European Heart Journal (2004) **25**, 656–662

Clinical research

Impact of diabetes mellitus on long-term survival in patients with congestive heart failure

Pascal de Groote[a], Nicolas Lamblin[a], Frédéric Mouquet[a], David Plichon[a], Eugène McFadden[b], Eric Van Belle[a], Christophe Bauters[a,*]

[a] *Hôpital Cardiologique, CHRU de Lille, Lille Cedex 59037, France*
[b] *Thoraxcenter, Erasmus Medical Centre, Rotterdam, The Netherlands*

Received 13 August 2003; revised 8 December 2003; accepted 15 January 2004

See page 629 for the editorial comment on this article [†]

KEYWORDS
Diabetes mellitus;
Heart failure;
Ischaemia;
Prognosis

Aims To test the hypothesis that diabetic status may be used as a prognostic indicator in heart failure (HF) patients.
Methods and results We studied 1246 consecutive patients with left ventricular dysfunction. All patients had a cardiopulmonary exercise test and an echocardiogram. Cardiac catheterisation was systematically performed to define HF aetiology. Twenty-two percent of the patients were diabetic (hypoglycaemic drugs or fasting blood glucose >126 mg/dL); in diabetic patients, HF aetiology was ischaemic in 58% vs. 40% in non-diabetic patients ($p < 0.0001$).

Clinical follow-up (median 1200 days) was obtained for 1241 patients. There was a statistically significant effect of diabetes mellitus on cardiac survival that differed according to HF aetiology (interaction $p < 0.01$). Diabetes mellitus was an independent predictor of cardiovascular mortality in ischaemic patients (HR = 1.54 [1.13; 2.09]; $p = 0.006$) but not in non-ischaemic patients (HR = 0.65 [0.39; 1.07]; $p = 0.09$). When diabetic patients were defined as patients receiving hypoglycaemic drugs at baseline, diabetes mellitus remained an independent predictor of cardiovascular mortality in ischaemic patients (HR = 1.43 [1.03; 1.98]; $p = 0.03$) while diabetes mellitus was associated with a statistically significant decrease in cardiovascular mortality in non-ischaemic patients (HR = 0.46 [0.23; 0.88]; $p = 0.02$).
Conclusion The prognostic impact of diabetes mellitus in HF patients is markedly influenced by the underlying aetiology and is particularly deleterious in those with ischaemic cardiomyopathy.

Introduction

Diabetes mellitus (DM) is a well-known and important risk factor for heart disease. While coronary artery disease is the most common cardiac manifestation in diabetic patients, diabetes mellitus also appears to be strongly linked to heart failure (HF).[1,2] Data obtained from the Framingham cohort have demonstrated an increased risk of HF in patients with diabetes mellitus.[3] Furthermore, 15–25% of patients with HF have DM.[4–6]

Retrospective analyses of the SOLVD trials have suggested that diabetic status may be useful as a prognostic indicator in HF patients. Shindler et al.[4] showed that both all-cause mortality and cardiovascular mortality at a mean follow-up of 3 years were significantly higher in

* Corresponding author. Tel.: +33-3-20-44-50-45; fax: +33-3-20-44-48-81.
E-mail address: cbauters@chru-lille.fr (C. Bauters).
[†] doi:10.1016/j.ehj.2004.02.028.

0195-668X/$ - see front matter
doi:10.1016/j.ehj.2004.01.010

diabetic than in non-diabetic HF patients. More recently, Dries et al.[7] suggested that the effect of diabetes mellitus on survival was modulated by HF aetiology: they found that diabetes mellitus was associated with an increased risk for all-cause mortality in patients with ischaemic HF, but not in patients with non-ischaemic HF. Moreover, it has been suggested that the increased mortality in patients with ischaemic cardiomyopathy compared with non-ischaemic cardiomyopathy (reviewed in Ref.[8]) may be limited to the diabetic subgroup.[7]

Although these results may have important clinical implications, the SOLVD database was limited by the lack of precise characterisation of diabetic status and of HF aetiology; in addition, important prognostic variables such as peak VO2 were not available for adjustment of statistical models.

Accordingly, we designed the present study to analyze the impact of diabetes mellitus on survival as a function of HF aetiology. We selected a group of 1246 consecutive patients with systolic HF who underwent prognostic evaluation in our institution; information on diabetes mellitus was recorded at baseline; coronary angiography was systematically performed to define HF aetiology.

