Influence of Diabetes on Left Ventricular Systolic and Diastolic Function and on Long-Term Outcome After Cardiac Resynchronization Therapy

Ulas Höke, md[1,2]
Joep Thijssen, md[1]
Rutger J. van Bommel, md[1]
Lieselot van Erven, md, phd[1]
Enno T. van der Velde, phd[1]

Eduard R. Holman, md, phd[1]
Martin J. Schalij, md, phd[1]
Jeroen J. Bax, md, phd[1]
Victoria Delgado, md, phd[1]
Nina Ajmone Marsan, md, phd[1]

OBJECTIVE—The influence of diabetes on cardiac resynchronization therapy (CRT) remains unclear. The aims of the current study were to 1) assess the changes in left ventricular (LV) systolic and diastolic function and 2) evaluate long-term prognosis in CRT recipients with diabetes.

RESEARCH DESIGN AND METHODS—A total of 710 CRT recipients (171 with diabetes) were included from an ongoing registry. Echocardiographic evaluation, including LV systolic and diastolic function assessment, was performed at baseline and 6-month follow-up. Response to CRT was defined as a reduction of ≥15% in LV end-systolic volume (LVESV) at the 6-month follow-up. During long-term follow-up (median = 38 months), all-cause mortality (primary end point) and cardiac death or heart failure hospitalization (secondary end point) were recorded.

RESULTS—At the 6-month follow-up, significant LV reverse remodeling was observed both in diabetic and non-diabetic patients. However, the response to CRT occurred more frequently in non-diabetic patients than in diabetic patients (57 vs. 45%, $P < 0.05$). Furthermore, a significant improvement in LV diastolic function was observed both in diabetic and non-diabetic patients, but was more pronounced in non-diabetic patients. The determinants of the response to CRT among diabetic patients were LV dyssynchrony, ischemic cardiomyopathy, and insulin use. Both primary and secondary end points were more frequent in diabetic patients ($P < 0.001$). Particularly, diabetes was independently associated with all-cause mortality together with ischemic cardiomyopathy, renal function, LVESV, LV dyssynchrony, and LV diastolic dysfunction.

CONCLUSIONS—Heart failure patients with diabetes exhibit significant improvements in LV systolic and diastolic function after CRT, although they are less pronounced than in non-diabetic patients. Diabetes was independently associated with all-cause mortality.

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D iabetes and heart failure (HF) are two major health care problems with worldwide growing prevalence and incidence (1,2). Their interrelationship is largely established (3–5), with diabetes being a well-known risk factor for the development of HF and an important prognostic factor among HF patients (6). The pathophysiological mechanisms underlying the association between diabetes and HF are still unclear but may include a higher risk of atherosclerosis and microvascular dysfunction (7), deposition of interstitial myocardial fibrosis (8), and specific neurohumoral deregulations (9). Any of these alterations may in fact lead to an impaired cardiac contractility (systolic dysfunction) and/or compliance (diastolic dysfunction), which are both independently associated with a significantly higher risk of HF development and long-term mortality (10,11).

Cardiac resynchronization therapy (CRT) is an established therapy in patients with drug-refractory HF and wide QRS duration, providing significant improvement of symptoms, left ventricular (LV) function, and long-term morbidity and mortality. The precise impact of diabetes on the efficacy of CRT still remains controversial (12–16). Therefore, the aim of the current study was to evaluate the potential differences in LV systolic and diastolic function improvement after CRT between diabetic and non-diabetic patients. Furthermore, the influence of diabetes on long-term outcome after CRT was assessed.

RESEARCH DESIGN AND METHODS

Patient population and protocol

A total of 710 consecutive CRT recipients from an ongoing, single-center registry were included in the present analysis (17). Patient data were prospectively collected in the departmental Cardiology Information System (EPD-Vision, Leiden University Medical Center) and retrospectively analyzed. Patients were selected for CRT according to the presence of LV ejection fraction (LVEF) ≤35%, HF symptoms despite optimal medical therapy, and a QRS duration ≥120 ms (18). The etiology of HF was considered ischemic in the presence of significant coronary artery disease (>50% stenosis in one or more major epicardial coronary arteries) on coronary angiography and/or a history of myocardial infarction or previous revascularization. Patients with recent myocardial infarction (<3 months) or decompensated HF were excluded. During the implantation procedure, LV lead position was assessed on fluoroscopy, as previously described (19).

