ESC European Society of Cardiology

European Heart Journal (2023) **44**, 4259–4269
https://doi.org/10.1093/eurheartj/ehad591

FASTTRACK CLINICAL RESEARCH
Clinical trials

Upgrade of right ventricular pacing to cardiac resynchronization therapy in heart failure: a randomized trial

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Received 13 July 2023; revised 20 August 2023; accepted 23 August 2023; online publish-ahead-of-print 26 August 2023

See the editorial comment for this article 'The BUDAPEST trial: a good grade for upgrades in heart failure with reduced ejection fraction', by C. Linde, https://doi.org/10.1093/eurheartj/ehad588.

Abstract

Background and Aims *De novo* implanted cardiac resynchronization 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, randomized, controlled trial, 360 symptomatic (New York Heart Association Classes 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 hospitalization, or <15% reduction of left ventricular end-systolic volume assessed at 12 months. Secondary outcomes included all-cause mortality or heart failure hospitalization.

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 0.06–0.19; $P < .001$). 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% confidence interval 0.16–0.47; $P < .001$). 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%)].

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

Structured Graphical Abstract

Key Question

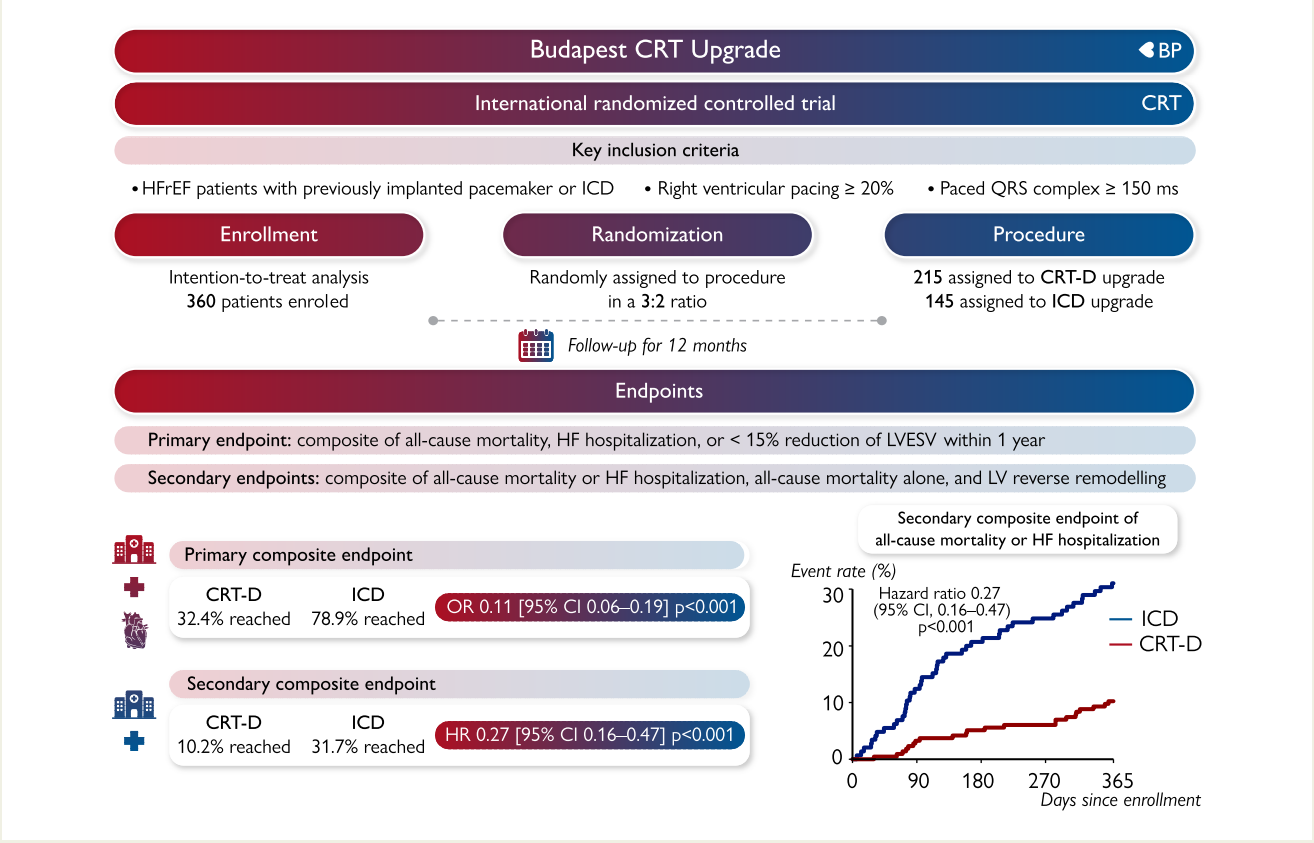
What is the efficacy and safety of cardiac resynchronization therapy (CRT-D) upgrade vs. implantable cardioverter defibrillator (ICD) in heart failure with reduced ejection fraction (HFrEF) patients with pacemaker or ICD, ≥ 20% right ventricular (RV) pacing burden and paced QRS complex duration ≥150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

Key Finding

In this randomized trial, CRT-D upgrade reduced the risk of all-cause mortality, heart failure 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.