Methods

Study population

We included 1246 consecutive patients who were referred to our centre between January 1991 and December 2001 for evaluation of LV systolic dysfunction. Patients were included if they were ambulatory, stable for at least 2 months, and had a LVEF $\leqslant$45%. Patients were excluded if they had a recent (<3 months) myocardial infarction, unstable angina, or coronary revascularisation. As part of the prognostic evaluation, the patients underwent echocardiography and a cardiopulmonary exercise test as previously described.[9] In addition, cardiac catheterisation was systematically performed to define the aetiology of LV dysfunction. Patients were classified as having an ischaemic aetiology if they had experienced a previous myocardial infarction and/or had significant (>50% stenosis in at least one major epicardial vessel on visual estimation) coronary artery disease at angiography. Sixteen patients refused coronary angiography and were classified as having an unknown aetiology. The information used for the present study was prospectively collected and entered in a database at the time of prognostic evaluation.

Patients were classified as diabetic if they were being treated with oral hypoglycaemic drugs or insulin, or if they had a previous history, documented on their medical chart, of elevated (>126 mg/dL) fasting blood glucose on at least two separate occasions in conjunction with ongoing dietary measures. Diabetic patients were classified in three categories depending on anti-diabetic management: (1) diet alone, (2) oral hypoglycaemic drugs (diet and oral hypoglycaemic drugs but no insulin), and (3) insulin (irrespective of other therapy).

Clinical follow-up

Clinical follow-up was performed at outpatient visits or by contacting the general practitioner or the cardiologist. Review of hospital records enabled us to complete some missing information. Finally, patients' municipal records were checked for mortality status. The range for the follow-up period was 185–4218 days. The primary endpoint of the study was cardiovascular mortality. The cause of cardiovascular death was determined after a detailed review of the circumstances of death and classified as (1) pump failure death; (2) sudden death; (3) vascular death (i.e., death related to myocardial infarction, stroke, or peripheral artery disease).

Statistical analysis

Statistical analysis was performed with SPSS software (version 9, Chicago, Illinois). Mean values $\pm$ SD were calculated for quantitative data. The quantitative variables were compared between groups using unpaired Student *t* tests. Qualitative variables were compared using the χ^2-test. Cardiac survival was estimated with the Kaplan–Meier method; differences were tested with a log rank test. Cardiac transplantations were censored at the time of transplantation. In addition to diabetes mellitus and HF aetiology, the parameters tested for possible association with cardiac survival were age, sex, body mass index, smoking habit, hypertension, hypercholesterolaemia, previous coronary artery bypass graft (CABG), number of coronary vessels with significant stenosis, atrial fibrillation, NYHA class, LVEF, heart rate, systolic blood pressure, diastolic blood pressure, peak VO2, treatment with ACE inhibitors, beta-blockers, digoxin or diuretics. A multivariate Cox proportional hazards analysis was performed to determine the independent predictors of survival. All the parameters significant to $p < 0.1$ in univariate analysis were entered in the Cox model. The assumption of proportional hazards was assessed with the log-minus-log survival plot. For continuous variables, the assumption of linearity was assessed by plotting residuals against independent variables. Values of $p < 0.05$ were considered significant.

Results

One thousand two hundred and forty-six patients were included in the study; 280 (22%) had DM; 549 (44%) had ischaemic cardiomyopathy while 681 (55%) had non-ischaemic cardiomyopathy; 16 patients (1%) did not have angiography and were classified as having an unknown aetiology. In diabetic patients, the aetiology of HF was classified as ischaemic in 58% of cases versus 40% in non-diabetic patients ($p < 0.0001$).

Baseline characteristics

The baseline characteristics of the study population stratified by HF aetiology and diabetic status are presented in Table 1. In both the ischaemic and non-ischaemic cohorts, diabetic patients were older, had higher BMI, and more often had a history of hypertension than their non-diabetic counterparts. Overall, patients from the ischaemic cohort were older ($p < 0.0001$) and more frequently male ($p < 0.0001$), smokers ($p < 0.0001$) and hypercholesterolaemic ($p < 0.0001$); they had a lower peak VO2 ($p < 0.0001$); and a higher proportion were receiving beta-blockers ($p < 0.0001$) than patients from the non-ischaemic cohort. The proportion of diabetic patients receiving insulin or oral hypoglycaemic drugs was higher in the ischaemic group ($p < 0.0001$).

