Cardiac Resynchronization Therapy and its Effects in Patients with type 2 DIAbetes Mellitus OPTimized in Automatic vs. Echo Guided Approach. Data from the DIA-OPTA Investigators

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Abstract

Objectives: To evaluate the effects of cardiac resynchronization therapy (CRTd) in patients with type 2 diabetes mellitus (T2DM) optimized via automatic vs. echocardiographic guided approach.

Background: Suboptimal optimization of atrio-ventricular (AV) and inter-ventricular (VV) timings reduces CRTd response. Thus, we hypothesize that automatic CRTd optimization could ameliorate clinical outcomes in T2DM patients.

Methods: We designed a prospective, multicenter study to recruit, from October 2016 to June 2019, 191 patients with T2DM and heart failure (HF) candidate to receive a CRTd. Study outcomes were CRTd responders rate, hospitalizations for HF worsening, cardiac deaths and all cause of deaths in T2DM patients treated with a CRTd and randomly optimized via automatic (n 93) vs. echocardiographic (n 98) guided approach at 12 months of follow-up.

Results: We had a significant difference in CRTd responders rate (68 (73.1%) vs. 58 (59.2%), p 0.038), and hospitalization for HF worsening (12 (16.1%) vs. 22 (22.4%), p 0.030) in automatic vs. echo-guided group of patients. At multivariate Cox regression analysis, automatic guided approach (3.636 [1.271-10.399], CI 95%, p 0.016) and baseline highest values of atrium pressure (automatic SonR values, 2.863 [1.537-6.231], CI 95%, p 0.006) predicted CRTd responders rate. In automatic group, we had significant difference in SonR values comparing CRTd responders vs. non responders (1.24 ± 0.72 g vs. 0.58 ± 0.46 g (follow-up), p 0.001), hospital admission for HF worsening events (0.48 ± 0.29 g vs. 1.18 ± 0.43 g, p 0.001), and cardiac deaths (1.13 ± 0.72 g vs. 0.65 ± 0.69 g, p 0.047).

Conclusions: automatic optimization increased CRTd responders rate, and reduced hospitalizations for HF worsening. Intriguingly, automatic CRTd and highest baseline values of SonR could predict the outcome of CRTd responders. Notably, there is a significant difference in SonR values for CRTd responders vs. non responders, hospitalizations for HF worsening and cardiac deaths.

Clinical trial: ClinicalTrials.gov Identifier NCT04547244;

Background

Type 2 diabetes mellitus (T2DM) is a risk factor negatively impacting on clinical prognosis for patients with heart failure (HF), and in those receiving a Cardiac resynchronization therapy with defibrillator (CRTd), (1). On other hand, CRTd could ameliorate clinical outcomes, because it shows a positive impact on both morbidity and mortality in treated patients (2). Notably, T2DM accounts about the 38% of patients treated with a CRTd (1), and the patients which do not respond to CRTd are defined “CRTd non responders”, and show worse prognosis (3). In this setting, T2DM is a leading cause of multiple and complex alterations of molecular, metabolic, electrical, and mechanical cardiac functions, which cause arrhythmias and worsening of cardiac pump (1). The worsening of cardiac pump is a relevant cause of hospitalizations and deaths in CRTd patients (1–5). However, a great effort has been invested in last

decades to develop new therapeutic approaches to improve the cardiac pump efficiency, the CRTd responders rate and the clinical outcomes in CRTd patients with T2DM. In this setting, the use of multipolar left-ventricular (LV) pacing leads, and the optimization of device programming mode has been seen as an important advancement in T2DM patients with CRTd (6, 7, 8). On other hand, also T2DM patients receiving a multipolar CRTd could experience a worse prognosis (6). In CRTd patients, this could be due to the reduction of cardiac pump, that is more evidenced in patients with the loss of atrioventricular (AV) and interventricular (IV) synchrony (9). Therefore, the optimization of AV and IV intervals could be a therapeutic target, to ameliorate the post implant CRTd effectiveness, and to increase the CRTd responders (8, 9). By the way, the echocardiography could be used to ameliorate the optimization of AV/IV intervals (9). On other hand, it showed contrasting results in clinical studies, and low application in clinical practice (9). Therefore, new techniques, as the intracardiac electrogram (IEGM) guided approach, have been proposed for the optimization of AV/IV intervals in CRTd patients (9). Indeed, IEGM guided approach is quicker, simpler and a reliable alternative to the echo guided approach for CRTd optimization (9). On other hand, also IEGM guided approach showed contrasting results in the optimization of CRTd (9), and for the optimization of CRTd patients authors showed its inferiority as compared to echocardiography approach for the hemodynamic outcome (9). Therefore, recently authors introduced an optimization technique non-IEGM based, that is correlated with LV dP/dt max and with heart hemodynamic function (8). To date, this non-IEGM technique evaluates the peak of endocardial acceleration during isovolumetric contraction of left ventricle, and its amplitude, registered as SonR signal, that is correlated with the contractile function of the heart (8, 10). Moreover, automatic vs. echocardiography guided approach could lead to an increase of CRTd response (10). Intriguingly, there are not studies designed to compare the effects of automatic vs. echocardiography guided approach to optimize AV/IV delays in T2DM patients treated with multipolar CRTd. Again, no study evidenced the modifications of SonR signals in T2DM patients with CRTd experiencing the main clinical outcomes. However, in the present study we evaluated CRTd responders rate, hospitalization for HF worsening and deaths (cardiac deaths and all cause of deaths) in T2DM patients with HF and multipolar CRTd randomly assigned to automatic vs. echocardiography guided optimization approach at 12 months of follow-up. Furthermore, we evaluated at baseline and at follow-up the values of SonR for CRTd responders, and in case of hospitalizations for HF worsening and deaths.

Methods

Study design

Between 1th January 2010 and 20th January 2019, we screened a population of 203 consecutive patients with T2DM, chronic HF and indication to receive a CRTd in an observational multicenter, randomized study (DIA-OPTA investigators). Figure 1. T2DM was diagnosed according to American Diabetes Association criteria (11). To establish T2DM patients treatment, the screened patients answered a specific questionnaire about medicines used for diabetes treatment, the date of the beginning and end of treatment, route of administration, and duration of use (11). The diagnosis of HF was made as

indicated by international guidelines on heart failure disease management (12). Moreover, only patients with T2DM and HF were enrolled in the study, according to inclusion/exclusion criteria. Figure 1. The study population respected the following inclusion/exclusion criteria:

Inclusion criteria

at least 18 years of age, T2DM diagnosis, with clinical history of stable chronic heart failure, New York Heart Association (NYHA) functional class II or III, sinus rhythm, left bundle branch block, severe left ventricle ejection fraction reduction (LVEF < 35%), stable sinus rhythm, and candidates to receive a CRT-d treatment (12).

Exclusion criteria

age < 18 or > 75 years, ejection fraction > 35%, previous implant of implantable cardioverter defibrillator (ICD), CRT-d and/or pacemaker, absence of informed patient consent, and any condition that would make survival for 1 year unlikely.

