

# Differences in clinical characteristics and reported quality of life of men and women undergoing cardiac resynchronization therapy

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## Abstract

**Aims** Response to cardiac resynchronization therapy (CRT) is known to be associated with a number of clinical characteristics, including QRS duration and morphology, gender, height, and the aetiology of heart failure (HF). We assessed the relation of gender and baseline characteristics with QRS duration and Kansas City Cardiomyopathy Questionnaire.

**Methods and results** AdaptResponse is a global randomized trial. The trial enrolled CRT-indicated patients with New York Heart Association classes II–IV HF, left bundle branch block (QRS  $\geq$  140 ms in men,  $\geq$ 130 ms in women), and baseline PR interval  $\leq$ 200 ms. In total, 3620 patients were randomized, including 1569 women (43.3%) approaching the actual proportion of women in the HF population. Women were older and more often New York Heart Association class III or IV than men (55.6% vs. 48.7%), had less frequent ischaemic cardiomyopathy (21.2% vs. 39.5%), and had a 5.1 ms shorter QRS duration than men. Women were more often depressed (18.5% vs. 9.7%), had a significantly lower Kansas City Cardiomyopathy Questionnaire score, and had differences in medication prescriptions.

**Conclusions** AdaptResponse is the largest randomized CRT trial and enrolled more women than any other landmark CRT trial. Women differed from men with regard to baseline characteristics and quality of life. Whether these differences translate into clinical outcome differences will be examined further in the AdaptResponse trial.

**Keywords** Cardiac resynchronization therapy outcome; LV pacing; AV conduction; Left bundle branch block; Gender differences in heart failure; Kansas City Cardiomyopathy Questionnaire

Received: 6 February 2020; Revised: 13 June 2020; Accepted: 13 July 2020

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Clinical trial registration: AdaptResponse ClinicalTrials.gov identifier NCT02205359.

## Introduction

Cardiac resynchronization therapy (CRT) is an established therapy for patients with symptomatic heart failure (HF), left ventricular (LV) systolic dysfunction, and a prolonged QRS duration, which reduces HF symptoms, hospitalizations, and mortality.<sup>1,2</sup> However, the benefit of CRT varies with limited clinical improvement or reverse remodelling observed in approximately 30–40% of device recipients.<sup>3</sup> Patient sex has

been reported to influence response to CRT, with an overall higher response rate, especially with regard to reverse remodelling, reported in women.<sup>4–8</sup> Other patient characteristics, including QRS morphology and duration, dyssynchrony, scar burden, cardiomyopathy aetiology, age, height, New York Heart Association (NYHA) class, and prior HF hospitalization, have all also been associated with the extent of clinical benefit with CRT.<sup>9–12</sup> As some of these characteristics differ between the sexes, the improved CRT response in women

might be secondary to the sex-related difference in patient characteristics associated with response.

To determine whether women should be treated differently from men, a better understanding of the independent effect of sex on outcome is crucial. A lower QRS duration cut-off criterion for left bundle branch block (LBBB) has already been proposed for women.<sup>13</sup> Although there are reports comparing CRT response by sex,<sup>4,5,8,9,14</sup> there is a need for confirmation and further investigation in randomized controlled clinical trials well represented with women. Unfortunately, women constitute only about 20–30% of the study population of previous CRT trials,<sup>15–20</sup> so the study results have primarily reflected outcomes in men. In order to understand potential differences between men and women, we must understand the differences in clinical characteristics and their impact on clinical outcomes.

The AdaptivCRT<sup>®21</sup> algorithm (Medtronic plc, USA) was designed to provide ongoing automated CRT optimization and to allow for more physiologic ventricular activation and greater device longevity in patients with normal atrioventricular (AV) conduction times by reducing unnecessary right ventricular pacing. Previously published evidence suggests improved clinical outcomes, predominantly in patients with LBBB and intact AV conduction.<sup>22–24</sup> The AdaptResponse trial seeks to test the hypothesis that the AdaptivCRT algorithm results in superior outcome compared with conventional CRT in CRT-indicated patients with normal AV conduction and LBBB.<sup>25</sup> The current report describes the sex-related differences in the baseline clinical characteristics and quality of life (QoL) of the patients randomized in the AdaptResponse trial and focuses specifically on factors associated with QRS duration.

## Methods

### AdaptResponse trial design

The design of the AdaptResponse trial has been reported in detail elsewhere.<sup>25</sup> Briefly, AdaptResponse is a global single-blinded randomized trial with blinded endpoint adjudication (ClinicalTrials.gov; identifier: NCT02205359), which compares AdaptivCRT to conventional CRT in patients with LBBB and PR interval  $\leq 200$  ms. The primary endpoint is the combined endpoint of all-cause mortality and intervention for HF decompensation.

### Inclusion and exclusion criteria

Patients could be included when they had (i) an indication for a CRT device according to the local scientific guidelines with an LV ejection fraction (LVEF)  $\leq 35\%$  and NYHA classes II, III, or IV symptoms despite optimal medical therapy; (ii) LBBB according to the Strauss criteria<sup>13</sup> as determined by the physician

(requires QRS duration  $\geq 140$  ms in men,  $\geq 130$  ms in women); (iii) normal AV conduction defined as PR interval  $\leq 200$  ms on electrocardiogram (ECG); and (iv) sinus rhythm at time of enrolment. Previous CRT was an exclusion criterion. The AdaptResponse design manuscript<sup>25</sup> provides details on the inclusion criteria and a complete overview of the exclusion criteria. Inclusion was based on investigator assessment of ECG criteria; however, screening ECGs were subsequently reviewed by a core laboratory that provided instructional feedback to investigators in case of deviation from the strict criteria.

