The Effect of Gender on Outcomes following Cardiac Resynchronization Therapy in Patients with a Narrow QRS Complex

A Subgroup Analysis of the EchoCRT Trial

Short title: Effect of gender on CRT in narrow QRS

Jan Steffel, M.D.[1]*, Niraj Varma*, M.D., Ph.D.[2*], Michele Robertson, B.Sc.[3], Jagmeet P. Singh, M.D.[4], Jeroen J. Bax, M.D., Ph.D.[5], Jeffrey S. Borer, M.D.[6], Kenneth Dickstein, M.D., Ph.D.[7], Ian Ford, M.D., Ph.D.[3], John Gorcsan III, M.D.[8], Daniel Gras, M.D.[9], Henry Krum, M.B., B.S., Ph.D.[10], Peter Sogaard, M.D., D.M.Sc.[11], Johannes Holzmeister, M.D.[1], Josep Brugada, M.D. Ph.D.[12], William T. Abraham, M.D., Ph.D.[13]* and Frank Ruschitzka, M.D.[1]*

*authors contributed equally

[1] Department of Cardiology, University Heart Center Zurich, Zurich, Switzerland

[2] Department of Cardiovascular Medicine, Cleveland Clinic, Cleveland, Ohio

[3] Robertson Centre for Biostatistics, University of Glasgow, Glasgow, United Kingdom

[4] Cardiac Arrhythmia Service, Massachusetts General Hospital, Harvard Medical School, Boston, MA

[5] Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands

[6] Division of Cardiovascular Medicine and Howard Gilmanand Ron and Jean Schiavone Institutes, State University of New York Downstate College of Medicine, New York

[7] University of Bergen, Stavanger University Hospital, Stavanger, Norway

[8] University of Pittsburgh, Pittsburgh, PA

[9] Nouvelles Cliniques Nantaises, Nantes, France

[10] Monash Centre of Cardiovascular Research and Education in Therapeutics, Melbourne, Australia

[11] Department of Cardiology and Clinical Institute, Aalborg University Hospital, Aalborg, Denmark

[12] Cardiology Department, Thorax Institute, Hospital Clinic, University of Barcelona, Barcelona, Spain

[13] Division of Cardiovascular Medicine, Ohio State University Medical Center, Davis Heart and Lung Research Institute, Columbus. OH

Correspondence:

Frank Ruschitzka, MD FESC FRCP

Head, Heart Failure Clinic and Transplantation

Deputy Head, Department of Cardiology

University Heart Center Zurich

Tel.: +41 44 255 11 11
Mail: frank.ruschitzka@gmail.com

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Abstract

Background: In EchoCRT, a randomized controlled trial evaluating the effect of CRT in patients with a QRS duration <130 msec 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 as compared with the control group. In this pre-specified subgroup analysis we evaluated the effect of gender 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 gender for the primary or any of the secondary endpoints. Numerically, a higher all-cause mortality was observed in male patients randomized to CRT-ON vs. CRT-OFF on univariable analysis (HR 1.83, 95% CI 1.08 - 3.12); however, no statistically significant interaction compared to females randomized to CRT-ON vs. CRT-OFF was noted (HR 0.99, p interaction = 0.56). There was no difference in the primary safety endpoint 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 due to the premature termination of the trial and the limited data. These results suggest that male gender may be a risk factor for harm by CRT in patients with narrow QRS width, an observation which deserves further investigation.

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Introduction

Cardiac resynchronization therapy (CRT) has been demonstrated to reduce morbidity and mortality in numerous large clinical trials, and has become an integral part of contemporary heart failure therapy. [1-3] The inclusion criteria of these trials form the basis of current guidelines, recommending CRT for patients with a severely reduced left ventricular ejection fraction (EF ≤ 35%), symptomatic chronic heart failure (CHF), and a QRS complex ≥ 120 msec.[4] Since the majority of CHF patients present with a narrow QRS complex,[5] the EchoCRT trial was designed to investigate the effect of CRT in patients with a QRS duration ≤ 130 msec together with echocardiographic evidence of left ventricular dyssynchrony.[6] The trial was terminated early due to futility, but also indicated an increased risk for all-cause mortality of 81% with CRT in this patient population. The gender distribution, as well as the reason for the overall increase in mortality observed in Echo CRT is presently still unclear.

