Primary Prevention Implantable Cardioverter Defibrillator (ICD) Therapy in Women—Data From a Multicenter French Registry

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Background—There are limited data describing sex specificities regarding implantable cardioverter defibrillators (ICDs) in the real-world European setting.

Methods and Results—Using a large multicenter cohort of consecutive patients referred for ICD implantation for primary prevention (2002–2012), in ischemic and nonischemic cardiomyopathy, we examined the sex differences in subjects' characteristics and outcomes. Of 5539 patients, only 837 (15.1%) were women and 53.8% received cardiac resynchronization therapy. Compared to men, women presented a significantly higher proportion of nonischemic cardiomyopathy (60.2% versus 36.2%, $P<0.001$), wider QRS complex width (QRS >120 ms: 74.6% versus 68.5%, $P=0.003$), higher New York Heart Association functional class (≥III in 54.2%♀ versus 47.8%♂, $P=0.014$), and lower prevalence of atrial fibrillation (18.7% versus 24.9%, $P<0.001$). During a 16 786 patient-years follow-up, overall, fewer appropriate therapies were observed in women (hazard ratio=0.59, 95% CI 0.45–0.76; $P<0.001$). By contrast, no sex-specific interaction was observed for inappropriate shocks (odds ratio ♀=0.84, 95% CI 0.50–1.39, $P=0.492$), early complications (odds ratio=1.00, 95% CI 0.75–1.32, $P=0.992$), and all-cause mortality (hazard ratio=0.87 95% CI 0.66–1.15, $P=0.324$). Analysis of sex-by- cardiac resynchronization therapy interaction shows than female cardiac resynchronization therapy recipients experienced fewer appropriate therapies than men (hazard ratio=0.62, 95% CI 0.50–0.77; $P<0.001$) and lower mortality (hazard ratio=0.68, 95% CI 0.47–0.97; $P=0.034$).

Conclusions—In our real-life registry, women account for the minority of ICD recipients and presented with a different clinical profile. Whereas female cardiac resynchronization therapy recipients had a lower incidence of appropriate ICD therapies and all-cause death than their male counterparts, the observed rates of inappropriate shocks and early complications in all ICD recipients were comparable.

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Key Words: death, sudden • heart failure • mortality • shock

Implantable cardioverter defibrillators (ICDs) are currently an effective and accepted treatment for improving the outcomes of selected patients with ischemic and nonischemic cardiomyopathy with heart failure and severe left ventricular dysfunction.[1–4] However, in the major randomized controlled trials determining guideline recommendations, women were markedly underrepresented.[1–4]

Accordingly, the existence of sex-related differences in outcomes among ICD recipients is still controversial. While in North American registries,[5] women seem to experience a

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lower incidence of appropriate therapies, these data were not confirmed in a large Dutch single-center prospective cohort study[6] and in the recent Nationwide Israeli-ICD registry.[7]

Data on sex-related survival differences are also contradictory. A large North American registry[5] and the Israeli-ICD registry[7] have shown no differences in all-cause death, while a 35% lower mortality was observed in women of the single-center Dutch cohort.[6]

Real-world data from European registries addressing these issues is still absent. In the present article, we aim to determine the proportion of female ICD recipients, as well as differences in terms of characteristics at implant and outcomes (therapies, overall and specific mortalities) in women compared to men.

Methods

We selected 5539 patients from the DAI-PP study (*Défibrillateur Automatique Implantable Prévention Primaire*; NCT01992458) for this analysis. To qualify for the study, patients had to be at least 18 years old at the time of ICD implantation. Overall, between 2002 and 2012, all patients with ischemic cardiomyopathy or nonischemic cardiomyopathy, implanted with an ICD (biventricular, single chamber, or dual chamber) in the setting of primary prevention in 12 reference French centers were considered and enrolled in the DAI-PP follow-up program. Primary prevention was defined when no prior history of sudden cardiac arrest and/or ventricular tachycardia/fibrillation was documented. Ischemic cardiomyopathy was defined as presence of myocardial dysfunction in the context of previous myocardial infarction and/or history of coronary artery disease with or without revascularization (angioplasty or bypass surgery).

Exclusion criteria included all patients having an ICD implant for secondary prevention purposes or for primary prevention without structural heart disease (including Brugada, long QT syndrome, among others) or structural heart disease other than ischemic or nonischemic cardiomyopathy (hypertrophy cardiomyopathy, noncompaction cardiomyopathy, and arrhythmogenic right ventricular dysplasia).

