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Effect of Cardiac Resynchronization Therapy in Patients with Diabetes Randomized in EchoCRT

Short title: Effect of diabetes in EchoCRT

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Abstract

Aims: Patients with heart failure (HF) and concomitant diabetes carry a poor prognosis. In this post-hoc subgroup analysis, we compared the outcomes of patients with and without diabetes randomized in EchoCRT.

Methods and Results: EchoCRT randomized patients with a QRS duration <130 msec and echocardiographic evidence of left ventricular dyssynchrony to CRT-ON vs. CRT-OFF following device implantation. At study entry, 328 patients (40.5%) had diabetes. The primary outcome (all-cause death or first hospitalization for worsening HF) occurred more frequently in patients with vs. without diabetes (32.6% vs. 23%, p=0.003). A significant treatment interaction was observed for the primary outcome indicating a higher risk for CRT-ON vs. –OFF in patients without (26.5% vs. 19.8%, hazard ratio (HR) 1.58; 95% confidence interval (CI) 1.08-2.31) vs. with diabetes (31.4% vs. 34%; HR 0.86; 95% CI 0.58 – 1.27; p interaction = 0.041). This effect was mainly driven by a lower rate in HF hospitalizations, but was only of borderline significance after multivariate adjustment (p=0.063). The most pronounced effect was observed in patients with non-ischemic cardiomyopathy, where a significantly reduced risk to reach the primary endpoint for CRT-ON vs. –OFF was observed in patients with (HR 0.27, p=0.003) vs. without diabetes (HR 1.79, p=0.038; p interaction 0.005). No treatment interaction by diabetes diagnosis was found for mortality endpoints.

Conclusion: In EchoCRT, heart failure patients with a narrow QRS complex and coexisting diabetes demonstrated a signal for less harm of CRT compared to patients without diabetes, which was driven by differences in HF hospitalizations.

Key words: Heart Failure; Cardiac Resynchronization Therapy; Narrow QRS; Diabetes.

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Introduction

Patients with diabetes mellitus have an elevated risk for cardiac events, including the development of heart failure. Conversely, the prognosis of patients with symptomatic heart failure and concomitant diabetes is dire, with both morbidity and mortality well in excess of that observed in patients without diabetes.[1-3] Cardiac resynchronization therapy (CRT) reduces morbidity and mortality in patients with symptomatic heart failure with reduced ejection fraction and a wide QRS complex,[4-7] and has become standard of care in the treatment of such patients.[8] Patients with diabetes have been demonstrated to derive at least a similar benefit from CRT than patients without diabetes based on several subanalyses of large randomized clinical trials.[9-12] In the same way, a substantial benefit of CRT was observed for diabetes patients in real world registries.[13, 14]

Based on the observation that a substantial proportion of heart failure patients presents with a narrow QRS complex,[15] the EchoCRT trial was conducted to assess the effect of CRT in patients with a QRS duration ≤ 130 msec who present with echocardiographic evidence of left ventricular dyssynchrony. The trial was terminated early due to futility, and demonstrated a relative increase in all-cause mortality of 81% with CRT in this patient population.[16] Evidence on the effect of CRT in heart failure patients with diabetes and a narrow QRS complex is scarce. While a more beneficial response appears possible as extrapolated from data on diabetes patients with a wide QRS complex,[11, 17] patients with diabetes are known to be more susceptible to arrhythmias and may thus be at higher risk in the context of a narrow QRS complex and biventricular pacing.[18] This post-hoc subgroup analysis was therefore performed to assess the efficacy and safety of CRT in patients with and without diabetes randomized in EchoCRT.

Methods

Study design and conduct

EchoCRT was an investigator-initiated, multicenter, international, randomized clinical trial. The results of the main trial including the methodology have been reported.[16] Patients were eligible if they were on optimized medical heart failure therapy, had a standard indication for an implantable cardioverter–defibrillator (ICD), were suffering from symptomatic heart failure (New York Heart Association (NYHA) class III or IV), had a left ventricular ejection fraction (EF) ≤ 35%, a QRS duration of < 130 msec, a left ventricular end-diastolic diameter (LVEDD) of ≥ 55 mm, and echocardiographic evidence of left ventricular dyssynchrony as previously defined.[16] After implantation of a Biotronik Lumax HF-T CRT-D system, patients were randomly assigned in a 1:1 ratio to have cardiac resynchronization turned on (CRT-ON group) or off (CRT-OFF control group). While physicians involved in the device implantation and follow-up were aware of the study-group assignments, heart-failure physicians, patients, and study personnel completing the follow-up assessments were not. The trial was designed by the executive committee and was sponsored by Biotronik with support for echocardiographic training and software provided by GE Healthcare. Diagnosis of diabetes was made at the discretion of the local study site investigators at enrollment into the trial. In cases where diagnosis of diabetes was unclear (n=13), diagnosis was made by the central study team according to available medical reports and concomitant medication.

