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Influence of Diabetes and Diabetes-Gender Interaction on the Risk of Death in Patients Hospitalized With Congestive Heart Failure

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OBJECTIVES The purpose of this study was to investigate the influence of diabetes on long-term mortality in a large cohort of patients hospitalized with heart failure (HF).

BACKGROUND Diabetes is common in HF patients, but information on the prognostic effect of diabetes is sparse.

METHODS The study is an analysis of survival data comprising 5,491 patients consecutively hospitalized with new or worsening HF and screened for entry into the Danish Investigations of Arrhythmia and Mortality on Dofetilide (DIAMOND). Screening, which included obtaining an echocardiogram in 95% of the patients, took place at Danish hospitals between 1993 and 1995. The follow-up time was five to eight years.

RESULTS A history of diabetes was found in 900 patients (16%), 41% of whom were female. Among the diabetic patients, 755 (84%) died during follow-up, compared with 3,200 (70%) among the non-diabetic patients, resulting in a risk ratio (RR) of death in diabetic patients of 1.5 (95% confidence interval [CI] 1.4 to 1.6, $p < 0.0001$). In a multivariate analysis, the RR of death in diabetic patients was 1.5 (CI 1.3 to 1.76, $p < 0.0001$), but a significant interaction between diabetes and gender was found. Diabetes increased the mortality risk more in women than in men, with the RR for diabetic men being 1.4 (95% CI 1.3 to 1.6, $p < 0.0001$) and 1.7 for diabetic women (95% CI 1.4 to 1.9, $p < 0.0001$). The effect of diabetes on mortality was similar in patients with depressed and normal left ventricular systolic function.

CONCLUSIONS Diabetes is a potent, independent risk factor for mortality in patients hospitalized with HF. The excess risk in diabetic patients appears to be particularly prominent in females. (J Am Coll Cardiol 2004;43:771–7) © 2004 by the American College of Cardiology Foundation

Diabetes mellitus is common in patients with heart failure (HF). In surveys and clinical trials of HF, the prevalence of diabetes ranges from 10% to more than 30% (1). When patients with pre-diabetic glucose abnormalities are included, the prevalence exceeds 40% (2). Information on the prognosis in diabetic patients with HF is sparse. Most of the available information is the result of post-hoc analysis of randomized trials in myocardial infarction (MI) and congestive HF (CHF). From analyses of studies in MI, it is well known that patients with diabetes have an increased mortality, which is largely attributable to their higher risk of developing post-MI HF (3–8). This increased risk of diabetes seems to be particularly evident in patients treated with insulin (3,6,9) or in those who are female (3,9). In the community setting, an increased incidence of HF has been reported in diabetic subjects, with female diabetic patients having a particularly increased risk of developing HF (10). The Framingham studies have demonstrated the importance of diabetes for long-term mortality in HF patients in the community (11). With regard to randomized studies, diabetes was found to be an independent risk factor for mortality and morbidity in both symptomatic and asymptomatic HF in the Studies Of Left Ventricular Dysfunction (SOLVD) (12). However, in terms of consecutive patients hospitalized with HF, no contemporary analysis on long-term prognosis in diabetic subjects exists. We used a large database of consecutive hospitalizations for HF to study the influence of diabetes on long-term prognosis and to evaluate the impact of other risk factors, particularly gender, on the prognosis in diabetic subjects.

METHODS

Patient population. The current study is an analysis of survival data comprising 5,491 patients screened for entry into the Danish Investigations of Arrhythmia and Mortality on Dofetilide in Congestive Heart Failure—the DIAMOND-CHF trial. Originally 5,548 patients were screened, but 57 patients were excluded from this study because follow-up was impossible due to misrecorded personal data. The DIAMOND trial was a multicenter, randomized, double-blinded, placebo-controlled study of the

