

## Gender-Related Safety and Efficacy of Cardiac Resynchronization Therapy

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### ABSTRACT

**Background:** Cardiac resynchronization therapy (CRT) is an established therapy for patients with chronic heart failure (CHF) and a broad QRS complex. Gender-related safety and efficacy data are necessary for informed patient decision-making for female patients with CHF. The aim of the study was to assess the effects of gender on the outcome of CRT in highly symptomatic heart failure patients.

**Hypothesis:** Gender may have an effect on the outcome of heart failure patients undergoing cardiac resynchronization therapy.

**Methods:** The study analyzed the 2-year follow-up of 393 New York Heart Association (NYHA) class III/IV patients with a class I CRT indication enrolled in the Management of Atrial Fibrillation Suppression in AF-HF Comorbidity Therapy (MASCOT) study.

**Results:** In female patients ( $n = 82$ ), compared with male patients ( $n = 311$ ), CHF was more often due to dilated cardiomyopathy (74% vs 44%, respectively;  $P < 0.0001$ ). Females also had a more impaired quality-of-life score and a smaller left ventricular end-diastolic diameter (LVEDD). Women were less likely than men to have received a CRT defibrillator (35% vs 61%, respectively;  $P < 0.0001$ ). After 2 years, the devices had delivered more biventricular pacing in women than in men ( $96\% \pm 13\%$  vs  $94\% \pm 13\%$ , respectively;  $P < 0.0004$ ). Women had a greater reduction in LVEDD than did men ( $-8.2 \text{ mm} \pm 11.1 \text{ mm}$  vs  $-1.1 \text{ mm} \pm 22.1 \text{ mm}$ , respectively;  $P < 0.02$ ). Both genders improved similarly in NYHA functional class. Women reported greater improvement than men in quality-of-life score ( $-21.1 \pm 26.5$  vs  $-16.2 \pm 22.1$ , respectively;  $P < 0.0001$ ). After adjustment for cardiovascular history, women had lower all-cause mortality ( $P = 0.0007$ ), less cardiac death ( $P = 0.04$ ), and fewer hospitalizations for worsening heart failure ( $P = 0.01$ ).

**Conclusions:** Females exhibited a better response to CRT than did males. Because females have such impressive benefits from CRT, improved screening and advocacy for CRT implantation in women should be considered.

### Introduction

Women and men respond differently to medical treatment of cardiovascular diseases.<sup>1,2</sup> The current management of patients with advanced chronic systolic heart failure (CHF)

includes medical as well as nonpharmacological treatment to alleviate symptoms, prevent major morbidity, and lower mortality.<sup>3</sup> Cardiac resynchronization therapy (CRT) is well established for patients with systolic CHF and bundle branch block on the resting electrocardiogram.<sup>4</sup>

Gender-related differences have been observed for nonpharmacological treatments such as implantable cardioverter-defibrillator therapy.<sup>5</sup> Data from CRT studies such as Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) and Cardiac Resynchronization–Heart Failure (CARE-HF) revealed no gender-related differences in survival,<sup>6,7</sup> whereas the Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy (MADIT-CRT) demonstrated a greater benefit for women compared with men from CRT with defibrillator (CRT-D) than from an

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implantable cardioverter-defibrillator alone.<sup>8,9</sup> For proper patient decision-making in female CHF patients, gender-specific safety and efficacy data based on publications are mandatory.<sup>10</sup> The purpose of the present analysis was to assess the effects of gender on the outcome of CRT.

### Patient Population and Methods

Patients included in this analysis were enrolled in the Management of Atrial Fibrillation Suppression in AF-HF Comorbidity Therapy (MASCOT) study and followed for 2 years.<sup>11</sup> Patients were eligible for enrollment if they presented with New York Heart Association (NYHA) functional class III or IV despite optimal medical therapy, had a QRS duration  $\geq 130$  ms, a left ventricular ejection fraction (LVEF)  $\leq 35\%$ , and a left ventricular end-diastolic diameter (LVEDD)  $\geq 55$  mm.<sup>4</sup> Exclusion criteria included permanent atrial fibrillation (AF) and myocardial infarction, cardiac surgery, or a coronary revascularization procedure within the previous 3 months. Implanted devices were the CRT-pacemakers (CRT-P) Frontier (model 5510) or Frontier II (model 5596) or the CRT-Ds Epic HF (model V-350) or Atlas HF (model V-341; all from St. Jude Medical, Sylmar, CA). The patients received a CRT-P or CRT-D device upon the clinical decision of each center.

