Cardiac resynchronization therapy (CRT) has been demonstrated to reduce morbidity and mortality in numerous large clinical trials, and it has become an integral part of contemporary heart failure therapy. The inclusion criteria of these trials form the basis of current guidelines, recommending CRT for patients with a severely reduced left ventricular ejection fraction of $\leq 35\%$, symptomatic chronic heart failure (CHF), and a QRS complex of $\geq 120$ ms. Because the majority of patients with CHF present with a narrow QRS complex, the EchoCRT trial was designed to investigate the effect of CRT in patients with a QRS duration of $<130$ ms together with echocardiographic evidence of left ventricular dyssynchrony. The trial was terminated early because of futility, but also indicated an increased risk for all-cause mortality of 81% with CRT in this patient population. The sex distribution, as well as the reason for the overall increase in mortality observed in EchoCRT is presently still unclear.

Sex-specific results of CRT have been suggested by some, but not all, previous studies. For example, the Cardiac Resynchronization–Heart Failure (CARE-HF) study was unable to find a sex-by-treatment interaction, whereas in MADIT (Multicenter Automatic Defibrillator Implantation)–CRT, women experienced a 79% reduction in the primary end point (death or heart failure) when compared with only 28%.

Background—In EchoCRT, a randomized controlled trial evaluating the effect of cardiac resynchronization therapy (CRT) in patients with a QRS duration of $<130$ ms and echocardiographic evidence of left ventricular dyssynchrony, the primary outcome (death from any cause or first hospitalization for worsening heart failure) occurred more frequently in the CRT-ON when compared with the control group. In this prespecified subgroup analysis, we evaluated the effect of sex on clinical outcome in EchoCRT.

Methods and Results—In EchoCRT, 585 (72%) of included patients were men. At baseline, male patients had a higher incidence of ischemic cardiomyopathy and longer QRS duration. On uni- and multivariable analysis, no significant interaction was observed regarding sex for the primary or any of the secondary end points. Numerically, a higher all-cause mortality was observed in male patients randomized to CRT-ON versus CRT-OFF on univariable analysis (hazard ratio, 1.83; 95% confidence interval, 1.08–3.12); however, no statistically significant interaction compared with females randomized to CRT-ON versus CRT-OFF was noted (hazard ratio, 0.99; $P$ interaction, 0.56). There was no difference in the primary safety end point of system-related complications, including CRT system- and implantation-related events.

Conclusions—The largest hazard for all-cause mortality in EchoCRT was observed in men randomized to CRT-ON: the comparison with women did not reach statistical significance, which may be because of the premature termination of the trial and the limited data. These results suggest that male sex may be a risk factor for harm by CRT in patients with narrow QRS width, an observation which deserves further investigation.

Clinical Trial Registration—URL: https://clinicaltrials.gov. Unique identifier: NCT00683696.

Key Words: cardiac resynchronization therapy • cardiomyopathy • female gender • heart failure • risk factor
WHAT IS KNOWN

- The EchoCRT trial investigated the effect of CRT in patients with a QRS duration <130 ms and echocardiographic evidence of left ventricular dyssynchrony. It was prematurely terminated due to futility, and it indicated an increased risk for all-cause mortality of 81% with CRT in this patient population.
- Gender-specific responses to CRT have been suggested by some, but not all, prior studies.

WHAT THE STUDY ADDS

- The largest hazard for all-cause mortality in EchoCRT was observed in men randomized to CRT-ON.
- The comparison with women did not reach statistical significance, which may be due to the premature termination of the trial.
- These results suggest that male sex may be a risk factor for harm by CRT in patients with a narrow QRS width.

in men. More recently, pronounced female advantage for CRT effect was seen at shorter (120–150 ms) QRS durations. Whether the lack of benefit for CRT shown in EchoCRT pertains to all patients, or whether male or female patients with a narrow QRS complex and echocardiographic signs of dyssynchrony may derive a benefit (or particularly pronounced harm) from CRT is presently unclear. The current prespecified subgroup analysis was, therefore, performed to assess the effect of sex on clinical outcome in EchoCRT.