Study population and intervention

The 191 enrolled patients with T2DM and HF respected the clinical indication for implantation of a de-novo multipolar CRTd, according to current international guidelines (12).

However, we randomly treated the T2DM patients with conventional CRTd implant (n 98) vs. SensoR CRTd (n 93), using a computer generating code program. The patients with conventional CRTd implant were optimized using echo-guided approach, and defined as “Echo-guided” group. The patients with automatic sensor guided CRTd were defined as “Automatic group”, and they were not optimized by echo-guided approach. Figure 1. However, in a time of 14 days after a successful CRTd implant, patients were randomized (2:1, respectively) to weekly automatic AV and IV delay optimization with SonR in Automatic group vs. echo-guided optimization in Echo group. The full description of CRTd implant, echocardiography evaluation and post CRTd implant optimization (Automatic vs. Echo group) is provided in supplementary file. At baseline and for all follow-up duration (6 and 12 months) the patients underwent full echocardiographic evaluation, and a global clinical status (NYHA) assessment, and CRTd interrogation (13). Before CRTd intervention and during follow-up, the baseline laboratory studies were determined by peripheral blood and enzymatic assays after an overnight fast (values of plasma glucose, HbA1c, B type natriuretic peptide (BNP) and serum lipids). In addition, at baseline, and during follow up we measured inflammatory markers as circulating serum levels of pro-inflammatory cytokines (tumor necrosis factor-α, TNF α, interleukin-6, IL6), systemic inflammatory markers (C reactive protein, CRP), and leucocytes and neutrophils count as previously reported (13). Thereafter, for each enrolled patients during clinical, instrumental assessment, device telemetric control (at implant, 10 days, 6, and 12 months after discharge) and visualization of hospital discharge schedules, we reported the effects of CRT-d in terms of

clinical outcomes, CRT responder rate, and clinical events as hospitalizations for HF worsening, all deaths. The study follow-up duration was 12 months.

Study endpoints

Primary endpoints were the rate of patients responders to CRTd, hospitalizations for HF worsening, cardiac deaths and all cause of deaths events comparing patients in Automatic vs. Echo-guided group. In addition, in Automatic group of patients we evaluated the SonR signals amplitude at baseline, and their variation at follow-up for the CRTd responders vs. non responders, and for the events of hospitalization for HF worsening, cardiac deaths and all cause of deaths. The study endpoints were evaluated for 12 months during visits and controls, and by hospital discharge schedules. The detailed description of study endpoints data collection and analysis is reported in supplementary file.

Ethical Committee and Clinical trial registration

Authors conducted the study in accordance with the Declaration of Helsinki. The Ethics Committees of all participating institutions approved the protocol. All patients were informed about the study nature, and gave their written informed, and signed consent to participate in the study. The study was registered in ClinicalTrials.gov, clinical trial number NCT04547244. The authors and investigators of DIA-OPTA study accepted full responsibility for the accuracy and completeness of the data and all analyses, and for the fidelity of this report of the trial protocol.

Statistical analysis

The collected data were analyzed by a qualified statistician. The T2DM patients with CRTd were divided in automatic group of patients vs. echo-guided group of patients (conventional group or controls), and during follow up visits, and controls in CRT-d responders vs. CRT-d non-responders. However, we supposed that the number of patients with alterations in primary and secondary endpoints was significantly different between the two groups of patients. Safety analyses were performed on data from all enrolled patients. Thus, we expressed the continuous variables as means and standard deviations, that were tested by two-tailed Student t test for paired or unpaired data, as appropriate, or by one-way analysis of variance (ANOVA) for more than two independent groups of data. The categorical variables were compared by Chi square or Fisher exact test where appropriate. We performed survival analysis by the Kaplan–Meier method, and we evaluated the predictors of the study endpoints by Cox regression models in patients with automatic as compared with echo-guided CRTd. However, we conducted an univariate analysis to examine the association between single principal clinic, echocardiographic, electrocardiographic characteristics, etc. and automatic CRTd effects, and 12 months study outcomes (CRTd responders rate, hospitalizations for HF worsening, all cause of deaths and cardiac deaths). However, Cox models were adjusted for; age, Body mass index, cholesterol, dyslipidemia, beta-blockers, ace-inhibitors, calcium inhibitors, etc. Therefore, only variables presenting a p value ≤ 0.25 at the univariate analysis were included in the model. We used a stepwise method with backward elimination. and we calculated odds ratios (OR) with 95% confidence intervals. The model was evaluated with Hosmer

and Lemeshow test. A 2-sided $p < 0.05$ was considered statistically significant. The statistical analysis was performed using the SPSS software package for Windows 17.0 (SPSS Inc., Chicago Illinois).

Results

In the present study we analyzed 191 T2DM patients with multipolar CRTd, divided in automatic CRTd group (n 93), vs. echo-guided group (conventional CRTd implant, n 98). Figure 1. Characteristics of study population at baseline are reported in table 1.

Table 1
Clinical characteristics of study population at baseline in overall, and automatic vs. echoguided patients.

PARAMETERS	OVERALL POPULATION (n 191)	AUTOMATIC (n 93)	ECHO GUIDED (n 98)	P value
Age	71 ± 6	71 ± 7	72 ± 6	0.426
Male (%)	134 (70.2)	63 (67.7)	71 (72.4)	0.431
Smokers (%)	97 (50.8)	46 (49.5)	51 (52)	0.407
Hypertension (%)	136 (71.2)	65 (69.9)	71 (72.5)	0.282
Dislipidemia (%)	71 (37.2)	35 (37.6)	36 (36.7)	0.462
Plasma glucose (mg/dl)	186.7 ± 22.1	185.5 ± 22.3	188.9 ± 22.0	0.367
HbA1c (mmol/mol)	57.9 ± 16.3	57.8 ± 16.2	58.1 ± 16.4	0.263
BMI > 30 kg/m^2(%)	15 (7.8)	8 (8.6)	7 (7.1)	0.791
COPD (%)	35 (18.3)	17 (18.3)	18 (18.4)	0.538
Renal disease (%)	35 (18.3)	16 (17.2)	19 (19.4)	0.105
Ischemic heartfailure (%)	131 (68.6%)	65 (69.9)	66 (67.4)	0.302
II NYHA class (%)	33 (25.2)	16 (24.6)	17 (25.8)	0.280
III NYHA class (%)	98 (74.8)	49 (75.4)	49 (74.2)	0.211
QRS duration (ms)	137.4 ± 9.2	137.5 ± 9.0	137.9 ± 9.4	0.930
6MWT	243.47 ± 41.83	241.18 ± 44.94	246.75 ± 40.74	0.371
SonR values (g)	/	0.24 ± 0.08	/	/
Echocardiographic parameters				
LVEF (%)	27 ±8	27 ± 5	28 ± 5	0.285
LVEDd (mm)	65 ± 8	66 ± 7	64 ± 9	0.101
LVESd (mm)	43 ± 8	41 ± 6	44 ± 9	0.291
LVEDv (ml)	205 ± 20	206 ± 18	203 ± 22	0.993
LVESv (ml)	146 ± 17	148 ± 15	145 ± 18	0.818
Mitral insufficiency				
+ (%)	96 (50.3)	45 (48.4)	51 (52.0)	0.359
++ (%)	78 (40.8)	38 (40.9)	40 (40.8)	0.556
+++ (%)	17 (8.9)	10 (10.7)	7 (7.2)	0.451

