Chapter 4

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

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Diabetes mellitus (DM) and heart failure (HF) are two major health care problems with worldwide growing prevalence and incidence.[1,2] Their inter-relationship is largely established,[3-5] being DM 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 DM and HF are still unclear, but may include a higher risk of atherosclerosis and microvascular dysfunction,[7] deposition of interstitial myocardial collagen leading to systolic and diastolic dysfunction,[8] and specific neurohumoral deregulations.[9]

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 DM on the efficacy of CRT remains still controversial.[10-14] Therefore, the aim of the present study was to evaluate potential differences in LV systolic and diastolic function improvement after CRT between DM and non-DM patients. Furthermore, the influence of DM 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.[15] Patient data were prospectively collected in the departmental Cardiology Information System (EPD-Vision®, Leiden University Medical Center, Leiden, the Netherlands) and retrospectively analyzed. Patients were selected for CRT according to the presence of left ventricular ejection fraction (LVEF) ≤35%, HF symptoms despite optimal medical therapy and a QRS duration ≥120 milliseconds.[16] The etiology of HF was considered ischemic in the presence of significant coronary artery disease (>50% stenosis in ≥1 major epicardial coronary artery) 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. All patients underwent extensive clinical evaluation and transthoracic 2-dimensional (2D) echocardiography assessment at baseline and 6 months after CRT. All patients were scheduled for regular 6-monthly visits to the outpatient clinic. The relation between the presence of DM and the effect of CRT on LV systolic and diastolic function at 6-month follow-up, as well as the clinical outcome during long-term follow-up after CRT, were evaluated.

Definition of diabetes mellitus

DM was defined as treated or presently diagnosed glucose intolerance, according to the World Health Organization criteria (fasting blood glucose of ≥7.0 mmol/L, or 2-hour oral glucose tolerance test glucose of ≥ 11.1 mmol/L).[17] According to the American Diabetes Association criteria, DM patients were stratified as having type 1 or type 2 diabetes.[18] Patients with exogenous insulin use as the cornerstone of their glycaemic control regimen were classified as insulin dependent. Hemoglobin A_{1c} (HbA_{1c}), a marker of glycaemic control level, was measured and expressed according to International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) 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 Minnesota living with Heart failure questionnaire (higher scores indicate poorer quality of life) and exercise capacity by 6-minute walk test (6MWT).[19-20] The renal function was evaluated with glomerular filtration rate (GFR) according to the equation of Cockcroft-Gault.[21]

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, General Electric Vingmed Ultrasound, Horten, Norway) equipped with a 3.5 MHz transducer. Complete 2D, 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, Horten, Norway). LV end-diastolic volume (LVEDV), end-systolic volume (LVESV) and LVEF were measured from the apical 2- and 4-chamber views according to the biplane Simpson's rule.[22] LV volumes were indexed by body surface area (BSA) and noted as LVEDVi and LVESVi, respectively. Patients with a reduction of ≥15% in LVESV at 6-months 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 non-responders.[23]

Mitral regurgitation severity was determined semi-quantitatively from color Doppler images obtained from the conventional parasternal long-axis and apical views.(24) 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 en inferior). A delay of ≥65 ms was defined as substantial LV dyssynchrony.[25] LV diastolic function evaluation included Doppler transmitral velocities and TDI-derived mitral annular motion velocities. In particular,

transmitral early (E) and late (A) diastolic velocities and the E-wave deceleration time were measured using the apical 4-chamber view with a 2 mm sample volume at the tips of the mitral leaflets. 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. LV diastolic dysfunction was graded (grade I, II, and III) according to E/A ratio, E-wave deceleration time and average E/E' based on current guidelines.[26]

Long-term follow-up and definition of endpoints

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

Statistical analysis

Results are presented as mean ± SD for continuous variables and as numbers and percentages for dichotomous data. Independent t–tests were used to compare continuous variables and $\chi 2$ tests for comparison of categorical variables. Differences at 6-month follow-up within and between the patient groups were compared by repeated-measures ANOVA, including interaction between group and time. The Wilcoxon signed rank test was used to test the change in non-parametric paired samples. In DM patients, univariable (binary) logistic regression identified the variables that are associated with response to CRT. A multivariable (binary) logistic regression was performed with relevant or statistically significant ($p<0.05$) clinical, echocardiographic and DM related variables to identify the independent predictors of response to CRT in DM patients. Survival was evaluated by the method of Kaplan-Meier and the effect of DM 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 ($p<0.05$) at the univariable analysis were entered in the multivariable Cox proportional hazards model. In case of colinearity of the variables, only one of these variables was entered in the multivariable model. All statistical tests were 2-sided and for all tests, a p-value <0.05 was considered statistically significant. Windows PASW Statistics software (SPSS version 18.0, PASW, 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±37ml/m²) with depressed LVEF (25±8%; Table 1).

