Short- and Long-term Prognosis of Patients With Acute Heart Failure With and Without Diabetes: Changes Over the Last Three Decades

Diabetes Care 2018;41:143–149 | https://doi.org/10.2337/dc17-0544

Jan C. van den Berge, Alina A. Constantinescu, Hendrik J. Boiten, Ron T. van Domburg, Jaap W. Deckers, and K. Martijn Akkerhuis

OBJECTIVE

We studied differences in long-term (i.e., 10 year) prognosis among patients with acute heart failure (HF) with and without diabetes over the last three decades. In addition, we investigated whether the degree of prognostic improvement in that period was comparable between patients with and without diabetes.

RESEARCH DESIGN AND METHODS

This prospective registry included all consecutive patients aged 18 years and older admitted to the Intensive Coronary Care Unit with acute HF in the period of 1985–2008. A total of 1,810 patients were included; 384 patients (21%) had diabetes. The outcome measure was the composite of all-cause mortality, heart transplantation, and left ventricular assist device implantation after 10-year follow-up.

RESULTS

The 10-year outcome in patients with diabetes was significantly worse than in those without diabetes (87% vs. 76%; adjusted hazard ratio [HR] 1.17 [95% CI 1.02–1.33]). Patients admitted in the last decade had a significantly lower 10-year event rate than patients admitted in the first two decades, both among patients without diabetes (adjusted HR 0.86 [95% CI 0.75–0.99]) and patients with diabetes (adjusted HR 0.80 [95% CI 0.63–1.00]).

CONCLUSIONS

The long-term outcome of patients with diabetes is worse than that of patients without diabetes. However, the long-term prognosis improved over time in both groups. Importantly, this improvement in long-term prognosis was comparable in patients with and without diabetes. Despite these promising results, more awareness for diabetes in patients with acute HF is necessary and there is still need for optimal treatment of diabetes in acute HF.

The prevalence of both heart failure (HF) and diabetes has increased over the last decades and is expected to do so in the upcoming decades (1,2). Therefore, the presence of diabetes in patients with HF is also likely to increase and this is anticipated to become a major health concern. The actual prevalence of diabetes in patients with acute HF in different registries has varied but may be as high as 45% (3). Because the

Department of Cardiology, Thoraxcenter, Erasmus Medical Center, Rotterdam, the Netherlands

Corresponding author: Jan C. van den Berge, j.vandenberge@erasmusmc.nl.

Received 16 March 2017 and accepted 9 September 2017.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc17-0544/-/DC1.

See accompanying articles, pp. 11, 14, 136, 150, and 156.

structure and function of the heart is directly influenced by the presence of diabetes, diabetes is to be considered to represent more than just a comorbid condition in HF (4).

Diabetes has been shown to be an independent risk factor for the development of HF (5,6). Moreover, this risk has been shown to be age and sex dependent. Compared with patients without diabetes, the presence of diabetes doubles the risk of HF in men, and the risk of developing HF in women may be as much as four times higher (5). These associations may even be stronger in younger patients (5). Furthermore, the presence of diabetes has been associated with a longer duration of hospitalization and higher rates of rehospitalization among patients with acute HF (7,8). Importantly, in patients with HF, it has been established that the presence of diabetes is not only associated with an increased cardiovascular morbidity but also with an increased mortality (9–13). However, the prognostic value of diabetes on in-hospital and long-term mortality among patients with acute HF is still controversial (7,14–19).

Since the 2000s, several new treatment modalities have been added to the therapeutic regimen of chronic HF, resulting in an improved prognosis of these patients (20–23). However, it has not been established whether the improvement of prognosis in patients with acute HF was influenced by the presence of diabetes. For these reasons, we studied differences in long-term prognosis among patients with acute HF with and without diabetes over the last three decades. In addition, we investigated whether the degree of prognostic improvement in that period was comparable between patients with and without diabetes.

