Impact of Adding Defibrillation Therapy to Cardiac Resynchronization: Analysis According to Underlying Myocardial Substrate

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ABSTRACT

Background: Non-ischemic dilated cardiomyopathy (DCM) patients may present a lower risk of ventricular arrhythmias compared to those with ischemic cardiomyopathy (ICM). In addition, DCM has been identified as a predictor of positive response to cardiac resynchronization therapy (CRT).

Objectives: We investigated the impact of additional implantable cardioverter defibrillator (ICD) over CRT, according to underlying heart disease, in a large population of primary prevention heart failure patients.

Methods: This was an observational multicentre European cohort study of 5,307 consecutive patients with DCM or ICM, no history of sustained ventricular arrhythmias, having CRT implantation with (CRT-D, n=4,037) or without (CRT-P, n=1,270) defibrillator. Propensity score and cause-of-death analyses were used to compare outcomes.

Results: After a mean follow-up of 41.4±29.0 months, ICM patients had better survival when implanted with CRT-D compared with CRT-P (HR for mortality adjusted on propensity score and all mortality predictors 0.76, 95% CI 0.62-0.92, p=0.005), whereas in DCM patients no such difference was observed (HR 0.92, 95% CI 0.73-1.16, p=0.49). Compared to CRT-D recipients, the excess mortality in CRT-P patients was related to sudden cardiac death in 8.0% among the ICM patients but only in 0.4% of the DCM patients.

Conclusion: In the setting of heart failure patients with CRT indication, DCM patients may not benefit from additional primary prevention ICD therapy as opposed to those with ICM.

KEY-WORDS: Implantable cardioverter-defibrillator; cardiac resynchronization therapy; cause of death analysis; sudden cardiac death; all-cause mortality; ischemic cardiomyopathy;

coronary artery disease; dilated cardiomyopathy; propensity score matching; propensity score weighting.

BRIEF ABSTRACT

In this observational multicentre cohort study of 5,307 patients with ischemic (ICM) or non-ischemic dilated cardiomyopathy (DCM), we investigated the impact of additional implantable cardioverter-defibrillator over cardiac resynchronization therapy (CRT) according to underlying heart disease. After a mean follow-up of 41.4±29.0 months, ICM patients had better survival when implanted with CRT-Defibrillator compared with CRT-Pacemaker (propensity score adjusted HR=0.76, 95%CI 0.62-0.92, p=0.005), whereas in DCM patients no such difference was observed (HR=0.93, 95%CI 0.74-1.17, p=0.52). The excess mortality in CRT-Pacemaker patients was related to sudden cardiac death in 8.0% among the ICM patients but only in 0.4% of the DCM patients.

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

ICM – Ischemic cardiomyopathy

PS – Propensity score

SCD – Sudden cardiac death

SMR – Standardized mortality ratio

INTRODUCTION

Cardiac resynchronization therapy (CRT) has been shown to improve survival of heart failure patients with ischemic (ICM) or non-ischemic dilated cardiomyopathy (DCM), prolonged QRS duration and severe left ventricular (LV) systolic dysfunction(1–3). The addition of an implantable cardioverter-defibrillator (ICD) in symptomatic patients with an LV ejection fraction of ≤35% is also recommended for primary prevention of sudden cardiac death (SCD; class I indication)(4–6). However, the issue of whether this recommendation is equally applicable to patients with DCM and ICM has been poorly addressed so far(7).

