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ORIGINAL RESEARCH

Upgrading Right Ventricular Pacing to Cardiac Resynchronization in HFrEF Patients Improves Symptoms and Functional Outcomes

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ABSTRACT

BACKGROUND In the BUDAPEST (Biventricular Upgrade on left ventricular reverse remodeling and clinical outcomes in patients with left ventricular Dysfunction and intermittent or permanent APical/SepTal right ventricular pacing)-CRT Upgrade randomized trial, the authors have demonstrated improved mortality and morbidity after cardiac resynchronization therapy (CRT) upgrade in patients with heart failure with reduced ejection fraction (HFrEF) with high right ventricular (RV) pacing burden.

OBJECTIVES This substudy sought to examine the impact of CRT upgrade on symptoms, functional outcome, and exercise capacity.

METHODS In the BUDAPEST-CRT Upgrade trial, 360 HFrEF patients with pacemaker or implantable cardioverter-defibrillator (ICD) and ≥20% RV pacing burden were randomly assigned (3:2) to cardiac resynchronization therapy with defibrillator (CRT-D) upgrade (n = 215) or ICD (n = 145). The prespecified tertiary endpoints were changes in quality of life (QoL) (EQ-5D-3L), NYHA functional class, 6-minute walk test, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels.

RESULTS Up to 12 months, NYHA functional class improved in the CRT-D upgrade arm compared with ICD only (adjusted OR: 0.50 [95% CI: 0.32-0.80]; $P = 0.003$). A remarkable decrease was observed in NT-proBNP levels in the CRT-D arm (adjusted difference −1,257 pg/mL [95% CI: −2,287 to −228]; $P = 0.017$). The progression of age-related worsening of QoL was moderated by CRT-D upgrade (EQ-5D-3L difference by each year: 0.015 [95% CI: 0.005-0.025]; P interaction = 0.003). However, exercise tolerance (6-minute walk test) remained unchanged in both groups.

CONCLUSIONS HFrEF patients with pacemaker/ICD and ≥20% RV pacing burden receiving CRT upgrade showed a substantial improvement in NYHA functional class and decrease in natriuretic peptide levels, as compared with ICD alone. Moreover, CRT-D upgrade could moderate the progression of worsening of QoL attributed to ageing in this vulnerable, elderly patient population. (Biventricular Upgrade on left ventricular reverse remodeling and clinical outcomes in patients with left ventricular Dysfunction and intermittent or permanent APical/SepTal right ventricular pacing [BUDAPEST]-CRT Upgrade trial) (JACC Heart Fail. 2024;■:■-■) © 2024 Published by Elsevier on behalf of the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

6MWT = 6-minute walk test

BMI = body mass index

CRT = cardiac resynchronization therapy

CRT-D = cardiac resynchronization therapy with defibrillator

HF = heart failure

HFrEF = heart failure with reduced ejection fraction

ICD = implantable cardioverter-defibrillator

LVEF = left ventricular ejection fraction

NT-proBNP = N-terminal pro-B-type natriuretic peptide

QoL = quality of life

RV = right ventricular

Heart failure (HF) patients have poor prognosis and experience high burden of life-restricting symptoms and poor quality of life (QoL).[1,2] Assessment and improvement of clinical status, functional capacity, and exercise tolerance in patients with HF is essential as it has been associated with morbidity and mortality.[3,4]

In a well-selected HF patient population, cardiac resynchronization therapy (CRT) reduces left ventricular mechanical dyssynchrony and leads to reverse remodeling.[5] By improving the cardiac function in mild and severe HF patients, de novo CRT implantation effectively reduces HF symptoms, improves QoL and exercise capacity.[5] Notably, the efficacy of CRT upgrade in patients with conventional pacemaker or implantable cardioverter-defibrillator (ICD) with pacing need has not been established yet.