RESEARCH DESIGN AND METHODS

Inclusion

The study population and the design of the study have been described previously (23). In brief, all patients aged 18 years and older admitted to the Intensive Coronary Care Unit (ICCU) with acute HF were included in this prospective registry. The inclusion period was from 1985 until 2008. All patients were recruited from the Erasmus Medical Center.

Patients were included when the admitting physician established a diagnosis of acute HF or cardiogenic shock. We included patients with acute, new-onset HF as well as patients with decompensated chronic HF. Patients admitted for acute HF caused by an acute coronary syndrome without evidence of sustained systolic or diastolic dysfunction were excluded. If a patient was admitted more than once with acute HF, only the first admission was taken into account.

Ethics Statement

This was a prospective cohort registry. During the enrollment of the patients, approval from the local research ethics committee to conduct this study was not required. The study was conducted according to the Declaration of Helsinki (24).

Baseline Variables

Patient records and discharge letters were used for the collection of the baseline variables. Age and sex were collected as demographic variables. The following clinical variables were collected: previous medical history, etiology of HF, left ventricular ejection fraction (LVEF), and BMI. Also, the type of treatment at the ICCU was registered.

Diabetes was considered to be present when patients received oral antidiabetic therapy and/or subcutaneous insulin prior to admission. The LVEF was classified into the following qualitative categories: good, moderate, and poor. Quantitative measures for LVEF were categorized as follows: $>$45%, 30–44%, and $<$30% for preserved, moderately depressed, and severely depressed LVEF, respectively. The etiology of HF was categorized into ischemic HF and nonischemic HF.

End Point

The outcome measure of this study was the composite of all-cause mortality, heart transplantation, and implantation of a left ventricular assist device (LVAD) 10 years after the initial hospitalization. Survival status was assessed by using the Municipal Civil Registries in January 2017 and was available for 98% of the included patients.

Statistical Analysis

The study population was categorized into three groups: patients admitted in 1985–1989, 1990–1999, and 2000–2008. We chose these time frames according to the development of HF therapy (in particular, ACE inhibitors and β-blockers). In the 1980s, there was no evidence-based therapy for HF. New drug therapy like ACE inhibitors and β-blockers was developed and subsequently implemented in daily practice in the 1990s, and it had become common practice to prescribe them in the 2000s. Therefore, we hypothesized that the prognosis of patients admitted in the first decade was worse and that the prognosis would improve in the second decade and continued to improve in the last decade. Moreover, we have also performed additional statistical analyses with the study population divided into three equal groups of periods of 8 years (1985–1992, 1993–2000, and 2001–2008) in order to make sure the results were not depending on the chosen time period.

Data were summarized as mean with SD for continuous variables and as frequencies with percentage for categorized variables. The Student *t* test or ANOVA was used for comparing continuous variables and the χ^2 test for comparing categorized variables.

Since the LVEF was not reported in 28% of the patients and the etiology was not reported in 12% of the patients, we applied multiple imputation. Baseline characteristics were used as predictors. Pooled means were given for LVEF and etiology.

The Kaplan-Meier method was used to present the cumulative event curves. The log-rank test was applied for comparing the Kaplan-Meier curves. Landmark analyses for the 30-day event-free survivors (defined as patients who did not reach the composite end point) were performed as secondary analyses. We used logistic regression for the 30-day outcome and the Cox proportional hazards model for the 1- and 10-year outcomes in order to evaluate the independent association between diabetes and the composite end point of all-cause mortality, heart transplantation, and LVAD implantation. In multivariable analysis for 30-day and 1-year outcome, adjustments were made for age, sex, BMI, atrial fibrillation at admission, etiology of HF, LVEF, and a history of HF, rhythm or conduction disorder, and hypertension. In the analysis of the 10-year outcome, corrections were made for age, sex, BMI, etiology of HF, LVEF, period of admission, and a history of myocardial infarction, HF, and rhythm or conduction disorder. All variables were categorical, except for age, which was retained as a continuous variable. Results of logistic regression and the Cox proportional hazards model were reported as odds ratios (ORs) and hazard ratios (HRs), respectively, with their corresponding 95% CI.

