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Sex-Related Procedural Aspects and Complications in CRT Survey II

A Multicenter European Experience in 11,088 Patients

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ABSTRACT

OBJECTIVES This study sought to compare sex difference for procedural aspects and complications in the European Society of Cardiology CRT Survey II, exploring whether adverse events were related to the type of CRT device implanted.

BACKGROUND Sex-related differences in procedural aspects and complications in patients undergoing cardiac resynchronization therapy (CRT) implantation has not been explored in a real-life population.

METHODS A post-hoc analysis of procedural data and complications in different sexes and factors associated with events was performed from data collected in the European Society of Cardiology CRT Survey II.

RESULTS Of all patients (n = 11,088) included, 24.3% were women. The mean age (70 years of age) of male and female recipients was similar. Female patients more frequently had an idiopathic cardiomyopathy (67.4% vs. 44.1%) and fewer comorbidities, including atrial fibrillation (34.8% vs. 42.8%), diabetes (29.1% vs. 32.1%), chronic obstructive lung disease (10.3% vs. 12.6%), and renal failure (28.7% vs. 31.9%), compared with men. More women compared with men had a pacemaker (56.6% vs. 46.3%) and much less often an implantable cardioverter-defibrillator (CRT-D) (19.0% vs. 34.7%) implant. Periprocedural event rate was the highest in women with CRT with defibrillator (7.1% vs. 4.8% in men), followed by women with a CRT with pacing (5.5% vs. 4.4% in men). The higher periprocedural event rate in CRT-D women was attributable primarily to the occurrence of pneumothorax (1.4%), coronary sinus dissection (2.1%), and pericardial tamponade (0.3%). The rate of in-hospital major adverse events (6.0%) and complications necessitating reoperation (4.0%) was not different among sex and device type.

CONCLUSIONS Women are more likely to experience adverse procedure-related events during CRT implantation. Thus, preventive strategies should be employed to minimize complication rate. (J Am Coll Cardiol EP 2019;5:1048–58) © 2019 by the American College of Cardiology Foundation.

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The well-documented superior clinical benefit from cardiac resynchronization therapy (CRT) in women compared with men (1–5) strongly contrasts a large sex gap in device implantation in patients receiving CRT, as documented by the most recent European Society of Cardiology (ESC) CRT Survey II (6). Over the last decade, this sex gap remained unchanged in Europe and was 27% and 24% in the ESC CRT Survey I and II, respectively (6,7). A similar (men received the majority of CRT implantations in the United States, accounting for 71.4% of all CRTs) and persistent (during 2002 to 2010) sex gap has been reported by Sridhar et al. (8) using the Nationwide Inpatient Sample database, the largest all-payer, inpatient database in the United States.

Until recently, less attention has been paid to sex differences in procedure-related adverse events. Procedure-related complications not only have an immediate effect on health care utilization, but also, if occurring more frequently in 1 sex, may represent a detrimental factor for a wider therapy adoption. At the same time, complication monitoring provides an opportunity for a sex-specific risk preventive strategy. Most of the current evidence of sex-related complications is limited to pacemaker and implantable cardioverter-defibrillator (ICD) (9,10). To date, the evaluation of the relationship between sex and procedure-related adverse events as result of CRT implantation was reported in 2 prospective randomized controlled trials (11,12) in which patients were randomized to a CRT with defibrillator (CRT-D) or an ICD alone. The lack of evidence may also be because women were significantly underrepresented in all major prospective clinical trials in CRT (13). Furthermore, one-third of CRT patients treated in real life receive CRT with pacing (CRT-P); in this sizable group of patients, there is no information about the procedural aspects, intra- or periprocedural adverse events, and whether frequency and characteristics are similar in men and women.

Therefore, in a large prospectively conducted European registry (ESC CRT Survey II), we investigated sex-related procedural aspects of a CRT implantation. Furthermore, we sought to determine whether female CRT patients have similar complication rates to male patients and whether sex-related rates and characteristics of intraprocedural adverse events were associated with the type of implanted device: CRT-D or CRT-P.

ABBREVIATIONS AND ACRONYMS

BMI = body mass index

CRT = cardiac resynchronization therapy

CRT-D = cardiac resynchronization therapy with defibrillator

CRT-P = cardiac resynchronization therapy with pacing

ESC = European Society of Cardiology

ICD = implantable cardioverter-defibrillator

LBBB = left bundle branch block

LV = left ventricular

METHODS

SURVEY DESIGN AND PATIENT RECRUITMENT. The design, rationale, and overall results of the ESC CRT Survey II have been presented in previous publications (2,14). The survey was designed as a joint ESC initiative between the European Heart Rhythm Association and the Heart Failure Association. In brief, between October 1, 2015, and December 31, 2016, 288 centers located in 42 ESC member countries enrolled 11,088 consecutive patients scheduled to receive a CRT. The Scientific Committee continuously monitored the progress of the data collection and took responsibility for a prospectively designed data analysis plan. The Scientific Committee was supported by National Coordinators who were responsible for obtaining national Institutional Review Board approval if required, soliciting each national center and distributing information from the Scientific Committee to individual implanters and centers.

DATA COLLECTION. A central database was created at the data management center, IHF GmbH (Ludwigshafen, Germany), which maintained and interrogated the database and performed analyses. Each implanting center completed a web-based electronic case report form containing demographic data, implant procedures, and outcomes including adverse events and complications during the index hospital stay. There was no attempt to collect post-discharge outcome data.

STATISTICAL ANALYSIS. Absolute numbers and proportions are shown for categorical variables to describe the patient population. Descriptive analysis

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Clinical Electrophysiology* author instructions page.