Main inclusion criteria and randomization 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 with 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 hospitalization, or <15% decrease in LVESV as the primary outcome. Secondary outcome of all-cause mortality and HF hospitalization also proved a substantially lower incidence in CRT-D patients compared with 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.

Keywords Cardiac resynchronization therapy • Upgrade • Right ventricular pacing • Pacing-induced cardiomyopathy • Heart failure

Introduction

The estimated number of patients undergoing pacemaker (PM) or implantable cardioverter defibrillator (ICD) implantation has surpassed 1 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) hospitalization 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 resynchronization 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 Heart Rhythm Society/Asia Pacific Heart Rhythm Society/Latin American Heart Rhythm Society 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 PM 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 >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 with ICD, in HFrEF patients with a non-CRT PM/ICD and intermittent or permanent RV pacing.[18] We hypothesized that cardiac resynchronization therapy with defibrillator (CRT-D) upgrade compared with ICD-only upgrade is associated with improved clinical outcomes, defined as risk for all-cause mortality, hospitalization 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, randomized, controlled trial. The study and the analysis were conducted with emphasis on strict adherence to the protocol and a preestablished 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. Enroled 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 (NYHA) Classes 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 severe valvular heart disease, or 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 (see Supplementary data online, *Table S1*).[19]

Those who met the inclusion criteria were randomly assigned to receive a CRT-D upgrade or ICD in a 3:2 ratio. Randomization 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 randomization.

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 electrocardiogram (ECG), echocardiography, cardiac implantable electronic device interrogation, 6-min walking test (6MWT), and EQ-5D-3L quality of life questionnaire testing (see Supplementary data online, *Table S2*). If a patient assigned to the ICD arm required HF hospitalization, 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 hospitalization, all-cause mortality within 1 year, or <15% reduction of LVESV from baseline to 12 months assessed by echocardiography. Secondary outcomes were the composite of all-cause mortality and HF hospitalizations, 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 hospitalization 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 (CIs). The prespecified adjustment factors were the following: age, sex, country, ischaemic aetiology, diabetes mellitus, secondary prevention

Table 1 Characteristics of the participants at baseline, according to randomization arm

Characteristics[a]	CRT-D ($n = 215$)	ICD ($n = 145$)
Age—years	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. (%)[b]		
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. (%)		
Ischaemic aetiology	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)
Hyperlipidaemia	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 ischaemic 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 hospitalization 12 months prior to enrollment	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)

Continued

Table 1 *Continued*

Characteristics[a]	CRT-D ($n = 215$)	ICD ($n = 145$)
Prior device type—no. (%)		
Pacemaker	150 (69.8)	94 (64.8)
Implantable cardioverter defibrillator	64 (29.8)	50 (34.5)
Cardiac resynchronization therapy with plug	1 (0.5)	1 (0.7)
Pacemaker interrogation		
Per cent right ventricular pacing prior to enrollment—%	85.4 ± 21.1	88.1 ± 18.8

ACE, angiotensin-converting enzyme; BMI, body mass index; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; MRA, mineralocorticoid receptor antagonist.
[a]Plus–minus values are means ± SD.

Table 2 Primary, secondary outcomes, and safety outcomes according to randomization arm

Endpoints	CRT-D ($n = 215$)	ICD ($n = 145$)	Measure of effect	Unadjusted hazard or odds ratio or difference (95% CI)	*P*-value	Adjusted hazard or odds ratio or difference (95% CI)[a]	*P*-value
Primary outcome							
Composite endpoint of all-cause death or heart failure hospitalization or <15% end-systolic volume decrease—no./total no. (%)	58/179 (32.4)	101/128 (78.9)	Odds ratio	0.13 (0.08 to 0.22)	<0.001	0.11 (0.06 to 0.19)	<0.001
Secondary outcomes							
Composite endpoint of all-cause death or heart failure hospitalization—no./total no. (%)	22/215 (10.2)	46/145 (31.7)	Hazard ratio	0.28 (0.17 to 0.46)	<0.001	0.27 (0.16 to 0.47)	<0.001
Death from any cause—no./total no. (%)	12/215 (5.6)	16/145 (11.0)	Hazard ratio	0.49 (0.23 to 1.04)	0.062	0.52 (0.23 to 1.16)	0.110
Changes in left ventricular end-diastolic volume from baseline to 12 months—mL (SD)	−40.9 (54.6)	−1.9 (47.1)	Difference	−38.95 (−51.54 to −26.35)	<0.001	−39.00 (−51.73 to −26.27)	<0.001
Changes in left ventricular ejection fraction from baseline to 12 months—% (SD)	11.0 (9.3)	1.2 (8.3)	Difference	9.83 (7.67 to 11.99)	<0.001	9.76 (7.55 to 11.98)	<0.001
Safety outcomes							
Successful procedures—no./total no. (%)	207/211 (98.0)	142/142 (100.0)					
Lead extraction during procedure—no./total no. (%)	32/211 (15.1)	16/142 (11.3)					
Patients with device—or procedure-related SAE—no./total no. (%)	25/211 (12.3)	11/142 (7.8)					
Ventricular tachycardia or ventricular fibrillation—no./total no. (%)	1/215 (0.5)	21/145 (14.5)					