All tests were two tailed, and *P* values <0.05 were considered statistically significant. All data were analyzed using SPSS software (SPSS 21.0, IBM Corp., Armonk, NY).

RESULTS

Baseline Characteristics

We identified 1,810 patients admitted with acute HF to our ICCU in the period of 1985 until 2008. Of these, 384 patients (21%) had diabetes. The prevalence of diabetes increased; in the 1980s, 14% of the patients had diabetes, compared with 21% in the 1990s and 27% in the most recent study period (*P* for trend <0.001). Baseline characteristics of patients with and without diabetes were different (Table 1). On average, patients with diabetes were 5 years older, were more often female, and had a higher BMI as compared with patients without diabetes. Furthermore, patients with diabetes more frequently had a history of hypertension, myocardial infarction, and coronary revascularization. Presence of diabetes was more commonly associated with ischemic HF, whereas patients without diabetes more often sustained HF of a nonischemic origin. The distribution of the left ventricular function was not influenced by the presence of diabetes.

Diabetes and Mortality

Compared with patients without diabetes, patients with diabetes less frequently reached the composite end point of all-cause mortality, heart transplantation, and LVAD implantation at 30 days (9% vs. 16%; unadjusted OR 0.51 [95% CI 0.35–0.75]) (Fig. 1). After multivariable adjustment, the difference in the 30-day event rate was somewhat attenuated but remained lower in patients with diabetes (adjusted OR 0.61 [95% CI 0.41–0.92]). The cumulative 1-year event rate was comparable between patients with and without diabetes (*P* = 0.13) (Fig. 1*A*). When the analysis was restricted to the 30-day event-free survivors only, the number of patients who reached the composite end point was almost identical in patients with diabetes and in those without diabetes (26% and 25%, respectively; *P* = 0.63) (Fig. 1*B*).

The number of patients who reached the composite end point of all-cause mortality, heart transplantation, and LVAD implantation after 10 years of follow-up was higher in patients with diabetes than in those without diabetes (87% vs. 76%; unadjusted HR 1.19 [95% CI 1.06–1.36]) (Fig. 1*A*), and this remained the case after multivariable adjustment (adjusted HR 1.17 [95% CI 1.02–1.33]). A more pronounced difference in the 10-year event rate between patients with and without diabetes became apparent when the analysis was restricted to the 30-day event-free survivors (adjusted HR 1.33 [95% CI 1.15–1.53]) (Fig. 1*B*).

Patients with diabetes more frequently had prior myocardial infarction, and an ischemic cause of HF was more common among these patients. However, since we did not find a significant interaction in the multivariable Cox proportional hazards model, neither between diabetes and previous myocardial infarction (*P* = 0.95) nor between diabetes and etiology of HF (*P* = 0.95), there was no difference in the impact on long-term outcome of these factors between patients with and without diabetes.

Long-term Prognosis Over Time

The baseline characteristics of patients with and without diabetes changed during the three decades of observation (Supplementary Table 1). With time, the presence of coronary revascularization, rhythm or conduction disorder, and hypertension became more frequent among both subgroups. In addition, the patients without diabetes were more commonly women and had less prior myocardial infarction over time. The distribution of the etiology of HF and LVEF remained stable over time in both patients with and without diabetes.