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Abbreviations and Acronyms

ACE	= angiotensin-converting enzyme
CHF	= congestive heart failure
CI	= confidence interval
DIAMOND	= Danish Investigations of Arrhythmia and Mortality on Dofetilide trial
HF	= heart failure
ICD-9-CM	= International Classification of Diseases-Ninth Revision-Clinical Modification
LV	= left ventricle/ventricular
LVEF	= left ventricular ejection fraction
MI	= myocardial infarction
NYHA	= New York Heart Association
RR	= risk ratio
WMI	= wall motion index

efficacy of a novel class III antiarrhythmic agent, dofetilide, in patients with acute MI or CHF. Details of the DIAMOND study design (13) and results of the DIAMOND-CHF trial (14) have been published previously. The 34 Danish hospitals participating in the DIAMOND-CHF study screened all patients admitted consecutively to their centers with new or worsening HF in the period between November 1993 and December 1995. In Denmark, HF patients are admitted to approximately 60 different hospitals, implying that more than half of the potential Danish hospitals participated in the study. Small county hospitals and university teaching hospitals participated in the study, and as such, it can be anticipated that the study population is highly representative of hospitalized HF patients in Denmark.

The patients should have been in New York Heart Association (NYHA) functional class III or IV at some time within the preceding month to be eligible for the DIAMOND-CHF study. Patients with acute MI within seven days before screening were excluded from the CHF part of the DIAMOND study. The screening procedure consisted of a clinical history, a physical examination, and an echocardiogram, which was recorded on videotape locally and evaluated in a central laboratory. The wall motion index (WMI), with use of a 16-segment model of the left ventricle (LV), was calculated using a reverse scoring system (15). WMI multiplied by 30 gives a rough estimate of percent left ventricular ejection fraction (LVEF). Left ventricular systolic function was obtained in 95% of the patients. New-onset CHF was defined as a CHF duration <1 month.

The diagnosis of diabetes was based on a self-report by the patient or by documentation in the patient's medical records. Diabetic subjects were classified according to both the types of diabetes (I or II) and the antidiabetic treatment regimen (diet alone, oral hypoglycemic agents, or insulin). Patients receiving both insulin and oral hypoglycemic agents were classified as treated with insulin.

Survival status was obtained from the Danish Central Personal Registry in July 2002, 8.5 years after screening of the first patient. The minimum follow-up time was five years. Four patients emigrated during follow-up, and they were censored at the time they left Denmark.

Statistics. Discrete variables were compared using the chi-square test, and continuous variables with the rank-sum test. Mortality curves were generated using Kaplan-Meier survival estimates. Multivariate analysis of mortality was made using Cox proportional hazards models. Covariates considered of potential prognostic impact by the authors were entered into the model. The assumptions of proportional hazards and linearity with regard to continuous variables were met for all variables studied. The interaction between diabetes and other risk factors (age, gender, WMI, history of ischemic heart disease, and history of hypertension) was tested by likelihood ratio test. The only relevant interaction found was between diabetes and gender. For this reason, separate variables were used for diabetes in males and females. Significance was accepted at $p < 0.05$. All calculations were made using the Statistical Analysis System software (SAS Institute, Cary, North Carolina).

Ethics. The study was conducted in accordance with the Declaration of Helsinki II and was approved by the Central Danish Ethics Committee. All patients gave their written, informed consent before screening.

RESULTS

Patient characteristics. Almost all patients were Caucasian (99.9%). A history of diabetes was found in 900 (16%) of the 5,491 patients. Type I diabetes accounted for 75 cases (8%) and type II for 825 cases (92%). In the diabetic group as a whole, 24% were treated with insulin, 51% with oral hypoglycemic agents, and 25% with diet alone. The median time since diagnosis of diabetes was 7.1 years. The baseline characteristics of patients with and without a history of diabetes are presented in Table 1. The duration of HF varied considerably in both groups, but the median duration was found to be longer for the diabetic group. Compared with non-diabetic patients, diabetic patients had a higher frequency of arterial hypertension and known ischemic heart disease. Left ventricular systolic function was slightly more impaired in patients with than in patients without diabetes. Systolic dysfunction, defined as WMI ≤1.2 (corresponding to LVEF ≤35%), was present in 54% of the diabetic subjects and in 45% of the non-diabetic subjects. Diabetic patients received more diuretics, digoxin, and angiotensin-converting enzyme (ACE) inhibitors, reflecting their higher frequency of previous cardiovascular disease.

Characteristics of diabetic women compared with diabetic men. Compared with diabetic men, diabetic women were older and had a longer duration of diabetes and a lower body mass index. The women smoked less and had a lower frequency of previous MI. Despite having similar NYHA functional class distribution and a higher use of diuretics, the women had better systolic function (Table 2). Similar differences between men and women were found among non-diabetic patients (Table 3).