All patients underwent extensive clinical evaluation and transthoracic two-dimensional echocardiography assessment at baseline and 6 months after CRT. The relation between the presence of diabetes and the effect of CRT on LV systolic and diastolic function at the 6-month follow-up, as well as the clinical outcome during long-term follow-up after CRT, was evaluated.

Definition of diabetes

Diabetes was defined as treated or presently diagnosed glucose intolerance, according to the World Health Organization criteria (fasting blood glucose ≥7.0 mmol/L, or 2-h oral glucose tolerance test glucose ≥11.1 mmol/L) (20). According to the American Diabetes Association criteria, diabetic patients were stratified as having type 1 or type 2 diabetes (21). Patients with exogenous insulin use as the cornerstone of their glycemic control regimen were classified as insulin dependent. HbA_{1c}, a marker of glycemic control level, was measured and expressed according to the International Federation of Clinical Chemistry and Laboratory Medicine in mmol/mol units.

Clinical evaluation

Clinical status was evaluated at baseline and 6-month follow-up, including the New York Heart Association (NYHA) functional class, quality-of-life score according to the Minnesota Living with Heart Failure Questionnaire (higher scores indicate poorer quality of life), and exercise capacity by 6-min walk test (22,23). The renal function was evaluated with the glomerular filtration rate (GFR) according to an equation from Cockcroft and Gault (24).

Echocardiographic evaluation

Echocardiographic studies were performed with patients in the left lateral decubitus position, using a commercially available ultrasound system (Vivid-7 and Vivid-E9; GE Vingmed Ultrasound, Horten, Norway) equipped with a 3.5-MHz transducer. Complete two-dimensional, color, pulsed, and continuous wave Doppler images were acquired according to standard techniques and digitally stored for offline analysis in cine-loop format (EchoPac 110.0.0; GE Vingmed Ultrasound). LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), and LVEF were measured from the apical two- and four-chamber views according to the biplane Simpson rule

(25). LV volumes were indexed by body surface area and noted as LVEDVi and LVESVi, respectively. Patients with a reduction of ≥15% in LVESV at the 6-month follow-up were considered responders to CRT, whereas patients who died before the 6-month follow-up, or who did not show a reduction of ≥15%, were classified as nonresponders (26).

Mitral regurgitation severity was determined semiquantitatively from color Doppler images obtained from the conventional parasternal long-axis and apical views (27). LV dyssynchrony was quantified using color-coded tissue Doppler imaging (TDI) as the maximum delay between peak systolic velocities among the four basal segments (septal, lateral, anterior, and inferior). A delay of ≥65 ms was defined as substantial LV dyssynchrony (28).

The presence of an impaired LV relaxation (LV diastolic dysfunction) was evaluated according to current recommendations, using transmitral flow Doppler velocities and TDI-derived mitral annular velocities (29,30). In particular, transmitral early (E) and late (A) diastolic velocities and the E-wave deceleration time were measured using the apical four-chamber view with a 2-mm sample volume at the tips of the mitral leaflets. An E/A ratio ≥2 and a shorter E-wave deceleration time identify an LV-restrictive filling pattern. Using TDI, the peak early diastolic myocardial velocities at septal and lateral borders of the mitral annulus were measured and averaged to calculate the mean early diastolic myocardial velocities (E′). The E/E′ ratio was therefore derived as a measure of LV filling pressures; a higher E/E′ ratio is associated with increased LV filling pressures. LV diastolic dysfunction was therefore graded (grade I, II, and III) according to a multiparametric approach, including E/A ratio, E-wave deceleration time, and average E/E′ based on current guidelines (29).

Long-term follow-up and definition of end points

The long-term follow-up was performed by medical chart review, outpatient clinical visits, and telephone contact. The primary end point was all-cause mortality, and the secondary end point was HF hospitalization, heart transplantation, or cardiac death (whichever came first). Cardiac deaths were classified as sudden cardiac death or death due to decompensated HF or other cardiac causes.

