Baseline clinical characteristics of heart failure patients with reduced ejection fraction enrolled in the BUDAPEST-CRT Upgrade trial

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Abstract

Aims The BUDAPEST-CRT Upgrade study is the first prospective, randomized, multicentre clinical trial investigating the outcomes after cardiac resynchronization therapy (CRT) upgrade in heart failure (HF) patients with intermittent or permanent right ventricular pacing (RVP) with wide paced QRS. This report describes the baseline clinical characteristics of the enrolled patients and compares them to cohorts from previous milestone CRT studies.

Methods and Results This international multicentre randomized controlled trial investigates 360 patients having a pacemaker (PM) or implantable cardioverter defibrillator (ICD) device for at least six months prior to enrollment, reduced left ventricular ejection fraction (LVEF≤35%), HF symptoms (New York Heart Association functional class II-IVa), wide paced QRS (>150 ms), and ≥20% of RVP burden without having a native left bundle branch block.

At enrollment, the mean age of the patients was 73±8 years; 89% were male, 97% of the patients were in NYHA II/III functional class, and 56% had atrial fibrillation. Enrolled patients predominantly had conventional PM devices, with a mean RVP burden of 86%. Thus, this is a patient cohort with advanced HF, low baseline LVEF (25%±7%), high N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels [2231 pg/mL (25th – 75th percentile 1254/4309 pg/mL)], and frequent HF hospitalizations during the preceding 12 months (50%).

Conclusion When compared with prior CRT trial cohorts, the BUDAPEST-CRT Upgrade study includes older patients with a strong male predominance and a high burden of atrial fibrillation and other comorbidities. Moreover, this cohort represents an advanced HF population with low LVEFs, high NT-proBNPs, and frequent previous HF events.

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Introduction

Cardiac resynchronization therapy (CRT) has been proven to reduce morbidity and mortality in patients with chronic heart failure (HF), low left ventricular (LV) ejection fraction (EF) and a wide QRS complex.[1-3] Despite having clear and detailed guidelines for patients with de novo implantations, data are limited for those already implanted with a conventional pacemaker (PM) or implantable cardioverter-defibrillator (ICD).[4-7] At the same time, the proportion of PM/ICD patients who develop HF and LV dysfunction constitute around 30% of all implantations,[8] and it is still increasing with time and by right ventricular (RV) pacing rate, showing a relatively high incidence of HF hospitalization and adverse clinical outcome. [9, 10]

Since chronic RV pacing induces intraventricular dyssynchrony with similar effects as native left bundle branch block (LBBB), such patients might also benefit from a CRT upgrade.[9-11]

As there were no prior prospective, randomized, controlled trials (RCTs) primarily aimed to investigate CRT upgrade vs. no upgrade, long-term survival, and clinical response were described by comparing CRT upgrade and de novo CRT patients showing no difference in outcomes in a recent meta-analysis.[12] Nevertheless, subgroup analysis from previous RCTs as RAFT trial showed no difference in the primary outcome (all-cause mortality and heart failure hospitalization) between CRT-D vs. ICD groups.[11] Moreover, the RAFT Upgrade substudy also highlighted the main concerns of physicians about the procedures and the lack of clear evidences.[13] Data about CRT upgrade patients might be influenced by a selection bias, and therefore, recommendations are less conclusive than for the de novo CRT candidates.[12] The current ESC Pacing and CRT guidelines refer to CRT upgrade as class IIa, level of evidence B, for patients with HF, LVEF≤ 35% despite optimal medical treatment

and a significant percentage of right ventricular pacing, without declaring an exact pacing burden.[4]

Thus, it is essential to define the proper patient population to benefit from CRT upgrades. The BUDAPEST-CRT Upgrade study is, to the best of our knowledge, the first multicentre, randomized, controlled trial designed to assess the effects of CRT upgrade on left ventricular reverse remodelling and clinical outcomes. We have previously published the rationale and the design of the trial.[14] The current report describes the baseline clinical characteristics of patients enrolled in the BUDAPEST-CRT Upgrade trial and compares them with cohorts of previous milestone studies.

Methods

Study design

The BUDAPEST-CRT Upgrade study is a prospective, multicentre, randomized controlled trial including 360 patients from 17 centers (Figure 1). Those patients who had symptomatic heart failure with reduced ejection fraction and PM or ICD at least six months prior to enrollment with >20% RV pacing rate were randomized in a 3:2 ratio to CRT-D or ICD stratified by site.[14]

Data management was conducted by the Sheba Medical Centre, Israel, and all data were registered in the electronic case report forms (eCRF) system. Echocardiographic images, pacemaker interrogation files, and ECGs were uploaded to the Biobankok core laboratory, Semmelweis University, Budapest.

The trial is registered on ClinicalTrials.gov (NCT02270840). The design of the study has been published.[14] Here, in this report, we briefly summarize the baseline clinical characteristics of the enrolled patients.

Study patients

Patients with low LVEF (<35%), HF symptoms [New York Heart Association class (NYHA) II-IVa], a wide paced QRS (>150 ms) and ≥20% right ventricular pacing without having intrinsic LBBB, right ventricular dilatation (RV diameter >50 mm), severe valve impairment or severe renal impairment (>200 μmol/l) could be enrolled.

Echocardiography was mandatory for the assessment of LVEF, chamber dimensions, and valves at baseline and at the 12-month follow-up. In the laboratory measurements, the measurement of serum creatinine level was mandatory, whereas the measurement of NT-proBNP was recommended only at baseline and follow-ups. In addition, ECG, pacemaker

interrogation, six-minute walk test distance (6MWT), and EQ-5D quality of life questionnaires were also mandatory at baseline and the 12-month follow-up.