Table 1. Baseline characteristics of the study population and comparing patients with (DM) and without diabetes mellitus (Non-DM)

	DM (n=171)	Non-DM (n=539)	p-value
Age, yrs	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/1.73m²	69±34	69±31	0.774
HbA_{1c}, 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**
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

Values are mean ± SD or n. Bold p-values are statistically significant. ACE-I/ARB-II = Angiotensin-Converting Enzyme Inhibitor/Angiotensin-Receptor Blockers II; BSA= Body Surface Area; HbA1c = Hemoglobin A_{1c}; GFR = GlomerularFiltration Rate, estimated according Cockroft-Gault equation; LV= Left Ventricular; LVEDVi= Left Ventricular End-Diastolic Volume index; LVEF= Left Ventricular Ejection Fraction; LVESVi= Left Ventricular End-Systolic Volume index; NYHA= New York Heart Association

DM 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 anti-diabetics were recorded in 138 (81%) patients. Baseline characteristics of DM and non-DM patients were compared and summarized in Table 1. Patients with DM were more likely to have lower quality-of-life, ischemic etiology of cardiomyopathy and to use diuretics and statins. In addition, DM patients had shorter mean QRS duration, smaller LV volumes (indexed) and lesser degree of mitral regurgitation as compared to non-DM patients. Of interest, the degree of LV diastolic dysfunction was comparable between the two groups; in particular, LV diastolic dysfunction grade II was observed in 43% of DM patients and in 39% of non-DM patients, while LV diastolic dysfunction grade III was present in 28% of DM and 27% of non-DM patients (p=0.514)

Diabetes mellitus 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 ($p<0.001$), 6MWT distance increased from 301±113 to 374±129 meters ($p<0.001$) 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 to 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 DM and non-DM patients, during follow-up after CRT, are displayed in Table 2. At 6 months follow-up, similar improvements in clinical characteristics were observed among DM and non-DM patients. Furthermore, significant LV reverse remodeling was observed in both groups, but the reduction in LVEDVi and LVESVi was more pronounced in non-DM patients as compared to DM patients (interaction group and time p-values in Table 2). In particular, the percentage of response to CRT was lower in the DM patients as compared to non-DM patients (45% vs. 57%, p=0.017). LV dyssynchrony before implantation was comparable between the 2 groups and the degree of resynchronization (reduction in LV dyssynchrony) was similar between DM and non-DM patients (67±48 to 37±36 ms in DM 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-DM patients as compared to

DM 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 DM patients (p<0.001) and from 27% to 13% among non-DM patients (p<0.001), while the percentage of patients with LV diastolic dysfunction grade II decreased from 43% to 38% among DM patients (p<0.001) and from 39% to 28% among non-DM patients (p<0.001). Of interest, 20% of non-DM patients normalized LV diastolic function as compared to 10% in DM patients (p<0.001).

In order to identify potential characteristics that might have an impact on LV reverse remodeling after CRT among DM-patients, a logistic regression analysis was performed to predict response to CRT. LV dyssynchrony (OR [95-%-CI]: 3.950 [1.851-8.430], p<0.001), ischemic etiology (OR [95-%-CI]: 0.409 [0.172-0.970], p=0.043) and insulin use (OR [95-%-CI]: 0.388 [0.123-0.931], p=0.036) were independent predictors of echocardiographic response to CRT in DM patients (Table 3).