The study was funded by public sources, including the French Institute of Health and Medical Research (INSERM) and the French Society of Cardiology, and was coordinated by Clinique Pasteur, Toulouse and the Paris Cardiovascular Research Center, European Georges Pompidou Hospital, Paris, in France. The study complied with the Declaration of Helsinki, and the data file of the DAI-PP study was declared to and authorized by the French data protection committee (Commission Nationale Informatique et Liberté, CNIL). Patients gave informed consent for anonymized use of their data.

Sample Characterization

All variables at the time of the procedure were defined and categorized according to the literature or common practice. In addition to the New York Heart Association (NYHA) functional class, we collected the etiology of the underlying heart disease (ischemic cardiomyopathy or nonischemic cardiomyopathy). Glomerular filtration rate was estimated with the formula of Cockroft–Gault and categorized in 2 categories ($\geq$60 and <60 mL/min); QRS duration was categorized as <120 and $\geq$120 ms. Atrial fibrillation (AF) was defined as a history of AF (paroxysmal or persistent), documented on standard ECG or 24-hour Holter monitoring. Comorbidities at the time of ICD implantation were systematically collected from review of medical records: cancer, chronic obstructive pulmonary disease, chronic renal failure, chronic liver disease, history of transient ischemic neurological attack, and others (including diabetes mellitus). The type of ICD device implanted (biventricular, single chamber or dual chamber—no indication on manufacturers) was recorded. Data on device programming was not collected and was left to the discretion of individual investigators, according to each patient's needs. Programming rules were based on high detection windows, as suggested by local guidelines at the time.[8] Furthermore, French guidelines did not recommend special programming adjustments, namely, cut-offs for therapy zones, based on sex. Information on medications at hospital discharge included β-blockers, amiodarone, Ic class anti-arrhythmic agents, sotalol, digoxin, calcium blockers, angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker, diuretics, anti-platelets, and vitamin K antagonists.

Follow-Up and Outcomes

Follow-up information was obtained from appointments every 4 to 6 months for device evaluation, according to French guidelines.[8] The different end points were occurrence of appropriate therapies, early complications, inappropriate shocks, as well as overall and specific mortalities.

Device interrogation printouts were checked by the local investigator for appropriate and inappropriate ICD therapy. Appropriate ICD therapy was defined as an episode of ventricular tachycardia/ventricular fibrillation resulting in a single or multiple shocks or/and anti-tachycardia pacing for arrhythmia termination. The date of the first appropriate ICD therapy was recorded, and the overall cumulative number of appropriate therapies was considered. The cause of inappropriate shock(s) was collected as well. Adjudication as appropriate or inappropriate therapy was undertaken by the local electrophysiology (EP) investigator.

Early complications (defined as those that appeared throughout the first 30 days after device implantation)

included lead-related complications (eg, failure of coronary sinus lead placement, rise of threshold, lead dislodgment with or without need of reintervention, phrenic nerve stimulation), bleeding (ecchymosis, hematoma, other bleeds requiring transfusion, and procedure-related anemia), sepsis, cardiac tamponade, pneumothorax, and death.

Vital status data were obtained from the hospital or the general practitioner, and were systematically controlled through the National Institute of Statistics Economical Studies (INSEE). Causes of death were obtained from the investigators and/or by the French Center on Medical Causes of Death (CépiDc–INSERM). The CépiDc–INSERM is an academic public institution focused on the analysis of circumstances and causes of death based on death certificate and medical records. Causes of deaths were classified according to the International Classification of Diseases (10th Revision). This information was reviewed by 2 investigators and causes of death were adjudicated after consideration of all the available information, and according to the following prespecified groups: cardiovascular (including progressive heart failure death, stroke), noncardiovascular, ICD-unresponsive sudden cardiac death (arrhythmic or not arrhythmic whenever the assessment was possible), ICD-related death, as well as unknown when the quality of the information could not allow the investigators to appropriately identify cause of death. Overall, cause of death assessment was possible among 682 patients (out of 826 deceased, 82.6%).

Statistical Analysis

Preparation of this report was in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for reporting of observational studies.[9]

Comparisons were performed between men and women. Chi-square was used for comparison of nominal variables and Student *t* test for continuous variables; the Levene's test was used to check the homogeneity of variance; when appropriate, nonparametric equivalent, Mann–Whitney test, was employed. When baseline differences were present, adjustment was performed using multivariate analysis with binary logistic regression. Results with $P<0.05$ were regarded as significant.