Device implantation and programming were described in detail previously [14] and in the Supplementary material.

Study endpoints

The primary end-point is the composite of clinical and echocardiographic parameters, including the first occurrence of an HF event, all-cause mortality, or less than 15% reduction in left ventricular end-systolic volume (LVESV) assessed by echocardiography from baseline to 12 months (Figure 1). Further endpoints were described previously. [14]

Comparison of BUDAPEST-CRT Upgrade trial subgroup characteristics and those of other clinical trial participants

The baseline clinical characteristics of patients randomized to CRT-D or ICD in the BUDAPEST-CRT Upgrade trial were compared. As there have been no randomized trials with patients having a CRT-D upgrade, patient cohorts of milestone trials comparing CRT-D patients with ICD patients, such as the Multicenter Automatic Defibrillator Implantation with Cardiac Resynchronization Therapy (MADIT-CRT), Resynchronization/Defibrillation for Ambulatory Heart Failure Trial (RAFT), and The Danish Study to Assess the Efficacy of ICDs in Patients with Nonischemic Systolic Heart Failure on Mortality (DANISH) trials and a trial that investigated patients with high degree AV block and LVEF ≤50% receiving CRT-D or ICD implantations, the Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block (BLOCK-HF) trial were compared with the

BUDAPEST-CRT Upgrade study population.[2, 11, 15, 16] Data of patients from large-scale registries, such as the European Society of Cardiology (ESC) CRT Survey II and its subgroup with CRT Upgrade patients, were also collected for comparison with the BUDAPEST-CRT Upgrade trial cohort.[8, 17]

Sample size calculation and statistical analysis

A total of 360 patients were 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 is 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, (iii) or the study ends while the patient is still being followed, in which case the patient is censored. All subjects were/are 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 attrition (drop out) 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.[14]

Descriptive statistics

Continuous variables with normal distributions are expressed as mean±SD, while those with non-normal distributions as medians with interquartile range (25th – 75th percentile).

Categorical variables are summarized with frequencies and percentages (n, %). Baseline clinical characteristics were compared between the CRT and ICD groups using an unpaired t-test for normally distributed continuous variables, the Mann–Whitney for non-normally distributed variables, while χ^2 – a test was used for dichotomous variables as appropriate. Comparing more subgroups by years (Supplementary Table 3a and 3b) were analysed by ANOVA.

Results

Enrollment of the study population

Patients were screened for enrollment between November 2014 and August 2021. Overall, 360 patients met the inclusion criteria (Supplementary Table 1) and were randomized at 17 sites from 6 countries (Supplementary Table 2). The top enrollers (7 sites with more than 10 patients) included 89% of the total cohort (Supplementary Table 2). The average inclusion rate was around 53 patients per year (Figure 2); throughout the inclusion period, there have been no relevant and systematic changes in the baseline clinical characteristics of the enrolled patient populations (Supplementary Table 3a and Table 3b), neither by years nor by the randomization result (CRT-D vs. ICD groups).

Baseline characteristics of participants

Among the participants enrolled in the study, the mean age was 72.8±7.7 years, and 88.9% were male (Table 1). Concomitant comorbidities were found in a high proportion of patients; 56.4% had a history of atrial fibrillation, 46.4% had a prior myocardial infarction, the majority of the patients had hypertension (80.3%), 45.8% had high cholesterol levels, and 35.6% had diabetes (Figure 3). The mean LVEF was severely reduced (24.8 ± 6.6%), predominantly due to ischemic heart failure (58.1%). The mean body mass index (BMI) was

28.7 ± 4.9, and 29.4% of the included patients were considered obese (assessed by the physicians). Valvular heart disease was present in 17.5%, with prior valvular surgery in 10.6%. Cerebrovascular event or transient ischemic attack was documented in 15.6%, peripheral vascular disease in 9.4%, and other chronic diseases in 53.3%. Altogether, 6.9% of the participants were currently smoking, 13.3% had chronic obstructive pulmonary disease (COPD), and 3.1% had bronchial asthma at the time of enrollment. Regarding major tachyarrhythmias, 32% of the patients had previous ventricular tachycardia or ventricular fibrillation, and almost half (49.4%) of the patients enrolled in the study had HF hospitalization within 12 months before randomization. Over two-thirds of the patients (67.8%) had a pacemaker, 31.7% had an ICD, and 0.6% had CRT with an unplugged LV lead before the index procedure.

Previously implanted pacemaker types were most frequently DDD pacemakers (64.8%), VVI (26.2%), and less frequently VDD (9%). Those previously implanted with an ICD device had DDD-ICD (47.4%) or VVI-ICD (47.4%) in the same proportion and VDD-ICD in some cases (5.3%). The right ventricular lead was typically positioned to the apical (48.2%) or septal part (44.9%). The device interrogation for RV pacing showed a very high pacing rate of 86.5 ± 20.2%. The proportion of patients by the severity of the symptoms was comparable; mild-moderate symptoms (NYHA functional class II) were found in 46.9% of patients, and severe symptoms (NYHA functional class III/IV) were found in 49.7% and 3.3% of patients, respectively. The mean creatinine was 112.7 ± 32.7 μmol/L, the median NT-proBNP was 2231 (1254-4309) pg/mL, and the six-minute walk test distance (6MWT) was 276.0 ± 116.4 m, whereas the calculated score of the EQ-5D quality of life questionnaire was 0.668 ± 0.289. Patients were well treated with guideline-recommended HF therapies at baseline, and 73.6% received an angiotensin-converting enzyme inhibitor (ACE-I), 18.3% received an angiotensin receptor blocker (ARB), 91.1% beta-blocker, and 62.5% received a mineralocorticoid

receptor antagonist (MRA). Only 5% of patients were taking an angiotensin receptor neprilysin inhibitor (ARNI) at enrollment, at the same time, the rate of ARNI administration at enrollment was significantly increased in the last years (Supplementary Table 3b). Approximately two-thirds of the participants received triple HF therapy (ACE-I/ARB + beta-blocker + MRA).