### Study Design

The MASCOT study was a multicenter, single-blind, randomized, parallel study that examined the safety and efficacy of a specific atrial overdrive pacing algorithm in CRT recipients during the 2-year follow-up.<sup>11</sup> For this purpose, the AF suppression algorithm was programmed either to "on" or "off." Follow-up visits were scheduled at hospital discharge and at 3, 6, 9, 12, and 24 months after device implantation. The study protocol was reviewed and approved by the institutional ethics committee of each participating medical center. All patients granted their informed consent to participate in the study.

### Data Collection and Analysis

The present analysis included the patients who completed the 2-year follow-up or died during the follow-up period. For each patient who died during the follow-up period, the reason for study termination, including a patient death form with a death classification, was completed. At each follow-up visit, the number of and reasons for hospital admissions were recorded.

All patients underwent echocardiography in the left lateral decubitus position before and 2 years after implantation. Echocardiographic changes after CRT were assessed by comparing left-ventricular end-systolic volume, left-ventricular end-diastolic volume (LVEDV), and LVEF from baseline measurements.

Changes in NYHA functional class and in the quality-of-life score were measured with the Minnesota Living with Heart Failure Questionnaire. These variables were used to describe the clinical outcome. Other variables for the clinical outcome were all-cause mortality, cardiac death, sudden death, sudden cardiac death, hospitalization, and hospitalization for worsening CHF. The presence of AF was also recorded.

### Statistical Analysis

Data collected from the 2 groups were compared at baseline and after final follow-up. Normality of the data was verified using box-and-whisker plots, normal probability plots, and Kolmogorov-Smirnov tests for normality. Baseline data for all patients with available data were included in the analysis presented in Table 1. Continuous variables from the normal distribution were compared using the 2-sample *t* test for independent variables. The nonparametric Wilcoxon signed-rank test was used for non-normal variables. Categorical variables were compared using the Fisher exact test or the  $\chi^2$  test, as applicable. A *P* value  $< 0.05$  was considered significant.

### Results

Between September 2003 and March 2006, 405 patients at 34 medical centers from 10 different countries were enrolled in the MASCOT trial (see Appendix). Twelve patients were excluded because they were not randomized in the MASCOT study and were excluded from the following analyses.

From the 393 patients analyzed, 21% of patients undergoing CRT implantation were female (Table 1). As compared with males, females had a lower body weight, a greater frequency of CHF due to dilated cardiomyopathy, a more impaired quality-of-life score, and a smaller LVEDD. Females more often received a CRT-P rather than a CRT-D.

### Changes During Follow-up

At the final follow-up, women had more frequent biventricular pacing (Table 2). In the echocardiographic assessment, women had a greater reduction in LVEDD (Figure 1). Left-ventricular ejection fraction improved in women, but men had a significantly greater improvement in LVEF. Both genders had a similar decrease of their NYHA functional class, with no statistically significant difference between women and men. Women reported an improvement in quality-of-life score that was nearly statistically significant.

### All-Cause Mortality and Heart Failure Hospitalization at Final Follow-up

After adjustment for cardiovascular history, women had lower all-cause mortality, less cardiac death, and fewer hospitalizations due to worsening heart failure (Figure 2). No differences were detected for sudden death, all-cause hospitalization, and the presence of AF at the last follow-up visit.

### Discussion

#### Gender Distribution in Cardiac Resynchronization Therapy Implantation

In MASCOT, 21% of patients undergoing CRT implantation were female. The frequency of females in 6 CRT studies ranged from 15.2% to 38%, with a mean value of 23.8% (Table 3). Even in more recent trials, the percentage of women receiving CRT remained unchanged,<sup>12,13</sup> and similar gender distribution has been observed in Medicare patients.<sup>14</sup> Our data contain similar rates as these reports with regard to gender distribution in CRT recipients.