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TABLE 1 Clinical Characteristics of 11,088 Patients by Sex Included in the European Society of Cardiology CRT Survey II

	Men (n = 8,366)	Women (n = 2,686)	p Value
Demographics			
Age, yrs	70 (62-76)	70 (62-77)	0.019
Age ≥75 yrs	31.2 (2,607/8,348)	34.5 (926/2,682)	
Currently enrolled in a clinical trial	8.1 (678/8,342)	8.9 (239/2,680)	0.197
Primary HF etiology			
Ischemic	50.7 (4,201/8,288)	25.3 (674/2,659)	<0.001
Nonischemic	44.1 (3,655/8,288)	67.4 (1,793/2,659)	
Other	5.2 (432/8,288)	7.2 (192/2,659)	
Past history and major comorbidity			
Myocardial infarction	41.5 (3,434/8,267)	19.7 (523/2,653)	<0.001
PCI/CABG	44.7 (3,691/8,266)	20.9 (554/2,652)	<0.001
Valvular heart disease	27.1 (2,239/8,264)	27.4 (726/2,650)	0.760
Valve surgery	32.6 (928/2,843)	28.0 (252/899)	0.009
Hypertension	64.1 (5,282/8,246)	63.3 (1,676/2,648)	0.477
Diabetes	32.1 (2,654/8,262)	29.1 (773/2,653)	0.004
Obstructive lung disease	12.6 (1,041/8,264)	10.3 (274/2,652)	0.002
Anemia	15.7 (1,295/8,260)	13.0 (345/2,650)	<0.001
eGFR <60 ml/min/1.73 m^2	31.9 (2,635/8,257)	28.7 (758/2,644)	0.002
HF hospitalization <1 yr	46.9 (3,872/8,259)	45.4 (1,204/2,653)	0.178
Atrial fibrillation	42.8 (3,534/8,264)	34.8 (922/2,650)	0.001
Paroxysmal	33.2 (1,173/3,534)	40.7 (375/922)	
Persistent	22.7 (802/3,534)	20.7 (191/922)	
Permanent	43.4 (1,533/3,534)	38.4 (354/922)	
Missing	0.7 (26/3,534)	0.2 (2/922)	
Previous device implant	25.0 (1,950/7,812)	18 (453/2518)	<0.001
PM	46.3 (1,131/2,444)	56.6 (340/601)	<0.001
ICD	34.7 (849/2,444)	19.0 (114/601)	<0.001

Values are median (interquartile range) or % (n/N).

CABG = coronary artery bypass grafting; CRT = cardiac resynchronization therapy; eGFR = estimated glomerular filtration rate; HF = heart failure; ICD = implantable cardioverter-defibrillator; PCI = percutaneous coronary intervention; PM = pacemaker.

using median and interquartile range were used to describe continuous variables. Binary variables (yes-no response variables) were compared between subgroups by the Pearson chi-square test and continuous variables (numeric values) were compared by the Mann-Whitney-Wilcoxon test. Odds ratios and 95% confidence intervals were calculated where appropriate. Multivariate analysis was performed using a logistic regression model including sex, device type, age, morphology, left bundle branch block (LBBB), intrinsic QRS duration, number of comorbidities, body mass index (BMI), region, and interaction between sex and device type. A significance level of 0.05 was assumed for the statistical tests and all p values are results of 2-tailed tests. All statistical analyses were performed using SAS statistical software version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS. Female patients referred for CRT represented 24.3% of the entire cohort (Table 1). Despite being of similar mean age (70 years of age), female patients more frequently had idiopathic cardiomyopathy (67.4% vs. 44.1%) and fewer comorbidities, including atrial fibrillation (34.8% vs. 42.8%), diabetes (29.1% vs. 32.1%), chronic obstructive lung disease (10.3% vs. 12.6%), and renal failure (28.7% vs. 31.9%), compared with men. More women had a previous pacemaker (56.6% vs. 46.3%) and much less often a previous ICD (19.0% vs. 34.7%). The choice of CRT device was significantly more often CRT-P in women (37.1%) compared with in men (26.5%) ($p < 0.0001$).

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS BY SEX AND DEVICE TYPE. The proportion of underweight women with a BMI <18.5 kg/m^2 was nearly twice (1.70%) that of male patients (0.76%) in both the CRT-P and CRT-D groups (Table 2). Heart failure severity defined by New York Heart Association functional class tended to be more severe in women than men. As shown in Table 2, LBBB QRS morphology was very frequent in female patients after receiving CRT-D; in contrast, right bundle branch block QRS morphology was infrequent in both CRT-P and CRT-D female patients, possibly reflecting less prevalence of ischemic heart disease. Women had smaller left ventricles than men (60 mm vs. 64 mm) and more often mitral regurgitation (81.5% vs. 79.3%), but less frequently had aortic stenosis (9.5% vs. 11.6%). A large QRS duration was the most frequent indication for CRT (67.9%), with a difference between men (59.2%) and women (63.2%) ($p < 0.001$). The second-most-frequent indication (22.8%) for CRT was an expectation to have a high proportion of right ventricular pacing. Significant differences were observed between CRT-D men (24.0%) and women (18.9%) ($p < 0.001$), with the subgroup of female CRT-D being the smallest 1 (9.1%).

Within the group of female patients (Table 2), there was no difference in the proportion of women presenting with nonischemic cardiomyopathy treated with CRT-P (68.2%) and CRT-D (67.3%). On the other hand, female patients with ischemic cardiomyopathy were more frequently treated with CRT-D (28.8% vs. 19.1%) (Table 2).