Table 1—Baseline characteristics of patients with and without diabetes

	Total population	Patients with diabetes	Patients without diabetes	*P* value*
No. of patients	1,810	384	1,426	
Age (years)	63.5 ± 14.8	67.1 ± 11.1	62.3 ± 15.5	<0.001
Male sex	1,153 (64)	223 (58)	930 (65)	0.01
BMI	25.1 ± 4.9	27.1 ± 6.3	24.6 ± 4.5	<0.001
Medical history				
Myocardial infarction	714 (39)	188 (49)	526 (37)	<0.001
Coronary revascularization†	390 (22)	108 (28)	282 (20)	<0.001
Heart surgery (not CABG)	237 (13)	38 (10)	199 (14)	0.04
Heart transplantation	9 (0.5)	1 (0.3)	8 (0.6)	0.69
Waiting for heart transplantation	35 (2)	4 (1)	31 (2)	0.15
HF	888 (49)	184 (48)	704 (49)	0.61
Rhythm or conduction disorder	445 (25)	83 (22)	362 (25)	0.13
Hypertension	590 (33)	184 (48)	406 (29)	<0.001
HF				
Etiology of HF				<0.001
Ischemic origin	845 (47)	239 (62)	606 (42)	
Nonischemic origin	965 (53)	145 (38)	820 (58)	
Atrial fibrillation at admission	391 (22)	75 (20)	316 (22)	0.27
LVEF				>0.05
Preserved	522 (29)	122 (32)	400 (28)	
Moderately depressed	427 (24)	91 (24)	336 (24)	
Severely depressed	861 (48)	171 (44)	690 (48)	

Data are *n* (%) or mean ± SD unless otherwise indicated. CABG, coronary artery bypass graft. *Comparison between patients with and without diabetes. †Percutaneous coronary intervention and/or CABG.