Baseline characteristics by sex

Since one of the most relevant differences in the baseline clinical characteristics was the low proportion of women, we have also analysed these parameters by sex (Supplementary Table 4). Beside the antropometric differences as height and weight disparities [height in women 161.4 ± 6.9 cm vs. men 174.7 ± 7.5 cm; p<0.0001, weight in women 72 kg (65.5-84.8) vs. men 85 kg (75.3-98); p<0.0001], there was a lower prevalence of ischemic events in the medical history [women 19 (47.5%) vs. men 190 (59.4%); p<0.0001] led by the rate of CABG [women 4 (10%) vs. men 82 (25.6%); p=0.03]. At the same time, women had shorter distance of 6MWT [women 224.5 m (141-300) vs. men 300 m (200-360); p=0.026], lower mean of serum creatinine level [women 87 μmol/L (67.3-135.8) vs. men 106 μmol/L (89-129); p=0.002] and smaller left ventricular dimensions [EDV in women 189 mL (154.2-229.4) vs. men 219.5 mL (180.2-277.9); p=0.01, ESV in women 140.8 mL (114.2-170.8) vs. men 164.6 mL (130.2-216.4); p=0.045].

Comparison of baseline demographics and clinical characteristics to prior CRT trials

The baseline clinical characteristics of the BUDAPEST-CRT Upgrade Study were similar to those of patients enrolled in the Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block (BLOCK-HF) trial (Table 2).[16] In the two trials, the mean age of the cohorts was approximately 71-73 years, which is ten years higher

than the average in other CRT trials.[2, 8, 11, 15-17] Comorbidities, such as hypertension, diabetes, or prior myocardial infarction, were also described in a similar proportion of enrolled subjects.[2, 11, 15, 16] However, despite these similarities, in the BUDAPEST-CRT Upgrade Study, male patients were overrepresented (89%), while more than half of our patients had atrial fibrillation, which is also much higher than in the MADIT-CRT, RAFT or DANISH trials.[2, 8, 11, 15-17]

The previously listed studies also show further characteristic differences in the NYHA functional class (Table 3). Only MADIT-CRT and BLOCK-HF included patients with NYHA functional class I, whereas BLOCK-HF and RAFT did not enroll patients with NYHA functional class IV.[2, 11, 16] In terms of these differences, patients enrolled in the BUDAPEST-CRT Upgrade Study had the highest prevalences of patients with NYHA functional class III and IV. Furthermore, based on the available laboratory and echocardiographic results, the patients included in the BUDAPEST-CRT Upgrade Study had the highest NT-proBNP, along with low 6MWT distances and LVEF values representing a very advanced heart failure cohort (Table 3). Concerning medical therapy, the use of MRA and amiodarone in the BUDAPEST-CRT Upgrade Study was outstanding compared to previous studies.[2, 8, 11, 15-17] At the same time, the use of ACE-Is, ARBs, beta-blockers, diuretics, and statins did not differ significantly from that in other CRT trials (Table 3).[2, 8, 11, 15-17]

Discussion

The BUDAPEST-CRT Upgrade study is the first multicentre, randomized, controlled trial that was designed to investigate the effects of CRT upgrade on echocardiographic response and outcomes in HF patients with intermittent or permanent RV pacing with a wide paced

QRS complex.[14] The baseline clinical characteristics of this contemporary HF cohort differed significantly from those of other CRT study populations.[2, 8, 11, 15-17]

In our patient cohort, the mean age was almost 73 years, ten years more than that in the previous RCTs investigating de novo CRT patients [2, 11, 15, 16] and still higher than the real-world data of the European CRT Survey II (62-76 years, with an average of 70).[8] However, in the BLOCK-HF trial, where subjects with a high degree AV block were enrolled, with a mean LVEF of 43%, a similarly aged cohort was described.[16] Since the prevalence of bradycardia increases with age, those who need conventional pacemaker implantation are often older.[18] Moreover, pacing-induced adverse cardiac effects and subsequent heart failure development are relatively slow processes, and evidently, such patients become candidates for CRT upgrades at an older age.[9, 10, 12]

Chronic right ventricular pacing also increases the incidence of heart failure and atrial fibrillation.[9, 10] At presentation, 56% of patients from our cohort were in atrial fibrillation, exceeding the rates of previous CRT trials.[2, 8, 11, 15-17] In MADIT-CRT, where mild heart failure patients were investigated, only 12% of patients had atrial fibrillation; in the BLOCK-HF trial, the percentage of patients with atrial fibrillation in the CRT-D and ICD subgroups was almost 50%, while in the European CRT Survey II, the percentage of patients with atrial fibrillation in among CRT upgrade patients was only 34.4%.[2, 16, 17] Older age, the presence and severity of heart failure, the high prevalence of tachy-brady syndrome, the need for CIED, and the high rate of right ventricular pacing all predispose patients to atrial fibrillation.[9, 19, 20] At the same time, a higher incidence of atrial fibrillation is also associated with the male sex consequently the prevalence of rapid atrial fibrillation and potentially indicated AV node ablation may be higher.[19] Nevertheless, a higher incidence of AV block can be observed in male patients.[21]

The proportion of male subjects was 89%, remarkably high in our cohort. Nevertheless, females are generally underrepresented in CRT trials, with a range between 20 and 28%.[2, 11, 15, 16] Based on the European CRT Survey II, which presented data from 11088 patients from everyday clinical practice, almost one-quarter of CRT recipients were females.[8] Whether the high predominance of males is due to male patients developing heart failure due to the high percentage of right ventricular pacing among males or to selection bias requires further investigation.