PROCEDURAL CHARACTERISTICS BY SEX AND DEVICE TYPE. Overall, there were minor differences in the implanting physician specialty, implantation procedure location, and duration (Tables 3 and 4,

TABLE 2 Pre-Implant Clinical Evaluation by Sex and Device Type

	Men		Women		
	CRT-P (n = 2,220)	CRT-D (n = 5,857)	CRT-P (n = 998)	CRT-D (n = 1,588)	p Value
Demographics					
Age, yrs	75 (67–81)	68 (61–74)	74 (67–80)	68 (61–74)	<0.001
Age ≥75 yrs	52.0 (1,154/2,219)	23.2 (1,359/5,856)	49.6 (495/998)	24.8 (394/1,587)	
BMI, kg/m^2	27 (24–30)	27 (25–31)	27 (24–30)	27 (24–31)	<0.001
<18.5 kg/m^2	0.9 (18/2,117)	0.7 (41/5,585)	2.0 (19/956)	1.5 (23/1,506)	
18.5–25 kg/m^2	30.9 (654/2,117)	26.1 (1,459/5,585)	32.2 (308/956)	28.3 (426/1,506)	
25–30 kg/m^2	42.0 (890/2,117)	43.5 (2,459/5,585)	36.3 (347/956)	37.5 (565/1,506)	
≥30 kg/m^2	26.2 (555/2,117)	29.7 (1,656/5,585)	29.5 (282/956)	32.7 (492/1,506)	
Primary HF etiology					<0.001
Ischemic	39.0 (862/2,209)	55.1 (3,210/5,825)	19.1 (189/991)	28.8 (453/1,575)	
Nonischemic	50.2 (1,110/2,209)	41.7 (2,429/5,825)	68.2 (676/991)	67.3 (1,060/1,575)	
Other	10.7 (237/2,209)	3.2 (186/5,825)	12.7 (126/991)	3.9 (62/1,575)	
Past history and major comorbidities					
Myocardial infarction	30.4 (671/2,207)	45.7 (2,656/5,816)	13.2 (131/990)	23.0 (363/1,576)	<0.001
Prior revascularization	33.3 (734/2,206)	48.9 (2,845/5,817)	15.2 (150/990)	24.2 (381/1,575)	<0.001
Valvular heart disease	30.1 (665/2,211)	26.0 (1,513/5,809)	30.9 (306/991)	25.0 (393/1,572)	<0.001
Hypertension	67.2 (1,480/2,201)	62.6 (3,635/5,804)	66.8 (659/987)	61.3 (965/1,574)	<0.001
Atrial fibrillation	51.6 (1,140/2,209)	39.2 (2,280/5,811)	46.0 (456/991)	27.8 (437/1,572)	<0.001
Obstructive lung disease	13.5 (298/2,210)	12.3 (713/5,811)	8.4 (83/991)	11.2 (177/1,574)	<0.001
Diabetes	30.6 (676/2,211)	32.4 (1,882/5,809)	28.5 (282/991)	29.5 (465/1,575)	0.020
Chronic kidney disease	36.8 (814/2,209)	29.9 (1,735/5,805)	32.1 (318/991)	26.8 (419/1,566)	<0.001
Anemia	19.3 (426/2,210)	14.3 (830/5,807)	14.6 (145/990)	11.9 (188/1,574)	<0.001
HF hospitalization during past year	43.9 (970/2,210)	47.8 (2,772/5,805)	45.6 (452/992)	45.4 (715/1,574)	0.013
NYHA functional class					<0.001
I	3.9 (86/2,194)	3.5 (200/5,770)	2.3 (23/987)	2.9 (46/1,567)	
II	32.7 (718/2,194)	40.4 (2,332/5,770)	31.5 (311/987)	38.4 (601/1,567)	
III	57.4 (1,259/2,194)	52.1 (3,009/5,770)	60.0 (592/987)	55.6 (872/1,567)	
IV	6.0 (131/2,194)	4.0 (229/5,770)	6.2 (61/987)	3.1 (48/1,567)	
ECG					
Heart rate, beats/min	70 (60–80)	70 (60–80)	72 (62–84)	72 (64–81)	<0.001
Atrial rhythm					
Sinus rhythm	56.7 (1,243/2,192)	71.7 (4,148/5,785)	64.6 (633/980)	81.5 (1,276/1,565)	<0.001
Atrial fibrillation	36.6 (803/2,192)	23.7 (1,372/5,785)	29.2 (286/980)	14.2 (223/1,565)	
Atrial paced	3.6 (79/2,192)	2.4 (141/5,785)	3.5 (34/980)	2.4 (37/1,565)	
PR interval, ms	188 (160–226)	184 (160–214)	180 (158–200)	174 (154–200)	<0.001
Intrinsic QRS duration, ms	160 (140–175)	160 (141–176)	158 (140/170)	160 (144–170)	<0.001
Normal QRS morphology	9.9 (216/2,185)	6.4 (367/5,761)	10.6 (104/977)	4.5 (71/1,562)	<0.001
LBBB	64.0 (1,398/2,185)	72.6 (4,183/5,761)	75.9 (742/977)	84.4 (1,318/1,562)	<0.001
RBBB	8.9 (195/2,185)	7.4 (428/5,761)	2.1 (21/977)	3.1 (48/1,562)	<0.001
Indeterminate	11.9 (260/2,185)	10.9 (627/5,761)	8.0 (78/977)	6.9 (107/1,562)	<0.001
Not available	5.5 (121/2,185)	3.0 (170/5,761)	3.6 (35/977)	1.3 (20/1,562)	<0.001
Echocardiographic findings					
LV ejection fraction, %	30 (25–38)	27 (20–30)	30 (25–36)	28 (22–32)	<0.001
LVEDD, mm	61 (56–67)	65 (60–70)	59 (52–65)	61 (56–66)	<0.001
Mitral regurgitation (any degree)	78.2 (1,607/2,054)	79.7 (4,321/5,307)	80.4 (721/897)	82.2 (1,189/1,447)	<0.001
Previous device implantation					
PM	79.8 (578/724)	31.2 (511/1,637)	81.6 (231/283)	34.1 (103/302)	<0.001
ICD	1.9 (14/724)	49.4 (809/1,637)	0.7 (2/283)	36.4 (110/302)	<0.001

Values are median (interquartile range) or % (n/N).

BMI = body mass index; CRT-D = cardiac resynchronization therapy with defibrillator; CRT-P = cardiac resynchronization therapy with pacing; ECG = electrocardiography; LBBB = left bundle branch block; LV = left ventricular function; LVEDD = left ventricular end-diastolic diameter; NYHA = New York Heart Association; RBBB = right bundle branch block; RV = right ventricular; other abbreviations as in Table 1.

