Upgrade of right ventricular pacing to cardiac resynchronisation therapy in heart failure: a randomised trial

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Abstract

Background and Aims *De novo* implanted cardiac resynchronisation therapy with defibrillator (CRT-D) reduces the risk of morbidity and mortality in patients with left bundle branch block, heart failure and reduced ejection fraction (HFrEF). However, among HFrEF patients with right ventricular pacing (RVP), the efficacy of CRT-D upgrade is uncertain.

Methods In this multicentre, randomised, controlled trial, 360 symptomatic (New York Heart Association class II-IVa) HFrEF patients with a pacemaker or implantable cardioverter defibrillator (ICD), high RVP burden ≥20%, and a wide, paced QRS complex duration ≥150 ms were randomly assigned to receive CRT-D upgrade (n=215) or ICD (n=145) in a 3:2 ratio. The primary outcome was the composite of all-cause mortality, heart failure hospitalisation or <15% reduction of left ventricular end-systolic volume assessed at 12 months. Secondary outcomes included all-cause mortality or heart failure hospitalisation.

Results Over a median follow-up of 12.4 months, the primary outcome occurred in 58/179 (32.4%) in the CRT-D arm vs. 101/128 (78.9%) in the ICD arm [odds ratio 0.11; 95% confidence interval (CI) 0.06–0.19; p<0.001]. All-cause mortality or heart failure hospitalization occurred in 22/215 (10%) in the CRT-D arm vs. 46/145 (32%) in the ICD arm (hazard ratio 0.27; 95% CI 0.16–0.47; p<0.001). The incidence of procedure- or device-related complications was similar between the two arms [CRT-D group 25/211 (12.3%) vs. ICD group 11/142 (7.8%)].

Conclusions In pacemaker or ICD patients with significant RVP burden and reduced ejection fraction, upgrade to CRT-D compared to ICD therapy reduced the combined risk of all-cause mortality, heart failure hospitalisation or absence of reverse remodelling.

Key Question

What is the efficacy and safety of cardiac resynchronization therapy (CRT-D) upgrade vs. implantable cardioverter defibrillator (ICD) in heart failure with reduced ejection fraction (HFrEF) patients with pacemaker or ICD, ≥ 20% right ventricular (RV) pacing burden and paced QRS complex duration ≥150ms?

Key Finding

In this randomized trial, CRT-D upgrade reduced the risk of all-cause mortality, HF hospitalization, and absence of reverse remodelling, as compared to ICD.

Take Home Message

CRT-D upgrade reduces morbidity and mortality in HFrEF patients with RV pacing.
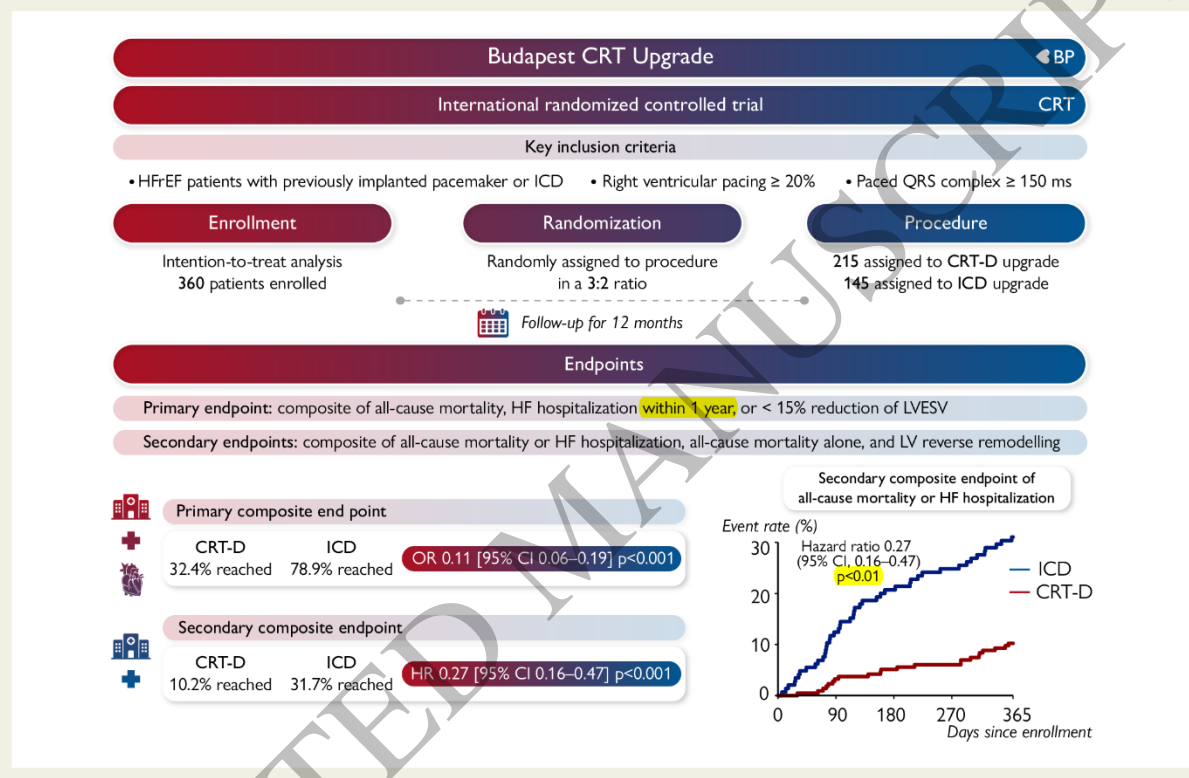
Structured Graphical Abstract

