Title: Risk of incident heart failure in patients with diabetes and asymptomatic left ventricular systolic dysfunction

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Abstract

Introduction: While it is well known that diabetes is 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-Prevention).

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

Results: Of the 4223 eligible participants, 647 patients (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 (24%) of the 3576 patients without diabetes developed HF, compared to 214 (33%) of the 647 patients with diabetes. In unadjusted analyses, patients with diabetes had a higher risk of development of HF (HR=1.53 [1.32-1.78], P<0.001), HF hospitalization (HR=2.04 [1.65-2.52], P<0.0001), and of the composite outcome of development of HF or cardiovascular death (HR=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 increased risk of death irrespective of diabetes status.

Keywords: Asymptomatic left ventricular dysfunction, heart failure, diabetes

Introduction

Heart failure (HF) and type 2 diabetes mellitus are two epidemics of modern times and many patients suffer from both conditions. Their coexistence places these individuals at very high risk of adverse cardiovascular outcomes, underscoring the importance of understanding the interactions between the two conditions.[1-6] It has long been recognized that patients with diabetes have a higher incidence of cardiovascular disease, including a two- to four-fold higher risk of heart failure, than people without diabetes.[7-11] However, we do not fully understand the link between diabetes and development of heart failure. For example, we still do not know whether diabetes causes heart failure directly or whether the higher risk of heart failure simply reflects the greater frequency of hypertension and myocardial infarction in patients with diabetes. Of course, if diabetes does directly promote the development of heart failure, it should also accelerate the development of heart failure in patients with pre-existing sub-clinical cardiac damage. To test this hypothesis, we examined the progression from asymptomatic left ventricular systolic dysfunction (ALVSD) to overt heart failure in patients with and without diabetes in the prevention arm of the Studies of Left Ventricular Dysfunction (SOLVD-P).

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 was designed to study the effect of enalapril on the development of heart failure 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 due to dyspnea or fatigue and were not receiving diuretics,

digoxin, or vasodilators for the treatment of HF (but could receive these for other indications such as hypertension and atrial fibrillation). According to the SOLVD protocol, participants had to exhibit no symptoms or signs of overt HF during a three-week run in period. During this period, patients received open-label enalapril for 2 to 7 days followed by open-label placebo for 14 to 17 days, after which they were randomly assigned 1:1 to double-blind enalapril or placebo.

Definition of diabetes mellitus

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 present analyzes we stratified patients by history of diabetes at baseline.

Outcomes

Patients were seen 2 and 6 weeks after randomization and at 4 months and then every 4 months until the end of study. The development of heart failure was a pre-specified endpoint, defined by the onset of symptoms and/or signs of "congestive heart failure" (shortness of breath on exertion or at rest, evidence of fluid retention such as peripheral edema, pulmonary congestion, jugular venous distension) which, in the opinion of the site investigator were sufficiently severe to warrant pharmacologic treatment. Hospital admission for HF and death due to heart failure were additional pre-specified HF endpoints (these were potentially overlapping, non-mutually exclusive events).

In the present analyses, we examined the following outcomes: i) development of HF, ii) hospitalization for HF, iii) death from cardiovascular (CV) causes and iv) death from any cause according to diabetes status at baseline (and in the case of all-cause death, also after development of heart failure).

Statistical analyses

Baseline characteristics were described by use of proportions for categorical variables and means with standard deviations for continuous variables. Baseline differences between patients with and without diabetes were tested by use of 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 non-cardiovascular causes as a competing risk by use of the Aalen-Johansen method.[15] Log rank test and Gray's test were used to analyze unadjusted differences, respectively. Event rates for each outcome of interest are presented per 1000 person years of follow-up. Cox proportional hazard models were used to compare the risk of patients with and without history of diabetes for all outcomes of interest, as well as the effect of enalapril on these outcomes according to diabetes status at baseline. The adjusted Cox regression models included information on age, gender, 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. Tests for interactions between atrial fibrillation and heart rate as well as angina at baseline and history of myocardial infarction in relation to all outcomes were preformed 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 hazard assumption. Furthermore analyses with blood pressure, creatinine and myocardial infarction as time-dependent covariates were carried out. The rate of total hospitalizations for HF was compared by use of negative binomial regression with logarithm of the duration of follow-up as the offset.[16]

Analyses were performed by use of Stata version 14 and R version 3.3.2.

Results

Baseline characteristics

A total of 4223 patients (99.9%) had information about history of diabetes recorded. Of these, 647 (15%) patients had a diagnosis of diabetes. Patients with diabetes were older (mean age 61 years compared with 58 years in patients without diabetes), more were women (15% vs 11%), they had a higher weight (mean 85 kg vs 82 kg), systolic blood pressure (130 mmHg vs 125 mmHg), and heart rate (78 bpm vs 74 bpm) and a different racial composition (77% whites and 16% blacks vs 88% whites and 8% blacks) (Table 1). History of hypertension and treatment with diuretics were also more common among patients with diabetes, compared to those without.

