

Sex-Specific Differences in Survival and Heart Failure Hospitalization After Cardiac Resynchronization Therapy With or Without Defibrillation

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Background—Women are underrepresented in cardiac resynchronization therapy (CRT) trials. Some studies suggest that women fare better than men after CRT. We sought to explore clinical outcomes in women and men undergoing CRT-defibrillation or CRT-pacing in real-world clinical practice.

Methods and Results—A national database (Hospital Episode Statistics for England) was used to quantify clinical outcomes in 43 730 patients (women: 10 890 [24.9%]; men: 32 840 [75.1%]) undergoing CRT over 7.6 years, (median follow-up 2.2 years, interquartile range, 1–4 years). In analysis of the total population, the primary end point of total mortality (adjusted hazard ratio [aHR], 0.73; 95% CI, 0.69–0.76) and the secondary end point of total mortality or heart failure hospitalization (aHR, 0.79, 95% CI 0.75–0.82) were lower in women, independent of known confounders. Total mortality (aHR, 0.73; 95% CI, 0.70–0.76) and total mortality or heart failure hospitalization (aHR, 0.79; 95% CI, 0.75–0.82) were lower for CRT-defibrillation than for CRT-pacing. In analyses of patients with (aHR, 0.89; 95% CI, 0.80–0.98) or without (aHR, 0.70; 95% CI, 0.66–0.73) a myocardial infarction, women had a lower total mortality. In sex-specific analyses, total mortality was lower after CRT-defibrillation in women (aHR, 0.83; $P=0.013$) and men (aHR, 0.69; $P<0.001$).

Conclusions—Compared with men, women lived longer and were less likely to be hospitalized for heart failure after CRT. In both sexes, CRT-defibrillation was superior to CRT-pacing with respect to survival and heart failure hospitalization. The longest survival after CRT was observed in women without a history of myocardial infarction. (*J Am Heart Assoc.* 2019;8:e013485. DOI: 10.1161/JAHA.119.013485.)

Key Words: cardiac resynchronization therapy • female sex • implantable cardioverter defibrillator

Cardiac resynchronization therapy (CRT) is a standard treatment for selected patients with heart failure (HF), impaired left ventricular (LV) function and a wide QRS complex. Sex-specific differences in the outcome of CRT

was first shown by the MIRACLE (Multicenter InSync Randomized Clinical Evaluation) study,¹ in which CRT was associated with a higher survival free of HF hospitalization in women than in men, compared with optimum pharmacologic therapy. A substudy of MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy) showed that survival and survival free of HF hospitalization from CRT-defibrillation (CRT-D) compared with implantable cardioverter-defibrillator (ICD) therapy was higher in women.² Data from the US National Cardiovascular Data Registry also showed that among patients with a left bundle branch block, the benefit from CRT-D over ICD was greater in women than in men.³ Better outcomes in women have also been reported by other observational studies.^{4–7} and meta-analyses.⁸ In contrast, sex-specific differences in survival were not observed in COMPANION (Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure)⁹ or CARE-HF (Cardiac Resynchronization Heart Failure).¹⁰

Randomized controlled trials are the cornerstone of evidence-based medicine. However, randomized controlled trials

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An accompanying Table S1 is available at <https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.013485>

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Clinical Perspective

What Is New?

- In this study of over 43 000 patients, women survived longer and were less likely to be hospitalized for heart failure after cardiac resynchronization therapy (CRT).
- In both women and men, survival and heart failure hospitalization were lower after CRT-defibrillation than after CRT-pacing, in both women and men.
- The lowest mortality after CRT was observed in women without a history of myocardial infarction.

What Are the Clinical Implications?

- The longer survival after CRT in women should be considered at the time of deciding on device therapy for women, in whom the uptake of device therapy is disproportionately low worldwide.

tend to comprise a small number of highly selected patients and a relatively short follow-up. On the other hand, studies using large administrative data sets have the advantage of large numbers and a long follow-up but typically lack granularity. In this context, there is a clear compromise between “wealth of numbers” and “wealth of detail.” Notwithstanding these constraints, it is useful to confirm whether the findings of randomized controlled trials are also observed in large data sets that reflect real-world clinical practice.

In this study, we explore sex-specific differences in the outcomes of CRT in a large, real-world population of CRT recipients over a long follow-up period. In addition, we address the relative benefits of CRT-D versus CRT-pacing (CRT-P) in women and men, with or without a history of myocardial infarction (MI).

Methods

Data Sources

This is a nonrandomized, retrospective study exploring total mortality and HF hospitalization after a first CRT device implantation. We have used the National Health Service Hospital Episode Statistics, a data warehouse containing data on all admissions to all public hospitals in England. Mortality data were linked with the Office of National Statistics. These data are available to the University Hospital Birmingham under a data-sharing agreement (section 251 of the National Health Service Act 2006), which obviates the need for ethics committee approval and patient consent. The data presented herein will not be made available to other researchers, as it is only provided to researchers with the conditions of this data sharing agreement. The study was approved by the Clinical

Audit Department at the Queen Elizabeth Hospital, which also waives patient consent. The study conforms to the Declaration of Helsinki.