We compared the adjusted outcomes of appropriate shock and death in men and women by using Cox proportional hazards regression analysis. Hazard curves were traced for comparison of men and women after adjustment for baseline differences.

Data were filled into a predefined data introduction electronic sheet made available to all participant Centers. After completion of follow-up, data from all Centers were merged and analyzed at the Paris Cardiovascular Research Center (Inserm U970, Cardiovascular Epidemiology Unit) using SAS program v9.3 (SAS Institute Inc, Cary, NC).

Results

The mean age of the sample was 62.5 ± 11.2 years. Among the 5539 patients included in the study, most (60.2%) had an ischemic cardiomyopathy and AF was present in 24.0%. Mean left ventricular ejection fraction and NYHA class were $26.7\pm7.2\%$ and $2.4\pm0.7\%$, respectively. Cardiac resynchronization therapy with defibrillator (CRT-D) was used in half of patients (53.8%). More information on baseline sample data and medical treatment at the time of implant can be found in Table 1.

Sex-Related Differences in Clinical Characteristics at Implant

Women accounted for 15.1% (n=837) of the whole study sample and had higher prevalence of patients in higher NYHA classes (NYHA ≥III: 54.2%♀ versus 47.8%♂, $P=0.014$). Men presented a higher prevalence of AF, ischemic cardiomyopathy, and had a higher prevalence of narrow QRS complex width (QRS <120 ms). No significant differences were found regarding age, mean left ventricular ejection fraction, and number of comorbidities.

On univariate analysis, women were more frequently implanted with CRT-D devices (61.0% versus 52.5%; $P<0.001$). However, after adjustment for baseline differences, this became no longer significant (odds ratio=1.28, 95% CI 0.98–1.66; $P=0.07$).

Women were more frequently treated with spironolactone and β-blockers. Conversely, men received amiodarone, vitamin K antagonists, and antiplatelet agents more frequently and had a trend for higher use of calcium channel blockers. However, after adjustment for baseline differences, only spironolactone was used more frequently among women (odds ratio=1.30, 95% CI 1.06–1.59; $P=0.014$), whereas all other drugs presented similar use among men and women (Table 1).

Appropriate and Inappropriate Therapies and Early Complications

No significant differences were observed in the occurrence of early complications (♂12.8% versus ♀13.3%; $P=0.789$; adjusted odds ratio=1.00, 95% CI 0.75–1.32; $P=0.992$) (Figure 1). Except for a higher incidence of pneumothorax in women (♂0.6% versus ♀1.9%, $P<0.001$), the remaining complication types were evenly distributed between sexes: bleeding (♂4.8% versus ♀3.2%), cardiac tamponade (0% in

Table 1. Baseline Sample Characteristics and Medication

Parameter	Global Sample (n=5539)	Male Sex (n=4702)	Female Sex (n=837)	P Value
Baseline data				
Age, y	62.5±11.2	62.6±11.0	62.0±12.4	0.245
Female sex	837 (15.1%)	—	—	—
NYHA I	10.6% (484)	11.0% (426)	8.2% (57)	0.014
NYHA II	40.7% (1861)	41.2% (1600)	37.6% (261)	
NYHA III	44.9% (2055)	43.9% (1703)	50.6% (352)	
NYHA IV	3.8% (176)	3.9% (151)	3.6% (25)	
Atrial fibrillation	1134 (24.0%)	1002 (24.9%)	132 (18.7%)	<0.001
Ischemic cardiomyopathy	3304 (60.2%)	2976 (63.8%)	328 (39.8%)	<0.001
Mean LVEF	26.7±7.2	26.7±6.9	27.0±8.5	0.343
QRS width <120 ms	1183 (30.5%)	1025 (31.5%)	158 (25.4%)	0.003
GFR <60 mL/min	1281 (39.6%)	1111 (40.1%)	170 (36.2%)	0.104
Number of comorbidities*	0.9±0.8	0.9±0.8	0.9±0.7	0.165
Single-chamber ICD	1258 (22.9%)	1095 (23.5%)	163 (19.6%)	<0.001
Double-chamber ICD	1280 (23.3%)	1119 (24.0%)	161 (19.4%)	
CRT-D	2952 (53.8%)	2446 (52.5%)	506 (61.0%)	
Medical therapy at the time of the implant				
ACEi or ARB	3263 (82.0%)	2780 (82.3%)	483 (80.0%)	0.161
Furosemide	2709 (68.1%)	2294 (68.0%)	415 (68.7%)	0.713
Spironolactone	1284 (32.3%)	1050 (31.1%)	234 (38.7%)	<0.001
Calcium channel blockers	79 (2.0%)	73 (2.2%)	6 (1.0%)	0.058
β-Blockers	3378 (84.9%)	2848 (84.4%)	530 (87.7%)	0.032
Amiodarone	902 (22.7%)	787 (23.3%)	115 (19.0%)	0.021
Digoxin	225 (5.7%)	189 (5.6%)	36 (6.0%)	0.723
Sotalol	21 (0.5%)	18 (0.5%)	3 (0.5%)	0.909
Class IC AA	4 (0.1%)	4 (0.1%)	0 (0%)	0.397
Antiplatelet agents	2278 (57.2%)	2007 (59.4%)	271 (44.9%)	<0.001
Vitamin K antagonists	1404 (35.3%)	1226 (36.2%)	178 (29.5%)	0.001