Statistical analysis

Results are presented as mean ± SD for continuous variables and as numbers and percentages for dichotomous data. Independent Student *t* tests were used to compare continuous variables, and χ^2 tests were used to compare categorical variables. The differences at the 6-month follow-up within and between the patient groups were compared by repeated-measures ANOVA, including the interaction between group and time. The Wilcoxon signed rank test was used to test the change in nonparametric paired samples. In diabetic patients, univariable (binary) logistic regression identified the variables that are associated with the response to CRT. A multivariable (binary) logistic regression was performed with relevant or statistically significant ($P < 0.05$) clinical, echocardiographic, and diabetes-related variables to identify the independent predictors of response to CRT in diabetic patients. Survival was evaluated by the Kaplan-Meier method, and the effect of diabetes on survival was evaluated with the Cox proportional hazards model. All relevant clinical and echocardiographic variables were included, and the variables that showed a statistically significant effect ($P < 0.05$) in the univariable analysis were entered in the multivariable Cox proportional hazards model. In the case of colinearity of the variables, only one of these variables was entered in the multivariable model. All statistical tests were two sided, and for all tests, a *P* value <0.05 was considered statistically significant. Windows PASW Statistics software (SPSS version 18.0; PASW Statistics, Chicago, IL) was used for data analyses.

RESULTS

Patient population

The study population consisted of 710 consecutive patients (536 men, mean age = 66 ± 10 years). All patients received optimal medical treatment, and echocardiography showed dilated LV (LVEDVi = 113 ± 40 mL/m²; LVESVi = 86 ± 37 mL/m²) with depressed LVEF (25 ± 8%) (Table 1).

Diabetes was present in 171 (24%) patients, with the majority having type 2 diabetes (158 patients, 93%). Exogenous insulin use was present in 33 (19%) patients, and dietary restrictions or oral antidiabetics were recorded in 138 (81%) patients. Baseline characteristics of diabetic and non-diabetic patients were compared and summarized in Table 1.

Table 1—*Baseline characteristics of the study population, comparing patients with diabetes (DM) and without diabetes (non-DM)*

	DM	Non-DM	P value
n	171	539	
Age, years	65.1 ± 9.1	66.5 ± 10.3	0.091
Male, n (%)	139 (81)	397 (74)	**0.043**
BSA, m²	2.00 ± 0.22	1.94 ± 0.21	**0.002**
Ischemic etiology, n (%)	124 (73)	281 (52)	**<0.001**
QRS duration, ms	158 ± 22	168 ± 26	**<0.001**
Left bundle branch block	110 (65)	383 (72)	0.095
Atrial fibrillation, n (%)	37 (22)	80 (16)	0.087
NYHA functional class	3.1 ± 0.3	3.1 ± 0.3	0.947
Quality-of-life score	42 ± 19	37 ± 16	**0.014**
6-min walking distance, m	282 ± 114	300 ± 117	0.108
GFR, mL/min/1.73 m²	69 ± 34	69 ± 31	0.774
HbA₁c, mmol/mol	54.7 ± 15.4	—	
β-Blockers, n (%)	125 (73)	380 (71)	0.514
ACE-I/ARB-II	150 (88)	483 (90)	0.488
Diuretics, n (%)	156 (91)	449 (83)	**0.011**
Aldactone, n (%)	84 (49)	263 (49)	0.940
Digoxin, n (%)	38 (22)	89 (17)	0.090
Statins, n (%)	121 (71)	274 (51)	**<0.001**
Oral anticoagulation or antiplatelet agents, n (%)	15 (91)	479 (89)	0.051
Biguanides, n (%)	107 (63)	—	—
Sulfonylureas, n (%)	69 (40)	—	—
Thiazolidinediones, n (%)	5 (3)	—	—
Insulin, n (%)	33 (19)	—	—
LVEDVi, mL/m²	103 ± 40	117 ± 41	**<0.001**
LVESVi, mL/m²	79 ± 36	89 ± 37	**0.001**
LVEF, %	25 ± 8	25 ± 8	0.830
LV dyssynchrony, ms	67 ± 48	69 ± 49	0.641
Mitral regurgitation ≥2,%	67 (41)	257 (50)	**0.032**
LV diastolic dysfunction grade	2.0 ± 0.8	1.9 ± 0.8	0.379
LV lead location			0.858
Lateral, n (%)	77 (52)	226 (49)	
Posterior, n (%)	54 (36)	182 (39)	
Anterior, n (%)	18 (12)	58 (12)	
Biventricular pacing, %	97.8 ± 8.4	97.8 ± 8.6	0.970

Values are mean ± SD or n (%) unless otherwise indicated. Bold P values are statistically significant. ACE-I/ARB-II, angiotensin-converting enzyme inhibitor/angiotensin receptor blockers II; BSA, body surface area.

