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Upgrades from Previous Cardiac Implantable Electronic Devices Compared to *De Novo* Cardiac Resynchronization Therapy Implantations: Results from CRT Survey-II in the Turkish Population

Önceki Kardiyak İmplante Edilebilir Cihazdan Upgrade İşleminin *De Novo* Kardiyak Resenkronizasyon Tedavisi İmplantasyonu ile Kıyaslanması: CRT Survey-II Çalışmasının Türk Popülasyonundaki Sonuçları

ORIGINAL ARTICLE
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ABSTRACT

Objective: Cardiac resynchronization therapy is the guideline-directed treatment option in selected heart failure with reduced left ventricular ejection fraction patients. Data regarding the contemporary clinical practice of cardiac resynchronization therapy in Turkey have been published recently. This sub-study aims to compare clinical and periprocedural characteristics between cardiac resynchronization therapy upgrade and *de novo* implantations.

Methods: Turkish arm of the Cardiac Resynchronization Therapy Survey-II was conducted between October 1, 2015, and December 31, 2016, at 16 centers. All consecutive patients who underwent an upgrade to cardiac resynchronization therapy system (n=60) or *de novo* cardiac resynchronization therapy implantation (n=335) were eligible.

Results: Distribution of age, gender, and heart failure etiology were similar in the 2 groups. Atrial fibrillation, valvular heart disease, and chronic kidney disease were more common in cardiac resynchronization therapy upgrade patients. Narrow intrinsic QRS duration and left ventricular ejection fraction being <25% were more common in cardiac resynchronization therapy upgrade patients. Successful first attempt rates were 100% and 98.8% in upgrade and *de novo* implantation groups. Rates of periprocedural complications were similar between the 2 groups (8.3% vs. 5.9%), but postprocedural adverse events during hospitalization were more common in cardiac resynchronization therapy upgrade patients (18.3% vs. 9.0%), with worsening heart failure being the most common reason. Prescription rates of angiotensin-converting enzyme inhibitors/angiotensin-II receptor blockers, mineralocorticoid receptor antagonists, and beta-blockers were >75% in both groups, and only beta-blockers were prescribed at rates of >90% in both groups.

Conclusion: Cardiac resynchronization therapy upgrades are performed with high procedural success rates and without excess periprocedural complication risk. Feared complications of cardiac resynchronization therapy upgrades due to the pre-existing device should not delay the procedure if indicated.

Keywords: Heart failure, device therapy, CRT upgrade, complications, adverse events

ÖZET

Amaç: Kardiyak resenkronizasyon tedavisi, seçili azalmış sol ventrikül ejeksiyon fraksiyonlu kalp yetmezliği hastalarında kılavuzlar tarafından önerilen tedavi seçeneğidir. Türkiye'deki çağdaş kardiyak resenkronizasyon tedavisi klinik uygulamasına ilişkin veriler yakın zamanda yayımlanmıştır. Bu altgrup çalışması, kardiyak resenkronizasyon tedavisine upgrade ve *de novo* implantasyon gruplarında klinik ve periprosedürel özellikleri kıyaslamayı hedeflemektedir.

Yöntemler: CRT Survey-II çalışmasının Türk kolu, 1 Ekim 2015-31 Aralık 2016 tarihleri arasında 16 merkezde gerçekleştirilmiştir. Kardiyak resenkronizasyon tedavisi sistemine upgrade edilen (n=60) ya da *de novo* kardiyak resenkronizasyon tedavisi implantasyonu gerçekleştirilen (n=335) ardışık tüm hastalar çalışmaya dahil edilmiştir.

Bulgular: Her iki grupta yaş, cinsiyet ve kalp yetmezliği etyolojisi benzerdi. Atriyal fibrilasyon, kalp kapak hastalığı ve kronik böbrek hastalığı; kardiyak resenkronizasyon tedavisine upgrade hastalarında daha sıktı. Kardiyak resenkronizasyon tedavisine upgrade hastalarında intrinsik QRS

süresi daha dar ve sol ventrikül ejeksiyon fraksiyonu daha sıklıkla <%25 idi. Başarılı ilk deneme hızı, upgrade ve *de novo* implantasyon gruplarında sırasıyla %100 ve %98,8'di. Her iki grupta periprosedürel komplikasyon hızları benzerdi (sırasıyla %8,3 ve %5,9). İşlem sonrası hastanede yatış süresince ortaya çıkan istenmeyen olaylar, kardiyak resenkronizasyon tedavisi upgrade grubunda daha sık olup (%18,3 vs. %9,0), bunların içinde en sıklıkla gözlenen kötüleşen kalp yetmezliğiydi. Anjiyotensin dönüştürücü enzim inhibitörleri/anjiyotensin-II reseptör blokörleri, mineralokortikoid reseptör antagonistleri ve beta blokörlerin reçete edilme hızları her iki grupta >%75 olup yalnızca beta blokörlerin her iki grupta reçete edilme hızı >%90 idi.