Gender specific results of CRT have been suggested by some, but not all, prior studies. CARE-HF or REVERSE were unable to find a gender-by-treatment interaction. In contrast, in MADIT-CRT, women experienced a 79% reduction in the primary endpoint (death or heart failure) as compared to only 28% in men. More recently, pronounced female advantage for CRT effect was seen at shorter (120-150 msec) QRS durations.[7, 8]

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 pre-specified subgroup analysis was therefore performed to assess the effect of gender 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.[6] 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 Centre for Biostatistics at the University of Glasgow. Patients were eligible if they had New York Heart

Association (NYHA) class III or IV heart failure; a left ventricular EF of 35% or less; a standard indication for an implantable cardioverter–defibrillator (ICD); optimized medical heart failure therapy; a QRS duration of less than 130 msec; a left ventricular end-diastolic diameter (LVEDD) of 55 mm or more; and echocardiographic evidence of left ventricular dyssynchrony as previously defined.[6] 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.

Endpoints

The primary efficacy outcome was the combination of death from any cause or first hospitalization for worsening heart failure.[6] The pre-specified secondary outcomes included all hospitalizations for worsening heart failure throughout the study; all-cause mortality, cardiovascular mortality; heart failure mortality and cardiovascular hospitalization.[6] 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 two-sample t-tests and chi-square (or Fisher's exact) tests for continuous and categorical variables, respectively.

Hazard ratios (HRs) for CRT-ON and CRT-OFF with 95% confidence intervals were calculated with the Cox proportional hazards models for male vs. female patients including the stratification factor of country in the model. Additionally, 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, QOL score, sitting DBP, ischemic cardiomyopathy, history of myocardial infarction, history of CABG, LVEDD, diuretic agent use). Interactions between males and females and

treatment (CRT=ON and CRT=OFF) were tested for in Cox models that included gender and treatment main effects and interaction terms. Time to event curves were estimated with the use of the Kaplan-Meier method. All tests were two-sided with a p value <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. Out 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 higher quality of life scores and higher use of diuretics. Other baseline parameters were comparable amongst the two groups.

Efficacy of CRT in male vs. female patients

There was no difference for male vs. female patients regarding the overall results of the trial, both unadjusted (Fig. 1, 2) and after multivariable adjustment for differences in baseline characteristics as outlined above (i.e. QRS width, walking distance, QOL score, sitting DBP, ischemic cardiomyopathy, history of myocardial infarction, history of CABG, LVEDD, diuretic agent use; Fig. 3). Numerically, however, both the increased hazard of CRT for the primary endpoint, as well as particularly for the mortality endpoints appeared to be driven mainly by an increased hazard in male patients. Most pronounced, cardiovascular mortality was increased 2.4-fold in male patients (HR 2.43 (95% CI 1.27 - 4.63), p=0.007 vs. HR 0.97 (95% CI 0.24 - 3.93), p=0.97 for the females), albeit with a non-significant interaction p-value. These observations were paralleled in the Kaplan Meier analyses as well as in the multivariable adjusted model (again, however, without significant interaction).

Device related complications in male vs. female patients

The primary safety endpoint (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 endpoint, 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 as compared to men). Overall, the difference between ICD lead related complications was similar and did not reach statistical significance.

Discussion

In the current pre-specified subgroup analysis, a trend indicating a worse outcome for males compared to 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 (i.e. harm in some neutralized by benefit in others). In contrast, male patients appear to be the main driver of worse outcomes of CRT-ON for the entire EchoCRT cohort. The lack of statistical significance may be due to the fact that the trial was prematurely terminated, resulting in a lack of statistical power both for the primary as for the secondary endpoints, which becomes even more relevant in subgroup analysis. 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 gender-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.[9] In MADIT-CRT, female patients randomized to CRT treatment had a 69% relative risk reduction to experience the primary endpoint of death or heart failure vs. ICD as compared to 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% vs. 35% risk reduction) and a significant reduction in all-cause mortality. Indeed, a reduction in all-cause mortality was primarily evident in women (HR 028, 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).[10] Finally, a large single center CRT