Table 1 Baseline characteristics stratified by heart failure aetiology and diabetes status

	Ischaemic cohort ($n = 549$)			Non-ischaemic cohort ($n = 681$)		
	Diabetes ($n = 164$)	No diabetes ($n = 385$)	p	Diabetes ($n = 112$)	No diabetes ($n = 569$)	p
Age (years)	60 ± 9	56 ± 11	<0.0001	56 ± 10	50 ± 12	<0.0001
Women	12 (7%)	33 (9%)	0.62	26 (23%)	117 (21%)	0.53
BMI, kg/m2	28 ± 4	26 ± 4	<0.0001	29 ± 5	26 ± 7	<0.0001
Smoker[a]	117 (71%)	297 (77%)	0.53	66 (59%)	330 (58%)	0.83
Hypertension	88 (54%)	113 (29%)	<0.0001	59 (53%)	158 (28%)	<0.0001
Hypercholesterolaemia	124 (76%)	273 (71%)	0.23	56 (50%)	204 (36%)	0.005
Previous CABG	25 (15%)	65 (17%)	0.64	NA	NA	–
Number of vessels with >50% stenosis	1.98 ± 0.94	1.81 ± 0.98	0.08	NA	NA	–
Atrial fibrillation	15 (9%)	27 (7%)	0.39	15 (13%)	80 (14%)	0.85
NYHA class III+IV	52 (32%)	113 (29%)	0.58	38 (34%)	140 (25%)	0.04
LVEF (%)	33 ± 11	31 ± 11	0.02	32 ± 10	33 ± 12	0.32
Heart rate at rest (beats/min)	84 ± 18	79 ± 19	0.01	94 ± 17	91 ± 19	0.21
SBP at rest (mm Hg)	127 ± 23	120 ± 22	0.002	129 ± 23	124 ± 23	0.27
DBP at rest (mm Hg)	80 ± 13	78 ± 12	0.24	83 ± 13	79 ± 19	0.16
Peak VO2 (ml/min/kg)	13.9 ± 3.9	15.4 ± 4.8	<0.0001	15.6 ± 4.8	17.6 ± 6.2	<0.0001
% Peak VO2	57 ± 17	57 ± 17	0.87	65 ± 19	63 ± 20	0.42
ACE inhibitors	150 (91%)	338 (88%)	0.21	106 (95%)	510 (90%)	0.09
Beta-blockers	65 (40%)	165 (43%)	0.48	18 (16%)	132 (23%)	0.10
Digoxin	70 (43%)	134 (35%)	0.08	81 (72%)	319 (56%)	0.001
Diuretics	124 (76%)	235 (61%)	0.001	98 (88%)	406 (71%)	<0.0001
Insulin	30 (18%)	NA	–	16 (14%)	NA	–
Oral hypoglycaemic drugs	109 (66%)	NA	–	63 (56%)	NA	–
Biguanides	43 (26%)	NA	–	21 (19%)	NA	–
Sulfamides	70 (43%)	NA	–	44 (39%)	NA	–

Values are mean ± SD or percent of patients.

BMI indicates body mass index; CABG, coronary bypass graft; NYHA, New York Heart Association functional classification; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure; DBP, diastolic blood pressure; VO2, oxygen consumption; % Peak VO2, % of maximal predicted VO2; ACE, angiotensin-converting enzyme.

[a] Smoker, indicates current or past smokers.

Survival in the overall study population

Clinical follow-up was obtained between June 2002 and September 2002 for 1241 (99.6%) patients; 5 patients were lost to follow-up (all in the non-diabetic group). During a median follow-up period of 1200 days, there were 334 cardiovascular deaths, 66 transplantations, and 51 non-cardiovascular deaths. Fig. 1 shows the cardiovascular mortality of diabetic versus non-diabetic patients. Diabetic patients had a significantly higher event rate ($p = 0.01$). The cardiovascular mortality rates at 2 and 5 years in diabetic compared to non-diabetic patients were 18% and 37% vs. 13% and 28%, respectively.

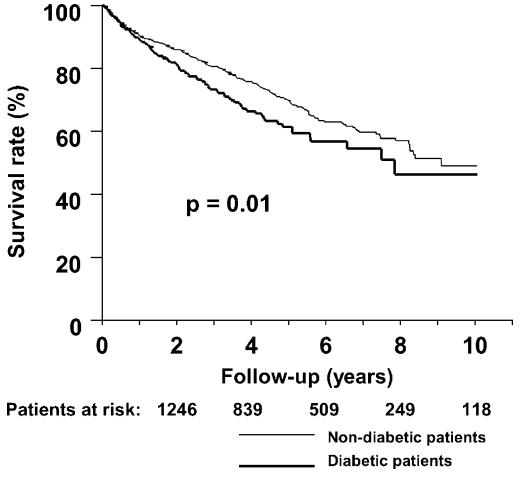

Fig. 1 Kaplan–Meier survival curve for cardiovascular mortality as a function of diabetic status at baseline (diabetes defined as treatment with hypoglycaemic drugs or fasting blood glucose >126 mg/dL).