Sonuç: Kardiyak resenkronizasyon tedavisine upgrade, artmış periprosedürel komplikasyon riski olmaksızın yüksek işlem başarısı ile gerçekleştirilmektedir. Kardiyak resenkronizasyon tedavisine upgrade işleminin mevcut cihaz kaynaklı korkulan komplikasyonları, endike işlemin ertelenmesine neden olmamalıdır.

Anahtar Kelimeler: Kalp yetmezliği, cihaz tedavisi, KRT upgrade, komplikasyonlar, istenmeyen olaylar

Cardiac resynchronization therapy (CRT) is the guideline-directed treatment option in selected patients with heart failure (HF) with reduced ejection fraction to improve morbidity and mortality.[1,2] Clinical CRT trials have focused on *de novo* implantation and upgrade patients are less represented. Although upgrade procedure has long been considered to be more complex and related to periprocedural complications due to a potential risk of damaging and extracting old leads,[3,4] an increasing trend of CRT upgrade procedures exists in recent years.

The majority of data comparing outcomes between upgrade and *de novo* CRT implantations are obtained from observational studies. A systematic review and meta-analysis that included papers published between 2006 and 2017 have compared outcomes between CRT upgrade and *de novo* implantations (n=16 papers; 468 205 *de novo* and 21 363 upgrade procedures).[5] All-cause mortality (crude relative risk [RR]: 1.19, 95% CI: 0.88-1.60, P =.27, I^2 = 90.1%) or HF events (crude RR: 0.96, 95% CI: 0.70-1.32, P =.81, I^2= 28.0%) did not differ between upgrade compared to *de novo* implantations.[5] In addition, QRSd narrowing (ΔQRS: 29.5 ms vs. 9.6 ms, P = .485), reverse remodeling, reflected with improvement in left ventricular ejection fraction (LVEF) (ΔEF: 9.35% vs. 6.85%, P = .235) and decrease in end-diastolic volume (EDV) (ΔEDV: 20 mL vs. 23.0 mL, P = .730), and clinical response reflected with improvement in New York Heart Association (NYHA) class (ΔNYHA: 0.70 vs. 0.74, P = .737) were similar in upgrade and *de novo* implantations.[5] Results with regard to periprocedural complication, however, have revealed contradictory findings.[4,6,7]

ABBREVIATIONS

AF	Atrial fibrillation
AV	Atrioventricular
BNP	Brain natriuretic peptide
CKD	Chronic kidney disease
CRT	Cardiac resynchronization therapy
ECG	Electrocardiography
EDV	End-diastolic volume
ESC	European Society of Cardiology
HF	Heart failure
ICD	Implantable cardioverter-defibrillator
LBBB	Left bundle branch block
LV	Left ventricular
LVEF	Left ventricular ejection fraction
NYHA	New York Heart Association
PPM	Permanent pacemaker
RV	Right ventricular

Data regarding the contemporary clinical practice of CRT in Turkey have been published recently, which was based on the European-wide performed CRT Survey-II.[8] However, differences in clinical and periprocedural characteristics between *de novo* implantation and upgrade groups have not been investigated in the Turkish population. Herein, we aimed to present relevant findings from the Turkish arm of CRT Survey-II registry.

Methods

Cardiac Resynchronization Therapy Survey-II was designed and conducted as a joint project of the European Heart Rhythm Association and Heart Failure Association.[9] The survey was undertaken in 42 European Society of Cardiology (ESC) member countries from October 1, 2015, to December 31, 2016. Annual cardiac device implantation profiles of participating centers, as well as characteristics of hospital facilities and implanters, were provided in the previous report.[8]

The study was in line with the principles of the Declaration of Helsinki and was approved by the Clinical Research Ethics Committee of Bahçeşehir University (2015-14/03).

Survey Population

All consecutive patients who underwent a *de novo* CRT implantation or an upgrade to a CRT system from an existing implantable cardioverter-defibrillator (ICD) or permanent pacemaker (PPM) were eligible for inclusion, regardless of the procedural success. Generator replacements and revisions of existing CRT devices were excluded.

Data Collection and Management

An internet-based electronic case report form was filled out for each patient. Data management and analysis were organized by IHF GmbH Institut für Herzinfarktforschung (Ludwigshafen). All percentages are presented relative to the total number of patients with available information. Absolute numbers and percentages are shown for categorical variables. Means (with standard deviations) or medians (with interquartile range [IQR]) are used for continuous variables. Categorical variables were compared between subgroups by the chi-square test and continuous variables by the Mann–Whitney–Wilcoxon test. A significance level of P < .05 was assumed for the statistical tests. All statistical analyses were performed using SAS statistical software (version 9.4, Cary, NC, USA).

Results

A total of 16 centers participated in the CRT Survey-II from Turkey. The number of patients that underwent *de novo*

implantation and CRT upgrade was 335 and 60, respectively. Of 60 patients who underwent CRT upgrade, 25.0% (15/60) had PPM and 75.0% (45/60) had ICD at baseline.