INTRODUCTION

The estimated number of patients undergoing pacemaker (PM) or implantable cardioverter defibrillator (ICD) implantation has surpassed one million devices per year worldwide and continues to rise due to the aging population(1, 2). Within a few years after implantation, around 30% of patients with PM or ICD devices experience left ventricular (LV) systolic dysfunction due to intraventricular dyssynchrony induced by right ventricular (RV) pacing, leading to a relatively high incidence of heart failure (HF) hospitalisation and associated

adverse clinical outcomes.(3-5) Among patients with HF and reduced ejection fraction (HFrEF), wide QRS complex with left bundle branch block (LBBB) morphology, and without prior pacing device implantation, a clear benefit from implantation of a *de novo* cardiac resynchronisation therapy (CRT) device implantation has been demonstrated.(6-9) Since RV pacing-induced dyssynchrony is comparable to intrinsic LBBB, patients with significant RV pacing burden and LV dysfunction appear to be at increased risk of further LV remodelling and adverse outcomes.(3, 4, 10, 11) To the best of our knowledge, in patients with HFrEF and prior implanted PM or ICD, the potential benefits of an upgrade to CRT on clinical outcomes have not been assessed.

Current European guidelines recommend upgrading to CRT in patients with a high burden of RV pacing as a Class IIa indication.(6, 12) The 2023 HRS/APHRS/LAHRS guidelines recommend biventricular pacing with a Class I level B for symptomatic high burden of RV pacing and an impaired LV function .(13)

Nevertheless, in patients with HFrEF and prior implanted pacemaker or ICD device, the potential benefits of an upgrade to CRT with regard to hard outcomes have not been established(14), as there are no randomized controlled trials properly powered to assess this question and looking at mortality and/or HF events. Additionally, data on the clinical impact of CRT upgrade procedures such as improvement of functional status, quality of life or risk reduction on hospitalization or mortality, were not definitive or unavailable.(14)

Moreover, previous data highlighted that indicated upgrade procedures are frequently not performed or deferred to a later, undetermined date in over 60% of the candidates.(15)

Because a substantial portion of patients with HFrEF and PM or ICD have a high burden of RV pacing,(16, 17) we hypothesized that they would be at risk for further adverse LV remodelling and might benefit from conversion to CRT.

Therefore, the **B**iventricular **U**pgrade on left ventricular reverse remodelling and clinical outcomes in patients with left ventricular **D**ysfunction and intermittent or permanent **AP**ical/**Se**p**T**al right ventricular pacing Upgrade CRT (BUDAPEST-CRT) trial aimed to compare the efficacy and safety of a CRT upgrade, compared to ICD, in HFrEF patients with a non-CRT PM/ICD and intermittent or permanent RV pacing.(18) We hypothesized that CRT-D upgrade compared to ICD only upgrade is associated with improved clinical outcomes, defined as risk for all-cause mortality, hospitalisation for HF or <15% reduction in LV end-systolic volume (LVESV) at 12 months.

METHODS

Study design

The BUDAPEST-CRT Upgrade trial was a prospective, phase III, multicentre, randomised, controlled trial. The study and the analysis were conducted with emphasis on strict adherence to the protocol and a pre-established statistical analysis plan, designed by the steering committee. The study protocol was approved by local and institutional ethics committees. The executive committee oversaw the progress of recruited patients and supervised the analysis of the data. Those authors who had access to the data vouch for the accuracy and completeness of the data, and all authors vouch for the adherence of the trial to the protocol.

All patients provided written informed consent. Enrolled were patients ≥ 18 years old implanted at least 6 months with a PM or an ICD presenting all the following: (i) reduced LV ejection fraction (LVEF, ≤35%), (ii) HF symptoms [New York Heart Association class (NYHA) II-IVa], (iii) wide paced QRS (≥150 ms), and (iv) ≥20% RV pacing burden, and treated with guideline-directed medical therapy. Patients were excluded if they were eligible for CRT by current guideline-directed criteria (had an intrinsic LBBB), had severe RV dilation (RV basal transversal diameter >50 mm by echocardiography), had evidence of

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severe valvular heart disease, had severe renal impairment (creatinine level >200 µmol/l). These patients frequently have a poor 1-year prognosis which makes them questionable candidates for defibrillator therapy. In addition, also patients who survived an acute myocardial infarction or coronary revascularization procedures in the previous 3 months were not eligible for inclusion. The trial design and baseline characteristics of patients have been previously described in detail.(19)

Those who met the inclusion criteria were randomly assigned to receive a CRT-D upgrade or ICD in a 3:2 ratio. Randomisation was based on permuted blocks of five, stratified by centre, generated from a web-based system. Clinicians and staff were blinded to the block size and to the fact that stratification was used until the last patient's last visit. Patients and physicians were not blinded to the randomisation.