registry found a significant 56% lower all-cause mortality in women compared to men on multivariable analysis.[11] When considered against QRS duration, female advantage (relative to male patients) was most pronounced at shorter (<150 msec) 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 COMPANION trial, no interaction by gender 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, in healthy women (as well as in EchoCRT), the QRS duration is on average 4-10msec shorter than that in male patients.[16, 17] As a result, male patients with a prolonged QRS complex may have relatively less electrical dyssynchrony and intracardiac conduction disturbance for any given absolute QRS duration as compared to women, which may explain the more favorable outcome of CRT in females. Possibly, in shorter QRS ranges as examined here, there is little if any dyssynchrony among males.[18] For these patients, ventricular stimulation itself may be associated with a worse outcome, similar to the development of pacemaker-mediated cardiomyopathy.[19] Indeed, separation of the KM curve for CRT-ON in males mostly occurs 1.5 – 2 years after implantation, which may indicate a detrimental effect of ventricular pacing on LV function in patients without relevant dyssynchrony, comparable to that of a pacer-mediated cardiomyopathy. In contrast, this phenomenon appears less pronounced in longer QRS durations (i.e., >150msec), after which the relative benefit of male and female patients appears more similar.[7, 8] In our subgroup analysis, male patients had larger LV diameters, longer QRS duration, and more frequently had ischemic cardiomyopathy, prior myocardial infarction and prior CABG. Although patients with prior myocardial infarction are generally less likely to respond to CRT[20] or become super-responders,[21] ischemic cardiomyopathy itself has not consistently been associated with a worse outcome in terms of hard endpoints in any of the major randomized clinical trials.[1, 22, 23] The gender pattern observed on univariable analysis was still evident after multivariable 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 to male patients. In absolute terms, women constitute a large proportion of the CHF population.[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 Euro CRT 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, likely due to smaller vessel diameter and body size.[11, 26] In our analysis, the system- / implantation-related complication rate was similar for men as compared to 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, especially since the trial did not meet its primary endpoint. Gender 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 Echo CRT is in line with other contemporary CRT trials, inclusion of a higher number of women may have increased statistical power for this subgroup analysis.

Conclusion

In the present pre-specified subgroup analysis of EchoCRT, a trend indicating a worse outcome for males compared to females can be observed with CRT-ON vs. CRT-OFF. This did not reach statistical significance, likely due to 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 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.

Conflict of Interest Statements

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References

1. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med*. 2005;352:1539-1549.
2. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, Kocovic DZ, Packer M, Clavell AL, Hayes DL, Ellestad M, Trupp RJ, Underwood J, Pickering F, Truex C, McAtee P, Messenger J. Cardiac resynchronization in chronic heart failure. *N Engl J Med*. 2002;346:1845-1853.
3. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, Carson P, DiCarlo L, DeMets D, White BG, DeVries DW, Feldman AM. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med*. 2004;350:2140-2150.
4. Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt OA, Cleland J, Deharo JC, Delgado V, Elliott PM, Gorenek B, Israel CW, Leclercq C, Linde C, Mont L, Padeletti L, Sutton R, Vardas PE, Guidelines ESCCfP, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S, Document R, Kirchhof P, Blomstrom-Lundqvist C, Badano LP, Aliyev F, Bansch D, Baumgartner H, Bsata W, Buser P, Charron P, Daubert JC, Dobreanu D, Faerestrand S, Hasdai D, Hoes AW, Le Heuzey JY, Mavrakis H, McDonagh T, Merino JL, Nawar MM, Nielsen JC, Pieske B, Poposka L, Ruschitzka F, Tendera M, Van Gelder IC, Wilson CM. 2013 esc guidelines on cardiac pacing and cardiac resynchronization therapy: The task force on cardiac pacing and resynchronization therapy of the european society of cardiology (esc). Developed in collaboration with the european heart rhythm association (ehra). *Eur Heart J*. 2013;34:2281-2329.
5. Khan NK, Goode KM, Cleland JG, Rigby AS, Freemantle N, Eastaugh J, Clark AL, de Silva R, Calvert MJ, Swedberg K, Komajda M, Mareev V, Follath F. Prevalence of ecg abnormalities in an international survey of patients with suspected or confirmed heart failure at death or discharge. *Eur J Heart Fail*. 2007;9:491-501.