Hypertension was the most frequently reported comorbidity, with almost 80%, which is two times higher than in the DANISH or RAFT trials.[11, 15] Despite the cohort's older mean age, the prevalences of diabetes and prior myocardial infarction were similar to those in other RCTs.[2, 11, 15, 16]

Heart failure was of ischemic etiology in 48% of the upgrade subgroup in the European CRT Survey II, while in the BUDAPEST-CRT Upgrade trial, 58% of the enrolled patients had a previous myocardial infarction and/or revascularization.[17] In the BUDAPEST trial, patients were implanted mostly with conventional pacemaker devices, followed by a very high (87%) right ventricular pacing rate. Almost 36% of the patients were pacemaker dependent, and 23% had a pacing rate in the 20-80% range. Previous data showed an association between apical pacing and poor outcomes.[22-24] In our cohort, there was no clear predominance in the previously implanted right ventricular lead position: septal and apical locations were used in 48% and 43% of patients, respectively.

In the BUDAPEST-CRT Upgrade study, patients presented at an advanced stage of heart failure; half of them were in NYHA class III at inclusion, with a median NT-proBNP level of almost 3500 pg/mL and a severely decreased LVEF (25%). Moreover, 49% had a hospitalization for heart failure worsening within 12 months prior to enrollment. This corresponds to a cohort with a more advanced HF stage than the European CRT Survey II:

those CRT upgrade-referred patients had a median EF of 30% and a natriuretic peptide level of 2800 pg/mL, although the percentage of patients with a NYHA functional class III also reached 55%.[17] These results strongly emphasize the clinical importance of proper timing of CRT upgrade in HFrEF patients.[25] As shown in a RAFT substudy, physicians deferred CRT upgrades to a later date in 9.6% of patients overall and in 11% of patients requiring battery replacement; in one-third of patients, the decision was based on the patients' preferences.[11] These uncertainties clearly necessitate further clarifications in the guidelines.[4, 5]

In summary, the BUDAPEST-CRT Upgrade trial is the first randomized, controlled trial involving patients with a previously implanted pacemaker or ICD with intermittent or permanent RV pacing in which outcomes after a CRT-D upgrade were investigated.

Our cohort's baseline clinical characteristics showed that patients referred for CRT upgrades represent an elderly, highly vulnerable, advanced heart failure population with a strong male predominance with a high burden of atrial fibrillation and other comorbidities.

Since the ever-growing proportion of CRT upgrade candidates requires more precise and extensive care, based on our opinion, these results will further help the physicians to properly identify those PM/ICD patients who have a higher risk for developing heart failure. Those patients with PM/ICDs and a higher burden of RV pacing rate need closer follow-up, especially those who are males with more comorbidities and particularly with atrial fibrillation.

The results of the BUDAPEST-CRT Upgrade trial will be available at the end of 2022 and will show the outcomes of CRT upgrade patients with respect to all-cause mortality, heart failure events, and echocardiographic response. The expected results may contribute to a more precise definition and extension of the current guidelines for CRT upgrade.

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Conflict of interest

B.M. reports grants from Boston Scientific, NRDIF Hungary, National Heart Program during the conduct of the study; personal fees from Biotronik, Abbott, Astra Zeneca, Novartis, Boehringer-Ingelheim and grants from Medtronic outside the submitted work. L.G. reports grants from Boston Scientific, NRDIF Hungary, National Heart Program, during the conduct of the study; personal fees from Biotronik, Medtronic, Abbott and Johnson & Johnson, outside the submitted work. E.Z. reports grants from Boston Scientific, NRDIF Hungary, National Heart Program, during the conduct of the study; personal fees from Medtronic, Biotronik, Abbott, Innomed and OrionPharma, outside the submitted work. I.O. reports grants from Boston Scientific, NRDIF Hungary, National Heart Program, during the conduct of the study; personal fees from Boston Scientific, Biotronik, Abbott, Medtronic, outside the submitted work. L.M. reports grants from Boston Scientific, NRDIF Hungary, National Heart Program, during the conduct of the study; personal fees from Medtronic, Abbott outside the

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Figure legends

Figure 1. The design of the BUDAPEST CRT Upgrade study

Figure 2. Inclusion rate by quarters from 2014 to 2021

Figure 3. The proportion of patients by comorbidities in the BUDAPEST CRT Upgrade study total cohort

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Table 1. Baseline clinical characteristics of patients in the BUDAPEST CRT upgrade study by treatment arm

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Table 1. Baseline clinical characteristics of patients in the BUDAPEST CRT upgrade study by treatment arm

	All patients (n=360)	**ICD (n=145)**	**CRT-D (n=215)**
Demographic Information			
Male, n (%)	320 (88.9)	135 (93.1)	185 (86.1)
Age (years), mean ± SD	72.8±7.7	72.6±8.3	72.9±7.3
Height (cm), mean ± SD	173.2±8.5	174.5±8.4	172.3±8.5
Weight (kg), mean ± SD	86.2±16.5	85.7±16.8	86.5±16.3
BMI (kg/m^2), mean ± SD	28.7±4.9	28.1±4.9	29.1±4.9
Medical History			
Ischemic etiology, n(%)	209 (58.1)	82 (56.6)	127 (59.1)
• MI. n (%)	167 (46.4)	65 (44.8)	102 (47.4)
• CABG, n (%)	86 (23.9)	33 (22.8)	53 (24.7)
• PCI, n (%)	140 (38.9)	55 (37.9)	85 (39.5)
Valve surgery, n (%)	38 (10.6)	10 (6.9)	28 (13.0)
CVA/TIA, n (%)	56 (15.6)	23 (15.9)	33 (15.3)
Post oncological disease, n (%)	34 (9.4)	14 (9.7)	20 (9.3)