For those patients with a previously implanted ICD assigned to the ICD arm, two options were provided per physician's discretion: no procedure; or CRT-D upgrade with the CRT-D function turned off. Previously implanted RV pacing leads could be extracted based on the physician's discretion.

Patients were clinically evaluated at regular follow-up visits performing 12-lead ECG, echocardiography, cardiac implantable electronic device interrogation, 6-minute walking test (6MWT), and EQ-5D-3L quality of life questionnaire testing. If a patient assigned to the ICD arm required HF hospitalisation, cross-over from ICD to CRT-D arm was left to the site investigators' discretion.

Outcomes

The primary outcome was the composite of the first occurrence of HF hospitalisation, all-cause mortality within 1 year, or less than 15% reduction of LVESV from baseline to 12 months assessed by echocardiography. Secondary outcomes were the composite of all-cause

mortality and HF hospitalisations, all-cause mortality alone, and reverse LV remodelling, defined as the change in LVEF, or LV end-diastolic volume (LVEDV) assessed by echocardiography from baseline to 12 months. Tertiary outcomes included the success rate and safety of implantations. An independent adjudication committee adjudicated the HF hospitalisation events in a blinded manner according to prespecified definitions. Echocardiographic recordings were evaluated by the Echocardiographic Core Laboratory of Semmelweis University without knowledge of treatment assignment.

Statistical analysis

A sample size of 360 patients was calculated to detect a statistically significant difference in the primary endpoint with 80% power and two-tailed alpha level of 5%, assuming 80% event rate in the ICD and 68% in the CRT-D arm with a 1% dropout per month.

The primary composite outcome was analysed using logistic regression due to its binary component and the effect size was expressed as adjusted and unadjusted odds ratios (OR) with associated 95% confidence intervals (CI). The prespecified adjustment factors were: age, sex, country, ischemic etiology, diabetes mellitus, secondary prevention ICD, atrial fibrillation, and baseline NYHA class. Time-to-event secondary outcomes (composite endpoint of all-cause mortality and HF hospitalisation; and all-cause mortality alone) were analysed by Cox proportional hazards models, change in LVEDV, and LVEF by linear regression. The adjustment factors were the same as for the primary outcome. The presented p-values and the width of the CIs were not adjusted for multiplicity. The primary outcome analysis was done in the modified intention-to-treat population: those who had missing results of the echocardiography component of the primary outcome and did not meet the primary

outcome through the other components (HF or death) were excluded (Supplementary Figure 1). However, they were included in all other analysis based on intention-to-treat principles. Sensitivity analyses included handling all patients with missing data from echocardiography as meeting the primary outcome, adding the delay of 12-month visit as an adjustment factor to the model, and per protocol population analysis. The per protocol population included those who completed the treatment originally allocated.

The consistency of the treatment effect on the primary outcome was assessed in prespecified subgroups by applying the main adjusted model of the primary outcome to each subgroup population (excluding the given subgroup's indicator variable from the adjustment factors). Statistical analyses were performed by using Stata version 15.0 (StataCorp., College Station, TX, USA).

An independent data monitoring committee reviewed the safety data and the results of a scheduled interim analysis according to the prespecified stopping boundaries described in the protocol. An independent statistician replicated and verified the analysis.

This trial is registered at ClinicalTrials.gov, NCT02270840.

RESULTS

Between November 24th, 2014 and August 13th, 2021, a total of 576 patients were assessed for eligibility, the reasons for exclusion are described in Supplementary Table 1. Finally, 360 patients were enrolled at 17 sites from seven countries, and randomly assigned to receive a CRT-D (n=215) or an ICD (n=145) upgrade procedure.

The clinical characteristics of the two groups were fairly balanced at baseline (Table 1), and previously described in detail.(19) The study population had a substantial burden of comorbidities: most importantly atrial fibrillation, prior myocardial infarction, or diabetes.

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Almost half of the patients experienced hospitalisation for HF within 12 months before enrollment (Table 1). The mean LVEF was $24.8 \pm 6.6\%$, and more than two-thirds of the patients had a pacemaker device (predominantly DDD) implanted with a high RV pacing burden (CRT-D group $85.4 \pm 21.1\%$, ICD group $88.1 \pm 18.8\%$).

Upgrade procedures failed in four (1.9%) patients assigned to the CRT-D arm due to unsuccessful LV lead implantation, while four (1.9%) patients in the CRT-D arm and one (0.7%) patient in the ICD arm were withdrawn before the procedure (Supplementary Figure 1) (Table 2). The patients were followed for a median of 12.4 months. Twenty-seven patients (18.6%) crossed over from the ICD arm to CRT-D with biventricular pacing activated. Altogether, 12 (5.6%) patients in the CRT-D and 16 (11.0%) patients in the ICD arm died during follow-up.

At the completion of the study, the vital status (dead or alive) was known for all patients, and all hospitalisations were reported by the centre investigators with no patients lost to follow-up. Changes in echocardiography-determined parameters could not be analysed in 36 patients in the CRT-D and 17 patients in the ICD arm, respectively.

