Sex specific outcomes with addition of defibrillation to resynchronization therapy in heart failure patients

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ABSTRACT

Objective: Among primary prevention heart failure patients receiving cardiac resynchronization therapy (CRT), the impact of additional implantable cardioverter defibrillator (ICD) treatment on outcomes and its interaction with sex remains uncertain. We aim to assess whether the addition of the ICD functionality to CRT devices offers a more pronounced survival benefit in men compared to women, as previous research has suggested.

Methods: Observational multicentre cohort study of 5,307 consecutive patients with ischaemic or non-ischaemic dilated cardiomyopathy and no history of sustained ventricular arrhythmias having CRT implantation with (CRT-D, n=4,037) or without (CRT-P, n=1,270) defibrillator functionality. Using propensity score (PS) matching and weighting and cause-of-death data, we assessed and compared the outcome of CRT-D vs. CRT-P patients. This analysis was stratified according to sex.

Results: After a mean follow-up of 41.4±29 months, no survival advantage of CRT-D vs. CRT-P was observed in both men and women after PS matching (HR=0.95, 95% CI 0.77-1.16, p=0.61, and HR=1.30, 95% CI 0.83-2.04, p=0.25, respectively). With inverse-probability weighting, a benefit of CRT-D was seen in male patients (HR 0.78, 95% CI 0.65-0.94, p=0.012) but not in women (HR 0.87, 95% CI 0.63-1.19, p=0.43). The excess mortality of CRT-P patients compared with CRT-D was related to SCD in 7.4% of cases in men but only 2.2% in women.

Conclusions: In primary prevention patients with CRT indication, the addition of a defibrillator might convey additional benefit only in well-selected male patients.

KEY-WORDS: Implantable cardioverter-defibrillator; cardiac resynchronization therapy; cause of death; sudden cardiac death; sudden arrhythmic death; all-cause mortality; sex; propensity score matching; propensity score weighting.

LIST OF ABBREVIATIONS

CI – Confidence interval

CRT-D – Cardiac resynchronization therapy defibrillator

CRT-P – Cardiac resynchronization therapy pacemaker

DCM – Dilated cardiomyopathy

GEE – Generalized estimating equation

ICD – Implantable cardioverter-defibrillator

IPTW – Inverse-probability-of-treatment weighting

PS – Propensity score

SCD – Sudden cardiac death

SMR – Standardized mortality ratio

KEY QUESTIONS

What is already known about this subject?

No randomized study has ever specifically compared the role of CRT with vs. without a defibrillator in primary prevention patients. Previous studies have suggested that sudden cardiac death accounts for only a limited part of the difference in overall mortality. The extent to which benefit from CRT-D differs according to sex requires further clarification.

What does this study add?

This study provides the first assessment on sex specific outcomes with the addition of the ICD to resynchronization therapy in heart failure patients. The addition of the ICD conveys additional benefit in well-selected male patients, but possibly not in women. Sudden cardiac death only accounts for 2.2% of the excess mortality in female CRT-P patients.

How might this impact on clinical practice?

Our results reinforce the importance of careful patient selection in both genders, but especially female sex, to optimize the benefit and subsequent cost-effectiveness of the ICD in patients with CRT indication.

INTRODUCTION

Cardiac resynchronization therapy (CRT) is a proven treatment for heart failure patients with prolonged QRS duration and severe left ventricular (LV) systolic impairment.(1,2) Its benefits include not only the improved functional capacity and quality of life but also the reduction in total mortality due to reduction of both progressive heart failure and sudden cardiac death (SCD).(3)

Except for an underpowered comparison in the COMPANION trial,(1) no randomized study has ever specifically compared the role of CRT with (CRT-D) vs. without (CRT-P) defibrillator (ICD) in patients with no history of ventricular arrhythmias. Previous observational studies(4–6) and meta-analyses(7) have shown that all-cause mortality rates are lower among CRT-D recipients with, however, SCD accounting for only a limited part of this difference.(5)

The extent to which benefit from CRT-D differs according to sex is of particular interest and requires further clarification. This large observational multicentre study compared CRT-D vs. CRT-P in both men and women using several propensity score (PS) methods and a cause-of-death analysis in order to determine whether the addition of the ICD functionality to CRT devices does indeed offer a more pronounced survival benefit in men compared to women.

