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RESEARCH ARTICLE

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

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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 (RV) pacing 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 6 months prior to enrolment, reduced left ventricular ejection fraction (LVEF ≤35%), HF symptoms (New York Heart Association [NYHA] functional class II–IVa), wide paced QRS (>150 ms), and ≥20% of RV pacing burden without having a native left bundle branch block. At enrolment, the mean age of the patients was 73 ± 8 years; 89% were male, 97% were in NYHA class II/III functional class, and 56% had atrial fibrillation. Enrolled patients predominantly had conventional PM devices, with a mean RV pacing 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 LVEF, high NT-proBNP, and frequent previous HF events.
Clinical Trial Registration: ClinicalTrials.gov NCT02270840.

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

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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 ejection fraction (LVEF) 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 left ventricular (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 versus 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 the Resynchronization/Defibrillation for Ambulatory Heart Failure Trial (RAFT) showed no difference in the primary outcome (all-cause mortality and HF hospitalization) between CRT with defibrillator (CRT-D) versus 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 European Society of Cardiology (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 RV 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 RCT designed to assess the effects of CRT upgrade on LV 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 RCT including 360 patients from 17 centres (*Figure 1*). Those patients who had symptomatic HF with reduced ejection fraction and PM or ICD at least 6 months prior to enrolment 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 Center, Israel, and all data were registered in the electronic case report forms system. Echocardiographic images, PM interrogation files, and electrocardiograms (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 [NYHA] class II–IVa), a wide paced QRS (>150 ms) and ≥20% RV pacing without having intrinsic LBBB, RV 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 N-terminal pro-B-type natriuretic peptide (NT-proBNP) was recommended only at baseline and follow-ups. In addition, ECG, PM interrogation, 6-min walk test (6MWT) distance, 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 online supplementary material.

Study endpoints

The primary endpoint is the composite of clinical and echocardiographic parameters, including the first occurrence of an HF event, all-cause mortality, or <15% reduction in LV end-systolic volume 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), 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 atrioventricular (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 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 versus ICD in a 3:2 ratio.