Table 1. Baseline Characteristics of 5,491 Patients With and Without a History of Diabetes

	Diabetics (n = 900)	Non-Diabetics (n = 4,591)	p Value
Age (yrs)	73 (55–85)	73 (52–86)	0.54
Male gender (%)	59	60	0.40
Body mass index (kg/m^2)	26 (20–36)	25 (19–34)	<0.0001
Smoking (%)	29	35	0.0003
Clinical history			
Ischemic heart disease (%)	64	55	<0.0001
Previous AMI (%)	39	36	0.11
Treated hypertension (%)	30	23	<0.0001
Atrial fibrillation (%)	27	24	0.06
Valvular heart disease (%)	3.0	3.9	0.18
CHF duration (months)	12 (0.07–156)	6 (0.07–120)	<0.0001
New-onset CHF (%)	30	41	<0.0001
WMI	1.2 (0.6–2.0)	1.4 (0.6–2.0)	<0.0001
NYHA class III or IV (%)	64	63	0.72
Medication on admission			
Beta-blockers (%)	13	13	0.62
ACE inhibitors (%)	37	25	<0.0001
Diuretics (%)	84	71	<0.0001
Digoxin (%)	43	31	<0.0001

Continuous variables are presented as the median value (5th to 95th percentiles).
ACE = angiotensin-converting enzyme; AMI = acute myocardial infarction; CHF = congestive heart failure; NYHA = New York Heart Association; WMI = wall motion index.

Mortality. Among the diabetic patients, 755 (84%) died during follow-up, compared with 3,200 (70%) among the non-diabetic patients (Fig. 1). Crude one-month and one-year mortality rates for patients without diabetes were 5% and 23%, respectively. The corresponding numbers for patients with diabetes were 7% and 31%. When evaluated in a univariate model, the risk ratio (RR) of death in diabetic patients compared with non-diabetic patients was 1.5 (95% confidence interval [CI] 1.4 to 1.6, $p < 0.0001$). To investigate whether the increased mortality in patients with diabetes reflected a higher prevalence of concomitant risk factors, a multivariate analysis, including age, gender, smoking, history of ischemic heart disease, previous MI, arterial hypertension, atrial fibrillation, NYHA functional class, and WMI as covariates, was performed. The RR of death in diabetic patients in this model was 1.5 (95% CI 1.3 to 1.6, $p < 0.0001$) (Table 4). Unfortunately, information on body mass index was missing for 791 patients (14%); therefore, this variable was not included in the multivariate model. Adding body mass index to the model, however, did not alter the results significantly. Similarly, data on new-onset CHF was missing for 437 patients (8%), and the addition of

Table 2. Baseline Characteristics of 900 Diabetic Patients According to Gender

	Women (n = 370)	Men (n = 530)	p Value
Age (yrs)	75 (57–87)	71 (54–83)	<0.0001
Body mass index (kg/m^2)	26 (19–38)	27 (21–35)	0.04
Smoking (%)	22	34	<0.0001
Clinical history			
Ischemic heart disease (%)	62	66	0.16
Previous AMI (%)	32	44	0.0005
Treated hypertension (%)	32	28	0.15
Atrial fibrillation (%)	25	28	0.44
Valvular heart disease (%)	3.0	3.0	0.97
CHF duration (months)	20 (0.07–180)	12 (0.07–144)	0.31
Diabetes duration (months)	8.0 (0.9–26.1)	6.6 (0.4–25.7)	0.02
WMI	1.4 (0.6–2.0)	1.1 (0.5–2.0)	<0.0001
NYHA class III or IV (%)	63	64	0.57
Medication on admission			
Beta-blockers (%)	14	13	0.96
ACE inhibitors (%)	32	40	0.01
Diuretics (%)	87	82	0.04
Digoxin (%)	44	43	0.66
Insulin (%)	28	21	0.03

Continuous variables are presented as the median value (5th to 95th percentiles).
Abbreviations as in Table 1.