TABLE 3 Implantation Procedure by Sex and Device Type

	Men		Women		
	CRT-P (n = 2,220)	CRT-D (n = 5,857)	CRT-P (n = 998)	CRT-D (n = 1,588)	p Value
Operator					0.00198
Electrophysiologist	76.7 (1,721/2,245)	77.3 (4,566/5,908)	80.6 (808/1,003)	74.6 (1,188/1,593)	
HF physician	6.2 (140/2,245)	4,7 (280/5,908)	4.9 (49/1,003)	4.5 (71/1,593)	
Invasive cardiologist	13.0 (292/2,245)	12.4 (733/5,908)	9.2 (92/1,003)	13.1 (209/1,593)	
Surgeon	3.4 (76/2,245)	4.2 (247/5,908)	4.3 (43/1,003)	5.8 (92/1,593)	
Other	0.7 (16/2,245)	1.4 (82/5,908)	1.1 (11/1,003)	2.1 (33/1,593)	
Procedure location					0.083
Cath lab	27.2 (611/2,245)	24.2 (1,425/5,895)	26.0 (260/1,001)	25.9 (412/1,588)	
Dedicated EP lab	28.3 (636/2,245)	30.9 (1,820/5,895)	32.3 (323/1,001)	32.1 (510/1,588)	
Device implantation lab	34.5 (775/2,245)	34.2 (2,015/5,895)	31.4 (314/1,001)	31.1 (494/1,588)	
Operating theatre	9.3 (209/2,245)	10.3 (605/5,865)	10.0 (100/1,001)	10.4 (165/1,588)	
Other	0.6 (14/2,245)	0.5 (30/5,865)	0.4 (4/1,001)	0.4 (7/1,588)	
Implantation procedure					
Duration, min	88 (62–120)	94 (68–125)	90 (64–120)	96 (70–120)	<0.001
Fluoroscopy time, min	13 (8–21)	14 (8–23)	12 (7–22)	14 (9–24)	<0.001
RV lead position					
Apex	54.5 (1,156/2,121)	63.3 (3,562/5,623)	56.0 (535/956)	66.1 (1,011/1,529)	<.0001
Septum	41.2 (873/2,121)	35.1 (1,974/5,623)	40.0 (382/956)	32.4 (496/1,529)	
RVOT	4.3 (92/2,121)	1.5 (87/5,623)	4.1 (39/956)	1.4 (22/1,529)	
LV lead placement					
Successful LV placement	99.8 (2,204/2,208)	99.4 (5,766/5,800)	99.3 (980/987)	99.0 (1,558/1,574)	0.009
Epicardial approach	9.3 (205/2,204)	9.0 (517/5,766)	8.5 (83/980)	10.3 (161/1,558)	
Reason for LV lead placement failure					0.992
CS not identified	25.0 (1/4)	17.6 (6/34)	14.3 (1/7)	18.8 (3/16)	
Extracardiac stimulation	0.0 (0/4)	0.0 (0/34)	0.0 (0/7)	0.0 (0/16)	
No suitable coronary vein	50.0 (2/4)	55.9 (19/34)	57.1 (4/7)	50.0 (8/16)	
Complication	0.0 (0/4)	5.9 (2/34)	14.3 (1/7)	6.3 (1/16)	
Other	25.0 (1/4)	20.6 (7,734)	14.3 (1/7)	25.0 (4/16)	

Values are % (n/N) or median (interquartile range).
CS = coronary sinus; EP = electrophysiology; RVOT = right ventricular outflow tract; other abbreviations as in Tables 1 and 2.

Figure 1). Implantation times were a median of 3 to 6 min longer for CRT-D than for CRT-P implantation, with a greater difference in men (Table 4). The success rate of a transvenous lead implantation approximated 90.0% in both men and women, and in CRT-P and CRT-D devices (Table 4). As indicated in Figure 1, irrespective of sex, the distribution of left ventricular (LV) unipolar, bipolar, and multipolar leads placed was different between CRT-P and CRT-D recipients. A multipolar LV lead was more frequently used in conjunction with CRT-D (60.0% vs. 51.0%) (Figure 1). The distribution of the LV lead position in anterior, lateral, and posterior sites was comparable between sex and device type (Figure 1); in contrast, LV lead was significantly ($p < 0.0001$) more frequently positioned in the basal part in women (17.0%) than in men (14.3%), especially when a CRT-D was implanted (Figure 1). LV lead position was most frequently optimized either by electrical delay or by paced QRS duration, without any preference for 1 method over the other (Figure 1).