Clinical outcomes according to diabetes status

During the median follow-up of 36 months (quartile 1-quartile 3, 26-47), 861 (24.1%) of the 3576 patients without diabetes 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 show 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 was1178 days, compared to 602 days in those with diabetes. As well as a higher risk of developing HF (Figure 1A), patients with diabetes also had a higher risk of HF hospitalization (Figure 1B) and of the composite endpoint of development of HF or cardiovascular death (Figure 1C), compared to patients without diabetes. Patients with diabetes were also at greater risk of death from any cause than those without diabetes (Figure 1D). The risk of each of these outcomes remained elevated in patients with diabetes when examined in adjusted Cox regression analyses (Table 2).

An incident myocardial infarction following randomization and prior to 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 compare to those without (adjusted HR=1.30 [1.11-1.52], P=0.001). Similarly, inclusion of systolic blood pressure or creatinine as time-dependent covariates did not weaken the association between diabetes and development of HF (adjusted HR=1.32 [1.12-1.54], P=0.001; HR=1.29 [1.10-1.50], P=0.002; respectively).

The total number of admissions to hospital for HF (taking account of repeat admissions) according to diabetes status is shown in Supplementary table 2. The crude rate of HF hospitalizations was 110 hospitalizations per 1000 person-years for patients with diabetes and 55 hospitalizations per 1000 person-years among patients without diabetes. This yielded an adjusted incidence rate-ratio of 1.93 [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 figure 1), HF hospitalization and the composite endpoint of HF hospitalization and cardiovascular death (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 figure 1).

Survival overall and following a HF event

In patients who did not develop HF, the risk of death over up to 4 years of follow-up was 14% [12%-16%] in those without diabetes at baseline and 22% [16%-27%] in those with diabetes (Figure 2). In those who did develop HF, the risk of death was 29% [25%-33%] in patients without diabetes at baseline and 37% [29%-45%] in those with diabetes. Focusing 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 1000 person years. The high mortality rate after development of HF was similar whether the first manifestation of HF was development of symptoms/signs or admission to hospital (Supplementary figure 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 developing HF had a significantly higher risk of subsequent death compared with patients who did not develop HF (Table 2). However, the *relative* risk of death in patients developing HF (compared to those not developing HF) was similar in participants with and without diabetes.

Effect of enalapril according to diabetes mellitus status

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

Discussion

The SOLVD Prevention trial remains the only detailed source of information on the natural history of ALVSD and, in particular, on the progression of ALVSD to symptomatic heart failure. As such this dataset also provided a unique opportunity to investigate whether diabetes accelerates the progression of ALVSD to symptomatic heart failure. And that is exactly what we found – patients

with diabetes were 1.5 to 2.0 times as likely to develop HF, or 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 heart failure were 2 to 3 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 account of repeat admissions) – with double the rate of admissions (110 versus 55) per 1000 person years 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-Prevention helps address this problem. Most patients in SOLVD-Prevention 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 accounting for these in a time-dependent co-variate analysis did not weaken the relationship between diabetes and development of HF. This indicates that diabetes can accelerate the risk of developing HF without the occurrence of further clinically recognized myocardial infarction. Of course patients might have experienced "silent" myocardial infarction, which may be more common in persons with diabetes.[20] Unfortunately, "silent" myocardial infarction was not collected in SOLVD-Prevention although, when it has been looked for, "silent" myocardial infarction has been uncommon, compared with recognized infarction and is unlikely to explain the excess risk of heart failure.

Apparently counterintuitively, we found that history of myocardial infarction was associated with lower likelihood of all outcomes. However, four out 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. Alternatively, the alternative underlying cause of left ventricular systolic dysfunction 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 to those without. Thus, among patients with symptomless left ventricular systolic dysfunction, higher systolic blood pressure does not seem to be a predictor of adverse outcomes. While this is clearly different that in patients with hypertension and cardiovascular disease more generally, it is also the pattern found in patients with HF and reduced ejection fraction where higher systolic pressure is associated with better outcomes (and low pressure with worse outcomes). Of course, patients with systolic dysfunction generally do not have substantially elevated blood pressure.