### Protocol and data collection

Written approval from the Institutional Review Board and/or Medical Ethics Committee was obtained at all sites and each patient provided written informed consent. After informed consent, data were collected on demographics, medical history, presenting signs and symptoms, comorbidities, and concomitant treatment. The EuroQol-5D Questionnaire (EQ-5D) and Kansas City Cardiomyopathy Questionnaire (KCCQ) were used as measures of general and health-related QoL. Case report form completion and handling was performed electronically using a secure, password-protected electronic data management system for clinical studies. After baseline assessment, patients were implanted with an AdaptivCRT capable device (Medtronic plc, Minneapolis, MN, USA) and randomized 1:1 to AdaptivCRT or conventional CRT.

### Time course of the AdaptResponse trial

The first enrolment took place on 5 August 2014 and enrolment was closed on 31 January 2019. Follow-up will continue until 1100 primary endpoint events have been accrued or predefined stopping criteria are met at an interim analysis.

### Statistical analysis

Descriptive statistics were used as appropriate according to the distribution of variables. Categorical data were reported as incidence (%) and continuous data as mean  $\pm$  standard deviation. Men and women were compared with Student's *t*-test for continuous variables, Fisher's exact test for nominal categorical variables, and the Cochran–Mantel–Haenszel test for trends in ordinal variables. Indexed QRS is derived by dividing QRS duration (ms) by body height (m) and indexed creatinine is derived by dividing the creatinine (mg/dL) value by body weight (kg) divided by 100.

A multivariable linear regression model was developed for QRS duration, using backward variable selection to reduce an initial model with 29 variables (known predictors of outcome in CRT patients and variables with large difference between men and women), forcing sex, age, height, NYHA class,

ischaemic aetiology, atrial fibrillation (AF), diabetes, chronic lung disease, and renal dysfunction to stay in the model. Interactions with sex were reviewed, but none were included in the final model. Body mass index is modelled as a partially linear effect with cut points at 18.5 and 30 kg/m<sup>2</sup>. Women with QRS duration < 140 ms were excluded to have balanced selection criteria.

All analyses were conducted in SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

## Results

A total of 3800 patients were recruited from 227 centres in 27 countries worldwide of which 3620 patients (95.3%) were randomized. The 180 subjects who were not randomized, including those who died ( $n = 8$ ), did not meet the eligibility criteria ( $n = 103$ , of which 49 did not meet the normal AV conduction criterion), did not have a successful device implantation ( $n = 56$ ), or revoked consent ( $n = 13$ ). The core laboratory reviewed the screening ECG of 3579 of the randomized patients (98.8%) and confirmed LBBB per Strauss criteria in 3472 (95.9%) and PR  $\leq 200$  ms in 3482 (96.2%). The Supporting Information summarizes the geographic distribution of subjects (Supporting Information, *Table S1*) and lists the participating investigators per country.

### Baseline characteristics

The baseline patient characteristics, laboratory findings, and QoL stratified by sex are presented in *Table 1*. AdaptResponse recruited a relatively high proportion of women, representing 43.3% of the randomized patients. A number of significant differences between the sexes was noted. In general, women were shorter and slightly older than men. Women were more often classified as NYHA class III or IV (55.6% vs. 48.7%), with a significantly smaller QRS duration ( $158.4 \pm 16.7$  vs.  $165.9 \pm 15.8$  ms) and PR interval ( $167.7 \pm 21.2$  vs.  $174.9 \pm 20.3$  ms), but larger indexed QRS ( $98.4 \pm 10.8$  vs.  $94.9 \pm 9.7$  ms/m). A smaller proportion of women had ischaemic cardiomyopathy (21.2% vs. 39.5%) or a history of myocardial infarction (12.6% vs. 23.7%).

Comorbidities such as AF (10.3% in women vs. 14.7% in men), peripheral vascular disease (3.8% vs. 6.6%), diabetes (32.6% vs. 36.2%), sleep apnoea (8.8% vs. 12.5%), and renal dysfunction (15.5% vs. 17.9%) were more common in men compared with women. In contrast, women had a higher incidence of anaemia (8.3% vs. 5.1%), chronic lung disease (16.2% vs. 13.7%), and depression (18.5% vs. 9.7%) and reported more often underweight (2.5% vs. 1.1%) or obesity (39.8% vs. 35.3%). Higher plasma levels of creatinine in men ( $1.09 \pm 0.76$  vs.  $1.27 \pm 0.89$  mg/dL) are explained by higher weight with indexed creatinine equal between sexes. In

women, lower plasma concentrations of haemoglobin ( $12.7 \pm 1.5$  vs.  $13.7 \pm 1.7$  g/dL) and increased incidence of hypothyroidism (14.0% vs. 5.2%) were observed.