The BUDAPEST (Biventricular Upgrade on left ventricular reverse remodeling and clinical outcomes in patients with left ventricular Dysfunction and intermittent or permanent APical/SepTal right ventricular pacing)-CRT Upgrade trial was the first, which investigated the efficacy of CRT upgrade in patients with intermittent or permanent right ventricular (RV) pacing and heart failure with reduced left ventricular ejection fraction (HFrEF), and despite the advanced-stage HF cohort, the trial provided robust data favoring cardiac resynchronization therapy with defibrillator (CRT-D) as compared with ICD alone on the combined risk of all-cause mortality, HF hospitalization, or absence of reverse remodeling.[6]

Whether the substantial treatment effect of the CRT upgrade could be also detected in symptoms, QoL, and exercise testing is uncertain. Accordingly, we aimed to examine the changes of NYHA functional class, EQ-5D-3L, 6-minute walk test (6MWT), and natriuretic peptide levels in the BUDAPEST-CRT Upgrade patient cohort.

METHODS

STUDY POPULATION. The BUDAPEST-CRT Upgrade trial was an investigator-initiated prospective, multicenter, randomized, controlled trial. The design, protocol, and the primary results of the BUDAPEST-CRT Upgrade trial have been previously published.[6-8] Altogether 360 patients were enrolled and randomly assigned to CRT-D upgrade (n = 215) or ICD (n = 145) in a 3:2 ratio, in 17 sites from Europe and Israel. Patients had been already implanted a pacemaker or ICD for at least 6 months before enrollment, reduced left ventricular ejection fraction (LVEF) (≤35%), HF symptoms (NYHA functional class II-IVa), wide paced QRS complex interval (>150 ms), and ≥20% of RV pacing burden and treated with guideline-directed medical therapy without having a native intrinsic left bundle branch block (**Central Illustration**). The study protocol was approved by local and institutional ethics committees.

DATA AND FOLLOW-UP. Enrolled patients were followed up for 12 months after randomization. In-office follow-up visits were done at 1, 6, and 12 months when clinical parameters, electrocardiogram and device interrogation results, echocardiographic, and biochemical parameters were collected. Additionally, the 6MWT and EQ-5D-3L QoL questionnaires were also mandatory at baseline and at the 12-month follow-up visit.

Echocardiographic data were submitted to the Echocardiography Core Laboratory for central assessment (Semmelweis University, Heart and Vascular Center, Budapest, Hungary). Left ventricular volumes and ejection fraction were calculated using the biplane Simpson method, at the baseline visit (after randomization and before implantation) and at the 12-month follow-up visit.

ENDPOINTS. The prespecified tertiary endpoints were changes in QoL, NYHA functional class, 6MWT, and natriuretic peptide levels. Change in NYHA functional class was assessed by the proportion of