Our sample included patients who had their first CRT device implantation between April 1, 2009, and December 1, 2016, in England. This period was chosen because of the introduction of reliable coding of CRT-D and CRT-P through the National Tariff. Second (“redo”) operations were excluded. The underlying etiology of cardiomyopathy or device indication (primary or secondary prevention) was not considered. Patients who had received an ICD without CRT were excluded. This study was undertaken in the context of the United Kingdom’s National Institute of Clinical Excellence (NICE) guidelines, which before 2007 recommended CRT-D only in the setting of secondary prevention. After 2007, the National Institute of Clinical Excellence recommended CRT-P rather than CRT-D for patients with nonischemic cardiomyopathy.¹¹ In 2014, the National Institute of Clinical Excellence recommended CRT-D for patients with nonischemic cardiomyopathy.¹¹ Consequently, up to 2014, a large proportion of patients with nonischemic cardiomyopathy received CRT-P rather than CRT-D.

End Points

The primary end point was total mortality. The secondary end point was total mortality or HF hospitalization, defined as the dominant diagnosis in the *International Classification of Diseases, Tenth Revision (ICD-10)* code I50, that is, the primary diagnosis of the first episode of HF in the hospital stay. Only data relating to the first event (death or HF hospitalization) were used in these analyses. Table S1 lists the codes used according to *ICD-10* and the Office of Population Censuses and Surveys Classification of Interventions and Procedures-4. Indicator specification and hospital-level mortality indicators (Health and Social Care Information Centre)¹² were used to minimize missing information.

Comorbidities

The Hospital Episode Statistics for England extends from 2002 to the present. Patients were regarded as having hypertension, diabetes mellitus, chronic kidney disease, and/or MI if these diagnoses appeared as primary or secondary diagnoses in any hospital stay before or at the time of device implantation.

Statistical Analysis

Continuous variables are expressed as mean (\pm SD) and compared using the Student *t* test. Categorical variables were compared using the chi-squared statistic. Kaplan–Meier curves and the log-rank test were used to assess observed cumulative survival. Cox proportional hazard models were

used to compare risks of total mortality and total mortality or HF hospitalization. Proportionality hypotheses were first verified by visual examination of log (survival) graphs to ensure parallel slopes, and then formally on the basis of Schoenfeld residuals after fitting Cox models. As the assumption of proportionality failed for age and device type, we fitted further Cox models to take into account these time-varying effects (ie, nonproportional effects). The presence of multiple interactions between explanatory variables with sex led to additional parallel analyses by sex. Statistical analyses were undertaken using Stata 14 (StataCorp, College Station, TX). A 2-sided $P \leq 0.05$ was considered statistically significant.

Results

Baseline Characteristics

Over the study period of 7.6 years, 43 730 patients underwent CRT implantation (women, 10 890 [24.9%]; men, 32 840 [75.1%]). More men (18 357 [55.9%]) than women (4283 [39.3%]) underwent CRT-D rather than CRT-P (Table). Because of the high numbers involved, statistically significant differences ($P < 0.001$) were observed with respect to all baseline characteristics, despite being numerically small. Women were younger (by 0.4 years) and were less likely to have hypertension (64.4% versus 67.8%), diabetes mellitus (24% versus 29%), chronic kidney disease (12.8% versus 15.1%), or MI (14% versus 22.3%).

Table. Characteristics of the Study Group

	Men	Women
N	32 840 (75.1)	10 890 (24.9)
Age, y	71.2±11	70.8±12.5
<60	4659 (14.19)	1747 (16.04)
60–69	7757 (23.62)	2344 (21.52)
70–79	12 687 (38.63)	4145 (38.06)
≥80	7737 (23.56)	2654 (24.37)
Hypertension	22 275 (67.83)	7013 (64.4)
Diabetes mellitus	9525 (29.0)	2616 (24.02)
Chronic kidney disease	4948 (15.07)	1394 (12.8)
MI	7328 (22.31)	1524 (13.99)
Device type		
CRT-D	18 357 (55.9)	4283 (39.33)
CRT-P	14 483 (44.1)	6607 (60.67)

Variables are expressed as n (%). All comparisons between women and men were significant ($P < 0.001$). CRT-D indicates cardiac resynchronization therapy–defibrillation; CRT-P, cardiac resynchronization therapy–pacing; MI, myocardial infarction.

Total Mortality

Over a median follow-up of 2.2 years (interquartile range, 1–4 years), a total of 11 030 patients (25.2%) died, corresponding to 2210 (20.3%) for women and 8820 (26.9%) for men. As shown in Figure 1, women had a lower total mortality than men ($P < 0.001$). When stratified according to device type, CRT-D in women was associated with the lowest absolute mortality (Figure 2). In multivariable analyses of the total population, total mortality (adjusted hazard ratio [aHR], 0.73; 95% CI, 0.70–0.76) after CRT was lower in women, independent of age; device type (CRT-P or CRT-D); or history of hypertension, diabetes mellitus, chronic kidney disease, or MI (Figure 3A). Similar findings emerged in within-sex analyses.