6. Ruschitzka F, Abraham WT, Singh JP, Bax JJ, Borer JS, Brugada J, Dickstein K, Ford I, Gorcsan J, 3rd, Gras D, Krum H, Sogaard P, Holzmeister J, Echo CRTSG. Cardiac-resynchronization therapy in heart failure with a narrow qrs complex. *N Engl J Med*. 2013;369:1395-1405.
7. Varma N, Manne M, Nguyen D, He J, Niebauer M, Tchou P. Probability and magnitude of response to cardiac resynchronization therapy according to qrs duration and gender in nonischemic cardiomyopathy and lbbb. *Heart Rhythm*. 2014;11:1139-1147.
8. Zusterzeel R, Selzman KA, Sanders WE, Canos DA, O'Callaghan KM, Carpenter JL, Pina IL, Strauss DG. Cardiac resynchronization therapy in women: Us food and drug administration meta-analysis of patient-level data. *JAMA internal medicine*. 2014;174:1340-1348.
9. Woo GW, Petersen-Stejskal S, Johnson JW, Conti JB, Aranda JA, Jr., Curtis AB. Ventricular reverse remodeling and 6-month outcomes in patients receiving cardiac resynchronization therapy: Analysis of the miracle study. *J Interv Card Electrophysiol*. 2005;12:107-113.
10. Raftopoulou M, Hall A. Cell migration: Rho gtpases lead the way. *Dev Biol*. 2004;265:23-32.
11. Zabarovskaja S, Gadler F, Braunschweig F, Stahlberg M, Hornsten J, Linde C, Lund LH. Women have better long-term prognosis than men after cardiac resynchronization therapy. *Europace*. 2012;14:1148-1155.
12. Saxon LA, Bristow MR, Boehmer J, Krueger S, Kass DA, De Marco T, Carson P, DiCarlo L, Feldman AM, Galle E, Ecklund F. Predictors of sudden cardiac death and appropriate shock in the comparison of medical therapy, pacing, and defibrillation in heart failure (companion) trial. *Circulation*. 2006;114:2766-2772.
13. Gasparini M, Regoli F, Ceriotti C, Galimberti P, Bragato R, De Vita S, Pini D, Andreuzzi B, Mangiavacchi M, Klersy C. Remission of left ventricular systolic dysfunction and of heart failure symptoms after cardiac resynchronization therapy: Temporal pattern and clinical predictors. *Am Heart J*. 2008;155:507-514.
14. Kutyifa V, Kloppe A, Zareba W, Solomon SD, McNitt S, Polonsky S, Barsheshet A, Merkely B, Lemke B, Nagy VK, Moss AJ, Goldenberg I. The influence of left ventricular ejection fraction on the effectiveness of cardiac resynchronization therapy: Madit-crt (multicenter automatic defibrillator implantation trial with cardiac resynchronization therapy). *J Am Coll Cardiol*. 2013;61:936-944.

15. Steffel J, Ruschitzka F. Superresponse to cardiac resynchronization therapy. *Circulation*. 2014;130:87-90.
16. Taneja T, Mahnert BW, Passman R, Goldberger J, Kadish A. Effects of sex and age on electrocardiographic and cardiac electrophysiological properties in adults. *Pacing Clin Electrophysiol*. 2001;24:16-21.
17. Casale PN, Devereux RB, Alonso DR, Campo E, Kligfield P. Improved sex-specific criteria of left ventricular hypertrophy for clinical and computer interpretation of electrocardiograms: Validation with autopsy findings. *Circulation*. 1987;75:565-572.
18. Arshad A, Moss AJ, Foster E, Padeletti L, Barsheshet A, Goldenberg I, Greenberg H, Hall WJ, McNitt S, Zareba W, Solomon S, Steinberg JS, Committee M-CE. Cardiac resynchronization therapy is more effective in women than in men: The madit-crt (multicenter automatic defibrillator implantation trial with cardiac resynchronization therapy) trial. *J Am Coll Cardiol*. 2011;57:813-820.
19. Wilkoff BL, Cook JR, Epstein AE, Greene HL, Hallstrom AP, Hsia H, Kutalek SP, Sharma A. Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator: The dual chamber and vvi implantable defibrillator (david) trial. *Jama*. 2002;288:3115-3123.
20. Diaz-Infante E, Mont L, Leal J, Garcia-Bolao I, Fernandez-Lozano I, Hernandez-Madrid A, Perez-Castellano N, Sitges M, Pavon-Jimenez R, Barba J, Cavero MA, Moya JL, Perez-Isla L, Brugada J, Investigators S. Predictors of lack of response to resynchronization therapy. *Am J Cardiol*. 2005;95:1436-1440.
21. Hsu JC, Solomon SD, Bourgoun M, McNitt S, Goldenberg I, Klein H, Moss AJ, Foster E. Predictors of super-response to cardiac resynchronization therapy and associated improvement in clinical outcome: The madit-crt (multicenter automatic defibrillator implantation trial with cardiac resynchronization therapy) study. *J Am Coll Cardiol*. 2012;59:2366-2373.
22. Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, Estes NA, 3rd, Foster E, Greenberg H, Higgins SL, Pfeffer MA, Solomon SD, Wilber D, Zareba W. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med*. 2009;361:1329-1338.
23. Tang AS, Wells GA, Talajic M, Arnold MO, Sheldon R, Connolly S, Hohnloser SH, Nichol G, Birnie DH, Sapp JL, Yee R, Healey JS, Rouleau JL. Cardiac-resynchronization therapy for mild-to-moderate heart failure. *N Engl J Med*. 2010;363:2385-2395.