Multivariate analysis was carried out to determine independent predictors of cardiovascular mortality. As shown in Table 2, seven variables were selected by the Cox model: age, ischaemic aetiology, NYHA class III or IV, LVEF, peak VO2, absence of beta-blocker therapy, and treatment with digoxin. Diabetes mellitus was not an independent predictor of cardiovascular mortality in this model (HR = 1.06 [0.80; 1.41]).

Survival in ischaemic and non-ischaemic subgroups

There was a significant interaction between HF aetiology and diabetes mellitus ($p < 0.01$), suggesting that diabetes mellitus had a different effect on survival in patients with ischaemic HF compared to those with non-ischaemic HF. Fig. 2(a) shows cardiovascular mortality as a function of HF aetiology in diabetic versus non-diabetic patients. In the non-ischaemic subgroup, there was a non-significant trend toward better survival in diabetic patients. By

Table 2 Predictors of cardiovascular mortality in the overall study population

Variable	Hazard ratio [95%CI]	*p*
Age	1.02 [1.01; 1.03]	0.0001
Ischaemic aetiology	2.05 [1.61; 2.62]	<0.0001
NYHA class III+IV	1.49 [1.18; 1.90]	0.001
LVEF	0.97 [0.96; 0.98]	<0.0001
Peak VO2	0.97 [0.96; 0.98]	<0.0001
Beta-blockers	0.69 [0.52; 0.92]	0.01
Digoxin	1.58 [1.24; 2.01]	0.0002
Diabetes	1.06 [0.80; 1.41]	0.29

NYHA, New York Heart Association functional classification; LVEF, left ventricular ejection fraction; VO2, oxygen consumption.

contrast, in the ischaemic subgroup, diabetics had a significantly worse prognosis than non-diabetics ($p < 0.003$). An ischaemic aetiology was associated with an increased cardiovascular mortality in diabetic patients ($p < 0.0001$) as well as in non-diabetic patients ($p = 0.0005$).

Further multivariate analysis was carried out separately in non-ischaemic and ischaemic patients (Table 3); 139 patients reached the endpoint of cardiovascular death in the non-ischaemic subgroup vs. 192 in the ischaemic sub-group. In patients with non-ischaemic cardiomyopathy, there was a trend ($p = 0.09$) toward better survival in diabetic patients; the 3 independent predictors of cardiovascular mortality were NYHA class III or IV, LVEF, and peak VO2. In patients with ischaemic cardiomyopathy, diabetes mellitus was an independent predictor of cardiovascular mortality (HR = 1.54 [1.13; 2.09]; $p = 0.006$); other variables retained in the model were age, NYHA class III or IV, LVEF, peak VO2, absence of beta-blocker therapy, and treatment with digoxin. Information on the cause of cardiovascular death is shown in Table 4. In patients with non-ischaemic cardiomyopathy, there were non-significant trends towards a diabetes-conferred decreased risk of pump failure death and sudden death. In contrast, in patients with ischaemic aetiology, there were non-significant trends for an increase in pump failure death and sudden death, and a significant increase in vascular death in patients with diabetes versus those without diabetes.

In the overall study population, the composite variable of aetiology and diabetic status was significantly