Comparison among sexes. AA indicates antiarrhythmic agent; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; CRT-D, cardiac resynchronization therapy with defibrillator; GFR, glomerular filtration rate; ICD, implantable cardioverter defibrillators; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.
*Number of comorbidities among the following: cancer, chronic kidney disease, chronic lung disease, hepatic failure, diabetes mellitus, and previous stroke.

both groups), infection (♂1.0% versus ♀0.8%), lead-related (♂3.4% versus ♀4.2%), and death (♂0.2% versus ♀0.1%) (all P=NS).

During 16 786 patient-years of follow-up, corresponding to a median of 994 days (95% CI 51–2623 without differences between sexes, P=0.997), appropriate therapies were documented in 1181 (22.3%) patients, corresponding to an annual incidence of 8.2 per 100 patient-years (95% CI 7.8–8.7) (Table 2). On univariate analysis, women had a significantly lower likelihood of receiving appropriate therapies (23.0%♂ versus 17.4%♀; P<0.001). After adjustment for all baseline intersex differences, on multivariate Cox-regression female sex remained an independent predictor of lower incidence of appropriate therapies (hazard ratio [HR]=0.59, 95% CI 0.45–0.76; P<0.001) (Figure 2). Even though the presence of CRT was not significantly associated with appropriate therapies (HR=0.978, 95% CI 0.80–1.20, P=0.830), analysis of different device strata suggests a larger effect size and more pronounced reduction in the incidence of appropriate therapies in female CRT-D recipients versus men (HR=0.49, 95% CI 0.34–0.70; P<0.001), than in their single- and dual-chamber ICD counterparts (HR=0.76, 95% CI 0.52–1.11; P=0.159) (Table 2).

Regarding inappropriate shocks, on univariate analysis, no sex-related benefit was observed (6.7% versus 6.7%; odds ratio=1.00, 95% CI 0.74–1.35, P=0.997). On binary logistic
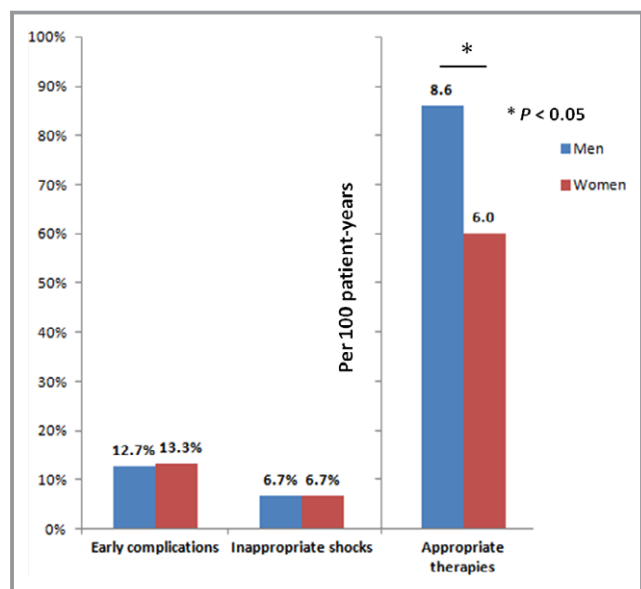
Figure 1. Overall view of outcomes in the male and female sex.

regression, after adjustment for baseline differences, the absence of sex-specific interaction was confirmed.