HF Hospitalization

In Kaplan–Meier survival analyses (Figure 1), women had a lower total mortality or HF hospitalization ($P < 0.001$). When stratified according to device type, CRT-D in women was associated with the lowest absolute total mortality or HF hospitalization (Figure 2). In multivariable analyses of the total population, total mortality or HF hospitalization was lower in women (aHR, 0.79; 95% CI, 0.75–0.82), independent of known confounders (Figure 3B). In within-sex analyses, CRT-D was superior to CRT-P with respect to total mortality or HF hospitalization in men (aHR, 0.76; 95% CI, 0.72–0.81), but not in women (aHR, 0.90; 95% CI, 0.80–1.01) (Figure 3B).

CRT-D Versus CRT-P

In the total population, CRT-D was associated with a lower total mortality (aHR, 0.70; 95% CI, 0.66–0.75) and total mortality or HF hospitalization (aHR, 0.78; 95% CI, 0.74–0.82) (Figures 2 and 3). In separate analyses of women and men, CRT-D was also associated with a lower mortality. With respect to total mortality or HF hospitalization, CRT-D was associated with a lower risk in men (aHR, 0.76; 95% CI, 0.72–0.81) but not in women (aHR, 0.90; 95% CI, 0.80–1.01) (Figures 2 and 3).

Influence of MI

In Kaplan–Meier survival analyses of patients with a history of MI, no differences in total mortality or total mortality or HF hospitalizations emerged between women and men (Figure 4). In multivariable analyses of patients with a history of MI, total mortality (aHR, 0.89; 95% CI, 0.80–0.98) and total mortality or HF hospitalization (aHR, 0.89; 95% CI, 0.82–0.98) after CRT were lower in women (Figure 5A). In patients without a history of MI, total mortality (aHR, 0.70; 95% CI,

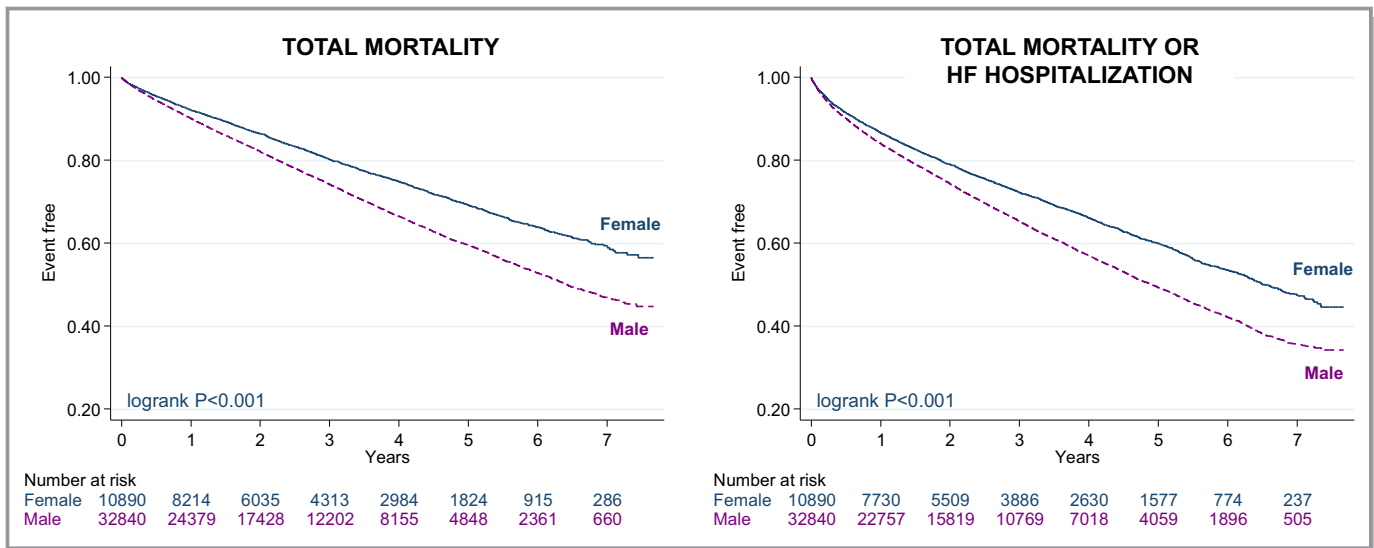


Figure 1. Clinical outcomes after cardiac resynchronization therapy according to sex.

0.66–0.73) and total mortality or HF hospitalization (aHR, 0.76; 95% CI, 0.73–0.80) after CRT were also lower in women (Figures 5B).

Discussion

Several findings have emerged from this study of a large, real-world population of patients undergoing CRT. First, women lived longer and were less likely to be hospitalized for HF after CRT. Second, total mortality and total mortality or HF hospitalization were lower after CRT-D than after CRT-P in both women and men. Third, survival after CRT in women was longest in those without a history of MI.