Patients with diabetes were more likely to have lower quality of life, have ischemic etiology of cardiomyopathy, and use diuretics and statins. In addition, diabetic patients had shorter mean QRS durations, smaller LV volumes (indexed), and lower degrees of mitral regurgitation, as compared with non-diabetic patients. The degree of LV diastolic dysfunction was comparable between the two groups; in particular, LV diastolic dysfunction grade II was observed in 43% of diabetic patients and 39% of non-diabetic patients, and LV diastolic dysfunction grade III was present in 28% of diabetic and 27% of non-diabetic patients (P = 0.514). Of interest, the distribution of the LV lead position was similar among the two groups.

Diabetes and clinical and echocardiographic changes after CRT

At 6 months follow-up, all evaluated parameters improved significantly in the entire population. NYHA functional class improved from 3.1 ± 0.3 to 2.1 ± 0.7 (P < 0.001), 6-min walk test distance increased from 301 ± 113 to 374 ± 129 m (P < 0.001), and quality-of-life score decreased from 38 ± 17 to 25 ± 18 (P < 0.001). In addition, LVEDVi decreased from 113 ± 40 to 102 ± 39 mL/m² (P < 0.001), LVESVi decreased from 86 ± 37 to 72 ± 34 mL/m² (P < 0.001), and consequently, LVEF increased from 25 ± 8 to 31 ± 9% (P < 0.001). In particular, a total of 371 patients (53%) were classified as responders to CRT. Furthermore, the percentage of mitral regurgitation ≥2 in the studied population decreased significantly as compared with the baseline, from 47 to 32% (P < 0.001). Also, LV diastolic function improved at 6 months follow-up in the entire patient population. The E/E′ ratio decreased from 21 ± 13 to 17 ± 12 cm/s (P < 0.001), and the diastolic dysfunction grade decreased from 1.9 ± 0.8 to 1.4 ± 0.9 (P < 0.001) among all CRT recipients.

Comparisons of clinical and echocardiographic data between diabetic and non-diabetic patients, during follow-up after CRT, are displayed in Table 2. At 6 months follow-up, similar improvements in clinical characteristics were observed among diabetic and non-diabetic patients. Furthermore, significant LV reverse remodeling was observed in both groups, but the reduction in LVEDVi and LVESVi was more pronounced in non-diabetic patients as compared with diabetic patients (interaction group and time P values in Table 2). In particular, the percentage of response to CRT was lower in the diabetic patients as compared with non-diabetic patients (45 vs. 57%, P = 0.017). LV dyssynchrony before implantation was comparable between the two groups, and the degree of resynchronization (reduction in LV dyssynchrony) was similar between diabetic and non-diabetic patients (67 ± 48 to 37 ± 36 ms in diabetes vs. 69 ± 49 to 38 ± 34 ms, interaction group and time P = 0.656) (Table 2).

Furthermore, the improvement in LV diastolic function at 6 months follow-up was more pronounced among non-diabetic patients compared with diabetic patients, including the measure of E′, E/E′, E-wave deceleration time, and overall LV diastolic dysfunction grade (interaction group and time P value in Table 2). In particular, the percentage of patients with LV diastolic dysfunction grade III decreased from 28 to 16% among diabetic patients (P < 0.001) and from 27 to 13% among non-diabetic patients (P < 0.001), and the percentage of patients with LV diastolic dysfunction grade II decreased from 43 to 38% among diabetic patients (P < 0.001) and from 39 to 28% among non-diabetic patients (P < 0.001). Of interest,

