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Gender, underutilization of cardiac resynchronization therapy, and prognostic impact of QRS prolongation and left bundle branch block in heart failure

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Aims It has been suggested that cardiac resynchronization therapy (CRT) is less utilized, dyssynchrony occurs at narrower QRS, and CRT is more beneficial in women compared with men. We tested the hypotheses that (i) CRT is more underutilized and (ii) QRS prolongation and left bundle branch block (LBBB) are more harmful in women.

Methods and results We studied 14 713 patients (28% women) with left ventricular ejection fraction (LVEF) <40% in the Swedish Heart Failure Registry. In women vs. men, CRT was present in 4 vs. 7% ($P < 0.001$) and was absent but with indication in 30 vs. 31% ($P = 0.826$). Next, among 13 782 patients (28% women) without CRT, 9% of women and 17% of men had non-specific intraventricular conduction delay (IVCD) and 27% of women and 24% of men had LBBB. One-year survival with narrow QRS was 85% in women and 88% in men, with IVCD 74 and 78%, and with LBBB 84 and 82%, respectively. Compared with narrow QRS, IVCD had a multivariable hazard ratio of 1.24 (95% CI 1.05–1.46, $P = 0.011$) in women and 1.30 (95% CI 1.19–1.42, $P < 0.001$) in men, and LBBB 1.03 (95% CI 0.91–1.16, $P = 0.651$) in women and 1.16 (95% CI 1.07–1.26, $P < 0.001$) in men, P for interaction between gender and QRS morphology, 0.241.

Conclusions While the proportion with CRT was lower in women, CRT was equally underutilized in both genders. QRS prolongation with or without LBBB was not more harmful in women than in men. Efforts to improve CRT implementation should be directed equally towards women and men.

Keywords Gender • Heart failure • QRS width • Left bundle branch block • Epidemiology • Cardiac resynchronization therapy

Introduction

Cardiac resynchronization therapy (CRT) is beneficial in New York Heart Association (NYHA) II–IV heart failure (HF) with electrical dyssynchrony.[1–6] Cardiac resynchronization therapy is generally underutilized in Europe.[7] Sub-group analysis of MADIT CRT[8] and REVERSE[9] indicates that CRT benefits are greater in the presence of left bundle branch block (LBBB) than with intraventricular conduction delay (IVCD) including right bundle branch block (RBBB). Recent guidelines therefore stress the presence of LBBB.[10–13]

It has been suggested that the benefit of CRT is greater in women.[14,15] Yet a majority of CRT recipients are men[1–6,16,17] suggesting a possible gender bias.[18] These reports present utilization of CRT, which is higher in men, and assume that the prevalence of CRT indication is similar in women and men. However, underlying morbidities in HF may differ as well as accompanying conduction disorders. Therefore, an alternate explanation could be that women correctly receive less CRT because they less often meet the selection criteria. The more appropriate comparison would then be underutilization in women vs. men.

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What's new?

- Women have been thought to receive less Cardiac resynchronization therapy (CRT) due to a gender bias and debated whether QRS width and LBBB morphology have the same prognostic implications in women and men. In this paper based on the national Swedish heart failure registry RiksSvikt, we demonstrated that
- Cardiac resynchronization therapy is not more underutilized in women compared with men and that
- QRS prolongation and LBBB are not more harmful in women compared with men.
- Efforts to improve CRT implementation should be directed equally towards women and men.

Moreover, even if CRT were not underutilized in women by current criteria, it is possible that women suffer adverse effects of dyssynchrony at narrower QRS. Women may thus have worse outcomes for a given QRS width and/or LBBB than men, suggesting that guidelines for CRT should be more lenient in women to enable women to receive CRT at smaller QRS widths. We have previously shown that QRS prolongation and LBBB are independent risk factors for mortality in HF patients.[19] However, the gender-specific risks were not tested and remain unknown.

Therefore, we tested the hypotheses that (i) CRT is more underutilized in women compared with men and (ii) QRS prolongation and LBBB are more harmful in women compared with men.

Methods

Study protocol

The Swedish Heart Failure Registry (RiksSvikt) has been previously described.[20,21] Establishment of the registry and registration and analysis of data were approved by a multisite ethics committee. The registry and this study conform to the Declaration of Helsinki.