Medications at baseline				
Amiodarone(%)	40 (20.9)	19 (20.4)	21 (21.4)	0.569
ACE inhibitors (%)	86 (45)	42 (45.2)	44 (44.9)	0.543
ARS blockers (%)	61 (31.9)	31 (33.3)	30 (30.6)	0.464
Sacubitril/valsartan (%)	47 (24.6)	23 (24.7)	24 (24.5)	0.551
Beta blockers:				
Carvedilol (%)	74 (38.7)	36 (38.7)	38 (38.8)	0.555
Bisoprolol (%)	62 (32.5)	32 (34.4)	30 (30.6)	0.539
Aspirin (%)	76 (39.8)	36 (38.7)	40 (40.8)	0.558
Tiklopidine(%)	5 (2.6)	2 (2.1)	3 (3.1)	0.525
Warfarin (%)	57 (29.8)	27 (29)	30 (30.6)	0.468
NOAC (%)	45 (23.6)	20 (21.5)	25 (25.5)	0.316
Calcium antagonist (%)	12 (6.3)	5 (5.4)	7 (7.1)	0.501
Ivabradine(%)	40 (20.9)	21 (22.6)	19 (19.4)	0.599
Digoxin (%)	57 (29.8)	27 (29)	30 (30.6)	0.468
Loop diuretics (%)	168 (88)	79 (84.9)	89 (90.8)	0.268
Aldosterone Blockers (%)	117 (61.3)	55 (59.1)	62 (63.3)	0.656
Statins (%)	142 (74.3)	69 (74.2)	73 (74.5)	0.461
Anti diabetic drugs, n (%)				
Insulin (%)	40 (20.9)	18 (19.3)	22 (22.4)	0.722
Metformin (%)	109 (57.1)	49 (52.7)	60 (61.2)	0.246
Sulfonylureas (%)	34 (17.8)	16 (17.2)	18 (18.4)	0.852
Thiazolidinediones (%)	22 (11.5)	10 (10.7)	12 (12.2)	0.823
GLP-1 agonist (%)	28 (14.7)	13 (14)	15 (15.3)	0.840

DPP-4 inhibitors (%):	40 (20.9)	18 (19.3)	22 (22.5)	0.722
Biomarkers				
Lymphocytes	7.95 ± 2.29	7.99 ± 2.23	7.83 ± 2.35	0.271
Neutrophiles	5.38 ± 1.92	5.40 ± 1.95	5.37 ± 1.90	0.421
BNP (pg/ml)	327.38 ± 18.61	321.04 ± 18.72	332.74 ± 19.55	0.667
CRP (mg/L)	9.84 ± 0.94	10.36 ± 1.03	9.36 ± 0.97	0.466
IL6 (pg/ml)	6.42 ± 0.05	6.38 ± 0.04	6.47 ± 0.06	0.272
TNFα (pg/ml)	6.31 ± 0.03	6.34 ± 0.03	6.29 ± 0.02	0.269

ACE: Angiotensin Converting Enzyme; ARS: Angiotensin Receptors; BMI: body mass index; BNP: B type natriuretic peptide; COPD: chronic obstructive pulmonary disease; CRP: C reactive protein; DPP-4: dipeptidyl peptidase-4; HbA1c: glycated hemoglobin 1Ac type; GLP-1: glucagone like peptide-1; IL-6: interleukine 6; LVEDd: left ventricle end diastolic diameter; LVEDv: left ventricle end diastolic volume; LVEF: left ventricle ejection fraction; LVESd: left ventricle end systolic diameter; LVESv: left ventricle end systolic volume; NYHA II, III: New York Heart Association II and III class; NOAC: new oral anti coagulation; SonR: values of SonR signals; TNFα: tumor necrosis factor alpha; 6MWT: 6 minutes walking test.* is for statistical significant (p <0.05).

At 6th month of follow up,

patients in automatic group vs. echo-guided group showed a significant reduction of NYHA class, BNP values (156.38 ± 19.26 vs. 203.55 ± 17.26 pg/ml, p 0.018), and inflammatory markers values, with amelioration of 6MWT (314.62 ± 26.73 vs. 238.84 ± 28.12). Table 2 a. These effects, comparing automatic vs. echo-guided group of patients, were linked to significant reduction of left ventricle systolic diameters/volumes and mitral valve insufficiency (p<0.05), and significant improvement of LVEF (35 ± 6 vs. 27 ± 5, p0.001). Table 2 a.

Table 2 A
Clinical characteristics of study population at 6th month of follow-up in overall, and automatic vs. echoguided patients.

6 months follow up			
PARAMETERS	**AUTOMATIC (n 93)**	**ECHO GUIDED (n 98)**	**P value**
BMI > 30 kg/m^2(%)	8 (8.6)	7 (7.1)	0.791
Plasma glucose (mg/dl)	179.8 ± 22.8	176.9 ± 21.3	0.261
HbA1c (mmol/mol)	54.9 ± 12.7	54.1 ± 11.9	0.167
I NYHA class	5 (5.4)	2 (2.0)	0.026*
II NYHA class	41 (44)	25 (25.5)	0.013*
III NYHA class	42 (45.1)	62 (63.3)	0.006*
IV NYHA class	5 (5.4)	9 (9.2)	0.408
QRS duration	122.1 ±9.5	123.2 ± 9.3	0.516
6MWT	314.62 ± 26.73	238.84 ± 28.12	0.023*
SonR values (g)	0.93 ± 0.08	/	/
Echocardiographic parameters			
LVEF (%)	35 ± 6	27 ± 5	0.001*
LVEDd (mm)	64 ± 6	65 ± 8	0.054
LVESd (mm)	38 ± 4	42 ± 5	0.001*
LVEDv (ml)	171 ± 25	182 ± 31	0.051
LVESv (ml)	111 ± 11	132 ± 16	0.001*
Mitral insufficiency			
+ (%)	47 (50.5)	35 (35.7)	0.021*
++ (%)	41 (44.1)	54 (55.1)	0.241
+++ (%)	5 (5.4)	9 (9.2)	0.408
Biomarkers			
Lymphocytes	7.29± 2.12	8.53 ± 2.17	0.001*
Neutrophiles	5.06± 1.82	5.41± 1.82	0.001*
BNP (pg/ml)	156.38 ± 19.26	203.55± 17.26	0.018*

CRP (mg/L)	7.29 ± 0.59	8.78 ± 0.81	0.049*
IL6 (pg/ml)	5.61± 0.03	6.19 ± 0.04	0.014*
TNFα (pg/ml)	5.36 ± 0.02	6.32± 0.02	0.007*
Study outcomes			
CRTd responders (%)	68 (73.1)	58 (59.2)	0.038*
Hospital admission for HF worsening (%)	11 (15.1)	17 (25.8)	0.084
Cardiac deaths (%)	1 (1.1)	2 (2)	0.061
All cause of deaths (%)	2 (2.1)	3 (3.1)	0.525

BMI: body mass index; BNP: B type natriuretic peptide; CRP: C reactive protein; HbA1c: glycated hemoglobin 1Ac type; IL-6: interleukine 6; LVEDd: left ventricle end diastolic diameter; LVEDv: left ventricle end diastolic volume; LVEF: left ventricle ejection fraction; LVESd: left ventricle end systolic diameter; LVESv: left ventricle end systolic volume; NYHA II, III: New York Heart Association II and III class; SonR: values of SonR signals; TNFα: tumor necrosis factor alpha; 6MWT: 6 minutes walking test.** is for statistical significant (p <0.05).