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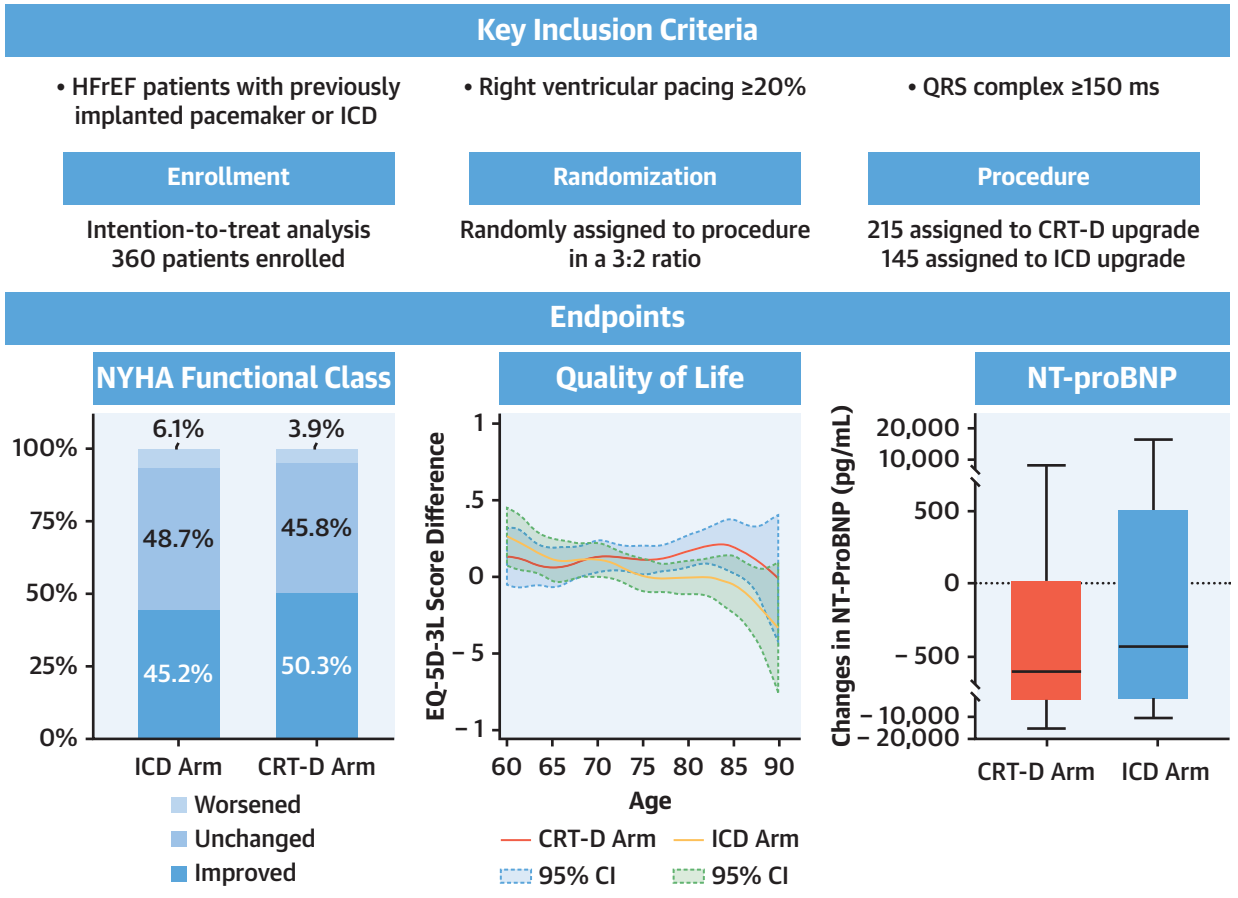
CENTRAL ILLUSTRATION **Tertiary Results of the Budapest-CRT Upgrade Trial**



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CRT = cardiac resynchronization therapy; CRT-D = cardiac resynchronization therapy with defibrillator; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; RV = right ventricular.

patients who improved or worsened 1 or 2 classes from baseline to 12 months or remained unchanged providing a 5-scale assessment due to patient death. Responder status was defined as >15% change of left ventricular end-systolic volume at 12 months.

STATISTICAL ANALYSIS. Continuous variables with normal distributions are expressed as mean ± SD, whereas those with non-normal distributions as median (25th-75th percentile). Categorical variables are summarized with frequencies and percentages.

Changes in N-terminal pro-B-type natriuretic peptide (NT-proBNP), 6MWT, and EQ-5D-3L score were analyzed by linear regression as adjusted and unadjusted differences between the treatment arms with associated 95% CIs. Assumptions of normality and homoscedasticity were checked graphically using histograms and residual plots. Change in NYHA functional class was studied with ordinal logistic regression and expressed as adjusted and unadjusted ORs with associated 95% CIs. When evaluations of

TABLE 1 Characteristics of the Participants According to Randomization Arm

	CRT-D (n = 215)	ICD (n = 145)
Changes in NYHA functional class from baseline to 12 mo		
Unchanged	83/181 (45.8)	56/115 (48.7)
Improved	91/181 (50.3)	52/115 (45.2)
Worsened	7/181 (3.9)	7/115 (6.1)
NT-proBNP		
Baseline, pg/mL (n = 282)	2,279 (1,223-4,234)	2,122 (1,336-4,476)
12-mo, pg/mL (n = 199)	1,097 (637-2,359)	1,533 (634-2,754)
EQ-5D-3L score		
Baseline (n = 360)	0.685 ± 0.283	0.656 ± 0.293
12-mo (n = 306)	0.837 ± 0.232	0.863 ± 0.209
6MWT		
Baseline, m (n = 309)	269.7 ± 116.1	285.4 ± 116.6
12-mo, m (n = 249)	312.1 ± 149.9	287.8 ± 170.3

Values are n/N (%), median (25th-75th percentile), or mean ± SD.