In the intention-to-treat (ITT) population, the primary outcome occurred in 58/179 (32.4%) patients in the CRT-D arm and 101/128 (78.9%) in the ICD arm [adjusted OR 0.11; 95% CI 0.06–0.19; P<0.001, Figure 1, Table 2, Supplementary Table 2](number needed to treat, NNT: 2.2). The composite of all-cause mortality and HF hospitalisation [adjusted hazard ratio (HR) 0.27, 95% CI 0.16–0.47; P<0.001] (Table 2, Figure 2A) (NNT: 4.7) as well as LV morphological and functional response (difference at 12 months in LVEDV, -39.00 mL, 95% CI -51.73 to -26.27; P<0.001, and difference at 12 months in LVEF, 9.76%, 95% CI 7.55–11.98; P<0.001) favoured CRT-D upgrading. There was no statistically significant difference in terms of all-cause mortality between the two arms (adjusted HR 0.52, 95% CI 0.23–1.16;

p=0.110). (Table 2, Figure 2B)(NNT: 18.5) showing that the secondary composite endpoint was mainly driven by reduction in heart failure hospitalisation (adjusted HR 0.24, 95% CI 0.13–0.43, p<0.001)(Figure 2C).

The beneficial effect of CRT-D upgrade on the primary outcome was consistent across all prespecified subgroups, including those defined according to baseline LVEF, RV pacing burden, age, or comorbidities (Figure 3).

Additionally, both sensitivity analysis handling patients with missing echocardiographic data and per protocol analysis as meeting the primary outcome also confirmed the robustness of the primary findings (Supplementary Table 3).

Regarding safety outcomes, the incidence of procedure- or device-related complications was similar between the two arms [CRT-D group 25/211 (12.3%) vs ICD group 11/142 (7.8%)](Table 2, Supplementary Table 4). Lead extraction was performed in 32/211 (15%) of the CRT-D and 16/142 (11%) of the ICD upgrade procedures. The occurrence of major ventricular arrhythmias was substantially lower in the CRT-D arm [1/215 patients (0.5%)] as compared to the ICD arm [21/145 patients (14.5%)] (Table 2).

DISCUSSION

In this international, randomised, controlled trial enrolling patients with HFrEF and significant RV pacing burden with a wide, paced QRS complex, CRT-D upgrade reduced the composite primary outcome of HF hospitalisations, deaths, and absence of reverse remodelling, as compared to ICD only treatment. CRT-D upgrade was associated with significantly fewer hospitalisation for HF or reduced all-cause mortality favoured CRT-D which was accompanied by improved LV reverse remodelling, when compared to ICD alone. Finally, CRT-D upgrade did not increase the rate of device- or procedure-related events

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during a 1-year follow-up when compared to ICD only therapy (Structured Graphical Abstract).

Due to the lack of strong evidence, guidelines established recommendations for CRT upgrade by referring to observational or small randomized studies or meta-analyses(20), and the class/level of recommendation for CRT upgrade were modified several times over the past decade (IB in 2013(21), IIb B in 2016(22), IIaB in 2018(12), 2021(6), and IB again in 2023(13)). This clearly shows an unmet need for more robust evidence and a randomized clinical trial. It was our ambition to provide high-quality evidence on the benefit of CRT-upgrade by designing BUDAPEST-CRT Upgrade trial to support the strategy of upgrading to CRT.

Several studies have demonstrated the harmful effects of RV pacing on short and long-term clinical outcomes, most likely due to inducing electromechanical dyssynchrony similar to intrinsic LBBB(3, 4). Other studies investigated patients with conventional pacemakers and preserved LVEF revealed that RV pacing rate of 20% or greater was associated with the development of pacing-induced cardiomyopathy.(5) The threshold, which defines significant RV pacing burden continues to be a matter of discussion and generally varies between 20-50%.(23)

The first trial, which investigated candidates with de novo device indication with an expectedly high pacing burden and LVEF ≤50%, was the Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block (BLOCK HF) trial. BLOCK-HF demonstrated the benefit of biventricular pacing with reduction in all-cause mortality, an urgent hospital care visit for HF requiring intravenous therapy, or a 15% or greater increase in LVESV index compared with RV pacing alone. However, contrary to pacing naïve patients, there is limited evidence to guide optimal upgrade strategy in patients with RV pacing who developed pacing-induced/aggravated LV dysfunction(24).

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The currently available evidence has been summarized in a recent systematic review and meta-analysis combining six randomized clinical trials (randomizing in total 161 patients) and 47 observational studies with 2644 patients showing an LVEF improvement by 8.4 increase as the primary endpoint. However, no conclusion on hard clinical outcomes could have been drawn from the existing data.(20)

Due to these uncertainties, CRT upgrade procedures are still not frequently performed in those with progressing pacing associated HF or this procedure is deferred to generator replacement or to a later, undetermined date, as revealed in the Resynchronization-Defibrillation for Ambulatory Heart Failure Trial study's (RAFT) subgroup analysis.(15) Therefore, we designed the BUDAPEST-CRT Upgrade trial to determine the benefit of CRT upgrade on hard clinical endpoints in symptomatic HF patients who already had an implanted device, and a reduced LVEF, and a 20% or higher RV pacing burden. The baseline clinical characteristics of our patients were quite similar to the BLOCK-HF cohort; e.g. mean age, however they had a considerably higher burden of comorbidities as compared with patients from registries or randomised controlled trials enrolling *de novo* CRT patients.(19) Our patients had more severe HF symptoms, higher N-terminal pro-B-type natriuretic peptide levels, and more reduced LV systolic function compared with other CRT study populations.(19) Moreover, more than half of the BUDAPEST-CRT Upgrade cohort had atrial fibrillation.

