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Rationale and design of the BUDAPEST-CRT Upgrade Study: a prospective, randomized, multicentre clinical trial

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Aims There is lack of conclusive evidence from randomized clinical trials on the efficacy and safety of upgrade to cardiac resynchronization therapy (CRT) in patients with implanted pacemakers (PM) or defibrillators (ICD) with reduced left ventricular ejection fraction (LVEF) and chronic heart failure (HF). The BUDAPEST-CRT Upgrade Study was designed to compare the efficacy and safety of CRT upgrade from conventional PM or ICD therapy in patients with intermittent or permanent right ventricular (RV) septal/apical pacing, reduced LVEF, and symptomatic HF.

Methods and results The BUDAPEST-CRT study is a prospective, randomized, multicentre, investigator-sponsored clinical trial. A total of 360 subjects will be enrolled with LVEF $\leq$ 35%, NYHA functional classes II–IVa, paced QRS $\geq$ 150 ms, and a RV pacing $\geq$ 20%. Patients will be followed for 12 months. Randomization is performed in a 3:2 ratio (CRT-D vs. ICD). The primary composite endpoint is all-cause mortality, a first HF event, or less than 15% reduction in left ventricular (LV) end-systolic volume at 12 months. Secondary endpoints are all-cause mortality, all-cause mortality or HF event, and LV volume reduction at 12 months. Tertiary endpoints include changes in quality of life, NYHA functional class, 6 min walk test, natriuretic peptides, and safety outcomes.

Conclusion The results of our prospective, randomized, multicentre clinical trial will provide important information on the role of cardiac resynchronization therapy with defibrillator (CRT-D) upgrade in patients with symptomatic HF, reduced LVEF, and wide-paced QRS with intermittent or permanent RV pacing.

Clinical trials.gov identifier NCT02270840.

Keywords Cardiac resynchronization therapy upgrade • Right ventricular pacing • Dyssynchrony • Randomized controlled trial • Study design • Pacing-induced heart failure

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What's new?

- Cardiac resynchronization therapy upgrade from a conventional pacemaker (PM) or implantable cardioverter defibrillator (ICD) takes a relatively high part of interventions. The patient selection and the optimal time of the procedures with measuring the risk–benefit ratio are according to the physician's discretion.
- While the current European Society of Cardiology guideline does not contain conclusive data (with more multicentre, randomized trials) on the superiority of cardiac resynchronization therapy with defibrillator (CRT-D) over ICD in patients with previously implanted PM or ICD devices with reduced left ventricular (LV) function and symptomatic heart failure (HF) who require intermittent or permanent ventricular pacing.
- The results of our prospective, randomized, multicentre clinical trial will provide important information on the role of CRT-D upgrade in patients with symptomatic HF (NYHA II–IVa), reduced LV ejection fraction (≤35%), and wide-paced QRS (≥150 ms) with intermittent or permanent right ventricular pacing (≥20%).

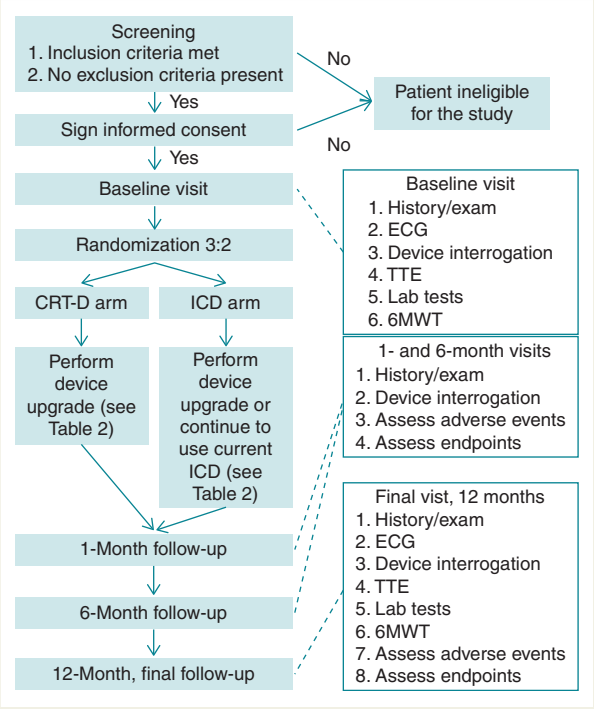

Figure 1 Study flowchart.