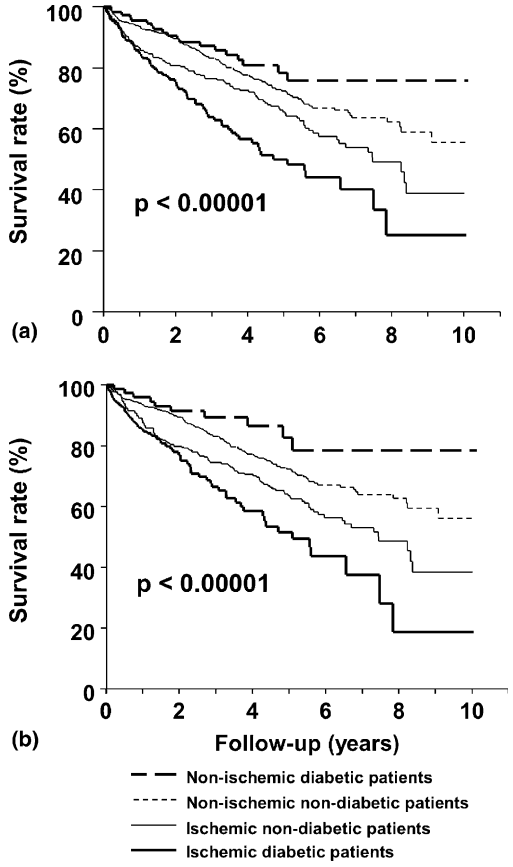

Fig. 2 Kaplan–Meier survival curve for cardiovascular mortality as a function of diabetic status and aetiology of left ventricular dysfunction. (a) Diabetes defined as treatment with hypoglycaemic drugs or fasting blood glucose >126 mg/dL. (b) Diabetes defined as treatment with hypoglycaemic drugs.

associated with survival ($p < 0.0001$) and was selected as the most powerful predictor of cardiovascular mortality (Wald $\chi^2 = 43$). Compared to non-ischaemic patients, the adjusted hazard ratio for cardiovascular death was 1.77 [1.35; 2.30] in ischaemic patients without diabetes and 2.68 [1.97; 3.64] in ischaemic patients with diabetes.

Finally, since the proportion of diabetic patients receiving diet alone differed in ischaemic versus non-ischaemic patients, the statistical analysis was repeated after defining diabetic patients as those receiving hypo-

Table 3 Predictors of cardiovascular mortality according to aetiology of left ventricular dysfunction: multivariate analysis

	Non-ischaemic ($n = 681$)		Ischaemic ($n = 549$)	
Variable	Hazard ratio [95%CI]	*p*	Hazard ratio [95%CI]	*p*
Age	1.01 [1.00; 1.03]	0.11	1.03 [1.01; 1.04]	0.0003
NYHA class III+IV	1.78 [1.19; 2.67]	0.005	1.46 [1.07; 1.98]	0.02
LVEF	0.97 [0.95; 0.99]	0.005	0.97 [0.95; 0.98]	<0.0001
Peak VO2	0.98 [0.97; 0.99]	<0.0001	0.97 [0.96; 0.98]	<0.0001
Beta-blockers	0.83 [0.48; 1.44]	0.54	0.69 [0.49; 0.98]	0.04
Digoxin	1.37 [0.92; 2.02]	0.11	1.73 [1.28; 2.36]	0.0005
Diabetes	0.65 [0.39; 1.07]	0.09	1.54 [1.13; 2.09]	0.006

NYHA, New York Heart Association functional classification; LVEF, left ventricular ejection fraction; DBP, diastolic blood pressure; VO2, oxygen consumption; % Peak VO2, % of maximal predicted VO2; ACE, angiotensin-converting enzyme.

Table 4 Impact of diabetes mellitus on the cause of cardiovascular death according to aetiology of left ventricular dysfunction

	Non-ischaemic ($n = 681$)		Ischaemic ($n = 549$)	
	Hazard ratio [95%CI]	p	Hazard ratio [95%CI]	p
Pump failure death	0.66 [0.34; 1.28]	0.29	1.20 [0.73; 1.98]	0.50
Sudden death	0.56 [0.24; 1.33]	0.19	1.40 [0.86; 2.27]	0.23
Vascular death[a]	NA		3.42 [1.52; 7.71]	0.003

NA, the number of vascular deaths in patients with non-ischaemic cardiomyopathy was too low to determine the hazard ratio.
[a] Vascular death includes myocardial infarction, stroke, and death from peripheral artery disease.

Table 5 Predictors of cardiovascular mortality according to aetiology of left ventricular dysfunction: multivariate analysis (Diabetes treated with hypoglycaemic drugs)

	Non-ischaemic ($n = 681$)		Ischaemic ($n = 549$)	
Variable	Hazard ratio [95%CI]	p	Hazard ratio [95%CI]	p
Age	1.01 [1.00; 1.03]	0.11	1.03 [1.01; 1.04]	0.0002
NYHA class III + IV	1.82 [1.22; 2.72]	0.003	1.45 [1.07; 1.97]	0.02
LVEF	0.98 [0.96; 0.99]	0.005	0.97 [0.95; 0.98]	<0.0001
Peak VO2	0.98 [0.97; 0.99]	<0.0001	0.97 [0.96; 0.98]	<0.0001
Beta-blockers	0.84 [0.49; 1.46]	0.56	0.70 [0.50; 0.99]	0.04
Digoxin	1.36 [0.92; 2.01]	0.12	1.76 [1.30; 1.98]	0.0003
Diabetes treated with hypoglycaemic drugs	0.46 [0.23; 0.88]	0.02	1.43 [1.03; 1.98]	0.03