METHODS

Study design and setting

Observational multicentre European cohort study of 5,307 consecutive patients with ischaemic or non-ischaemic dilated cardiomyopathy (DCM) having CRT-D or CRT-P

implantation between 2002 and 2012. The indications for CRT-P vs. CRT-D were as per the *European Society of Cardiology* and *European Heart Rhythm Association* guidelines for those treated in French and Swedish Hospitals and the *National Institute for Health and Care Excellence* (NICE) guidance [https://www.nice.org.uk/guidance/ta120] for patients treated in the UK. Using PS weighting and matching to account for differences in baseline characteristics and a cause-of-death analysis, we assessed and compared the outcome of CRT-D vs. CRT-P patients and their risk of SCD. This analysis was stratified according to sex.

This study complies with the *Declaration of Helsinki*. The data collection and analysis were approved by the individual sites' institutional review board or ethics committee.

Sample characterization

During the pre-specified study inclusion period, 5,651 patients received successful CRT implantation in 44 French, British and Swedish Hospital centers. Three-hundred and forty-four were excluded due to lack of follow-up data (n=89) or missing/inconclusive data on aetiology (n=255). The remaining **5,307 patients** represent the study group- **4,037 (76.1%) received CRT-D (all primary prevention)** while the remaining **1,270 (23.9%) received CRT-P**. Most patients from our cohort have been included and described in more detail in previous studies(5,6,8,9). Ischaemic cardiomyopathy was defined as the presence of systolic dysfunction associated with a history of myocardial infarction and/or the presence of significant coronary artery disease documented on a coronary angiogram. Individual patient data were collected at each participating medical centre. These included demographic characteristics, aetiology (ischaemic vs. dilated non-ischaemic), comorbidities at the time of CRT implantation including renal dysfunction (glomerular filtration rate stratified as ≥60 ml/min, 30-59 ml/min and <30 ml/min), history of atrial fibrillation (regardless of type),

chronic obstructive pulmonary disease (COPD), previous cerebrovascular events, Diabetes Mellitus and cancer, type of device (CRT-D vs. CRT-P), LV ejection fraction, and medication including beta-blocker, class III antiarrhythmics, angiotensin-converting enzyme inhibitor (ACEi) or angiotensin-II receptor blocker (ARA-II) and aldosterone antagonist. Of all procedures, 12.7% (n=674) were upgrades from pre-existing devices. Data on device programming was not routinely collected and was left at the discretion of the patients' physicians.

Follow-up and Study Endpoints

Follow-up visits were defined according to each centre's protocol but there was little variance between hospitals. In general, patients were followed at 6-month intervals. Unscheduled visits and/or remote ICD interrogations were performed in case of ICD shocks in patients with CRT-D.

The primary endpoint was all-cause mortality, while SCD was a secondary endpoint.

Investigators at each enrolling centre recorded all major clinical events. In the DAI-PP registry(8) and CeRtiTuDe cohort study,(5) vital status data were obtained from the hospital or the general practitioner, and were systematically controlled through the National Institute of Statistics Economical Studies. Causes of death were obtained by the investigators and/or by the French Center on Medical Causes of Death (CepiDc–INSERM). In the CeRtiTuDe cohort study, a Clinical Events Committee verified the accuracy of outcome data collected by the investigators by contacting the attending physicians as required, on a yearly basis, focusing on the vital status and on the specific modes and causes of death. Mortality data in patients treated in the UK were collected by at least two different investigators through the analysis of death certificates and necropsy results, clinical notes

from hospital admissions and information provided by the patients' General Practitioners. Mortality data in Swedish patients was gathered from the Swedish Death and Hospitalization registry and the Swedish pacemaker registry and crosschecked with manual assessment of preoperative medical records.