PVD, n (%)	34 (9.4)	13 (9.0)	21 (9.8)
Obesity as per physicians' discretion, n (%)	106 (29.4)	34 (23.4)	72 (33.5)
Obesity as per BMI>30, n (%)	127 (35.3)	46 (31.7)	81 (37.7)
Diabetes, n (%)	128 (35.6)	45 (31.0)	83 (38.6)
Hyperlipidaemia, n (%)	165 (45.8)	70 (48.3)	95 (44.2)
Hypertension, n (%)	289 (80.3)	111 (76.6)	178 (82.8)
Current smoking, n (%)	25 (6.9)	7 (4.8)	18 (8.4)
Asthma, n (%)	11 (3.1)	3 (2.1)	8 (3.7)
COPD, n (%)	48 (13.3)	18 (12.4)	30 (14.0)
Known valvular heart disease, n (%)	63 (17.5)	29 (20.0)	34 (15.8)
History of VT/VF, n (%)	84 (23.3)	37 (25.5)	47 (21.9)
AF, n (%)	203 (56.4)	87 (60.0)	116 (54.0)
HF hospitalization 12 months prior to enrollment, n (%)	178 (49.4)	77 (53.1)	101 (47.0)
Other chronic disease, n (%)	192 (53.3)	81 (55.9)	111 (51.6)
Prior device type			

PM, n (%)	244 (67.8)	94 (64.8)	150 (69.8)
ICD, n (%)	114 (31.7)	50 (34.5)	64 (29.8)
CRT with plug, n (%)	2 (0.6)	1 (0.7)	1 (0.5)
Prior pacemaker type			
DDD, n (%)	158 (64.8)	63 (67.0)	95 (63.3)
VDD, n (%)	22 (9.0)	9 (9.6)	13 (8.7)
VVI, n (%)	64 (26.2)	22 (23.4)	42 (28.0)
Types of ICDs			
DDD-ICD, n (%)	54 (47.4)	26 (52.0)	28 (43.8)
VDD-ICD, n (%)	6 (5.3)	2 (4.0)	4 (6.3)
VVI-ICD, n (%)	54 (47.4)	22 (44.0)	32 (50.0)
RV lead location			
Apical, n (%)	131 (48.2)	52 (46.8)	79 (49.1)
Septal, n (%)	122 (44.9)	50 (45.0)	72 (44.7)
Other, n (%)	19 (7.0)	9 (8.1)	10 (6.2)
Pacemaker interrogation			
Percent RV pacing prior to enrollment (%), mean ± SD	86.5±20.2	88.1±18.8	85.4±21.1
Clinical status			
Current NYHA functional class			
I, n (%)	0 (0)	0 (0)	0 (0)
II, n (%)	169 (46.9)	64 (44.1)	105 (48.8)
III, n (%)	179 (49.7)	78 (53.8)	101 (47.0)

IVa, n (%)	12 (3.3)	3 (2.1)	9 (4.2)
Six minute walk test (m), mean ± SD	276.0±116.4	285.4±116.6	269.7±116.1
EQ-5D 3L score, mean ± SD	0.668±0.289	0.656±0.293	0.685±0.283
Laboratory			
NT-pro-BNP (pg/mL), median (25th – 75th percentile)	2231.0 (1254.0-4309.0)	2122.0 (1336.0-4476.0)	2279.5 (1223.3-4234.0)
Creatinine (µmol/L), mean ± SD	112.7±32.7	114.3±30.4	111.6±34.2
Clinical assessment			
Systolic Blood Pressure (mmHg), mean ± SD	123.6±15.7	121.1±15.0	125.3±15.9
Diastolic Blood Pressure (mmHg), mean ± SD	74.5±10.3	73.9±10.0	74.8±10.5
Heart Rate (bpm), mean ± SD	70.2±10.2	70.5±11.0	70.1±9.5
Baseline Medications			
ACE-I, n (%)	265 (73.6)	108 (74.5)	157 (73.0)
ARB, n (%)	66 (18.3)	23 (15.9)	43 (20.0)
B-blockers, n (%)	328 (91.1)	131 (90.3)	197 (91.6)

Ca^{2+} Channel blocker, n (%)	39 (10.8)	10 (6.9)	29 (13.5)
Statins, n (%)	252 (70.0)	103 (71.0)	149 (69.3)
Loop diuretics, n (%)	288 (80.0)	118 (81.4)	170 (79.1)
Amiodarone, n (%)	87 (24.2)	35 (24.1)	52 (24.2)
Mineralo-corticoid receptor antagonist, n (%)	225 (62.5)	91 (62.8)	134 (62.3)
Oral Anti-coagulants, n (%)	212 (58.9)	86 (59.3)	126 (58.6)
Sotalol, n (%)	3 (0.8)	0 (0)	3 (1.4)
Platelets antagonists, n (%)	197 (54.7)	77 (53.1)	120 (55.8)
Digoxin, n (%)	34 (9.4)	17 (11.7)	17 (7.9)
Other, n (%)	234 (65.0)	91 (62.8)	143 (66.5)
• ARNI, n (%)	21 (5.8)	10 (6.9)	11 (5.1)