At 12th month of follow up,

patients in automatic group vs. echo-guided group showed a significant reduction of NYHA class, BNP values (148.41 ± 16.40 vs. 197.26 ± 19.12 pg/ml, p 0.001), and inflammatory markers values, with higher values of 6MWT (319.37 ± 26.92 vs. 227.92 ± 28.19), significant reduction of left ventricle systolic diameters/volumes and mitral valve insufficiency (p<0.05), and significant improvement of LVEF (36 ± 6 vs. 27 ± 5, p 0.001). Table 2 b.

Table 2 B
Clinical characteristics of study population at 12th month of follow-up in overall, and automatic vs. echoguided patients.

12 months follow up			
PARAMETERS	**AUTOMATIC (n 93)**	**ECHO GUIDED (n 98)**	**P value**
BMI > 30 kg/m^2(%)	7 (7.5)	6 (6.1)	0.622
Plasma glucose (mg/dl)	173.5 ± 21.7	171.2 ± 20.9	0.171
HbA1c (mmol/mol)	52.9 ± 12.1	52.3 ± 12.0	0.122
I NYHA class	6 (6.4)	2 (2.0)	0.016*
II NYHA class	45 (48.4)	21 (21.4)	0.010*
III NYHA class	38 (40.9)	66 (67.3)	0.001*
IV NYHA class	4 (4.3)	10 (10.2)	0.021*
QRS duration	121.6 ±9.6	122.9 ± 9.1	0.251
6MWT	319.37 ± 26.92	227.92 ± 28.19	0.005*
SonR values (g)	1.09 ± 0.07	/	/
Echocardiographic parameters			
LVEF (%)	36 ± 6	27 ± 5	0.001*
LVEDd (mm)	63 ± 5	65 ± 8	0.051
LVESd (mm)	35 ± 4	38 ± 5	0.001*
LVEDv (ml)	165 ± 24	178 ± 41	0.054
LVESv (ml)	109 ± 12	126 ± 18	0.001*
Mitral insufficiency			
+ (%)	50 (53.8)	31 (31.6)	0.040*
++ (%)	38 (40.9)	57 (58.2)	0.004*
+++ (%)	5 (5.4)	10 (10.2)	0.285
Biomarkers			
Lymphocytes	7.12± 1.27	8.48 ± 1.18	0.001*
Neutrophiles	4.87 ± 1.85	5.69 ± 2.31	0.001*
BNP (pg/ml)	148.41 ± 16.40	197.26± 19.12	0.001*

CRP (mg/L)	7.24 ± 0.56	8.69 ± 0.83	0.036*
IL6 (pg/ml)	5.55± 0.03	6.31 ± 0.03	0.011*
TNFα (pg/ml)	5.35 ± 0.02	6.31± 0.02	0.005*
Study outcomes			
CRTd responders (%)	68 (73.1)	58 (59.2)	0.038*
Hospital admission for HF worsening (%)	12 (16.1)	22 (22.4)	0.030*
Cardiac deaths (%)	4 (4.3)	7 (7.1)	0.538
All cause of deaths (%)	7 (7.5)	11 (11.2)	0.461

BMI: body mass index; BNP: B type natriuretic peptide; CRP: C reactive protein; HbA1c: glycated hemoglobin 1Ac type; IL-6: interleukine 6; LVEDd: left ventricle end diastolic diameter; LVEDv: left ventricle end diastolic volume; LVEF: left ventricle ejection fraction; LVESd: left ventricle end systolic diameter; LVESv: left ventricle end systolic volume; NYHA II, III: New York Heart Association II and III class; SonR: values of SonR signals; TNFα: tumor necrosis factor alpha; 6MWT: 6 minutes walking test.** is for statistical significant (p <0.05).

As primary study endpoints,

comparing patients in automatic vs. echo-guided group, we had at 6 months of follow-up a significant higher rate of CRTd responders (68 (73.1%) vs. 58 (59.2%), p value 0.038), and at 12 months of follow-up a significant higher rate of CRTd responders (68 (73.1%) vs. 58 (59.2%), p value 0.038), with lower rate of hospitalization for HF worsening (12 (16.1%) vs. 22 (22.4%), p value 0.030). Table 2a, b.

Intriguingly, in CRTd patients of automatic group at baseline we did find significant difference in SonR values comparing CRTd responders vs. non responders (0.27 ± 0.07 g vs. 0.195 ± 0.05 g, p 0.055), patients with vs. those without hospital admission for HF worsening (0.25 ± 0.08 g vs. 0.24 ± 0.08 g, p 0.468), patients with vs. those without all cause of deaths (0.26 ± 0.05 g vs. 0.24 ± 0.08 g, p 0.642) and patients with vs. those without cardiac deaths (0.27 ± 0.04 g vs. 0.24 ± 0.08 g, p 0.358). Figure 2. At follow-up end, this trend was confirmed only for all cause of deaths (0.81 ± 0.19 g vs. 1.10 ± 0.08 g, p 0.437), while there was a statistical significant difference in SonR values comparing CRTd responders vs. non responders (1.24 ± 0.72 g vs. 0.58 ± 0.46 g (follow-up), p 0.001), hospital admission for HF worsening events (0.48 ± 0.29 g vs. 1.18 ± 0.43 g, p 0.001), and cardiac deaths (1.13 ± 0.72 g vs. 0.65 ± 0.69 g, p 0.047). Figure 2.

At multivariate Cox regression analysis, automatic CRTd (HR 3.636, [1.271-10.399] CI 95%, p 0.016), and baseline SonR values (HR 2.863, [1.537-6.231] CI 95%, p 0.006) were predictors of CRTD responders rate. Table 3.

Table 3 A
Multivariate Cox regression analysis for parameters associated with CRT responders.