Table 2—Changes in clinical and echocardiographic variables after 6 months' CRT in HF patients with diabetes (DM) and without diabetes (non-DM)

Variable	DM (n = 171)		Non-DM (n = 539)		P value between groups	P value, interaction group and time
	Baseline	Follow-up	Baseline	Follow-up		
NYHA functional class	3.1 ± 0.3	2.2 ± 0.7*	3.1 ± 0.3	2.1 ± 0.7*	0.451	0.179
Quality-of-life score	42 ± 19	267 ± 21*	37 ± 16	25 ± 17*	**0.049**	0.299
6-min walking distance, m	282 ± 114	357 ± 127*	300 ± 117	379 ± 128*	0.130	0.413
LVEDVi, mL/m^2	103 ± 40	97 ± 37*	117 ± 41	103 ± 39*	**0.007**	**0.001**
LVESVi, mL/m^2	79 ± 36	68 ± 32*	89 ± 37	72 ± 34*	**0.027**	**0.003**
LVEF, %	25 ± 8	31 ± 9*	25 ± 8	31 ± 9*	0.572	0.768
LV dyssynchrony, ms	67 ± 48	37 ± 36*	69 ± 49	38 ± 34*	0.932	0.656
Mitral regurgitation ≥2,%	41	26	50	35	**0.026**	0.790
E/A ratio	1.76 ± 1.32	1.52 ± 1.14*	1.81 ± 1.69	1.42 ± 1.15*	0.859	0.317
E-wave deceleration time, ms	169 ± 71	191 ± 75*	176 ± 73	183 ± 67†	0.966	0.063
E′, cm/s	4.50 ± 1.75	4.73 ± 1.70†	4.37 ± 1.82	5.17 ± 1.74*	0.288	**0.004**
E/E′ ratio	21 ± 11	19 ± 12†	21 ± 14	15 ± 12*	0.063	**0.007**
LV diastolic dysfunction grade	2.0 ± 0.8	1.6 ± 0.9*	1.9 ± 0.8	1.3 ± 0.9*	**0.035**	0.027

Values are mean ± SD unless otherwise indicated. Bold P values are statistically significant. *P < 0.001, baseline vs. follow-up. †P = not significant, baseline vs. follow-up.

20% of non-diabetic patients normalized LV diastolic function, compared with 10% of diabetic patients (P < 0.001).

In order to identify potential characteristics that might have an impact on LV reverse remodeling after CRT among diabetic patients, a logistic regression analysis was performed to predict response to CRT. LV dyssynchrony (odds ratio 3.950 [95% CI 1.851–8.430], P < 0.001), ischemic etiology (0.409 [0.172–0.970], P = 0.043), and insulin use (0.388 [0.123–0.931], P = 0.036) were independent predictors of echocardiographic response to CRT in diabetic patients. Furthermore, none of the other tested parameters in the logistic regression analysis (age, sex, atrial fibrillation, QRS duration, percentage of biventricular pacing, GFR, HbA$_{1c}$, biguanide use, sulfonylurea use, thiazolidinedione use, LVEDVi, LVESVi, LVEF, and LV diastolic dysfunction) independently predicted the response to CRT (see online appendix for univariable and multivariable analysis of predictors of response to CRT among diabetic patients).

Diabetes and long-term prognosis after CRT

During a median follow-up of 38 months (interquartile range 22–64 months), the primary end point of all-cause mortality was recorded in 255 (36%) patients. Cardiac death occurred in 160 (63%) patients, including decompensated HF in 132 (83%), sudden cardiac death in 15 (9%), and other cardiac causes in 13 (8%). Cardiac death was more frequently

observed among diabetic patients (75 vs. 56%, P = 0.004) compared with non-diabetic patients and was mainly caused by decompensated HF (89 vs. 78%, P < 0.001). Additionally, six patients (2%) underwent heart transplantation, and HF hospitalizations were recorded in 100 (14%) patients.

The overall survival (primary end point) was worse in diabetic versus non-diabetic patients. The Kaplan-Meier curves show a significant survival difference between the two groups from the third year after implantation (log rank P = 0.001) (Fig. 1A). In particular, respective 3- and 5-year survival rates were 79% (95% CI 76–83%) and 68% (63–73%) in non-diabetic patients compared with 70% (63–78%) and 50% (40–59%) in diabetic patients.