SCD was defined as any unexpected and unexplained death due to cardiac causes which occurred within one hour from the start or acute deterioration of any cardiac-related symptoms, or that occurred within 24 h of the patient last being seen alive and stable, and where no other plausible cause for a sudden death was found during autopsy or reported in the death certificates. Heart failure death was defined as death resulting from progressive circulatory collapse with gradual deterioration of heart failure symptoms and signs over a period of a few days, weeks or months. Unknown cause of death was defined as those cases where insufficient information was available to make a reasonable assumption as to the immediate cause of death.

Statistical Analysis (full statistical section in the supplementary material)

Statistical analysis was performed using *IBM SPSS Statistics*, v.24. P values <0.05 (two-sided) were considered statistically significant. Handling of **missing data** with multiple imputation is described in the supplementary material section. Briefly, five datasets with imputed data were created, all tests were performed in each dataset and a pooled result presented.

Methods for comparison CRT-D vs. CRT-P

Propensity scores were obtained for all study patients and three different PS methods were used: matching, inverse-probability-of-treatment weighting (IPTW) and standardized-mortality-ratio (SMR) weighting.(10,11) The rationale for using three different PS methods rather than one lies in the fact that each of these methods provides an answer

to a different question. Relying on one method only would lead to a biased estimation of the true ICD treatment effect. Proportional hazards regression adjusting for mortality predictors was then conducted after matching or weighting had been performed. In addition, a cause-of-death analysis was conducted as a supplementary analysis, with a focus on SCD.

Obtainment of propensity scores

We included all baseline covariates that were shown to affect the primary outcome:(12) age, sex, LV ejection fraction, NYHA class, QRS duration, aetiology (ischaemic vs. non-ischaemic), *de novo* implantation vs. upgrade, history of atrial fibrillation, cerebrovascular event, Diabetes Mellitus, malignancy, renal dysfunction (severe if GFR <30 ml/min, moderate if 30-59 ml/min) and COPD, treatment with beta-blockers, class III antiarrhythmics, ACEi/ARA-II and aldosterone antagonists.

Propensity score matching

Greedy nearest neighbour matching within a specified caliper width (0.01) and without replacement was used for forming pairs of CRT-D and CRT-P patients matched on the PS. Given the number of CRT-D patients is significantly higher than that of CRT-P patients, the matched analysis estimates the treatment effect of the ICD in CRT patients who more closely resemble those who receive CRT-P than their CRT-D counterparts. As patients with the lowest PS are often not deemed fit for an ICD, PS matching was repeated after excluding those with a PS <20th percentile. After matching, proportional hazards regression was used to compare survival outcomes in both device groups.

Three methods were used for ***assessing balance in PS matched groups***, including a comparison of standardized differences in the means of continuous and binary covariates between treatment groups(10) (details in supplementary material).

Propensity score weighting

Two PS weighting methods were used.(11) The first one, known as IPTW-weighted estimator, estimates the treatment effect in a population whose distribution of risk factors is similar to that found in all study subjects. The second weighting method, known as the SMR-weighted estimator, estimates the treatment effect in a population whose distribution of risk factors is more similar to that found in CRT-D study subjects only. Then, we performed proportional hazards regression with robust variance estimation to account for the sample weights, adjusting for the type of device, all other mortality predictors and the PS, with each subject being weighted according to the weighting methods described before.

Power analysis

The ALTITUDE survival study revealed a 3.5-year mortality rate of 41.5% in CRT-P patients(13). The largest meta-analysis on CRT-D vs. CRT-P revealed an unadjusted 31% lower relative risk of all-cause mortality in CRT-D patients.(8) Therefore, we estimate that a sample size of 430 patients (215 per group) followed for ≥3.5 years would be required to provide 80% power to detect a 31% difference in treatment effect on all-cause mortality (two-tailed alpha level=0.05).