Table 2. Changes in clinical and echocardiographic variables after six months CRT in heart failure patients with (DM) and without diabetes mellitus (Non-DM)

Variable	DM n = 171		Non-DM n = 539		p-value	p-value
	Baseline	Follow-up	Baseline	Follow-up	between groups	interaction group and time
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/m²	103±40	97±37*	117±41	103±39*	**0.007**	**0.001**
LVESVi, ml/m²	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. Bold p-values are statistically significant. For abbreviations see Table 1. * p<0.001, baseline vs. follow-up; †p= not significant, baseline vs. follow-up

Table 3. Predictors of response to CRT (defined as ≥15% reduction in left ventricular end-systolic volume at 6-month follow-up) in patients with diabetes mellitus

	Univariable analysis			Multivariable analysis		
	OR	**CI 95%**	**p-value**	**OR**	**CI 95%**	**p-value**
Age (per year)	1.006	0.993 – 1.020	0.359	0.997	0.955 - 1.042	0.904
Male gender	0.739	0.533 – 1.023	0.068	0.690	0.266-1.787	0.445
Ischemic etiology	0.575	0.433 – 0.764	**<0.001**	0.409	0.172 – 0.970	**0.043**
QRS duration per ms	1.011	1.004-1.017	**0.001**	1.011	0.994-1.029	0.216
GFR (per ml/min/1.73m² increase)	1.001	0.997 – 1.005	0.671			
HbA_{1c} (per mmol/mol)	0.989	0.960 – 1.019	0.484			
Insulin use	0.404	0.177 – 0.922	**0.031**	0.338	0.123 - 0.931	**0.036**
LVEDVi (per ml/m²)	1.003	0.999 – 1.006	0.118			
LVESVi (per ml/m²)	1.003	0.999 – 1.007	0.149	1.003	0.992-1.014	0.616
LVEF (per %)	0.995	0.978 – 1.012	0.549			
LV dyssynchrony (≥ 65 ms)	3.520	1.901-6.518	< **0.001**	3.950	1.851 – 8.430	< **0.001**
LV diastolic dysfunction grade I (reference group)			0.987			
Grade II (vs. reference group)	1.066	0.494-2.300	0.870			
Grade III (vs. reference group)	1.033	0.443-2.405	0.941			
Mitral regurgitation grade ≥ 2	0.887	0.669-1.177	0.406	1.041	0.481-2.250	0.919

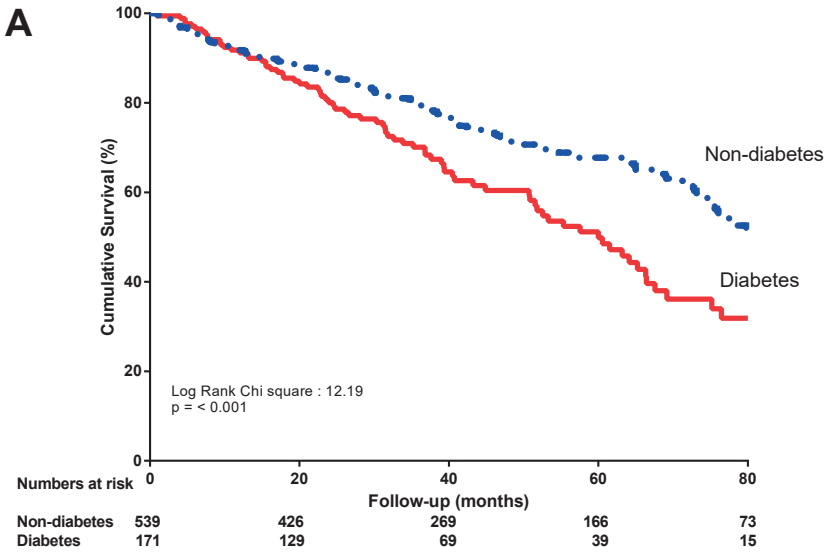
Bold p-values are statistically significant. HbA1c = Hemoglobin A1c; GFR = Glomerular Filtration Rate, estimated according Cockroft-Gault equation; LV= Left Ventricular; LVEDVi = Left Ventricular End-Diastolic Volume index; LVEF= Left Ventricular Ejection Fraction; LVESVi= Left Ventricular End-Systolic Volume index

Diabetes mellitus and long-term prognosis after CRT

During a median follow-up of 38 months (interquartile range 22-64 months), the primary endpoint of all-cause mortality was recorded in 255 (36%) patients. Cardiac death occurred in 160 (63%) patients, including decompensated heart failure in 132 (83%), sudden cardiac death in 15 (9%) and other cardiac causes in 13 (8%). Cardiac death was more frequently observed among DM patients (75% vs. 56%, p=0.004) as compared to non-DM patients and was mainly caused by decompensated heart failure (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 endpoint) was worse in DM versus non-DM 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; Figure 1A). In particular, respective 3- and 5-year survival rates were 79% (95-% CI: 76%-83%) and 68% (95-CI: 63%-73%) in non-DM patients compared with 70% (95%-CI: 63%-78%) and 50% (95%-CI: 40%-59%) in DM patients.