NYHA, New York Heart Association functional classification; LVEF, left ventricular ejection fraction; VO2, oxygen consumption.

glycaemic agents (oral or insulin) at baseline (205 patients; 16%). Similar results were obtained. Diabetes mellitus was not an independent predictor of cardiovascular mortality in the overall study population (HR = 1.08 [0.82; 1.43]). A statistically significant interaction was again observed between HF aetiology and diabetes mellitus ($p < 0.01$) (Fig. 2(b)). As shown in Table 5, diabetes mellitus was an independent predictor of cardiovascular mortality in patients with ischaemic cardiomyopathy (HR = 1.43 [1.03; 1.98]; $p = 0.03$) while in patients with non-ischaemic cardiomyopathy, diabetes mellitus was associated with a decreased cardiovascular mortality (HR = 0.46 [0.23; 0.88]; $p = 0.02$).

Discussion

Our results demonstrate that the prognostic impact of diabetes mellitus in patients with heart failure is markedly influenced by the underlying aetiology. Diabetes mellitus was an independent predictor of cardiovascular mortality in patients with ischaemic cardiomyopathy; by contrast, diabetes mellitus was associated with a trend toward better survival in patients with non-ischaemic cardiomyopathy.

Diabetes mellitus in HF patients

Clinical studies and registries have linked DM with HF. In the SOLVD clinical trials, 15% of patients had DM in the prevention arm and 26% in the treatment arm.[4] In the EPICAL study, a registry of consecutive patients hospitalised for advanced chronic HF due to left ventricular systolic dysfunction, 26% of patients had a history of type I or type II DM.[6] In the present study, the proportion of diabetic patients was 22% in the overall study population and was higher in the ischaemic subgroup (30%) than in the non-ischaemic subgroup (16%). A higher prevalence of diabetes mellitus in ischaemic HF has also been observed in other studies[5–7] and suggests that part of the increased risk of HF encountered in diabetic patients is related to the increased prevalence of underlying coronary artery disease. However, the 16% rate of diabetes mellitus in our patients with non-ischaemic HF is much higher than the 4—6% prevalence of diabetes mellitus observed in age-matched control populations.[3] This strongly suggests that other mechanisms directly or indirectly related to diabetic status may have contributed to the development of heart failure (reviewed in Refs.[1,2]). Co-morbidities, such as hypertension, were more frequent in diabetic patients, a fact that could explain some of the excess risk associated with diabetes; a specific diabetic cardiomyopathy may also be implicated in some patients.

Diabetes mellitus as a prognostic indicator in HF patients

Our results concur with those of Dries et al.[7] and confirm the deleterious impact of diabetes mellitus in patients with ischaemic HF. The design of our study, however, differed markedly from that of Dries and our results provide significant new insights into the complex relationship between diabetic status and prognosis in heart failure.

Firstly, diabetes mellitus remains independently associated with cardiovascular mortality in ischaemic HF, even when powerful prognostic variables like peak VO2 are entered into the multivariate model. At least two explanations may account for the negative interaction between DM and the ischaemic aetiology of heart failure. Diabetic HF patients may have a higher risk of coronary plaque rupture and thrombosis.[10,11] Recurrent myocardial infarction is a major cause of death in patients with ischaemic HF;[12] in addition, non-fatal myocardial infarction may further deteriorate left ventricular function in patients with ischaemic HF. Our observation that diabetes mellitus is associated with an increased risk of vascular death in patients with ischaemic HF supports this hypothesis. Furthermore, abnormalities in myocardial metabolism, such as impaired myocardial glucose uptake, may be especially deleterious in diabetic patients with ischaemic HF.[13,14] The increased turnover of free fatty acids seen in diabetic patients may further impair myocardial glucose utilisation via inhibition of pyruvate dehydrogenase and may have other deleterious consequences such as changes in myocardial gene expression resulting in myocyte hypertrophy with impaired contractile function, or production of free radicals.[1,15] In the present study, diabetes was associated with a 20% increase in the risk of pump failure death in diabetic patients. However, this was not a statistically significant trend, which can only be taken as hypothesis-generating because breaking down cardiovascular mortality into its main components automatically reduces the power of the comparison. The figure is consistent with the 44% increase reported in the paper by Dries et al. and in the recent analysis of the BEST database by Domanski et al.[16]