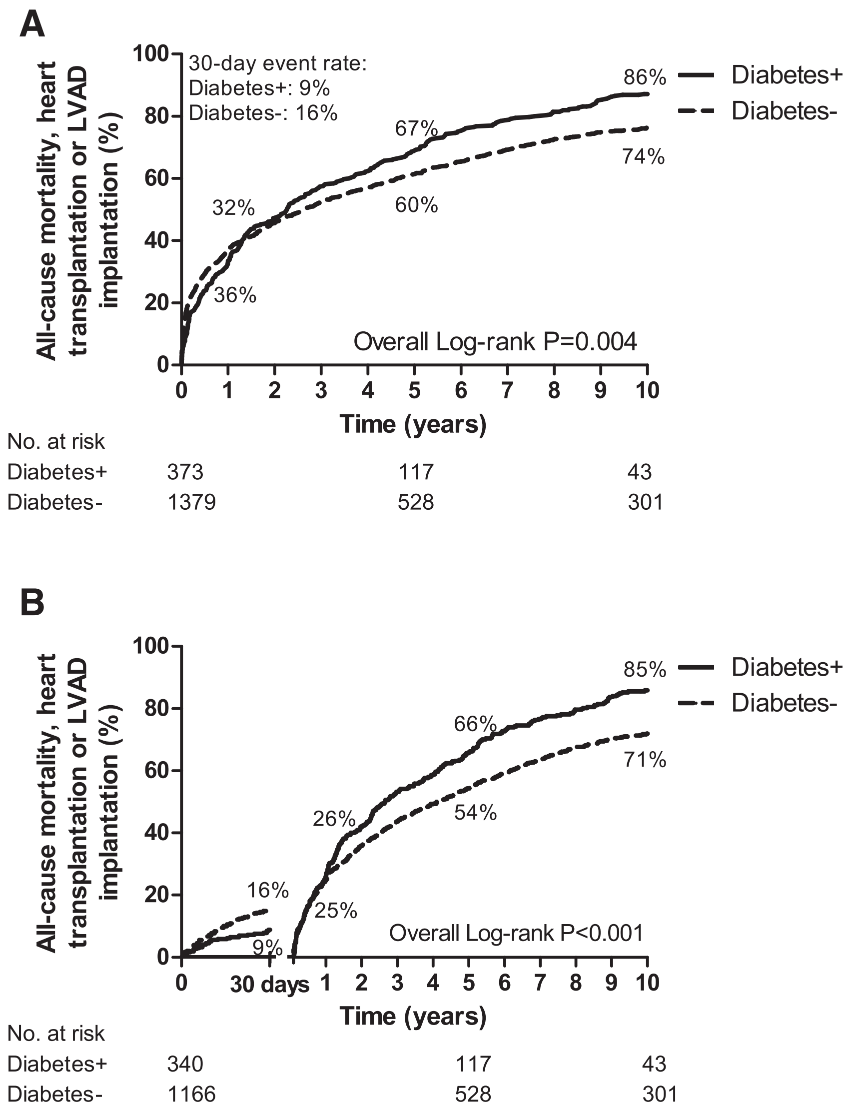

Figure 1—Kaplan-Meier curve of the cumulative incidence of reaching the composite end point of all-cause mortality, heart transplantation, and LVAD implantation in the total population (*A*) and a landmark analysis in the 30-day event-free survivors (*B*): patients with diabetes vs. those without diabetes.

The short- and long-term event rate of patients admitted in the second decade was comparable with the outcome in the first decade. This holds for both patients with and without diabetes. For the purpose of comparison with the outcome of patients studied in the most recent time period, patients admitted from 1985 until 1999 were pooled into one group. This comparison demonstrated that the 1-year outcome did not significantly improve over time—neither in patients with diabetes nor in those without diabetes (adjusted HR 0.93 [95% CI 0.64–1.36] and adjusted HR 0.92 [95% CI 0.76–1.12], respectively). In contrast, the long-term event rate showed improvement, both in acute HF patients with and without diabetes (Fig. 2). Patients without diabetes admitted in the last decade less frequently reached the composite end point 10 years after initial hospitalization than patients admitted in the first two decades (adjusted HR 0.86 [95% CI 0.75–0.99]). A similar improvement in long-term outcome was found among the patients with diabetes (adjusted HR 0.80 [95% CI 0.63–1.00]). This improvement in long-term outcome over time was more pronounced in both patients without and with diabetes when the analysis was restricted to the 30-day event-free survivors (adjusted HR 0.81 [95% CI 0.69–0.95] and adjusted HR 0.74 [95% CI 0.58–0.95], respectively).

When we analyzed the temporal trend in the long-term prognosis of the patients divided into three equal groups of periods of 8 years, we found that the prognosis of patients admitted in the first period (1985–1992) was comparable with the outcome in the patients admitted in the period 1993–2000. Therefore, we pooled these patients into one group and compared their long-term outcome with the outcome in patients admitted in the period 2001–2008 (Fig. 3). The outcome of these analyses was comparable to the results of the analyses in patients divided according to the decades. Hence, we can conclude that the results were not dependent on the division of the data set in the chosen time periods.

CONCLUSIONS

In this cohort study of patients with acute HF, studied over a period of 24 years, the prevalence of diabetes increased over time, with almost 30% of the patients found to have diabetes in the last decade. This study shows that among patients with acute HF, the presence of diabetes is associated with a clear prognostic disadvantage long-term (i.e., at 10 years) when compared with those without diabetes. More important, we clearly demonstrated that the temporal reduction in long-term outcome (i.e., the composite of all-cause mortality, heart transplantation, and LVAD implantation) in patients admitted with acute HF, achieved in the last decade, was at least as high in patients with diabetes and in those without diabetes.

Short- and Long-term Outcome in Patients With and Without Diabetes

This study added results to the controversial evidence available in literature about the prognostic impact of diabetes on the 1-year prognosis among patients admitted with acute HF. We found that patients with and without diabetes equally reached the composite end point of all-cause mortality, heart transplantation, and LVAD implantation after 1-year follow-up. This endorsed the findings by others who reported a comparable prognosis in patients with and without diabetes (19). However, our findings were also in contrast with previous studies. DIAMOND-CHF (Danish Investigations of Arrhythmia and Mortality on Dofetilide in Congestive Heart Failure) was a large Danish trial with >5,000 patients reporting higher 1-year mortality rates among