Total Mortality and HF Hospitalization

We have found that CRT was associated with a better survival and survival free of HF hospitalization in women. These findings are in keeping with a substudy of MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy), the magnitude of the benefit from CRT-D versus ICD in terms of survival or survival free of HF hospitalization was better in women (25% of the study population) than in men.² They are also consistent with the findings from MIRACLE,¹ in which women had a better survival free of HF hospitalization than men, compared with optimum pharmacologic therapy. Moreover, they are in line with registry data from the US

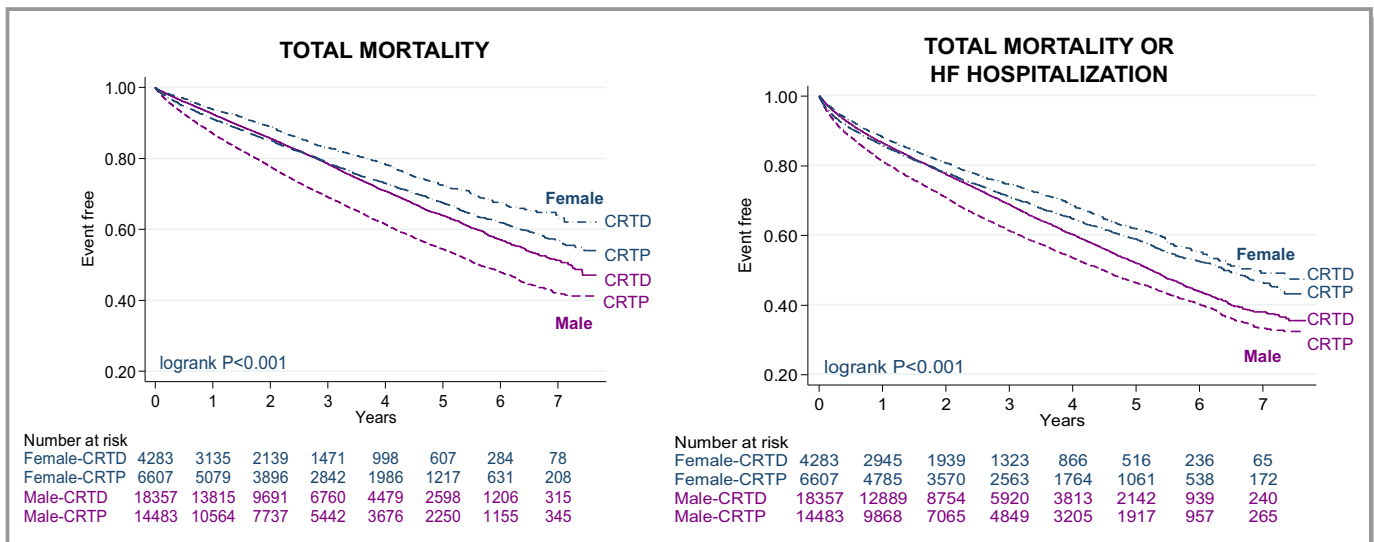


Figure 2. Clinical outcomes after cardiac resynchronization therapy according to sex and device type. Kaplan–Meier survival curves for study end points according to sex and device type. CRT-D indicates cardiac resynchronization therapy–defibrillation; CRT-P, cardiac resynchronization therapy–pacing; HF, heart failure.