	Univariate analysis HR (95% CI)	**p value**	**Multivariate analysis HR (95% CI)**	**p value**
Age	0.102 [0.11-0.968]	0.048	0.713 [0.007-1.773]	0.276
Automatic	0.795 [0.567-1.115]	0.184	**3.636 [1.271-10.399]**	**0.016***
Beta blockers	1.176 [0.806-1.716]	0.401	1.156 [0.745-1.793]	0.517
BNP	1.001 [0.989-1.101]	0.868	1.001 [0.889-1.007]	0.816
COPD	1.446 [0.948-2.204]	0.087	1.527 [0.935-2.495]	0.091
CRP	1.101 [0.992-1.280]	0.274	1.017 [0.995-1.041]	0.136
HbA1c	1.118 [0.851-1.315]	0.643	1.181 [0.922-1.472]	0.123
Hypertension	0.898 [0.619-1.302]	0.569	0.895 [0.561-1.430]	0.644
LVEF	1.006 [0.970-1.044]	0.736	1.036 [0.993-1.081]	0.102
NYHA 3	1.176 [0.840-1.647]	0.345	1.829 [0.923-3.626]	0.084
Obesity	1.497 [1.290-1.852]	0.011	1.330 [0.829-1.843]	0.082
QRS duration	0.989 [0.971-1.008]	0.255	0.991 [0.971-1.011]	0.379
SonR	10.2 [5.227-19.952]	0.002	**2.863 [1.537-6.231]**	**0.006***
6MWT	1.001 [0.993-1.007]	0.926	1.010 [0.993-1.007]	0.994

* is for statistical significant ($p < 0.05$). BNP: B type natriuretic peptide; COPD: chronic obstructive pulmonary disease; CRP: C reactive protein; HbA1c: glycated hemoglobin 1Ac type; LVEF: left ventricle ejection fraction; NYHA 3: New York Heart Association 3 class; SonR: values of SonR signals; 6MWT: 6 minutes walking test.

Table 3 B

Multivariate Cox regression analysis for parameters associated with hospitalization for heart failure.

	Univariate analysis HR (95% CI)	p value	**Multivariate analysis** HR (95% CI)	p value
Age	1.012 [0.873-1.322]	0.958	0.997 [0.671-1.201]	0.240
Automatic	0.795 [0.567-1.115]	0.184	1.166 [0.118-1.504]	0.895
Beta blockers	1.301 [0.587-2.885]	0.517	0.844 [0.336-2.122]	0.718
BNP	1.002 [1.001-1.301]	0.011	1.002 [1.001-1.040]	0.125
COPD	0.561 [0.276-1.141]	0.111	2.364 [0.907-6.158]	0.078
CRP	1.011 [0.978-1.046]	0.507	1.032 [0.982-1.084]	0.219
HbA1c	1.142 [0.816-1.913]	0.143	0.915 [0.589-1.541]	0.762
Hypertension	1.991 [1.003-3.952]	0.049	2.503 [0.809-7.745]	0.111
LVEF	1.029 [0.956-1.108]	0.443	1.061 [0.960-1.172]	0.245
NYHA 3	0.531 [0.258-1.096]	0.087	0.962 [0.289-3.202]	0.950
Obesity	0.905 [0.276-2.965]	0.869	1.093 [0.220-5.429]	0.913
QRS duration	0.964 [0.927-1.020]	0.066	0.960 [0.919-1.003]	0.069
SonR	0.074 [0.004-1.292]	0.074	0.679 [0.118-1.154]	0.932
6MWT	0.999 [0.985-1.013]	0.891	0.995 [0.980-1.011]	0.552

* is for statistical significant ($p < 0.05$). BNP: B type natriuretic peptide; COPD: chronic obstructive pulmonary disease; CRP: C reactive protein; HbA1c: glycated hemoglobin 1Ac type; LVEF: left ventricle ejection fraction; NYHA 3: New York Heart Association 3 class; SonR: values of SonR signals; 6MWT: 6 minutes walking test.

Table 3 C
Multivariate Cox regression analysis for parameters associated with cardiac deaths.

	Univariate analysis HR (95% CI)	p value	**Multivariate analysis** HR (95% CI)	p value
Age	0.953 [0.795-1.541]	0.543	1.362 [0.632-1.872]	0.361
Automatic	1.670 [0.489-5.705]	0.413	0.111 [0.001-2.583]	0.427
Beta blockers	2.099 [0.525-3.024]	0.176	1.095 [0.048-1.435]	0.945
BNP	1.001 [0.998-1.004]	0.681	0.999 [0.996-1.003]	0.679
COPD	1.119 [0.031-1.447]	0.072	2.138 [0.942-4.002]	0.401
CRP	0.913 [0.807-1.034]	0.151	0.903 [0.734-1.112]	0.338
HbA1c	1.601 [0.925-2.563]	0.142	3.224 [0.841-4.389]	0.106
Hypertension	0.226 [0.029-1.764]	0.156	0.515 [0.026-1.019]	0.663
LVEF	1.127 [0.964-1.316]	0.133	1.126 [0.855-1.482]	0.397
NYHA 3	0.615 [0.180-2.102]	0.439	0.458 [0.008-2.618]	0.705
Obesity	2.283 [0.002-3.248]	0.521	0.759 [0.001-1.621]	0.993
QRS duration	0.951 [0.885-1.021]	0.164	0.897 [0.782-1.016]	0.087
SonR	0.056 [0.001-8.699]	0.263	0.010 [0.001-5.267]	0.520
6MWT	0.992 [0.968-1.016]	0.509	0.973 [0.919-1.031]	0.355

* is for statistical significant ($p < 0.05$). BNP: B type natriuretic peptide; COPD: chronic obstructive pulmonary disease; CRP: C reactive protein; HbA1c: glycated hemoglobin 1Ac type; LVEF: left ventricle ejection fraction; NYHA 3: New York Heart Association 3 class; SonR: values of SonR signals; 6MWT: 6 minutes walking test.

Table 3 D
Multivariate Cox regression analysis for parameters associated with all cause deaths.

	Univariate analysis HR (95% CI)	p value	**Multivariate analysis** HR (95% CI)	p value
Age	1.782 [1.053-2.302]	0.001	1.362 [0.809-1.780]	0.563
Automatic	1.471 [0.570-3.795]	0.425	1.744 [0.270-2.713]	0.179
Beta blockers	2.009 [0.582-6.490]	0.270	3.338 [0.684-6.781]	0.096
BNP	0.999 [0.996-1.002]	0.434	0.998 [0.994-1.021]	0.258
COPD	0.268 [0.106-0.680]	0.006	2.802 [0.493-5.192]	0.245
CRP	0.918 [0.837-1.007]	0.070	0.915 [0.792-1.057]	0.915
HbA1c	0.832 [0.503-1.742]	0.430	0.587 [0.201-3.105]	0.224
Hypertension	0.027 [0.001-1.801]	0.092	0.898 [0.648-1.547]	0.936
LVEF	1.008 [0.916-1.110]	0.869	0.879 [0.001-5.644]	0.713
NYHA 3	0.292 [0.096-0.888]	0.030	1.966 [0.030-3.082]	0.465
Obesity	2.289 [0.014-3.766]	0.407	0.468 [0.009-1.821]	0.099
QRS duration	0.958 [0.907-1.012]	0.128	0.958 [0.885-1.037]	0.284
SonR	0.191 [0.005-7.540]	0.378	1.684 [0.101-5.647]	0.713
6MWT	1.009 [0.991-1.028]	0.339	1.004 [0.977-1.031]	0.791

* is for statistical significant ($p < 0.05$). BNP: B type natriuretic peptide; COPD: chronic obstructive pulmonary disease; CRP: C reactive protein; HbA1c: glycated hemoglobin 1Ac type; LVEF: left ventricle ejection fraction; NYHA 3: New York Heart Association 3 class; SonR: values of SonR signals; 6MWT: 6 minutes walking test.