Table 3. Baseline Characteristics of 4,591 Non-Diabetic Patients According to Gender

	Women (n = 1,819)	Men (n = 2,772)	p Value
Age (yrs)	75 (56–88)	72 (50–85)	<0.0001
Body mass index (kg/m^2)	24 (18–34)	26 (20–34)	<0.0001
Smoking (%)	28	40	<0.0001
Clinical history			
Ischemic heart disease (%)	51	58	<0.0001
Previous AMI (%)	28	42	<0.0001
Treated hypertension (%)	26	21	0.0004
Atrial fibrillation (%)	22	25	0.01
Valvular heart disease (%)	5.0	3.3	0.006
CHF duration (months)	5 (0.07–192)	6 (0.07–120)	0.17
WMI	1.7 (0.6–2.0)	1.2 (0.5–2.0)	<0.0001
NYHA class III or IV (%)	63	63	0.81
Medication on admission			
Beta-blockers (%)	14	12	0.17
ACE inhibitors (%)	20	28	<0.0001
Diuretics (%)	74	69	0.002
Digoxin (%)	32	31	0.49

Continuous variables are presented as the median value (5th to 95th percentiles).
Abbreviations as in Table 1.

this variable, likewise, did not change the independent impact of diabetes on mortality (RR 1.4, $p < 0.0001$), nor was the result changed significantly by the addition of treatment with ACE inhibitors, beta-blockers, or digoxin or whether or not the patients were included in the randomized DIAMOND study. In the former multivariate model (including randomization status and treatment with ACE inhibitors, beta-blockers, or digoxin) and in a model including only age, diabetes, and gender, a significant interaction between diabetes and gender was found ($p = 0.03$ and $p = 0.01$, respectively). Consequently, a new multivariate model including the same nine covariates, besides separate variables for diabetes in men and diabetes in women, was created. This model revealed that the interaction between diabetes and gender reflected that diabetes increased the mortality risk more in women than in men, with the RR for diabetic men being 1.4 (95% CI 1.3 to 1.6, $p < 0.0001$) and 1.7 for diabetic women (95% CI 1.4 to 1.9, $p < 0.0001$). In patients without diabetes, males had a higher mortality, but the opposite was found for diabetic patients, where the females had the highest mortality rate (Fig. 2). During follow-up, 70% of the non-diabetic men and 69% of the non-diabetic women died. The corresponding numbers for the diabetic men and women were 83% and 85%. Other significant interactions between diabetes and the remaining parameters in the multivariate model were not found.

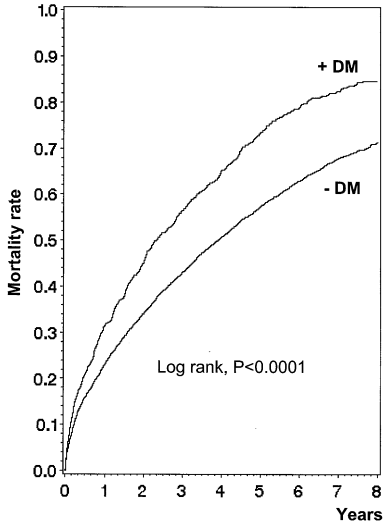

Figure 1. Cumulative mortality from all causes in patients with and without diabetes. +DM = diabetic patients; −DM = non-diabetic patients.

To test if the presented results also apply to the subgroup of HF patients with LV systolic dysfunction, we performed the same analyses in those who had WMI ≤1.2. Essentially, we found similar results. Diabetes was an independent risk factor of death (RR estimate of 1.5) in both the univariate and multivariate models. Furthermore, in the multivariate model, the interaction between diabetes and gender was also significant ($p = 0.03$).

The group of type I diabetic patients ($n = 75$) was too small to allow for separate statistical analysis. Instead, we analyzed the mortality data by classifying the diabetic patients into three subgroups according to the antidiabetic treatment regimen (diet, tablets, and insulin). Compared with the other two groups, the patients in the insulin-treated group were younger and had a longer duration of diabetes and a tendency toward a higher frequency of previous ischemic heart disease and MI. Mortality during follow-up was 83% in the diet-treated group, 84% in the group treated with tablets, and 86% in the insulin-treated group ($p = 0.59$ by log-rank). When the findings were adjusted for the important differences in age and gender, insulin therapy was a significant risk factor for mortality (RR 1.39, 95% CI 1.07 to 1.80; $p = 0.02$). However, when further risk factors were allowed into the model, this effect