Our study cohort represents a patient population with cardiomyopathy with severe LV dysfunction and HF due to or aggravated by RV pacing. Based on the current guidelines these patients are indicated for primary preventative upgrade to ICD therapy. However, limited outcome data are available for adding CRT to ICD therapy. We believe that our results contribute to accepting CRT-D upgrade as the therapy of choice in such patients including those with atrial fibrillation and will help clinical decision making. The sensitivity analysis, in

which patients with missing echocardiographic data were considered to meet the primary outcome, also confirmed the robustness of the primary result, even during this relatively short follow-up period (12 months).

Regarding the secondary outcomes, the risk of all-cause mortality or HF hospitalisation was substantially lower in CRT-D patients as compared to ICD patients up to 12 months. This beneficial effect could also be detected in LV reverse remodelling and related lower incidence of major arrhythmias. These may reflect direct and indirect effects on the decreased risk of major arrhythmias as similar beneficial effects were also described in previous *de novo* CRT trials.(25)

There are some specific considerations that worth discussion. Patients were recruited only from a few high-enrolling tertiary centres, and the overall recruitment rate was relatively low, but several other factors – both clinical and organisational - might have contributed to the relatively long recruitment time of 7 years in 17 sites. Upgrading conventional pacing to CRT is in general perceived as complex procedure associated with several caveats. Overall, procedural complications of upgrades are higher than those of *de novo* implants. Among the randomized and observational studies of biventricular pacing upgrade, complications were observed in about 10% (mainly infections, pneumothorax, cardiac perforation and lead related complications).(14) This prolongs procedure duration with increased risk of infection and might necessitate extraction of redundant lead/-s. Such procedures are therefore less appealing for the implanter with resulting biventricular upgrade deferral especially in multimorbid and/or frail patients. However, our results demonstrated that CRT-D upgrade was a safe procedure in certified, high-volume centres even with lead removal in such a vulnerable patient cohort.

The BUDAPEST-CRT Upgrade trial also proved a homogeneous treatment effect of CRT-D compared to ICD alone in all the prespecified subgroups. The subgroup analysis by sex was

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compromised by the male predominance in both arms (CRT-D 86.1% and ICD 93.1%). Additionally, despite of choosing an RV pacing burden of 20% for inclusion criteria (as the majority of relevant studies have similarly specified this value(26-29)), a relatively high median RV pacing burden could be observed in the total cohort, therefore the prespecified subgroup analysis was restricted to a higher pacing rate. Notably, the previously implanted devices' indications were not investigated in detail, as the protocol of the trial focused rather on the pacing burden.

Some further limitations of this trial should be noted. The specific inclusion and exclusion criteria may limit the generalizability of our findings as in all randomized trials, however, we followed everyday clinical practice and excluded only those with severe concomitant disease, which could influence the outcome. Patients assigned to the ICD arm could be also implanted with a CRT-D device with the CRT capability turned off or remain with an ICD with no procedure, which could have reduced the observed occurrence of procedure-related complications. The relatively slow recruitment (in detail discussed above) and a proportion of missing echocardiographic data were certainly also influenced by more than two years of the COVID-19 pandemic with consequent lockdowns in participating countries.

However, the overall use of guideline-directed medical therapy was high (renin–angiotensin–aldosterone system inhibition was used in more than 97% of the patients, beta-blocker therapy in approximately 90%, and mineralocorticoid receptor antagonist in 62%) and did not change substantially over time. The only exception was the administration of ARNI (sacubitril/valsartan), which became available in the participating countries only during the course of the trial.

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The proportion of women were higher in the CRT-D group, therefore added female as a covariate for adjustment. The mean body mass index was statistically (with 1 kg/m^2 unit) higher in CRT-D group, however this difference may have no clinical impact.

While a greater number of patients had missing echocardiographic data in the ICD arm at 12 months, the sensitivity analysis showed similar results to the primary analysis. Additionally, further investigations are warranted to compare the CRT upgrade with more physiological conduction system pacing.

CONCLUSIONS

Among patients with HF and reduced LVEF with intermittent or permanent RV pacing, CRT-D upgrade resulted in a lower incidence of the composite of all-cause mortality, HF hospitalisation, or less than 15% decrease in LVESV as compared with ICD therapy only. The CRT upgrade procedure proved to be a safe procedure in this sick patient population in certified, high-volume centres. Overall, these findings support performing CRT upgrade in HF patients with reduced LVEF and a PM or ICD device with intermittent or permanent RV pacing to reduce morbidity and mortality.

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Figure legends

Structured Graphical Abstract

Main inclusion criteria and randomisation by arms showing the result of 360 patients (215 CRT-D vs. 145 ICD) analysed by intention-to-treat. Primary and secondary outcomes showing a substantial treatment effect of CRT-D compared to ICD alone. Among patients with HF and reduced LVEF with intermittent or permanent RV pacing, CRT-D upgrade resulted in a lower incidence of the composite of all-cause mortality, HF hospitalisation, or less than 15% decrease in LVESV as the primary outcome. Secondary outcome of all-cause mortality and HF hospitalisation also proved a substantially lower incidence in CRT-D patients compared to ICD.