Between 11 May 2000 and 5 June 2013, there were 85 291 registrations from 68 of ~80 hospitals and 102 of 1000 primary care outpatient clinics in Sweden. We included first registrations from patients with left ventricular ejection fraction (LVEF) <40% and any NYHA class, and excluded patients without CRT in whom CRT indications could not be assessed (e.g. QRS and/or LBBB missing or not registered due to pacemaker and/or paced EKG) as well as re-registrations. This left 14 713 patients for Hypothesis 1. Thereafter, 931 patients with existing CRT were excluded leaving 13 782 patients for Hypothesis 2 (Supplementary material online, *Appendix Figure S1*, Flow Chart). For this study, we made no distinction between patients who received or were eligible for a CRT device with or without defibrillation capabilities (CRT-D vs. CRT-*P*). Moreover, we defined the underutilization of CRT as the proportion of patients who are current potential CRT candidates[10–13] but do not have CRT.

Hypothesis 1

Hypothesis 1 tested whether CRT is even more underutilized in women than in men, i.e. whether more women lack CRT despite having an indication. In men and women separately, we compared the proportions with CRT, without CRT but with indication, and without CRT without indication (*Table 1*). A CRT indication was defined as meeting the criteria in the most recent EHRA/ESC guidelines[13], based on NYHA class, LVEF, QRS duration and morphology, and depending on NYHA class, presence, or absence of atrial fibrillation (*Table 1*).

Table 1 Distribution of 14 713 patients for hypothesis 1

Patient category	Women *n* (%)	Men *n* (%)	*P**
CRT yes[a]	156 (4%)	775 (7%)	<0.001
CRT no but indication[b] yes	1237 (30%)	3243 (31%)	0.826
CRT no and indication[b] no	2688 (66%)	6614 (62%)	<0.001
Total[c]	4081 (100%)	10 632 (100%)	

[a]Patients with CRT are shown here but excluded from further analysis (flow chart, Supplementary material online, *Appendix Figure S1*).
[b]Indication for CRT adapted from ESC guidelines on Cardiac Pacing and Cardiac Resynchronization Therapy 2013: EF ≤ 39% and NYHA III–IV and QRS ≥ 120 or EF ≤ 39% and NYHA II and QRS ≥ 120 and chronic AF = NO.
[c]Total may not equal 100% due to rounding.
**P* is for difference in women vs. men with Fisher's exact test.

Consistency analyses for Hypothesis 1

Categorization and availability of data in the registry do not allow a perfect match to the guidelines criteria.[10–13] In the registry, LVEF is reported in 10% increments. First, LVEF was thus categorized as <30, 30–39, 40–49, and ≥50%. We excluded LVEF 40–49% and ≥50%. In Sweden, LVEF is overwhelmingly reported in 5–10% increments. Therefore, for LVEF 30–39%, we assumed that a vast majority had a reported LVEF of 30% or 35% and that very few had 36–39%. Thus, in the main analysis the patients in the LVEF 30–39% category were considered to meet CRT criteria. However, we performed a conservative consistency analysis where only patients with LVEF <30% were considered for CRT indication, and patients with LVEF 30–39% were considered not to have CRT indication (Supplementary material online, *Appendix Table S1A*).

In the absence of LBBB and moderately prolonged QRS (120–149 ms), CRT is indicated but the evidence is weaker. Therefore, we also performed a consistency analysis where LBBB was required for CRT indication if QRS width was 120–149 ms (Supplementary material online, *Appendix Table S1B*).

Guidelines recommend CRT also in patients who meet NYHA and LVEF criteria and have a concomitant indication for conventional pacing.[12,13] The registry contains data on the presence of conventional pacemakers but no information on the initial indication for cardiac pacing. Upgrade to CRT was not taken into account. Therefore, we may have underestimated the total number of patients with an indication for CRT.

Finally, some important background variables for patients with CRT compared with those without but with an indication were analysed (Supplementary material online, *Appendix Table S2*).

Hypothesis 2

Hypothesis 2 tested whether non-specific IVCD and/or LBBB are more harmful in women than in men. Right bundle branch block is not reported in the registry and thus encompassed by IVCD. In this analysis, patients with CRT were excluded. For the main risk analysis, QRS width was categorized as ≥120 vs. <120 ms. Patients were categorized into three groups: QRS <120 ms (narrow), QRS ≥120 ms without LBBB (IVCD) and QRS ≥120 ms with LBBB (*Figure 1* and *Table 2*). QRS width contains more physiological and statistical information as a continuous variable, but the dichotomization at the 120 ms cut-off is clinically more useful and allows distinction of LBBB. We also performed a separate risk analysis where QRS was analysed as a continuous variable.