Methods

Study Design and Conduct

The EchoCRT study was an investigator-initiated, international, multicenter, randomized clinical trial. The outcome results of the main trial, as well as the methodology have previously been reported. In brief, the trial (sponsored by Biotronik) was designed by the executive committee with support for echocardiographic training and software provided by GE Healthcare. All study results were independently analyzed at the Robertson Center for Biostatistics at the University of Glasgow. Patients were eligible if they had New York Heart Association class III or IV heart failure, a left ventricular ejection fraction of ≤35%, a standard indication for a implantable cardioverter–defibrillator (ICD), optimized medical heart failure therapy, a QRS duration of less than 130 ms, a left ventricular end-diastolic diameter of ≥55 mm, and echocardiographic evidence of left ventricular dyssynchrony as previously defined. After implantation of a Biotronik Lumax HF-T CRT-D system, patients were randomly assigned in a 1:1 ratio to have CRT capability turned on (the CRT group) or to have CRT capability turned off (the control group). Device-implanting physicians were aware of the study-group assignments, but the patients, heart failure physicians, and study personnel completing the follow-up assessments were unaware of the group assignments. The trial protocol was approved by the institutional review board at each participating center, and all subjects provided written informed consent.

End Points

The primary efficacy outcome was the combination of death from any cause or first hospitalization for worsening heart failure. The prespecified secondary outcomes included all hospitalizations for worsening heart failure throughout the study: all-cause mortality, cardiovascular mortality, heart failure mortality, and cardiovascular hospitalization. The primary safety outcome was freedom from CRT-D-related complications at 6 months in the implanted population. Complications were defined as adverse events that require additional invasive intervention to resolve, related to the implanted CRT system, including the device and leads. In addition, system-related complications during the whole trial were analyzed by treatment group.

Statistical Analysis

All analyses were performed according to the intention-to-treat principle. Baseline characteristics were compared with the use of 2-sample t tests and χ² (or Fisher exact) tests for continuous and categorical variables, respectively.

Hazard ratios (HRs) for CRT-ON and CRT-OFF with 95% confidence intervals (CIs) were calculated with the Cox proportional hazards model. The comparison with women did not reach statistical significance, which may be due to the premature termination of the trial. In addition, a multivariable Cox proportional hazards model was performed to account for differences across randomized treatment groups in baseline characteristics between males and females (QRS width, walking distance, quality of life [QOL] as determined by the Minnesota Living With Heart Failure Questionnaire score, sitting diastolic blood pressure, ischemic cardiomyopathy, history of myocardial infarction, history of coronary artery bypass grafting, left ventricular end-diastolic diameter, and diuretic agent use). Interactions between males and females and treatment (CRT=ON and CRT=OFF) were tested for in Cox models that included sex and treatment main effects and interaction terms. Time-to-event curves were estimated with the use of the Kaplan–Meier method. All tests were 2 sided with a P value of ≤0.05 considered to be significant. Analyses were performed using SAS for Windows version 9.2.

Results

Baseline Characteristics

Metrics at trial entry are summarized in Table 1. Of 809 randomized patients, 224 (27.7%) were females. Male patients had longer QRS complex duration, longer walking distance, slightly higher diastolic blood pressure, larger LV diameters, and more frequently had ischemic cardiomyopathy or related interventions. In contrast, women had worse heart failure related quality of life (QOL) and higher use of diuretics. Other baseline parameters were comparable among the 2 groups.