Table 1. Baseline Characteristics of Male and Female Subjects

	Male, n = 311	Female, n = 82	P Value	OR (95% CI)
<b>Demographic data</b>				
Age, y	67.80 ± 9.53	67.76 ± 9.47	0.90	NA
Weight, kg	78.48 ± 14.26	68.81 ± 13.21	<0.0001	NA
Height, m	1.72 ± 0.07	1.61 ± 0.06	0.003	
BMI, kg/m <sup>2</sup>	26.46 ± 4.08	26.67 ± 4.74	0.90	
Body surface area, m <sup>2</sup>	1.91 ± 0.18	1.72 ± 0.16	<0.0001	
SBP, mm Hg	119.74 ± 18.27	118.41 ± 19.34	0.69	NA
DBP, mm Hg	72.02 ± 10.78	69.39 ± 10.70	0.12	NA
QoL score	42.32 ± 20.91	54.18 ± 20.04	<0.0001	NA
<b>NYHA functional class, n (%)</b>				
III	265 (85.21)	73 (89.02)	0.09	NA
IV	44 (14.15)	7 (8.54)		
<b>CHF etiology, n (%)</b>			<0.0001	0.27 (0.16–0.47)
Ischemic etiology	173 (55.63)	21 (25.61)		
Dilated cardiomyopathy	138 (44.37)	61 (74.39)		
<b>Medications, n (%)</b>				
ACEI	215 (69.13)	65 (79.27)	0.07	1.71 (0.95–3.07)
ARB	57 (18.33)	14 (17.07)	0.79	0.92 (0.48–1.75)
β-Blocker	220 (70.74)	63 (76.83)	0.27	1.37 (0.78–2.42)
Diuretic	294 (94.53)	77 (93.90)	0.82	0.89 (0.32–2.49)
Spironolactone	63 (20.26)	18 (21.95)	0.74	0.9 (0.5–1.63)
Digitalis	74 (23.79)	33 (40.24)	0.0029	2.16 (1.29–3.6)
Antiarrhythmic drugs	108 (34.73)	11 (13.41)	0.0002	0.29 (0.15–0.57)
<b>Comorbidities, n (%)</b>				
DM	89 (28.62)	23 (28.05)	0.92	1.03 (0.6–1.77)
HT	143 (45.98)	34 (41.46)	0.46	1.2 (0.73–1.97)
Chronic renal insufficiency	46 (14.79)	7 (8.54)	0.14	1.86 (0.81–4.29)
<b>History of AF, n (%)</b>				
Paroxysmal AF	34 (10.93)	10 (12.20)	0.75	0.88 (0.42–1.87)
Persistent AF	0 (0)	0 (0)	NA	NA
<b>12-lead ECG</b>				
QRS duration, ms	162.24 ± 25.98	168.25 ± 36.06	0.30	NA
AF at baseline, yes, n (%)	60 (19.29)	10 (12.20)	0.14	0.58 (0.28–1.19)
<b>Echocardiographic parameters</b>				
LVEDD, mm	71.21 ± 9.85	66.89 ± 9.41	0.0009	NA
LVEF, %	25.22 ± 6.48	25.30 ± 7.11	0.68	NA
Left atrial diameter, longitudinal view	47.91 ± 8.59	44.93 ± 10.75	0.02	NA

Table 1. Continued

	Male, n = 311	Female, n = 82	P Value	OR (95% CI)
Device type, n (%)				
CRT-P	119 (38.26)	53 (64.63)	<0.0001	0.34 (0.2–0.56)
CRT-D	192 (61.74)	29 (35.37)		
Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; BMI, body mass index; CHF, chronic heart failure; CI, confidence interval; CRT, cardiac resynchronization therapy; CRT-D, CRT-defibrillator; CRT-P, CRT-pacemaker; DBP, diastolic blood pressure; DM, diabetes mellitus; ECG, electrocardiogram; HT, hypertension; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; NA, not applicable; NYHA, New York Heart Association; OR, odds ratio; QoL, quality of life; SBP, systolic blood pressure.				