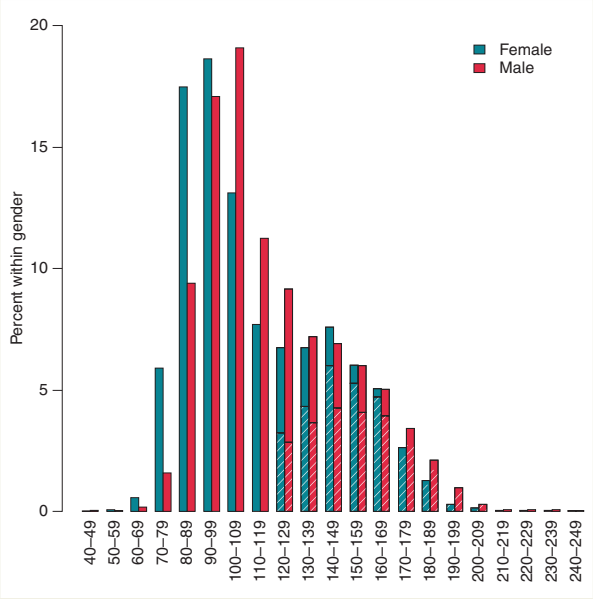

Figure 1 Distribution of QRS width (ms) and proportions with LBBB among women and men. The percentage of patients within each gender with QRS widths in 10 ms intervals is given as well as the proportion of women and men reported to have LBBB (hashed bars). Women had narrower QRS, but once QRS was ≥120 ms, LBBB was more common as a proportion and in absolute terms in women compared with men. As QRS widened, the proportion of patients with LBBB increased in both genders. Data not imputed.

Statistical analysis

All analyses were performed in R version 2.15.3 (R Foundation for Statistical Computing, Vienna, Austria). The level of significance was set to 5% and all reported *P*-values are two-sided.

For Hypothesis 1, percentages for women vs. men were compared with Fisher's exact test (*Table 1 and* Supplementary material online, *Appendix Table S1A and B*). Moreover, the clinical characteristics of patients with CRT indications who were treated and not treated with a CRT were compared (Supplementary material online, *Appendix Table S2*).

For Hypothesis 2, QRS width and LBBB by gender were depicted in a histogram (*Figure 1*) and descriptive statistics in women vs. men were compared with Fisher's exact test for categorical variables and *t*-test for continuous variables (selected variables shown in *Table 2;* complete variables shown in Supplementary material online, *Appendix Table S3*). Survival for narrow QRS, IVCD, and LBBB was charted with the Kaplan–Meier method separately for women and men (*Figure 2*). Univariable and multivariable Cox regressions, using the Efron method for tie handling, were performed separately for IVCD/LBBB as a categorical variable compared with narrow QRS and for QRS width as a continuous variable (where LBBB yes/no was not included in the model, due to potential covariance with QRS width). Some baseline variables had missing data. Supplementary material online, *Appendix Table S3*, specifies 41–42 clinically relevant baseline variables that were used in the models and percentage missing for each variable. In the Cox regressions, to avoid bias and confounding due to variables missing at random, multiple imputation ($n = 10$) was performed for all variables with missing data, using predictive mean matching with QRS width as a continuous variable and the variables in Supplementary material online, *Appendix Table S3*. The outcome, survival, was included as the Nelson–Aalen estimator in the imputation model, although not imputed itself since it contained no missing values. Imputation corrections to the resulting standard errors were performed. The same imputed values were used for all regression and sub-group analyses.

The main analyses were performed in the overall population with adjustment for the numbered variables in Supplementary material online, *Appendix Table S3*, QRS morphology (narrow, IVCD, or LBBB) and the interaction between gender and QRS morphology. The modelling of an interaction effect renders a similar interpretation as if the data had been analysed separately in gender sub-groups, but with the additional benefit of also being able to statistically test differences between women and men in effects of IVCD and LBBB on mortality. For the analysis with QRS as a continuous variable, the hazard ratio (HR) is not easily interpreted when modelling the interaction between gender and QRS width, so here the HR are instead taken from separate analyses in the female and male sub-groups. However, the *P*-value from the interaction effect is presented.