Finally, the Kaplan curves show the cumulative survival free from CRTd non responders, hospitalization for HF worsening, cardiac deaths and all cause of deaths in automatic vs. echo-guided CRTd group of patients. Figure 3.

Discussion

In the present study, we investigated the effects of automatic vs. echo-guided CRTd optimization in patients with T2DM. Here, in T2DM patients we reported the ameliorative effects of automatic vs. echo-guided CRTd optimization approach in terms of significant increase of CRTd responders and significant reduction of hospital admissions for HF worsening at follow-up end of 12 months ($p < 0.05$). Notably, for first time in literature we investigated at baseline (CRTd implant) and for all follow-up the values of SonR in the Automatic group of T2DM patients with CRTd. Thus, there were significant modifications of SonR

values in CRTd responders vs. non responders patients, and for hospital admissions for HF worsening and for events of cardiac deaths. Finally, and clinically relevant, for T2DM patients the choice of SonR guided automatic CRTd implant could predict a 3.6 folds higher possibility to be CRTd responder. In addition, the patients with higher values of SonR at baseline could have a 2.8 folds higher possibility to become CRTd responders. Indeed, the automatic right atrium lead sensor could assess the peak of highest values of atrium pressure (8). The peak of atrium pressure, as indicated by SonR values, is linked to LV dP/dt max at baseline, and to the endocardial acceleration during isovolumetric contraction of left ventricle (8, 10). Therefore, the amplitude of SonR values is correlated with the hemodynamic heart function, and specifically with the contractile heart function (8, 10). However, we could speculate that modifications of cardiac contractility correspond to modifications of dP/dT values, and to modifications of SonR signals. Furthermore, in HF patients with T2DM the automatic vs. echo-guided CRTd optmization could significantly reduce the levels of inflammatory biomarkers (CRP, IL6, TNFa), and of BNP values, via its favorable hemodynamic and clinical effects. The reduction of inflammatory burden, and of BNP values at 6th and 12th month of follow up has been observed in a previous study conducted on T2DM patients with HF and treated by multipolar CRTd (1, 6). Indeed, both inflammatory burden and BNP expression are over-expressed in a condition of HF, and in HF patients with depressed cardiac pump (1, 6). In this context, BNP is a valuable marker of HF, and a predictor of hospitalizations for HF worsening and worse prognosis in CRTd patients (1, 6, 13). However, BNP could be relapsed in condition of stable and unstable HF, and used for risk stratification in patients with acute and chronic HF (14). Therefore, BNP is independently a marker of worse prognosis for patients with the failure of cardiac pump (14), and in those treated with CRTd (1, 6, 13, 15, 16). Consequently, T2DM patients with severe reduction of cardiac pump, as evidenced by lowest LVEF values at echocardiography, could experience a worse clinical prognosis (1, 6, 15, 16). To date, the cardiac pump reduction in T2DM failing heart patients treated with CRTd, could be caused by advanced degree of anatomical ventricular remodeling (15, 16, 17), and reflected by the loss of synchronism during diastolic and systolic cardiac phases (8, 10). In this setting, the alterations in AV/IV intervals are linked to and could mark CRTd patients that evidence the loss of cardiac synchronism (18). To date, CRTd patients with evidenced AV/IV delays are those that could experience worse prognosis by the loss of AV and IV synchronism, and by the worsening of cardiac pump (18). In this setting, automatic CRTd could monitor the modifications of dP/dT values induced by CRTd therapy, by the registration of different values of SonR signals (8, 10). Consequently, the modifications of SonR values in the different stages of HF could induce an automatic optimization of AV/IV intervals (10). Thus, the reduction of AV/IV delays could consequently lead to best cardiac synchronism in Automatic group (10). However, we might speculate that this automatic optimization of AV/IV delays could consequently ameliorate the hemodynamic function of heart, with improvement of cardiac pump.

Therefore, the improvement of cardiac pump could lead to the amelioration of clinical outcomes in T2DM patients with CRTd, such as previously observed in overall population of CRTd patients (10). In addition, we reported an increase of LVEF, with reverse remodeling, and amelioration of NYHA class and clinical status in T2DM patients, which expressed at baseline highest SonR values, as an index of better AV/IV synchronism. However, the best optimization of AV/IV delays could lead to best clinical outcomes for

CRTd patients (8, 10). In our study, we observed and confirmed these results in a selective population of T2DM with CRTd. Again, for first time in literature, we monitored the modification of SonR values for 12 months of follow-up in T2DM patients with CRTd regards CRTd responders rate, hospitalizations for HF worsening, cardiac deaths and all cause of deaths. Thus, we might speculate that the automatic CRTd optimization has been showed to be superior as compared to echo guided optimization to achieve CRTd responders target, and to reduce hospitalizations for HF worsening in T2DM patients. However, we could summarize the most important functions of automatic CRTd as monitor and activator of cardiac remodeling processes, that are involved in clinical prognosis of CRTd patients. Therefore, it could be relevant to identify at baseline T2DM patients with higher values of dP/dT signals, as patients with lower AV/IV delays and best cardiac synchronism (18). To date, it looks intuitive to say that these patients could experience a higher possibility to become CRTd responders and to experience best clinical prognosis. This point is relevant, because it opens a new scenario in the possibility to identify and to treat at best we can T2DM patients with CRTd with different stages of cardiac dyssynchrony. However, we might speculate that this could drive towards specific treatments that in addition to automatic guided optimization of AV/IV delays could result in best clinical response in T2DM patients with CRTd. Finally, this could be used to ameliorate CRTd responders and to reduce worse prognosis in failing heart patients with T2DM.

Study limitations.

This study has few limitations. As first, the small sample size and the duration of follow-up could influence study results, that have to be applied in a future study with larger size of T2DM patients, and at more long term follow up analysis. In addition, in the present study by the loss of an experimental animal model of HF with automatic vs. echo-guided CRTd, we did not practice cardiac biopsy to show the different inflammation/fibrosis for the main study outcomes. In addition, we did not use a continuous monitoring systems for arrhythmias detection and devices interventions as described by authors (18), and this may affect the study outcomes. However, further studies are needed to better understand the pleiotropic functions of automatic SonaR guided CRTd therapy, and its cardiovascular effects in terms of AV/IV synchronism and best clinical outcomes. Therefore, a larger clinical trial may be adequate to assess all these pathogenic processes in a population of failing heart patients with T2DM treated by automatic SonaR guided CRTd. This may be applied in clinical practice to reduce hospitalizations, and to improve CRTd response in failing heart patients with T2DM.