6MWT = 6-minute walk test; CRT-D = cardiac resynchronization therapy with defibrillator; ICD = implantable cardioverter-defibrillator; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

trial patients were unavailable due to death, to get unbiased estimates of the treatment effect, imputed values were used as 0 m (6MWT) or 0 score (EQ-5D-3L) or a fifth grade (NYHA functional class) as it was outlined in the statistical analysis plan. Imputed values were used for 28 of 360 patients (8%), 16 of 145 (11%) in the ICD only, and 12 of 215 (6%) in the CRT-D upgrade arms. Additionally, a sensitivity analysis was carried out with only those patients who were alive and had available data at the end of the follow-up (Supplemental Table 1). The interaction between age and treatment on QoL and exercise capacity was analyzed by linear regression models with interaction terms, the results were graphically presented by smooth lines using restricted cubic splines. The analyses were based on intention-to-treat principle.

The prespecified subgroups were defined by age, body mass index (BMI), renal function, LVEF at enrollment, atrial arrhythmias at enrollment, history of diabetes, history of any ischemic event, NT-proBNP at enrollment, NYHA functional class, and the percent of RV pacing at enrollment.

The prespecified adjustment factors were age, sex, country, ischemic etiology, diabetes mellitus, secondary prevention ICD, atrial fibrillation, and baseline NYHA functional class. For the changes in NT-proBNP levels, BMI was also included as an adjustment factor. Statistical analyses were performed by using Stata version 18.0 (StataCorp).

Values of $P < 0.05$ were considered statistically significant.