24. Lund LH, Mancini D. Heart failure in women. *The Medical clinics of North America*. 2004;88:1321-1345, xii.
25. Dickstein K, Bogale N, Priori S, Auricchio A, Cleland JG, Gitt A, Limbourg T, Linde C, van Veldhuisen DJ, Brugada J. The european cardiac resynchronization therapy survey. *Eur Heart J*. 2009;30:2450-2460.
26. Peterson PN, Daugherty SL, Wang Y, Vidaillet HJ, Heidenreich PA, Curtis JP, Masoudi FA, National Cardiovascular Data R. Gender differences in procedure-related adverse events in patients receiving implantable cardioverter-defibrillator therapy. *Circulation*. 2009;119:1078-1084.

Tables

Tab. 1: Baseline characteristics

For categorical variables number and percentage are reported; for continuous variables mean and standard deviation are reported (except for BNP and NT-proBNP where median and inter-quartile range are presented). * p-value not reported due to small numbers.

Variable	Females	Males	P-value
Age (years)	57.5 (13.62)	58.2 (12.38)	0.482
QRS width (msec; site)	102.4 (12.89)	106.3 (12.70)	**<0.001**
QRS width (msec; core)	102.3 (13.35)	107.1 (12.01)	**<0.001**
Walking distance (m)	286.7 (120.64)	340.4 (116.84)	<0.001
Quality of life score	54.4 (24.15)	50.0 (24.21)	**0.021**
NYHA Classification			
I	0 (0.00%)	5 (0.85%)	*
II	3 (1.34%)	16 (2.74%)	
III	213 (95.09%)	546 (93.33%)	
IV	8 (3.57%)	18 (3.08%)	
BNP (pg/ml)	225.0 (102.00, 471.00)	251.0 (75.00, 515.00)	0.927
NT-proBNP (pg/ml)	1275.0 (610.00, 2124.0)	1095.5 (449.50, 2408.5)	0.604
Sitting SBP (mmHg)	117.6 (18.11)	119.3 (19.87)	0.271
Sitting DBP (mmHg)	71.4 (11.18)	73.3 (12.20)	**0.039**
BMI (kg/m2)	31.7 (14.80)	30.5 (10.98)	0.212
Ischemic cardiomyopathy	88 (39.29%)	344 (58.90%)	**<0.001**
MI > 3 months ago	66 (29.46%)	256 (43.76%)	**<0.001**
PCI > 3 months ago	70 (31.25%)	218 (37.26%)	0.110
CABG > 3 months ago	23 (10.27%)	128 (21.88%)	**<0.001**
Hypertension	146 (66.06%)	387 (66.61%)	0.884
Congenital heart disease	2 (0.92%)	14 (2.42%)	0.259
Prior ischemic stroke or TIA	27 (12.22%)	69 (11.86%)	0.888
Diabetes mellitus	95 (42.79%)	225 (38.53%)	0.269
Chronic lung disease	40 (18.02%)	109 (18.79%)	0.801
Chronic kidney disease	22 (9.95%)	86 (14.78%)	0.074
LVEF Biplane (%)	27.2 (5.39)	26.9 (5.63)	0.477
LV end diastolic dimeter (mm)	64.1 (6.84)	67.3 (7.62)	**<0.001**
Qualified by TDI and/or radial dyssynchrony			
Tissue Doppler imaging only	50 (22.32%)	152 (26.03%)	0.050
Radial strain only	42 (18.75%)	143 (24.49%)	
TDI and radial strain	132 (58.93%)	289 (49.49%)	
Medication at study entry			
ACE inhibitor or ARB	212 (94.64%)	555 (94.87%)	0.896
Aldosterone antagonist	130 (58.04%)	355 (60.68%)	0.492
Beta-blocker	216 (96.43%)	566 (96.75%)	0.828
Diuretic agent	206 (91.96%)	492 (84.10%)	**0.004**