Endpoints

The primary combined efficacy outcome consisted of the combination of death from any cause or first hospitalization for worsening heart failure.[16] The pre-specified secondary outcomes included time to first hospitalization for worsening heart failure; all-cause

mortality; cardiovascular mortality; and cardiovascular hospitalization.[16] The primary safety outcome was freedom from CRT-D related complications at 6 months in the implanted population.

Statistical analysis

All study results were independently analyzed at the Robertson Centre for Biostatistics at the University of Glasgow. All analyses were performed by intention-to-treat. Baseline characteristics were compared with the use of chi-square (or Fisher's exact) and two-sample t-tests for categorical and continuous variables, respectively. Hazard ratios (HRs) for CRT-OFF and CRT-ON (with 95% confidence intervals) were calculated with the Cox proportional hazards models for patients with vs. without diabetes, stratified for country. In addition, a multivariable Cox proportional hazards model was performed to account for differences across randomized treatment groups in baseline characteristics between patients with and without diabetes (age, gender, sitting systolic blood pressure, body mass index, ischemic cardiomyopathy, history of coronary artery bypass graft and chronic kidney disease). Interactions between patients with and without diabetes (CRT=ON and CRT=OFF) were tested for in Cox models that included diabetes and treatment main effects and interaction terms. Time to event curves were estimated with the use of the Kaplan-Meier method. All tests were two-sided; a p value <0.05 was considered significant.

Results

Baseline characteristics

Patient characteristics at trial entry are shown in Table 1. Out of 809 randomized patients, 328 (40.5%) had a diagnosis of diabetes at baseline. In 3 patients, the status of diabetes could not be definitely assessed. Of the 328 patients with diabetes at baseline, 172

(52.4%) were randomized to CRT-ON and 156 (47.6%) to CRT-OFF. Of the 478 patients without diabetes, 230 (48.1%) were randomized to CRT-ON and 248 (51.9%) to CRT-OFF. Baseline characteristics by group allocation and diabetes status are shown in Supplementary Table 1. There was no significant difference in group allocation to CRT-ON between patients with vs. without diabetes (p=0.228). Patients with diabetes were older, had a higher average body mass index (BMI), more frequently had hypertension, chronic kidney disease, thyroid disease, and more frequently had underlying ischemic cardiomyopathy and prior coronary artery bypass grafting. They achieved a shorter walking distance, reported worse heart failure-related quality of life and were more frequently treated with diuretics, nitrates, statins and aspirin.

Outcomes in patients with vs. without diabetes

Outcomes and event rates in patients with and without diabetes are summarized in Table 2. The primary combined outcome (death from any cause or first hospitalization for worsening heart failure) occurred more frequently in patients with vs. without diabetes (32.6% vs. 23.0%, p=0.008 in fully adjusted analysis). Patients with vs. without diabetes also had a higher event rates for heart failure hospitalizations (28.1% vs. 20.1%, p=0.001 all-cause mortality (11.9% vs. 6.7%, p=0.03 in fully adjusted analysis) and non-cardiovascular infections (17.1% vs. 9.8%, p=0.002). In contrast, there was no significant difference in the primary safety outcome of freedom from complications related to the CRT-D system at 6 months between patients with vs. without diabetes (91.2% vs. 88.1% respectively, p=0.17 in unadjusted analysis; Table 3). Multivariate adjustment did not significantly alter this result.

Efficacy of CRT in patients with vs. without diabetes

A significant treatment interaction was observed for the primary outcome indicating a higher risk for CRT-ON vs. –OFF in patients without (26.5% vs. 19.8%; hazard ratio (HR)

1.58; 95% confidence interval (CI) 1.08 – 2.31) vs. with diabetes (31.4% vs. 34.0%, HR 0.86; 95% CI 0.58 – 1.27; p interaction =0.041, Figs. 1A & 2). This effect was mainly driven by a significant treatment interaction for worsening heart failure hospitalizations, for which a higher risk for CRT-ON vs. –OFF was observed in patients without diabetes (23.0% vs. 17.3%; HR 1.57 (95% CI 1.05 – 2.35) compared to with diabetes (26.2% vs. 30.1%; HR 0.80 (95% CI 0.53 – 1.22); p interaction 0.035). Similarly, cardiovascular hospitalizations were more frequent in CRT-ON vs. –OFF in patients without as compared to with diabetes (p interaction = 0.029). The interaction by diabetes status for the primary endpoint remained borderline significant (p interaction=0.063) after adjustment for baseline parameters (Fig. 3).