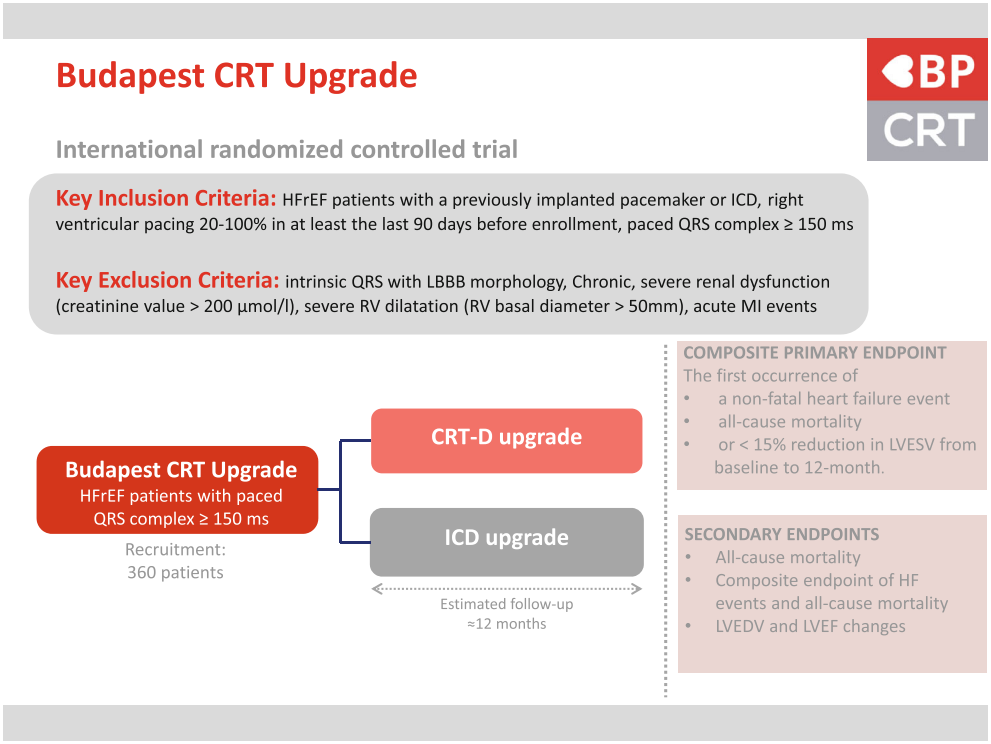

Figure 1 Design of the BUDAPEST-CRT Upgrade study. CRT-D, cardiac resynchronization therapy with defibrillator; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter defibrillator; LBBB, left bundle branch block; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MI, myocardial infarction; RV, right ventricular.

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 vs. 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 ± standard deviation, while those with non-normal distributions as medians with interquartile range (25th–75th percentile). Categorical variables are summarized with frequencies and percentages. 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 test was used for dichotomous variables as appropriate. Comparisons of more subgroups by years (see online supplementary *Table S3*) were analysed by ANOVA.

Results

Enrolment of the study population

Patients were screened for enrolment between November 2014 and August 2021. Overall, 360 patients met the inclusion criteria (online supplementary *Table S1*) and were randomized at 17 sites from six countries (online supplementary *Table S2*). The top enrollers (seven sites with more than 10 patients) included 89% of the total cohort (online supplementary *Table S2*). 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 (online supplementary *Table S3*), 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%

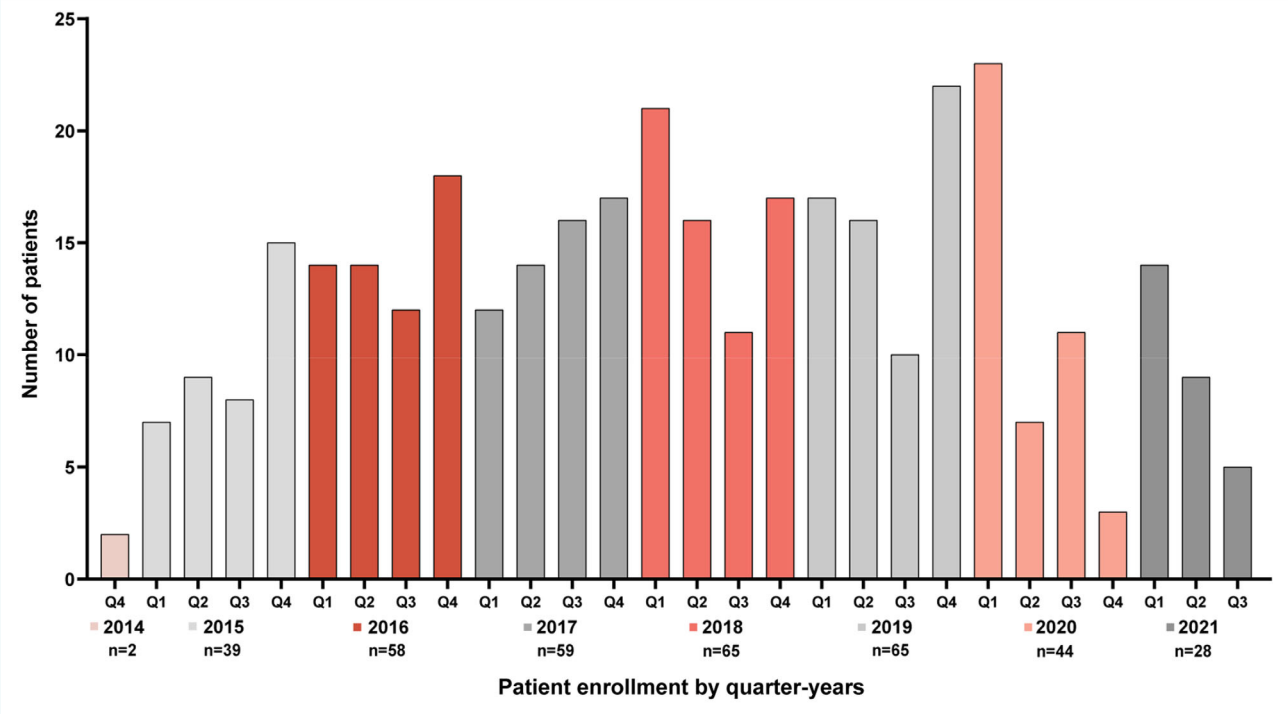

Figure 2 Inclusion rate by quarters from 2014 to 2021.