RESULTS

Tables 1-2 show the baseline characteristics of all CRT-D and CRT-P patients before PS matching. CRT-P patients were older than those receiving CRT-D and had more advanced heart failure and comorbidity. They received upgrade to CRT more often than CRT-D patients and were less often on standard heart failure medication. Ischaemic cardiomyopathy was more frequent in CRT-D patients. Men were much more likely to receive CRT-D compared with women.

Median follow-up in the 3,792 surviving patients (71.5%) was 34 months (interquartile range 22-60 months). Unadjusted mortality incidence rates in male patients were 87.1 vs. 145.4 per 1,000 patient-years in CRT-D vs. CRT-P recipients, respectively. In female patients, unadjusted incidence rates were 56.5 vs. 97.3 per 1,000 patient-years in those receiving CRT-D vs. CRT-P, respectively.

Propensity score analysis in male patients

Matching was performed in all imputed datasets and comparison between device groups was performed using cox regression analysis adjusting for mortality predictors. Both groups were very well balanced (**supplementary material**). The HR for all-cause mortality varied between 0.90-0.98 in all imputed datasets. The pooled HR was 0.95 (95%CI 0.77-1.16), p=0.61 **(table 3)**. PS matching was repeated after excluding patients with a PS ≤20th percentile: HR 0.87 (0.64-1.17), p= 0.35. In other words, even after excluding those patients who might not have been deemed fit for an ICD, male CRT-P patients as currently seen in clinical practice would not benefit from the addition of the ICD. **Figure 1** illustrates the cumulative survival in male CRT-D and CRT-P patients after unadjusted and propensity score-matched analyses.

In the IPTW-weighted population, the resultant pooled HR after multiple adjustments as well as considering PS was 0.78 (0.65-0.94), p=0.012. In the SMR-weighted population, the pooled HR was 0.73 (0.59-0.89) (p=0.003).

Propensity score analysis in female patients

Both propensity score-matched groups were well balanced (**supplementary material**). The adjusted HR for all-cause mortality varied between 1.1-1.48 in all imputed

datasets. The pooled HR was 1.3 (95%CI 0.83-2.04), p=0.25 **[table 3]**. Matching was repeated after excluding patients with a PS ≤20th percentile: HR 0.97 (0.65-1.45), p=0.90. **Figure 2** illustrates the cumulative survival in female CRT-D and CRT-P patients after unadjusted and propensity score-matched analyses.

In the IPTW-weighted population, the resultant pooled HR after adjusting for all mortality predictors and the PS was 0.87 (0.63-1.19), p=0.43. In the SMR-weighted population, the pooled HR was 0.81 (0.56-1.18), p=0.27.

Propensity score analysis in the original population without imputed data corroborated the results obtained in the imputed datasets (more data in the **supplementary material**).

Cause-of-death analysis in men and women

Cause of death data was obtained for 71% of patients who died during follow-up. Overall, 60.1% of known deaths were due to non-sudden cardiovascular death, 9.1% were SCD, 1.5% device-related deaths and 29.3% non-cardiovascular deaths. **Figure 3** presents an unadjusted comparison between CRT-D and CRT-P regarding each specific cause of death. In both device groups, SCD was more frequent in men than in women (**Figure 4)** and the proportion of deaths due to SCD was also higher in male vs. female patients (10.1% vs. 7.4% in CRT-D patients, and 8.3% vs. 5.5% in CRT-P patients). The excess mortality of CRT-P patients compared with CRT-D was related to SCD in 7.4% of cases in men but only 2.2% in women. Sudden cardiac death rates were very low amongst female patients with non-ischaemic DCM regardless of device (2.4 vs. 1.8 per 1000 patient-years in CRT-D and CRT-P patients, respectively). In women with ischaemic cardiomyopathy, SCD rates in CRT-D and CRT-P patients were 9 and 2.2 per 1000 patient-years, respectively. After computing the

cumulative incidence of the event from incidence rates, the number needed to treat (NNT) to prevent one SCD in women with ischaemic cardiomyopathy would be 148.