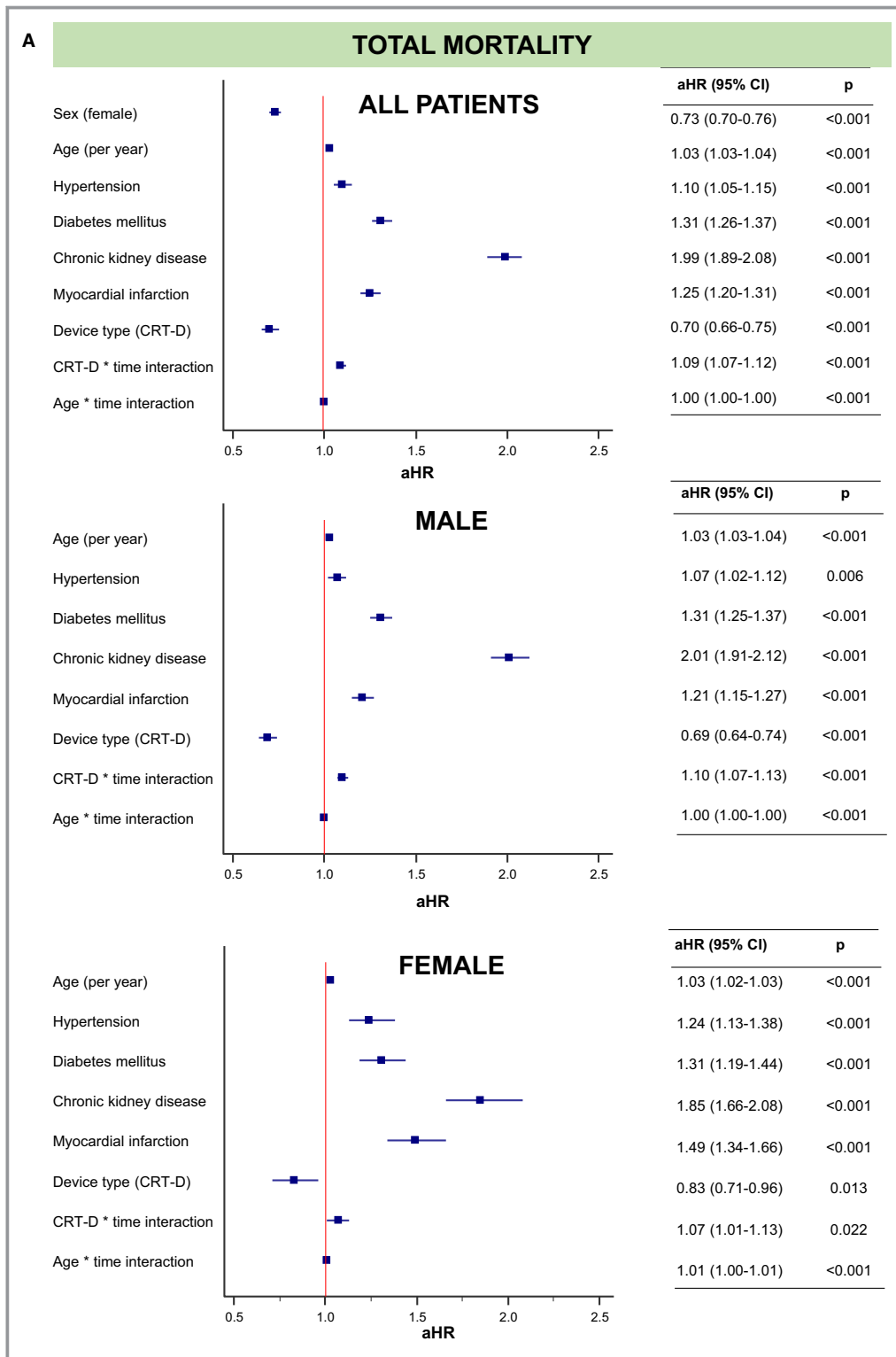


Figure 3. Multivariable analyses. Analyses refer to (A) total mortality and (B) total mortality or heart failure (HF) hospitalization. Results are shown in terms of adjusted hazard ratios (aHR) and 95% CI. CRT-D indicates cardiac resynchronization therapy–defibrillation.

National Cardiovascular Data Registry, in which benefit from CRT-D over ICD was greater in women than in men with a left bundle branch block.³ In a metaanalysis of 33 434

patients from 72 studies, women had an ~33% reduction in total mortality and 20% reduction in total mortality or HF hospitalization after CRT.⁸ This is comparable with the