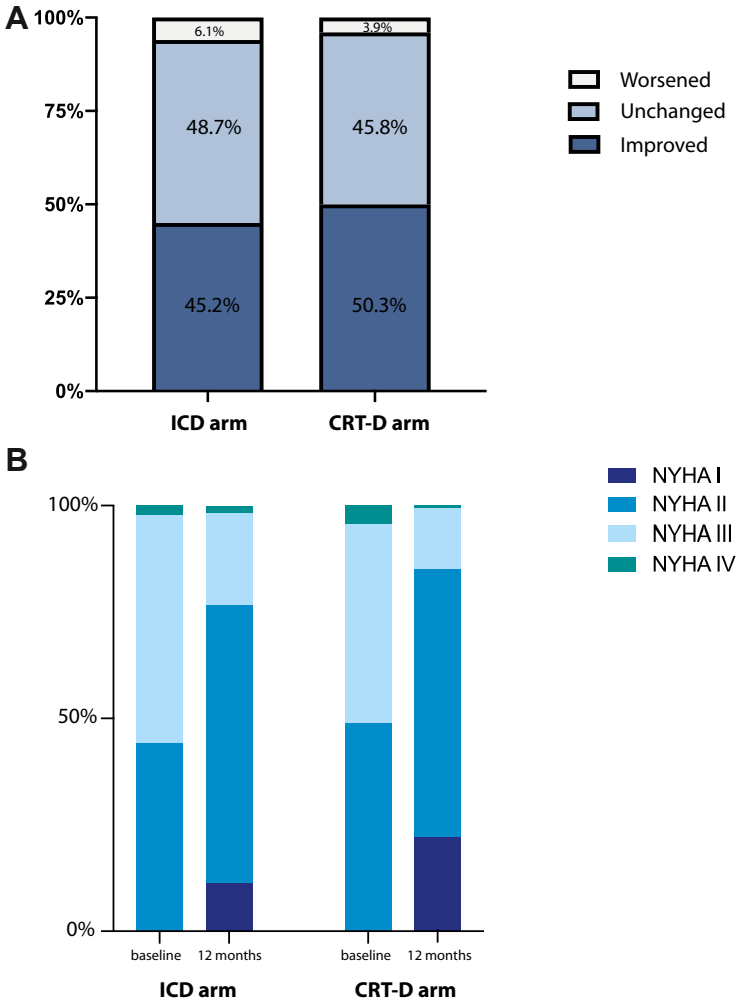
RESULTS

BASELINE CLINICAL CHARACTERISTICS. The baseline clinical characteristics were reported previously.[8] Briefly, the mean age of the total cohort was 72.8 ± 7.7 years, and male sex was predominant (88.9%). Also, patients presented with severely reduced LVEF, with a mean of 24.8 ± 6.6%. At enrollment, more than one-half of the patients were moderately or severely symptomatic, NYHA functional class III-IVa, with 110 patients (51%) in the CRT-D and 81 (56%) in the ICD arm, respectively. 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 approximately 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, which became available in the participating countries only during the course of the trial.

FUNCTIONAL RESPONSE, QoL. Over a median follow-up of 12.4 months, NYHA functional class improved in 50.3% of the patients in the CRT-D upgrade arm and in 45.2% of the patients in the ICD arm, remained unchanged in 45.8% and 48.7%, and worsened in 3.9% and 6.1%, respectively (**Table 1**, **Figure 1**). At the 12-month follow-up, there was 50% higher odds to have at least 1 class improvement of NYHA functional class in the CRT-D upgrade arm as compared with the ICD-only group (adjusted OR: 0.50 [95% CI: 0.32-0.80]; $P = 0.003$) (**Table 2**). When these changes were assessed by echocardiographic response, responder patients show a higher rate of improvement or unchanged status compared with nonresponders (responders 98% vs nonresponders 92%) for 12 months (Supplemental Figure 1).

At baseline, patients had poor exercise tolerance, their 6MWT was low:[8] 285.4 ± 116.6 m in the ICD group and 269.7 ± 116.1 m the CRT-D upgrade group (**Table 1**). The changes in the 6MWT were similar in the 2 groups (adjusted difference 10.0 m [95% CI: −23.3 to 43.3]; $P = 0.553$) (**Table 2**). These changes were also evaluated based on responder status in both arms. In responder patients, the mean difference was 61.7 ± 92.9 m, in nonresponders 40.9 ± 112.7 m. The changes were comparable in the 2 patient groups (unadjusted difference 20.8 m [95% CI: −8.7 to 50.2]; $P = 0.165$ and adjusted difference 22.0 m [95% CI: −10.5 to 54.6]; $P = 0.128$). We could not detect a significant difference in the 6MWT in responders on the CRT-D arm (unadjusted difference 14.33 m [95% CI: −26.7 to 55.4]; $P = 0.491$ and

FIGURE 1 Changes and Proportional Changes of NYHA Functional Class by Treatment Arms



(A) Proportional changes of NYHA functional class by treatment arms during 12 months: Bar chart comparing the changes of NYHA functional class in the cardiac resynchronization therapy with defibrillator (CRT-D) upgrade and implantable cardioverter-defibrillator (ICD) upgrade alone arms, showing a favorable outcome on symptoms in the CRT-D upgrade arm. (B) Changes of NYHA functional class by treatment arms during 12 months: Bar chart comparing the changes of NYHA functional class in the CRT-D upgrade and ICD upgrade alone arms.

adjusted difference 23.9 m [95% CI: −17.6 to 65.4]; P = 0.256).

Subgroup analysis showed that the only patient subgroup gaining benefit regarding exercise capacity were patients >75 years of age (unadjusted difference 51.8 m [95% CI: 6.3-98.3]; P = 0.026; interaction P = 0.057) (Supplemental Figures 2 to 4). In patients >75 years of age, the modelled 6MWT distance decreased in the ICD arm (mean difference −1.9 ± 97.3 m) and increased in the CRT-D upgrade arm (mean difference 49.9 ± 112.0 m) (Supplemental Figure 4).