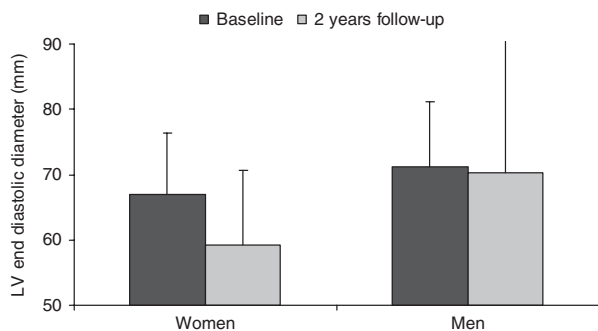
Table 2. Clinical Efficacy Outcome at 24 Months or Termination of the Study

	Male, n = 311	Female, n = 82	P Value	OR (95% CI)
Atrial pacing (%)	54.11 ± 40.36	58.26 ± 39.61	0.28	NA
Ventricular pacing (%)	94.53 ± 13.71	96.32 ± 13.68	0.0004	NA
Effect on NYHA functional class				
Difference between baseline and last NYHA class	−1.04 ± 0.80	−1.00 ± 0.70	0.79	NA
Patients who improved ≥1 NYHA class, n (%)	154 (78.57)	41 (75.93)	0.68	1.16 (0.57–2.37)
Effect on LVEF				
Difference between baseline and last LVEF (%)	13.32 ± 13.02	7.23 ± 11.62	0.02	NA
Patients who improved ≥5% in LVEF (%)	15 (13.39)	3 (10.34)	0.14	0.52 (0.22–1.24)
Effect on LVEDD				
Difference between baseline and last LVEDD (%)	−1.14 ± 22.05	−8.27 ± 11.14	0.02	NA
Effect on QoL score				
Difference between baseline and final QoL (%)	−16.20 ± 22.19	−21.19 ± 26.56	<0.0001	NA
Clinical outcome, n (%)				
All-cause mortality	62 (19.94)	4 (4.88)	0.0007	4.86 (1.71–13.8)
Cardiac death	30 (9.65)	2 (2.44)	0.04	4.27 (1.0–18.3)
Sudden death	14 (4.50)	2 (2.44)	0.54	1.89 (0.42–8.47)
Sudden cardiac death	10 (3.22)	1 (1.22)	0.47	2.69 (0.34–21.3)
Hospitalization	129 (41)	31 (37)	0.55	1.17 (0.71–1.92)
Hospitalization due to worsening HF	73 (23.47)	9 (10.98)	0.01	2.49 (1.19–5.22)
AF at last visit	27 (8.68)	6 (7.32)	0.82	1.2 (0.48–3.02)
Abbreviations: AF, atrial fibrillation; CI, confidence interval; HF, heart failure; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; NA, not applicable; NYHA, New York Heart Association; OR, odds ratio; QoL, quality of life.				

The prevalence of CHF is equally distributed between genders in epidemiological surveys.<sup>15,16</sup> Between 2002 and 2004, more US women than men were admitted to the hospital due to worsening CHF.<sup>14</sup> Although there may be equal prevalence of CHF in men and women, women are more likely to have diastolic heart failure with preserved systolic function. It is possible that, in many cases, women may not be considered candidates for CRT based on having preserved systolic function. On the other hand, gender disparities and underutilization of therapies have been previously reported for other diagnostic and therapeutic procedures in women with cardiovascular diseases.<sup>17</sup> It

is not clear whether the observed differences are based on gender disparities or they result from underutilization similar to other procedures.

Not surprisingly, women had lower body weight and a smaller LVEDV. The most consistent gender-related difference was the more frequent etiology of CHF due to dilated cardiomyopathy in women compared with men.<sup>12,18–22</sup> One exception is a report from Lilli and co-workers.<sup>23</sup> This difference may be the result of the greater incidence of coronary artery disease in men. As women had smaller heart diameters as measured by echocardiography (eg, the LVEDD),