The proportional hazard assumption was investigated for the scaled Schoenfeld residuals from the multivariable models and the dfbetas (a measure of how much the HR changes due to the deletion of a single observation) from the models were inspected to detect extreme outliers.[19] As a result, location (in- vs. outpatient) was modelled as a strata variable since it was deemed not to fulfil the proportional hazard assumption. All continuous variables were modelled using restricted cubic splines (enabling possible non-linear relationships between these variables and the outcome to be modelled) with four degrees of freedom,[22] except QRS width itself, in order to achieve an easily interpreted effect estimate. Visual inspection of the functional form of the partial residuals from the model and the martingale residuals did, however, show linearity for QRS width.

Results

Hypothesis 1: CRT utilization in women and men among

Hypothesis 1 was analysed in 14 713 individual patients (*Table 1*). Of 4081 women and 10 632 men, 4% of women and 7% of men had CRT ($P < 0.001$). Importantly, of all patients in the study 30% of women and 31% of men ($P = 0.826$) met CRT eligibility criteria but had no CRT. In consistency analyses of LVEF <30%, 18% of women vs. 19% of men ($P = 0.011$) met CRT eligibility criteria but had no CRT (Supplementary material online, *Appendix Table S1A*). In consistency analysis where LBBB was required if QRS was 120–149 ms, 24% of women vs. 21% of men ($P = 0.001$) met CRT eligibility criteria but had no CRT (Supplementary material online, *Appendix Table S1A*).Thus, irrespective of analysis, a large and similar proportion of both genders lacked CRT despite an indication. Compared with patients with CRT, patients who lacked CRT despite an indication were older, less frequently cared for by cardiology specialists, had slightly higher EF and more atrial fibrillation and slightly less use of HF medications, but similar NYHA class and prevalence of diabetes and ischaemic heart disease (Supplementary material online, *Appendix Table S2*).

Hypothesis 2: Risk associated with QRS prolongation and LBBB

Figure 1 shows distribution of QRS width and LBBB in women and men. Women had narrower QRS, but once QRS was ≥120 ms, LBBB was more common in women (27%) compared with men

Table 2 Selected baseline characteristics according to QRS width, LBBB and gender of 13 782 patients (3925 women and 9857 men) for hypothesis 2