The baseline mean EQ-5D-3L score was 0.685 ± 0.283 in the CRT-D upgrade and 0.656 ± 0.293 in the ICD-only group. At 1 year, the mean EQ-5D-3L score was 0.837 ± 0.232 in the CRT-D upgrade group and 0.863 ± 0.209 in the ICD-only group (Table 1). Changes in QoL did not differ significantly in the 2 treatment arms (adjusted mean difference at 12 months, EQ-5D-3L score 0.03 [95% CI: −0.05 to 0.11]; P = 0.417), or in responders vs nonresponders (adjusted mean difference at 12 months, EQ-5D-3L score 0.01 [95% CI: −0.06 to 0.08]; P = 0.76) (Table 2). Improvement in QoL seemed to be higher in older patients (>75 years of age) (unadjusted EQ-5D-3L score difference: 0.17 [95% CI: 0.05-0.29]; P = 0.006) and patients with a BMI <30 kg/m^2 (unadjusted EQ-5D-3L score

TABLE 2 Outcomes by Randomization Arm, Parameter Changes From Baseline to 12 Months

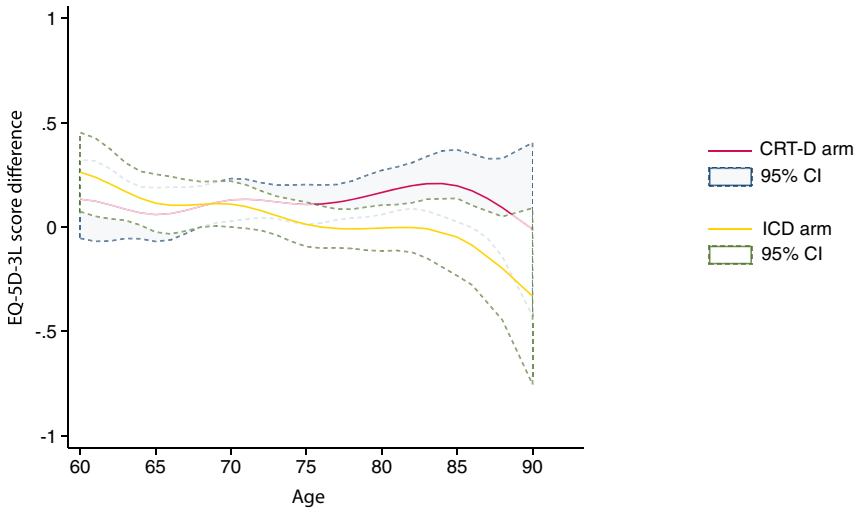
Endpoints	Unadjusted OR or Difference (95% CI)	*P* Value	Adjusted OR or Difference (95% CI)	*P* Value
Changes in NYHA functional class (n = 296)	OR: 0.50 (0.32 to 0.78)	0.002	OR: 0.50 (0.32 to 0.80)	0.003
Changes in NT-proBNP, pg/mL (n = 176)	−950 (−2,000 to 99)	0.076	−1,257 (−2,287 to −228)	0.017
Changes in EQ-5D-3L, score (n = 306)	0.06 (−0.02 to 0.14)	0.15	0.03 (−0.05 to 0.11)	0.42
Changes in 6-MWT, m (n = 219)	13.0 (−19.7 to 45.8)	0.43	10.0 (−23.3 to 43.3)	0.55

Abbreviations as in Table 1.

difference: 0.11 [95% CI: 0.02-0.21]; $P = 0.014$) (Supplemental Figure 5). In patients >75 years of age, the EQ-5D-3L score decreased in the ICD arm (modelled mean EQ-5D-3L score difference −0.11 ± 0.31), whereas it improved in the CRT-D arm (modelled mean EQ-5D-3L score difference 0.16 ± 0.34) (Supplemental Figure 6). An age-dependent treatment effect difference was observed in the QoL favoring CRT-D treatment. The yearly change of EQ-5D-3L was higher by 0.015 (95% CI: 0.005-0.025; $P = 0.003$) on average in this patient group (Figure 2).