### Kansas City Cardiomyopathy Questionnaire and EuroQol-5D Questionnaire

Women had a significantly lower score on all KCCQ domains except self-efficacy (*Figure 1*). Large differences were seen for physical limitation ( $62.4 \pm 25.1$  vs.  $72.3 \pm 24.3$ ), symptom frequency ( $63.1 \pm 26.1$  vs.  $71.6 \pm 24.9$ ), symptom burden ( $65.2 \pm 24.9$  vs.  $73.4 \pm 23.7$ ), and in the clinical summary score ( $63.3 \pm 23.1$  vs.  $72.4 \pm 22.1$ ), all  $P < 0.0001$ . The overall summary score was  $57.9 \pm 23.7$  in women and  $65.9 \pm 23.3$  in men,  $P < 0.0001$ . The EQ-5D questionnaire also showed significant differences between sexes. Women reported more frequent problems in each of the five dimensions (*Figure 2A*), including 46.5% vs. 36.4% having problems walking, 58.5% vs. 42.2% having problems performing usual activities, and 48.7% vs. 34.2% being anxious or depressed. The self-rated overall health score ( $61.9 \pm 20.1$  vs.  $64.2 \pm 19.3$ ,  $P < 0.001$ , *Figure 2B*) was also lower in women.

### Medication

*Table 2* summarizes the baseline cardiovascular medication and shows sex-related differences in treatment. Women received less angiotensin-converting enzyme inhibitors than men (47.5% vs. 54.6%) but were more often prescribed angiotensin receptor blockers (37.6% vs. 30.6%). The use of diuretics was higher in women (68.1% vs. 60.9%). No differences were seen for beta-blockers, mineralocorticoid receptor antagonists, angiotensin receptor neprilysin inhibitors, or ivabradine. Vasodilators (10.4% vs. 12.8%), antiarrhythmic drugs (5.7% vs. 9.6%), anticoagulants (10.9% vs. 15.9%), antiplatelets (49.3% vs. 59.1%), and statins (42.3% vs. 51.2%) were more frequently prescribed to men.

### Dependence of QRS duration on sex and height

Multivariable linear regression was used to assess the relation of QRS duration with sex, height, and other baseline covariates. Because men in the study were limited to QRS  $\geq 140$  ms, 146 women with QRS < 140 ms were excluded from this analysis to have balanced selection criteria. Sex, height, body mass index, LVEF, PR interval, diabetes, chronic lung disease, and the prescription of loop diuretics were identified to be independently associated with QRS duration (*Table 3*). Among patients with QRS duration  $\geq 140$  ms, women had a 5.1 ms shorter QRS duration than men. In the

Table 1 Baseline characteristics

Baseline characteristics	All patients (N = 3620)	Females (N = 1569)	Males (N = 2051)	P value <sup>a</sup>
<b>Patient demographics</b>				
Age (years)	64.9 ± 11.0	65.4 ± 11.0	64.5 ± 11.0	0.013
Height (cm)	169.0 ± 10.5	161.1 ± 7.4	175.1 ± 8.1	<0.0001
BMI (kg/m <sup>2</sup> )	28.9 ± 6.5	29.2 ± 7.0	28.7 ± 6.1	0.019
Underweight (BMI < 18.5)	61 (1.7%)	39 (2.5%)	22 (1.1%)	0.002
Obese (BMI > 30)	1348 (37.2%)	625 (39.8%)	723 (35.3%)	0.005
<b>Physical assessment</b>				
Heart rate (bpm)	72.0 ± 12.2	73.0 ± 11.9	71.1 ± 12.5	<0.0001
Systolic blood pressure (mmHg)	125.5 ± 19.7	125.5 ± 19.9	125.6 ± 19.6	0.94
LVEF (%)	25.5 ± 6.3	25.8 ± 6.2	25.3 ± 6.3	0.008
QRS duration (ms) <sup>b</sup>	162.6 ± 16.6	158.4 ± 16.7	165.9 ± 15.8	<0.0001
QRS duration excluding <140 ms	163.8 ± 15.9	160.8 ± 15.6	165.9 ± 15.8	<0.0001
Indexed QRS duration (ms/m)	96.4 ± 10.4	98.4 ± 10.8	94.9 ± 9.7	<0.0001
PR interval (ms)	171.8 ± 21.0	167.7 ± 21.2	174.9 ± 20.3	<0.0001
Dyspnoea	1068 (29.5%)	484 (30.8%)	584 (28.5%)	0.12
Rales/crackles	183 (5.1%)	69 (4.4%)	114 (5.6%)	0.13
Murmurs (systolic or diastolic)	512 (14.1%)	246 (15.7%)	266 (13.0%)	0.024
S3 gallop	128 (3.5%)	54 (3.4%)	74 (3.6%)	1.00
Peripheral oedema	501 (13.8%)	228 (14.5%)	273 (13.3%)	0.31
<b>Blood chemistry<sup>c</sup></b>				
Creatinine (mg/dL)	1.19 ± 0.84	1.09 ± 0.76	1.27 ± 0.89	<0.0001
Creatinine, indexed for weight (mg/dL/100 kg)	1.55 ± 1.32	1.54 ± 1.32	1.55 ± 1.32	0.78
GFR (mL/min/1.73 m <sup>2</sup> )	62.0 ± 20.4	59.6 ± 19.7	63.8 ± 20.8	<0.0001
Haemoglobin (g/dL)	13.3 ± 1.7	12.7 ± 1.5	13.7 ± 1.7	<0.0001
Sodium (mmol/L)	139.0 ± 3.9	139.3 ± 3.5	138.8 ± 4.2	<0.001
Potassium (mmol/L)	4.33 ± 0.50	4.28 ± 0.50	4.37 ± 0.50	<0.0001
<b>Heart failure history and symptoms</b>				
Time since heart failure diagnosis (months)	28.0 ± 45.0	26.9 ± 44.6	28.9 ± 45.2	0.26
Prior hospitalization for heart failure (N, %)	1744 (48.2%)	763 (48.6%)	981 (47.8%)	0.97
<b>NYHA class</b>				
Class II	1748 (48.3%)	696 (44.4%)	1052 (51.3%)	<0.001
Class III	1824 (50.4%)	860 (54.8%)	964 (47.0%)	
Class IV	48 (1.3%)	13 (0.8%)	35 (1.7%)	
<b>Cardiovascular medical history</b>				
Dilated/congestive cardiomyopathy	2380 (65.7%)	1179 (75.1%)	1201 (58.6%)	<0.0001
Ischaemic cardiomyopathy	1143 (31.6%)	332 (21.2%)	811 (39.5%)	<0.0001
Mycardial infarction	684 (18.9%)	197 (12.6%)	487 (23.7%)	<0.0001
Hypertension	2,198 (60.7%)	945 (60.2%)	1,253 (61.1%)	0.66
Pulmonary hypertension	211 (5.8%)	108 (6.9%)	103 (5.0%)	0.018
Mitral valve disease	582 (16.1%)	291 (18.5%)	291 (14.2%)	<0.001
Previous ICD	227 (6.3%)	61 (3.9%)	166 (8.1%)	<0.0001
Previous pacemaker	37 (1.0%)	12 (0.8%)	25 (1.2%)	0.24
Atrial fibrillation	462 (12.8%)	161 (10.3%)	301 (14.7%)	<0.0001
AV block	175 (4.8%)	55 (3.5%)	120 (5.9%)	0.001
Left bundle branch block	3617 (99.9%)	1567 (99.9%)	2050 (100.0%)	1.00
Stroke	221 (6.1%)	93 (5.9%)	128 (6.2%)	0.73
Peripheral vascular disease	195 (5.4%)	59 (3.8%)	136 (6.6%)	<0.001