DISCUSSION

Main findings

In primary prevention patients with CRT indication, the addition of a defibrillator might convey additional benefit only in well-selected male patients. The potential lack of benefit of the ICD in female CRT patients is likely a result of their lower risk of SCD (especially in those with non-ischaemic DCM), which represents only 2.2% of the excess mortality compared with CRT-P.

Cardiac resynchronization therapy with or without an ICD: careful patient selection is warranted

Multiple observational studies and meta-analyses(4–7,14) have been performed to compare CRT-D vs. CRT-P, but results have been inconclusive. The marked differences in baseline characteristics between both groups have made it difficult to establish whether the better outcome of CRT-D patients translates causality or is mostly due to patient selection. When studying an effect of any treatment intervention on patient outcome, a randomized controlled trial is the only method that allows for a conclusion on causality. This consideration notwithstanding, PS analysis allows for adjustment for observed prognostic factors and can provide valuable data. However, different PS methods provide different answers to different questions and therefore do not always estimate the same effect exactly.(10,11) When using PS matching in our population, a significant number of the more

numerous CRT-D group were expectedly excluded given the lack of a control CRT-P patient. The outcome is that PS matching estimated the effect of the ICD on patients who were in general more similar to CRT-P patients. Quite importantly, we repeated the analysis after excluding the patients with the lowest PS who would possibly not be considered for an ICD. On the other hand, IPTW estimated the effect on average mortality if the entire population was shifted from CRT-P to CRT-D, while SMR-weighting estimated the effect of the ICD on patients more similar to those who ultimately receive it. Thus, the populations to which each estimate applies are qualitatively different from one another.

In our cohort, no significant benefit of the ICD was seen in male patients whose general characteristics more closely matched those of patients receiving CRT-P, even after excluding those with the lowest PS for whom ICD implantation could be deemed inappropriate. However, there was a clear benefit in patients with higher PS. This is a good example of the importance of patient selection that goes much beyond LV ejection fraction. Different risk scores can reliably predict competing risk of non-sudden death and help with patient selection(15–17) Compared with a biventricular pacemaker, CRT-D seems beneficial in primary prevention male patients at lower competing risk of non-sudden death, but its benefit decreases with increasing comorbidity. Male patients with ischaemic cardiomyopathy seem to be at the highest risk of SCD and therefore the absolute benefit of the ICD may be highest in this group as long as the risk of non-sudden death is low.

On the other hand, no significant benefit of the ICD was seen in female CRT patients after PS matching and weighting. This may have several explanations. Firstly, women in general have a lower susceptibility to ventricular arrhythmia compared with men(18) and are less vulnerable to sudden death than men regardless of the presence of coronary artery disease,(19) as our study confirmed. Amongst heart failure patients potentially eligible for a

primary prevention ICD, women are at lower risk of sudden death compared with men, and fewer of their deaths are sudden throughout a spectrum of all-cause mortality risk, irrespective of heart failure severity.(20) Female patients implanted with an ICD/CRT-D experience fewer appropriate ICD therapies than men.(8,18,21) Secondly, female sex is a known predictor of CRT response independent of baseline aetiology(22,23) and responders and super-responders to CRT are at significantly lower risk of mortality and ventricular arrhythmias.(24,25) Thirdly, women have a higher prevalence of non-ischaemic cardiomyopathy which has recently been shown to associate with smaller benefit from the ICD.(26) Fourthly, female patients are at higher risk of device-related complications(27) which may cause additional morbidity and mortality. It is noteworthy that CRT-D associates with a higher risk of complications compared with any other device.(14,27) Finally, this study may not have been powered to detect a small effect size in women given the much lower number of female patients compared with their male counterparts. Nevertheless, subgroup analyses of SCD-HeFT, DEFINITE and DANISH suggested that the benefit of the ICD in women was much less pronounced than in men and potentially non-existent, especially in the context of non-ischaemic cardiomyopathy.(26) The benefit of the ICD in CRT studies decreases with increasing percentage of female patients.(7) Our study suggests that female patients with ischaemic cardiomyopathy have a lower risk of SCD when given CRT-D but the NNT is impractically large given the overall low risk of SCD in women regardless of etiology and device. Further research is required to specifically select those female patients with ischaemic cardiomyopathy who may potentially benefit from CRT-D. Meanwhile, an upgrade of CRT-P to CRT-D in the very few cases where sustained VT is documented during follow-up may remain a safe and more cost-effective alternative to systematic CRT-D implantation in female patients.