CRT-D, cardiac resynchronization therapy with defibrillator; ICD, implantable cardioverter defibrillator; NYHA class, New York Heart Association class; SAE, serious adverse event.
[a]Adjusted for variables considered strong predictors of the outcome: age, sex, country, ischaemic aetiology, diabetes, secondary prevention, atrial fibrillation, and baseline NYHA class.

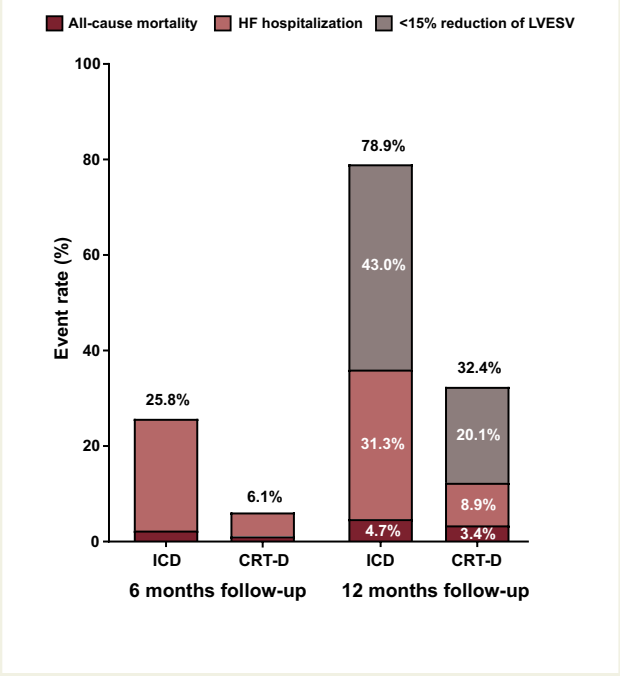


Figure 1 Event rate of the primary composite outcome in the implantable cardioverter defibrillator and cardiac resynchronization therapy with defibrillator arms and its components: first occurrence of heart failure hospitalization with or without subsequent all-cause death, all-cause death without previous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

ICD, atrial fibrillation, and baseline NYHA class. Time-to-event secondary outcomes (composite endpoint of all-cause mortality and HF hospitalization 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 (ITT) 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 (see Supplementary data online, *Figure S1*). However, they were included in all other analysis based on ITT 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 24 November 2014 and 13 August 2021, a total of 576 patients were assessed for eligibility, and the reasons for exclusion are described in Supplementary data online, *Table S3*. Finally, 360 patients were enroled 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. Almost half of the patients experienced hospitalization for HF within 12 months before enrollment (*Table 1*). The mean LVEF was 24.8 ± 6.6%, and more than two-thirds of the patients had a PM device (predominantly DDD) implanted with a high RV pacing burden (CRT-D group 85.4 ± 21.1%; ICD group 88.1 ± 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 (see Supplementary data online, *Figure S1*; *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 hospitalizations 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 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; $P < .001$, *Figure 1* and *Table 2*; see Supplementary data online, *Table S4*) [number needed to treat (NNT): 2.2]. The composite of all-cause mortality and HF hospitalization [adjusted hazard ratio (HR) 0.27, 95% CI 0.16–0.47; $P < .001$] (*Table 2* and *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; $P < .001$, and difference at 12 months in LVEF, 9.76%, 95% CI 7.55–11.98; $P < .001$) 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* and *Figure 2B*) (NNT: 18.5), showing that the secondary composite endpoint was mainly driven by reduction in HF hospitalization (adjusted HR 0.24, 95% CI 0.13–0.43, $P < .001$) (*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 (see Supplementary data online, *Table S5*).