An exploratory post-hoc analysis revealed that patients with non-ischemic cardiomyopathy were the main driver of this effect. Of the 374 patients with non-ischemic cardiomyopathy, 125 had a diagnosis of diabetes of which 64 (51.2%) were randomized to CRT-ON. A significantly reduced risk to reach the primary efficacy endpoint for CRT-ON vs. –OFF was observed in patients with (25.01% vs. 32.8%, HR 0.27 (95% CI 0.11 – 0.65), p=0.005) as compared to without diabetes (29.2% vs. 17.1%; HR 1.79 (95% CI 1.03 – 3.11), p=0.04) in patients with non-ischemic cardiomyopathy after multivariate adjustment (p interaction 0.005). In contrast, no difference in events was observed for CRT-ON vs. –OFF in ischemic cardiomyopathy (HR 1.09 (95% CI 0.67 – 1.78), p=0.72) vs. HR 1.10 (95% CI 0.62 – 1.97), p=0.74) for diabetes vs. non-diabetes patients, respectively, after multivariate adjustment (p interaction 0.96).

There was no treatment interaction for all-cause mortality (Fig 1B), as well as heart failure and cardiovascular mortality in patients with vs. without diabetes, both unadjusted (Fig. 2) and after adjustment for baseline differences (Fig. 3). Indeed, in the fully adjusted analysis, the hazard ratio for all-cause mortality in the CRT-ON vs. CRT-OFF group was 1.58 (95% CI 0.78 – 3.20) in patients with diabetes and 1.60 (95% CI 0.77 – 3.32) in patients without diabetes (p interaction 0.98).

Discussion

The current subgroup analysis of EchoCRT reveals three important key findings. First, in this population of heart failure patients with a narrow QRS complex and echocardiographic signs of dyssynchrony, patients with diabetes show less evidence of harm by CRT than patients without diabetes. Second, these differences in the primary outcome are primarily driven by differences in heart failure hospitalizations. Third, although patients with diabetes had an overall higher morbidity and mortality, no significant differences in CRT-D- or implant-related complications were seen between patients with or without diabetes.

The presence of diabetes poses a challenge in the everyday treatment of patients with heart failure, with a worse prognosis observed in a multitude of clinical trials and registries.[1-3] Conversely, patients with diabetes enrolled in the pivotal CRT trials generally fared worse than those without diabetes. In CARE-HF, the risk of all-cause mortality was increased by 30% in patients with as compared to without diabetes by the end of the extension period.[9] Also in MADIT-CRT patients with diabetes more frequently reached the primary endpoint as compared to those without diabetes (26.6% vs. 18%).[11] In COMPANION, a numerically increased risk for mortality and / or HF hospitalization was observed in patients with diabetes, which was not significant after multivariate adjustment.[10] Our data demonstrating an increased risk for both HF hospitalization and all-cause mortality in diabetes patients are hence in line with the results from previous landmark trials in diabetes patients receiving CRT.

In those same trials, patients with diabetes derived at least a similar if not greater benefit from CRT than those without diabetes. In CARE-HF, patients randomized to CRT pacemaker vs. optimal medical therapy had a similar reduction in all endpoints independent of concomitant diabetes.[9] In COMPANION, a reduction of all major morbidity and/or mortality endpoints was observed in the combined cohort of diabetes patients receiving CRT-P or CRT-

D compared with diabetes patients on optimal medical therapy.[10] In MADIT-CRT, a consistent effect of CRT-D as compared to ICD therapy was observed in patients with and without diabetes, with a suggestion of an earlier and greater benefit from CRT-D in patients with diabetes.[11] Importantly in the latter trial, the benefit of CRT appear larger in diabetes patients with non-ischemic cardiomyopathy than in ischemic cardiomyopathy, although there was no statistically significant interaction (HR 0.30 vs. HR 0.59; p int = 0.10).[19] This observation led us to further post-hoc dissect the effect of CRT in patients with diabetes and non-ischemic cardiomyopathy. In line with MADIT-CRT, CRT was associated with a 76% reduced risk for the primary composite endpoint in patients with non-ischemic cardiomyopathy and coexisting diabetes in our study, which is almost identical to the 70% relative risk reduction observed in MADIT-CRT.[19] In contrast, a 79% increased relative risk for the primary outcome with CRT was observed in patients with non-ischemic cardiomyopathy without diabetes.

The mechanism underlying this differential effect is presently unclear, but may be related to a different pathophysiology of diabetic cardiomyopathy in patients with vs. without clinically apparent coronary artery disease. Indeed, patients with diabetes may develop overt heart failure in the absence of coronary artery disease,[20] which may be related to a variety of pathophysiological changes including metabolic disturbances, myocardial fibrosis, small vessel disease, cardiac autonomic neuropathy and insulin resistance.[21] In the Framingham Study cohort, patients with diabetes had increased LV mass and wall thickness on echocardiography, which remains significant even after adjusting for confounding factors.[22] Whether and how these factors may be involved in the differential effect observed in EchoCRT currently remains elusive and will require further study. The premature termination of the trial as well as the absolute low number of events precludes further meaningful sub-subanalysis within the group of non-ischemic diabetic patients, including investigation of individuals who potentially profit more of CRT such as women.