Similarly as shown in Figure 1B, the secondary endpoint of HF hospitalizations and cardiac death was more frequent in DM patients when compared with non-DM



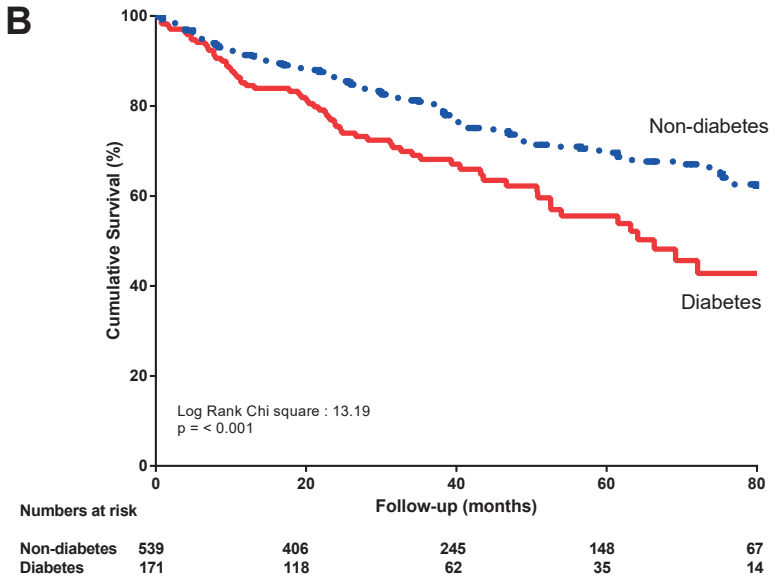


Figure 1. Panel A. Kaplan-Meier survival curves for the time to all-cause mortality (primary end point) in diabetes versus non-diabetes patients. Panel B. Kaplan-Meier survival curves for the time to cardiac death and heart failure hospitalization (secondary endpoint) in diabetes versus non-diabetes patients (1B).

patients ($\chi 2$ 13.19, log rank p<0.001)

Finally, DM was tested as independent predictor of mortality using the Cox proportional hazards model. After adjusting for age, gender, ischemic etiology, NYHA functional class, presence of atrial fibrillation, GFR, LVESVi, significant LV dyssynchrony, LV diastolic dysfunction grade and mitral regurgitation ≥2, DM remained as strong independent predictor of all-cause mortality (HR [95%-CI]: 1.593 [1.092-2.324], p=0.016; Table 4) together with ischemic etiology, renal dysfunction, LVESVi, lack of significant LV dyssynchrony and LV diastolic dysfunction grade.

DISCUSSION

Key findings of the present study are: (1) significant improvement in LV systolic function was observed both in DM and non-DM patients after CRT, but was more pronounced in non-DM patients; (2) the improvement in LV diastolic dysfunction after CRT was more pronounced among larger? non-DM patients as compared to

Table 4. Univariable and multivariable Cox proportional hazards model for all-cause mortality in the overall population

	Univariable			Multivariable Model		
	HR	**CI 95%**	**p-value**	**HR**	**CI 95%**	**p-value**
Age (per year)	1.025	1.012-1.039	< **0.001**	0.989	0.966-1.1013	0.379
Male gender	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**
QRS duration (per ms)	0.997	0.992-1.002	0.223			
Left bundle branch block	0.810	0.624-1.051	0.112			
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 mellitus	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			
Quality-of-life score (per point)	1.021	1.013-1.029	< **0.001**			
6-min walking distance (per m)	0.996	0.995-0.997	< **0.001**			
GFR (per ml/min/1.73m² increase)	0.977	0.971-0.982	< **0.001**	0.977	0.969 - 0.985	< **0.001**
LVEDVi (per ml/m²)	1.004	1.001-1.007	**0.007**			
LVESVi (per ml/m²)	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**

Table 4. Univariable and multivariable Cox proportional hazards model for all-cause mortality in the overall population (*continued*)

	Univariable			Multivariable Model		
	HR	**CI 95%**	**p-value**	**HR**	**CI 95%**	**p-value**
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. HbA1c = Hemoglobin A_{1c}; GFR = Glomerular Filtration Rate, estimated according Cockroft-Gault equation; LV= Left Ventricular; LVEDVi = Left Ventricular End-Diastolic Volume index; LVEF= Left Ventricular Ejection Fraction; LVESVi= Left Ventricular End-Systolic Volume index

DM patients; (3) and finally, the long-term outcome after CRT was superior in non-DM patients when compared to DM patients with DM as independent predictor of all-cause mortality in CRT recipients.