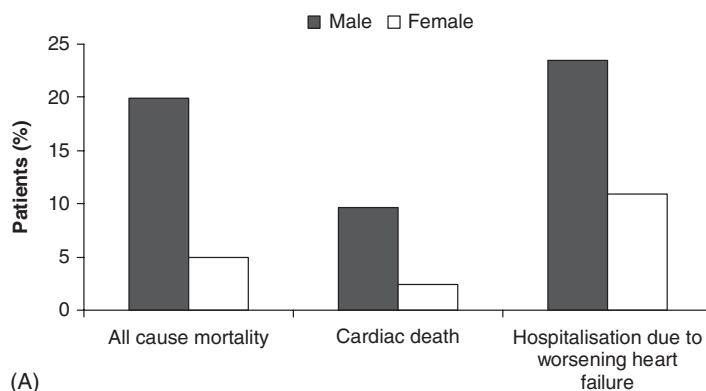


**Figure 1.** At baseline, women had a significantly smaller LV end-diastolic diameter than did men ( $P = 0.0009$ ); after 2-year follow-up, women had a significantly greater reduction of LV end-diastolic diameter than did men ( $P < 0.02$ ). Abbreviations: LV, left ventricular.

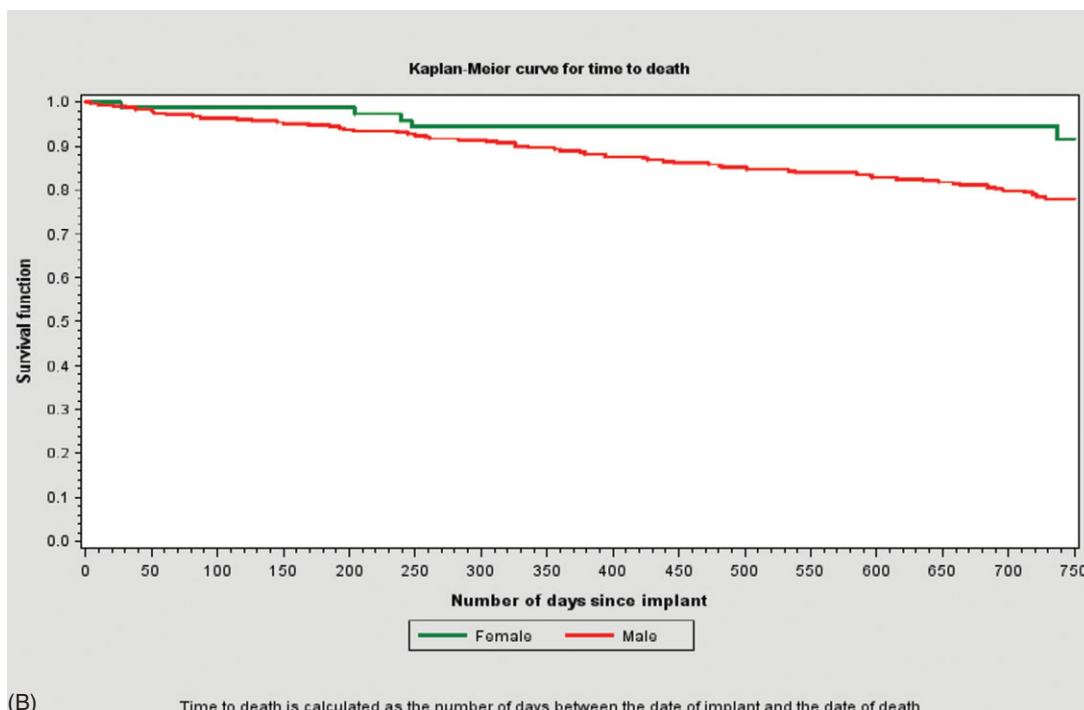
this may translate into gender-specific effects on cardiac remodeling.<sup>24</sup> The assumption, however, that lower body weight and decreased body height, and thus a smaller female body volume, accounts for the gender differences in response to CRT was not supported in the analysis of Cheng et al.<sup>25</sup> In addition, patients with CHF of ischemic etiology had an established indication for an implantable defibrillator very early. These patients, who were mainly male, seemed to receive a CRT-D more often than did patients whose CHF was due to dilated cardiomyopathy, who were mainly female.

### Echocardiographic Changes After Cardiac Resynchronization Therapy Implantation

The echocardiographic assessments after 2-year follow-up revealed a greater reduction of LVEDD in women compared with men. A more pronounced improvement of LVEF,



(A)



(B)

Time to death is calculated as the number of days between the date of implant and the date of death

**Figure 2.** (A) After 2-year follow-up, women had lower all-cause mortality ( $P = 0.008$ ), lower cardiac mortality ( $P = 0.04$ ), and fewer hospitalizations due to worsening heart failure ( $P = 0.045$ ) than did men. (B) The Kaplan-Meier curve for time to death shows a significantly better survival for women than for men ( $P = 0.006$ ).