The trend towards less harm in the primary composite endpoint in diabetes patients randomized to CRT-ON was primarily driven by differences in heart failure hospitalizations. No difference in all-cause mortality for CRT-ON vs. –OFF was observed among patients with and without diabetes. This is in contrast to MADIT-CRT where CRT reduced all-cause mortality to a significantly higher extent in insulin-treated diabetes patients compared to orally treated diabetes patients and patients without diabetes in a recent subanalysis of the trial.[11, 17]

The reasons for the differential effect of CRT between diabetes patients with a narrow and a wide QRS complex are unclear. On the one hand, several mechanisms for a worse outcome in diabetes patients receiving CRT may be conceivable, such as myocardial fibrosis, microvascular dysfunction, lipid accumulation, altered autonomic tone, or side-effects of anti-glycemic drugs, hypoglycemia in particular.[23-25] Combined these phenomena may make patients with diabetes more prone to any potential pro-arrhythmogenic effect of CRT in the context of a narrow QRS complex. On the other hand, CRT has been shown to improve the metabolomic profile of heart failure patients and CRT-mediated restoration of glucose metabolism may be especially advantageous for insulin-treated diabetes patients.[26, 27] Finally, based on a small study, patients with diabetes may have more pronounced echocardiographic dyssynchrony despite similar QRS duration than non-diabetic patients, making them potentially more amendable to cardiac resynchronization.[28] However, no significant differences in the extent of echocardiographic dyssynchrony were found at baseline or at 6 months in patients with as compared to without diabetes in EchoCRT[29], although the dyssynchrony entry criteria may have created a bias in this regard. In addition, none of these observations readily explain the different response between EchoCRT and MADIT-CRT patients, and further investigations are required to elucidate the underlying mechanisms involved.

Limitations

Any subgroup analysis, including the current investigation of patients with diabetes should by definition be interpreted as hypothesis generating. According to the current 2016 European Society of Cardiology heart failure guidelines CRT is not recommended for patients with a QRS duration < 130ms, independent of the presence or absence of diabetes.[30] As EchoCRT demonstrated an excess of mortality of patients randomized to CRT, the trial was stopped prematurely, thus reducing the statistical power of any subgroup analysis. As such, for some analyses event rates were relatively low, particularly when assessing the sub-subgroup of non-ischemic vs. ischemic cardiomyopathy. The trial excluded patients with atrial fibrillation and advanced renal insufficiency, hence selection bias in the diabetes patients included in the study cannot be excluded. Glucose and HbA1c levels were not available at the time of diagnosis or during follow-up. As a result, misclassification may have occurred in some patients. Furthermore, no sub-subgroup analyses could be performed according to glycemic control (e.g. low vs. high HbA1c). Also, information on the type of diabetes was not available. Given the age and characteristics of the study population, it is very likely that the majority of patients had a diagnosis of type 2 diabetes. Finally, detailed information on the antidiabetic treatments were not available and thus no analyses by oral and non-oral antidiabetic medications (i.e. insulin use) could be performed.

Conclusion

In the present subgroup analysis of EchoCRT on patients with heart failure and a narrow QRS complex, a signal for less harm of CRT was found in patients with vs. without diabetes. This effect was mainly observed in patients with non-ischemic cardiomyopathy and

was driven by differences in heart failure hospitalizations without significant differences in mortality. These results, together with the consistent data from the other large CRT trials, may help clinical decision making in the “grey zone” of CRT indications. Further studies are required to analyze the underlying mechanisms of these results in order to maximize the benefit of CRT in this difficult to treat patient population.

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Conflict of Interest Statements