Introduction

Cardiac resynchronization therapy (CRT) reduces morbidity and mortality in selected patients with heart failure (HF) and broad QRS complex (≥130 ms). Large randomized clinical trials have shown improvement in cardiac function and decreased HF events or all-cause mortality, mainly in patients with *de novo* CRT device implantations.[1–4] However, 28% of CRT implantations in Europe are upgrade procedures after previously implanted cardiac devices.[5] To date, there are no conclusive data on the superiority of cardiac resynchronization therapy with defibrillator (CRT-D) over implantable cardioverter defibrillator (ICD) in patients with previously implanted pacemaker (PM) or ICD devices with reduced left ventricular (LV) function and symptomatic HF who require intermittent or permanent ventricular pacing. Furthermore, recent data indicated that upgrade procedures to biventricular pacing are associated with a relatively high complication rate,[6] suggesting that more conclusive data are required before a general recommendation for an upgrade to a CRT system can be made.

Study design

Study objectives

The aim of the BUDAPEST-CRT Upgrade Study is to investigate the safety and efficacy of upgrading to CRT from existing previously implanted PM or defibrillators, during a 12-month follow-up time in patients with reduced ejection fraction (LVEF ≤ 35%), symptomatic heart failure (NYHA II–IVa), and intermittent or permanent right ventricular (RV) pacing (≥20%, with paced QRS complex ≥150 ms), compared with therapy with ICD only.

The primary endpoint of the study is the composite of clinical and echocardiographic parameters including the first occurrence of a non-fatal HF event, or all-cause mortality, or less than 15% reduction in LVESV from baseline to 12 months, determined by echocardiography.

Secondary endpoints are all-cause mortality, the composite endpoint of death or HF events, and changes in left ventricular ejection fraction (LVEF) and left ventricular end-diastolic volume from baseline to 12 months.

Tertiary endpoints are safety endpoints related to procedure success as well as changes in functional (NYHA) class, biomarker parameters (NT-pro-BNP) after 1 year, quality of life, and 6 min walk test.

Study design

This is a prospective, international, multicentre, randomized controlled clinical trial conducted in 30 European and Israeli investigational centres. The study will be conducted in accordance with the Helsinki Declaration, the good clinical practice, and the applicable regulatory requirements.[7] All patients will provide their written informed consent prior to enrolment (*Figure 1*).

Patient population

Patients with chronic cardiomyopathy (regardless of aetiology), reduced LVEF (≤35%), and symptomatic HF (NYHA functional classes II–IVa) despite optimized medical treatment, who have a single- or dual-chamber PM or ICD implanted at least 6 months before enrolment (with ≥20% RV pacing in the time period of ≥90 days prior to enrolment, paced QRS duration ≥150 ms).

The intrinsic rhythm is required to assess at enrolment in order to exclude patients with typical Left Bundle Branch Block (LBBB) morphology. Patients with atrial fibrillation/flutter or atrial tachycardia can also be enrolled. The rate or frequency control management