(Continues)

Table 1 (continued)

Baseline characteristics N (%) or mean $\pm$ standard deviation	All patients (N = 3620)	Females (N = 1569)	Males (N = 2051)	P value <sup>a</sup>
Renal dysfunction	611 (16.9%)	243 (15.5%)	368 (17.9%)	0.054
Diabetes	1254 (34.6%)	511 (32.6%)	743 (36.2%)	0.024
Anaemia	236 (6.5%)	131 (8.3%)	105 (5.1%)	<0.001
Hypothyroidism	327 (9.0%)	220 (14.0%)	107 (5.2%)	<0.0001
Sleep apnoea	395 (10.9%)	138 (8.8%)	257 (12.5%)	<0.001
Chronic lung disease	534 (14.8%)	254 (16.2%)	280 (13.7%)	0.033
Asthma	237 (6.5%)	147 (9.4%)	90 (4.4%)	<0.0001
Chronic obstructive pulmonary disease	328 (9.1%)	126 (8.0%)	202 (9.8%)	0.062
Cancer	226 (6.2%)	105 (6.7%)	121 (5.9%)	0.33
Depression	489 (13.5%)	291 (18.5%)	198 (9.7%)	<0.0001
Current smoker	439 (12.1%)	157 (10.0%)	282 (13.7%)	<0.001
Quality of Life				
EQ-5D health score (VAS)	63.2 $\pm$ 19.7	61.9 $\pm$ 20.1	64.2 $\pm$ 19.3	<0.001
KCCQ overall summary score	62.4 $\pm$ 23.8	57.9 $\pm$ 23.7	65.9 $\pm$ 23.3	<0.0001

AV, atrioventricular; BMI, body mass index; EQ-5D, EuroQol-5D Questionnaire; GFR, glomerular filtration rate; ICD, implantable cardioverter defibrillator; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; VAS, visual analog scale.

<sup>a</sup>P values compare male and female patients. Tests used are Student's t-test, Fisher's exact test, and Cochran-Mantel-Haenszel test for trend.

<sup>b</sup>Inclusion criterion was QRS  $\geq$  130 in women and  $\geq$  140 in men.

<sup>c</sup>Blood chemistry collected only when done as part of standard practice.

model, 2.8 ms of this difference was attributed to sex and 2.0 ms to the difference in height (Figure 3).

## Discussion

This manuscript describes sex differences in the baseline clinical characteristics and QoL of patients randomized in the AdaptResponse trial, which is the largest randomized CRT study to date, and recruited the highest percentage of female patients (43.3% of those randomized), approaching the actual proportion of women among patients with HF with reduced ejection fraction.<sup>1</sup> The most important findings were that, compared with men, women more often had advanced HF symptoms, were more often depressed, and scored significantly lower on measures of QoL despite having less comorbidities and less frequent ischaemic cardiomyopathy.<sup>26</sup> Differences in medication prescriptions were also noted. QRS duration remained shorter in women even when other baseline variables, including shorter height, were accounted for.