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Tables

Table 1: Baseline characteristics

Variable	Diabetes (n=328)	No diabetes (n=478)	P-value
Assigned to CRT=ON	172 (52.4%)	230 (48.1%)	0.228
Age (years)	59.7 (10.8)	56.8 (13.8)	**0.001**
Males	231 (70.4%)	353 (73.9%)	0.285
QRS width (site; msec)	105.3 (12.5)	105.2 (13.1)	0.843
QRS width (core; msec)	105.2 (11.78)	106.2 (13.1)	0.291
6-minute walking distance (m)	291.8 (112.8)	348.5 (119.9)	**<0.001**
Quality of life score (MLHFQ)	53.7 (24.1)	49.4 (24.2)	**0.014**
BNP (pg/ml)	229.0 (104.0, 574.0)	268.0 (84.0, 540.0)	0.988
NT-proBNP (pg/ml)	1054.0 (449.5, 2221.0)	1158.0 (539.0, 2356.0)	0.463
Sitting SBP (mmHg)	119.1 (19.4)	118.6 (19.5)	0.727
Sitting DBP (mmHg)	72.3 (11.9)	73.2 (12.0)	0.300
BMI (kg/m2)	32.6 (15.1)	29.7 (9.5)	**<0.001**
Ischemic cardiomyopathy	203 (61.9%)	228 (47.8%)	**<0.001**
MI > 3 months ago	143 (43.6%)	179 (37.5%)	0.080
PCI > 3 months ago	129 (39.3%)	158 (33.1%)	0.068
CABG more than 3 months ago	75 (22.9%)	75 (15.7%)	**0.010**
Hypertension	264 (81.0%)	267 (56.5%)	**<0.001**
Congenital heart disease	2 (0.6%)	14 (3.0%)	**0.019**
Prior ischemic stroke or TIA	47 (14.5%)	48 (10.1%)	0.061
Chronic lung disease	60 (18.5%)	88 (18.5%)	0.982
Chronic kidney disease	69 (21.2%)	39 (8.2%)	**<0.001**
Thyroid disease	36 (11.0%)	33 (6.9%)	**0.043**

LVEF Biplane (%)	27.2 (5.2)	26.9 (5.8)	0.466
LV end diastolic dimeter (mm)	65.5 (7.0)	67.0 (7.8)	**0.005**
LV lead location optimal	207 (79.0%)	314 (79.7%)	0.831
Qualified by TDI and/or radial dyssynchrony			0.437
Tissue Doppler imaging only	85 (25.9%)	116 (24.3%)	
Radial strain only	81 (24.7%)	104 (21.8%)	
Tissue Doppler imaging and radial strain	162 (49.4%)	257 (53.9%)	
NYHA classification			*
I	0 (0.00%)	5 (1.1%)	
II	7 (2.1%)	12 (2.5%)	
III	310 (94.5%)	447 (93.5%)	
IV	11 (3.4%)	14 (2.9%)	
Concomitant medication			
ACE inhibitor or ARB	309 (94.2%)	456 (95.4%)	0.450
Aldosterone antagonist	189 (57.6%)	295 (61.7%)	0.244
Beta-blocker	321 (97.9%)	458 (95.8%)	0.112
Diuretic agent	295 (89.9%)	400 (83.7%)	**0.011**
Nitrate	97 (29.6%)	90 (18.8%)	**<0.001**
Antidiabetic medication	283 (86.3%)	5 (1.1%)	**<0.001**
Statin	254 (77.4%)	294 (61.5%)	**<0.001**
Aspirin	235 (71.7%)	294 (61.5%)	**0.003**
Anticoagulant	75 (22.9%)	136 (28.5%)	0.076
Amiodarone	28 (8.5%)	43 (9.0%)	0.821
Digoxin	65 (19.8%)	84 (17.6%)	0.420

Antiarrhythmic drugs	84 (25.6%)	124 (25.9%)	0.916

For categorical variables number and percentage are reported; for continuous variables mean and standard deviation are reported (except for BNP and NT-proBNP where median and inter-quartile range are presented). * p-value not reported due to small numbers.

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide, CRT, cardiac resynchronization therapy; BMI, body mass index; DBP, diastolic blood pressure, LV, left ventricular; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MLHFQ, Minnesota Living with Heart Failure Questionnaire; NYHA, New-York Heart Association; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; TIA, transient ischemic attack

Table 2: Efficacy outcomes in patients with and without diabetes

Endpoint	Diabetes (n=328)	No diabetes (n=478)	HR (95% CI)*	P-value	Fully adjusted HR (95% CI)**	P-value
Death or WHF hospitalization	107 (32.6%)	110 (23.0%)	1.66 (1.26, 2.17)	**<0.001**	1.48 (1.10, 1.97)	**0.008**
WHF hospitalization	92 (28.1%)	96 (20.1%)	1.61 (1.20, 2.16)	**0.001**	1.45 (1.06, 1.98)	**0.020**
All-cause mortality	39 (11.9%)	32 (6.7%)	2.08 (1.29, 3.36)	**0.003**	1.79 (1.06, 3.03)	**0.030**
Cardiovascular mortality	33 (10.1%)	21 (4.4%)	2.80 (1.59, 4.92)	**<0.001**	2.41 (1.30, 4.45)	**0.005**
Heart failure mortality	16 (4.9%)	11 (2.3%)	2.69 (1.22, 5.97)	**0.015**	2.45 (1.03, 5.78)	**0.042**
Cardiovascular hospitalization	121 (36.9%)	162 (33.9%)	1.24 (0.97, 1.57)	0.081	1.09 (0.84, 1.40)	0.529