Limitations of our study

The main limitation of this study is its non-randomized nature. PS methods only account for measured baseline parameters, which means estimates of treatment effect may still be susceptible to bias due to unmeasured confounding variables. In addition, the number of male patients was expectedly much higher than that of female patients, which means our observations regarding the impact of CRT-D in men were more robust than those in women. The female cohort was not large enough for an interaction analysis to be powered and therefore external validation of our findings would be welcome. Some caution is needed before concluding on heterogeneity on the basis of separate tests of treatment effect within each subgroup.(28)

The cause-of-death analysis should also be interpreted with caution. Occasionally the mechanism of death is very difficult to determine even when the data is collected prospectively. The percentage of patients whose cause of death was unknown was higher in CRT-P recipients. As a result, we chose all-cause mortality as the primary endpoint because it is unambiguous and easy to collect.

CONCLUSIONS

In primary prevention patients with ischaemic or non-ischaemic DCM and CRT indication, the addition of the ICD conveys additional benefit in well-selected male patients but not female patients.

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FIGURE LEGENDS

Figure 1– Survival curves comparing CRT-D vs. CRT-P in **male** patients

Figure 2– Survival curves comparing CRT-D vs. CRT-P in **female** patients

Figure 3– Cause-of-death analysis: forest-plots comparing CRT-D vs. CRT-P in both genders

Figure 4- Cause-of-death analysis: forest-plots comparing male vs. female sex in both device groups

Table 1–Baseline characteristics of study group according to device

Variable	CRT-D (n=4037)	CRT-P (n=1270)	p-value
Age (years)	65.2±10.7	73±10.1	<0.001
Male sex	84.6% (3417)	57.6% (732)	<0.001
Left ventricular ejection fraction (%)	25.5±7.7	27.1±9.1	<0.001
NYHA class (mean)	2.9±2.1	3.3±3.0	<0.001
NYHA class ≥3	69.9% (2821)	83.1% (1056)	<0.001
QRS duration <120 ms **120-150 ms** **>150 ms**	9% (360) 38.1% (1540) 52.9% (2137)	6% (77) 29.7% (377) 64.3% (816)	<0.001
Ischaemic aetiology	51.9% (2094)	46.3% (588)	0.001
De novo CRT implantation **Upgrade to CRT**	88.8% (3584) 11.2% (453)	78.7% (1000) 21.3% (270)	<0.001
History of atrial fibrillation	32.9% (1327)	33% (419)	0.9
History of stroke or transient ischaemic attack	6.5% (262)	9.4% (119)	0.008
History of chronic obstructive pulmonary disease	13.7% (554)	14.3% (182)	0.5
History of Diabetes Mellitus	22.4% (905)	18.9% (240)	0.008
History of cancer	9.8% (396)	12.7% (161)	0.001
Glomerular filtration rate ≥60 ml/min **30-59 ml/min** **<30 ml/min**	22.8% (919) 40.6% (1639) 36.6% (1479)	31.6% (401) 48.3% (614) 20.1% (255)	<0.001
On beta-blockers	81.2% (3277)	62% (787)	<0.001
On ACEI/ARA-II	84.5% (3410)	77.5% (984)	<0.001
On aldosterone antagonists	45.9% (1852)	42.6% (540)	<0.001
Class III antiarrhythmic drugs*	28.8% (1161)	17.9% (227)	<0.001
Mean follow-up in surviving patients (months)	41.2±30	42±26	0.48