Total and Specific Mortalities

Death occurred in 15.2% (6.0 per 100 patient-years; 95% CI 5.6–6.3). Despite the fact that women experienced a slightly lower annual mortality rate (5.0 per 100 patient years ♂ versus 4.2 per 100 patient years ♀) on univariate Cox-regression, after adjustments for all baseline differences, this was no longer observed: female sex was not an independent predictor of mortality (HR=0.87, 95% CI 0.66–1.15; P=0.324). By contrast, AF (HR=1.41; 95% CI 1.13–1.77, P=0.003), NYHA ≥III (HR=2.25; 95% CI 1.81–2.79, P<0.001), left ventricular ejection fraction <30% (HR=1.50; 95% CI 1.21–1.86, P<0.001), ischemic heart disease (HR=1.66, 95% CI 1.34–2.00, P<0.001), and glomerular filtration rate ≤60 mL/min (HR=2.31, 95% CI 1.88–2.84, P<0.001) were associated with increased mortality.

On Cox-regression multivariate analysis, when restricting the analysis only to patients implanted with CRT-Ds, a significant survival benefit was seen in women implanted with a CRT-D (HR=0.68, 95% CI 0.47–0.97; P=0.034) (Table 2). In their single- and dual-chamber ICD counterparts, this was not observed (HR=1.50, 95% CI 0.96–2.34; P=0.072). The P-value for this sex by device interaction was 0.070. Kaplan–Meier curves illustrating this interaction (Figure 3) show that male and female patients implanted with CRT-Ds diverge right from the beginning. On the other hand, for female and male patients implanted with single- and dual-chamber ICDs, curves are overlapping for the first 4 years, and suddenly

diverge after that, at a time where only close to 100 female patients are being followed. These curves also show that male patients with CRT-Ds do much worse than males implanted with single- and dual- chamber ICDs. This difference is not as pronounced in female patients.

The specific analysis of causes of death (Table 3), after adjustment for baseline differences, revealed a significant interaction of sex with CRT as regards nonarrhythmic cardiovascular mortality: women with single- and dual-chamber ICD implants fared worse than men (HR=2.49, 95% CI 1.40–4.45, P=0.002), but those implanted with CRT-Ds were less likely to die of nonarrhythmic cardiovascular causes (HR=0.50, 95% CI 0.35–0.99, P=0.048).

Discussion

Our multicentric real-world data show that similar to randomized controlled trials[10] and other registries of ICD recipients in daily clinical practice,[11–13] women account for only a minority of our cohort. Also, they present with a different clinical profile, with higher prevalence of nonischemic cardiomyopathy, more advanced heart failure, broader QRS complex width, and lower prevalence of AF. Women, overall, presented with lower incidence of appropriate ICD therapies and similar mortality compared with men. However, our results suggest that differences in sex-related outcomes in primary prevention ICDs may be observed among CRT recipients. Whereas female CRT-D recipients present with lower mortality and incidence of appropriate ICD interventions than their male counterparts, outcomes of single- and dual-chamber ICD recipients seem to be more comparable.

Our findings, suggesting a lower incidence of appropriate ICD therapies among women, have also been reproduced in other studies: the prospective Ontario registry[5] and a single-center North American propensity-matched observational study.[14] However, only the latter has shown that this effect was more pronounced among CRT-D recipients.[14] This is similar to what we observed in our cohort, where the lower incidence of appropriate therapies among women was mostly driven by a significant difference in CRT-D recipients. We believe these differences may partially result from different clinical risk profiles or ethnic/regional factors in the different samples. Therefore, identifying specific subgroups of primary prevention ICD female recipients who can derive higher benefit from this therapy may be of interest. CRT response, discussed below, may also play a role.

The underlying causes for the more favorable arrhythmic profile of women are not entirely clear but may be related to the lower propensity to sustained ventricular tachycardia in the nonischemic heart failure setting[15,16] but also for ischemic cardiomyopathy–associated sudden cardiac

Table 2. Study Outcomes in the Global Sample: Analysis by Sex and Device Interaction