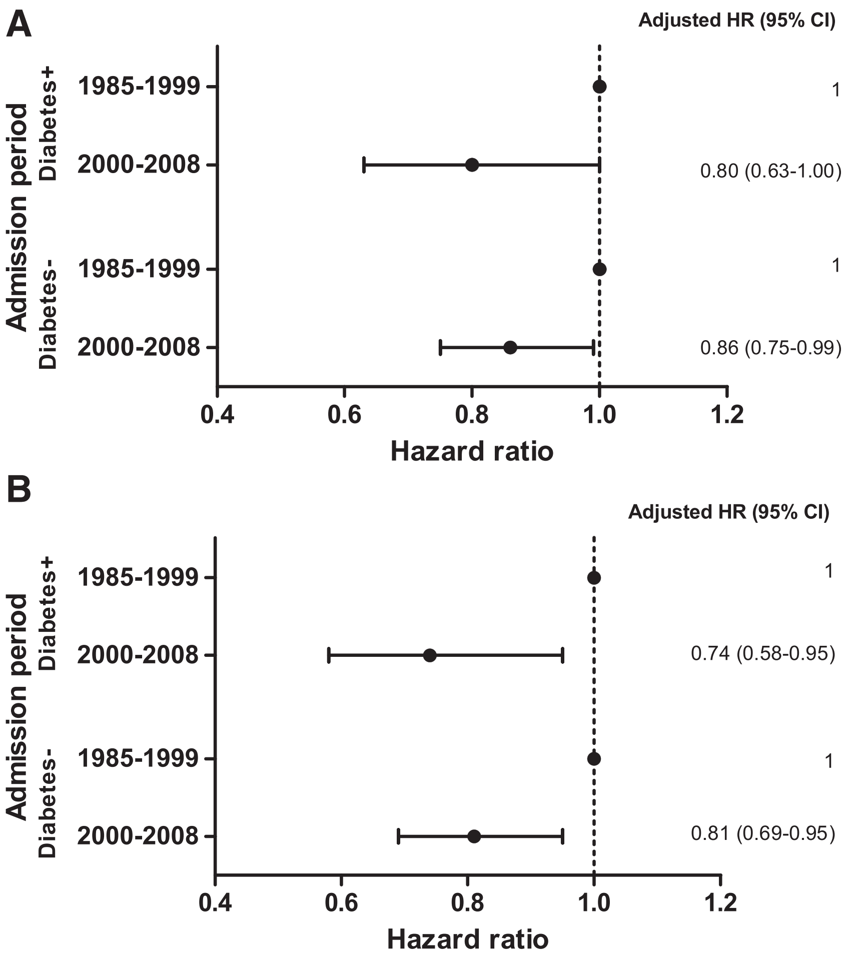

Figure 2—Multivariable-adjusted trends in 10-year prognosis among patients with acute HF: patients with diabetes vs. those without diabetes. Analyses were separately done in the total population (*A*) and in the 30-day event-free survivors (*B*). The data set was divided according to the three decades.

patients with diabetes (14). Two other European registries also found a prognostic disadvantage of diabetes on the 1-year prognosis (15,18). Last, a large retrospective Scottish population study also found a prognostic disadvantage after 1-year follow-up of patients with diabetes (16). A potential reason for these discrepancies is the difference in the study population. Generally, patients in our study were younger, more commonly had a myocardial infarction or HF in their history, and were less frequently found to have a history of hypertension.

Importantly, after a longer follow-up duration, acute HF patients with diabetes had a prognostic disadvantage compared with those without diabetes. This resulted in higher 10-year event rates among patients with diabetes. These results confirmed the results reported by others (14,25,26).

The poorer long-term prognosis in patients with diabetes is an important finding and has implications for the future. Since the incidence of diabetes in HF patients is likely to further increase in the future, this will become a major health care problem with high morbidity and mortality, as well as high costs for society (27). Therefore, it is important to recognize diabetes in patients with HF and to start an adequate therapy for the diabetes. However, there is little evidence for the best therapy of glycemic control in HF patients in practice (28). For that reason, more future clinical research is required for the medical treatment of diabetes in patients with HF. We believe that better glycemic control in that specific subset of patients may contribute to a further improvement in prognosis.