Variable	QRS <120 ms 'Narrow QRS' *N* = 8187 (60% of total)			QRS ≥120 ms and LBBB no 'IVCD' *N* = 2013 (15% of total)			QRS ≥120 ms and LBBB yes 'LBBB' *N* = 3427 (25% of total)		
	Women *N* = 2493 (64% of women)	Men *N* = 5788 (59% of men)	*P*	Women *N* = 363 (9% of women)	Men *N* = 1660 (17% of men)	*P*	Women *N* = 1069 (27% of women)	Men *N* = 2409 (24% of men)	*P*
Follow-up time, median (range), days	895 (1–4515)	960 (1–4179)		670 (1–3700)	782 (1–4505)		828 (1–4127)	841 (1–4093)	
No. of dead	901 (36%)	1776 (31%)		188 (52%)	807 (49%)		392 (37%)	1020 (42%)	
Demographics									
Age (years)	72 ± 13	68 ± 13	<0.001	76 ± 11	73 ± 11	<0.001	74 ± 11	72 ± 11	0.001
Caregiver medical specialty			0.056			0.140			0.911
Cardiology	1350 (56%)	3274 (58%)		167 (48%)	832 (52%)		543 (52%)	1230 (52%)	
Internal medicine/geriatrics	1078 (44%)	2379 (42%)		184 (52%)	766 (48%)		497 (48%)	1116 (48%)	
Follow-up referral specialty			<0.001			0.001			0.001
Cardiology/internal medicine	1630 (69%)	4342 (79%)		210 (63%)	1117 (72%)		693 (69%)	1710 (75%)	
Other	69 (3%)	134 (2%)		7 (2%)	41 (3%)		38 (4%)	84 (4%)	
Primary care	653 (28%)	1040 (19%)		118 (35%)	393 (25%)		272 (27%)	480 (21%)	
Follow-up referral to outpatient HF nurse clinic	1170 (50%)	3097 (56%)	<0.001	161 (48%)	807 (52%)	0.227	501 (50%)	1191 (53%)	0.150
Clinical									
NYHA			<0.001			0.005			0.613
I	175 (7%)	641 (11%)		14 (4%)	120 (7%)		77 (7%)	200 (8%)	
II	1147 (46%)	2826 (49%)		140 (39%)	710 (43%)		445 (42%)	1023 (42%)	
III	1025 (41%)	2088 (36%)		176 (48%)	734 (44%)		487 (46%)	1053 (44%)	
IV	146 (6%)	233 (4%)		33 (9%)	96 (6%)		60 (6%)	133 (6%)	
LVEF			<0.001			0.145			<0.001
30–39%	1470 (59%)	2870 (50%)		176 (48%)	733 (44%)		449 (42%)	842 (35%)	
<30%	1023 (41%)	2918 (50%)		187 (52%)	927 (56%)		620 (58%)	1567 (65%)	
Chronic atrial fibrillation	831 (33%)	2189 (38%)	<0.001	99 (27%)	613 (37%)	<0.001	221 (21%)	735 (31%)	<0.001
Blood pressure, mm Hg									
Systolic	126 ± 22	124 ± 21	0.031	125 ± 23	123 ± 20	0.101	126 ± 20	122 ± 20	<0.001
Diastolic	73 ± 12	75 ± 13	<0.001	71 ± 13	72 ± 12	0.149	72 ± 11	72 ± 12	0.918
Heart rate, beats per minute	76 ± 16	75 ± 16	0.040	75 ± 17	72 ± 16	0.007	73 ± 15	71 ± 15	<0.001
Laboratory									
Creatinine clearance, mL/min	61 ± 31	80 ± 39	<0.001	51 ± 29	67 ± 33	<0.001	59 ± 32	70 ± 33	<0.001
Haemoglobin, g/L	130 ± 15	139 ± 17	<0.001	128 ± 15	136 ± 17	<0.001	130 ± 15	137 ± 17	<0.001
NT-proBNP, ng/L	6122 ± 8205	4726 ± 6716	<0.001	8931 ± 11374	6382 ± 8473	0.027	6124 ± 8534	5329 ± 7509	0.113
Medical history									
Hypertension	1147 (47%)	2445 (44%)	0.005	191 (54%)	721 (45%)	0.002	486 (47%)	983 (43%)	0.026
Diabetes mellitus	519 (21%)	1310 (23%)	0.073	103 (28%)	488 (29%)	0.750	244 (23%)	597 (25%)	0.229
Ischaemic heart disease	1078 (46%)	2711 (50%)	0.001	195 (55%)	989 (62%)	0.016	430 (43%)	1276 (56%)	<0.001
History of revascularization	506 (20%)	1702 (30%)	<0.001	94 (26%)	605 (37%)	<0.001	175 (16%)	731 (31%)	<0.001
Dilated Cardiomyopathy	363 (15%)	1100 (19%)	<0.001	47 (13%)	295 (18%)	0.021	246 (24%)	608 (26%)	0.198
Valve disease	522 (21%)	900 (16%)	<0.001	103 (29%)	356 (22%)	0.004	256 (24%)	505 (21%)	0.056

History of valve intervention	96 (4%)	210 (4%)	0.657	18 (5%)	103 (6%)	0.395	60(6%)	166 (7%)	0.158
Lung disease	438 (18%)	869 (15%)	0.005	59 (16%)	280 (17%)	0.816	195(19%)	382 (16%)	0.093
Medications									
ACE-inhibitor	1711 (69%)	4404 (76%)	<0.001	233 (64%)	1180(71%)	0.011	721 (68%)	1710 (71%)	0.037
Angiotensin receptor blocker	551 (22%)	1118 (20%)	0.003	93 (26%)	377 (23%)	0.242	289 (27%)	557 (23%)	0.011
β-blocker	2284 (92%)	5358 (93%)	0.204	324 (90%)	1473 (89%)	0.853	951 (89%)	2146 (89%)	0.953
Aldosterone antagonist	772 (31%)	1855 (32%)	0.367	124 (34%)	562 (34%)	0.951	411 (39%)	883 (37%)	0.269
Digoxin	473 (19%)	1107 (19%)	0.879	54 (15%)	302 (18%)	0.148	143 (13%)	352 (15%)	0.371
Diuretic	1988 (80%)	4326 (75%)	<0.001	310 (86%)	1400 (85%)	0.627	873 (82%)	1915 (80%)	0.104
Nitrate	373 (15%)	677 (12%)	<0.001	81 (22%)	287 (17%)	0.030	168 (16%)	412 (17%)	0.349
Platelet inhibitor	1239 (50%)	2800 (49%)	0.280	224 (62%)	876 (53%)	0.002	576 (54%)	1316 (55%)	0.767
Oral anticoagulant	916 (37%)	2533 (44%)	<0.001	103 (28%)	670 (40%)	<0.001	277 (26%)	903 (38%)	<0.001
Statin	506 (20%)	1702 (30%)	<0.001	94 (26%)	605 (37%)	0.037	175 (16%)	731 (31%)	<0.001