<u>Tab. 2:</u> Primary Safety Endpoint in female and male patients (complication-free rate within 6 months of implantation)

	Female patients (%) Complication-Free (n total =237)	**Male patients (%) Complication-Free (n total =618)**	**p int**
CRT-D system	216 (91.14%)	569 (92.07%)	0.66
Implant procedure	232 (97.89%)	605 (97.90%)	1
Other	236 (99.58%)	617 (99.84%)	0.50
Any of the above	210 (88.61%)	556 (89.97%)	0.56

Tab. 3: CRT system related serious adverse events during the whole trial

N = Number of events; N pts = Number of patients with events

	Female patients				**Male patients**				**p int**
	CRT=ON (N= 110)		***CRT=OFF (N= 114)***		***CRT=ON (N=294)***		***CRT=OFF (N=291)***		
	N	N pts.	N	N pts.	N	N pts.	N	N pts.	
CRT system related	26	19 (17.27%)	7	7 (6.14%)	48	36 (12.24%)	25	22 (7.56%)	0.25
ICD lead	10	9 (8.18%)	2	2 (1.75%)	16	14 (4.76%)	11	11 (3.78%)	0.13
RA pacing lead	7	5 (4.55%)	1	1 (0.88%)	14	13 (4.42%)	4	4 (1.37%)	0.70
LV pacing lead	7	6 (5.45%)	2	2 (1.75%)	14	12 (4.08%)	2	2 (0.69%)	0.57
Implantation related	6	6 (5.45%)	3	3 (2.63%)	13	11 (3.74%)	15	13 (4.47%)	0.26

Figure Legends

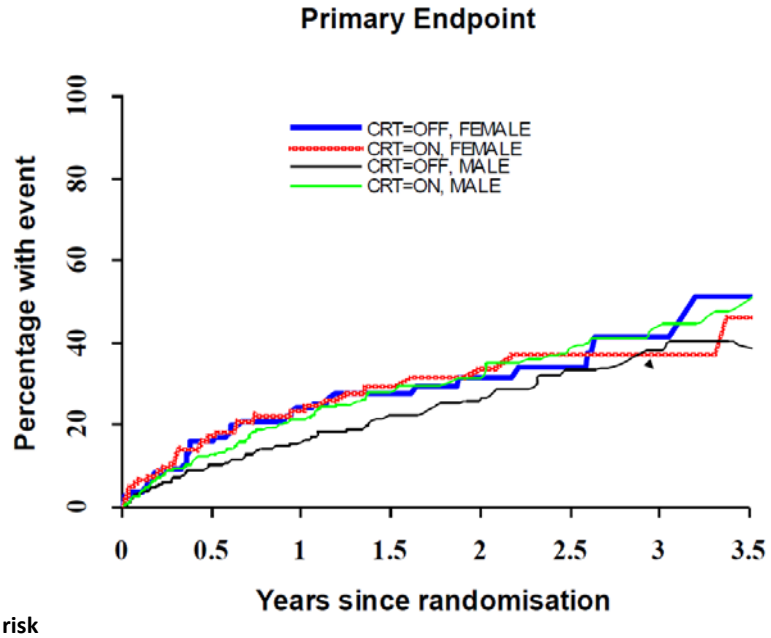
Fig 1.: Kaplan–Meier Estimates for Primary-Outcome Events, stratified by gender.
Kaplan–Meier curves for the primary composite efficacy outcome of death from any cause or hospitalization for heart failure, as well as the secondary endpoints in patients randomized to CRT-ON and CRT-OFF , stratified by gender.