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%)]

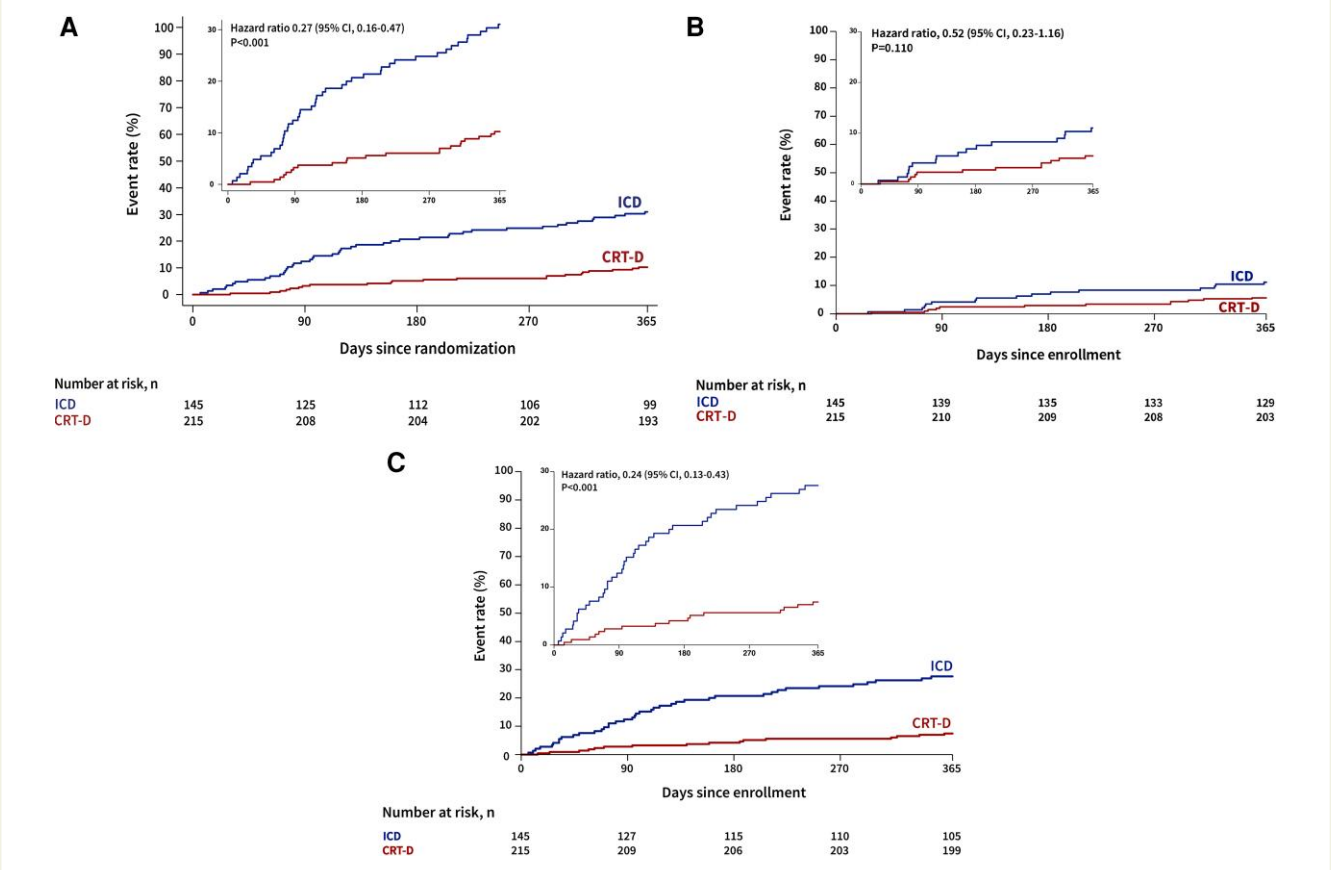


Figure 2 (*A*) All-cause mortality and heart failure hospitalization. (*B*) All-cause mortality. (*C*) Heart failure hospitalization. Kaplan–Meier estimates for secondary outcomes. (*A*) The Kaplan–Meier curves for the secondary composite outcome of first occurrence of all-cause mortality or heart failure hospitalization. (*B*) The Kaplan–Meier curves for death from any cause. (*C*) The Kaplan–Meier curves for heart failure hospitalization. CI, confidence interval; CRT-D, cardiac resynchronization therapy with defibrillator; ICD, implantable cardioverter defibrillator.

(*Table 2*; Supplementary data online, *Table S6*). 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 with the ICD arm [21/145 patients (14.5%)] (*Table 2*).