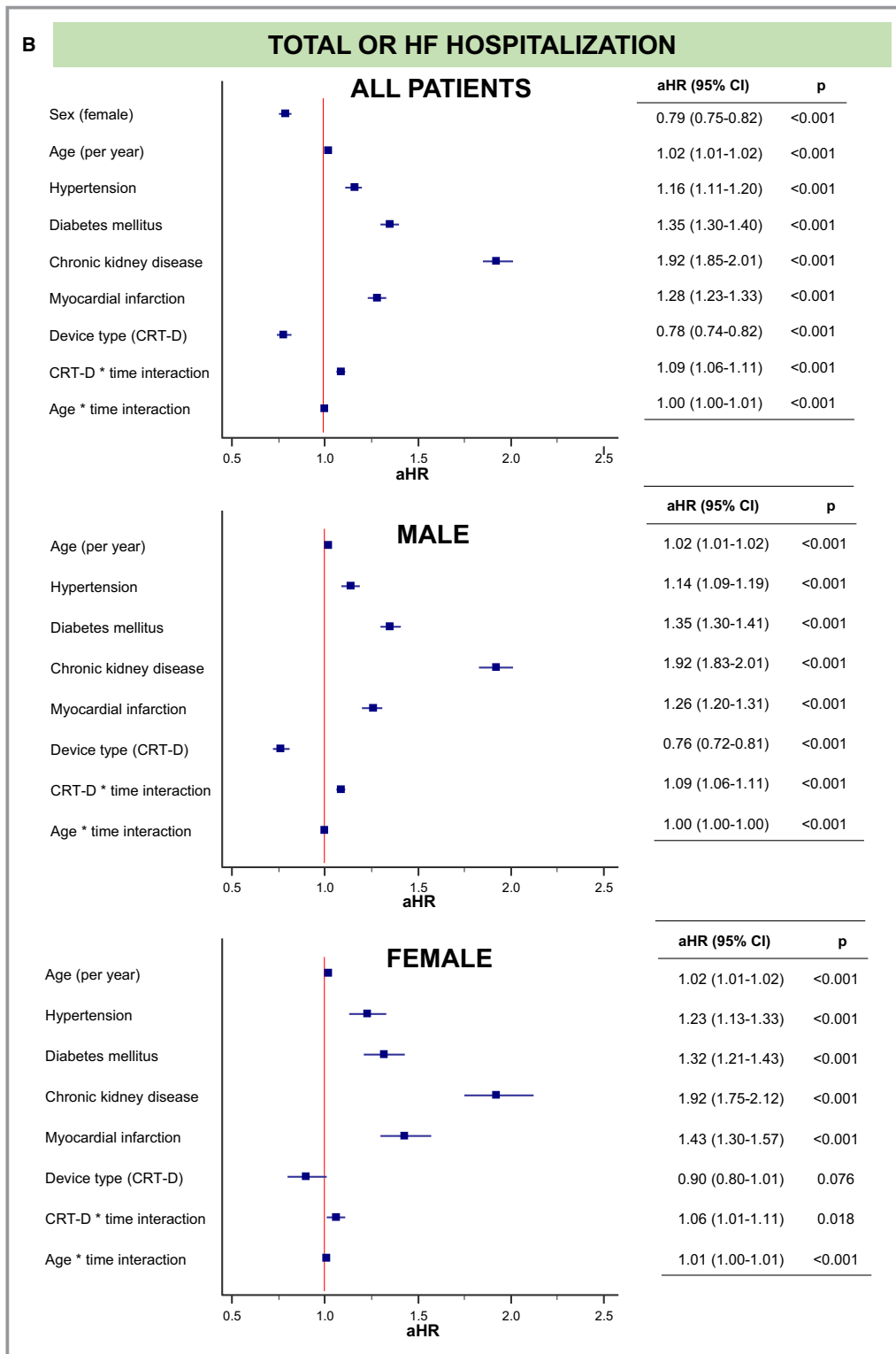


Figure 3. Continued

reductions observed after CRT in women versus men in the present study (27% and 21%, respectively).

The reasons for better outcomes after CRT in women are unclear. We have observed, however, that women were less

likely to have had an MI (14% versus 22%, respectively) and that the survival advantage of women over men after CRT was higher in those without a history of MI. This suggests that at least some of the survival benefit from CRT in women over men relates to

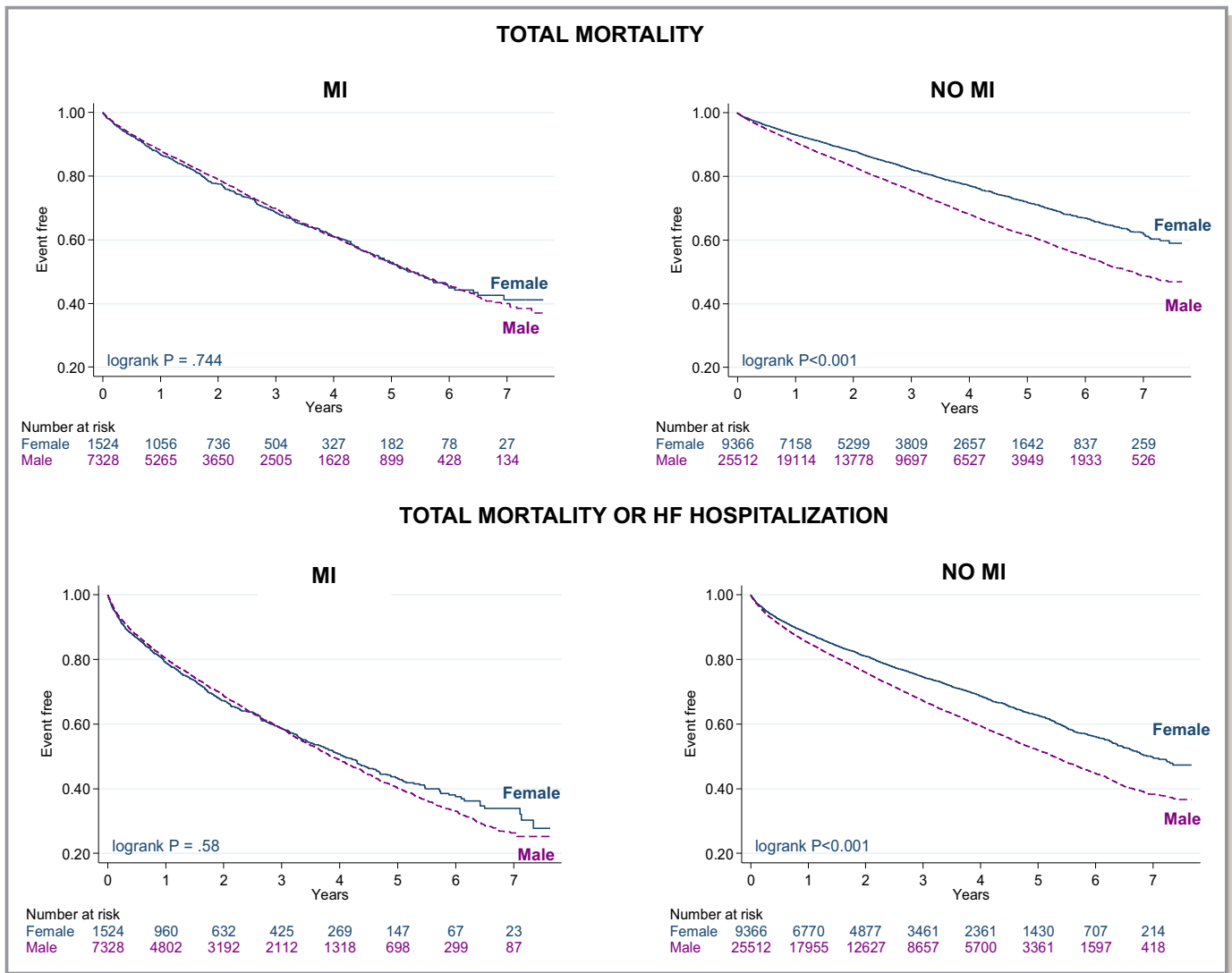


Figure 4. Clinical outcomes after cardiac resynchronization therapy according to sex and history of MI. Kaplan–Meier survival curves according to sex and history of MI. HF indicates heart failure; MI, myocardial infarction.