Table 1 Inclusion and exclusion criteria in the study

Inclusion criteria	Exclusion criteria
(1) Age: over 18 years	(1) CABG or PCI ≤ 3 months ago or planned
(2) Cardiomyopathy with LVEF ≤ 35%, ischaemic or non-ischaemic	(2) AMI ≤ 3 months ago
(3) Single- or dual-chamber PM or ICD implanted ≥6 months prior to enrolment (battery depletion or another indication for upgrade is not required)	(3) Unstable angina
(4) RV pacing ≥20% in the prior ≥90 days (use of algorithms to avoid ventricular pacing is recommended, per discretion of the clinician)	(4) Planned cardiac transplant
(5) Paced QRS duration ≥ 150 ms	(5) Acute myocarditis
(6) Symptomatic HF with NYHA functional classes II–IVa ≥3 months prior to enrolment, despite optimized medical therapy	(6) Infiltrative cardiomyopathy
(7) Informed consent	(7) Hypertrophic cardiomyopathy
	(8) Severe primary mitral, aortic, or tricuspid valve stenosis or insufficiency
	(9) Tricuspid valve prosthesis
	(10) Severe RV dysfunction (RV basal diameter > 50 mm)
	(11) Chronic severe renal dysfunction (creatinine > 200 μmol/L)
	(12) Pregnant women of planned pregnancy
	(13) Subjects who are unable or unwilling to cooperate with the study protocol
	(14) Any comorbidity that is likely to interfere with the conduct of the study
	(15) Participation in another trial
	(16) Patients geographically not stable or unavailable for follow-up
	(17) Intrinsic QRS with typical LBBB morphology

Table 2 Study interventions

CRT-D group	ICD group
1. Existing PM Addition of RV defibrillator lead Addition of RA pacing lead (unless already has one or has permanent AF) Addition of LV pacing lead Extraction of old RV PM lead optional (physician's judgement) Any revision of the old lead(s) and device pocket, as necessary Generator change to CRT-D	1. Existing PM Addition of RV defibrillator lead Addition of RA pacing lead optional (physician's judgement, unless already has one or has permanent AF) Extraction of old RV PM lead optional (physician's judgement) Any revision of the old lead(s) and device pocket, as necessary Generator change to VVI or DDD ICD,
2. Existing ICD Addition of RA pacing lead (unless already has one or has permanent AF) Addition of LV pacing lead Any revision of the old lead(s) and device pocket, as necessary Generator change to CRT-D	2. Existing ICD Continue with existing device Addition of RA pacing lead and upgrading to a DDD ICD is optional (physician's judgement, unless already has one or has permanent AF)

is based on the physician's discretion before the enrolment and during the follow-up.

Detailed inclusion and exclusion criteria are listed in *Table 1*.

Patient enrolment and randomization

After signing the written informed consent, eligible patients will undergo a baseline evaluation including clinical history, physical examination, assessment of NYHA class, 12-lead ECG with paced and non-paced QRS complexes using VVI 40 bpm settings, echocardiography, device interrogation for assessment of RV pacing percentage, assessment of quality of life, 6 min walk test, and optional blood test for assessment of NT-pro-BNP (*Figure 1*).

Subjects meeting all inclusion criteria, without having any of the exclusion criteria, will be randomized to the CRT-D group (upgrade of the existing device into CRT-D) or the ICD group (either continued ICD therapy in patients currently implanted with an ICD or upgrade to an ICD from an existing PM).

Among patients randomized to the control group who require ICD implantation, it is possible to implant a CRT-D device with or without the LV lead implanted at the same time, but LV pacing has to be turned off and the device has to be programmed to VVI/DDD ICD. The decision of implanting a CRT-D device with the LV lead deactivated for the ICD arm is left to the discretion of the principal investigator at each site and will be recorded in the electronic CRF system. The randomization will be performed in a 3:2 ratio (CRT-D:ICD).

A total of 360 patients will be enrolled in the study.

Trial intervention

Device upgrades will be performed within 14 business days from randomization. Patients assigned to the CRT-D group and those with a PM, assigned to the ICD group, will undergo the device upgrade procedure (*Table 2*). Patient with an existing ICD, assigned to the ICD group, may not need a procedure unless a generator replacement, system revision, or upgrade to a dual-chamber system is indicated by the enrolling physician. Decisions about lead