Temporal Trends in Long-term Prognosis

Several previous studies have reported trends in long-term outcome (20–23), but temporal trends among acute HF patients stratified by the presence of diabetes have not been described previously—neither short-term trends nor long-term trends. Novel treatment modalities for HF, like ACE inhibitors, β-blockers, mineralocorticoid receptor antagonists, implantable cardioverter defibrillators, and cardiac resynchronization therapy, have all been implemented in clinical practice in the last decades. This change in the therapeutic regimen was associated with a lower long-term mortality in the total population with acute HF (20–23), and it caused the improved long-term prognosis of the patients without diabetes.

However, our study cannot definitely elucidate the mechanisms that resulted in the improved long-term prognosis among the subgroup with diabetes. Since the novel treatment modalities have been found to have comparable mortality benefit in patients both with and without diabetes (27), it is possible that this is the (only) reason for the improved long-term prognosis among the acute HF patients with diabetes. On the other hand, previous studies among patients with diabetes (not in an acute HF population) showed an improved survival over the last decades (29,30), which was attributed to a growing awareness of diabetes, more focus on cardiovascular prevention by treating comorbidities, and an improvement in the treatment of acute myocardial infarction (29–31). We hypothesized that the improved prognosis among acute HF patients with diabetes may be a result of the combination of both above-mentioned potential mechanisms. Therefore, despite the impaired prognosis associated with diabetes in acute HF, patients admitted with acute HF both with diabetes and without diabetes showed a comparable improvement over time in long-term prognosis.

Thirty-Day Outcome of Patients With and Without Diabetes

Contrary to expectations, we found that patients with acute HF with diabetes less frequently reached the composite end point at 30 days than those without diabetes. This is not a unique finding, but data on this topic vary. Some studies reported comparable in-hospital mortality in patients with and without diabetes (7), but other analyses described worse in-hospital outcome in patients with diabetes (17,18). A large Scottish database reported that diabetes was associated with lower 30-day