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

The beneficial effect of CRT on LV remodeling and function has been widely reported.[27,28] Specific analyses exploring the influence of DM 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-DM versus DM patients.[10-14] Conversely, sub-analyses from CRT clinical trials showed similar improvements in LV performance in DM and non-DM patients.[11-13] However, these results are difficult to translate outside the setting 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 DM and non DM patients. However, LV reverse remodeling was more pronounced in non-DM patients. This finding could not be related to the degree of resynchronization, since the reduction in LV dyssynchrony was similar between the 2 groups. However, several potential DM-related pathophysiological mechanisms might contribute to the relatively limited LV reverse remodeling in DM patients: 1) higher incidence of coronary artery disease and therefore a larger myocardial scar burden and recurrence of ischemia, 2) reduced microvascular blood flow[29], 3) increased myocardial fat and interstitial fibrotic tissue content,[8,30] 4) advanced glycation end- product deposition[31] and 5) neurohumoral and autonomic functional changes.[9]

In order to explore which baseline characteristics might help to predict response to CRT specifically among DM patients, we evaluated the association of glycaemic

control level and insulin use with LV reverse remodeling after CRT, together with other important clinical and echocardiographic variables. Previous studies suggested that exogenous insulin use, a well-known predictor of HF, [5,11] may play an important role in the myocardial compensatory capacity. Decreased insulin availability can impair energy-independent transport of glucose across the cell membrane resulting in a shift toward fatty acid metabolism and increased myocardial oxygen utilization.[30] Results from the multivariate analysis in the current study suggested that insulin use, together with LV dyssynchrony and ischemic etiology were independent predictors of response to CRT in DM patients. In line with this observation, data from the CArdiac REsynchronization in Heart Failure trial (CARE-HF) revealed that insulin use was predictive of all-cause mortality in CRT recipients.[11]

Impact of diabetes mellitus on response to CRT: LV diastolic function

LV diastolic dysfunction is common in DM patients irrespective of the LV systolic function.[31] 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.[31] Particularly advanced glycation end-products may lead to cardiac dysfunction by causing an abnormal vasodilator response in the coronary microcirculation and increasing myocardial stiffness directly by crosslinking collagen or reducing bioavailability of nitric oxide. [8,31,32]

The contribution of LV diastolic dysfunction to the development of cardiomyopathy in DM patients is well known, but so far no studies have specifically focused on the changes in LV diastolic function after CRT in patients with DM. In the current study, significant improvement in LV diastolic function after CRT was observed both in DM and non-DM patients, but this improvement was more pronounced in non-DM patients. The magnitude of improvement in LV diastolic function might partially be related to the extent of LV reverse remodeling after CRT.[33]

Impact of diabetes mellitus on long-term prognosis after CRT

Conflicting results on the long-term survival benefit after CRT in DM patients have been reported. The Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure trial (COMPANION) reported similar survival in DM and non-DM patients.[11,34] In contrast, the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT),[12] demonstrated that DM patients had worse outcome with higher all-cause mortality and more HF hospitalization rates.[12] The results of the current study also suggest a worse prognosis in CRT recipients with DM as compared with non-DM patients.[15,35] Moreover, the current study extensively explored potential predictors of long-term outcome including clinical

and echocardiographic characteristics. DM was an independent determinant of all-cause mortality together with renal function, LVESVi, LV dyssynchrony and LV diastolic dysfunction grade III. Similarly, recent data obtained in a large CRT registry demonstrated that HbA_{1c} as an expression of poorly regulated glycaemic control was predictive of worse outcome at short-term follow-up after CRT.[36] 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 present study.

Study limitations

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

CONCLUSIONS

DM 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 DM patients as compared to non-DM patients. Furthermore, the presence of DM was independently associated with an increased risk of all-cause mortality.

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