Secondly, in the non-ischaemic cohort, diabetes mellitus was associated with a decreased cardiovascular mortality; the difference in outcome was statistically significant when diabetic patients were restricted to those receiving hypoglycaemic drugs. We cannot firmly exclude the possibility that this finding reflects an alpha error. However, our cohort included 681 patients with non-ischaemic HF, a greater number than in either the SOLVD prevention or treatment arms. In the study by Dries et al.,[7] the SOLVD database was reanalysed and diabetic status had no impact (either deleterious or beneficial) on survival in patients with non-ischaemic HF. This discrepancy may be related to the fact that in the present study cardiac catheterisation was systematically performed to clarify the underlying aetiology. On the other hand, in the SOLVD study, the definition of the aetiology was based on the judgment of the investigators at the participating sites and did not routinely include either non-invasive testing or cardiac catheterisation to determine the underlying cause. Thus, in SOLVD, a significant number of diabetic patients with silent ischaemia (with a worse prognosis) could have been included in the non-ischaemic cohort. Similarly, in the recent report of the BEST database,[16] no information was available regarding the proportion of patients classified as having non-ischaemic cardiomyopathy who actually underwent coronary angiography.

At least two explanations may account for this intriguing finding of decreased cardiovascular mortality. Due to differences in pathophysiology, the natural history of diabetic non-ischaemic cardiomyopathy may be less severe than that of other causes of non-ischaemic HF; alternatively, diabetic patients may have had more intensive medical follow-up than non-diabetic patients because they are recognised as a population at high risk of cardiac disease.

Ischaemic aetiology was associated with increased mortality irrespective of diabetic status while in the study of Dries et al. the deleterious impact of ischaemic aetiology was restricted to the diabetic subgroup. As suggested above, differences in the technique(s) used for defining ischaemic aetiology may account for these discordant results.

Finally, the finding that diabetes was not an independent predictor of mortality in the overall group is at first sight surprising and appears to run counter to the findings of previous studies. Since the deleterious impact of diabetes is limited to patients with an ischaemic aetiology, the proportion of ischaemic patients in the overall cohort will have a primordial impact on global mortality. In our patients, only 45% were classified as ischaemic whereas in the study of Dries et al., 82% were classified as ischaemic. Furthermore, other variables that are nowadays recognised to be powerful prognostic indicators, such as peak VO2, were also included in our multivariate model. This was not the case in many previous studies.

Clinical implications

Risk stratification is an important step before defining the optimal treatment strategy for a patient with congestive heart failure, particularly given the limited availability of some therapies such as cardiac transplantation. Variables such as NYHA classification, LVEF or peak VO2 are routinely used to predict clinical outcome in HF patients.[9,17,18] Our study indicates that HF aetiology and diabetic status may be used in addition to these classic prognostic indicators to refine risk stratification in HF patients. Characterisation of the ischaemic/non-ischaemic origin improves risk stratification in the overall cohort of HF patients. Since the determination of HF aetiology based on the presence/absence of symptoms or on non-invasive testing may be inaccurate, we determined aetiology with coronary angiography. In the not too distant future, parameters obtained with new imaging modalities like magnetic resonance imaging or multislice computed tomography may help to predict outcome of HF patients in clinical practice. The knowledge of diabetic status also improves risk stratification but our results clearly demonstrate that its use as a prognostic indicator requires a precise knowledge of HF aetiology.

In addition, in view of the very poor outcome of diabetic patients with ischaemic HF, it may also be of interest to determine whether any specific therapeutic approach may be beneficial in this high-risk subgroup. A strategy of "aggressive" secondary prevention is now

routinely advocated in diabetic patients;[19,20] prospective studies are needed to determine if an attitude of ''systematic" revascularisation is superior to medical therapy for diabetic patients with ischaemic HF. Finally, whether improved metabolic control might favourably influence the outcome of diabetic patients with ischaemic HF could also be determined prospectively. These studies would also clarify whether the preferred treatment for diabetes mellitus should be an insulin-sensitising regimen or an insulin-providing regimen.

Study limitations

This was a retrospective study; although we recorded anti-diabetic management at baseline, information on the duration of diabetes or on diabetic control (such as HbA1c) was not available. As our patients were consecutive referrals to a tertiary centre for further evaluation, we cannot exclude a referral bias. Notably, there was a male predominance in our population and extrapolation of the findings to female patients should be performed with caution; in addition, a high proportion of our patients were smokers. On the other hand, it must be pointed out that our study is strengthened by a clear characterisation of HF aetiology and a systematic prognostic evaluation in a large series of consecutive patients.