the etiology of the underlying cardiomyopathy. In this respect, several studies have shown that CRT in women is better in those with nonischemic cardiomyopathy.^{7,13,14} In multivariable analyses comprising MI as a covariable, the HR for CRT-D versus CRT-P was lower in men (0.69; $P < 0.001$) than in women (0.83; $P = 0.013$), suggesting a lower efficacy of CRT-D in women.

Another explanation for a sex-specific difference in CRT response may relate to QRS duration, which is shorter in healthy women and in women undergoing CRT.¹⁵ Accordingly, conduction disturbances and LV dyssynchrony may be more prevalent in women at a given QRS duration, perhaps accounting for their superior benefit from CRT. Another contributing factor may be the correlation between QRS duration and cardiac as well as body size.¹⁶ In this respect, it is possible that men have a longer QRS duration simply because of LV mass and body size, rather than LV dyssynchrony.¹⁷

The possible effects of estrogen and testosterone on CRT response has not been explored. It is noteworthy that in the Danish Osteoporosis Prevention Study, hormone replacement therapy in women was associated with a reduced lower risk of the composite end point of mortality, HF, and MI.¹⁸ On the other hand, hormone replacement therapy is associated with lower LV end-diastolic volumes and left atrial volumes,¹⁹ both of which have been associated with better clinical outcomes in patients with HF. These findings raise the possibility that menopausal status may influence the CRT response. Unfortunately, our data set does not include menopausal status.

CRT-D Versus CRT-P

Individual studies and metaanalyses⁸ on sex-specific differences in outcomes after CRT have used different comparators, and it is