Baseline echocardiographic parameters			
	All patients (n=360)	ICD (n=145)	CRT-D (n=215)
LVEDV (mL), mean ± SD	229.3±77.9	226.6±74.5	231.2±80.3
LVESV (mL), mean ± SD	173.7±65.5	171.2±63.9	175.5±66.7

LVEF (%), mean ± SD	24.8±6.6	25.0±6.3	24.7±6.8

ACE-I-angiotensin-converting enzyme inhibitor; AF-atrial fibrillation; ARB-angiotensin receptor blocker; ARNI- angiotensin receptor–neprilysin inhibitor; BMI-body mass index; CABG-coronary artery bypass grafting; COPD-chronic obstructive pulmonary disease; CRT-cardiac resynchronization therapy; CVA- Cerebrovascular accident; LVEDV- left ventricular end-diastolic volume; LVEF- left ventricular ejection fraction; LVESV- left ventricular end-systolic volume; HF-heart failure; ICD-implantable cardioverter defibrillator; MI-myocardial infarction; NT-proBNP-N-Terminal pro-B-type natriuretic peptid; NYHA-New York Heart Association; PCI-percutan coronary intervention; PM-pacemaker; PVD-peripheral vascular disease; RV-right ventricular; TIA-transient ischemic attack; VF-ventricular fibrillation; VT-ventricular tachycardia

Table 2. Comparison of baseline clinical characteristics of patients enrolled in the BUDAPEST CRT upgrade trial and previous randomized control trials

	Budapest CRT Upgrade		**BLOCK HF (only CRT-D/ICD)**		**ESC CRT survey II**	**ESC CRT survey Upgrade**	**MADIT-CRT**		**RAFT**		**DANISH**	
	CRT-D (n=215)	ICD (n=145)	CRT-D (n=106)	ICD (n=101)	CRT (*n* = 1088)	Upgrades PM/ICD (*n* = 2398)	CRT-D (n=1089)	ICD (n=731)	CRT-D (n=894)	ICD (n=904)	PM/CRT (n=560)	ICD/CRT-D (n=556)
Age (years), mean ± SD	72.9±7.3	72.6±8.3	72.0±9.3	71.0±10	70 (62-76)	72 (64-78)	65±11	64±11	66.1±9.3	66.2±9.4	63 (56–70)	64 (56–72)

Sex – male, n (%)	185 (86.1)	135 (93.1)	87 (82.1)	81 (80.2)	8366 (76)	1947 (81.2)	814 (74.7)	553 (75.6)	758 (84.8)	732 (81.0)	404 (72)	405 (73)
BMI or >30, n (%) ; or mean ± SD; or median (25th – 75th percentile)	29.1±4.9	28.1±4.9	-	-	27 (25-31)	27 (25–31)	35.9%	36.4%	-	-	26.8 (23.8–30.1)	26.8 (23.9–30.5)
HT, n (%)	178 (82.8)	111 (76.6)	84 (79.2)	87 (86.1)	6962 (64)	1550 (65.5)	-	-	402 (45.0)	397 (43.9)	167 (30)	181 (33)
Diabetes	83	45	47	37	3428	763	329/108	223/729	293	313	112 (20)	99

Mellitus , n (%)	(38.6)	(31.0)	(44.3)	(36.6)	(31)	(32.2)	8 (30.2)	(30.6)	(32.8)	(34.6)		(18)
MI or ischemic etiology, n (%)	102 (47.4)	65 (44.8)	56 (52.8)	47 (46.5)	3957 (36)	957 (40.3)	5988 (54.9)	401(54.9)	614 (68.7)	587 (64.9)	-	-
HLP, n (%)	95 (44.2)	70 (48.3)	-	-	-	-	-	-	-	-	-	-
Current smoking ,n (%)	18 (8.4)	7 (4.8)	-	-	-	-	122/1069 (11.4)	92/717 (12.8)	121 (13.5)	127 (14.0)	-	-
AF, n (%)	116 (54.0)	87 (60.0)	44 (41.5)	52 (51.5)	2778 (26)	810 (34.4)	118/1063 (11.1)	90/717 (12.6)	114 (12.8)	115 (12.7)	113 (20)	135 (24)

AF-atrial fibrillation; BMI-body mass index; ; HLP-hyperlipidaemia; HT-hypertension; MI-myocardial infarction

Table 3. Comparison of baseline physical examination, laboratory tests, pharmacological treatment and echocardiographic parameters of patients enrolled in the BUDAPEST CRT upgrade trial and previous observational studies

	Budapest CRT Upgrade		BLOCK HF (only CRT-D/ICD)		ESC CRT survey II	ESC CRT survey Upgrade	MADIT-CRT		RAFT		DANISH	
	CRT-D (n=215)	ICD (n=145)	CRT-D (n=106)	ICD (n=101)	CRT (*n* = 11 088)	Upgrades PM/ICD (*n* = 2398)	CRT-D (n=1089)	ICD (n=731)	CRT-D (n=894)	ICD (n=904)	PM/CRT (n=560)	ICD/CRT-D (n=556)
Systolic BP, mean ± SD; or median (25th – 75th percentile)	125.3±15.9	121.1±15.0	-	-	122 (110–137)	120 (110–134)	124±17	121±18	-	-	124 (111–138)	123 (110–139)
Diastolic BP, mean ± SD;	74.8±10.5	73.9±10.0	-	-	72 (66-80)	70 (65–80)	72±10	71±10	-	-	74 (66–82)	74 (65–81)