* adjusted for country (p-value from Wald test). ** adjusted for country, randomized treatment group, age, gender, sitting systolic blood pressure, body mass index, ischemic cardiomyopathy, history of coronary artery bypass graft and history of chronic kidney disease (p-value from Wald test). Abbreviations: WHF, worsening heart failure

Table 3: Primary safety outcome (freedom from complications related to the CRT-D system at 6 months) in patients with and without diabetes

Endpoint	Diabetes (n=328)	No Diabetes (n=478)	P-value
Subjects (%) Complication-Free			
CRT-D system	306 (93.3%)	432 (90.4%)	0.15
Implant procedure	322 (98.2%)	467 (97.7%)	0.65
Other	327 (99.7%)	477 (99.8%)	0.79
Any of the above	299 (91.2%)	421 (88.1%)	0.17

Supplementary Table S1: Baseline characteristics by diabetes and randomization group

Variable	Diabetes, CRT=ON (n=172)	Diabetes, CRT=OFF (n=156)	No diabetes, CRT=ON (n=230)	No diabetes, CRT=OFF (n=248)
Age (years)	59.6 (10.5)	59.7 (11.2)	56.0 (14.3)	57.4 (13.3)
Males	128 (74.4%)	103 (66.0%)	165 (71.7%)	188 (75.8%)
QRS width (site)	105.1 (12.3)	105.6 (12.7)	104.9 (13.7)	105.4 (12.7)
QRS width (core)	105.1 (12.0)	105.3 (11.5)	106.8 (13.8)	105.6 (12.5)
Walking distance (m)	299.0 (113.7)	283.6 (111.7)	350.2 (117.9)	346.9 (121.9)
Quality of life score	54.4 (24.7)	52.9 (23.5)	49.0 (23.9)	49.8 (24.6)
BNP (pg/ml)	213.0 (108.0, 498.0)	276.0 (100.0, 683.0)	266.5 (74.0, 626.0)	271.0 (106.0, 500.5)
NT-proBNP (pg/ml)	1230.0 (472.0, 2520.0)	927.0 (410.0, 1997.0)	1335.0 (556.0, 2579.0)	1071.5 (533.5, 2080.5)
Sitting SBP (mmHg)	118.3 (19.5)	120.0 (19.3)	117.0 (19.9)	120.1 (19.0)
Sitting DBP (mmHg)	72.1 (11.4)	72.4 (12.5)	73.1 (12.6)	73.2 (11.4)
BMI (kg/m2)	32.1 (15.4)	33.2 (14.9)	29.4 (7.7)	29.9 (10.9)
Ischemic cardiomyopathy	108 (62.8%)	95 (60.9%)	110 (47.8%)	118 (47.8%)
Non-ischemic cardiomyopathy	64 (37.2%)	61 (39.1%)	120 (52.2%)	129 (52.0%)

Myocardial infarction more than 3 months ago	80 (46.5%)	63 (40.4%)	87 (37.8%)	92 (37.1%)
Percutaneous coronary intervention more than 3 months ago	74 (43.0%)	55 (35.3%)	82 (35.7%)	76 (30.7%)
CABG more than 3 months ago	44 (25.6%)	31 (19.9%)	33 (14.4%)	42 (16.9%)
Hypertension	138 (80.7%)	126 (81.3%)	122 (53.7%)	145 (58.9%)
Congenital heart disease	1 (0.6%)	1 (0.7%)	5 (2.2%)	9 (3.7%)
Prior ischemic stroke or TIA	24 (14.1%)	23 (14.8%)	24 (10.5%)	24 (9.8%)
Chronic lung disease	30 (17.5%)	30 (19.5%)	39 (17.1%)	49 (19.8%)
Chronic kidney disease	40 (23.5%)	29 (18.7%)	26 (11.3%)	13 (5.3%)
Thyroid disease	14 (8.2%)	22 (14.1%)	19 (8.3%)	14 (5.7%)
LVEF Biplane (%)	27.1 (5.5)	27.3 (4.8)	27.0 (5.8)	26.8 (5.8)
LV end diastolic dimeter (mm)	65.9 (6.9)	65.1 (7.2)	67.3 (8.1)	66.8 (7.5)
LV lead location optimal	102 (75.6%)	105 (82.7%)	155 (83.3%)	159 (76.4%)
Qualified by TDI and/or radial dyssynchrony				
Tissue Doppler imaging only	41 (23.8%)	44 (28.2%)	54 (23.6%)	62 (25.0%)
Radial strain only	40 (23.3%)	41 (26.3%)	45 (19.7%)	59 (23.8%)
Tissue Doppler imaging and	91 (52.9%)	71 (45.5%)	130 (56.8%)	127 (51.2%)