Discussion

In this international, randomized, controlled trial enroling patients with HFrEF and significant RV pacing burden with a wide paced QRS complex, CRT-D upgrade reduced the composite primary outcome of HF hospitalizations, deaths, and absence of reverse remodelling, as compared with ICD-only treatment. Cardiac resynchronization therapy with defibrillator upgrade was associated with significantly fewer hospitalizations for HF or reduced all-cause mortality, favouring CRT-D that was accompanied by improved LV reverse remodelling, when compared with ICD alone. Finally, CRT-D upgrade did not increase the rate of device- or procedure-related events during a 1-year follow-up when compared with 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 was modified several times over the past decade (IB in 2013,[21] IIb B in 2016,[22] IIaB in 2018[12] and 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 that investigated patients with conventional PM and preserved LVEF revealed that an 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% and 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.

The 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

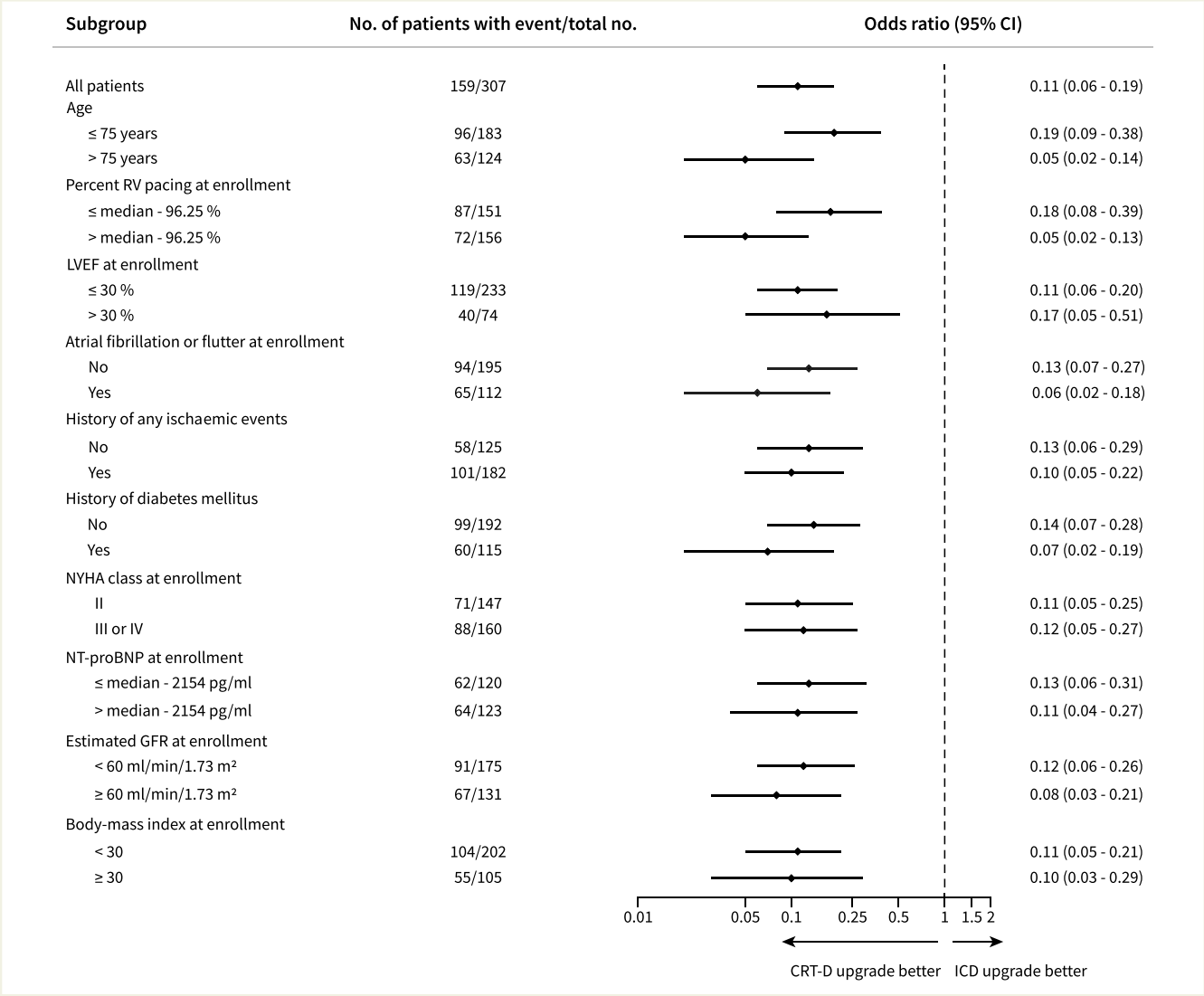


Figure 3 Primary composite outcome, according to prespecified subgroups.