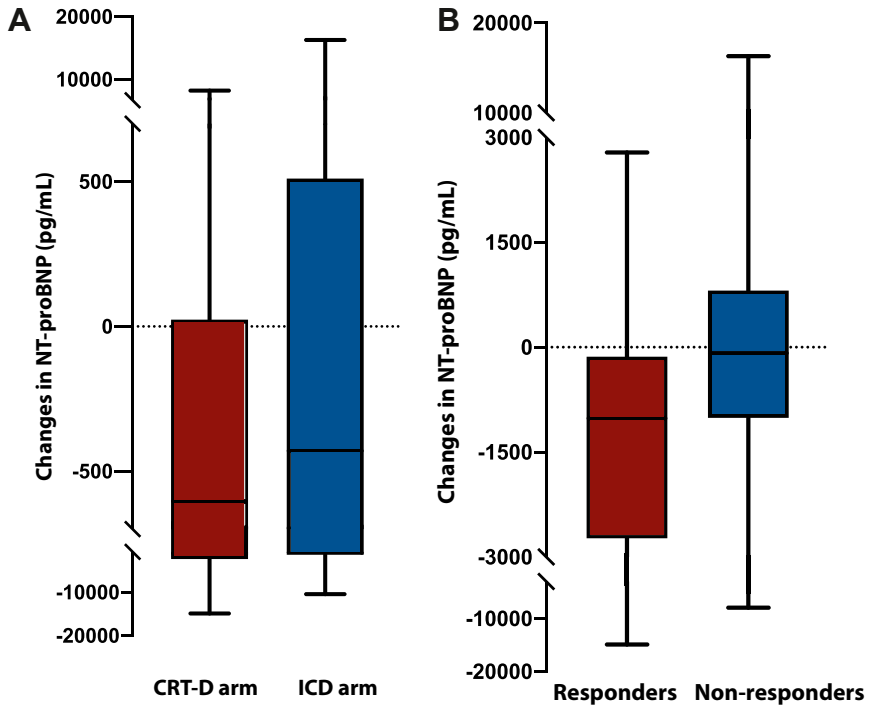
NATRIURETIC PEPTIDE LEVEL CHANGES. The median NT-proBNP was 2,231 pg/mL (25th-75th percentile: 1,254-4,309 pg/mL) at enrollment, 2,279 pg/mL (25th-75th percentile: 1,223-4,234 pg/mL) in the CRT-D arm and 2,122 pg/mL (25th-75th percentile: 1,336-4,476 pg/mL) in the ICD arm. At 1 year, the median NT-proBNP levels were 1,097 pg/mL (25th-75th percentile: 636-2,359 pg/mL) and 1,533 pg/mL (25th-75th percentile: 634-2,754 pg/mL) in the CRT-D and ICD arms, respectively (Table 1). According to the unadjusted model, there was a borderline association between the treatment arm and NT-proBNP levels (950 pg/mL [95% CI: −2,000 to 99 pg/mL]; $P = 0.076$) and a statistically significant association according to the adjusted model (adjusted difference −1,641 pg/mL [95% CI: −2,347 to −335 pg/mL]; $P = 0.009$) (Table 2, Figure 3A). In responders, the changes in NT-proBNP levels were significantly greater than in nonresponders (unadjusted difference −2,255 pg/mL [95% CI: 3,258 to −1,252 pg/mL]; $P < 0.001$ and adjusted difference −1,479 pg/mL [95% CI: −2,650 to −308 pg/mL]; $P = 0.014$) (Figure 3B).

FIGURE 2 Change in Quality of Life Score by Age and Treatment Arm



Change in quality of life score (EQ-5D-3L) by age and treatment arm: EQ-5D-3L score difference by age according to treatment arms analyzed by linear regression models with interaction terms, graphically presented by restricted cubic splines. Abbreviations as in Figure 1.

FIGURE 3 Changes of NT-proBNP From Baseline to 12 Months by Treatment Arms and Responder Status



(A) Changes of NT-proBNP from baseline to 12 months by treatment arms: box and whiskers plots of the changes of natriuretic peptide levels by treatments arms. (B) Changes of NT-proBNP from baseline to 12 months by responder status: box and whiskers plots of the changes of natriuretic peptide levels by responder status.