Conclusions

Our study results evidenced that automatic vs. echo guided CRTd optimization increased significantly the CRTd responders rate, and reduced hospitalizations for HF worsening in T2DM patients. To date, SonR signals showed a significant modification regards CRTd responders, hospitalizations for HF worsening events, and cardiac deaths. Notably and clinically relevant, the automatic guided optimization of AV/IV delays could increase of more than 3 folds the possibility to become CRTd responders, and baseline

highest values of SonR signals could characterize patients with 2.8 folds higher possibility to become CRTd responders. Therefore,

we could suggest to opt for automatic SonaR guided CRTd implant to reach the best cardiac synchronism, and to increase the possibility for a T2DM patient to become CRTd responder and to experience best clinical prognosis.

Abbreviations

AV: atrioventricular;

BNP: B type natriuretic peptide;

CRP: C reactive protein;

CRTd: Cardiac resynchronization therapy with defibrillator;

HbA1c: glycated hemoglobin 1Ac type;

HF: heart failure;

ICD: implantable cardioverter defibrillator;

IEGM: intracardiac electrogram;

IL6: interleukin-6;

IV: interventricular;

LV: left-ventricular;

LVEF: left ventricle ejection fraction;

NYHA**:** New York Heart Association;

TNF α: tumor necrosis factor-α;

T2DM: type 2 diabetes mellitus;

6MWT: six minutes walking test

Declarations

Ethics approval and consent to participate:

Ethical Committee of University of Campania “Luigi Vanvitelli”, Catholic University of Sacred Heart, Gemelli Molise and Vecchio Pellegrini Hospital approved the research protocol and gave the consent to participate in the study.

Consent for publication:

authors give the full consent to publish the present article.

Availability of data and material:

data and study materials are available.

Competing interests:

C.S edited and wrote the research project and the full manuscript.

Funding:

none to declare.

Authors' contributions:

Ce.S: wrote the research project and the full manuscript. P.P: data collection and interpretation; Ce.S, M.S, A.R, and V.D: performed CRTd implants; G.P, R.M, M.M: study revision editing, and data analysis; R.M: manuscript editing.

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Conflict of interest:

none.

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Figures

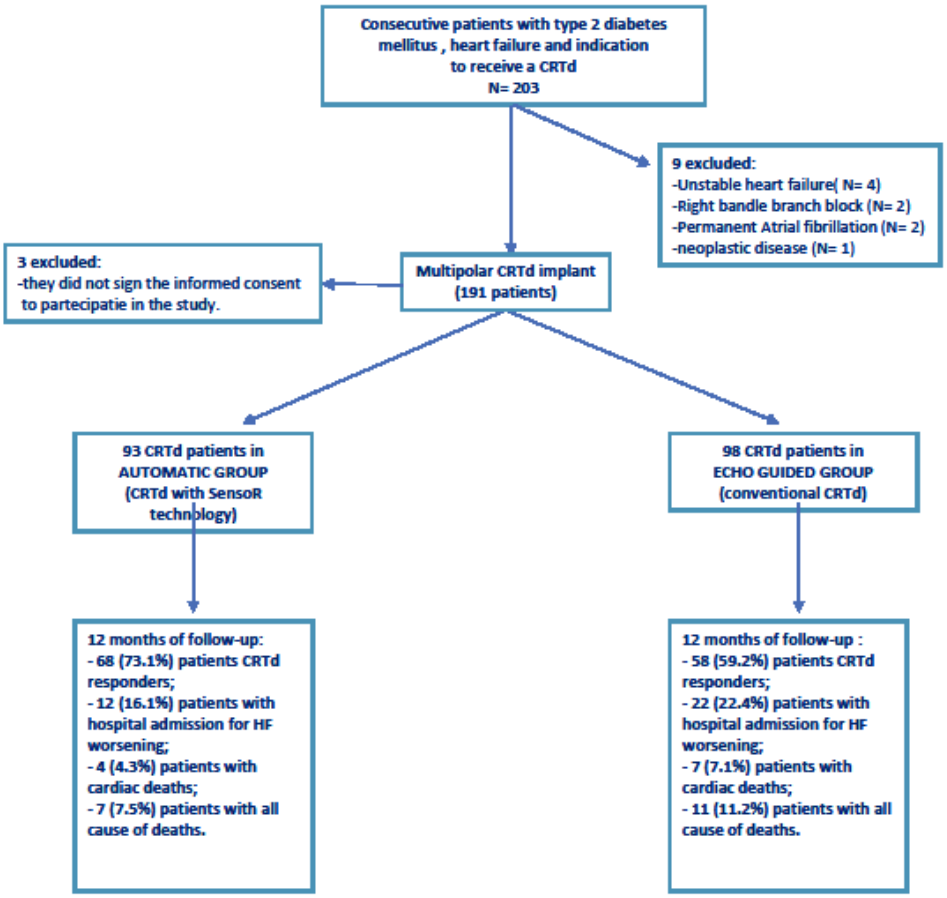

Figure 1

Representation of study flow chart. CRTd: cardiac resynchronization therapy with a defibrillator; HF: heart failure.