Patients with DCM may have a lower underlying risk of ventricular arrhythmias and sudden cardiac death (SCD) compared with those with ICM, and the former are also known to better respond to CRT(8, 9), despite the fact the benefit from CRT in absolute terms may be greater in ICM patients due to their higher event rate(10). Response to CRT further decreases the risk of ventricular arrhythmias, SCD and all-cause mortality(11–16). The very recently published DANISH study suggested that primary prevention patients with DCM may not derive a mortality benefit from the ICD regardless of whether the patient received CRT(17), although a possible benefit was seen in a sensitivity analysis of younger patients. Additionally, the benefit of CRT-Defibrillator (CRT-D) compared with CRT-Pacemaker (CRT-P) has been suggested to be more pronounced in studies with higher percentage of ICM patients(18). Improved medical therapy over the years has reduced the overall risk of mortality but also SCD among heart failure patients. These aforementioned observations raise the question as to how much additional benefit DCM patients would obtain with an ICD over and above CRT therapy.

In this large observational multicentre European study, we therefore aimed to compare the outcome of CRT-D vs. CRT-P patients according to the underlying aetiology of cardiomyopathy.

METHODS

Study design and setting

Data were obtained from a large European consortium comprising French, UK and Swedish centres between 2002 and 2012, incorporating 5,651 consecutive patients with no history of sustained ventricular arrhythmia receiving CRT-D or CRT-P(19–22). The overall purpose of the consortium is to assess the outcomes of heart failure patients receiving CRT, with or without a defibrillator. Out of these patients who received successful CRT implantation, 344 were excluded due to missing follow-up data (n=89) and presence of a cardiomyopathy other than ICM or DCM (n=255), and eventually **5,307 patients were included in the study population: 2,682 with ICM and 2,625 with DCM**.

The indications for CRT-P vs. CRT-D were as per the *European Society of Cardiology* and *European Heart Rhythm Association* guidelines(23) for those treated in French and Swedish Hospitals and the *National Institute for Health and Care Excellence* (NICE) guidelines [https://www.nice.org.uk/guidance/ta120] for patients treated in the UK.

Using cause-of-death and propensity score analyses(24, 25), we assessed and compared the outcome of CRT-D vs. CRT-P patients according to their underlying aetiology.

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

Of the **5,307 patients**, **4037 (76.1%) received CRT-D** while the remaining **1270 (23.9%) received CRT-P**. All procedures were new implants or upgrades from a standard pacemaker. Patients receiving generator replacement were not included. Ischemic 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 (defined as the presence of a ≥70% obstructive lesion in one of the main coronary arteries). Data collected included demographic characteristics, aetiology of cardiomyopathy, presence of renal dysfunction (glomerular filtration rate ≥60 ml/min, 30-59 ml/min and <30 ml/min, estimated by The Modification of Diet in Renal Disease (MDRD) Study equation), atrial fibrillation, chronic obstructive pulmonary disease, cerebrovascular event, diabetes mellitus, cancer, type of device (CRT-D vs. CRT-P), *de novo* CRT implantation vs. upgrade procedure, LV ejection fraction, and medication including beta-blocker, class III antiarrhythmic drug, angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARA-II) and aldosterone antagonist. Data on device programming was not routinely collected and was left at the discretion of the implanting physicians.

Follow-up and Study Endpoints

Patients were generally followed at 6-month intervals, but additional unscheduled visits or remote ICD interrogations were performed in CRT-D patients receiving ICD shocks.

The primary endpoint of the study was all-cause mortality. A secondary cause-of-death analysis was performed to complement the primary analysis, with a focus on SCD vs. non-SCD and an assessment of the percent excess mortality related to SCD. Methods for cause-of-death data collection have been described elsewhere(19, 20). Briefly, in the DAI-PP registry(19) and CeRtiTuDe cohort study(20), vital status data were obtained by the investigators and/or by the French Center on Medical Causes of Death, and were systematically controlled through the National Institute of Statistics Economical Studies. Mortality data in patients treated in the UK were collected by the 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 were gathered from the Swedish Death and Hospitalization registry and the Swedish pacemaker registry and crosschecked with manual assessment of electronic medical records.