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]

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, 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 randomized controlled trials enroling *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 hospitalization was substantially lower in CRT-D patients as compared with 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-enroling tertiary centres, and the overall recruitment rate was relatively low, but several other factors—both clinical and organizational—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 with ICD alone in all the prespecified subgroups. The subgroup analysis by sex was compromised by the male predominance in both arms (CRT-D 86.1% and ICD 93.1%). Additionally, despite 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 >2 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 >97% of the patients, beta-blocker therapy in ∼90%, and mineralocorticoid receptor antagonist in 62%) and did not change substantially over time. The only exception was the administration of angiotensin receptor–neprilysin inhibitor (ARNI) (sacubitril/valsartan), which became available in the participating countries only during the course of the trial.

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 hospitalization, or <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.

Acknowledgements

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Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

B.M. reports grants from Boston Scientific, NRDIF Hungary, and National Heart Program during the conduct of the study; personal fees from Biotronik, Abbott, AstraZeneca, Novartis, and Boehringer-Ingelheim; and grants from Medtronic outside the submitted work. I.O. reports lecture and advisory fees from Abbott, Biotronik, Boston Scientific, Medtronic, and Vitatro and travel grants from Abbott, Biotronik, Boston Scientific, and Medtronic. At.K. reports grants from Bolyai Research Scholarship and FK 'OTKA' Research Grant from NKFIH outside the submitted work; stock from CardioSight, Inc. and stock option from Argus Cognitive, Inc. outside the submitted work; and personal fees from Argus Cognitive, Inc. and CardioSight Hungary LLC outside the submitted work. G.D. reports research grants to institution from Medtronic and Biotronik and lecture and advisory fees from Medtronic, Biotronik, and Abbott. L.G. reports support for the present manuscript from Vitatron Medical, Boston Scientific, Abbott Laboratories, Medtronic Hungary, and Biotronik Hungary; consulting fees from Medtronic Hungary and Abbott

Hungary; honoraria; travel grants; participation on a data safety monitoring board or advisory board; and role in other board and committee (FESC, FEHRA, President of the Scientific Committee of the Hungarian Society of Cardiology, Past President of the Working Group on Cardiac Arrhythmias and Pacing, and EHRA Scientific Programme Board). An.K. reports grants from Bolyai Research Scholarship outside the submitted work; consulting fees from Medtronic; honoraria from AstraZeneca, Bayer, Boehringer Ingelheim, Biotronik, Novartis; payment for expert testimony from Boehringer Ingelheim and Boston Scientific; travel grants from AstraZeneca and Novartis; participation on a data safety monitoring board or advisory board for Boehringer Ingelheim and Boston Scientific; and role in other board and committee (committee member of Hungarian Society of Cardiology and secretary of the Working Group on Cardiac Arrhythmias and Pacing, Hungarian Society of Cardiology). S.D.S. reports grants to institution from Actelion, Alnylam, Amgen, AstraZeneca, Bellerophon, Bayer, BMS, Celladon, Cytokinetics, Eidos, Gilead, GSK, Ionis, Lilly, Mesoblast, MyoKardia, NIH/NHLBI, Neurotronik, Novartis, NovoNordisk, Respicardia, Sanofi Pasteur, Theracos, and US2.AI and consulting fees outside the scope of the current work from Abbott, Action, Akros, Alnylam, Amgen, Arena, AstraZeneca, Bayer, Boeringer-Ingelheim, BMS, Cardior, Cardurion, Corvia, Cytokinetics, Daiichi-Sankyo, GSK, Lilly, Merck, Myokardia, Novartis, Roche, Theracos, Quantum Genomics, Cardurion, Janssen, Cardiac Dimensions, Tenaya, Sanofi-Pasteur, Dinaqor, Tremeau, CellProThera, Moderna, American Regent, Sarepta, Lexicon, Anacardio, Akros, and Valo. Z.S. reports consulting fees and honoraria from Boston Scientific, Medtronic, and Biotronik. V.K. reports grants from Boston Scientific, ZOLL, Biotronik, Spire Inc, and NIH; consulting fees from Biotronik and ZOLL; and honoraria from Abbott Medical and Medtronic. R.H. reports institutional grants from Abbott, Biotronik, and Slovak Research and Development Agency; honoraria from Abbott and Medtronic; and travel grants from the European Society of Cardiology and Pfizer. He is also the president of the Slovak Heart Rhythm Association. E.Z. reports lecture and advisory fees outside the submitted work from Biotronik, Medtronic, Boston Scientific, SJM-Abbott, Orion, AstraZeneca, Richter, and Zoll Medical; travel grants for advisory meetings outside the submitted work from Biotronik, Medtronic, and Richter; and two Hungarian patents outside of this work. The other authors declare no conflict of interest for this contribution.

Data Availability

Data are available upon reasonable request.