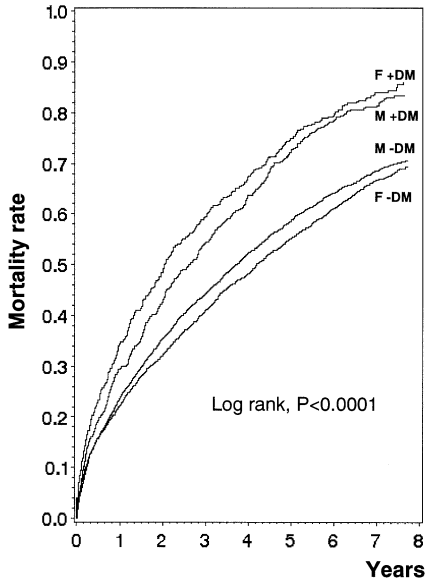

Figure 2. Cumulative mortality from all causes in patients with and without diabetes for each gender. +DM = diabetic patients; −DM = non-diabetic patients; F = females; M = males.

of insulin therapy versus diet treatment disappeared (RR 1.18, 95% CI 0.87 to 1.62; p = 0.29).

DISCUSSION

Major results. The present study is the first large investigation providing data on long-term prognosis and LV systolic function in diabetic patients derived from a cohort of consecutive patients hospitalized with HF. In general, a comparison of studies on diabetes and HF is difficult because of variability in the definition of disease entities. Most studies, however, define diabetes by history, as was the case in our study. The age and gender distribution of our cohort is similar to those found in contemporary studies of unselected HF patients (11,16–18). Because the prevalence of diabetes is highly associated with age and gender, this figure should be compared with other studies of a relatively unselected nature. The diabetes frequency of the present study (16%) is close to the findings in a French survey (19%) (17), in a British study (16%) (18), and in the earlier Framingham Heart Study (19%) (11), but is somewhat less than in contemporary U.S. cohorts, where the frequencies are above 30% (19,20). This discrepancy probably reflects the difference in the diabetes prevalence between Europe and the U.S.

Long-term mortality in diabetic patients from HF cohorts has only been investigated in a limited number of studies. Among 652 patients from the Framingham Heart Study with new-onset of HF and a mean follow-up of 3.9 years, diabetes emerged as a risk factor for mortality (11). This was also the case in a large Scottish cohort study (16). However, the interpretation of this study is difficult, as diabetes was defined by International Classification of Diseases-Ninth Revision-Clinical Modification (ICD-9-CM) codes, resulting in a diabetes prevalence of only 3%. In a prospective cohort of 435 patients admitted to a hospital with HF, diabetes had no impact on one-year mortality (19).

Table 4. Long-Term Mortality Risk in Diabetic Patients Compared With Non-Diabetic Patients: Results of Univariate and Multivariate Models

	RR (95% CI)	p Value
Univariate	1.5 (1.4–1.6)	<0.0001
Multivariate model 1*	1.5 (1.4–1.7)	<0.0001
Multivariate model 2†	1.5 (1.3–1.6)	<0.0001

*Including age and gender as covariates. †Including age, gender, smoking, history of ischemic heart disease, previous myocardial infarction, arterial hypertension, atrial fibrillation, New York Heart Association class, and wall motion index as covariates.
CI = confidence interval; RR = risk ratio.

Additional information on the prognostic influence of diabetes can be obtained from a few studies in selected populations with HF. In the SOLVD trials and registry, comprising patients with LV dysfunction, diabetes was found to be an independent risk factor of long-term mortality and HF-related hospitalizations, with the adjusted RR for mortality being 1.3 (12). In a hospitalized HF population of patients ≤65 years old, diabetes requiring insulin treatment was an independent predictor of long-term mortality (21). Diabetes determined by ICD-9-CM codes and adjusted for age and gender revealed a 20% increased long-term mortality in a large investigation of hospital records in older adults (≥67 years old) with HF (22). In contrast, diabetes had no prognostic impact on long-term mortality in the Cardiac Insufficiency BIsoprolol Study II (CIBIS-II), which included HF patients in NYHA functional class III or IV and with LVEF ≤35% (23). Likewise, diabetes had no prognostic value in a trial of 471 patients with advanced HF (24). The present study adds to information on the prognosis of consecutive hospitalized HF patients, showing that diabetic symptomatic patients both with and without LV dysfunction have about a 50% increased mortality rate compared with patients without diabetes, independent of conventional risk factors.