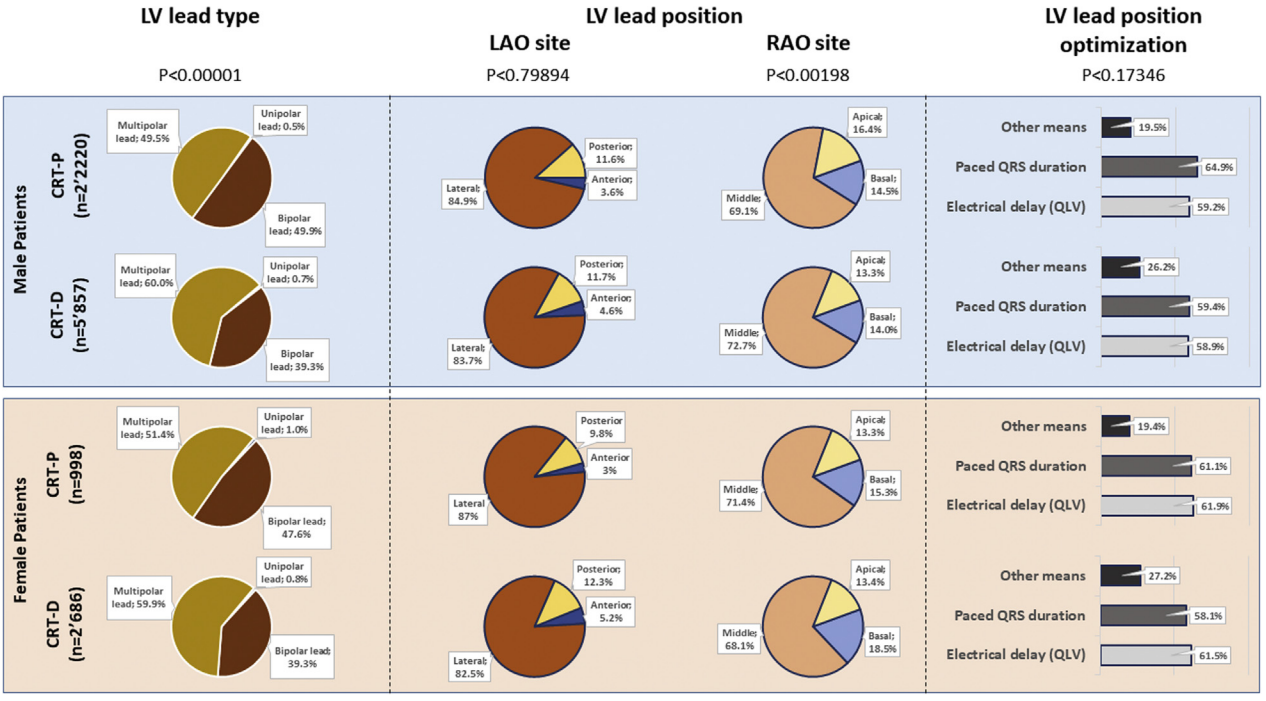
TABLE 4 Discharge Status by Sex and Device Type

	Men		Women	
	CRT-P (n = 2,220)	CRT-D (n = 5,857)	CRT-P (n = 998)	CRT-D (n = 1,588)
Alive	99.2 (2,175/2,193)	99.7 (5,762/5,778)	99.4 (980/986)	99.9 (1,567/1,568)
Death	0.8 (18/2,193)	0.3 (16/5,778)	0.7 (7/986)	0.1 (1/1,568)
Cardiovascular death	72.2 (13/18)	87.5 (14/16)	50.0 (3/6)	0.0 (0/1)
Progressive heart failure	44.4 (8/18)	56.3 (9/16)	0.0 (0/6)	0.0 (0/1)

Values are % (n/N). $p < 0.001$.
Abbreviations as in Table 2.

PERIPROCEDURAL EVENTS, ADVERSE EVENTS, AND DEATHS BY SEX AND DEVICE TYPE. Periprocedural event rate was the highest in women implanted with a CRT-D, followed by women treated with a CRT-P (Table 4, Central Illustration). The higher periprocedural event rate in CRT-D women was mainly

FIGURE 1 LV Lead Characteristics, Position, and Optimization Position in Women and Men Implanted With Either CRT-D or CRT-P



The distribution of LV lead characteristics, LV lead position, and LV lead optimization is indicated in the **upper panels** for male patients and in the **lower panels** for female patients. The implanted LV leads were either unipolar, bipolar, or quadripolar (multipolar). The longitudinal (apex-base) and circumferential (anterior-inferior) position of the LV lead was assessed using the right and left anterior view oblique, respectively. The LV lead position was optimized either targeting a pre-procedurally and noninvasively determined area with late peak shortening, or by selecting the LV site providing the shortest QRS duration (paced QRS duration), or the location at the LV wall with the longest electrical delay as compared to the Q-wave on surface ECG (Q-LV interval) determined invasively and during the implant procedure.
CRT-D = cardiac resynchronization therapy with defibrillator; CRT-P = cardiac resynchronization therapy with pacing; LAO = left anterior oblique; LV = left ventricular; RAO = right anterior oblique.

attributable to pneumothorax, coronary sinus dissection, and pericardial tamponade (**Central Illustration**). Although the rate of in-hospital major adverse events and complications necessitating reoperation was not statistically significant among sex and device type (**Figure 2**), there was a trend toward higher proportion of phrenic nerve stimulation, lead dislocation, and other complications in women (**Figure 3**).

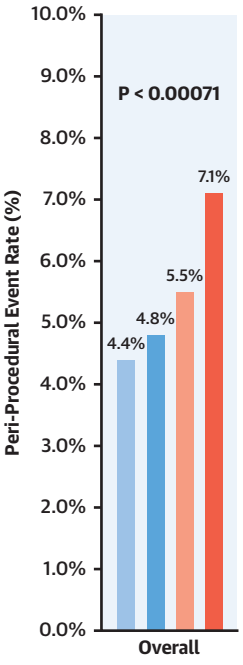
A logistic regression analysis for all successful implantations was conducted (Online Table 1) showing that female sex, number of comorbidities, and BMI had a significant influence on periprocedural events, whereas BMI, in contrast to female sex and the number of comorbidities, had a protective effect on periprocedural event occurrence. Type of device, age ≥75 years, QRS morphology and duration, and region identified as macro area (West Europe, East Europe, Middle East, non-European ESC countries) where the CRT implantation was performed, as well as the interaction between sex and device type, were not significantly associated with occurrence of periprocedural events (Online Table 1). The model showed a good fit ($p < 0.4714$). Interestingly, in the subgroup analysis for the complications, anemia (odds ratio: 1.94; 95% confidence interval: 1.33 to 2.03; $p < 0.001$) and chronic renal failure (odds ratio: 1.26; 95% confidence interval: 1.05 to 1.51; $p < 0.011$) represented the main contributors to the effect seen in the logistic regression model.

