclusion, in patients with ALVSD, diabetes is associated with an increased risk of developing HF, HF hospitalization, and cardiovascular death. The relative risk of death in patients who develop HF (vs. those who do not) is similarly high, irrespective of diabetes status. This information might help in the development of strategies to prevent the transition from ALVSD to overt HF.

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