CI, confidence interval; CRT-D, cardiac resynchronization therapy with defibrillator; HF, heart failure; HR, hazard ratio; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; OR, odds ratio; RV, right ventricular.

Figure 1. Event rate of the primary composite outcome in the ICD and CRT-D arms and its components: first occurrence of heart failure (HF) hospitalization with or without subsequent all-cause death, all-cause death without previous HF hospitalization, and <15% reduction in left ventricular end-systolic volume (LVESV) assessed at 12-month visit by echocardiography in patients without previous HF hospitalization.

Figure 2. (A) All-cause mortality and heart failure hospitalisation. **(B)** All-cause mortality. **(C)** Heart failure hospitalisation. Kaplan–Meier estimates for secondary outcomes. Panel A shows the Kaplan–Meier curves for the secondary composite outcome of first occurrence of all-cause mortality or HF hospitalisation. Panel B shows the Kaplan–Meier curves for death from any cause. Panel C shows the Kaplan–Meier curves for heart failure hospitalisation. CI, confidence interval.

Figure 3. Primary composite outcome, according to prespecified subgroups.

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Figure 1
206x228 mm (x DPI)

Figure 2
135x94 mm (x DPI)

Figure 3
134x92 mm (x DPI)

22

Figure 4
134x91 mm (x DPI)

Subgroup	No. of patients with event/total no.		Odds ratio (95% CI)
All patients	159/307		0.11 (0.06 - 0.19)
Age			
≤ 75 years	96/183		0.19 (0.09 - 0.38)
> 75 years	63/124		0.05 (0.02 - 0.14)
Percent RV pacing at enrollment			
≤ median - 96.25 %	87/151		0.18 (0.08 - 0.39)
> median - 96.25 %	72/156		0.05 (0.02 - 0.13)
LVEF at enrollment			
≤ 30 %	119/233		0.11 (0.06 - 0.20)
> 30 %	40/74		0.17 (0.05 - 0.51)
Atrial fibrillation or flutter at enrollment			
No	94/195		0.13 (0.07 - 0.27)
Yes	65/112		0.06 (0.02 - 0.18)
History of any ischemic events			
No	58/125		0.13 (0.06 - 0.29)
Yes	101/182		0.10 (0.05 - 0.22)
History of diabetes mellitus			
No	99/192		0.14 (0.07 - 0.28)
Yes	60/115		0.07 (0.02 - 0.19)
NYHA class at enrollment			
II	71/147		0.11 (0.05 - 0.25)
III or IV	88/160		0.12 (0.05 - 0.27)
NT-proBNP at enrollment			
≤ median - 2154 pg/ml	62/120		0.13 (0.06 - 0.31)
> median - 2154 pg/ml	64/123		0.11 (0.04 - 0.27)
Estimated GFR at enrollment			
< 60 ml/min/1.73 m²	91/175		0.12 (0.06 - 0.26)
≥ 60 ml/min/1.73 m²	67/131		0.08 (0.03 - 0.21)
Body-mass index at enrollment			
< 30	104/202		0.11 (0.05 - 0.21)
≥ 30	55/105		0.10 (0.03 - 0.29)