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 ischaemic HF (58.1%). The mean body mass index (BMI) was 28.7 ± 4.9 kg/m^2, 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 ischaemic 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, and 3.1% had bronchial asthma at the time of enrolment. 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 PM, 31.7% had an ICD, and 0.6% had CRT with an unplugged LV lead before the index procedure.

Previously implanted PM types were most frequently DDD PMs (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 RV 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 6MWT distance 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 enrolment, at the same time, the rate of ARNI administration at enrolment was significantly increased in the last years (online supplementary *Table S3B*). 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 (online supplementary *Table S4*). Beside the anthropometric 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 ischaemic events in the medical history (19 women [47.5%] vs. 190 men [59.4%]; $p < 0.0001$) driven by the rate of coronary artery bypass grafting (4 women [10%] vs. 82 men [25.6%]; $p = 0.03$). At the same time, women had shorter distance of 6MWT (women

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 ($n = 215$)
Demographics			
Male sex, *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, *n* (%)			
Ischaemic eatiology	209 (58.1)	82 (56.6)	127 (59.1)
MI, *n* (%)	167 (46.4)	65 (44.8)	102 (47.4)
CABG	86 (23.9)	33 (22.8)	53 (24.7)
PCI	140 (38.9)	55 (37.9)	85 (39.5)
Valve surgery	38 (10.6)	10 (6.9)	28 (13.0)
CVA/TIA	56 (15.6)	23 (15.9)	33 (15.3)
Post-oncological disease	34 (9.4)	14 (9.7)	20 (9.3)
PVD	34 (9.4)	13 (9.0)	21 (9.8)
Obesity as per physicians' discretion	106 (29.4)	34 (23.4)	72 (33.5)
Obesity as per BMI >30 kg/m^2	127 (35.3)	46 (31.7)	81 (37.7)
Diabetes	128 (35.6)	45 (31.0)	83 (38.6)
Hyperlipidaemia	165 (45.8)	70 (48.3)	95 (44.2)
Hypertension	289 (80.3)	111 (76.6)	178 (82.8)
Current smoking	25 (6.9)	7 (4.8)	18 (8.4)
Asthma	11 (3.1)	3 (2.1)	8 (3.7)
COPD	48 (13.3)	18 (12.4)	30 (14.0)
Known valvular heart disease	63 (17.5)	29 (20.0)	34 (15.8)
History of VT/VF	84 (23.3)	37 (25.5)	47 (21.9)
AF	203 (56.4)	87 (60.0)	116 (54.0)
HF hospitalization 12 months prior to enrolment	178 (49.4)	77 (53.1)	101 (47.0)
Other chronic disease	192 (53.3)	81 (55.9)	111 (51.6)
Prior device type, *n* (%)			
PM	244 (67.8)	94 (64.8)	150 (69.8)
ICD	114 (31.7)	50 (34.5)	64 (29.8)
CRT with plug	2 (0.6)	1 (0.7)	1 (0.5)
Prior pacemaker type, *n* (%)			
DDD	158 (64.8)	63 (67.0)	95 (63.3)
VDD	22 (9.0)	9 (9.6)	13 (8.7)
VVI	64 (26.2)	22 (23.4)	42 (28.0)
Types of ICD, *n* (%)			
DDD-ICD	54 (47.4)	26 (52.0)	28 (43.8)
VDD-ICD	6 (5.3)	2 (4.0)	4 (6.3)
VVI-ICD	54 (47.4)	22 (44.0)	32 (50.0)
RV lead location, *n* (%)			
Apical	131 (48.2)	52 (46.8)	79 (49.1)
Septal	122 (44.9)	50 (45.0)	72 (44.7)
Other	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, *n* (%)			
I	0 (0)	0 (0)	0 (0)
II	169 (46.9)	64 (44.1)	105 (48.8)
III	179 (49.7)	78 (53.8)	101 (47.0)
IVa	12 (3.3)	3 (2.1)	9 (4.2)
6-min 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