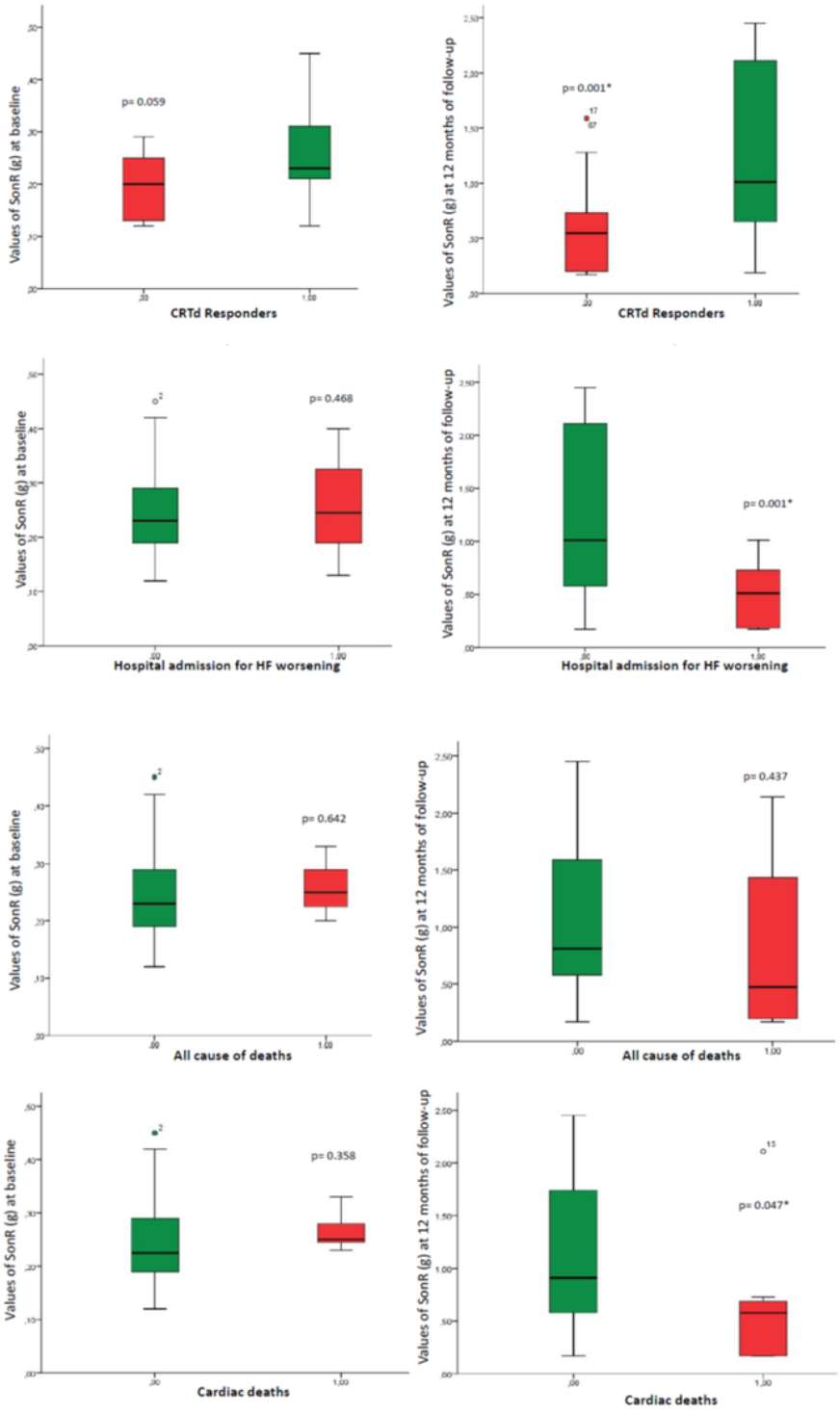

Figure 2

In upper part the SonR values (g) at baseline (left part) and at follow-up end in CRTd responders (green color) vs. CRTd non responders (red color) with the corresponding p value. In lower part the SonR values in g at baseline (left part) and at follow-up end in patients with hospital admission for heart failure (HF) worsening (red color) vs. patients without hospital admission for heart failure (HF) worsening (green color) with the corresponding p value. * is for statistical significant (p <0.05). B. In upper part the SonR

values in g at baseline (left part) and at follow-up end for patients with all cause of deaths (red color) vs. survived patients (green color) with the corresponding p value. In lower part the SonR values in g at baseline (left part) and at follow-up end in patients with cardiac deaths (red color) vs. survived patients (green color) with the corresponding p value. * is for statistical significant (p <0.05).

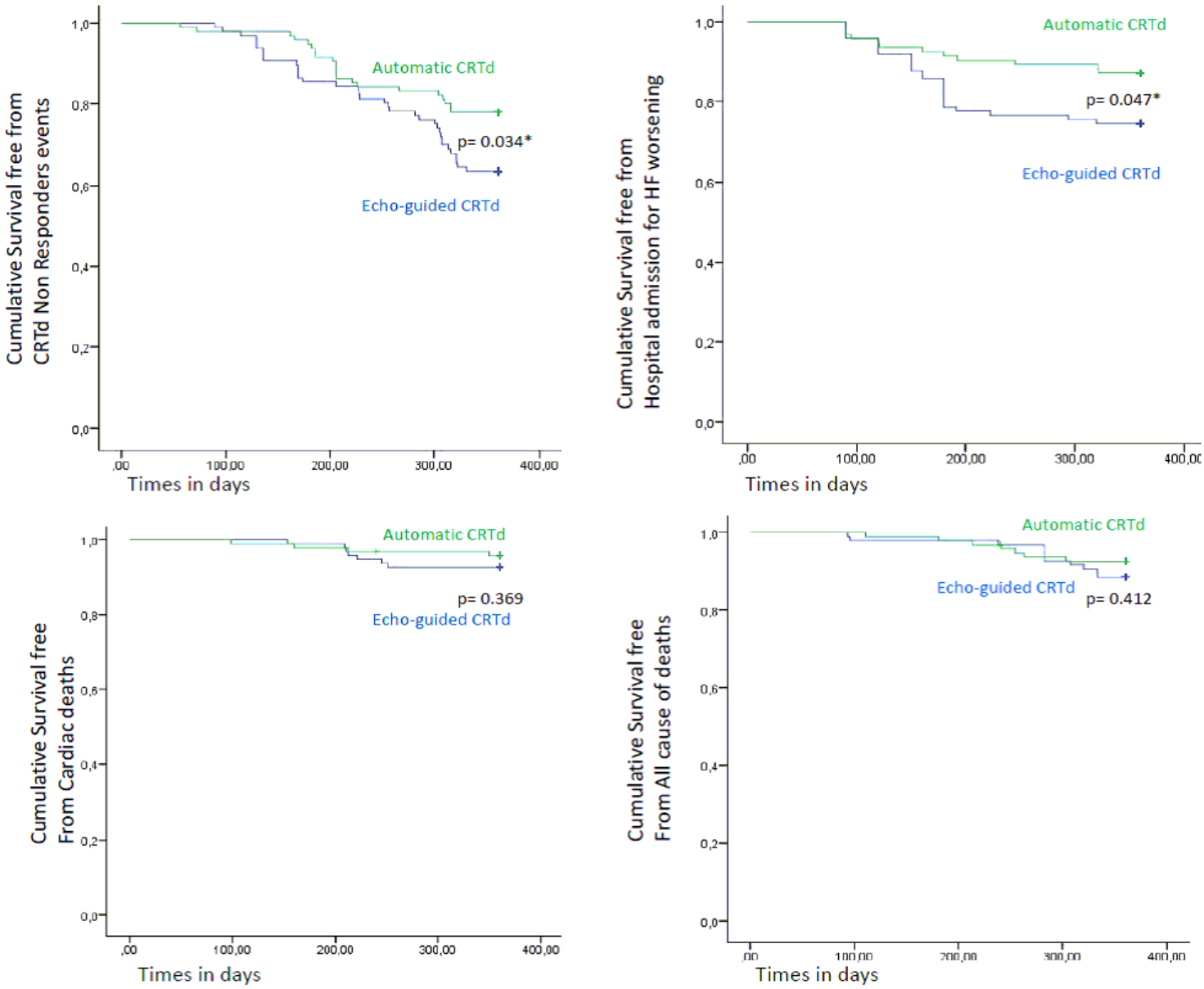

Figure 3

Kaplan curves for “cumulative survival free” at 360 days of follow-up from Cardiac Resynchronization therapy with a defibrillator (CRTd) response (upper left, p<0.05), hospital admission for heart failure (HF) worsening (upper right, p<0.05), cardiac deaths (lower left, p>0.05) and all cause of deaths (lower right, p>0.05) comparing patients in Automatic CRTd group (green color) vs. Acho-guided CRTd group (blue color). * is for statistical significant (p <0.05).

Supplementary Files

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