Indeed, in the multivariable analysis, diabetes emerged as a significant predictor of developing HF. Other significant predictors included high heart rate, low LVEF, black race, higher creatinine, age, and NYHA class, along with history of COPD. This 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 heart failure (although baseline creatinine was similar in patients with and without diabetes).[21, 22] Interestingly, heart rate was higher in patients with diabetes despite a similar prevalence of atrial fibrillation and similar use of

beta-blockers and digoxin in patients with and without diabetes. It is possible that autonomic neuropathy might also contribute to the HF risk related to diabetes and this finding is also of interest in light of the benefit of heart rate-lowering therapy in patients with heart failure and reduced ejection fraction.[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, our 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. Unfortunately, such treatments were not recorded in SOLVD-Prevention, although when this trial was conducted there were relatively few choices available (largely sulfonylureas and insulin). Sulfonylureas and insulin have both been associated with an increased risk of HF when compared to other treatments in observational studies, although there was no increase with insulin in a recent large randomized placebo-controlled trial.[25-27] The significance of this question has been highlighted in recent diabetes trials. Two with DPP-4 inhibitors raised concerns that the agents studied might increase the risk of developing HF whereas two other trials with SGLT2 inhibitors have clearly shown the opposite.[28-31] Unfortunately, in none of these trials was the heart failure phenotype described.

Strengths and limitations

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. This was a retrospective analysis. 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, allow both of

these 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 development of HF might be even higher than the results we report.

Conclusion

In patients with ALVSD; diabetes mellitus is associated with an increased risk of developing HF, HF hospitalization and cardiovascular death. The relative risk of death in patients developing HF (compared to those not developing HF) was similar 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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Guarantor: Dr. Rasmus Rørth is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Table 1: Baseline characteristics of patients with and without diabetes.

	No diabetes	Diabetes	P-values
Patients, n (%)	3576 (85)	647 (15)	
Age, mean ± SD	58 ± 11	61 ± 9	< 0.0001
Male sex, n (%)	3195 (89%)	552 (85%)	0.003
Race, n (%)			< 0.0001
White	3160 (88%)	494 (76%)	
Black	301 (8%)	102 (16%)	
Other	112 (3%)	50 (8%)	
Enalapril treatment, n (%)	1781 (50%)	326 (50%)	
NYHA class, n (%)			0.38
I	2403 (67%)	417 (64%)	
II	1169 (33%)	229 (35%)	
III	4 (0.1%)	1 (0.2%)	
Weight (kg), mean ± SD	81 ± 14	85 ± 15	< 0.0001
Current Smokers, n (%)	865 (24%)	129 (20%)	0.16
Ejection Fraction	0.28 ± 0.06	0.29 ± 0.05	0.11
Blood pressure (mm Hg)			
Systolic	125 ± 16	130 ± 17	< 0.0001
Diastolic	78 ± 10	78 ± 10	0.52
Heart Rate (beats/min)	74 ± 12	78 ± 13	< 0.0001
Sodium	140 ± 3	139 ± 3	< 0.0001
Potassium	4.3 ± 0.4	4.4 ± 0.4	0.22
Creatinine (µmol/l)	101 ± 23	102 ± 26	0.41
Medical history			
Myocardial infarction	2873 (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	1226 (34%)	341 (53%)	< 0.0001
Angina pectoris*	1186 (33%)	245 (38%)	0.05
Drug therapy, n (%)			
Diuretics	560 (16%)	145 (22%)	< 0.0001
Digoxin	446 (12%)	82 (13%)	0.89
Beta-blockers	848 (24%)	167 (26%)	0.25
Antiplatelet agents	1921 (54%)	371 (57%)	0.08
Anticoagulant agents	444 (12%)	54 (8%)	0.003
Antiarrhythmic drugs	569 (16%)	68 (11%)	0.0004
Calcium-channel blockers	1216 (34%)	259 (40%)	0.02

Abbreviations: SD - Standard deviation, COPD - Chronic obstructive pulmonary disease, * at baseline

Table 2: Event rates and hazard ratios for all outcomes according to diabetes status.

	No. events	Crude rate per 1000 py	Unadjusted HR (95% CI)	P- values	Adjusted HR* (95% CI)	P- values
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	1120	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.)	

Abbreviations: HR=Hazard Ratio; PY=Person years; HF=Heart failure; CV= Cardiovascular.

*****Adjusted for age gender, treatment effect, race, NYHA class, smoking status, ejection fraction, systolic blood pressure, heart rate, creatinine levels, angina at baseline and history of myocardial infarction, COPD, stroke, atrial fibrillation and hypertension.

Figure legends:

Figure 1: Cumulative incidence of development of heart failure HF (A), HF hospitalization (B), with death as competing risk among patients with and without diabetes. Risk of developing HF, HF Hospitalization or cardiovascular death with non-cardiovascular death as competing risk among patients with and without diabetes **(C)**. Risk of death among patients with and without diabetes (D).

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