or median (25th – 75th percentile)												
NYHA I, n (%)	0 (0)	0 (0)	11 (10.4)	16 (15.8)	370 (3)	60 (2.5)						
NYHA II, n (%)	105 (48.8)	64 (44.1)	67 (63.2)	58 (57.4)	4083 (38)	778 (33)			708 (79.2)	730 (80.8)	300 (54)	297 (53)
NYHA III, n (%)	101 (47)	78 (53.8)	28 (26.4)	27 (26.7)	5909 (55)	1392 (59.1)	109 (10.0)*	73 (10.0)*	186 (20.8)	174 (19.2)	253 (45)	252 (45)
NYHA IV, n (%)	9 (4.2)	3 (2.1)			486 (5)	127 (5.4)					7 (1)	7 (1)
NT-proBNP (pg/mL), mean ± SD; or median (25th – 75th percentile)	2279.5 (1223.3-4234.0)	2122.0 (1336.0-4476.0)	-	-	2400 (1049–5517)	2811 (1264–6818)	-	-	-	-	1110 (547–2166)	1244 (616–2321)
Creatinine	111.6±34.2	114.3±30.4	-	-	100 (83–	108 (88–	1.2±0.4	1.2±0.4	-	-	-	-

(μmol/L), mean ± SD; or median (25th – 75th percentile)					129)	139)						
6 MWT (m), mean ± SD	269.7±116.1	285.4±116.6	-	-	-	-	359±107	363±108	351.3±106.7 (N=789)	354.9±110.1 (N=765)	-	-
ACEi, n (%)	157 (73.0)	108 (74.5)	-	-	9163 (86) [#]	1925 (83.7) [#]	839 (77.0)	563 (77.0)	859 (96.1) [#]	878 (97.1) [#]	544 (97)	533 (96)
ARB, n (%)	43 (20.0)	23 (15.9)	-	-			227 (20.8)	148 (20.2)				
BB, n (%)	197 (91.6)	131 (90.3)	-	-	9472 (89)	2046 (88.6)	1016 (93.3)	681 (93.2)	808 (90.4)	805 (89.0)	517(92)	509 (92)
MRA, n (%)	134 (62.3)	91 (62.8)	-	-	6682 (63)	1377 (60.1)	352 (32.3)	226 (30.9)	372 (41.6)	378 (41.8)	320 (57)	326 (59)
Loop	170 (79.1)	118 (81.4)	-	-	8621	>80%	824	533	757 (84.7)	756 (83.6)	-	-

diuretics or diuretics, n (%)					(81)		(75.7)	(72.9)				
Amiodarone, n (%)	52 (24.2)	35 (24.1)	-	-	1825 (17)	507 (22.2)	78 (7.2)	51 (7.0)	140 (15.7)	124 (13.7)	32 (6)	34 (6)
Digitalis, n (%)	17 (7.9)	17 (11.7)	-	-	1100 (10)	266 (11.6)	291 (26.7)	177 (24.2)	301 (33.7)	756 (83.6)	-	-
Statin, n (%)	149 (69.3)	103 (71.0)	-	-	-	-	735 (67.5)	491 (67.2)	607 (67.9)	618 (68.4)	-	-
LVEF, mean ± SD; or median (25th – 75th percentile)	24.6±6.9	24.9±6.3	33.0±7.8	32.9±8.0	29 (23–34)	30 (22–34)	-	-	-	-	25 (20–30)	25 (20–30)
LVEDV (ml),	231.9±80.8	227.3±74.4	-	-	-	-	245±60	251±65	-	-	-	-

mean ± SD												
LVESV (ml), mean ± SD	176.3±67.1	171.8±63.8	-	-	-	-	175±48	179±53	-	-	-	-

ACE-I-angiotensin-converting enzyme inhibitor; ARB-angiotensin receptor blocker; B-beta-blocker; BP-blood pressure; LVEDV- left ventricular end-diastolic volume; LVEF- left ventricular ejection fraction; LVESV- left ventricular end-systolic volume; MRA-mineralocorticoid receptor antagonist; NT-proBNP-N-Terminal pro-B-type natriuretic peptide; NYHA-New York Heart Association; 6 MWT-6-minute walk test.