Efficacy of CRT in Male Versus Female Patients

There was no difference for male versus female patients regarding the overall results of the trial, both unadjusted (Figures 1 and 2) and after multivariable adjustment for differences in baseline characteristics as outlined above (ie, QRS width, walking distance, QOL score, sitting diastolic blood pressure, ischemic cardiomyopathy, history of myocardial infarction, history of CABG, left ventricular end-diastolic diameter, and diuretic agent use; Figure 3). Numerically, however, both the increased hazard of CRT for the primary end point, and especially the mortality end points, seemed to be driven mainly by an increased hazard in male patients. Strikingly, cardiovascular mortality was increased 2.4-fold in male patients (HR, 2.43 [95% CI, 1.27–4.63]; P=0.007 versus HR, 0.97 [95% CI, 0.24–3.93], P=0.97 for the females), albeit with a nonsignificant interaction P value. These observations were paralleled in the Kaplan–Meier analyses and in the multivariable adjusted model (again, however, without significant interaction).
Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Females</th>
<th>Males</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>57.5 (13.62)</td>
<td>58.2 (12.38)</td>
<td>0.482</td>
</tr>
<tr>
<td>QRS width (ms; site)</td>
<td>102.4 (12.89)</td>
<td>106.3 (12.70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>QRS width (ms; core)</td>
<td>102.3 (13.35)</td>
<td>107.1 (12.01)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Walking distance (m)</td>
<td>286.7 (120.64)</td>
<td>340.4 (116.84)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Quality of life score</td>
<td>54.4 (24.15)</td>
<td>50.0 (24.21)</td>
<td>0.021</td>
</tr>
<tr>
<td>NYHA classification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>0 (0.00%)</td>
<td>5 (0.85%)</td>
<td>*</td>
</tr>
<tr>
<td>II</td>
<td>3 (1.34%)</td>
<td>16 (2.74%)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>213 (95.09%)</td>
<td>546 (93.33%)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>8 (3.57%)</td>
<td>18 (3.08%)</td>
<td></td>
</tr>
<tr>
<td>BNP (pg/mL)</td>
<td>225.0 (102.00, 471.00)</td>
<td>251.0 (75.00, 515.00)</td>
<td>0.927</td>
</tr>
<tr>
<td>NT-proBNP (pg/mL)</td>
<td>1275.0 (610.00, 2124.0)</td>
<td>1095.5 (449.50, 2408.5)</td>
<td>0.604</td>
</tr>
<tr>
<td>Sitting SBP (mm Hg)</td>
<td>117.6 (18.11)</td>
<td>119.3 (19.87)</td>
<td>0.271</td>
</tr>
<tr>
<td>Sitting DBP (mm Hg)</td>
<td>71.4 (11.18)</td>
<td>73.3 (12.20)</td>
<td>0.039</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>31.7 (14.80)</td>
<td>30.5 (10.98)</td>
<td>0.212</td>
</tr>
<tr>
<td>Ischemic cardiomyopathy</td>
<td>88 (39.29%)</td>
<td>344 (58.90%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MI &gt;3 mo ago</td>
<td>66 (29.46%)</td>
<td>256 (43.76%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PCI &gt;3 mo ago</td>
<td>70 (31.25%)</td>
<td>218 (37.26%)</td>
<td>0.110</td>
</tr>
<tr>
<td>CAGB &gt;3 mo ago</td>
<td>23 (10.27%)</td>
<td>128 (21.88%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>146 (66.66%)</td>
<td>387 (66.61%)</td>
<td>0.884</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>2 (0.92%)</td>
<td>14 (2.42%)</td>
<td>0.259</td>
</tr>
<tr>
<td>Previous ischemic stroke or TIA</td>
<td>27 (12.22%)</td>
<td>69 (11.86%)</td>
<td>0.888</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>95 (42.79%)</td>
<td>225 (38.53%)</td>
<td>0.269</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>40 (18.02%)</td>
<td>109 (18.79%)</td>
<td>0.801</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>22 (9.95%)</td>
<td>86 (14.78%)</td>
<td>0.074</td>
</tr>
<tr>
<td>LVEF biplane (%)</td>
<td>27.2 (5.39)</td>
<td>26.9 (5.63)</td>
<td>0.477</td>
</tr>
<tr>
<td>LV end-diastolic diameter (mm)</td>
<td>64.1 (6.84)</td>
<td>67.3 (7.62)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Qualified by Tissue Doppler Imaging and radial dyssynchrony</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tissue Doppler Imaging only</td>
<td>50 (22.32%)</td>
<td>152 (26.03%)</td>
<td>0.050</td>
</tr>
<tr>
<td>Radial strain only</td>
<td>42 (18.75%)</td>
<td>143 (24.49%)</td>
<td></td>
</tr>
<tr>
<td>TDI and radial strain</td>
<td>132 (58.93%)</td>
<td>289 (49.49%)</td>
<td></td>
</tr>
<tr>
<td>Medication at study entry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td>212 (94.64%)</td>
<td>555 (94.87%)</td>
<td>0.896</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>130 (58.04%)</td>
<td>355 (60.68%)</td>
<td>0.492</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>216 (96.43%)</td>
<td>566 (96.75%)</td>
<td>0.828</td>
</tr>
<tr>
<td>Diuretic agent</td>
<td>206 (91.96%)</td>
<td>492 (84.10%)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

For categorical variables, number and percentage are reported; for continuous variables, mean and SD are reported (except for BNP and NT-proBNP where median and interquartile range are presented). ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; DBP diastolic blood pressure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NT-proBNP, N-terminal pro b-type natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; TIA, transient ischemic attack; and SBP, systolic blood pressure.

*P value not reported because of small numbers.
Steffel et al  Effect of Gender on CRT in Narrow QRS

Device-Related Complications in Male Versus Female Patients
The primary safety end point (freedom from device-related complications at 6 months) in the implanted population (237 females and 618 males) is presented in Table 2. There were no differences in the primary safety end point, including CRT system- and implantation-related events. Device-related complications occurring during the whole trial in male and female patients are summarized in Table 3. 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.