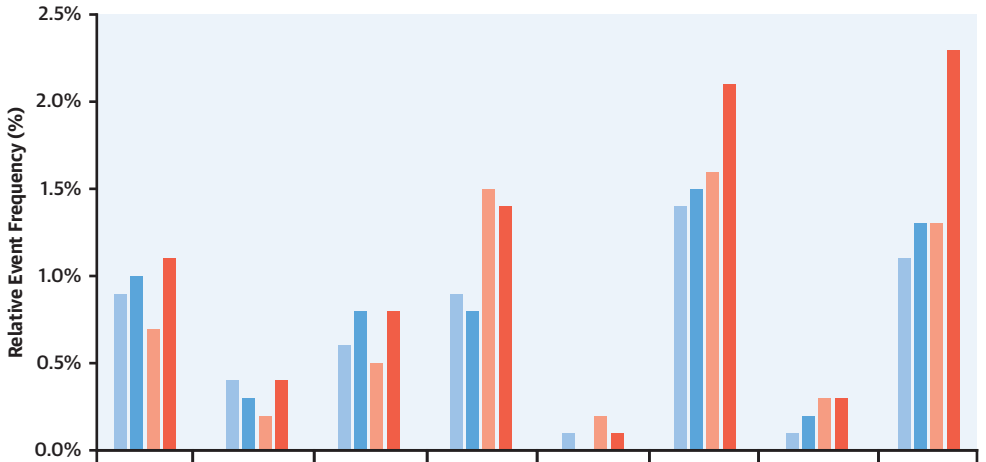
The overall perioperative death rate ranged from 0.1% to 0.8%. There was no difference in the death rate between women and men, but CRT-P patients of each sex experienced the highest death rate compared with CRT-D patients (**Table 4**), probably reflecting the higher age, more severe heart failure, and comorbidities of these patients.

DISCUSSION

To the best of our knowledge, the present study represents the largest comparison of procedural success and complications in patients implanted with

CENTRAL ILLUSTRATION **Frequency of Periprocedural Complications by Sex and Device Type**





	Bleeding	Requiring Intervention	Pocket Hematoma	PNX	Hemoth.	CS Dissection	Pericardial Tamponade	Others
Males CRT-P	0.9%	0.4%	0.6%	0.9%	0.1%	1.4%	0.1%	1.1%
Male CRT-D	1.0%	0.3%	0.8%	0.8%	0.0%	1.5%	0.2%	1.3%
Female CRT-P	0.7%	0.2%	0.5%	1.5%	0.2%	1.6%	0.3%	1.3%
Female CRT-D	1.1%	0.4%	0.8%	1.4%	0.1%	2.1%	0.3%	2.3%

Auricchio, A. et al. J Am Coll Cardiol EP. 2019;5(9):1048–58.

The total peri-procedural event rate and the relative frequency of each peri-procedural complication is reported. In some patients, more than 1 complication may have occurred. CRT-D = cardiac resynchronization therapy with defibrillator; CRT-P = cardiac resynchronization therapy with pacing; CS = coronary sinus; Hemoth. = hemothorax; PNX = pneumothorax.

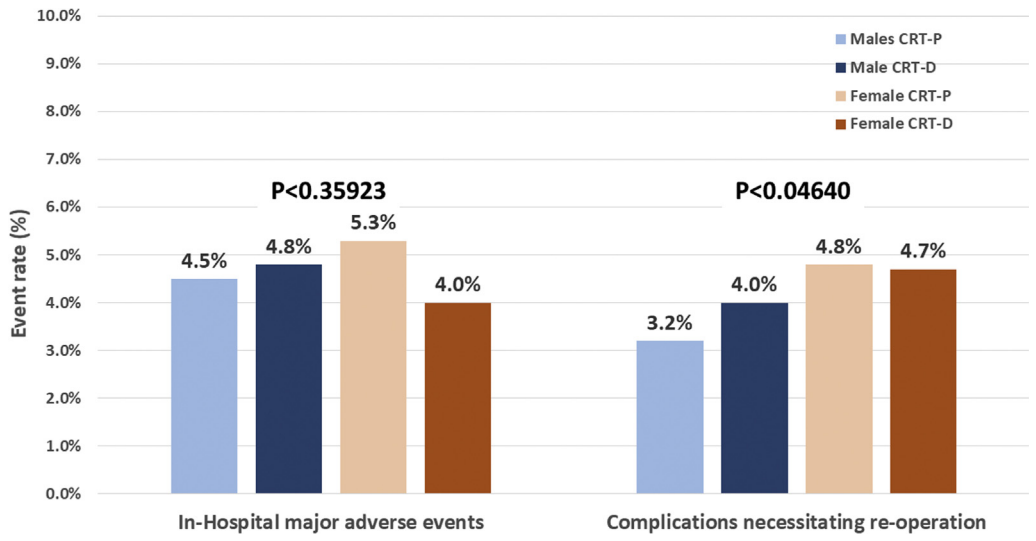
either a CRT-P or a CRT-D in Europe with respect to sex. We found that female patients more often experienced intra- and periprocedural complications such as pneumothorax, pericardial tamponade, and coronary sinus dissection. Furthermore, lead dislodgment was frequent in CRT-D patients, particularly in women. Our results support the development of preventive strategies to minimize complications. Such actions may improve outcome of CRT patients, in particular in female patients.

IMPORTANCE OF INVESTIGATING SEX-RELATED DIFFERENCE IN CRT PROCEDURE. The study of sex-related differences in cardiovascular procedures and related outcomes is an expanding area of cardiology research. The current survey represents the largest cohort on present CRT implantation across a wide set of European geographies and patients, and includes a large amount of female patients (n = 2,638), enabling the study of sex differences outside of randomized clinical trials.

It is well known that female patients derive large benefit from CRT (1–5). The significant reverse remodeling and better outcome observed in female patients is usually attributed to a lower incidence of ischemic cardiomyopathy, higher incidence of LBBB, and body mass index <30 kg/m^2, as well as smaller height (4,15). Our observation not only is in line with that of a large French-UK-Sweden cohort study (16) indicating a lower incidence of atrial fibrillation and diabetes in female patients compared with male patients, but also expands previous knowledge. Indeed, in addition to these clinical characteristics, female patients included in the ESC CRT Survey II had a lower frequency of comorbidities including renal dysfunction. They were also more frequently implanted with an LV lead in the basal position, had narrower paced QRS complex during CRT, and had a larger QRS reduction during CRT pacing compared with men. All these factors are associated with positive response to CRT. Whether they significantly contribute to a better outcome of our patients is unknown because this survey was not designed to report on short- and long-term outcomes.