Unadjusted Analysis				
	Event Rate, % (n)			
Outcome	Global Sample (n=5539)	Male Sex (n=4702)	Female Sex (n=837)	P Value
Appropriate therapies	8.2 per 100 patient years (95% CI 7.8–8.7)	8.6 per 100 patient years (95% CI 8.1–9.1)	6.0 per 100 patient years (95% CI 5.1–7.1)	<0.001
Early complications	710 (12.8%)	599 (12.7%)	111 (13.3%)	0.785
Inappropriate shocks	355 (6.7%)	302 (6.7%)	53 (6.7%)	0.997
Mortality	4.9 per 100 patient years (95% CI 4.6–5.3)	5.0 per 100 patient years (95% CI 4.7–5.4)	4.2 per 100 patient years (95% CI 3.5–5.1)	0.01
Multivariate-Adjusted Analysis* Odds Ratio/Hazard Ratio (95% CI)—All Patients				
Appropriate therapies	HR=0.59 (0.45–0.76)		<0.001	
Early complications	OR=1.00 (0.75–1.32)		0.992	
Inappropriate shocks	OR=0.84 (0.50–1.39)		0.492	
Mortality	HR=0.87 (0.66–1.15)		0.324	
VVI and DDD-ICD patients				
Appropriate therapies	HR=0.76 (0.52–1.11)		0.159	
Early complications	OR=0.83 (0.48–1.43)		0.498	
Inappropriate shocks	OR=0.61 (0.28–1.31)		0.609	
Mortality	HR=1.50 (0.96–2.34)		0.072	
CRT-D patients				
Appropriate therapies	HR=0.49 (0.34–0.70)		<0.001	
Early complications	OR=1.10 (0.78–1.55)		0.574	
Inappropriate shocks	OR=1.08 (0.54–2.18)		0.828	
Mortality	HR=0.68 (0.47–0.97)		0.034	

CRT-D indicates cardiac resynchronization therapy with defibrillator; DDD-ICD, dual chamber device-implantable cardioverter defibrillators; HR, hazard ratio; OR, odds ratio; VVI, single chamber device.

*Adjusted for baseline differences in New York Heart Association class, atrial fibrillation, ischemic cardiomyopathy, QRS width, use of CRT-D, treatment with β-blockers, amiodarone, spironolactone, calcium channel blockers, antiplatelet agents, and vitamin K antagonists.

death.[17–19] In our sample, despite having more women with nonischemic cardiomyopathy, the overall reduction in arrhythmic burden was still present even after adjustment for baseline differences. Several mechanisms have been proposed for sex differences regarding the risk of ventricular arrhythmia: higher resting heart rate, different autonomic response to stress, degree of vagal activation, differences in cardiac repolarization, hormonal differences affecting arrhythmic vulnerability, genetic variants influencing QT interval length or adrenergic receptors, and even nutritional factors, adherence to a low-risk lifestyle, and behavioral and psychological factors.[20–31] Overall, the interplay between vulnerable substrate (underlying structural and electric heart substrate), triggers, and autonomic tone may be slightly different.[30]

The reason for the sex-related benefit among women implanted with CRT-D is still unclear. Arhsad et al have proposed 2 hypothetical explanations[32]: first, a likely possible greater risk of progression to overt heart failure among women, resulting in a greater preventive benefit of CRT-D therapy. Second, women may have, on average, a 10 ms shorter QRS duration than men in subjects without heart disease.[33] Therefore, on a relative basis, for the same degree of QRS duration, more pronounced conduction disturbances and cardiac dyssynchrony may occur in women, explaining the higher response to cardiac resynchronization therapy. Thus, a higher prevalence of response to CRT and reverse remodeling, as observed in the MADIT-CRT trial,[32] can possibly explain the survival and arrhythmic benefit of our population.