Baseline Characteristics

Baseline characteristics of the study population are shown in Table 1. Age and gender distribution were similar between the 2 groups (*P*=.263 and .092, respectively). Heart failure etiology distribution was also similar (*P* = .438). Elective admission was less common in CRT upgrade patients (70.0% vs. 86.9%, *P* =.001).

Atrial fibrillation (AF) (31.7% vs. 18.8%, *P*=.024), valvular heart disease (50.0% vs. 28.1%, *P*=.001), and chronic kidney disease (CKD) (38.3% vs. 22.5%, *P*=.009) were more common in CRT upgrade patients.

Pre-implantation Clinical Characteristics and Laboratory Test Results

Pre-implantation clinical characteristics and laboratory test results of the study population are given in Table 2. CRT upgrade patients had lower body mass index (mean 24.9 vs. 26.5 kg/m^2, *P* = .033). Brain natriuretic peptide (BNP), N-terminal-BNP, hemoglobin, and serum creatinine levels were similar between the 2 groups (*P* = .370, *P* = .055, *P* = .332 and *P* = .330, respectively).

Pre-implantation Electrocardiography and LVEF Characteristics

Pre-implantation electrocardiography (ECG) and LVEF characteristics are shown in Table 3. Heart rate was slower (median:

Table 1. Baseline Characteristics of the Study Population

	CRT Upgrade (n=60)	*De Novo* Implantation (n=335)	*P*
Age (years)	61.1±13.5	64.2±10.9	.263
Age (%)			
<65	56.7 (34/60)	47.8 (160/335)	
65≤ age <75	30.0 (18/60)	35.8 (120/335)	
≥75	13.3 (8/60)	16.4 (55/335)	
Gender: male (%)	80.0 (48/60)	69.3 (232/335)	.092
Primary heart failure etiology (%)			.438
Ischemic	56.7 (34/60)	51.3 (172/335)	
Non-ischemic	43.3 (26/60)	48.4 (162/335)	
Other	0	0.3 (1/335)	
Patient admission (%)			
Elective admission	70.0 (42/60)	86.9 (291/335)	.001*
Referral from another center	16.7 (10/60)	22.7 (76/335)	.298
Currently enrolled in a clinical trial	0	10.5 (35/334)	.009*
Myocardial infarction (%)	50.0 (30/60)	41.5 (139/335)	.220
Prior revascularization (PCI/CABG) (%)	55.0 (33/60)	48.1 (161/335)	.322
Hypertension (%)	63.3 (38/60)	56.1 (188/335)	.298
Atrial fibrillation (%)	31.7 (19/60)	18.8 (63/335)	.024*
Type of atrial fibrillation (%)			.652
Paroxysmal	21.1 (4/19)	27.0 (17/63)	
Persistent	42.1 (8/19)	39.7 (25/63)	
Permanent	36.8 (7/19)	33.3 (21/63)	
Valvular heart disease (%)	50.0 (30/60)	28.1 (94/335)	.001*
Valve surgery/procedure (%)	18.8 (6/32)	17.5 (22/126)	.865
Aortic valve replacement	66.7 (4/6)	45.5 (10/22)	.357
Mitral valve replacement	50.0 (3/6)	59.1 (13/22)	.690
Mitral valve repair	33.3 (2/6)	9.1 (2/22)	.133
Other	0	9.1 (2/22)	.443
Obstructive lung disease (%)	3.3 (2/60)	11.9 (40/335)	.046*
Diabetes mellitus (%)	33.3 (20/60)	31.6 (106/335)	.796
Anemia (%)	30.0 (18/60)	23.9 (80/335)	.312
Chronic kidney disease (%)	38.3 (23/60)	22.5 (75/334)	.009*
Dialysis (%)	0	5.3 (4/75)	.258
Heart failure hospitalization during past year (%)	55.0 (33/60)	50.7 (170/335)	.544

CABG, coronary artery bypass grafting; CRT, cardiac resynchronization therapy; PCI, percutaneous coronary intervention. *A *P* value <.05 denotes statistical significance.

Table 2. Preimplantation Clinical Characteristics and Laboratory Test Results of the Study Population

	CRT Upgrade (n=60)	*De Novo* Implantation (n=335)	*P*
NYHA class (%)			.279
I	1.7 (1/60)	3.0 (10/335)	
II	56.7 (34/60)	44.5 (149/335)	
III	33.3 (20/60)	46.9 (157/335)	
IV	8.3 (5/60)	5.7 (19/335)	
BMI (kg/m^2)	24.9 ± 4.1	26.5 ± 4.7 (n=327)	.033*
BMI class (%)			
< 18.5	6.7 (4/60)	2.8 (9/327)	
18.5 ≤ BMI <25	38.3 (23/60)	34.9 (114/327)	
25 ≤ BMI <30	45.0 (27/60)	41.6 (136/327)	
≥30	10.0 (6/60)	20.8 (68/327)	
Diastolic BP (mm Hg)	73.8 ± 12.6	75.9 ± 11.8	.209
Systolic BP (mm Hg)	121.0 ± 18.1	124.3 ± 19.4	.249
NT-pro BNP (pg/mL)	250 (150, 300) (n=4)	650 (230, 2126) (n=49)	.055
BNP (pg/mL)	675 (200, 1143) (n=28)	545 (181, 900) (n=78)	.370
Hemoglobin (g/dL)	13.1 ± 1.7	12.9 ± 1.8 (n=329)	.332
Serum creatinine (μmol/L)	96 (80, 124)	89 (78, 116)	.330