Table 3 Study procedures

Visit/evaluation	Patient enrolment visit Day 0	Device implantation and programming Within 14 days	1 month FU visit Day 30	6 months FU visit Day 180	12 months FU visit Day 365
Inclusion criteria	×				
Exclusion criteria	×				
Signed informed consent	×				
Clinical history	×		×	×	×
Physical examination	×		×	×	×
Assessment of NYHA class	×		×	×	×
12-Lead ECG (paced)	×				×
12-Lead ECG (at VVI 40 bpm)	×				×
Echocardiography	×				×
Device interrogation (print, save, upload)	×		×	×	×
Blood test (NP-pro-BNP)	x[1]				x[1]
6 Min walk test	x[2]				×
Randomization	×				
Assessment of clinical endpoints			x[3]	x[3]	x[3]
Assessment of post-implantation complications			×		
SAE, AE, UADE, USADE	×	×	×	×	×
Quality-of-life assessment using EQ-5D	x[2]				×

1, Optional; 2, after the randomization but before implantation; 3, clinical endpoints; SAE, serious adverse event; AE, adverse event; UADE, unanticipated adverse device effect; USADE, unanticipated serious adverse device effect.

extraction are left to the individual judgement of each physicians based on the actual recommendations.[8]

Use of Boston Scientific Corporation (Marlborough, MA, USA) ICDs or CRT-D is encouraged in the study; however, it is left to the physician's discretion to even use device manufactured by other companies. All devices implanted in the study have a CE certificate and will be implanted according to their instruction for use and current guidelines.[9] In the ICD arm, choosing single- or dual-chamber device is left to the physician's decision. In the CRT-D arm, the LV lead is recommended to be implanted in the lateral or posterolateral side branch of the coronary sinus. Transvenous implantation is strongly preferred; however, alternative methods are also accepted if the transvenous attempt fails.

Follow-up

Patients will be followed up for 12 months after randomization (*Figure 1*). The estimated duration of enrolment period is 36 months, which may be extended depending on the recruitment rate.

Regular, in-office follow-ups will be performed at 1, 6, and 12 months. Clinical parameters, ECG, device, echocardiographic, and biochemical parameters will be collected at each follow-up visit and stored in a central electronic database (*Table 3*).

Echocardiography assessment

After enrolment, a detailed echocardiographic report will be submitted to the Echocardiography Core Laboratory for central assessment (Semmelweis University, Heart and Vascular Center, Budapest, Hungary). Left ventricular volumes and ejection fraction will be calculated using the biplane Simpson method. Echocardiographic images will be obtained at baseline visit (after randomization and before implantation) and at the 12-month follow-up visit. A detailed echocardiographic protocol has been prepared and will be sent to the enrolling centres for standard acquisition of the echocardiographic images. All sonographers in the study will be certified by the Echocardiography Core Laboratory according to the international standards.

Device interrogation and programming

Lead impedance, sensing, and pacing parameters will be determined for each lead. Device settings, Holter recording data including RV pacing percentage, and all available tachyarrhythmia episodes with EGMs will be interrogated. All retrieved data will be printed, saved to a disk or a USB, and uploaded to a digital archive maintained by the Coordination and Data Centre.

A DDD(R) or VVI(R) mode is required with base rate setting between 40 and 70 bpm. Atrio-ventricular (AV) delay should be programmed in DDD(R) devices to minimize RV pacing by using SMART AV delay[10] or echocardiographic optimization or fixed values (sensed AV delay 120–140 ms/paced AV delay 140–160 ms). Recommended tachycardia therapy settings are as follows: VT zone between 170 and 200 bpm monitor zone without therapy, or VT therapy in case of secondary prevention with a duration delay of 2.5 s. Ventricular fibrillation (VF) zone is over 200 bpm with a 2.5 s delay, ATP during charging (8 pulses at 88% of the tachycardia cycle length) and subsequent shocks (first shock DFT + 10 or 30 J, subsequent shocks should be maximum energy shocks).