SCD was defined as an unexpected sudden death due to cardiac causes which occurred within one hour from the start or acute deterioration of any cardiac-related symptoms, or that which occurred within 24 hours of the patient last being seen alive and stable, with no other plausible cause for a sudden death found during autopsy or reported in the death certificates. Non-SCD included all remaining cardiovascular deaths which did not fulfil the criteria for SCD and also for non-cardiovascular deaths. When insufficient information was available to make a reasonable assumption of the cause of death, the death was classified as unknown.

Statistical Analysis (complete section in the supplementary material)

Statistical analysis was performed using *IBM SPSS Statistics*, v.24. Baseline characteristics were described with mean±standard deviation for continuous data and counts and proportions for categorical data. The Kolmogorov-Smirnov test was used to test the normal distribution of continuous variables. The Chi-square test, Student's t-test and non-parametric equivalent tests were used when appropriate. P values <0.05 (two-sided) were considered statistically significant.

Missing data were assumed to be random and treated with multiple imputation by chained equations. However, the results of an analysis restricted to complete cases are also presented.

The outcome of CRT-D vs. CRT-P patients was compared using proportional hazards regression with adjustment on the propensity score (PS) and all mortality predictors in univariate analysis. This analysis was complemented with PS matching and PS weighting,

which provided different answers to different questions(24, 25). In the context of this investigation, the former estimated the effect of the ICD in CRT patients whose general characteristics more closely match those generally seen in CRT-P patients, while the latter assessed the benefit of the ICD in CRT patients who more closely resemble the group of patients who typically receive a CRT-D.

For obtaining the PS, we included all baseline covariates that were shown to affect the outcome(26): age, sex, LV ejection fraction, NYHA class, QRS duration, aetiology, *de novo* implantation vs. upgrade, history of atrial fibrillation, cerebrovascular event, diabetes mellitus, malignancy, renal dysfunction and chronic lung disease, treatment with beta-blockers, class III anti-arrhythmic drugs, ACEi or ARA-II and aldosterone antagonists. All of the variables were collected at baseline.

Firstly, we compared the outcome of CRT-D vs. CRT-P patients across both etiologies by using covariate adjustment with the PS. Using this approach, the outcome variable was regressed on treatment status, the estimated PS and mortality predictors and the effect of the ICD was determined using the estimated regression coefficient from the fitted regression model. Secondly, 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(27). In order to assess the balance on the newly created PS matched sample, we compared standardized differences in the means of continuous and binary covariates between treatment groups(24). After the matched sample had been created and shown to be well balanced, comparison between device groups was performed using proportional hazards regression analysis adjusting for mortality predictors. Thirdly, a PS weighting method, known as the standardized mortality ratio (SMR) estimator(25), was used to estimate the treatment effect of the ICD in a population whose distribution of risk factors is more similar to that found in the CRT-D subjects only, that is, the average treatment effect

for the treated. Then, we used proportional hazards regression with robust variance estimation, adjusting on the type of device (CRT-D vs. CRT-P), all other mortality predictors and the PS, with each subject being weighted according to the weighting method described before.

We estimated that a sample size of 430 patients (215 per group) followed for at least 3.5 years would be required to provide 80% power to detect a 31% difference in treatment effect on all-cause mortality between groups(18) at a two-tailed alpha level of 0.05 and taking into account a 3.5 year [equivalent to the mean follow-up duration of our CRT-P patients] mortality rate of 41.5% in CRT-P patients, as seen in the ALTITUDE survival study(28).

RESULTS

Baseline characteristics of the entire population are reported in tables 1-3. CRT-P patients were older, more often female, had more advanced heart failure and comorbidity and received more frequently CRT upgrade rather than *de novo* implantation than those receiving CRT-D. Ischemic cardiomyopathy was more frequent in CRT-D patients (51.6% vs. 46.3%, $p<0.001$).