BMI, body mass index; BNP, brain natriuretic peptide; BP, blood pressure; NYHA, New York Heart Association. *A *P* value <.05 denotes statistical significance.

Table 3. Preimplantation Electrocardiography and LVEF Characteristics of the Study Population

	CRT Upgrade (n=60)	*De Novo* Implantation (n=335)	*P*
Heart rate (bpm)	75 (70, 88)	80 (70, 90)	.030*
Atrial rhythm (%)			<.001*
Sinus	66.7 (40/60)	85.1 (285/335)†	
Atrial fibrillation	25.0 (15/60)	13.1 (44/335)†	
Atrial paced	3.3 (2/60)	0	
Other	5.0 (3/60)	1.8 (6/335)	
PR interval (ms)	145 (130, 155) (n=37)	150 (130, 180) (n=288)	.100
AV block II/III (%)	33.3 (20/60)	4.8 (16/335)	<.001*
Intrinsic QRS duration (ms)	141±16 (n=41)	152±19 (n=335)	<.001*
Intrinsic QRS duration (%)			
Intrinsic QRSd <120	4.9 (2/41)	3.3 (11/335)	
120≤ Intrinsic QRSd <130	14.6 (6/41)	5.4 (18/335)†	
130≤ Intrinsic QRSd <150	41.5 (17/41)	23.6 (79/335)†	
150 ≤ Intrinsic QRSd <180	39.0 (16/41)	59.7 (200/335)†	
Intrinsic QRSd ≥ 180	0	8.1 (27/335)	
QRS morphology (%)			
Normal	1.7 (1/59)	3.0 (10/335)	.579
Left bundle branch block	55.9 (33/59)	84.2 (282/335)	<.001*
Right bundle branch block	1.7 (1/59)	1.8 (6/335)	.959
Indeterminate	25.4 (15/59)	11.3 (38/335)	.003*
Not available	15.3 (9/59)	0	<.001*
AV node ablation in patients with AF (%)	20.0 (3/15)	27.3 (12/44)	.576
Performed	66.7 (2/3)	41.7 (5/12)	
Planned	33.3 (1/3)	58.3 (7/12)	
LVEF by any method (%)	25 (18, 30)	25 (20, 30)	.006*
LVEF by any method (%)			
LVEF by any method <25	50.0 (30/60)	31.0 (104/335)†	
25 ≤ LVEF by any method ≤ 35	48.3 (29/60)	66.3 (222/335)†	
LVEF by any method > 35	1.7 (1/60)	2.7 (9/335)	

AF, atrial fibrillation; AV, atrioventricular; LVEF, left ventricular ejection fraction; QRSd, QRS duration. *A *P* value <.05 denotes statistical significance. †Indicates statistical significance for this row, calculated using the odds ratios including 95% CIs.

Table 4. Details with Respect to Successful CRT Implantation in the Study Population

	CRT Upgrade (n=60)	*De Novo* Implantation (n=335)	*P*
Type of device (%)			.295
CRT-pacemaker	0	1.8 (6/331)	
CRT-defibrillator	100.0 (60/60)	98.2 (325/331)	
Duration (minutes)	64 (40, 90)	76 (55, 116)	.002*
Fluoroscopy time (minutes)	15 (4, 25)	19 (11, 30)	.005*
Prophylactic antibiotics (%)	100.0 (60/60)	99.7 (330/331)	.670
Test shock (%)	0	2.1 (7/330)	.259
Left ventricular lead placement successful (%)	98.3 (59/60)	97.3 (322/331)	.635
Lead placement epicardially (%)	6.8 (4/59)	12.7 (41/322)	
Left ventricular lead placement unsuccessful (%)	1.7 (1/60)	2.7 (9/331)	.635
Coronary sinus not identified	0	22.2 (2/9)	
Extracardiac simulation	0	0	
No suitable coronary vein	100.0 % (1/1)	66.7 (6/9)	
Complication	0	0	
Other	0	11.1 (1/9)	
Left ventricular lead type (%)			.105
Unipolar	5.0 (3/60)	2.7 (9/330)	
Bipolar	55.0 (33/60)	70.0 (231/330)†	
Multipolar	40.0 (24/60)	27.3 (90/330)†	
Coronary venogram performed (%)	88.3 (53/60)	90.9 (301/331)	.526
Venogram performed with occlusion (%)	13.2 (7/53)	30.0 (90/300)	.012*
Dilatation of coronary vein performed (%)	5.0 (3/60)	8.8 (29/331)	.328
Phrenic nerve stimulation tested (%)	71.7 (43/60)	70.4 (233/331)	.842
Left ventricular lead position evaluation (%)			.038*
Biplane x-ray projection	61.7 (37/60)	80.5 (243/302)†	
Monoplane LAO	36.7 (22/60)	17.2 (52/302)†	
Monoplane RAO	1.7 (1/60)	2.3 (7/302)	
LAO site evaluation (%)			.363
Anterior	13.6 (8/59)	9.5 (31/325)	
Lateral	69.5 (41/59)	70.5 (229/325)	
Posterior	16.9 (10/59)	20.0 (65/325)	
RAO site evaluation (%)			.009*
Basal	22.0 (13/59)	17.5 (57/325)	
Middle	78.0 (46/59)	65.5 (213/325)	
Apical	0	16.9 (55/325)	
Left ventricular lead position optimized (%)	42.4 (25/59)	37.8 (125/331)	.503
Electrical delay such as	0	40.0 (50/125)	
Paced QRS duration	40.0 (10/25)	69.6 (87/125)†	
Other means	100.0 (25/25)	54.8 (68/124)	