The cause of the increased risk in patients with diabetes is not known. Most likely, a higher prevalence of hypertension and ischemic heart disease involving more widespread and distal coronary arteriosclerosis plays an important role. The existence of a specific diabetic cardiomyopathy giving rise to LV diastolic dysfunction is another factor of potential negative influence on outcome (25). Also, we cannot exclude the possibility of a selection bias, implying that the diabetic patients have HF at a more advanced stage when hospitalized, and that such a situation is not completely accounted for by adding WMI and NYHA functional class to the regression models.

Interaction between diabetes and other variables. An important finding in this study is the diabetes–gender interaction. Previous reports have indicated that diabetes has a greater impact on women than on men with regard to the prognosis of HF, but a formal interaction analysis was

not applied in these studies (3,9,11). Also, there seems to be a similar experience with regard to the prognosis in coronary heart disease, although it is not a consistent finding (26,27). Very little is known about the mechanism underlying the gender difference in risk from diabetes in HF patients. It is possible that part of the explanation is a clustering of risk factors in diabetic women, which we were not able to control for, such as the level of high-density lipoprotein and apolipoprotein B (26,28). Angiographic data suggest a tendency toward more extensive coronary artery disease in diabetic women (29). Data from human studies in aortic stenosis and hypertension have revealed gender differences in LV hypertrophic responses (30). Moreover, in individuals without cardiovascular disease, it has been found that diabetes in women is independently associated with increased LV wall thickness and mass (31). This may result in a higher frequency of LV diastolic dysfunction, explaining the relative mismatch between symptoms and systolic function in women. However, the impact of isolated or coexisting diastolic dysfunction on prognosis is unknown. Lastly, it is possible that diabetic women with HF are admitted to the hospital only at a later stage, thereby introducing a selection bias (30).

In the present study, we did not find a significant interaction between diabetes and HF etiology (i.e., ischemic vs. non-ischemic HF). This is in contrast to recently published, important results from SOLVD (32), where it was found that diabetes was associated with an increased mortality only in patients with underlying ischemic heart disease. The reason for the discrepancy between the two studies is not clear. However, it should be considered that a definite diagnosis of ischemic heart disease has not been attempted in all patients in either study, and the condition is therefore likely to be underdiagnosed. Furthermore, a major difference between the studies exists in that a large part of the population in the study by Dries et al. (32) was recruited from the prevention arm of SOLVD. These patients, per definition, had systolic dysfunction but no clinical HF, and thus the results may not be comparable to those obtained in a population of patients hospitalized with HF.

In contrast to what has been described in studies of MI, we did not find a significantly higher mortality rate in the insulin-treated patients compared with the non-insulin-treated diabetic patients. However, there was a trend toward a higher mortality rate in insulin-treated subjects when age and other risk factors where controlled for. It is possible that the lack of a significant difference in mortality between the diabetic groups can simply be the result of a type 2 statistical error (i.e., the low number of patients treated with insulin).

Study limitations. The limitations of this study relate mainly to the definitions of diabetes and HF. Unfortunately, no data on the glycometabolic state were available. It can be anticipated that a significant proportion of the non-diabetic patients have undiagnosed diabetes. If these patients also have an increased mortality risk, the presented results are likely to underestimate the real difference between patients with and without diabetes. With regard to the definition of HF, this diagnosis was based on clinical judgment by the investigators, but it was a requirement that the patients had to be in NYHA functional class III or IV within the preceding month. It is possible that the study includes some patients who, if reevaluated, would turn out not to suffer from HF but from other conditions such as pulmonary disease. Therefore, it is reassuring that when performing the survival analysis including only patients with at least moderately depressed LV systolic function, similar results were obtained.

A point of concern is the significant baseline differences between diabetic and non-diabetic patients, which may confound the survival analyses. Efforts have been made in the multivariate analyses to correct for potential confounding, but one cannot exclude the possibility that other confounders that we were not able to include in the models exist.

Conclusions. The present study demonstrates that patients with diabetes represent a high-risk group in HF. Acknowledging this finding is important because therapy with ACE inhibitors (33) and beta-blockers (34) seems to have at least the same relative effect in these patients and, thereby, a greater absolute effect when compared with non-diabetic patients. In conclusion, diabetes is an important risk factor for mortality in HF patients, and the effect of diabetes appears to be most prominent in females.

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