Regarding inappropriate shocks, all existing data have found a similar risk in both men and women,[5,9,34] as we have observed. Furthermore, we have assessed the underlying reasons for inappropriate therapies and found no intersex differences (namely, a similar incidence of supraventricular tachycardia despite the fact that AF was more frequent among men).
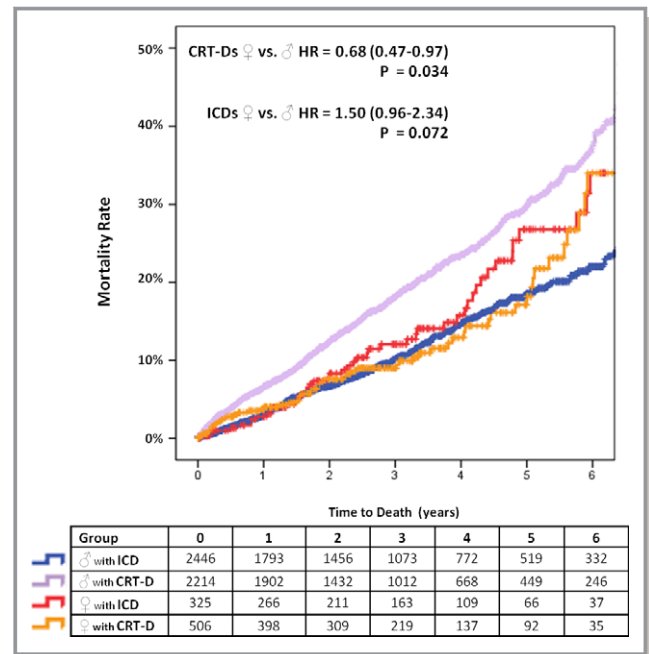
Our data do not reproduce the previously described increased risk of complications in women. MacFadden and
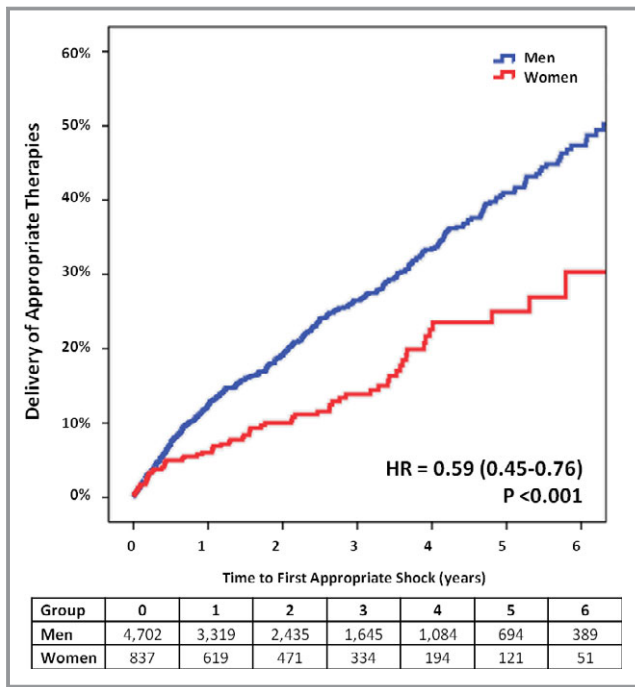
Figure 2. Adjusted event curves for first appropriate therapy. HR indicates hazard ratio. Adjusted for baseline differences in New York Heart Association class, atrial fibrillation, ischemic cardiomyopathy, QRS width, use of cardiac resynchronization therapy with defibrillator, treatment with β-blockers, amiodarone, spironolactone, calcium channel blockers, antiplatelet agents, and vitamin K antagonists.

Figure 3. Adjusted event-curves for overall mortality in men and women. CRT-D indicates cardiac resynchronization therapy with defibrillator; HR, hazard ratio; ICD, single- or dual-chamber implantable cardioverter defibrillator. Adjusted for baseline differences in New York Heart Association class, atrial fibrillation, ischemic cardiomyopathy, QRS width, use of CRT-D, treatment with β-blockers, amiodarone, spironolactone, calcium channel blockers, antiplatelet agents, and vitamin K antagonists.

colleagues reported a 50% significantly higher (5.4% versus 3.3%) occurrence of any major or minor complications in women at 45-day follow-up.[5] Recent data from the United States *National Cardiovascular Data Registry ICD Registry* show that device-related complications are more common in women (7.2% versus 4.8%; $P<0.001$).[35] Unlike the latter study, we observed no differences regarding 30-day mortality and observed a much lower rate of cardiac tamponade. Possible explanations for the observed lack of sex-related differences and the overall higher complication rate in our sample may be the very inclusive definition of end points such as bleeding events and lead-related complications, and having local investigator-adjudicated end points instead of using the Centers for Medicare and Medicaid Services inpatient claims. Lastly, the use antiplatelet agents and oral anticoagulants in our sample was more common in males, which may account for the numerically, but not statistically significant, higher rate of bleeding observed in male patients.

As regards mode of death, we have observed that the incidence of specific causes of death in women, namely, nonarrhythmic cardiovascular mortality, may depend on the type of implanted device. In single- or dual-chamber ICD recipients, nonarrhythmic cardiovascular death occurred more commonly in women whereas in those implanted with a CRT-

D it happened less frequently. These findings are contrary to previously published data showing no sex-related differences in cause of death.[6,36] We believe this may occur because these 2 studies have smaller samples, and therefore are not statistically powered to assess for interactions between sex, device type, and specific mortalities. In patients who are eligible for an ICD, it is known that sudden cardiac death seems to occur less frequently in women.[37] Our data seem to suggest that after device implantation, the favorable arrhythmic profile may still exist because, notwithstanding the similar incidence of ICD unresponsive sudden death, women present with fewer appropriate therapies, which can be considered, to a certain level, a sudden cardiac death surrogate.