Fig 2: Effect of CRT in female (upper, black) and male (lower, red) patients.
Hazard ratio (HR; 95% confidence interval (CI)) adjusted for country and p-value from Wald test are presented.

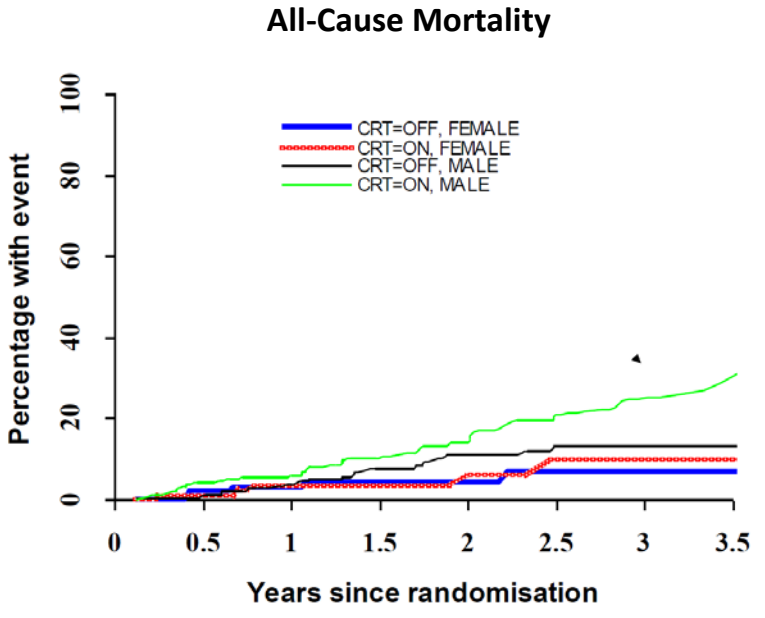
Fig. 3: Effect of CRT in female (upper, black) and male (lower, red) patients after multivariable adjustment
Hazard ratio (95% confidence interval) adjusted for country, QRS width, walking distance, QOL score, sitting DBP, ischemic cardiomyopathy, history of myocardial infarction, history of CABG, LVEDD, diuretic agent use (p-value from Wald test.)

Fig 1.: Kaplan–Meier Estimates for Primary-Outcome Events, stratified by gender.

Kaplan–Meier curves for the primary composite efficacy outcome of death from any cause or hospitalization for heart failure, as well as the secondary endpoints in patients randomized to CRT-ON and CRT-OFF , stratified by gender.



No. At risk								
CRT=OFF, FEMALE	114	86	67	49	32	19	12	2
CRT=ON, FEMALE	110	73	56	38	27	16	9	5
CRT=OFF, MALE	291	216	169	117	87	52	32	13
CRT=ON, MALE	294	224	167	117	76	49	33	14



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CRT=OFF, FEMALE	114	86	67	49	32	19	12	2
CRT=ON, FEMALE	110	73	56	38	27	16	9	5
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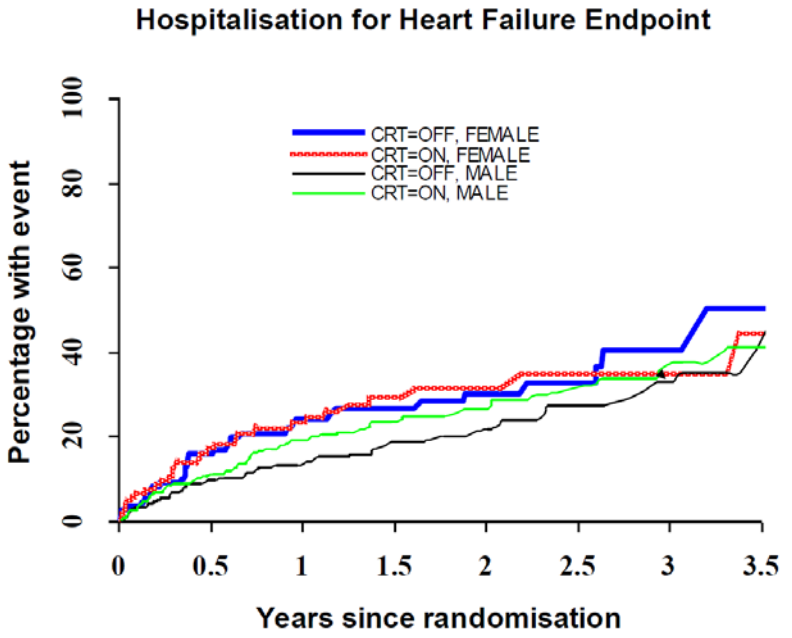