Assessment of endpoints

Ascertainment of the endpoints of death and HF events will be performed by the site investigators. The assessment of HF events are

Table 4 Indication for upgrade to CRT in patients with existing PM or ICD

ESC/EHRA 2013[9]	CRT is indicated in HF patients with LVEF < 35% and high percentage of ventricular pacing who remain in NYHA class III and ambulatory IV despite adequate medical treatment. Remark: Patients should generally not be implanted during admission for acute decompensated HF. In such patients, guideline-indicated medical treatment should be optimized and the patient reviewed as an out-patient after stabilization. It is recognized that this may not always be possible.	Class I LOE B
ACCF/AHA/HRS 2012[11]	CRT can be useful for patients on GDMT who have LVEF ≤ 35% and are undergoing new or replacement device placement with anticipated requirement for significant (>40%) ventricular pacing.	Class IIa LOE C
ESC/HFA 2012[12]	CRT is recommended as an alternative to conventional RV pacing in patients with HF-REF who have a standard indication for pacing or who require a generator change or revision of a conventional PM.	No specific recommendations for CRT upgrade

ESC/EHRA, European Society of Cardiology/European Heart Rhythm Association; GDMT, Guideline determined medical therapy; ACCF/AHA/HRS, American College of Cardiology Foundation/American Heart Association/Heart Rhythm Society; ESC/HFA, European Society of Cardiology/Heart Failure Association.

based on the physicians' discretion. Clinical signs and symptoms are required that are responsive to intravenous decongestive therapy or an augmented decongestive regimen with oral or parenteral medications during hospitalization.

Death should be reported immediately. An independent HF and Death committee blinded to treatment group or clinical characteristics of the patients will review HF and death events. An event will be classified as a HF event (i) if the patient had symptoms and/or signs consistent with congestive HF and (ii) received intravenous diuretic and/or positive inotropic therapy for longer than 2 h or (iii) received an augmented oral or intravenous HF therapy during an in-hospital stay due to worsening of HF. An independent, blinded Arrhythmia Adjudication Committee will review atrial and ventricular arrhythmia episodes.

Safety plan/study termination

A Data Safety Monitoring Board (DSMB) will perform pre-specified scheduled interim safety analysis following the enrolment of 30 and 60% of study population. The statistical design will permit early termination of the trial if CRT efficacy is meaningfully greater than that hypothesized for ICD only, or ICD-only efficacy is meaningfully greater than that hypothesized for CRT. The study will be terminated if the DSMB identifies a significant harm with an implanted CRT-D over an ICD during the interim safety analysis.

Statistical analysis

The main objective of this study is to demonstrate a reduction in the primary composite clinical and echocardiographic endpoint after CRT upgrade (superiority of CRT-D upgrade vs. ICD only). Analyses will be performed (i) on an intention-to-treat basis (without regard to device actually implanted/revised) and (ii) on efficacy basis, censoring follow-up when a patient crosses over to a different device. The primary analyses will be stratified by the percentage of baseline RV pacing as pre-specified in the study.

Sample size and statistical methods

A total of 360 patients will be enrolled and randomized to CRT-D vs. ICD in a 3:2 ratio. The null hypothesis for the primary endpoint is that the hazard rate, which is assumed to be constant across all study intervals, is identical in the two groups (CRT-D v. ICD). The hypothesis will be tested in a study in which subjects are entered and followed up until (i) the primary composite endpoint occurs, (ii) the patient drops out of the study, or (iii) the study ends while the patient is still being followed, in which case the patient is censored. All subjects will be followed up for 12 months.

Power was calculated *a priori* based on a hazard ratio of 0.7 and a primary composite endpoint event rate of 80% in the ICD group over 12 months. The power calculation was based on higher RV pacing rates, while no data is available <40%. Although the risk seems to correlate with RV pacing, the exact correlation is unclear. The attrition (dropout) rate was assumed at 0.01/interval. An instantaneous hazard rate of 0.134 for the ICD group and 0.094 for the CRT-D group was assumed—this equals to a median survival time of 5.17 intervals in the ICD group and 7.38 intervals in the CRT-D group, a cumulative event-free survival at 12 intervals of 0.2 for the ICD group and 0.32 for the CRT-D group. The two-tailed alpha was set at 0.05. A total of 144 patients will be entered into the ICD group and 216 into the CRT-D group to achieve a power of 80.1% to yield a statistically significant result.