Discussion
In the current prespecified subgroup analysis, a trend indicating a worse outcome for males compared with females can be observed. Indeed, on Kaplan–Meier analysis, the event curve for CRT-ON in women is almost a perfect match to that of CRT-OFF in women as well as in men, possibly indicating a balanced effect (ie, harm in some neutralized by benefit in others). In contrast, male patients seem to be the main driver of worse outcomes of CRT-ON for the entire EchoCRT cohort. The lack of statistical significance may be because of the fact that the trial was prematurely terminated, resulting in a lack of statistical power both for the primary and for the secondary end points, which becomes even more relevant in subgroup analyses. It is tempting to speculate that had the trial been terminated as planned, a statistically significant interaction may have been observed.
Our results indicating potential sex-specific differences in CRT effect are consistent with several other large outcome studies, extending those observations to the narrow QRS range studied here. In the early Multicenter InSync Randomized Clinical Evaluation (MIRACLE) Study, women, but not men, receiving CRT had a longer time to first hospitalization for CHF as well as time to first CHF hospitalization or death. In MADIT-CRT, female patients randomized to CRT treatment had a 69% relative risk reduction to experience the primary end point of death or heart failure versus ICD when compared with men, who only had 28% relative risk reduction (P interaction <0.001). This effect was driven both by a significant reduction in heart failure hospitalization (70% versus 35% risk reduction) and a significant reduction in all-cause mortality. Indeed, a reduction in all-cause mortality was primarily evident in women (HR, 0.28; 95% CI, 0.10–0.79), but not in men (HR, 1.05; 95% CI, 0.70–1.57; P interaction=0.03). A similar trend was also observed in the Resynchronization–Defibrillation for Ambulatory Heart Failure Trial (RAFT), the other large study investigating CRT in oligosymptomatic patients (P interaction=0.09). Finally, a large single-center CRT registry found a significant 56%
Defibrillation in Heart Failure (COMPANION) trial, no inter-

Similarly in the Comparison of Medical Therapy, Pacing, and

hazard for sudden cardiac death or appropriate shocks.3,12

little if any dyssynchrony among males.18 For these patients,

Possibly, in shorter QRS ranges as examined here, there is

explain the more favorable outcome of CRT in females.

Indeed, in healthy women (as well as in EchoCRT), the QRS

duration is on average 4 to 10 ms shorter than that in male

patients.16,17 As a result, male patients with a prolonged QRS

duration is on average 4 to 10 ms shorter than that in male

patients.16,17 As a result, male patients with a prolonged QRS

cardiac conduction disturbance for any given absolute

dys synchrony, comparable with that of a pacer-mediated

cardiomyopathy. In contrast, this phenomenon seems

less pronounced in longer QRS durations (ie, >150 ms), after

which the relative benefit of male and female patients seems

more similar.7,8 In our subgroup analysis, male patients had

larger LV diameters, longer QRS duration, and more fre-

quently had ischemic cardiomyopathy, previous myocardial

infarction and previous CABG. Although patients with

previous myocardial infarction are generally less likely to

respond to CRT20 or become super-responders,21 ischemic

cardiomyopathy itself has not consistently been associated

with a worse outcome in terms of hard end points in any

of the major randomized clinical trials.1,2,23 The sex pattern

observed on univariable analysis was still evident after mul-

tivariable adjustment, indicating an effect independent of, or

at least in addition to those parameters.

In spite of the increasing evidence of a similar, if not more

pronounced benefit of CRT in women, CRT remains largely

underused in female compared with male patients. In absolute

terms, women constitute a large proportion of the population

with CHF.11,24 This is in sharp contrast to the proportion of

women included in CRT trials (including EchoCRT), ranging

from 17.2% (RAFT) to 32% (COMPANION).2,3,6 Similarly,

CRT remains underused in daily clinical practice, as shown

by only 27% females implanted in the EuroCRT survey.25

Our current analysis cannot readily supply an answer to this

phenomenon. A larger concern for complications after device

implantation, both from female patients as well as from the

referring/implanting physician has been suggested, probably

because of smaller vessel diameter and body size.11,26 In our

analysis, the system-/implantation-related complication rate

was similar for men when compared with women, indicating

that this factor per se should not discourage CRT implants

in women.