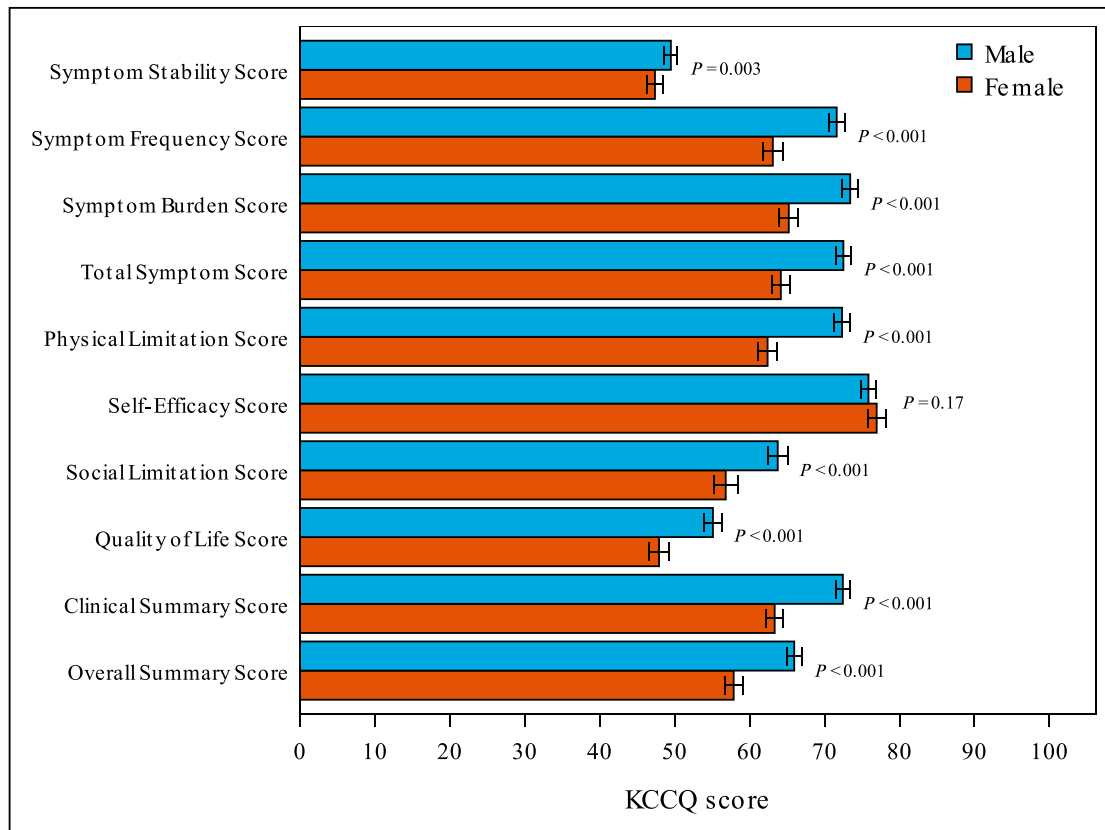
Historically, in clinical CRT trials, women have only represented roughly 20–30% of the study population (Table 4). Consequently, CRT trial results and meta-analyses primarily reflect outcomes in men, rendering it inherently difficult to interpret possible differences between the sexes in response to CRT. Underrepresentation of women in CRT trials may be the result of the fact that men are actually more often referred and historically enrol more frequently in HF trials.<sup>29</sup> In addition, some evidence suggests that men are treated more aggressively for heart disease and are more likely to receive guideline-recommended treatment, which is suggestive of potential referral bias.<sup>30,31</sup>

AdaptResponse differs from previous CRT studies in the inclusion criteria. The trial has exclusively enrolled patients with LBBB and without AV block. Compared with previous CRT trials (Table 4), AdaptResponse enrolled more women, more patients with NYHA class II (48%), fewer patients with ischaemic heart disease, patients received less angiotensin-converting enzyme inhibitor/angiotensin receptor blocker and loop diuretics, less patients had a history of AF, and more patients had diabetes.

Adding multiple inclusion criteria not previously used in CRT trials has likely contributed to the increased female enrolment in AdaptResponse. The lower QRS duration cut-off for women has broadened our patient cohort, potentially encouraging female enrolment. Restricting patient selection to LBBB may also have played a role because CRT trials have reported a higher proportion of LBBB in women.<sup>5,32</sup> Additionally, it has been reported that female CRT patients have a shorter PR interval than men.<sup>33,34</sup> The inclusion criterion of intact AV conduction has therefore selected more women than men. We analysed and could not confirm a correlation between female gender of the site's primary investigator and enrolment of female patients in AdaptResponse.



**FIGURE 1** Kansas City Cardiomyopathy Questionnaire (KCCQ). Women had a significantly lower score on all KCCQ domains except self-efficacy ( $P = 0.17$ ). Bars represent the average score by gender for the different KCCQ domains, with associated 95% confidence interval. Annotations are  $P$  values from Student's  $t$ -test.



Irrespective of patient sex, the inclusion criteria may have selected patients who are less sick (normal AV conduction and absence of permanent atrial arrhythmias) and are expected to benefit from CRT (LBBB).