radial strain				
NYHA classification				
I	0 (0.0%)	0 (0.0%)	2 (0.9%)	3 (1.2%)
II	5 (2.9%)	2 (1.3%)	2 (0.9%)	10 (4.0%)
III	162 (94.2%)	148 (94.9%)	221 (96.1%)	226 (91.1%)
IV	5 (2.9%)	6 (3.9%)	5 (2.17%)	9 (3.6%)
Concomitant medication				
ACE inhibitor or ARB	163 (94.8%)	146 (93.6%)	218 (94.8%)	238 (96.0%)
Aldosterone antagonist	101 (58.7%)	88 (56.4%)	145 (63.0%)	150 (60.5%)
Beta-blocker	167 (97.1%)	154 (98.7%)	218 (94.8%)	240 (96.8%)
Diuretic agent	152 (88.4%)	143 (91.7%)	192 (83.5%)	208 (83.9%)
Nitrate	52 (30.2%)	45 (28.9%)	45 (19.6%)	45 (18.2%)
Antidiabetic medication	146 (84.9%)	137 (87.8%)	2 (0.9%)	3 (1.2%)
Statin	135 (78.5%)	119 (76.3%)	144 (62.6%)	150 (60.5%)
Aspirin	131 (76.2%)	104 (66.7%)	134 (58.3%)	160 (64.5%)
Anticoagulant	38 (22.1%)	37 (23.7%)	65 (28.3%)	71 (28.6%)
Amiodarone	14 (8.1%)	14 (9.0%)	28 (12.2%)	15 (6.1%)
Digoxin	35 (20.4%)	30 (19.2%)	45 (19.6%)	39 (15.7%)

Antiarrhythmic drugs	43 (25.0%)	41 (26.3%)	67 (29.1%)	57 (23.0%)

Figures

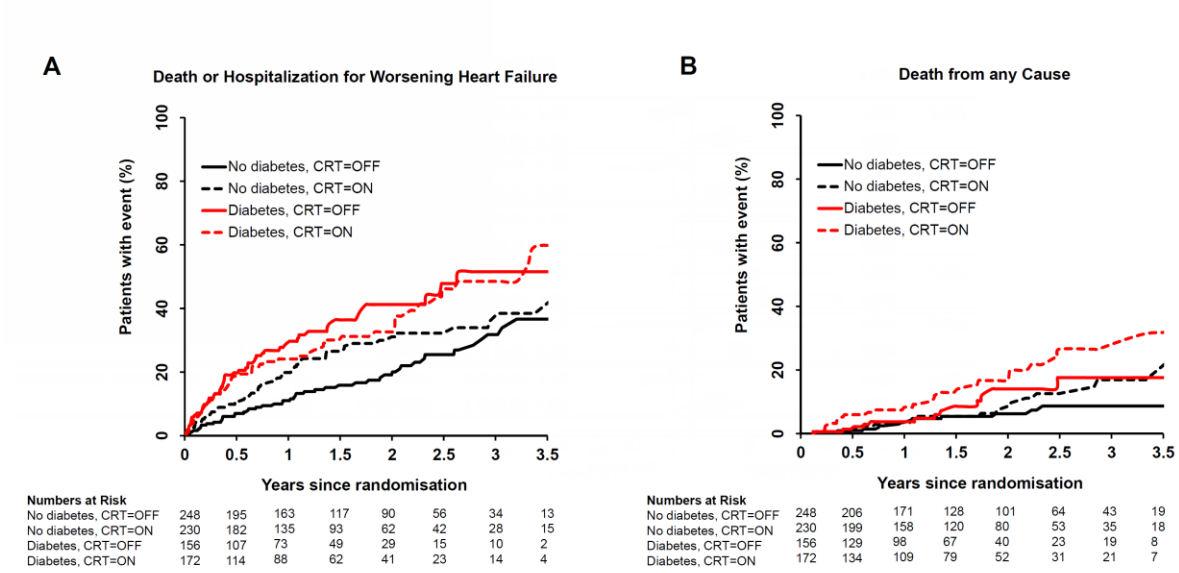

Figure 1: Kaplan–Meier Estimates for primary outcome and all-cause mortality events, stratified by diabetes.

Kaplan–Meier curves for (A) the primary composite efficacy outcome of death from any cause or hospitalization for heart failure and (B) death from any cause in patients with and without diabetes, randomized to CRT-ON and CRT-OFF.