Numbers are *n* (%) for categorical variables and mean ± standard deviation for continuous variables, with the exception of follow-up times which is median (range).
P with Fisher's exact test for categorical variables and *t*-test for continuous variables.
Percentages may not add to 100% because of rounding.
A complete list of variables is available in Supplementary material online, *Appendix Table S2*.
IVCD, intraventricular conduction delay.
LBBB, left bundle branch block.

Figure 2 Kaplan–Meier survival by gender and QRS/LBBB group. When visually comparing women vs. men, women had worse survival with narrow QRS and IVCD, and better survival with LBBB. When comparing QRS morphology, for both genders, narrow QRS was least harmful, followed by LBBB and then IVCD. Given a wide QRS, the presence of LBBB vs. IVCD conferred a greater advantage in women compared with in men.

(24%) (Supplementary material online, *Appendix Table S3*). As QRS widened, the proportion with LBBB increased in both genders. LBBB with a QRS duration of >150 ms present in 50% of women and 56% of men (Supplementary material online, *Appendix Table S2*).

Supplementary material online, *Appendix Table S3* shows all baseline characteristics used in subsequent multivariable modelling according to gender and QRS morphology, whereas *Table 2* shows selected baseline characteristics. Intraventricular conduction delay was less (9 vs. 17%) and LBBB more common in women (27% vs. 24%). In both women and men, patients with narrow QRS had the least severe disease, patients with IVCD had more ischaemic heart disease, and patients with dilated cardiomyopathy had more LBBB. All three QRS groups and genders were similarly treated by cardiologists. Follow-up referral to cardiology and to HF nurse was slightly higher in men compared with women, but was not different in patients with IVCD or LBBB compared with narrow QRS and was similar between the three QRS groups. Women were older than men, had more hypertension and higher blood pressure, less ischaemic heart disease, and previous revascularization and less chronic atrial fibrillation. Importantly, these differences between men and women were similar regardless of QRS morphology.

Kaplan–Meier survival curves by women and men in relation to QRS morphology (*Figure 2*)

One-year survival with narrow QRS was 85% in women and 88% in men, with IVCD 74 and 78%, and with LBBB 84 and 82%, respectively. When visually comparing survival by gender and QRS morphology,

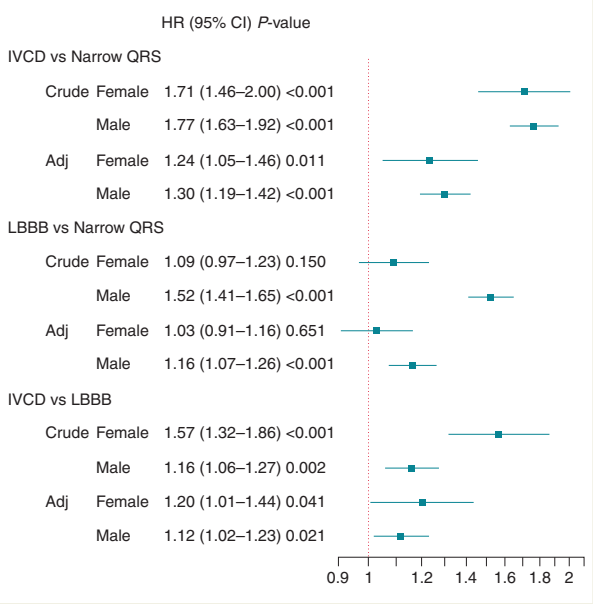

Figure 3 Forest plots depicting HRs for all-cause mortality associated with different QRS morphologies in women and men. Cox regressions were performed in the overall population with adjustment for the interaction between gender and QRS morphology. Hazard ratios are displayed for the listed gender sub-groups. HR, hazard ratio; CI, confidence interval; LBBB, left bundle branch block; IVCD, intraventricular conduction delay.

women had worse survival than men with narrow QRS and IVCD, and better survival with LBBB. When comparing QRS morphology for both genders, narrow QRS was least harmful, followed by LBBB and then IVCD. Given a wide QRS, the presence of LBBB vs. IVCD conferred a greater advantage in women compared with men.