DISCUSSION

The BUDAPEST-CRT Upgrade trial enrolled HFrEF patients with high burden of chronic RV pacing. In the present paper, we report the results of the tertiary endpoints. Despite the advanced-stage HF patient cohort, patients clearly experienced a significant improvement in NYHA functional class, in age-related deterioration of QoL, and a decrease of natriuretic peptide levels after CRT-D upgrade as compared with ICD alone.

De novo CRT implantation's treatment effect on functional response, relief of HF symptoms, and change in NT-proBNP is well-established.[9-12] However, data from patients undergoing CRT upgrade procedures are available only from meta-analyses and observational studies.[13-15] To our best knowledge, this is the first, randomized, controlled trial that describes an improvement in HF symptoms, natriuretic peptide levels, and QoL with CRT upgrade compared with ICD alone.

The beneficial functional response after CRT upgrade is observed mainly in patients with positive echocardiographic response. Such structural changes are usually paralleled by improved HF symptoms, translating into up 1 grade NYHA functional class improvement.[16] In our advanced-stage HF cohort, more than one-half of the patients improved by at least 1 NYHA functional class during the 12 months, which was also associated with an echocardiographic positive response.

Improvement of natriuretic peptide levels after CRT upgrade was uncertain. In a meta-analysis with a limited number (n = 85) of patients, no improvement could be observed after the procedure.[16] In the BUDAPEST-CRT Upgrade cohort, from a relatively high median value of NT-proBNP, it decreased to approximately 1,000 pg/mL, which was proved to be an important cutoff value in predicting a better response in HFrEF patients.[21] The positive change correlated with a better echocardiographic response: in CRT responders a 1.5 times greater NT-proBNP decrease could be observed in 12 months as compared with nonresponders.

These beneficial changes after a device implantation may turn into an improved QoL; however, this

endpoint was incomprehensively detected in de novo CRT trials. The differences in outcome and the perception of QoL are partly associated with the different sensitivity of the tests, as well as the characteristics of the patient cohorts. Most frequently it is measured by the MLHFQ (Minnesota Living with Heart Failure Questionnaire) or the KCCQ (Kansas City Cardiomyopathy Questionnaire) or EQ-5D. Even though the EQ-5D-3L is not specified for HF patients like the MLHFQ, it enables a simple, rapid, and general assessment of QoL and has been implemented in HF patients eligible for CRT.[17,18] As previously stated,[8] the patient cohort in the BUDAPEST-CRT Upgrade trial was older than patients enrolled in prior CRT studies,[19,20] and patients were burdened with comorbidities,[8] but they still showed a better outcome and improved QoL after CRT-D upgrade during 12 months as compared with ICD alone.

Severe comorbidity profile including reduced mobility of our patient cohort may have resulted in lower baseline 6MWT values compared with prior de novo CRT trials,[8,19,20] and despite the beneficial treatment effect in the clinical outcome, we did not observe a significant difference between the 2 treatment arms at 12 months.

STUDY LIMITATIONS. First, when data were missing at baseline or at 12 months' follow-up, values were imputed for those who have died, otherwise changes could not be evaluated. Second, the specific inclusion and exclusion criteria may limit the generalizability of our findings as in all randomized trials. Third, these analyses were performed on the basis of intention-to-treat principles, which may result in better outcome in the ICD arm.

CONCLUSIONS

Patients with HF and reduced LVEF with high RV pacing burden showed a clear improvement in NYHA functional class, reduction of natriuretic peptide levels, and a reduced age-related deterioration of QoL during the 12-month follow-up after CRT-D upgrade compared to ICD alone.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: These data provide further understanding of the clinical benefit of CRT upgrade procedures in the HFrEF patient population.

TRANSLATIONAL OUTLOOK IMPLICATIONS: These findings support the need of performing CRT upgrade procedure as soon as possible in HFrEF patients. Further randomized controlled trials are to be conducted in heart failure patients with mildly reduced ejection fraction with resynchronization therapy.

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APPENDIX For supplemental figures and tables, please see the online version of this paper.