Table 1 (Continued)

	All patients (n = 360)	ICD (n = 145)	CRT-D (n = 215)
Laboratory			
NT-proBNP (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, *n* (%)			
ACE-I	265 (73.6)	108 (74.5)	157 (73.0)
ARB	66 (18.3)	23 (15.9)	43 (20.0)
Beta-blockers	328 (91.1)	131 (90.3)	197 (91.6)
Calcium channel blocker	39 (10.8)	10 (6.9)	29 (13.5)
Statins	252 (70.0)	103 (71.0)	149 (69.3)
Loop diuretics	288 (80.0)	118 (81.4)	170 (79.1)
Amiodarone	87 (24.2)	35 (24.1)	52 (24.2)
MRA	225 (62.5)	91 (62.8)	134 (62.3)
Oral anticoagulants	212 (58.9)	86 (59.3)	126 (58.6)
Sotalol	3 (0.8)	0 (0)	3 (1.4)
Platelet antagonists	197 (54.7)	77 (53.1)	120 (55.8)
Digoxin	34 (9.4)	17 (11.7)	17 (7.9)
Other	234 (65.0)	91 (62.8)	143 (66.5)
ARNI	21 (5.8)	10 (6.9)	11 (5.1)
Baseline echocardiographic parameters			
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 graft; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy with defibrillator; CVA, cerebrovascular accident; HF, heart failure; ICD, implantable cardioverter defibrillator; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PM, pacemaker; PVD, peripheral vascular disease; RV, right ventricular; SD, standard deviation; TIA, transient ischaemic attack; VF, ventricular fibrillation; VT, ventricular tachycardia.

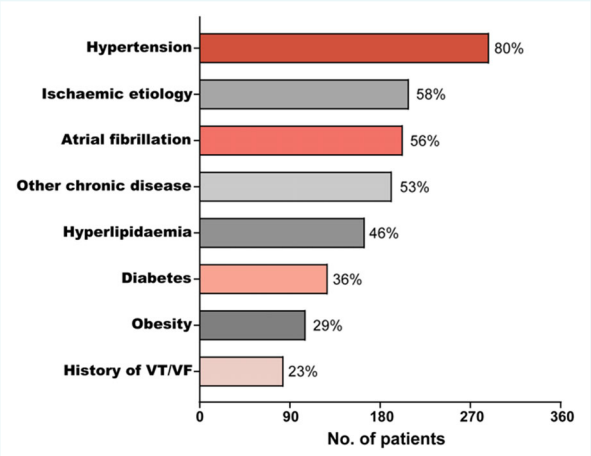

Figure 3 Proportion of patients by comorbidities in the BUDAPEST-CRT Upgrade study total cohort. VF, ventricular fibrillation; VT, ventricular tachycardia.

224.5 m [141–300] vs. men 300 m [200–360]; p = 0.026), lower mean serum creatinine level (women 87 μmol/L [67.3–135.8] vs. men 106 μmol/L [89–129]; p = 0.002) and smaller LV dimensions (end-diastolic volume in women 189 ml [154.2–229.4] vs. men 219.5 ml [180.2–277.9]; p = 0.01; end-systolic volume 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 cardiac resynchronization therapy trials

The baseline clinical characteristics of the BUDAPEST-CRT Upgrade study were similar to those of patients enrolled in the BLOCK-HF trial[16] (*Table 2*). In the two trials, the mean age of the cohorts was ~71–73 years, which is 10 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

Table 2 Comparison of baseline clinical characteristics of patients enrolled in the BUDAPEST-CRT Upgrade trial and previous studies