COMPARISON OF PRESENT SURVEY TO RANDOMIZED CONTROLLED TRIALS AND REGISTRIES. Previous multicenter U.S. cohorts (National Inpatient Sample)

FIGURE 2 Frequency of Major Adverse Events and Complications Necessitating Reoperation After CRT Implantation by Sex and Device Type

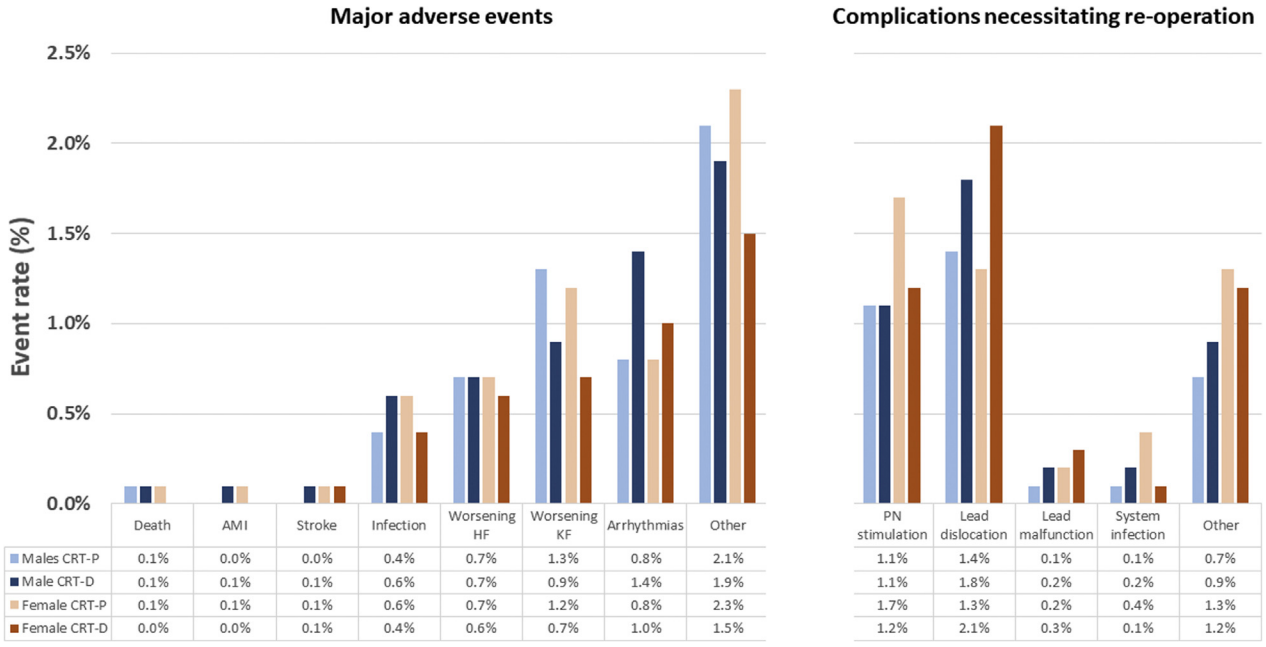


Female CRT patients had the highest complication rate necessitating re-operation. The in-hospital adverse events were comparable high between male and female patients. Abbreviations as in Figure 1.

assessing CRT implant patterns (1,8,17) similarly identified a predominance of CRT-D implantation, although of higher magnitude (about 85%) in comparison with our survey. Similar to our findings, patients receiving CRT-P were older, less likely to be men, less likely to have ischemic heart disease, and more likely to have atrial fibrillation (8,17). In the Nationwide Inpatient Sample by Shridhar et al. (8), the mortality associated with CRT-P implants was higher compared with CRT-D implants (1.4% vs. 0.8%; $p < 0.001$). Consistent with this observation, in the ESC CRT Survey II there was a similar difference but much lower mortality. This increased mortality with CRT-P is likely because of the fact that in the real world, CRT-P recipients usually represent patients whose life expectancy is low and do not qualify for ICD insertion. These patients also have greater comorbidities and often present with noncardiac life-threatening diseases, such as malignancies. As reported by Shridhar et al. (8), the rates of pericardial effusion and pneumothorax in CRT-P patients were noted to be slightly higher. The greater prevalence of comorbidities in CRT-P recipients may possibly explain these observations. On the other hand, the rates of hematoma formation associated with CRT-D in both the Nationwide Inpatient Sample and our survey were higher than the rates of CRT-P; the larger size of CRT-D devices may potentially contribute to the higher hematoma rates with these devices.

Two randomized controlled trials, MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy) (11) and Echo-CRT (Echocardiography Guided Cardiac Resynchronization Therapy) (12), have to date reported on sex-related complications. In the Echo-CRT study (6), the rate of ICD lead–related complications was numerically higher in women in the CRT-ON group, which was counterbalanced by a numerically lower rate of ICD lead complications in the CRT-OFF group in women (both when compared with men). Overall, the difference between ICD lead-related complications was similar and did not reach statistical significance. In contrast, in MADIT-CRT study (11) women were more likely than men were (6.3% vs. 2.7%; $p < 0.0001$) to develop procedure-related adverse events during CRT-D and ICD insertion. This was mainly driven by increased rates of pneumothorax and hemothorax in women (3.3% vs. 0.9%; $p < 0.0001$). Women were also more likely to develop device-related infections that required reoperation (2.0% vs. 0.9%; $p < 0.01$) and tended to have higher rates of coronary sinus dissection (0.9% vs. 0.4%; $p < 0.172$). Interestingly, both the MADIT-CRT trial and our survey included patients who were, on average, 6 to 8 years older than those included in the Echo-CRT trial, and with a much lower BMI (MADIT-CRT men: 28.9 kg/m^2, women: 28.1 kg/m^2; ESC CRT Survey II: 27 kg/m^2 in both men and women) than