Conclusions

The prognostic impact of diabetes mellitus in patients with heart failure is markedly influenced by the underlying aetiology and is particularly deleterious in those with ischaemic cardiomyopathy. Further studies are needed to determine whether specific therapeutic approaches may be beneficial in diabetic patients with ischaemic cardiomyopathy.

References

1. Solang L, Malmberg K, Ryden L. Diabetes mellitus and congestive heart failure. Further knowledge needed. *Eur Heart J* 1999;**20**:789–95.
2. Bauters C, Lamblin N, Mc Fadden EP et al. Influence of diabetes mellitus on heart failure risk and outcome. *Cardiovasc Diabetol* 2003;**2**:1.
3. Kannel WB, McGee DL. Diabetes and cardiovascular disease. The Framingham study. *JAMA* 1979;**241**:2035–8.
4. Shindler DM, Kostis JB, Yusuf S et al. Diabetes mellitus, a predictor of morbidity and mortality in the Studies of Left Ventricular Dysfunction (SOLVD) Trials and Registry. *Am J Cardiol* 1996;**77**:1017–20.
5. Ryden L, Armstrong PW, Cleland JG et al. Efficacy and safety of high-dose lisinopril in chronic heart failure patients at high cardiovascular risk, including those with diabetes mellitus. Results from the ATLAS trial. *Eur Heart J* 2000;**21**:1967–78.
6. Zannad F, Braincon S, Juilliere Y et al. Incidence, clinical and etiologic features, and outcomes of advanced chronic heart failure: the EPICAL Study. Epidemiologie de l'Insuffisance Cardiaque Avancee en Lorraine. *J Am Coll Cardiol* 1999;**33**:734–42.
7. Dries DL, Sweitzer NK, Drazner MH et al. Prognostic impact of diabetes mellitus in patients with heart failure according to the aetiology of left ventricular systolic dysfunction. *J Am Coll Cardiol* 2001;**38**:421–8.
8. Follath F, Cleland JG, Klein W et al. Etiology and response to drug treatment in heart failure. *J Am Coll Cardiol* 1998;**32**:1167–72.
9. de Groote P, Millaire A, Foucher-Hossein C et al. Right ventricular ejection fraction is an independent predictor of survival in patients with moderate heart failure. *J Am Coll Cardiol* 1998;**32**:948–54.
10. Haffner SM, Lehto S, Ronnemaa T et al. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med* 1998;**339**:229–34.
11. Burke AP, Kolodgie FD, Farb A et al. Healed plaque ruptures and sudden coronary death: evidence that subclinical rupture has a role in plaque progression. *Circulation* 2001;**103**:934–40.
12. Uretsky BF, Thygesen K, Armstrong PW et al. Acute coronary findings at autopsy in heart failure patients with sudden death: results from the assessment of treatment with lisinopril and survival (ATLAS) trial. *Circulation* 2000;**102**:611–6.
13. Ingebretsen CG, Moreau P, Hawelu-Johnson C et al. Performance of diabetic rat hearts: effects of anoxia and increased work. *Am J Physiol* 1980;**239**:H614–20.
14. Savabi F, Kirsch A. Altered functional activity and anoxic tolerance in diabetic rat isolated atria. *Arch Biochem Biophys* 1990;**279**:183–7.
15. Young ME, McNulty P, Taegtmeyer H. Adaptation and maladaptation of the heart in diabetes: Part II: potential mechanisms. *Circulation* 2002;**105**:1861–70.
16. Domanski M, Krause-Steinrauf H, Deedwania P et al. The effect of diabetes on outcomes of patients with advanced heart failure in the BEST trial. *J Am Coll Cardiol* 2003;**42**:914–22.
17. Mancini DM, Eisen H, Kussmaul W, Mull R et al. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. *Circulation* 1991;**83**:778–86.
18. Cohn JN, Johnson GR, Shabetai R et al. Ejection fraction, peak exercise oxygen consumption, cardiothoracic ratio, ventricular arrhythmias, and plasma norepinephrine as determinants of prognosis in heart failure. The V-HeFT VA Cooperative Studies Group. *Circulation* 1993;**87**:VI5–VI16.
19. Yusuf S, Sleight P, Pogue J et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000;**342**:145–53.
20. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;**360**:7–22.