Table 3. Gender Distribution in Studies Assessing the Outcome of Cardiac Resynchronization Therapy Patients

Author	Publication and Year	Total Population	Women, No. (%)	Men, No. (%)
Cleland et al <sup>7</sup>	N Engl J Med 2005	409	105 (26)	304 (74)
Bleeker et al <sup>18</sup>	Pacing Clin Electrophysiol 2005	173	36 (20.8)	137 (79.2)
Lilli et al <sup>23</sup>	Pacing Clin Electrophysiol 2007	195	46 (23.5)	149 (76.5)
Zardkoohi et al <sup>19</sup>	Pacing Clin Electrophysiol 2007	117	26 (22.2)	91 (77.8)
Alaeddini et al <sup>14</sup> registry	Pacing Clin Electrophysiol 2008	2590	659 (25)	1931 (75)
		26593	6928 (26)	19646 (74)
		42196	11286 (27)	30889 (73)
Moss et al <sup>8</sup>	N Engl J Med 2009	1089	275 (25.3)	814 (74.7)
Dickstein et al <sup>30</sup>	Eur Heart J 2009	2438	659 (27)	1779 (73)
Tang et al <sup>31</sup>	N Engl J Med 2010	894	136 (15.2)	758 (84.8)
Leyva et al <sup>20</sup>	Pacing Clin Electrophysiol 2011	550	122 (22)	428 (78)
Mooyaart et al <sup>12</sup>	Am J Cardiol 2011	578	147 (25.4)	431 (74.6)
Xu et al <sup>21</sup>	J Cardiovasc Electrophysiol 2012	728	166 (22.8)	562 (77.2)
Zabarovskaja et al <sup>13</sup>	Europace 2012	619	118 (19)	501 (81)
Celikyurt et al <sup>32</sup>	Clin Cardiol 2013	105	40 (38)	65 (62)
All (with exception of Alaeddini et al)		7895	1876 (23.8)	6019 (76.2)

however, was seen in men. Both are valid echocardiographic findings of beneficial reverse remodeling and indicate gender-related differences in cardiac remodeling. Two other investigations had similar findings but also demonstrated a greater improvement of the LVEF in women than in men.<sup>21,23</sup> An additional reason for these results may reflect the observation that ventricular remodeling occurs more often in patients with a smaller baseline LVEDD, which was more often present in women.<sup>26</sup>

### Mortality and Morbidity After Cardiac Resynchronization Therapy Implantation

No significant gender-related differences in overall survival were reported in the COMPANION and CARE-HF trials, as well as in 3 additional investigations.<sup>6,7,18,19,23</sup> A multinomial logistic regression analysis to identify risk factors for death after CRT implantation found a nonsignificant *P* value for male gender.<sup>27</sup> In a retrospective cohort study, Xu et al reported fewer deaths in women compared with men over a median follow-up of 3.7 years.<sup>21</sup> After adjusting for multiple variables, the survival benefit from CRT was not statistically different between men and women.

Because ischemic etiology has been identified as a predictor of death after CRT implantation, we performed a multivariate analysis.<sup>17</sup> Adjusting for this confounder, we observed an improved survival in women compared with men. Our results are similar to those from a study including 555 patients and with median follow-up of 36.2 months. Female gender was independently associated with lower mortality after CRT, and the benefit continuously increased after device implantation.<sup>20</sup> In the study from

Mooyaart et al with 578 patients, women had a lower 2-year all-cause mortality rate compared with men (8% vs 15%, respectively).<sup>12</sup> Our study supports the gender-specific responses to CRT and points out that the additional benefit for women is evident as early as 2 years after implantation.