CRT, cardiac resynchronization therapy; LAO, left anterior oblique; RAO, right anterior oblique. *A *P* value <.05 denotes statistical significance. †Indicates statistical significance for this row, calculated using the odds ratios including 95% CIs.

75 vs. 80 bpm, *P* = .030) and 2°/3° atrioventricular (AV) block was more common (33.3% vs. 4.8%, *P* < .001) in CRT upgrade patients. Intrinsic QRS duration (QRSd) was narrower (mean: 141 vs. 152 ms, *P* < .001), yet 80.5% had an intrinsic QRSd ≥ 130 ms. Left bundle branch block was found to be less (55.9% vs. 84.2%, *P* < .001) and indeterminate rhythm was more common (25.4% vs. 11.3%, *P* = .003) in CRT upgrade patients.

In the CRT upgrade group, 15 of 19 patients with AF (78.9%) had persistent or permanent AF. Of these 15 patients with AF, AV node ablation was either performed or planned in 3 patients (20.0%). In the *de novo* implantation group, 46 of 63 patients with AF (73.0%) had persistent or permanent AF. Of these 46 patients with AF, 44 had data regarding AV node ablation which showed that AV node ablation was either performed or planned in 12 of 44 patients (27.3%). AV node ablation (either performed or planned) rates were similar in the 2 groups (*P*=.576) (Table 3).

A greater proportion of CRT upgrade patients had LVEF< 25% (50.0% vs. 31.0%, *P* < .05) (Table 3).

Clinical Indications for CRT

In the CRT upgrade group, the indications were as follows: (1) HF or left ventricular (LV) dysfunction and indication for ICD

Table 5. Periprocedural Evaluation in the Study Population

	CRT Upgrade (n=60)	*De Novo* Implantation (n=335)	*P*
Periprocedural complications following attempts (%)	8.3 (5/60)	5.9 (20/338)	.477
Death	0	0	-
Bleeding	20.0 (1/5)	40.0 (8/20)	.405
Requiring intervention	100.0 (1/1)	25.0 (2/8)	
Pocket hematoma	0	75.0 (6/8)	
Pneumothorax	0	5.0 (1/20)	.610
Hemothorax	0	0	-
Coronary sinus dissection	0	20.0 (4/20)	.275
Pericardial tamponade	20.0 (1/5)	5.0 (1/20)	.269
Other	60.0 (3/5)	30.0 (6/20)	.211
Post-implantation ECG			
Paced QRS duration (ms)	124±15 (n= 59)	123±17 (n= 328)	.585
Paced-intrinsic QRS duration (ms)	-14 (-25, -2) (n= 41)	-30 (-45, -15) (n= 328)	<.001*
Device programming			
AV programming performed prior to discharge (%)	75.0 (45/60)	71.2 (237/333)	.544
VV programming performed prior to discharge (%)	76.7 (46/60)	74.7 (248/332)	.746
Device-based software optimization for AV or VV (%)			.364
If yes, was it	71.7 (43/60)	65.7 (218/332)	.003*
Automatic	2.3 (1/43)	21.6 (47/218)†	
Manual	97.7 (42/43)	78.4 (171/218)†	

AV, atrioventricular; ECG, electrocardiogram; VV, ventriculoventricular. *A P value <.05 denotes statistical significance. †Indicates statistical significance for this row, calculated using the odds ratios including 95% CIs.

(56.7%), (2) HF with wide QRS (53.3%), and (3) PM indication and expected a high percentage of right ventricular (RV) pacing (33.3%). Heart failure with wide QRS was a less common (vs. 74.6%, *P* = .001) PM indication and expected a high percentage of RV pacing was a more common (vs. 3.9%, *P* < .001) indication in the upgrade group compared with the *de novo* implantation group.