Limitations

This analysis has a number of limitations. First, the retrospective nature of this registry could have led to information bias. Second, device programming may have been a source of some interindividual variability, but this factor has been minimized by proposed programming rules recommending no differences based on sex.[8] Last, no central adjudication for classification of appropriate and inappropriate therapies was used in this registry.

Table 3. Causes of Death: Analysis by Sex and Device Interaction

Cause of Death	n (% of Total Deaths) All Patients (n=826)	All Patients, Unadjusted Analysis n (% of Patients)		
		Male Sex	Female Sex	P Value
Sudden death	64 (7.7%)	54 (1.2%)	10 (1.2%)	0.908
ICD-related	14 (1.7%)	14 (0.3%)	0 (0%)	0.114
Cardiovascular causes	407 (49.3%)	350 (7.6%)	57 (7.0%)	0.518
Noncardiovascular	197 (23.8%)	181 (3.9%)	16 (2.0%)	0.005
Unknown	144 (17.4%)	121 (2.6%)	23 (2.8%)	0.770
Cause of Death	n (% of Total Deaths) VVI or DDD-ICD (n=315)	VVI or DDD-ICD Patients, Unadjusted Analysis n (% of Patients)		
		Male Sex	Female Sex	P Value
Sudden death	28 (8.9%)	22 (1.0%)	6 (1.9%)	0.168
ICD-related	4 (1.3%)	4 (0.2%)	0 (0%)	0.444
Cardiovascular causes	142 (45.1%)	116 (5.4%)	26 (8.3%)	0.042
Noncardiovascular	83 (26.3%)	76 (3.5%)	7 (2.2%)	0.228
Unknown	58 (18.4%)	51 (2.4%)	7 (2.2%)	0.871
Cause of Death	n (% of Total Deaths) CRT-D Patients (n=500)	CRT-D Patients, Unadjusted Analysis n (% of Patients)		
		Male Sex	Female Sex	P Value
Sudden death	35 (7.0%)	31 (1.3%)	4 (0.8%)	0.372
ICD-related	10 (2.0%)	10 (0.4%)	0 (0%)	0.151
Cardiovascular causes	259 (51.8%)	229 (9.5%)	30 (6.0%)	0.014
Noncardiovascular	112 (22.4%)	104 (4.3%)	8 (1.6%)	0.004
Unknown	84 (16.8%)	68 (2.8%)	16 (3.2%)	0.626
Multivariate-Adjusted Cox Regression* ♀ vs ♂—Hazard Ratio (95% CI)				
Death due to noncardiovascular causes All patients		HR=0.63 (0.30–1.31)		0.206
Death due to cardiovascular causes ICD patients		HR=2.49 (1.40–4.45)		0.002
Death due to cardiovascular causes CRT-D patients		HR=0.59 (0.35–0.99)		0.048
Death due to noncardiovascular causes CRT-D patients		HR=0.59 (0.23–1.50)		0.267

CRT-D indicates cardiac resynchronization therapy with defibrillator; DDD-ICD, dual chamber device-implantable cardioverter defibrillators; HR, hazard ratio; ICD, implantable cardioverter defibrillators; NYHA, New York Heart Association; VVI, single chamber device.
*Adjusted for baseline differences in NYHA class, atrial fibrillation, ischemic cardiomyopathy, QRS width, use of CRT-D, treatment with β-blockers, amiodarone, spironolactone, calcium channel blockers, antiplatelet agents, and vitamin K antagonists.

Conclusions

In our real-life registry, women seem to account for the minority of ICD recipients and present with a different clinical profile. Even though the incidence of early complications and inappropriate shocks was similar, lower all-cause mortality and incidence of appropriate therapies was observed in female CRT-D recipients compared with men. Among single- and dual-chamber ICD recipients, the incidence of ICD therapies was comparable but nonarrhythmic cardiovascular death was more common in women.

Appendix

The following investigators and institutions participated in the conception of the registry, and in the organization, collection, storage, and analysis of the data:

Co-principal Investigators: Serge Boveda, MD, Clinique Pasteur, Toulouse; Eloi Marijon, MD, PhD, Hôpital Européen Georges Pompidou, Paris, France. Conceived, designed and organized the registry in 2009.

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