Similarly, as shown in Fig. 1B, the secondary end point of HF hospitalizations and cardiac death was more frequent in diabetic patients when compared with non-diabetic patients (χ^2 = 13.19, log rank P < 0.001).

Finally, diabetes was tested as independent predictor of mortality using the Cox proportional hazards model. After adjusting for age, sex, ischemic etiology, NYHA functional class, presence of atrial fibrillation, GFR, LVESVi, significant LV dyssynchrony, LV diastolic dysfunction grade, and mitral regurgitation ≥2, diabetes remained as a strong independent predictor of all-cause mortality (hazard ratio [HR] 1.593 [95% CI 1.092–2.324], P = 0.016) (Table 3) together with ischemic etiology, renal dysfunction, LVESVi,

lack of significant LV dyssynchrony, and LV diastolic dysfunction grade.

CONCLUSIONS—The key findings of this study are as follows: 1) A significant improvement in LV systolic function was observed both in diabetic and non-diabetic patients after CRT, but was more pronounced in non-diabetic patients; 2) the improvement in LV diastolic dysfunction after CRT was more pronounced among non-diabetic patients than in diabetic patients; and 3) the long-term outcome after CRT was superior in non-diabetic patients when compared with diabetic patients, with diabetic as independent predictor of all-cause mortality in CRT recipients.

Impact of diabetes on response to CRT: LV dimensions and systolic function

The beneficial effect of CRT on LV remodeling and function has been widely reported (31,32). Specific analyses exploring the influence of diabetes on LV reverse remodeling and improvement of function after CRT have also been performed but provided contradictory results. Initial single-center studies, with small patient populations, reported more pronounced improvement in LV function after CRT among non-diabetic versus diabetic patients (12,16). Conversely, subanalyses from CRT clinical trials showed similar improvements in LV performance in diabetic and non-diabetic patients (13–15). However, these results are difficult to translate outside the setting
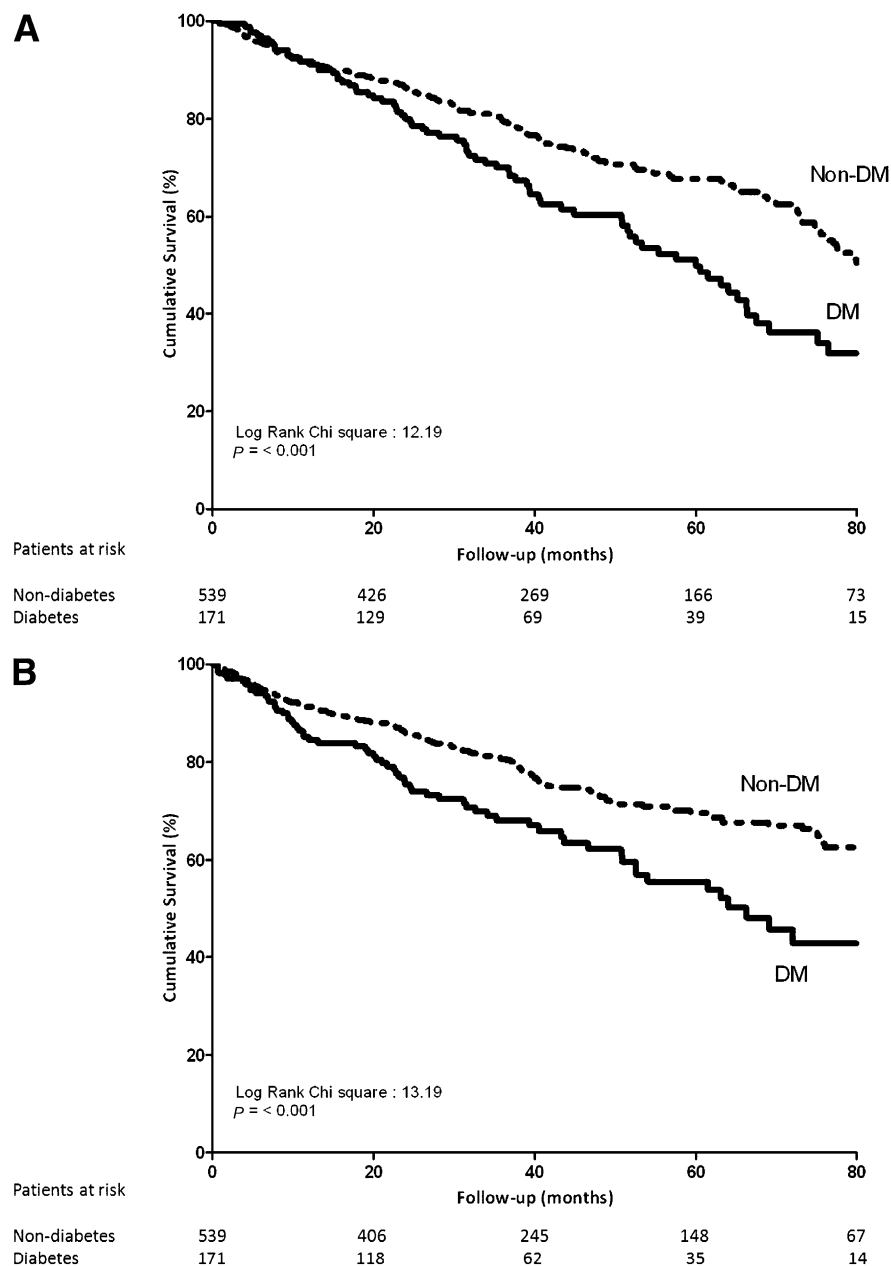
Figure 1—A: *Kaplan-Meier survival curves for the time to all-cause mortality (primary end point) in diabetic versus non-diabetic patients.* B: *Kaplan-Meier survival curves for the time to cardiac death and heart failure hospitalization (secondary end point) in diabetic (DM) versus non-diabetic (non-DM) patients.*