Details with respect to CRT implantation procedure

All CRT upgrade patients were successfully implanted at the first attempt, where 331 of 335 patients (98.8%) underwent successful *de novo* implantation (3 of them were successfully implanted in the second attempt). Reasons for unsuccessful attempts in *de novo* implantation patients were unsuccessful LV lead placement in 6 patients and pericardial tamponade in 1 patient. Median time from admission to implantation was longer in CRT upgrade patients (median: 3, IQR: 2-7 days vs. median: 2, IQR: 1-3 days, *P* = .001).

Details with respect to successful CRT attempt

Details with respect to successful CRT attempt in the study population are provided in Table 4. The procedure (median: 64 minute vs. 76 minute, *P* = .002) and fluoroscopy (median: 15 minute vs. 19 minute, *P* = .005) lasted shorter in CRT upgrade patients. Multipolar LV lead was more frequently preferred in CRT upgrade patients (40.0% vs. 27.3%, *P* < .05).

Periprocedural and postprocedural evaluation

Periprocedural complications are listed in Table 5. Rates of periprocedural complications were similar between the 2 groups. Narrowing in QRSd was less in CRT upgrade patients (median: −14 ms vs. −30 ms, *P* < .001).

Post-implantation status

Post-implantation status in the study population is detailed in Table 6. Total hospital stay was longer in CRT upgrade patients (median: 5 days vs. 3 days, *P* < .001). Postprocedural adverse events during hospitalization were more common in CRT upgrade patients (18.3% vs. 9.0%, *P* = .028), mostly driven by worsening HF being more common in CRT upgrade patients (8.3% vs. 0.6%, *P* < .001). Adverse events and complications that necessitated an intervention are listed in Table 7.

Device remote monitoring at follow-up was planned in only 6.7% of CRT upgrade patients and 12.0% of *de novo* implantation patients, comparable in both groups (*P* = .227).

Drug therapy at discharge

Drug therapy at discharge in the study population is shown in Table 7. Angiotensin-converting enzyme inhibitors/angiotensin-II receptor blockers, mineralocorticoid receptor antagonists, and beta-blockers were prescribed to >75% of patients in the 2 groups, with only beta-blockers being prescribed to >90% of patients in both groups. Digoxin (29.3% vs. 13.8%, *P* = .003), amiodarone (25.0% vs. 11.9%, *P* = .009), and other antiarrhythmic drugs (7.1% vs. 1.3%, *P* = .005) were more commonly prescribed to CRT upgrade patients. Oral anticoagulants were also prescribed more frequently to CRT upgrade patients (41.7% vs. 28.0%, *P* = .034).

Discussion

This cross-sectional study shows that although constituting less than one-fifth of CRT implantation procedures between October 1, 2015, to December 31, 2016, in 16 participating Turkish centers, CRT upgrade had similar periprocedural success

Table 6. Post-implantation Status in the Study Population

	CRT Upgrade (n=60)	*De Novo* Implantation (n=335)	*P*
Total length of hospital stay (days)	5 (3, 10)	3 (2, 5)	<.001*
Discharge status (%)			.677
Alive	100.0 (60/60)	99.7 (333/334)	
Death	0	0.3 (1/334)	
Cardiovascular death		100.0 (1/1)	
Adverse event during hospitalization after procedure	18.3 (11/60)	9.0 (30/335)	.028*
Myocardial infarction	0	1	.672
Stroke	0	0	-
Infection	5.0 (3/60)	1.5 (5/335)	.076
Worsening heart failure	8.3 (5/60)	0.6 (2/335)	<.001*
Worsening renal function	5.0 (3/60)	3.3 (11/335)	.508
Arrhythmias	5.0 (3/60)	2.7 (9/335)	.336
Other	0	1.5 (5/335)	.341
Complications that necessitated an intervention	3.3 (2/60)	3.0 (10/335)	.885
Phrenic nerve stimulation	1.7 (1/60)	0.3 (1/335)	.169
Lead dislocation or displacement	0	2.4 (8/335)	.227
Infection	1.7 (1/60)	0.3 (1/335)	.169
Other	1.7 (1/60)	0	.018*
Follow-up (%)			
Will the device be monitored by telemetry	6.7 (4/60)	12.0 (40/333)	.227

*A *P* value <.05 denotes statistical significance.

and complication rates with *de novo* implantation. On the other hand, upgrade procedure was associated with a longer hospital stay, increased adverse event rates during hospitalization, and less narrowing in QRSd. This has been the first study to compare periprocedural characteristics in Turkish patients undergoing an upgrade or *de novo* CRT implantations.