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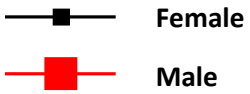
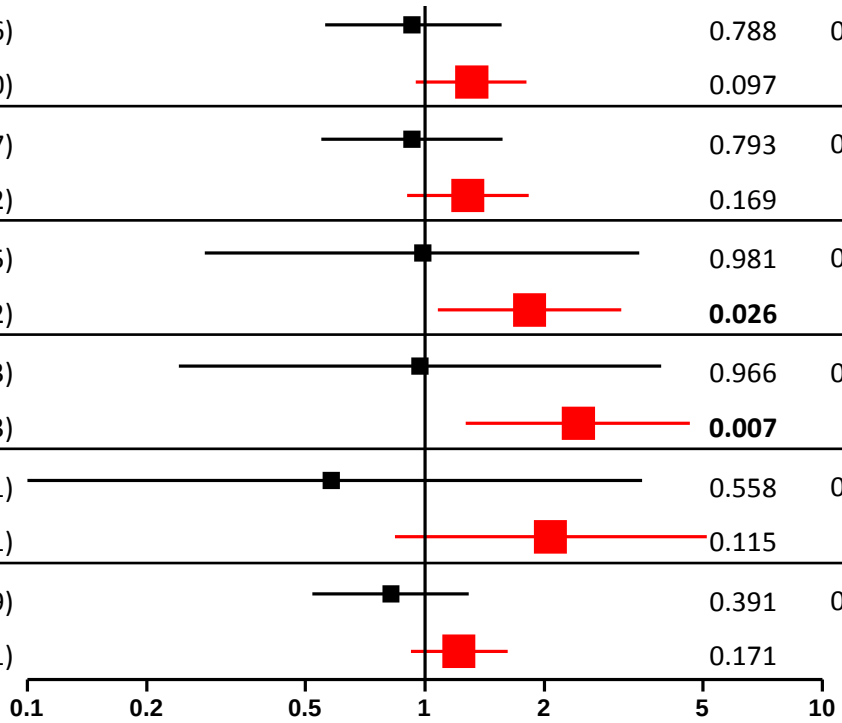


Endpoint	CRT=OFF	CRT=ON	Adjusted HR (95% CI)	P-value	p int.
Death or WHF	34 (29.82%)	30 (27.27%)	0.93 (0.56 - 1.56)	0.788	0.428
hospitalisation	68 (23.37%)	86 (29.25%)	1.31 (0.95 - 1.80)	0.097	
WHF hospitalisation	33 (28.95%)	29 (26.36%)	0.93 (0.55 - 1.57)	0.793	0.474
	57 (19.59%)	70 (23.81%)	1.28 (0.90 - 1.82)	0.169	
All cause mortality	5 (4.39%)	5 (4.55%)	0.99 (0.28 - 3.45)	0.981	0.560
	21 (7.22%)	40 (13.61%)	1.83 (1.08 - 3.12)	**0.026**	
Cardiovascular mortality	4 (3.51%)	4 (3.64%)	0.97 (0.24 - 3.93)	0.966	0.371
	13 (4.47%)	33 (11.22%)	2.43 (1.27 - 4.63)	**0.007**	
Heart failure mortality	3 (2.63%)	2 (1.82%)	0.58 (0.10 - 3.51)	0.558	0.322
	7 (2.41%)	15 (5.10%)	2.07 (0.84 - 5.11)	0.115	
Cardiovascular	45 (39.47%)	37 (33.64%)	0.82 (0.52 - 1.29)	0.391	0.249
hospitalisation	92 (31.62%)	110 (37.41%)	1.22 (0.92 - 1.61)	0.171	



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Hazard ratio (95% confidence interval) adjusted for country, QRS width, walking distance, QOL score, sitting DBP, ischemic cardiomyopathy, history of myocardial infarction, history of CABG, LVEDD, diuretic agent use (p-value from Wald test.)