Possible explanations for these findings in our analysis can be the higher percentage of biventricular pacing in women. The importance of biventricular pacing with regard to outcomes has been previously reported.<sup>21</sup> One reason for this difference may be the trend toward more frequent AF in men compared with women, in combination with a better rate control in the case of AF. Women received digitalis more frequently than men, but the occurrence of AF is not significantly different and the prescription of  $\beta$ -blockers was similar in both groups. Second, males had more often received antiarrhythmic drugs. Thirdly, as discussed previously, women may have a more robust response to CRT.<sup>28</sup> Fourthly, the reduction in end-diastolic volume in the MADIT-CRT trial was a predictor for better prognosis after device implantation.<sup>29</sup> In our study, these changes occurred more frequently in women than in men. Because the definitive underlying mechanisms remain unclear, there is a need to better understand the mechanisms responsible for these gender-related differences.

### Study Limitations

This is a post hoc analysis that was not part of the original endpoints of the MASCOT trial. The randomization in MASCOT evaluating the overdrive pacing algorithm should not have an impact on this post hoc analysis, because randomization was similar in men and women. The study

was not powered to detect differences in mortality for the 2 groups. Finally, there were differences in the percentages of male and females receiving a CRT-D. However, there is yet no evidence of improved patient survival with CRT-D instead of CRT-P.<sup>6</sup>

## Conclusion

After adjusting for confounders, mainly for the etiology of CHF, female gender significantly contributed in our analysis to a better long-term outcome of CRT. Because females have such impressive benefits from CRT, improved screening and advocacy for CRT implantation in women should be considered.

## Appendix

The following investigators and institutions participated in the Management of Atrial Fibrillation Suppression in AF-HF Comorbidity Therapy Study (MASCOT): Fiorenzo Acquatì, Ospedale Valduce, Como, Italy; Francesco Alessandrini, Università Cattolica del Sacro Cuore, Campobasso, Italy; Maria-Grazia Bongiorno, Ospedale Cisanello, Pisa, Italy; Johannes Brachmann, Klinikum Coburg, Coburg, Germany; Valeria Calvi, Ospedale Ferrarotto, Catania, Italy; Ngai-yin Chan, Princess Margaret Hospital, Hong Kong, China; Per Dahl Christensen, Sygehus Viborg, Viborg, Denmark; Pierre Fiorello, CMC Parly II, Le Chesnay, France; Daniel Flammang, Centre Hospitalier Général Girac, Saint Michel, France; Francesco Foti, Ospedale di Melegnano, Melegnano, Italy; Robert Frank, Hôpital Pitié-Salpêtrière, Paris, France; Antonio Fusco, Clinica Pederzoli, Peschiera del Garda, Italy; Grahame Goode, Blackpool Victoria Hospital, Blackpool, United Kingdom; Daniel Gras, Nouvelles Cliniques Nantaises, Nantes, France; Michael Gruska, Hanusch Krankenhaus, Vienna, Austria; Gaël Jauvert, InParys, Saint-Cloud, France; Salem Kachboura, CHU Abderrahmane Mami, Ariana, Tunisia; Gert Kaltofen, Klinikum Chemnitz gGmbH Krankenhaus, Chemnitz, Germany; Wolfgang Kiowski, Herzgefäß Zentrum Klinik im Park, Zürich, Zürich, Switzerland; Francesco Lisi, Azienda Ospedaliera Cannizzaro, Catania, Italy; Themistoklis Maounis, Onassis Cardiac Surgery Center, Athens, Greece; Eraldo Occhetta, Ospedale Maggiore della Carità, Novara, Italy; Luigi Padeletti, Ospedale Careggi, Florence, Italy; Olivier Piot, Centre Cardiologique du Nord, St. Denis, France; Jean-Ernest Poulard, Centre Hospitalier Général, Abbeville, France; Jean-Luc Rey, CHRU Hôpital Sud, Amiens, France; Nadir Saoudi, Centre Hospitalier Princesse Grace, Monaco; Andreas Schuchert, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany; Olivier Thomas, Clinique Ambroise Paré, Neuilly-sur-Seine, France; Bernardo Tuccillo, Ospedale Loreto Mare, Naples, Italy; Thomas Vesterlund, Aalborg Hospital, Aalborg, Denmark; Paul Vock, A.ö. KH der Stadt St. Pölten, St Pölten, Austria; Arnd Weide, Kardiologische Gemeinschaftspraxis, Hannover, Germany; Paolo Zecchi, Policlinico Gemelli, Rome, Italy.

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