Although our data are not generalizable to the whole country, 15.2% of the CRT implants in the study sample were upgraded to CRT. This seems to be even lower than the average European proportion in the CRT Survey-II, which was 23.2%.[6] Previously suggested reasons for less performance of CRT upgrades in potential candidates include the fear of increased complication risk, the concern of increased cost when performed prior to expected generator change date, and lack of RCT data demonstrating the efficacy of upgrade.[10] It has been speculated that unwillingness to perform a CRT upgrade at follow-up might even stimulate clinicians to implant a *de novo* CRT device in HF patients despite the presence of a clearer indication for implantation of a conventional device.[11]

Our data suggest that CRT upgrades could be performed with a comparable procedural success and risk of periprocedural complications. This is in line with data from the entire CRT Survey-II cohort[6] that have investigated periprocedural characteristics of CRT practice patterns across 42 ESC member countries (n=2396 upgrades and n=7933 *de novo* implantations). CRT Survey-II has shown similar procedural success (97.1% vs. 97.3%, *P*=.544) and periprocedural complication rates (5.1% vs. 5.7%, *P*=.256) in upgrade and *de novo* implantation groups, respectively.[6] The most common periprocedural complication was coronary sinus dissection, making up 33.6% of the periprocedural complications.[6] In the Turkish arm of CRT Survey-II, all of the 60 patients undergoing CRT upgrade (100.0%) had successful implantation and 8.3% of the upgrade patients experienced a periprocedural complication. Despite the lack of a statistical comparison between the entire European and Turkish cohorts, a numerically higher prevalence of complication risk was observed in the Turkish cohort. However, it should be noted that the number of patients undergoing CRT upgrade was markedly lower than the corresponding number in the entire European cohort and that coronary sinus dissection was not among these complications. Of the 5 periprocedural complications observed in the Turkish cohort, 1 was bleeding requiring intervention, 1 was pericardial tamponade, and 3 were classified as "others."

A recent study from the United States with the largest single-center cohort of CRT upgrade patients aiming to compare procedural success and complication rates at 90 days between upgrade (n=549) and *de novo* (n=947) procedures has supported CRT Survey-II data, demonstrating similar rates (procedural success: 96% vs. 97%, respectively; *P*=.28 and 90-day complication: 4.6% vs. 5.1%, respectively, *P* = .70).[7] With non-LV lead dislodgement or malfunction (1.4%) and deep vein thrombosis (1.3%) being the most common complications in both groups, rates of none of the specific complications differed between CRT upgrade and *de novo* implantation groups.[7] Mortality rates were also similar in these 2 groups (2.9% vs. 1.8%, *P* = .20).[7] This study is important to show that CRT upgrades are not more

Table 7. Drug Therapy at Discharge in the Study Population

	CRT Upgrade (n=60)	*De Novo* Implantation (n=335)	*P*
Loop diuretic (%)	77.6 (45/58)	82.5 (274/332)	.368
ACEi/ARB (%)	82.8 (48/58)	90.6 (300/331)	.072
Mineralocorticoid receptor antagonist (%)	75.9 (44/58)	78.4 (257/328)	.673
Beta blocker (%)	94.9 (56/59)	96.1 (319/332)	.676
Ivabradine (%)	8.8 (5/57)	16.6 (53/320)	.133
Digoxin (%)	29.3 (17/58)	13.8 (44/318)	.003*
Calcium channel blocker (%)	3.6 (2/56)	4.1 (13/318)	.856
Amiodarone (%)	25.0 (14/56)	11.9 (38/319)	.009*
Other anti-arrhythmic agent (%)	7.1 (4/56)	1.3 (4/318)	.005*
Oral anticoagulant (%)	41.7 (25/60)	28.0 (91/325)	.034*
Warfarin	52.0 (13/25)	52.7 (48/91)	.947
Dabigatran	4.0 (1/25)	12.1 (11/91)	.240
Rivaroxaban	28.0 (7/25)	24.2 (22/91)	.696
Apixaban	16.0 (4/25)	11.0 (10/91)	.496
Anti-platelet agent (%)	53.3 (32/60)	65.4 (219/335)	.074
Aspirin	57.4 (31/54)	63.1 (200/317)	.426
Clopidogrel	3.7 (2/54)	16.1 (51/317)	.016*
Ticagrelor	0	0.3 (1/317)	.679
Prasugrel	0	0.6 (2/317)	.558
None	40.7 (22/54)	30.9 (98/317)	.154
Dual and triple therapy (%)			
Dual antiplatelet therapy	1.9 (1/54)	11.0 (35/317)	.035*
Oral anticoagulation and P2Y12 inhibitor	5.0 (3/60)	3.1 (10/325)	.449
Triple therapy	5.0 (3/60)	1.8 (6/325)	.137

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker. *A *P* value <.05 denotes statistical significance.

complication-prone than *de novo* implantations not only during the periprocedural phase but also at 90-day follow-up. In addition, this study highlights the fact that when optimally managed, even the presence of veno oclusive disease, which is a commonly feared pre-existing condition in CRT upgrade candidates, does not result in increased risk of upper extremity deep vein thrombosis (95% CI for difference: 1.5%-2.2%, *P* = 1.00) or the composite rate of unsuccessful LV lead placement or complication (95% CI for difference: 5.2%-5.6%, *P* = 1.00).[7]