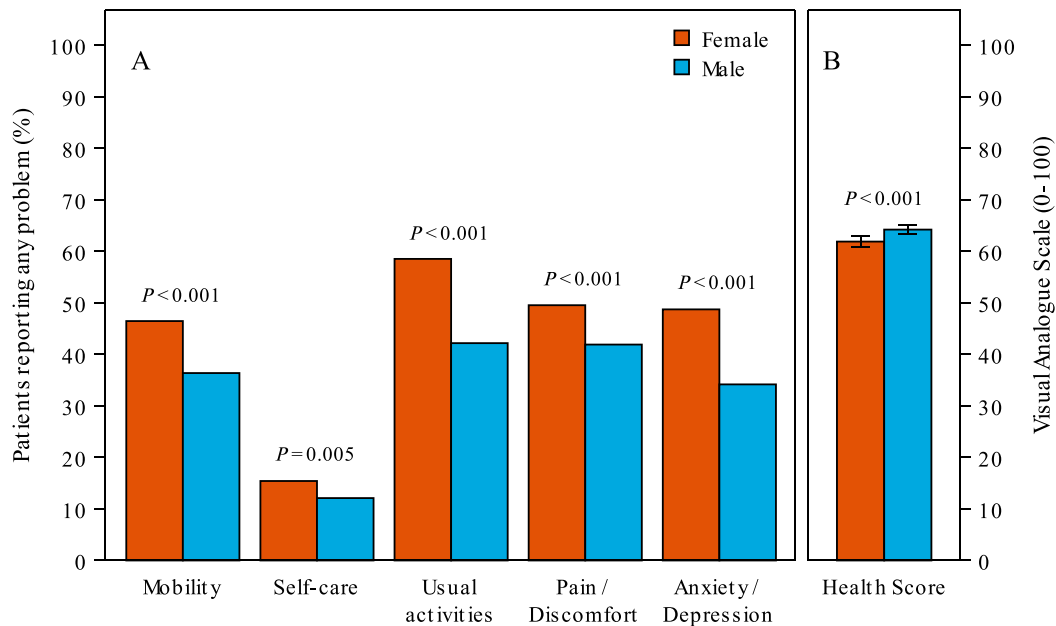
The current analysis identified considerable differences in baseline characteristics between male and female CRT recipients. In line with previous CRT studies, women were less likely to have an ischaemic aetiology of cardiomyopathy (*Table 1*). Furthermore, also in concordance with other studies, there was a striking difference in the pattern of comorbidities between the sexes. Men were more likely to have AF and renal dysfunction compared with women,<sup>7,35</sup> both factors that have been associated with poorer prognosis and higher risk of death in patients with a previous myocardial infarction and low LVEF.<sup>36</sup>

Interestingly, despite having less comorbid conditions and similar time since HF diagnosis, women had a higher HF symptom burden, as evidenced by the NYHA class distribution and the KCCQ physical limitation and total symptom scores. The adverse impact of the disease on well-being is also greater in women, as seen from the KCCQ QoL score, the EQ-5D health score, and the higher incidence of

depression. These findings are in line with a previous report on patients with HF with reduced ejection fraction in pharmacological trials.<sup>32</sup>

An important finding in the early CRT trials, including Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) trial, Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT), and Resynchronization–Defibrillation for Ambulatory Heart Failure Trial (RAFT), was the observation of substantially better outcome in women than men.<sup>7,19,20,35</sup> A potential explanation could be that women more frequently have LBBB and non-ischaemic cardiomyopathy, which are both related to an improved response to CRT,<sup>11</sup> due to greater LV reverse remodelling.<sup>37</sup> Indeed, a meta-analysis of these three major CRT trials demonstrated a 76% reduction of mortality among female CRT recipients with LBBB and QRS duration of 130–150 ms, without similar benefit reported in men.<sup>5</sup> In addition, women have smaller hearts and a shorter QRS duration at baseline compared with men and may therefore have complete LBBB at a shorter QRS duration.<sup>13</sup> Several reports have also suggested that women benefit from CRT at shorter QRS durations than men.<sup>4,7,38</sup> It has been suggested

**FIGURE 2** The EQ-5D score. (A) The five descriptive questions of the EQ-5D-3L Questionnaire for dimensions mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. These were reported with three answer categories indicating no, some, or extreme problems. The bars indicate the percentage of patients reporting any problems, including the latter two answer categories. The annotated *P* values are from Fisher's exact tests and compare by sex. (B) Summary of self-rated health collected on a visual analog scale (range 0–100). The bars show the mean health score annotated with 95% confidence interval for the mean and a *P* value from Student's *t*-test comparing sexes.