0.01 0.05 0.1 0.25 0.5 1 1.5 2
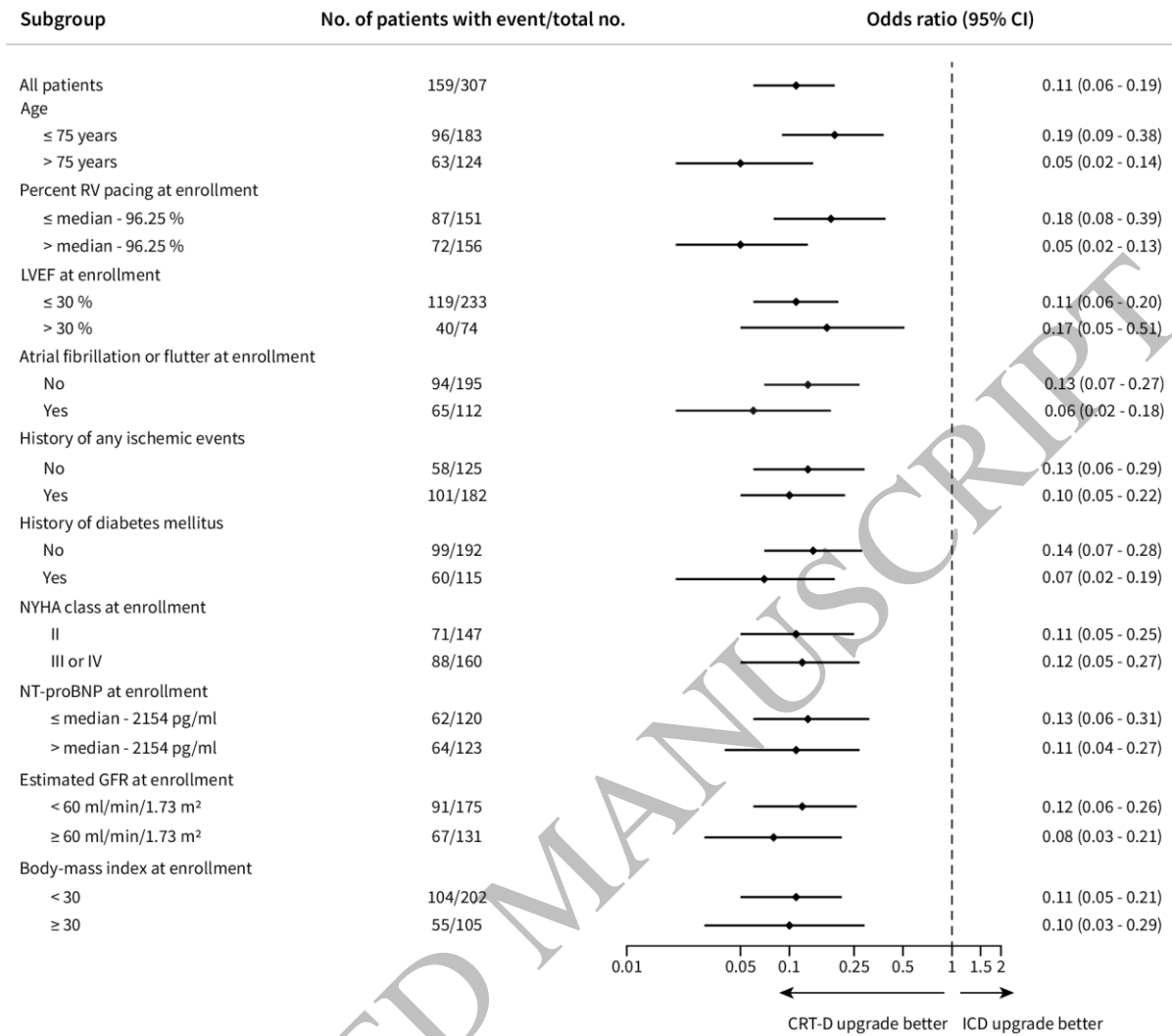
← CRT-D upgrade better   ICD upgrade better →
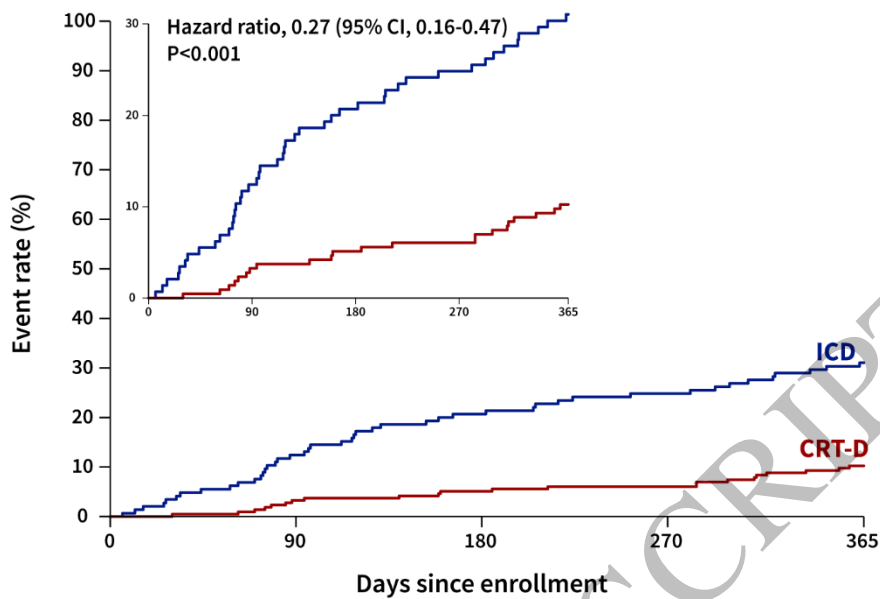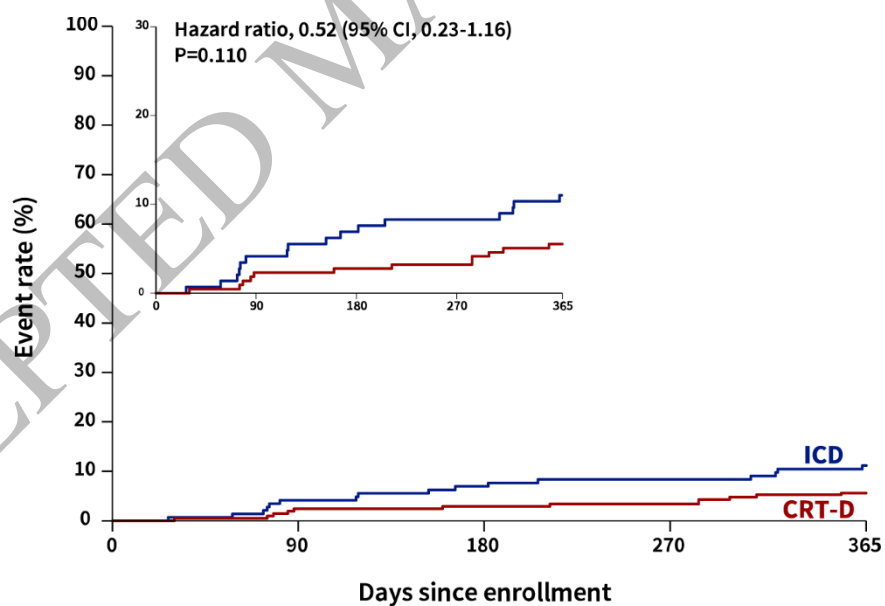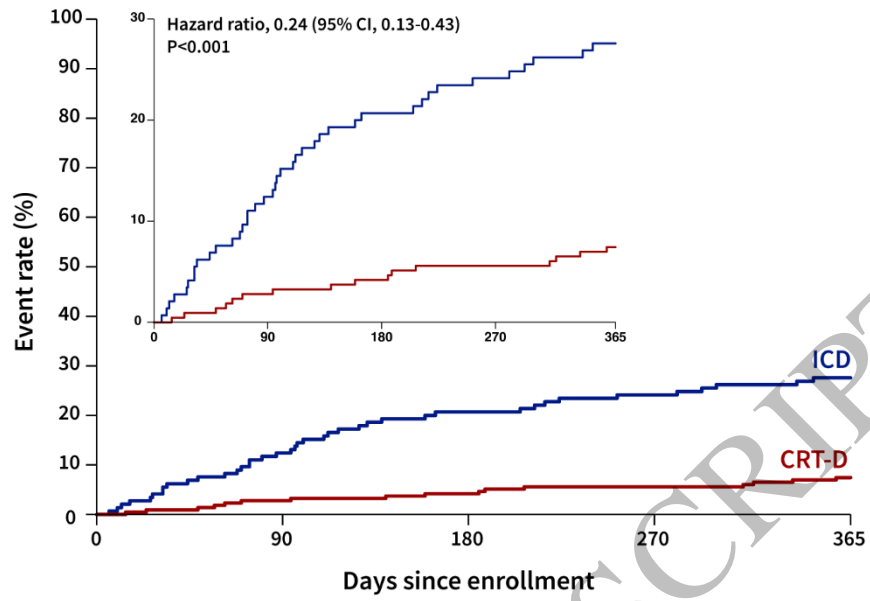
Table 1. Characteristics of the Participants at Baseline, According to Randomisation Arm