During a mean follow-up of 41.4±29 months, 1535 patients died, including 887 patients with ischemic cardiomyopathy (645 with CRT-D, 242 with CRT-P) and 648 with non-ischemic cardiomyopathy (420 with CRT-D, 228 with CRT-P). Crude mortality incidence rates in ischemic cardiomyopathy patients were 96.5 (95% CI 89.7-103.8) vs. 143.4 (95% CI 127.2-160.6) per 1,000 patient-years in CRT-D vs. CRT-P recipients, respectively ($p<0.0001$). In DCM patients, crude incidence rates were 66.2 (95% CI 60.3-72.6) vs. 105 (95% CI 93.1-118.9) per 1,000 patient-years in those receiving CRT-D vs. CRT-P, respectively ($p<0.0001$). **Figure 1** illustrates unadjusted Kaplan-Meier survival curves for the four study groups.

CRT-D vs. CRT-P in ischemic cardiomyopathy

Patients with ICM had a more favourable outcome as a group when implanted with CRT-D compared with CRT-P (adjusted HR 0.76, 95% CI 0.62-0.92, p=0.005) (**figure 2**). The number needed to treat with CRT-D to prevent one additional death over CRT-P during a device battery life of 5 years was 12.5. In the SMR-weighted population, the pooled HR after multiple adjustment as well as considering the PS was 0.65 (95% CI 0.52-0.82, p=0.002). With PS matching (n=922), and after confirming that both groups were very well balanced **(table 4)**, the pooled HR was 0.89 (95% CI 0.71-1.12, p=0.34). These results show that CRT-D was superior to CRT-P, with the benefit seen in patients whose general characteristics best matched those typically seen in CRT-D recipients (that is, with higher propensity scores translating into younger age, higher prevalence of males and less advanced comorbidity). The excess mortality of CRT-P compared to CRT-D in patients with ICM was related to SCD in 8.0% of cases: SCD incidence rate was 8.5 per 1000 patient-years of follow-up in CRT-D vs. 13.2 per 1000 patient-years in CRT-P group.

CRT-D vs. CRT-P in non-ischemic dilated cardiomyopathy

In DCM patients, there was no significant difference in survival between those receiving CRT-D vs. CRT-P (adjusted HR 0.92, 95% CI 0.73-1.16, p=0.49) (**figure 2**). In the SMR-weighted population, the pooled HR was 0.93 (95% CI 0.72-1.19, p=0.6). With PS matching (n=988), and after confirming that both groups were very well balanced **(table 4)**, the pooled HR was 1.01 (95% CI 0.77-1.32, p=0.96). These results show that, regardless of the PS method used, CRT-D was not associated with a significantly better outcome. When performing an analysis according to age sub-group (<68 and ≥68 years old, as per the DANISH trial(17)), results did not vary, with no differences seen between device groups

irrespective of age subgroup. In patients with DCM, the excess mortality of CRT-P compared with CRT-D was related to SCD in only 0.4% of cases: SCD incidence rate was 3.9 per 1000 patient-years of follow-up in CRT-D vs. 4.1 per 1000 patient-years in CRT-P.

Propensity score analysis in the original population without imputed data

The analysis performed in the original database corroborated the results obtained in the imputed datasets. A benefit of the ICD was seen in ICM patients (HR adjusted for the propensity score, age, gender, NYHA class and LV ejection fraction 0.79, 95% CI 0.65-0.97, p=0.025, while no benefit was seen in patients with DCM (HR 0.90, 95% CI 0.71-1.15, p=0.39).

DISCUSSION

This large European multicentre study of patients with CRT indication and no history of sustained ventricular arrhythmias suggests that the addition of an ICD over CRT is beneficial in well selected patients with ICM but does not convey a significant survival benefit in patients with non-ischemic DCM. The excess crude mortality of DCM patients with CRT-P compared to CRT-D is the result of higher non-SCD rates. This study, in concert with the recently presented DANISH data(17), suggests that selecting CRT-D (versus CRT-P) implantation in a DCM patient with no history of ventricular arrhythmias needs careful consideration as the evidence for a putative additional benefit appears questionable.