Our data show that CRT upgrade procedure was associated with longer hospital stays and increased rates of adverse events during hospitalization that were managed in accordance with clinical practice guidelines.[1,12] These vary from data of the entire European CRT Survey-II cohort, which revealed similar length of hospital stay and adverse event rates during hospitalization in both groups.[6] Less patients being electively admitted for CRT upgrade and longer median time from admission to implantation in the Turkish cohort may reflect a more decompensated status at admission. AF, CKD, valvular heart disease, and chronic obstructive pulmonary disease were also considerably more prevalent, and LVEF was significantly lower in patients undergoing CRT upgrade in the Turkish population, reflecting a sicker patient profile. These factors may have contributed to the higher adverse event rate during hospitalization after the procedure, which was mostly driven by a higher incidence of worsening HF. It may also be speculated that less utilization of biplane x-ray projection for the evaluation of LV lead position in CRT upgrade patients may have resulted in this finding. Whether differences exist between 2 groups regarding the amount of administered contrast medium has not been assessed in the current study.

Our study has shown less QRSd narrowing in the CRT upgrade group. This may be explained by several features of patients in the upgrade group, including (1) narrow intrinsic QRSd, (2) left bundle branch block (LBBB) being less common as the intrinsic QRS morphology, (3) sinus rhythm being less common and AV node ablation being performed or planned only in 20% of patients with AF, (4) PPM indication and expected high percentage of RV pacing being a more common indication, and (5) having a greater burden of co-morbidities. In addition, time lag before the upgrade procedure (reflected with considerably higher LVEF at the time of index RV pacing) may have potentially contributed to interferences in expected reverse remodeling as suggested in a previous paper.[13] Even though findings from our study do not provide evidence regarding postprocedural clinical response rates, controversial results exist regarding clinical outcomes after upgrade compared to *de novo* implantation.[14-16] Authors of the observational study reporting unfavorable clinical outcomes (fewer patients experiencing improvement of at least 1 New York Heart Association functional class, improvement of LVEF, and decrease of LV end-diastolic diameter determined using echocardiography at 6-month follow-up; increased all-cause mortality at mean 37-month follow-up) after CRT upgrade (n=177) when compared to *de novo* implantation

(n=375) have suggested that abovementioned factors may have contributed to reduced benefit.[14]

Due to limitations in the sample size, differences in QRSd narrowing have not been compared between patients upgraded from PPMs and ICDs in the current study. A recent study has highlighted the impact of baseline native LBBB (n=628) versus chronic RV pacing (n=233) in patients undergoing CRT implantation on survival free of LV assist device implantation or heart transplantation at mean 6.5-year follow-up, where patients with chronic RV pacing had inferior survival compared to native LBBB (log-rank $P < .001$) and similar outcomes with both right bundle branch block (log-rank $P = .60$) and non-specific intraventricular conduction defect (log-rank $P = .50$).[16] Nevertheless, both mean and proportional improvements in LVEF evaluated using echocardiography were found to be similar at 3- to 6-month follow-up in chronic RV pacing patients compared with native LBBB and superior to non-LBBB groups.[16] Patient demographic and co-morbidity profiles may partly explain why similar improvement in LVEF has not translated into a survival benefit in the CRT upgrade group compared to patients with baseline LBBB.[16]

Limitations

There are several limitations of this study. First, the nationwide generalizability of the data is low since this survey was answered on a voluntary basis from 16 centers located in 6 cities. In addition, certain characteristics of participating implanters, such as expertise in CRT upgrade procedures and working at high-volume and/or referral hospitals with suitable facilities, may have impacted the results. Second, a selection bias cannot be excluded, sites might have been less reluctant to share unsuccessful attempts, complications, or adverse events. Third, the relatively small sample size has limited comparing periprocedural characteristics between patients upgraded from PPM and ICDs. Fourth, definitions for co-morbidities were lacking, and these might have led to variations between centers. Furthermore, more detailed descriptive data on the procedural complexity of CRT upgrades, such as the number of implanted and explanted leads, were not collected in the current study. Of note, due to the nature of the study, follow-up characteristics are not present.

Conclusion

Findings from CRT Survey-II registry undertaken in 16 Turkish centers show that CRT upgrade is performed with high procedural success rates and without excess periprocedural complication risk. These emphasize the fact that feared complications of CRT upgrade by the physicians due to the pre-existing lead(s) and generator should not delay the procedure if indicated provided that it is undertaken by cardiologists with certain level of expertise. Variations in co-morbidity profiles, CRT indications, and baseline ECG morphologies in upgrade and *de novo* patient populations may account for differences in the course of hospitalization for the procedure, as well as in the extent of post-procedural QRSd narrowing. Findings from this study are also important to highlight the underutilization of mainstay of pharmacological agents in the treatment of HF, as well as a potential for telemonitorization strategies to be incorporated into clinical practice, although the situation was comparable with *de novo* implantation.

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