and 5) neurohumoral and autonomic functional changes (9).

To explore which baseline characteristics might help to predict the response to CRT specifically among diabetic patients, the association of glycemic control level and insulin use with LV reverse remodeling after CRT was evaluated, together with other important clinical and echocardiographic variables. Previous studies suggested that exogenous insulin use, a well-known predictor of HF (5,13), may play an important role in the myocardial compensatory capacity. Decreased insulin availability can impair the energy-independent transport of glucose across the cell membrane, resulting in a shift toward fatty acid metabolism and increased myocardial oxygen utilization (34). Results from the multivariable analysis in the current study suggested that insulin use, LV dyssynchrony, and ischemic etiology were independent predictors of the response to CRT in diabetic patients, whereas the level of glycemic control prior to CRT implantation influenced the response to CRT. In line with this observation, data from the Cardiac Resynchronization in Heart Failure (CARE-HF) trial revealed that insulin use was predictive of all-cause mortality in CRT recipients (13). Furthermore, insulin use in a population with a high prevalence of type 2 diabetes probably reflects a long history of diabetes and/or poorly controlled diabetes under oral antidiabetic medication.

Impact of diabetes on response to CRT: LV diastolic function

LV diastolic dysfunction is common in diabetic patients irrespective of the LV systolic function and is significantly associated with a poor prognosis and higher mortality rates (10,11). The mechanisms responsible for the increased myocardial stiffness among these patients might be relative myocardial hypertrophy and, more importantly, myocardial deposition of collagen and advanced glycation end products (11).

The contribution of LV diastolic dysfunction to the development of cardiomyopathy in diabetic patients is well known, but so far, no studies have specifically focused on the changes in LV diastolic function after CRT in patients with diabetes. In the current study, a significant improvement in LV diastolic function after CRT was observed both in diabetic and non-diabetic patients, but this improvement was more pronounced in non-diabetic patients. The magnitude

of the clinical trials, i.e., when patients are not selected according to specific inclusion criteria and are less closely monitored. In the current tertiary referral hospital registry, CRT resulted in significant LV function improvement both in diabetic and non-diabetic patients. However, LV reverse remodeling was more pronounced in non-diabetic patients. This finding could not be related to the degree of resynchronization, since the reduction in LV dyssynchrony was similar

between the two groups. However, several potential diabetes-related pathophysiological mechanisms might contribute to the relatively limited LV reverse remodeling in diabetic patients: 1) higher incidence of coronary artery disease and therefore a larger myocardial scar burden and recurrence of ischemia, 2) reduced microvascular blood flow (33), 3) increased myocardial fat and interstitial fibrotic tissue content (8,34), 4) advanced glycation end product deposition (11),