The use of the ICD confers a survival benefit in primary prevention heart failure patients with severe ischemic cardiomyopathy, as shown in the SCD-HeFT(29) and Multicenter Automatic Defibrillator Implantation Trial (MADIT) II(30) trials. Its role in patients with non-ischemic DCM is less clear due to the smaller number of DCM patients included in primary prevention ICD trials such as *The Cardiomyopathy Trial* (CAT)(31),

AMIOVIRT(32), Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE)(33) and SCD-HeFT(29). In fact, none of these studies revealed a statistically significant benefit of the ICD in the context of non-ischemic DCM. While a meta-analysis of these trials suggested a reduced mortality risk in ICD patients compared with those receiving medical therapy, the very recently published DANISH trial(17) concluded that prophylactic ICD implantation in patients with symptomatic systolic heart failure of non-ischemic aetiology was not associated with a significantly lower long-term rate of all-cause death than was medical therapy.

However, whilst the utility of the ICD in the non-ischemic patient without CRT has been the subject of various studies, albeit with inconclusive results, the role of the ICD in CRT-eligible candidates remains to be determined. The COMPANION trial revealed that the combination of CRT plus ICD is of benefit in both ischemic and non-ischemic patients compared with medical therapy alone(7), but to the best of our knowledge no aetiology-stratified comparison between CRT-D and CRT-P was performed. In the DANISH trial, the effect of ICD implantation was independent of CRT status, suggesting that the lack of benefit of the ICD in non-ischemic patients is independent of whether the patient received CRT(17). The improved background medical treatment for heart failure in DANISH may have also contributed to the smaller effect size of the ICD compared with DCM patients enrolled in previous randomized trials. A recent meta-analysis has suggested that the benefit of the ICD in CRT patients is more pronounced in studies with higher percentage of ischemic cardiomyopathy patients and may not be seen in the context of non-ischemic DCM(18).

The present multicentre study corroborates these findings, suggesting that CRT-D is superior to biventricular pacing alone in ischemic cardiomyopathy but not in non-ischemic DCM. In the latter, the use of CRT-D was not of benefit even in patients with higher mean PS, as shown by SMR weighting, which assessed the benefit of the ICD in CRT patients

whose general characteristics best match those of patients who would typically receive a CRT-D. These results reinforce the need for an appropriate patient selection based on the estimated risk of non-sudden death, which is known to correlate with the degree of comorbidity and frailty of the patient(34–36), and the risk of ventricular arrhythmias(37). Patient selection based on LV ejection fraction alone is clearly insufficient.

There are several potential explanations for the lack of benefit of CRT-D compared with CRT-P in DCM patients with no history of ventricular arrhythmias. First, the use of competing risks analysis on data from the ATLAS study, a multicentre randomized trial of Lisinopril in patients with chronic heart failure, has shown that sudden death is most closely related to markers of ischemic heart disease(38). In their derivation of a risk model for the prediction of the risk of SCD in heart failure patients without ICDs, Shadman et al found a higher risk of SCD in patients with ischemic cardiomyopathy in their proportional hazards model (supplementary material)(39). A recent meta-analysis on the mode of death of CRT patients has shown a higher rate of SCD in studies with higher percentage of ischemic cardiomyopathy patients [unpublished data: Barra et al, Causes of death in patients with cardiac resynchronization therapy with or without a defibrillator: a systematic review and proportional meta-analysis]. Patients with non-ischemic cardiomyopathy are less prone to death from arrhythmia than those with ischemic heart disease as our results suggest, hence reducing the absolute impact of any therapy predominantly targeting SCD. Advances and improvements in medical treatment and CRT may have reduced the overall risk of death from both heart failure and arrhythmia. In addition, CRT has been shown to reduce the risk of SCD even in the absence of the ICD(40). In the Certitude cohort study, the higher all-cause mortality rate in CRT-P patients was almost entirely the result of higher number of progressive heart failure related- or non-cardiac deaths, while SCD was only slightly more frequent(20). Second, non-ischemic DCM is a known predictor of better response to CRT