**Table 2** Baseline medication

Medication prescribed N (%)	All patients (N = 3620)	Females (N = 1569)	Males (N = 2051)	<i>P</i> value <sup>a</sup>
Beta-blocker	3237 (89.4%)	1413 (90.1%)	1824 (88.9%)	0.42
ACE inhibitor, ARB <sup>b</sup> or both	3036 (83.9%)	1313 (83.7%)	1723 (84.0%)	0.59
ACE inhibitor	1865 (51.5%)	746 (47.5%)	1119 (54.6%)	<0.0001
ARB <sup>b</sup>	1218 (33.6%)	590 (37.6%)	628 (30.6%)	<0.0001
ARNI <sup>b</sup>	369 (10.2%)	152 (9.7%)	217 (10.6%)	0.37
MRA	1703 (47.0%)	744 (47.4%)	959 (46.8%)	0.79
Ivabradine	133 (3.7%)	59 (3.8%)	74 (3.6%)	0.86
Diuretic <sup>c</sup>	2318 (64.0%)	1069 (68.1%)	1249 (60.9%)	<0.0001
Loop	2161 (59.7%)	995 (63.4%)	1166 (56.9%)	<0.0001
Thiazide	273 (7.5%)	125 (8.0%)	148 (7.2%)	0.45
Potassium sparing	10 (0.3%)	7 (0.4%)	3 (0.1%)	0.11
Digitalis glycosides	177 (4.9%)	80 (5.1%)	97 (4.7%)	0.64
Antiarrhythmic	286 (7.9%)	90 (5.7%)	196 (9.6%)	<0.0001
Calcium channel blocker	245 (6.8%)	102 (6.5%)	143 (7.0%)	0.59
Vasodilator	426 (11.8%)	163 (10.4%)	263 (12.8%)	0.022
Anticoagulant	497 (13.7%)	171 (10.9%)	326 (15.9%)	<0.0001
Antiplatelet	1987 (54.9%)	774 (49.3%)	1213 (59.1%)	<0.0001
Statin	1713 (47.3%)	663 (42.3%)	1050 (51.2%)	<0.0001

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; MRA, mineralocorticoid receptor antagonist.

<sup>a</sup>*P* values compare male and female patients. Test used is Student's *t*-test.

<sup>b</sup>Patients who receive an ARNI are also included in the ARB count.

<sup>c</sup>Diuretic total includes all patients with one or more medications that are classified as loop diuretic, thiazide, or potassium sparing diuretic.

that shorter height<sup>9</sup> and longer QRS duration,<sup>39</sup> rather than sex, are independent predictors of greater beneficial effect of CRT and that sex may act as a surrogate for height,

QRS, LV dimensions, or HF aetiology. Importantly, our analysis of QRS duration (*Table 3*) shows that in AdaptResponse, even when accounting for height, aetiology, and other

**Table 3** Multivariable linear regression model for QRS duration

Variable <sup>a</sup>	Effect on QRS duration (ms)	95% confidence interval	P value
Intercept <sup>b</sup>	164.5		
Female	-2.81	-4.23 to -1.40	<0.0001
Age	-0.02 per year	-0.07 to 0.03	0.50
Height	0.15 per cm	0.08 to 0.21	<0.0001
BMI	0.41 per kg/m <sup>2c</sup>	0.25 to 0.57	<0.0001
NYHA class III/IV	0.08 vs. class II	-0.96 to 1.13	0.87
LVEF	-0.35 per percent	-0.43 to -0.26	<0.0001
PR interval	0.08 per ms	0.05 to 0.11	<0.0001
Ischaemic aetiology	-0.76	-1.93 to 0.41	0.20
Atrial fibrillation	0.58	-0.99 to 2.14	0.47
Diabetes	-2.21	-3.34 to -1.09	0.0001
Chronic lung disease	-2.33	-3.78 to -0.88	0.002
Renal dysfunction	-0.58	-1.99 to 0.84	0.42
Loop diuretics	1.76	0.68 to 2.83	0.001

BMI, body mass index; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

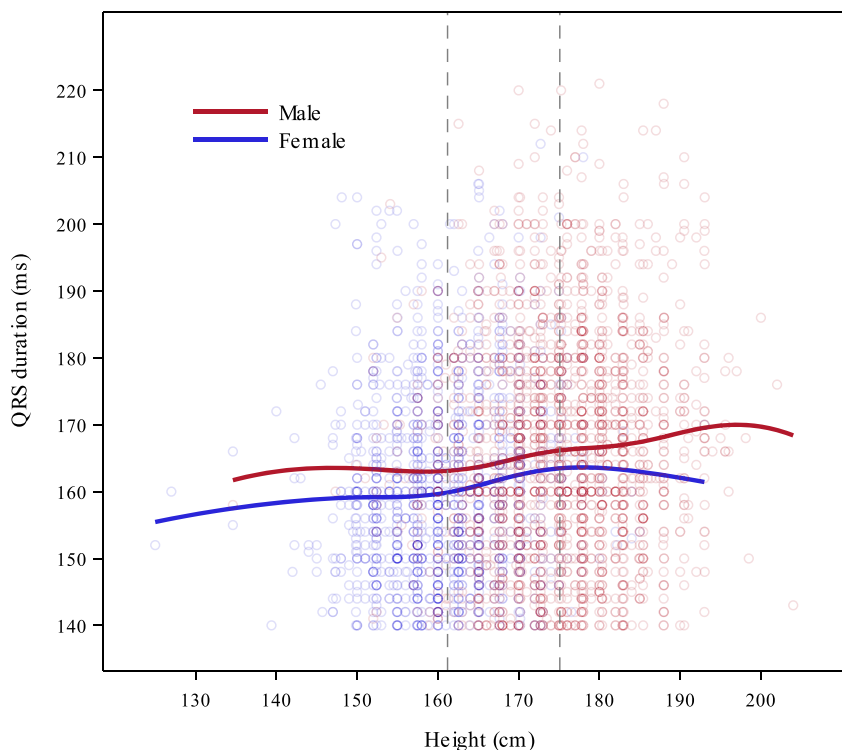
A total of 146 female patients with QRS < 140 ms were excluded.