Table 3—*Univariable and multivariable Cox proportional hazards model for all-cause mortality in the overall population*

	Univariable model			Multivariable model		
	HR	95% CI	P value	HR	95% CI	P value
Age (per year)	1.025	1.012–1.039	<0.001	0.989	0.966–1.013	0.379
Male	1.637	1.196–2.240	0.002	1.938	0.980–2.738	0.060
Ischemic etiology	1.635	1.266–2.112	<0.001	1.797	1.162–2.779	0.008
NYHA functional class IV	2.019	1.417–2.876	<0.001	1.450	0.835–2.519	0.187
Atrial fibrillation	1.655	1.226–2.261	0.001	1.182	0.739–1.890	0.485
Diabetes	1.608	1.229–2.105	0.001	1.593	1.092–2.324	0.016
Insulin use	0.752	0.413–1.370	0.352			
HbA$_{1c}$ (per mmol/mol)	1.004	0.973–1.037	0.798			
GFR (per mL/min/1.73 m^2 increase)	0.977	0.971–0.982	<0.001	0.977	0.969–0.985	<0.001
LVESVi (per mL/m^2)	1.005	1.002–1.008	0.001	1.005	1.000–1.010	0.030
LVEF (per %)	0.971	0.956–0.987	<0.001			
LV dyssynchrony (≥65 ms)	0.683	0.529–0.881	0.003	0.631	0.439–0.909	0.013
LV diastolic dysfunction grade I (reference group)			<0.001			0.004
Grade II (vs. reference group)	1.833	1.185–2.836	0.006	1.543	0.958–2.552	0.074
Grade III (vs. reference group)	2.739	1.75–4.285	<0.001	2.167	1.423–4.199	0.001
Mitral regurgitation grade ≥2	1.384	1.079–1.774	0.011	1.182	0.803–1.740	0.396

Bold *P* values are statistically significant.

of improvement in LV diastolic function might partially be related to the extent of LV reverse remodeling after CRT (35). In addition, significant LV diastolic dysfunction might persist despite an improvement in LV systolic function. Sustained LV diastolic dysfunction may have a significant impact on exercise capacity (15,16) and, most importantly, on long-term outcome.

Impact of diabetes on long-term prognosis after CRT

Conflicting results on the long-term survival benefit after CRT in diabetic patients have been reported. The Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial reported similar survival in diabetic and non-diabetic patients (13,36). In contrast, the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) (14) demonstrated that diabetic patients had a worse outcome with higher all-cause mortality and more HF hospitalization rates (14). The results of the current study also suggest a worse prognosis in CRT recipients with diabetes than non-diabetic patients (17,37). Moreover, the current study extensively explored the potential predictors of long-term outcome, including clinical and echocardiographic characteristics. Diabetes was an independent determinant of all-cause mortality, together with renal function, LVESVi, LV dyssynchrony, and LV

diastolic dysfunction grade III. Similarly, the recent data obtained in a large CRT registry demonstrated that HbA$_{1c}$ as an expression of poorly regulated glycemic control was predictive of a worse outcome at short-term follow-up after CRT (38). In contrast, at longer-term follow-up, the glycemic control may significantly change over time, and therefore, this variable may no longer influence the long-term outcome, as observed in the current study.

Study limitations

Data on the mean duration of diabetes prior to the implantation, mean duration of insulin therapy, or changes in antidiabetic regimen during follow-up were not systematically available. This information could have allowed a more accurate analysis of the impact of glycemic control on outcome after CRT in diabetic patients.

Conclusion

Diabetic patients experienced a significant benefit from CRT in terms of functional parameters and LV diastolic and systolic function. However, the magnitude of LV reverse remodeling and LV diastolic function improvement was less pronounced in diabetic patients as compared with non-diabetic patients. Furthermore, the presence of diabetes was independently associated with an increased risk of all-cause mortality.

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