compared with ischemic heart failure(8, 9, 41). DCM patients experience greater improvement in left ventricular systolic function and reverse remodeling while also sustaining a greater survival benefit(8). CRT responders are at significantly lower risk of ventricular arrhythmias(11–15). As patients with non-ischemic DCM are more likely to respond to CRT, their subsequent risk of ventricular arrhythmias may be lower, thus reducing the favourable impact of the ICD.

Limitations of our study

The main limitation of this study is its observational non-randomized nature. The use of propensity score analysis allows for an adjustment on observed variables but residual confounding due to non-observed parameters may still persist. A conclusion on causality can only be achieved through a randomized controlled trial. Nevertheless, considering the large size of our cohort and the use of multiple complementary methods for assessing the effect of the ICD, our results are robust. Also, as CRT-P patients are usually older and have more advanced heart failure and comorbidity than their CRT-D counterparts, any residual confounding would tend to bias the outcome in favour of CRT-D and cannot explain the lack of benefit of the ICD in non-ischemic patients.

Data on inpatient vs. elective implantation was not systematically collected. Inpatients would in theory be at higher risk. However, given that no patient had a history of sustained ventricular arrhythmias, CRT implantation as an inpatient would only be justified on the basis of a recent heart failure decompensation. NYHA class ≥3 and/or NYHA class 4 were much more frequently seen among CRT-P patients, suggesting that these would be more likely to receive their device as an inpatient. This would in theory put them at higher risk, but still the outcome of CRT-P patients in the setting of non-ischemic DCM was similar to that of CRT-D patients.

Also, the most appropriate statistical method for assessing heterogeneity of treatment effects is through a formal test of interaction(42). However, this study lacks the power to detect heterogeneity in treatment effect through a formal test of interaction. Detecting an interaction of the same magnitude as the overall effect would require a sample at least four times as large, and this increases dramatically for more subtle interactions(42). An impractically large cohort of CRT-P patients would be required for an interaction analysis to be powered.

Finally, it must be kept in mind that this study was not powered to show small differences in treatment effect between CRT-D and CRT-P patients with non-ischemic cardiomyopathy. Yet, given the very low risk of SCD amongst patients with non-ischemic cardiomyopathy regardless of device, a very large number of patients would be needed for a statistically significant benefit to be shown. Such small benefit would nonetheless translate into an impractically high number needed to treat.

CONCLUSIONS

Our data suggest that, in CRT-eligible heart failure patients with no history of ventricular arrhythmias, the addition of the ICD conveys a significant survival benefit in patients with ischemic cardiomyopathy but not in patients with non-ischemic DCM.

PERSPECTIVES

Competency in Medical Knowledge 1: Selection of cardiac resynchronization therapy (CRT) defibrillator (CRT-D) or biventricular pacemaker in heart failure patients without a history of ventricular arrhythmias must consider several clinical factors but also the patient's values and preferences.

Competency in Medical Knowledge 1: Patients with non-ischemic dilated cardiomyopathy (DCM) are at lower risk of life-threatening ventricular arrhythmias compared with those with ischemic cardiomyopathy (ICM).

Competency in Patient Care 1: The heart failure patient with ICM and CRT indication should be made aware that the addition of the defibrillator may reduce his risk of sudden cardiac death, although this may come at the cost of increased risk of complications.

Competency in Patient Care 2: The heart failure patient with DCM, no previous history of ventricular arrhythmias and with CRT indication should be made aware that the addition of the defibrillator is unlikely to provide any significant survival benefit but may expose him to increased risk of complications.

Competency in Interpersonal & Communication Skills: It is mandatory to discuss all the pros and cons of the defibrillator with patients who are candidates for CRT.