<sup>a</sup>Variables removed from model: prior heart failure hospitalization, dilated cardiomyopathy, coronary artery disease, myocardial infarction, hypertension, mitral valve disease, stroke, peripheral vascular disease, anaemia, hypothyroidism, sleep apnoea, cancer, depression, beta-blocker, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker.

<sup>b</sup>Intercept represents a male patient, 65 years, height 175 cm, BMI 29 kg/m<sup>2</sup>, LVEF 30%, PR interval 180 ms, NYHA class II, no comorbidities, no diuretics.

<sup>c</sup>QRS duration increases for BMI between 18.5 and 30.

**FIGURE 3** Relation of QRS duration with height and gender. Solid curves represent the smoothed average QRS duration for height and gender (penalized B-splines). Vertical dashed lines represent average height for women and men.



baseline characteristics, women remained to have shorter QRS duration.

The current investigation of differences in patient characteristics will be used in outcome analyses that will

account for confounding factors and address the question whether sex is linked to response and, if so, whether this is attributed to sex alone or to sex-associated patient characteristics.



Table 4 Comparison between CRT trials

Parameter	MIRACLE <sup>15</sup>	COMPANION <sup>16</sup>	CARE-HF <sup>17,27</sup>	REVERSE <sup>18</sup>	MADIT-CRT <sup>19</sup>	RAFT <sup>20</sup>	NCDR <sup>4</sup>	ESC CRT Survey II <sup>28</sup>	AdaptResponse
Patients without CRT (n)	225	308	404	0	0	0	0	0	0
Patients CRT-P (n)	228	617	409	99	0	0	0	3256	161
Patients CRT-D (n)	0	595	0	509	1089	894	24 152	7513	3449
FU duration (months)	6	16	29	12	28	40	0	NR	Ongoing
Age (years)	65	67	65	63	65	66	69	70	65
Women (%)	32	33	27	21.5	26	17	41	24	43
Ischaemic heart disease (%)	54	55	38	55	14	69	51	45	31
NYHA I/II (%)	0	0	0	100	100	79	14	41	48
MLWHF	59	NR	45	28	NR	42	NR	NR	NR
Six-minute hall walk (m)	298	262	NR	395	359	351	NR	NR	NR
LVEF (%)	22	21	26	27	24	23	24	29	26
QRS (ms)	166	160	165	153	NR	157	156	160	163
Heart rate (bpm)	74	72	70	67	NR	NR	NR	70	72
Systolic BP mmHg	114	111	117	125	124	NR	NR	122	126
ACEi/ARB (%)	92	89	95	97	98	96	85 <sup>a</sup>	86 <sup>a</sup>	83
Beta-blockers(%)	59	68	72	95	93	90	89 <sup>a</sup>	89 <sup>a</sup>	89
Diuretics (%)	94	95	99	80	75	85	NR	81 <sup>a</sup>	64
AF (%)	NR	NR	21	17	11	13	NR	41	13
Diabetes (%)	NR	41	21	23	30	33	37	31	35
LBBB (%)	NR	71	NR	77	70	73	100	73	99 <sup>b</sup>

ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BP, blood pressure; CARE-HF, The Cardiac Resynchronization - Heart Failure trial; COMPANION, The Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure trial; CRT, cardiac resynchronization therapy; ESC, European Society of Cardiology; FU, follow-up; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; MADIT-CRT, Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy; MIRACLE, Multicenter InSync Randomized Clinical Evaluation trial; MLWHF, Minnesota Living with Heart Failure Questionnaire; NCDR, National Cardiovascular Data Registry; NR, not reported; NYHA, New York Heart Association; RAFT, Resynchronization-Defibrillation for Ambulatory Heart Failure Trial; REVERSE, Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction.

<sup>a</sup>At discharge.

<sup>b</sup>Investigator reported.

## Conclusions

In the largest CRT trial to date, women showed a higher HF symptom burden and differed from men in a large number of clinical characteristics, including characteristics known to be associated with response to CRT. In particular, accounting for other clinical factors, QRS duration was shorter in women.

## Conflict of interest

B.L.W. participated in Physician Advisory Committees of Medtronic, Abbott, Philips and reports honoraria from Medtronic, Abbott, Philips. D.B. is a mid-career investigator supported by the Heart and Stroke Foundation of Ontario and by the University of Ottawa Chair in Electrophysiology Research. He has received major research funding from Medtronic, Boston Scientific, Boehringer Ingelheim, Bayer, Biotronik, Pfizer, and Bristol Myers Squibb. M.R.G. is a consultant to Medtronic and Boston Scientific and receives honoraria from Medtronic, Boston Scientific, and EBR. A.S.H., K.

K., and W.M. have no conflicts of interest to disclose. S.J. and B.G. are employed by Medtronic. C.L. participated in a Medtronic advisory board and reports honoraria received from Medtronic, Biotronik, LivaNova, Boston Scientific, and Abbott. G.F. participated in committees of trials sponsored by Bayer, Novartis, Servier, Vifor, BI, and Medtronic.

## Funding

The AdaptResponse study is funded in its entirety by Medtronic plc.

## Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Data S1.** Supporting information

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