	BUDAPEST-CRT Upgrade		BLOCK-HF (only CRT-D/ICD)		ESC CRT Survey II	ESC CRT Survey Upgrades PM/ICD (*n* = 2398)	MADIT-CRT		RAFT		DANISH	
	CRT-D (*n* = 215)	ICD (*n* = 145)	CRT-D (*n* = 106)	ICD (*n* = 101)	CRT (*n* = 11 088)		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, or median (25th–75th percentile)	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)
Male sex, *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 (kg/m^2), mean ± SD or >30 (%); 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 mellitus, *n* (%)	83 (38.6)	45 (31.0)	47 (44.3)	37 (36.6)	3428 (31)	763 (32.2)	329/1088 (30.2)	223/729 (30.6)	293 (32.8)	313 (34.6)	112 (20)	99 (18)
MI or ischaemic aetiology, *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; CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy with defibrillator; HLP, hyperlipidaemia; HT, hypertension; ICD, implantable cardioverter defibrillator; MI, myocardial infarction; PM, pacemaker; SD, standard deviation.

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 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 enrol 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 prevalence of patients with NYHA functional class III and IV. Furthermore, based on the available laboratory and echocardiographic results, 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 HF 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 RCT 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, 10 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 PM implantation are often older.[18] Moreover, pacing-induced adverse cardiac effects and subsequent HF development are relatively slow processes, and evidently, such patients become candidates for CRT upgrades at an older age.[9,10,12]

Chronic RV pacing also increases the incidence of HF 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 HF 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 among CRT upgrade patients was only 34.4%.[2,16,17] Older age, the presence and severity of HF, the high prevalence of tachy-brady syndrome, the need for cardiac implantable electronic device, and the high rate of RV 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

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 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; or median (25th–75th percentile)	74.8 ± 10.5	73.9 ± 10.0	–	–	72 (66–80)	70 (65–80)	72 ± 10	71 ± 10	–	–	74 (66–82)	74 (65–81)
NYHA class, *n* (%)												
I	0 (0)	0 (0)	11 (10.4)	16 (15.8)	370 (3)	60 (2.5)						
II	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)
III	101 (47)	78 (53.8)	28 (26.4)	27 (26.7)	5909 (55)	1392 (59.1)	109 (10.0)[a]	73 (10.0)[a]	186 (20.8)	174 (19.2)	253 (45)	252 (45)
IV	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 (μmol/L), mean ± SD; or median (25th–75th percentile)	111.6 ± 34.2	114.3 ± 30.4	–	–	100 (83–129)	108 (88–139)	1.2 ± 0.4	1.2 ± 0.4	–	–	–	–
6MWT (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)	–	–
ACE-I, *n* (%)	157 (73.0)	108 (74.5)	–	–	9163 (86)[b]	1925 (83.7)[b]	839 (77.0)	563 (77.0)	859 (96.1)[b]	878 (97.1)[b]	544 (97)	533 (96)
ARB, *n* (%)	43 (20.0)	23 (15.9)	–	–			227 (20.8)	148 (20.2)				
Beta-blockers, *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 diuretics or diuretics, *n* (%)	170 (79.1)	118 (81.4)	–	–	8621 (81)	>80%	824 (75.7)	533 (72.9)	757 (84.7)	756 (83.6)	–	–
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), mean ± SD	231.9 ± 80.8	227.3 ± 74.4	–	–	–	–	245 ± 60	251 ± 65	–	–	–	–
LVESV (ml), mean ± SD	176.3 ± 67.1	171.8 ± 63.8	–	–	–	–	175 ± 48	179 ± 53	–	–	–	–

6MWT, 6-min walk test; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy with defibrillator; ICD, implantable cardioverter defibrillator; 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; SD, standard deviation.

[a]NYHA class III and IV.

[b]ACE-I or ARB.

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 11 088 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 HF due to the high percentage of RV 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 ischaemic aetiology 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 PM devices, followed by a very high (87%) RV pacing rate. Almost 36% of the patients were PM-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 RV 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 HF; 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 HF worsening within 12 months prior to enrolment. 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 ejection fraction 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 patients with HF with reduced ejection fraction.[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 RCT involving patients with a previously implanted PM or ICD with intermittent or permanent RV pacing in which outcomes after a CRT-D upgrade were investigated.

Our cohort baseline clinical characteristics showed that patients referred for CRT upgrades represent an elderly, highly vulnerable, advanced HF 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 HF. 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, HF events, and echocardiographic response. The expected results may contribute to a more precise definition and extension of the current guidelines for CRT upgrade.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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