Discussion

Several guidelines have been published on optimal patient selection for CRT implantation; however, recommendations on CRT upgrades are still ambiguous without any details for the different causes for chronic RV pacing (*Table 4*). The 2013 European Society of Cardiology (ESC)/European Heart Rhythm Association (EHRA) guidelines recommend CRT upgrade in patients with LVEF < 35%, NYHA III and IVa, and high percentage of ventricular pacing—although the cited evidence stands for *de novo* CRT implantations and crossover trials as opposed to upgrades from existing devices, with level of evidence 'B' and class I indication.[9] The 2012 ACCF/AHA/HRS guidelines are listing CRT upgrade with IIa indication, level of evidence 'C' for patients with LVEF ≤ 35%, and a need for at least 40% ventricular pacing, for both new implants and device replacements.[11] The 2012 ESC/HFA

guidelines,[12] the 2013 Appropriate Use Criteria document, endorsed by the ACCF/HRS/AHA,[13] and the most recent 2015 ESC/EHRA guideline on ventricular arrhythmias and sudden cardiac death do not provide any recommendations on CRT upgrade.[14]

Effects of chronic right ventricular pacing

Large randomized trials have shown that chronic RV pacing is associated with an increased risk of HF, atrial fibrillation, and mortality.[9,15] The Dual-Chamber and VVI Implantable Defibrillator (DAVID) trial demonstrated worse outcomes in patients with reduced LVEF and dual-chamber ICD programming to DDDR 70 bpm when compared with patients with VVI 40 bpm pacing. Every 10% increase in RV pacing increased the risk of death or HF hospitalization by 16%. The most significant separation was observed with 40% RV pacing, strongly predicting death or HF hospitalization (HR = 5.2, $P = 0.008$).[16]

Another multicentre, randomized clinical trial, the Mode Selection Trial, confirmed the correlation of RV pacing and impaired clinical outcome in patients with preserved LVEF and sinus node dysfunction. The risk of HF hospitalization linearly increased with RV pacing up to 40%.[15]

In contrast, Olshansky *et al.* suggested that reducing RV pacing does not necessarily eliminate the risk of an adverse outcome. In the INTRINSIC RV study, patients were categorized into six groups based on increasing RV pacing rates. A significant difference was found between rates concerning patients' age, history of ventricular tachycardia, atrial fibrillation, atrial flutter, and amiodarone therapy. Adjusting for these parameters, the best outcome was seen in patients with RV pacing between 10 and 19% (2.8% event rate over a median follow-up of 11.6 months). Increasing RV pacing has been found predictive of death or HF hospitalization ($P = 0.003$). Other than expected, patients with rare RV pacing (0–9%) experienced worse outcome (8.1% event rate, $P = 0.016$), although a lower RV pacing rate may be advantageous to improve AV dyssynchrony.[17]

Possible benefits and limitations of cardiac resynchronization therapy in patients with heart failure and intermittent pacing

Small crossover trials have compared RV pacing only to CRT in patients with symptomatic bradycardia and reduced LVEF. They showed that CRT reduced mortality, HF hospitalization, and lead to reverse ventricular remodelling.[9,18] For the first time, the Biventricular vs. Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block Trial (BLOCK HF) showed that CRT is superior to RV pacing in patients with AV block, LVEF $\leq$ 50%, and HF class NYHA I–III. After a median follow-up of 37 months, primary endpoints (time to death from any cause, HF visit that required intravenous therapy, or $\geq$15% increase in LVESV index) occurred in 190 of 342 patients (55.6%) in the RV pacing group, compared with 160 of 349 (45.8%) in the CRT group (HR = 0.6–0.9, posterior probability of HR $<1 = 0.9978$). The LV lead-related complications occurred in 6.4% of patients in the CRT-treated group.[9]

The Homburg Biventricular Pacing Evaluation trial compared CRT with RV pacing in patients with bradycardia and LV dysfunction (LV end-diastolic diameter $\geq$60 mm and LVEF $\leq$ 40%). Three months of RV pacing vs. biventricular pacing were studied in 30 patients. Improved echocardiographic parameters, laboratory values, and quality of life scores, as well as improved peak exercise capacity, were found only with biventricular pacing.[9]