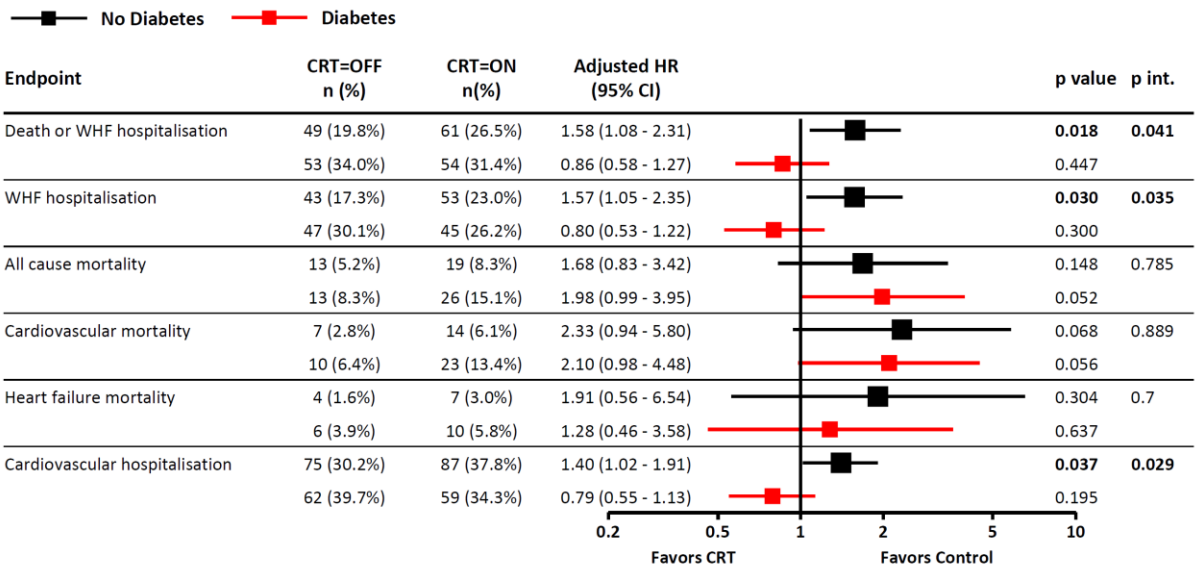

Figure 2: Effect of CRT in patients with (lower, red) and without (upper, black) diabetes.

Hazard ratio (HR; 95% confidence interval (CI)) adjusted for country and p-value from Wald test are presented. Abbreviations: WHF, worsening heart failure.

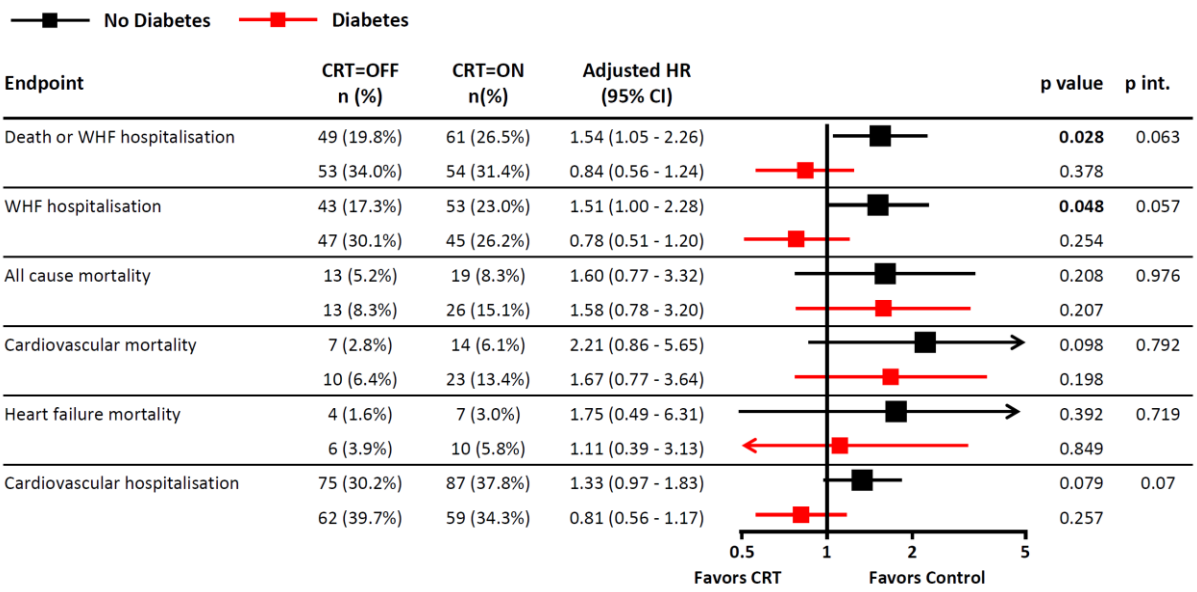

Figure 3: Effect of CRT in patients with (lower, red) and without (upper, black) diabetes after multivariable adjustment

Hazard ratio (HR; 95% confidence interval (CI)) adjusted for country, age, gender, sitting systolic blood pressure, body mass index, ischemic cardiomyopathy, history of coronary artery bypass graft and history of chronic kidney disease (p-value from Wald test).

Abbreviations: WHF, worsening heart failure.