FIGURE 3 Overview of Major Adverse Events and Reasons for Reoperation After CRT Implantation by Sex and Device Type



	Death	AMI	Stroke	Infection	Worsening HF	Worsening KF	Arrhythmias	Other
Males CRT-P	0.1%	0.0%	0.0%	0.4%	0.7%	1.3%	0.8%	2.1%
Male CRT-D	0.1%	0.1%	0.1%	0.6%	0.7%	0.9%	1.4%	1.9%
Female CRT-P	0.1%	0.1%	0.1%	0.6%	0.7%	1.2%	0.8%	2.3%
Female CRT-D	0.0%	0.0%	0.1%	0.4%	0.6%	0.7%	1.0%	1.5%

	PN stimulation	Lead dislocation	Lead malfunction	System infection	Other
Males CRT-P	1.1%	1.4%	0.1%	0.1%	0.7%
Male CRT-D	1.1%	1.8%	0.2%	0.2%	0.9%
Female CRT-P	1.7%	1.3%	0.2%	0.4%	1.3%
Female CRT-D	1.2%	2.1%	0.3%	0.1%	1.2%

Detailed presentation of the major adverse events and complication necessitating re-operation in male and female patients. AMI = acute myocardial infarction; HF = heart failure; KF = acute kidney failure; PN = phrenic nerve; other abbreviations as in Figure 1.

patients in the Echo-CRT trial cohort (men: 31.7 kg/m^2, women: 30.5 kg/m^2). Age and BMI were strongly associated to complication occurrence and may explain the remarkable differences between Echo-CRT trial and the MADIT-CRT trial and our survey.

Our findings reflect previous observations from the Danish Cardiovascular Implantable Electronic Device Registry (10) and the U.S. National Cardiovascular Data Registry report (18). In the Danish registry, low body weight, female sex, and complex procedures were associated with more complications. In particular, women had a 30% higher risk of any complication, mainly due to pneumothorax and cardiac perforation. The U.S. National Cardiovascular Data Registry indicated that any device-related complication was more common in women compared with men (7.2% vs. 4.8%, $p < 0.001$); even after exclusion of 30-day mortality, device-related complications remained higher in women (5.9% vs. 3.9%, $p < 0.001$). In particular, women had a significantly higher rate of 30-day pneumothorax requiring intervention, hematoma requiring evacuation, cardiac tamponade, and 90-day mechanical complications requiring revision when compared with men. There was no sex differences in occurrence of 90-day device-related infection or recurrent ICD implant.

Unlike most of the prospective randomized controlled trials or registries on CRT (6,8,11,12), our survey included a very large group of female CRT-P and CRT-D patients. Consistent with recent data from a large registry cohort conducted in France and the United Kingdom, which showed on that the addition of the defibrillator in patients receiving CRT associates with a higher risk of device-related complications compared with CRT (19), our study indicated a trend toward higher intra- and perioperative complication rate in CRT-D patients with a higher risk in women. However, our study is the first one comparing CRT-P to CRT-D in a female patient cohort; female CRT-P patients experienced similar complications types compared with female CRT-D patients, albeit less frequently.

The underlying explanations of sex differences in complication rate may include differences in body composition, including smaller vascular and cardiac dimensions, lower body weight, and hormonal differences, whereas those related to device type are less understood. The occurrence of a pneumothorax and hemothorax is nearly always associated with subclavian vein puncture, and a lower BMI is frequently associated with this complication. Echo-guided puncture (20) or the use of alternative

approaches to avoid direct subclavian puncture (21), especially in female patients with a low BMI, could represent a preventive strategy to possibly reduce or abolish the occurrence of pneumothorax, hemothorax, inadvertent arterial puncture, thoracic duct injury, and brachial plexus injuries.

STUDY LIMITATIONS. Surveys are an important source of information describing the implementation of clinical practice guidelines. However, surveys have their own limitations that need to be acknowledged and to be considered during interpretation of the findings. Furthermore, differences in practice between countries can skew the results. Although the importance of consecutive patient inclusion was emphasized during the data collection, we cannot confirm that all patients were included consecutively. Height and weight were not captured due to anonymity and data protection laws. The registry did not record the type of lead fixation (active or passive fixation) implanted in each chamber; thus, it is not possible to establish whether the use of passive fixation lead may help decrease the occurrence of perforation or tamponade especially in women. The survey also did not record system manufacturer to evaluate whether some complications where more frequently associated with some implanting tools. The accuracy of the data has not been audited and there is a potential for investigator selection bias.

CONCLUSIONS

Women are more likely to experience adverse procedure-related events after CRT implantation. The identification and management of procedure-related risk factors is warranted to reduce or abolish the occurrence of some complications in all patients. Risk factor analyses are particularly relevant with respect to the female population, in which more frequent complications may jeopardize the larger clinical benefit from CRT.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Sex differences in procedure-related adverse events is an important research field. Procedure-related complications not only have an immediate effect on health care utilization, but also, if occurring more frequently in 1 sex, may represent a detrimental factor for a wider therapy adoption. At the same time, complication monitoring provides an opportunity for a sex-specific risk preventive strategy. Periprocedural event rate was the highest in women implanted with a CRT-D followed by women treated with a CRT-P.

TRANSLATIONAL OUTLOOK: The underlying explanations of sex differences in complication rate may include differences in body composition, including smaller vascular and cardiac dimensions, lower body weight, and hormonal differences, whereas those related to device type are less understood. Future studies shall evaluate the role of preventive strategies for some specific complications (e.g., pneumothorax and hemothorax) in female CRT patients.

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KEY WORDS **cardiac devices, cardiac resynchronization therapy, complications, female, European practice, heart failure, survey**

APPENDIX **For a supplemental table, please see the online version of this paper.**