The Conventional vs. Multisite Pacing for BradyArrhythmia Therapy (COMBAT) crossover study compared CRT vs. RV pacing in 60 patients with AV block, LVEF $<$ 40%, and HF with NYHA classes II–IV. After a follow-up of 17.5 months, the quality of life, NYHA class, and echocardiographic parameters improved in patients with CRT. Overall mortality was significantly higher in patients with RV pacing alone (86.7% vs. 13.3%, $P = 0.012$).[18] Studies performed in patients with preserved LVEF also demonstrated benefit with CRT, showing increased reverse LV remodelling.[9]

The Long term from the Pacing to Avoid Cardiac Enlargement trial investigated the clinical outcomes of 149 patients with CRT, randomized to 1 year of RV or biventricular pacing after an extended follow-up of 5 years (mean 4.8 $\pm$ 1.5 years). In the RV pacing group, LVEF and LVESV worsened progressively during 1-year, 2-year, and long-term follow-ups, whereas both parameters remained unchanged in the CRT group (LVEF difference, respectively, $P < 0.001$). However, patients with RV pacing needed significantly more HF hospitalization (23.9%) than CRT patients (14.6%).[19] In summary, chronic biventricular pacing seems to be superior to RV-only pacing, but the results cannot be extrapolated to patients with intermittent or chronic pacing who developed worsening of HF only recently.

The RD-CHF study upgraded 56 patients from VVI pacing (NYHA III and IV, and LV dyssynchrony) to CRT at the time of generator replacement. The study had a 3-month crossover design with RV pacing only or CRT. Cardiac resynchronization therapy pacing significantly improved NYHA class, 6MWT, and quality of life.[9]

In the Resynchronization–Defibrillation for Ambulatory Heart Failure Trial (RAFT) study, 644 of 1346 enrolled (48%) patients underwent *de novo* CRT implantation, 80 patients were upgraded to CRT from a previously implanted ICD device, and 60 patients underwent CRT upgrade 6 months after the end of the initial study. The success rate was 95.2% for *de novo*, 96.3% for upgrade, and 90.0% for post-trial CRT upgrade sub-study ($P = 0.402$). The acute complication rate was 26.2% for *de novo*, 18.8% for upgrade, and 3.4% for the sub-study CRT upgrade ($P < 0.001$), most commonly due to LV lead dislodgement. The main reasons for not attempting upgrade in the sub-study group were patient preference (31.9%), NYHA class I (17.0%), and QRS $<$ 150 ms (13.1%). The authors conclude that the success of CRT upgrade is high and that the complication rates are similar to *de novo* CRT implantation.[20] However, in the prospective REPLACE Registry with 1750 patients undergoing device replacement, those who required upgrade experienced a high rate of major complications during a 6-month follow-up time (18% vs. only 4%).

There is still limited information concerning the efficacy and safety of CRT upgrade among patients with LV dysfunction and intermittent RV pacing, particularly in patients with moderate symptoms with lower percentage of RV pacing, or with a narrow QRS ($<$150 ms). Patients who receive CRT-D upgrade may experience additional benefits, but this needs to be proved in a prospective study. Therefore, we have designed the BUDAPEST-CRT Upgrade Study.

Conclusion

The BUDAPEST-CRT Upgrade Study will evaluate the efficacy and safety of CRT-D upgrade when compared with ICD therapy in patients with previously implanted PM or ICD devices, reduced LVEF $\leq$ 35%, symptomatic heart failure (NYHA II–IVa), and intermittent or permanent RV pacing with wide-paced QRS $\geq$ 150 ms. Our study results will provide conclusive data on the effects of CRT-D upgrade procedure in this patient population and confirm the indication of CRT-D upgrade.

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Conflict of interest: none declared.