Translational Outlook: Additional research is needed to establish a risk score which may help Physicians select the patients who are more likely to benefit from CRT-D compared with a biventricular pacemaker.

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FIGURE LEGENDS

Figure 1

Unadjusted Kaplan-Meier survival curves for the four study groups.

Legends: CRT-D- Cardiac resynchronization therapy defibrillator; CRT-P- Cardiac resynchronization therapy pacemaker; N- Number

Figure 2

Survival curves comparing CRT-D vs. CRT-P using cox regression with adjustment on the propensity score and all mortality predictors.

Legends: CRT-D- Cardiac resynchronization therapy defibrillator; CRT-P- Cardiac resynchronization therapy pacemaker; HR- Hazard ratio; N- Number

Table 1–Baseline characteristics of study group (n=5307)

	CRT-D (n=4037)	CRT-P (n=1270)	p-value
Age (years)	65.2±10.7	73±10.1	<0.001
Male gender	84.6% (3417)	57.6% (732)	<0.001
LV 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
Ischemic aetiology	51.9% (2094)	46.3% (588)	0.001
De novo CRT implantation **Upgrade**	88.8% (3584) 11.2% (453)	78.7% (1000) 21.3% (270)	<0.001
History of atrial fibrillation	35.7% (1440)	35.0% (444)	0.7
History of stroke or transient ischemic attack	6.5% (262)	9.4% (119)	0.008
History of lung disease	13.7% (554)	14.3% (182)	0.55
History of Diabetes Mellitus	22.4% (905)	18.9% (240)	0.008
History of cancer	9.8% (396)	12.7% (161)	0.001
Renal dysfunction **GFR ≥60 ml/min** **GFR 30-59 ml/min** **GFR <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	40.3% (1627)	40.1% (509)	0.8
On 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; GFR- Glomerular filtration rate; LV- Left ventricular

Table 2–Baseline characteristics of ischemic cardiomyopathy patients (n=2682)

	CRT-D (n=2094)	CRT-P (n=588)	p-value
Age (years)	67.8±9.3	74.8±8.6	<0.001
Male gender	92.5% (1936)	68.5% (403)	<0.001
LV ejection fraction (%)	26.1±8.0	26.7±8.0	0.16
NYHA class (mean)	2.8±0.6	3.0±0.5	<0.001
NYHA class ≥3	72.9% (1526)	86.4% (508)	<0.001
QRS duration **<120 ms** **120-150 ms** **>150 ms**	 8.6% (180) 41.1% (861) 50.3% (1053)	 5.6% (33) 29.8% (175) 64.6% (380)	<0.001
De novo CRT implantation **Upgrade**	87.5% (1832) 12.5% (262)	78.1% (459) 21.9% (129)	<0.001
History of atrial fibrillation	38.5% (806)	32.1% (189)	0.002
History of stroke or transient ischemic attack	7.5% (158)	11.7% (69)	0.004
History of lung disease	14.7% (307)	15.5% (91)	0.6
History of Diabetes Mellitus	33.7% (706)	23.6% (139)	<0.001
History of cancer	214 (10.2%)	80 (13.6%)	0.016
Renal dysfunction **GFR ≥60 ml/min** **GFR 30-59 ml/min** **GFR <30 ml/min**	 20.6% (431) 45.3% (948) 34.1% (715)	 27.6% (162) 49.3% (290) 23.1% (136)	<0.001
On beta-blockers	80.6% (1688)	64.3% (378)	<0.001
On ACEI/ARA-II	82.1% (1719)	76.5% (450)	<0.001
On aldosterone antagonists	38.4% (803)	38.9% (229)	0.5
On class III antiarrhythmic drugs	27.5% (576)	17.0% (100)	<0.001
Mean follow-up in surviving patients (months)	38.3±28.4	34.5±25.2	0.002