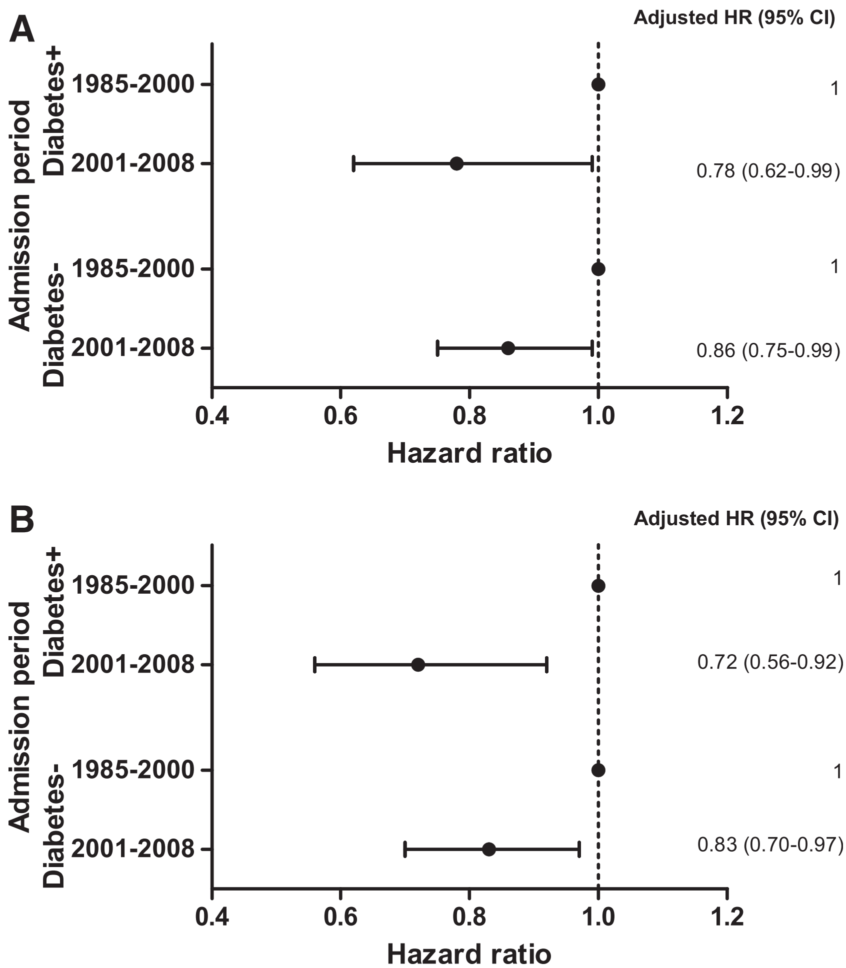

Figure 3—Multivariable-adjusted trends in 10-year prognosis among patients with acute HF: patients with diabetes vs. those without diabetes. Analyses were separately done in the total population (*A*) and in the 30-day event-free survivors (*B*). The data set was divided according to the three groups of equal length in years.

mortality (16). The hypothesis put forward by these investigators was that patients with diabetes would most likely have a better ejection fraction than subjects without diabetes. Since the authors were unable to adjust for LVEF, they could not establish this hypothesis. When we adjusted for LVEF in our analyses, we found that, despite this, patients with diabetes continued to have a better 30-day outcome.

We think there might be two potential reasons for this prognostic disadvantage of the patients without diabetes in our study. First, the patients without diabetes who reached the composite end point within 30 days were most likely predominantly patients with end-stage HF or, given the fact that patients without diabetes were more often treated with mechanical circulatory support, patients with cardiogenic shock. It is well known that cardiogenic shock is associated with elevated in-hospital mortality (32,33). The second reason why patients without diabetes were found to have a poorer 30-day prognosis may be due to the fact that the patients in our survey were admitted to an intensive care unit. A lower in-hospital mortality among patients with diabetes admitted at a general intensive care unit has also been described by Graham et al. (34) and Martin et al. (35). These two studies constitute the largest reports that investigated the in-hospital prognosis among patients with diabetes admitted to the general intensive care unit. However, the mechanism of the lower in-hospital mortality among these patients with diabetes admitted to an intensive care unit was not stipulated.

Strengths and Limitations

This study has several strengths. First, we studied long-term outcome (i.e., 10 years) in a large population of patients with acute HF over a study period of 24 years. Furthermore, this is the first study reporting temporal trends in prognosis among acute HF patients with and without diabetes.

Despite these unique strengths, some limitations should be acknowledged. First, this study was performed in a single center. Therefore, this could result in a lower external validity. Furthermore, no distinction was made between type 1 and type 2 diabetes. Also, any information regarding the development of diabetes during follow-up among the patients without diabetes at baseline was not available. The development of diabetes during follow-up may have also influenced the prognosis. Finally, information about drug therapy of diabetes was not reported in our database. This may be of added value because the type of diabetes treatment could influence HF symptoms, hospitalization, and mortality (36–38).

Conclusion

In conclusion, we showed that patients admitted with acute HF had a poor prognosis. Moreover, the long-term outcome (i.e., the composite of all-cause mortality, heart transplantation, and LVAD implantation) of patients with diabetes is worse as compared with those without diabetes. However, the long-term mortality prognosis improved over time as a result of an improved treatment of HF. Importantly, this improvement in long-term prognosis was at least as high in patients without diabetes as in those with diabetes. This study not only emphasizes the need to improve the treatment of HF but also emphasizes the need for optimal treatment of diabetes in acute HF as well as the need to create more awareness for diabetes in patients with acute HF.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. J.C.v.d.B. acquired data, performed the statistical analysis, interpreted the data, and wrote the manuscript. A.A.C. and H.J.B. reviewed the manuscript. R.T.v.D. designed the study, contributed to analysis, interpreted the data, and reviewed the manuscript. J.W.D. designed the study, interpreted the data, and reviewed and edited the manuscript. K.M.A. interpreted the data and reviewed and edited the manuscript. J.W.D. 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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