References

1. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E *et al.* Cardiac resynchronization in chronic heart failure. *New Eng J Med* 2002;**346**:1845–53.
2. 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. *New Eng J Med* 2004;**350**:2140–50.
3. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L *et al.* The effect of cardiac resynchronization on morbidity and mortality in heart failure. *New Eng J Med* 2005;**352**:1539–49.
4. Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP *et al.* Cardiac-resynchronization therapy for the prevention of heart-failure events. *New Eng J Med* 2009;**361**:1329–38.
5. Bogale N, Witte K, Priori S, Cleland J, Auricchio A, Gadler F *et al.* The European Cardiac Resynchronization Therapy Survey: comparison of outcomes between de novo cardiac resynchronization therapy implantations and upgrades. *Eur J Heart Fail* 2011;**13**:974–83.
6. Poole JE, Gleva MJ, Mela T, Chung MK, Uslan DZ, Borge R *et al.* Complication rates associated with pacemaker or implantable cardioverter-defibrillator generator replacements and upgrade procedures: results from the REPLACE registry. *Circulation* 2010;**122**:1553–61.
7. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 2013;**310**:2191–4.
8. Wilkoff BL, Love CJ, Byrd CL, Bongiorni MG, Carrillo RG, Crossley GH 3rd *et al.* Transvenous lead extraction: Heart Rhythm Society expert consensus on facilities, training, indications, and patient management: this document was endorsed by the American Heart Association (AHA). *Heart Rhythm* 2009;**6**:1085–104.
9. 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.
10. Ellenbogen KA, Gold MR, Meyer TE, Fernndez Lozano I, Mittal S, Waggoner AD *et al.* Primary results from the SmartDelay determined AV optimization: a comparison to other AV delay methods used in cardiac resynchronization therapy (SMART-AV) trial: a randomized trial comparing empirical, echocardiography-guided, and algorithmic atrioventricular delay programming in cardiac resynchronization therapy. *Circulation* 2010;**122**:2660–8.
11. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA 3rd, Freedman RA, Gettes LS *et al.* 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2013;**61**:e6–75.
12. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K *et al.* ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2012;**33**:1787–847.
13. Russo AM, Stainback RF, Bailey SR, Epstein AE, Heidenreich PA, Jessup M *et al.* ACCF/HRS/AHA/ASE/HFSA/SCAI/SCCT/SCMR 2013 appropriate use criteria for implantable cardioverter-defibrillators and cardiac resynchronization therapy: a report of the American College of Cardiology Foundation appropriate use criteria task force, Heart Rhythm Society, American Heart Association, American Society of Echocardiography, Heart Failure Society of America, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance. *Heart Rhythm* 2013;**10**:e11–58.
14. Authors/Task Force M, Priori SG, Blomstrom-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J *et al.* 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: the Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC) Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *Europace* 2015;**17**:1601–87.
15. Sweeney MO, Hellkamp AS, Ellenbogen KA, Greenspon AJ, Freedman RA, Lee KL *et al.* Adverse effect of ventricular pacing on heart failure and atrial fibrillation among patients with normal baseline QRS duration in a clinical trial of pacemaker therapy for sinus node dysfunction. *Circulation* 2003;**107**:2932–7.
16. Sharma AD, Rizo-Patron C, Hallstrom AP, O'Neill GP, Rothbart S, Martins JB *et al.* Percent right ventricular pacing predicts outcomes in the DAVID trial. *Heart Rhythm* 2005;**2**:830–4.
17. Olshansky B, Day JD, Lerew DR, Brown S, Stolen KQ, Investigators IRS. Eliminating right ventricular pacing may not be best for patients requiring implantable cardioverter-defibrillators. *Heart Rhythm* 2007;**4**:886–91.
18. Martinelli Filho M, de Siqueira SF, Costa R, Greco OT, Moreira LF, D'Avila A *et al.* Conventional versus biventricular pacing in heart failure and bradyarrhythmia: the COMBAT study. *J Card Fail* 2010;**16**:293–300.
19. Yu CM, Fang F, Luo XX, Zhang Q, Azlan H, Razali O. Long-term follow-up results of the pacing to avoid cardiac enlargement (PACE) trial. *Eur J Heart Fail* 2014;**16**:1016–25.
20. 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.