ACEI- Angiotensin converting enzyme inhibitor; ARA-II- Type 2 angiotensin receptor antagonist; CRT-Cardiac resynchronization therapy; GFR- Glomerular filtration rate; LV- Left ventricular

Table 3–Baseline characteristics of non-ischemic dilated cardiomyopathy patients (n=2625)

	CRT-D (n=1943)	CRT-P (n=682)	p-value
Age (years)	62.4±11.3	71.4±11.2	<0.001
Male gender	76.2% (1481)	48.2% (329)	<0.001
LV ejection fraction (%)	24.9±7.2	27.5±9.8	<0.001
NYHA class (mean)	2.7±0.6	2.9±0.6	<0.001
NYHA class ≥3	66.6% (1295)	82.1% (560)	<0.001
QRS duration **<120 ms** **120-150 ms** **>150 ms**	 9.3% (180) 34.9% (678) 55.8% (1085)	 6.5% (44) 29.6% (202) 63.9% (436)	0.001
De novo CRT implantation **Upgrade**	90.2% (1752) 9.8% (191)	79.3% (541) 20.7% (141)	<0.001
History of atrial fibrillation	32.8% (637)	37.5% (256)	0.01
History of stroke or transient ischemic attack	5.4% (104)	7.9% (54)	0.03
History of lung disease	12.8% (248)	13.5% (92)	0.6
History of Diabetes Mellitus	21.7% (422)	13.6% (93)	<0.001
History of cancer	9.4% (182)	12.0% (82)	0.008
Renal dysfunction **GFR ≥60 ml/min** **GFR 30-59 ml/min** **GFR <30 ml/min**	 25.2% (489) 35.5% (690) 39.3% (764)	 35.2% (240) 47.5% (324) 17.3% (118)	<0.001
On beta-blockers	81.7% (1588)	60.0% (409)	<0.001
On ACEI/ARA-II	84.6% (1643)	77.3% (527)	<0.001
On aldosterone antagonists	42.7% (830)	41.8% (285)	0.7
On class III antiarrhythmic drugs	30.1% (584)	18.6% (127)	<0.001
Mean follow-up in surviving patients (months)	39.2±29.8	38.1±26.7	0.4

ACEI- Angiotensin converting enzyme inhibitor; ARA-II- Type 2 angiotensin receptor antagonist; CRT-Cardiac resynchronization therapy; GFR- Glomerular filtration rate; LV- Left ventricular

Table 4– Comparison of standardized differences in the means of continuous and binary variables covariates between treatment groups before and after propensity score matching

	Ischemic cardiomyopathy		Non-ischemic cardiomyopathy	
	Standardized difference before PSM	**Standardized difference after PSM**	**Standardized difference before PSM**	**Standardized difference after PSM**
Age (years)	0.80	0.025	0.80	0.01
Gender	0.63	0.025	0.6	0.02
LV ejection fraction (%)	0.06	0	0.31	0.01
NYHA class (mean)	0.40	0	0.42	0
QRS duration (stratum)	0.27	0.1	0.16	0.02
Upgrade	0.24	0	0.31	0.03
History of atrial fibrillation	0.17	0.04	0.08	0.02
History of stroke or transient ischemic attack	0.1	0.03	0.03	0.04
History of lung disease	0.03	0.03	0.03	0
History of Diabetes Mellitus	0.22	0	0.21	0
History of cancer	0.09	0.03	0.1	0.03
Renal dysfunction (stratum)	0.25	0.01	0.43	0
On beta-blockers	0.36	0.02	0.50	0.02
On ACEI/ARA-II	0.12	0.025	0.18	0.025
On aldosterone antagonists	0.18	0.02	0.25	0.04
On class III antiarrhythmic drugs	0.24	0.025	0.26	0.02

ACEI- Angiotensin converting enzyme inhibitor; ARA-II- Type 2 angiotensin receptor antagonist; LV- Left ventricular; NYHA- New York Heart Association; PSM- Propensity score matching