Risk for all-cause mortality with regard to QRS morphology

Figure 3 depicts univariable and multivariable HRs for all-cause mortality associated with different QRS morphologies for women and men separately modelled using interaction effects between gender and QRS morphology. Compared with narrow QRS, IVCD was associated with a multivariable HR of 1.24 (95% CI 1.05–1.46, $P = 0.011$) in women and of 1.30 (95% CI 1.19–1.42, $P < 0.001$) in men. Left bundle branch block was associated with a multivariable HR of 1.03 (95% CI 0.91–1.16, $P = 0.651$) in women and 1.16 (95% CI 1.07–1.26, $P < 0.001$) in men, *P*-value for interaction between QRS group and gender is 0.241. Intraventricular conduction delay appeared to be more harmful than LBBB in both women and men, which was confirmed by the direct comparison of IVCD vs. LBBB: multivariable HR 1.20 (95% CI 1.01–1.44, $P = 0.041$) in women and 1.12 (95% CI 1.02–1.23, $P = 0.021$) in men. Thus, after adjusting for confounding variables, IVCD was harmful in both women and men and LBBB was harmful only in men and IVCD was more harmful than LBBB in both women and men. However, the interaction between QRS morphology and gender was not significant, suggesting that IVCD or LBBB was not definitively shown to entail different risks in women vs. men (*Figure 3*).

When the risk was assessed with QRS width as a continuous rather than a categorical variable (data not shown), the multivariable HR for each 10 ms increase in QRS width was 1.02 (95% CI 1.0–1.04, $P = 0.038$) in women and 1.03 (95% CI 1.02–1.04, $P < 0.001$) in men, *P* for interaction, 0.219. Thus, after adjusting for confounding variables, there was an additional risk of 2–3% for mortality for each 10 ms of increment of QRS width in both women and men, with no difference in risk between women and men.

Discussion

It has been suggested that CRT is less utilized, dyssynchrony occurs at narrower QRS and CRT is more beneficial in women compared with men. Indeed, CRT was slightly more utilized in men than in women. However, in this study we assessed underutilization, i.e. the prevalence of women and men who do not have CRT but have a potential CRT indication. We show that CRT is equally underutilized in women and men, reflecting general underutilization rather than a gender bias. We also show that IVCD and LBBB are not more harmful in women compared with men. Thus, our findings do not confirm the hypothesis that women should have more lenient criteria (e.g. narrower QRS) for CRT, although this remains to be proven in clinical studies.

Generally, CRT is underutilized[7] despite substantial benefits.[1–6] First, it has been believed that women were underrepresented in CRT trials.[1–6] Secondly, it has been believed that CRT is more underutilized in women in clinical practice.[14,17,18] In this study, we confirm that the majority of CRT recipients are men. However, although 30% of women and 31% of men were without CRT despite an indication was equal between genders, the absolute number of men was nearly three-fold that of women, suggesting that the CRT trials may not have entailed selection bias but actually represented the unselective clinical practice reported here. The fact that untreated patients more often were not cared for by cardiology specialists stresses the importance of level of care for awareness of new therapies such as CRT. We have previously shown that such awareness is the highest in cardiology specialists, [23]

Women have also been suggested to benefit more from CRT[14,15] and at lower QRS widths[8,15] further fuelling the fear that women are deprived CRT. This belief is probably reinforced by suggestion of under-prescription of ICDs in women.[24] To our knowledge it has not been confirmed if the reason for less CRT implants in women is a true bias or if men indeed more often meet the CRT criteria. We studied gender-related CRT underutilization and indications in an entire HF registry population, rather than looking at actual implantation patterns in a device-based registry, study, or database. We first tested whether CRT was underutilized in women (Hypothesis 1). Although significantly less women (4%) than men (7%) were in fact treated with CRT, the proportion of the much larger groups of both women and men with a potential indication for CRT who were not treated was close to identical between genders. If CRT were more underutilized in women, the reason might also be gender-related differences in contraindications to CRT. With regard to patients in NYHA IV HF, CRT is only indicated in ambulatory patients.[13] However, although women were older, they did not have more severe HF and were otherwise not markedly more ill either in the overall study population or in the group without CRT but with an indication. Therefore, we believe that the problem is a

general and serious underutilization of CRT rather than gender bias or a comorbidity profile disfavouring women. We acknowledge that the magnitude of underutilization in Sweden—a country with mid low implantation rate, may not be representative for all European countries. Irrespective of implantation rates, we have no reason to believe that gender distribution of those implanted with CRT or not differs in the European countries irrespective of high or low implantation rates.