ACEI- Angiotensin converting enzyme inhibitor; ARA-II- Type 2 angiotensin receptor antagonist; CRT- Cardiac resynchronization therapy; NYHA- New York Heart Association

* Prescribed to treat non-sustained VT for at least 6 months

Table 2–Baseline characteristics of study group according to sex

Variable	Male sex (n=4149)	Female sex (n=1158)	p-value
Age (years)	66.8±10.8	67.9±11.8	0.007
CRT-Defibrillator	82.3% (3417)	53.5% (620)	<0.001
Left ventricular ejection fraction (%)	25.7±7.9	26.7±8.4	<0.001
NYHA class (mean)	2.77±0.65	2.78±0.66	0.77
NYHA class ≥3	73.2% (3035)	73.8% (855)	0.8
QRS duration <120 ms **120-150 ms** **>150 ms**	8.7% (361) 35.7% (1480) 55.6% (2308)	6.5% (76) 37.7% (436) 55.8% (646)	0.06
Ischaemic aetiology	56.4% (2339)	29.6% (343)	<0.001
De novo CRT implantation **Upgrade to CRT**	85.8% (3562) 14.2% (587)	88.2% (1022) 11.8% (136)	0.06
History of atrial fibrillation	35.5% (1473)	29% (336)	<0.001
History of stroke or transient ischaemic attack	7.2% (299)	7.2% (83)	0.9
History of chronic obstructive pulmonary disease	14% (582)	13.4% (155)	0.5
History of Diabetes Mellitus	26.9% (1118)	20.9% (242)	0.001
History of cancer	9.1% (378)	15.5% (179)	<0.001
Glomerular filtration rate ≥60 ml/min **30-59 ml/min** **<30 ml/min**	24.4% (1012) 42.3% (1755) 33.3% (1382)	26.7% (309) 42.9% (497) 30.4% (352)	0.26
On beta-blockers	76.9% (3190)	75.5% (874)	0.32
On ACEI/ARA-II	81.8% (3394)	81.5% (944)	0.8
On aldosterone antagonists	43.9% (1821)	49.3% (571)	<0.001
On class III antiarrhythmic drugs*	27.3% (1133)	21.9% (254)	0.001
Mean follow-up in surviving patients (months)	37.4±28	40.8±29	<0.001

ACEI- Angiotensin converting enzyme inhibitor; ARA-II- Type 2 angiotensin receptor antagonist; CRT- Cardiac resynchronization therapy; NYHA- New York Heart Association

* Prescribed to treat non-sustained VT for at least 6 months

Table 3 – Hazard ratios for all-cause mortality with CRT-D vs. CRT-P in after propensity-score matching

MALE patients			
Imputed dataset	**Number of patients (1:1 matching)**	**Hazard ratio and 95% CI**	**P value**
1	1268	0.978 (0.808-1.183)	0.817
2	1286	0.895 (0.741-1.083)	0.255
3	1292	0.952 (0.789-1.148)	0.606
4	1254	0.968 (0.795-1.179)	0.748
5	1306	0.942 (0.780-1.138)	0.534
Pooled	-	0.947 (0.771-1.164)	0.606
FEMALE patients			
Imputed dataset	**Number of patients (1:1 matching)**	**Hazard ratio and 95% CI**	**P value**
1	590	1.257 (0.850-1.861)	0.252
2	570	1.350 (0.916-1.990)	0.129
3	568	1.294 (0.884-1.894)	0.184
4	586	1.099 (0.750-1.610)	0.629
5	590	1.479 (1.007-2.173)	0.046
Pooled	-	1.298 (0.825-2.041)	0.254