Characteristics[*]	CRT-D (n = 215)	ICD (n = 145)
Age – yrs	72.9 ± 7.3	72.6 ± 8.3
Male sex – no. (%)	185 (86.1)	135 (93.1)
BMI – kg/m^2	29.1 ± 4.9	28.1 ± 4.9
NYHA class – no. (%) [#]		
II	105 (48.8)	64 (44.1)
III	101 (47.0)	78 (53.8)
IVa	9 (4.2)	3 (2.1)
Echocardiographic parameters		
Left ventricular end-diastolic volume – mL	231.2 ± 80.3	226.6 ± 74.5
Left ventricular end-systolic volume – mL	175.5 ± 66.7	171.2 ± 63.9
Left ventricular ejection fraction – %	24.7 ± 6.8	25.0 ± 6.3
Medical history – no. (%)		
Ischemic etiology	127 (59.1)	82 (56.6)
Myocardial infarction	102 (47.4)	65 (44.8)
Coronary artery bypass graft	53 (24.7)	33 (22.8)
Percutaneous coronary intervention	85 (39.5)	55 (37.9)
Hypertension	178 (82.8)	111 (76.6)
Diabetes	83 (38.6)	45 (31.0)
Hyperlipidemia	95 (44.2)	70 (48.3)
Asthma	8 (3.7)	3 (2.1)
Chronic obstructive pulmonary disease	30 (14.0)	18 (12.4)

Current smoking	18 (8.4)	7 (4.8)
Known valvular heart disease	34 (15.8)	29 (20.0)
Valve surgery	28 (13.0)	10 (6.9)
Cerebrovascular accident or transient ischemic attack	33 (15.3)	23 (15.9)
Peripheral vascular disease	21 (9.8)	13 (9.0)
Atrial fibrillation	116 (54.0)	87 (60.0)
History of ventricular tachycardia or ventricular fibrillation	47 (21.9)	37 (25.5)
Heart failure hospitalisation 12 months prior to enrolment	101 (47.0)	77 (53.1)
Baseline medication – no. (%)		
ACE inhibitor	157 (73.0)	108 (74.5)
ARB	43 (20.0)	23 (15.9)
ARNI	11 (5.1)	10 (6.9)
Beta-blockers	197 (91.6)	131 (90.3)
MRA	134 (62.3)	91 (62.8)
Loop diuretics	170 (79.1)	118 (81.4)
Calcium channel blocker	29 (13.5)	10 (6.9)
Amiodarone	52 (24.2)	35 (24.1)
Digoxin	17 (7.9)	17 (11.7)
Prior device type – no. (%)		
Pacemaker	150 (69.8)	94 (64.8)
Implantable cardioverter defibrillator	64 (29.8)	50 (34.5)
Cardiac resynchronisation therapy with plug	1 (0.5)	1 (0.7)

26

Pacemaker interrogation		
Percent right ventricular pacing prior to enrollment – %	85.4 ± 21.1	88.1 ± 18.8

* Plus-minus values are means ± SD.

ACE denotes angiotensin-converting enzyme, BMI body mass index, ARB angiotensin receptor blocker, ARNI angiotensin receptor–neprilysin inhibitor, MRA mineralocorticoid receptor antagonis