Funding

The BUDAPEST CRT Upgrade study was an investigator-initiated research trial, sponsored by Semmelweis University, receiving an unrestricted grant from Boston Scientific to conduct the study. The trial was supported by the 'National Heart Program' (Project no. NVKP_16-1–2016-0017) with support provided by the National Research Development and Innovation Fund of Hungary, financed under the NVKP_16 funding scheme. Additionally, Project no. RRF-2.3.1-21-2022-00003 has been implemented with the support provided by the European Union. These sources played no role in the design, execution, or analysis of the trial results. An.K. and At.K. were supported by the Bolyai Janos Research Scholarship by the Hungarian Academy of Sciences.

Ethical Approval

The study protocol was approved by local and institutional ethics committees.

Pre-registered Clinical Trial Number

NCT02270840 on clinicaltrials.gov.

References

1. Mond HG, Proclemer A. The 11th world survey of cardiac pacing and implantable cardioverter-defibrillators: calendar year 2009—a World Society of Arrhythmia's project. *Pacing Clin Electrophysiol* 2011;**34**:1013–27. https://doi.org/10.1111/j.1540-8159.2011.03150.x
2. Greenspon AJ, Patel JD, Lau E, Ochoa JA, Frisch DR, Ho RT, *et al.* Trends in permanent pacemaker implantation in the United States from 1993 to 2009: increasing complexity of patients and procedures. *J Am Coll Cardiol* 2012;**60**:1540–5. https://doi.org/10.1016/j.jacc.2012.07.017
3. Lamas GA, Lee KL, Sweeney MO, Silverman R, Leon A, Yee R, *et al.* Ventricular pacing or dual-chamber pacing for sinus-node dysfunction. *N Engl J Med* 2002;**346**:1854–62. https://doi.org/10.1056/NEJMoa013040
4. Wilkoff BL, Cook JR, Epstein AE, Greene HL, Hallstrom AP, Hsia H, *et al.* Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator: the Dual Chamber and VVI Implantable Defibrillator (DAVID) trial. *JAMA* 2002;**288**:3115–23. https://doi.org/10.1001/jama.288.24.3115
5. Kiehl EL, Makki T, Kumar R, Gumber D, Kwon DH, Rickard JW, *et al.* Incidence and predictors of right ventricular pacing-induced cardiomyopathy in patients with complete atrioventricular block and preserved left ventricular systolic function. *Heart Rhythm* 2016;**13**:2272–8. https://doi.org/10.1016/j.hrthm.2016.09.027
6. Glikson M, Nielsen JC, Kronborg MB, Michowitz Y, Auricchio A, Barbash IM, *et al.* 2021 ESC guidelines on cardiac pacing and cardiac resynchronization therapy. *Eur Heart J* 2021;**42**:3427–520. https://doi.org/10.1093/eurheartj/ehab364
7. Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, *et al.* Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med* 2009;**361**:1329–38. https://doi.org/10.1056/NEJMoa0906431
8. Cleland JGF, Daubert J-C, Erdmann E, Freemantle N, Gras D, Kappenberger L, *et al.* The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005;**352**:1539–49. https://doi.org/10.1056/NEJMoa050496
9. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, *et al.* Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004;**350**:2140–50. https://doi.org/10.1056/NEJMoa032423
10. Tang AS, Wells GA, Talajic M, Arnold MO, Sheldon R, Connolly S, *et al.* Cardiac-resynchronization therapy for mild-to-moderate heart failure. *N Engl J Med* 2010;**363**:2385–95. https://doi.org/10.1056/NEJMoa1009540
11. Kosztin A, Vamos M, Aradi D, Schwertner WR, Kovacs A, Nagy KV, *et al.* De novo implantation vs. upgrade cardiac resynchronization therapy: a systematic review and meta-analysis. *Heart Fail Rev* 2018;**23**:15–26. https://doi.org/10.1007/s10741-017-9652-1
12. Kusumoto FM, Schoenfeld MH, Barrett C, Edgerton JR, Ellenbogen KA, Gold MR, *et al.* 2018 ACC/AHA/HRS guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, and the Heart Rhythm Society. *Circulation* 2019;**140**:e333–e81. https://doi.org/10.1161/CIR.0000000000000627
13. Chung MK, Patton KK, Lau CP, Dal Forno ARJ, Al-Khatib SM, Arora V, *et al.* 2023 HRS/APHRS/LAHRS guideline on cardiac physiologic pacing for the avoidance and mitigation of heart failure. *Heart Rhythm* 2023;**20**:e17–e91. https://doi.org/10.1016/j.hrthm.2023.03.1538
14. Slotwiner DJ, Raitt MH, Del-Carpio Munoz F, Mulpuru SK, Nasser N, Peterson PN. Impact of physiologic pacing versus right ventricular pacing among patients with left ventricular ejection fraction greater than 35%: a systematic review for the 2018 ACC/AHA/HRS guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2019;**74**:988–1008. https://doi.org/10.1016/j.jacc.2018.10.045
15. Essebag V, Joza J, Birnie DH, Sapp JL, Sterns LD, Philippon F, *et al.* Incidence, predictors, and procedural results of upgrade to resynchronization therapy: the RAFT upgrade substudy. *Circ Arrhythm Electrophysiol* 2015;**8**:152–8. https://doi.org/10.1161/CIRCEP.114.001997
16. Cheung JW, Ip JE, Markowitz SM, Liu CF, Thomas G, Feldman DN, *et al.* Trends and outcomes of cardiac resynchronization therapy upgrade procedures: a comparative analysis using a United States National Database 2003-2013. *Heart Rhythm* 2017;**14**:1043–50. https://doi.org/10.1016/j.hrthm.2017.02.017
17. Linde CM, Normand C, Bogale N, Auricchio A, Sterlinski M, Marinskis G, *et al.* Upgrades from a previous device compared to de novo cardiac resynchronization therapy in the European Society of Cardiology CRT Survey II. *Eur J Heart Fail* 2018;**20**:1457–68. https://doi.org/10.1002/ejhf.1235
18. Merkely B, Kosztin A, Roka A, Geller L, Zima E, Kovacs A, *et al.* Rationale and design of the BUDAPEST-CRT Upgrade Study: a prospective, randomized, multicentre clinical trial. *Europace* 2017;**19**:1549–55. https://doi.org/10.1093/europace/euw193