In our study, more women than men had LBBB. It has been hypothesized that LBBB in men more often than in women may be associated with conditions that also prolong QRS duration but do not necessarily cause LV dyssynchrony such as left ventricular hypertrophy.[25] Moreover, healthy women have smaller hearts and on average 6 ms shorter QRS duration.[26] It is thus fair to assume that women may also have dyssynchrony at shorter QRS widths than men. Our findings confirm the observation that women have smaller QRS width *(Figure 1)* and have LBBB at narrower QRS, suggesting that women would derive a benefit from CRT at LBBBs with shorter QRS widths. In a sub-study of MADIT CRT,[15] women benefited from CRT over all QRS widths even down to 130 ms,[8] whereas men only benefited if QRS was >140 ms.

We[19] and others[27] observed that LBBB and/or QRS prolongation were independent predictors of mortality, but these studies did not assess gender differences. In a study from Medicare, Bilchik[28] reported more favourable outcomes in CRT recipients with baseline LBBB compared with RBBB or IVCD, but gender differences with respect to BBB were not reported. Loring *et al.*[29] reported that pre-CRT LBBB predicted better survival in women compared to men. We did not study the effects of CRT, e.g. in relation to intrinsic QRS widths or LBBB at CRT implantation. However, in patients without CRT, we were able to provide a detailed and rigorous gender-based risk assessment for QRS width and morphology (Hypothesis 2). First, IVCD was harmful in both women and men, whereas LBBB appeared to be harmful in men only. However, the gender interaction was not significant, allowing only the conclusion that the risk associated with IVCD and LBBB is likely elevated but cannot be shown to be different for women vs. men. Likewise, incremental QRS prolongation was similarly harmful in women and men.

In LBBB, the septum contracts first against a non-activated LV free wall followed by LV free wall contraction when the septum is already relaxed, leading to a LV dyssynchrony. However, the conduction pattern in LBBB may vary and be linked to different IVCDs[30] in different individuals and disease conditions and may even differ between genders. In contrast, in RBBB it is the right ventricle that contracts dyssynchronously with a mostly normal LV contraction. Our study confirmed the evidence that IVCD (which included RBBB) may be linked to worse outcomes than LBBB.[28,31] This may be due to the higher prevalence of ischaemic heart disease with IVCD in our study and in other studies.[28,31] The comparisons of wide vs. narrow QRS and LBBB vs. non-LBBB should be interpreted more carefully, since they do not permit adjustment for the reciprocal variable (LBBB and QRS width, respectively). However, findings were consistent with the main analyses and there were again no interactions with gender. Thus, we could not confirm that present guideline recommendations for CRT[12,13] would exclude women who might benefit from CRT.

Limitations

Limitations due to missing data are discussed in the Methods. Moreover, ECG assessment of QRS width and bundle branch morphology was left to the individual physician and was not validated. In addition, we could not assess whether patients with potential CRT indication had contraindications. Our analysis is a snap-shot of CRT prevalence and we cannot rule out that patients without CRT may have received CRT during follow-up or improved such that CRT may no longer be indicated. Follow-up referral to cardiologists and HF nurse clinics were similar in patients with narrow QRS vs. IVCD or LBBB, suggesting that the discharging clinician may not have considered CRT or at least did not immediately plan CRT to any significant extent. Secondly, since only 4% of women and 7% of men had CRT at this time, it is unlikely that a significant proportion of the 30–31% with an indication would receive CRT in the foreseeable future.

Conclusions

We confirmed that CRT is slightly less utilized in women compared with men. However, the relevant question is extent of *under*utilization,[7] which was considerable but not different between genders, suggesting a general underutilization rather than gender bias. Furthermore, we showed that QRS prolongation in ms as a continuous variable and IVCD and LBBB are independent risk factors for mortality in HF with reduced ejection fraction in both women and men, but that LBBB was less harmful than IVCD in both genders and that LBBB possibly may be, if anything, less harmful in women than in men.

Thus, while efforts should be made to improve utilization of CRT in general, we found no evidence why these efforts should be more intense in women or why QRS or LBBB criteria for CRT should be different for women.

Supplementary material

Supplementary material is available at *Europace* online.

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