*NYHA III and NYHA IV, # ACEi or ARB

FIGURES

Figure 1. The design of the BUDAPEST CRT Upgrade study

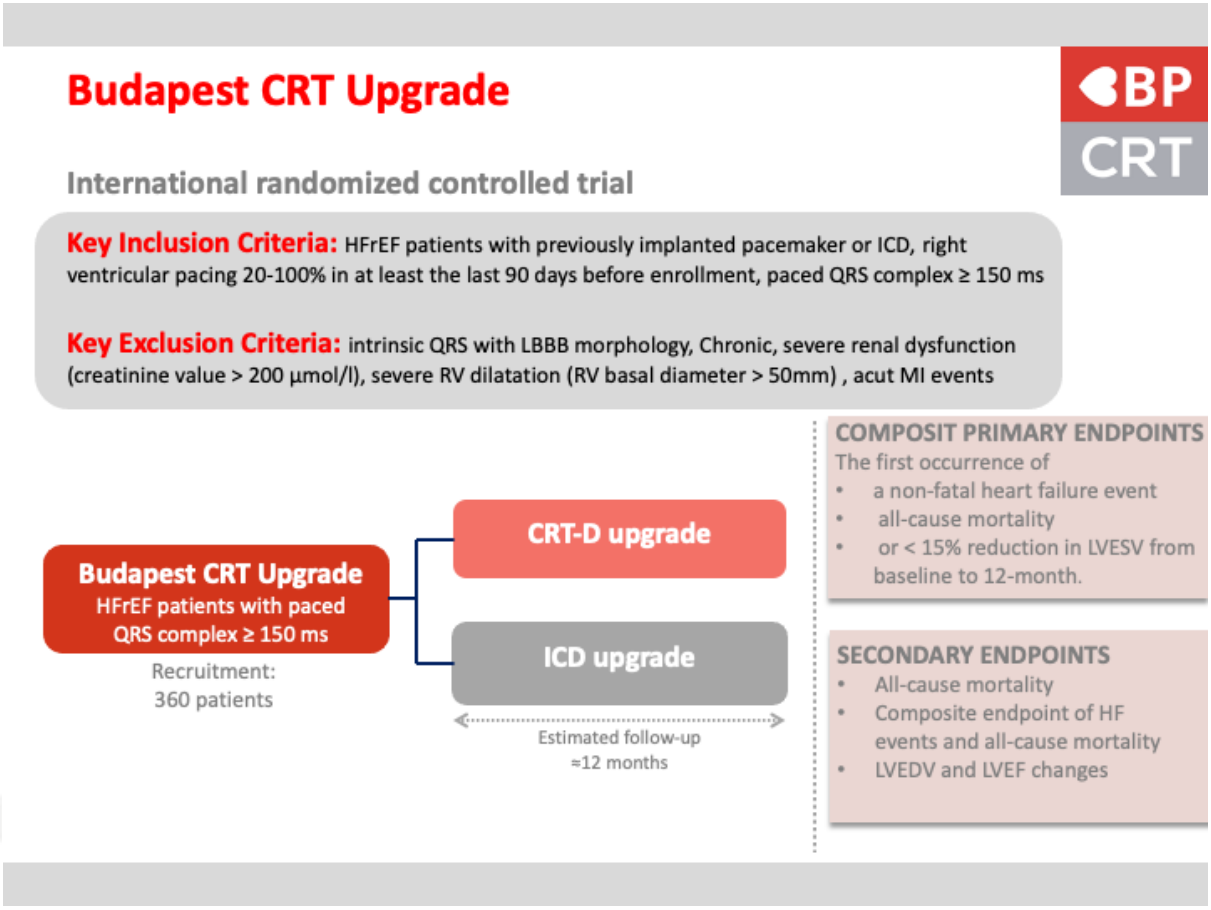

Figure 2. Inclusion rate by quarters from 2014 to 2021

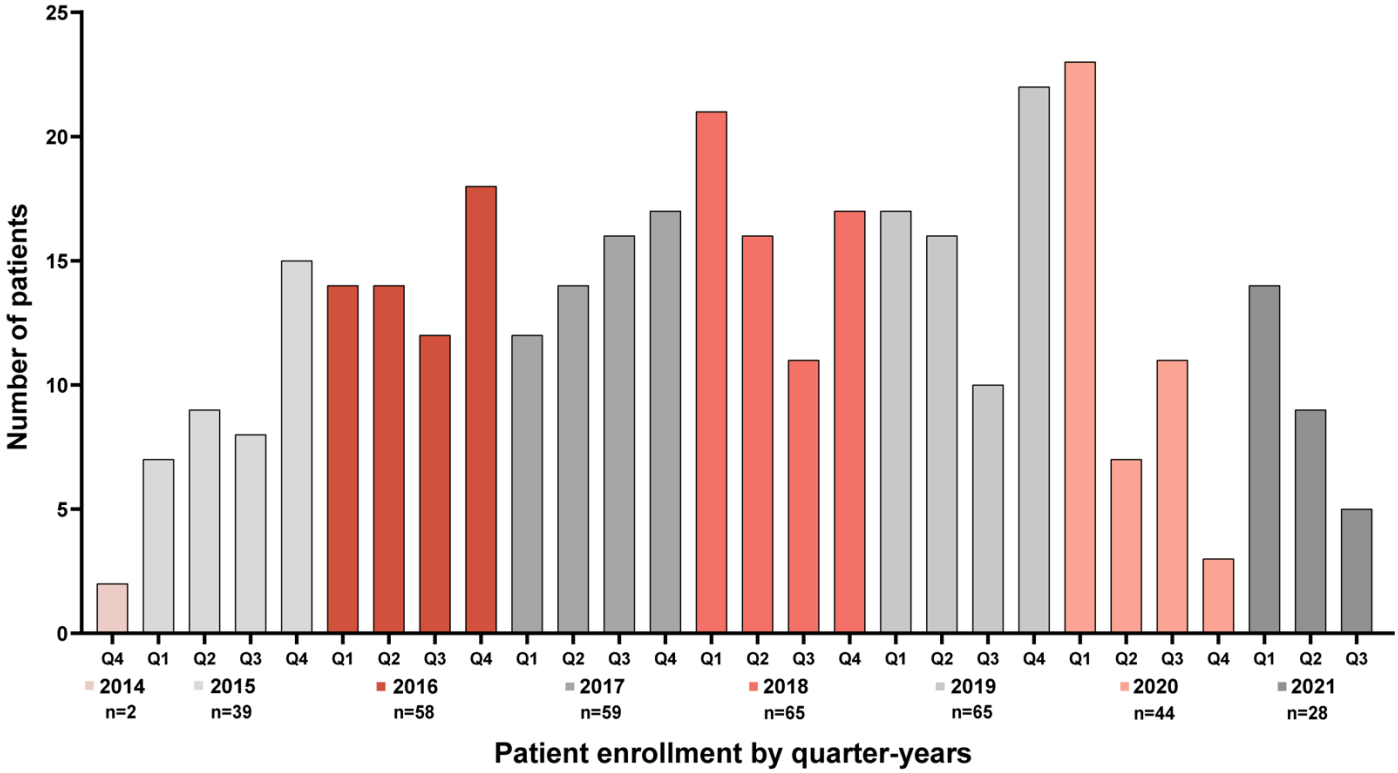

Figure 3. The proportion of patients by comorbidities in the BUDAPEST CRT Upgrade study total cohort