19. Merkely B, Geller L, Zima E, Osztheimer I, Molnar L, Foldesi C, *et al.* Baseline clinical characteristics of heart failure patients with reduced ejection fraction enrolled in the BUDAPEST-CRT Upgrade trial. *Eur J Heart Fail* 2022;**24**:1652–61. https://doi.org/10.1002/ejhf.2609
20. Kaza N, Htun V, Miyazawa A, Simader F, Porter B, Howard JP, *et al.* Upgrading right ventricular pacemakers to biventricular pacing or conduction system pacing: a systematic review and meta-analysis. *Europace* 2023;**25**:1077–86. https://doi.org/10.1093/europace/euac188
21. Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt OA, *et al.* 2013 ESC guidelines on cardiac pacing and cardiac resynchronization therapy: the task force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). *Europace* 2013;**15**:1070–118. https://doi.org/10.1093/europace/eut206
22. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, *et al.* 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016;**37**:2129–200. https://doi.org/10.1093/eurheartj/ehw128
23. Somma V, Ha FJ, Palmer S, Mohamed U, Agarwal S. Pacing-induced cardiomyopathy: a systematic review and meta-analysis of definition, prevalence, risk factors, and management. *Heart Rhythm* 2023;**20**:282–90. https://doi.org/10.1016/j.hrthm.2022.09.019
24. Leclercq C, Cazeau S, Lellouche D, Fossati F, Anselme F, Davy JM, *et al.* Upgrading from single chamber right ventricular to biventricular pacing in permanently paced patients with worsening heart failure: the RD-CHF study. *Pacing Clin Electrophysiol* 2007;**30**:S23–30. https://doi.org/10.1111/j.1540-8159.2007.00598.x
25. Barsheshet A, Wang PJ, Moss AJ, Solomon SD, Al-Ahmad A, McNitt S, *et al.* Reverse remodeling and the risk of ventricular tachyarrhythmias in the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy). *J Am Coll Cardiol* 2011;**57**:2416–23. https://doi.org/10.1016/j.jacc.2010.12.041
26. Abdelrahman M, Subzposh FA, Beer D, Durr B, Naperkowski A, Sun H, *et al.* Clinical outcomes of his bundle pacing compared to right ventricular pacing. *J Am Coll Cardiol* 2018;**71**:2319–30. https://doi.org/10.1016/j.jacc.2018.02.048
27. Khurshid S, Obeng-Gyimah E, Supple GE, Schaller R, Lin D, Owens AT, *et al.* Reversal of pacing-induced cardiomyopathy following cardiac resynchronization therapy. *JACC Clin Electrophysiol* 2018;**4**:168–77. https://doi.org/10.1016/j.jacep.2017.10.002
28. Vijayaraman P, Herweg B, Dandamudi G, Mittal S, Bhatt AG, Marcantoni L, *et al.* Outcomes of His-bundle pacing upgrade after long-term right ventricular pacing and/or pacing-induced cardiomyopathy: insights into disease progression. *Heart Rhythm* 2019;**16**:1554–61. https://doi.org/10.1016/j.hrthm.2019.03.026
29. Li DL, Yoneda ZT, Issa TZ, Shoemaker MB, Montgomery JA. Prevalence and predictors of pacing-induced cardiomyopathy in young adult patients (< 60 years) with pacemakers. *J Cardiovasc Electrophysiol* 2021;**32**:1961–8. https://doi.org/10.1111/jce.15029