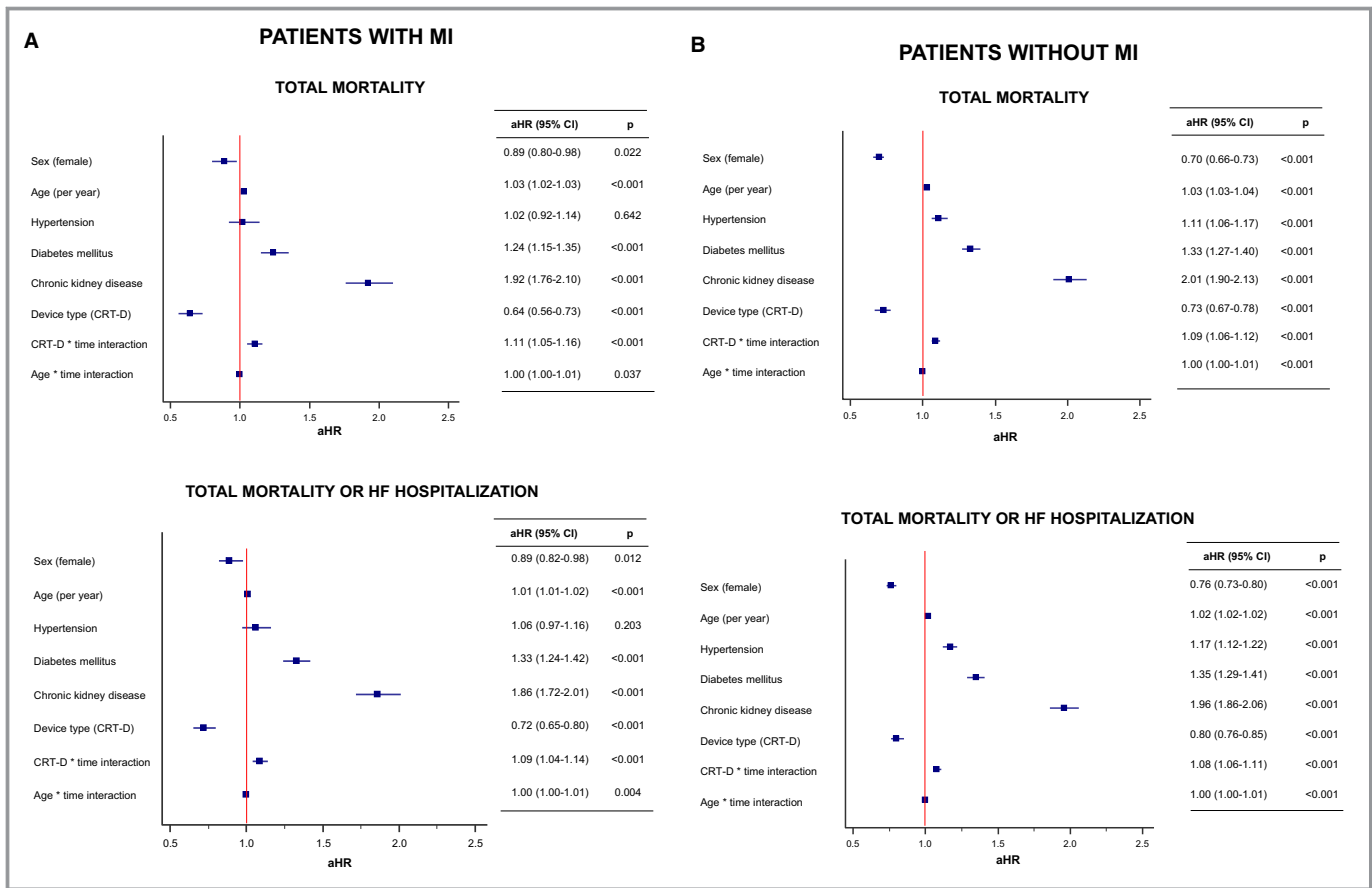


Figure 5. Multivariable analyses: influence of myocardial infarction (MI). Analyses refer to patients with (A) or without (B) a history of MI. Results are shown in terms of adjusted hazard ratio (aHR) and 95% CI. CRT-D indicates cardiac resynchronization therapy–defibrillation; HF, heart failure.

therefore difficult to determine whether the more favorable effects of CRT in women are due to resynchronization or defibrillation. In this respect, the MADIT-CRT subanalysis, which compared CRT-D with ICD, found more favorable outcomes in women,² suggesting that the survival benefit from CRT-D over ICD in women was due to resynchronization per se. Arguably, the answer to this question lies in comparisons of CRT-D versus CRT-P. In a recent retrospective study of propensity-matched (inverse-probability weighting) cohorts of 209 CRT-D recipients and 209 CRT-P recipients CRT-D was not associated with a survival benefit over CRT-P in women (HR, 0.87; 95% CI, 0.63–1.19).²⁰ In the present study, however, we found that survival was better in both women and men after both CRT-D and CRT-P. In separate analyses, the difference in survival between CRT-D and CRT-P was more pronounced in men (31%) than in women (17%), suggesting that defibrillation is more effective in men.

Uptake of CRT in Women

We found a lower proportion of women than men undergoing CRT, amounting to 25% of the study population. These findings are in keeping with the 2008 European CRT survey in

which 27% of CRT recipients were women.²¹ Admittedly, the lower proportion of CRT female recipients could simply be due to a lower prevalence of HF in women, rather than a lower utilization in potential CRT candidates. In this respect, a national audit of 55 959 patients over 45 years with a new diagnosis of HF in the period 2000 to 2017 in England, the proportion of women and men were 47.8% and 52.2%, respectively.²² The disparity between the relative incidence of HF in women (47.8%) and the proportion of women receiving CRT in the present study (25%) raises the possibility of a bias toward underutilization of CRT in women. Further studies on CRT implantation rates in women with indications for CRT are needed to clarify this issue.

Limitations

This study has the typical limitations of an observational, retrospective study using data from administrative databases, which typically lack granularity. First, we do not have data on the etiology of the underlying cardiomyopathy, LV function, QRS duration or morphology, or medication, all of which have been

linked to the response to CRT in women.² Second, comorbidities tend to be underreported in our administrative database,²³ although we have no reason to believe that this underreporting was different in women versus men. Third, we have not included optimum pharmacologic therapy group, and therefore we cannot comment on the relative benefits of CRT versus optimum pharmacologic therapy. Fourth, to explore the relative benefits of CRT-D over CRT-P, we used history of MI as a surrogate. This, however, does not equate to an underlying ischemic etiology of heart failure. Finally, as for the findings of fewer HF hospitalizations after CRT-D than after CRT-P in men, we should consider that hospitalizations coded as an HF hospitalization may have been provoked or associated with treated ventricular arrhythmias. Unfortunately, we have no data on concurrent ventricular arrhythmias or ICD therapies delivered.

Conclusions

We have found that in a large, real-world population of patients undergoing CRT, women survived longer and were less likely to be hospitalized for HF after CRT. In both women and men, CRT-D was superior to CRT-P with respect to survival and survival free of HF hospitalization. The lowest survival after CRT was observed in women without a history of MI. These factors should be considered at the time of deciding on device therapy for women, in whom the uptake of device therapy is disproportionately low worldwide.

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Disclosures

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SUPPLEMENTAL MATERIAL

Table S1. Diagnostic and procedural codes

	OPCS-4
CRT-D	K596
CRT-P	K6[0.1]7
	ICD10
Hypertension	I10
Diabetes mellitus	E1[0.1.3.4][1.5.6.8.9]
Chronic kidney disease	N18
Heart failure	I50

Corresponding diagnostic codes were obtained from the International Classification of Diseases 10th revision (ICD-10), and the Office of Population Censuses and Surveys Classification of Interventions and Procedures version 4 (OPCS-4) for procedural codes.