Limitations

Although prespecified, this subgroup analysis of EchoCRT

should by definition be interpreted as hypothesis generating.

lower all-cause mortality in women compared with men on

multivariable analysis.11 When considered against QRS dur-

ation, female advantage (relative to male patients) was most

pronounced at shorter (<150 ms) QRS durations.7 In contrast,

some other studies have failed to demonstrate a significant

difference between men and women, including CARE-HF.1

Similarly in the Comparison of Medical Therapy, Pacing, and

Defibrillation in Heart Failure (COMPANION) trial, no inter-

action by sex was observed, although women did have a lower

hazard for sudden cardiac death or appropriate shocks.3,12

The reason for these differences is just as elusive as the

mechanism underlying a potentially more pronounced

benefit of CRT in women. Several explanations have been

brought forward, including a higher proportion of ischemic

cardiomyopathies as well as larger LV diameters in males.

Indeed, the latter may play an important role, consistent with

a point of no return in the natural course of CHF after which

reverse LV remodeling —and, as a consequence, response to

CRT—becomes less likely.13–15 Another hypothesis is related

to the difference in QRS duration between men and women.

Indeed, male patients had a more similar.7,8 In our subgroup analysis, male patients had

larger LV diameters, longer QRS duration, and more fre-

quently had ischemic cardiomyopathy, previous myocardial

infarction and previous CABG. Although patients with

previous myocardial infarction are generally less likely to

respond to CRT20 or become super-responders,21 ischemic

cardiomyopathy itself has not consistently been associated

with a worse outcome in terms of hard end points in any

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was similar for men when compared with women, indicating

that this factor per se should not discourage CRT implants

in women.

Limitations

Although prespecified, this subgroup analysis of EchoCRT

should by definition be interpreted as hypothesis generating.

Table 2. Primary Safety End Point in Female and Male

Patients (Complication-Free Rate Within 6 Months of

Implantation)

<table>
<thead>
<tr>
<th></th>
<th>Female Patients (%)</th>
<th>Male Patients (%)</th>
<th>P Int</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRT-D system</td>
<td>216 (91.14)</td>
<td>569 (92.07)</td>
<td>0.66</td>
</tr>
<tr>
<td>Implant procedure</td>
<td>232 (97.89)</td>
<td>605 (97.90)</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>236 (99.58)</td>
<td>617 (99.84)</td>
<td>0.50</td>
</tr>
<tr>
<td>Any of the above</td>
<td>210 (88.61)</td>
<td>556 (89.97)</td>
<td>0.56</td>
</tr>
</tbody>
</table>

CRT indicates cardiac resynchronization therapy.

Table 3. CRT System–Related Serious Adverse Events During the Whole Trial

<table>
<thead>
<tr>
<th></th>
<th>Female Patients</th>
<th>Male Patients</th>
<th>P Int</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CRT=ON (n=110)</td>
<td>CRT=OFF (n=114)</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>N Pts (%)</td>
<td>N Pts (%)</td>
<td></td>
</tr>
<tr>
<td>CRT system related</td>
<td>26 (18.18)</td>
<td>7 (6.14)</td>
<td>0.25</td>
</tr>
<tr>
<td>ICD lead</td>
<td>10 (9.81)</td>
<td>2 (1.75)</td>
<td>0.13</td>
</tr>
<tr>
<td>RA pacing lead</td>
<td>7 (6.54)</td>
<td>2 (1.75)</td>
<td>0.70</td>
</tr>
<tr>
<td>LV pacing lead</td>
<td>7 (6.54)</td>
<td>2 (1.75)</td>
<td>0.57</td>
</tr>
<tr>
<td>Implantation related</td>
<td>6 (5.45)</td>
<td>3 (2.63)</td>
<td>0.26</td>
</tr>
</tbody>
</table>

CRT indicates cardiac resynchronization therapy; ICD, implantable cardioverter–defibrillator; LV, left ventricle; N, number of events; N Pts, number of patients with events; and RA, right atrial.
especially because the trial did not meet its primary end point. Sex was not a stratification factor at trial entry leaving the possibility of unmeasured residual confounding. Moreover, the trial was prematurely terminated, further reducing the statistical power of any subgroup analysis. Although the proportion of women included in EchoCRT is in line with other contemporary CRT trials, inclusion of a higher number of women may have increased statistical power for this subgroup analysis.

Conclusions

In the present prespecified subgroup analysis of EchoCRT, a trend indicating a worse outcome for males compared with females can be observed with CRT-ON versus CRT-OFF. This did not reach statistical significance, probably because of lack of power resulting from the premature termination of the trial. These data extend findings from previous large randomized trials and support the use of CRT in female patients if indicated according to the current guidelines. Importantly, these data serve as a reminder to use caution with CRT implantation in men with a narrow QRS complex irrespective of the presence of mechanical dyssynchrony.

Appendix

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Disclosures

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