Patients upgraded to cardiac resynchronization therapy due to pacing-induced cardiomyopathy are at low risk of life-threatening ventricular arrhythmias: a long-term cause-of-death analysis

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ABSTRACT

Aims: Upgrade to cardiac resynchronization therapy (CRT) should be offered to patients who have developed pacing-induced cardiomyopathy with conventional right ventricular pacing. The extent to which those patients would also benefit from defibrillator back-up at the time of CRT upgrade is, however, unknown.

Methods: Retrospective observational cohort study of 199 patients with pacing-induced cardiomyopathy (without history of sustained ventricular arrhythmia), including 104 upgraded to CRT-Pacemaker (CRT-P) and 95 upgraded to CRT-Defibrillator (CRT-D). The incidence of ventricular arrhythmias and, through a cause-of-death analysis based on clinical data and necropsy results, the risk of sudden arrhythmic death were assessed and compared between the two groups.

Results: During a mean follow-up of 66±24 months, 40 (38.5%) CRT-P patients died: three from primary arrhythmic death, while the remaining died of different causes (especially progressive heart failure), giving an incidence of 6.2 sudden arrhythmic deaths per 1000 patient-years. No episode of sustained VT was observed in the study group. There were no sudden arrhythmic deaths in the CRT-D group during a shorter follow-up, but the small and non-significant difference in all-cause mortality between CRT-P and CRT-D groups was mostly accounted for by an increase in non-sudden death. Women upgraded to CRT were at particularly low risk of all-cause mortality compared with men (HR 0.232, p=0.048).

Conclusion: Our findings suggest that patients who develop pacing-induced cardiomyopathy and are upgraded to CRT may not derive any significant benefit from the addition of the defibrillator in the absence of a history of ventricular arrhythmias.

KEYWORDS

Cardiac resynchronization therapy; pacemaker; implantable cardioverter-defibrillator; ventricular arrhythmias; cause-of-death; sudden arrhythmic death.

CONDENSED ABSTRACT

In our retrospective cohort study of 199 patients with pacing induced cardiomyopathy submitted to CRT upgrade, we have found that the risk of sustained ventricular tachycardia or sudden arrhythmic death is very low, and any increased mortality risk in those receiving CRT-P compared with CRT-D is mostly accounted for by an increase in non-sudden death.

WHAT'S NEW?

- Our study provides the largest and longest-term cause-of-death analysis in patients with pacing-induced cardiomyopathy based on post-mortem examinations and death certificates. We have found that the annual risk of sudden arrhythmic death or sustained ventricular arrhythmias in these patients is very low, and similar to a control group implanted with CRT with a defibrillator.

- The small difference in all-cause mortality between CRT-Pacemaker and CRT-Defibrillator in patients with pacing-induced cardiomyopathy is mostly accounted for by an increase in non-sudden death.

- Our results suggest that an upgrade to CRT-Defibrillator in patients with pacing-induced cardiomyopathy may convey no additional benefit when compared with upgrade to CRT-Pacemaker, and the cost-effectiveness ratio of such approach would be above generally accepted benchmarks for therapeutic interventions.

INTRODUCTION

Chronic right ventricular (RV) pacing may have deleterious effects on cardiac structure and function. The cumulative percentage of RV pacing has been shown to associate with the risk of adverse outcomes regardless of baseline LV systolic function (1–3). The upgrade to cardiac resynchronization therapy (CRT) may partially reverse this phenomenon, especially among those with heart failure (4-6). In addition, the benefit conferred by an upgrade to CRT is not inferior to that obtained from *de novo* CRT implantation (4,5).

Despite the lack of large randomized trials, the 2013 European guidelines on cardiac pacing and CRT state that *there is sufficient evidence that, in patients paced for conventional bradycardia indications who, during follow-up, develop severe symptoms of HF and have depressed EF, an upgrading to CRT pacing is likely to reduce hospitalization and improve their symptoms and cardiac performance* (6). Upgrade from conventional pacemaker or implantable cardioverter-defibrillator (ICD) to CRT is thus a class 1 Level of Evidence B indication in heart failure patients with LV ejection fraction <35% and high percentage of ventricular pacing who remain in New York Heart Association (NYHA) class III and ambulatory class IV despite adequate medical treatment (6).

However, whether this specific patient population should also receive defibrillator back-up at the time of CRT upgrade is unknown. On one hand, the majority of CRT upgrades are performed in patients with an LV ejection fraction <35%, thus fulfilling ICD implantation criteria according to the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) (7). On the other hand, some studies suggested that *de novo* CRT-P patients and those upgraded from pacemaker to CRT-defibrillator (CRT-D) have a low annual risk of sustained ventricular arrhythmias and sudden cardiac death (8–10). In addition, chronically RV paced heart failure

patients may respond even better to CRT with greater improvements in ejection fraction and intraventricular dyssynchrony than heart failure patients without RV pacing (11). Despite CRT upgrades making up almost one third of all CRT implants in the European CRT survey (12), no previous study has ever assessed the risk of sudden arrhythmic death in patients with pacing-induced cardiomyopathy.

This study sought to assess, using a cause-of-death analysis approach, the long-term risk of sudden arrhythmic death and ventricular arrhythmias in patients with pacing-induced cardiomyopathy submitted to upgrade to CRT-P (without defibrillator back-up), compared to patients receiving CRT-D.

METHODS

Study design

Retrospective analysis of 104 consecutive patients with pacing-induced cardiomyopathy upgraded to CRT-P in Papworth Hospital between January 2006 and December 2013. We assessed the long-term outcome of these patients, the incidence of sustained and non-sustained ventricular arrhythmias and, through a cause-of-death analysis, their risk of sudden arrhythmic death. We further compared this cohort with a control group of 95 patients with pacing-induced cardiomyopathy and no history of sustained ventricular arrhythmias receiving an upgrade to CRT-D. The latter group was included in the DAI-PP study (*Defibrillateur Automatique Implantable Prevention Primaire;* NCT01992458) (13). We hypothesised that patients with pacing-induced cardiomyopathy could be safely upgraded to a CRT-P device only.

This study complies with the *Declaration of Helsinki* and was approved by our institutional ethics review board.

Patients' eligibility criteria, procedural details and follow-up

During the pre-specified study inclusion period, 170 consecutive patients with previously implanted pacemakers were upgraded to CRT at Papworth Hospital NHS Foundation Trust. This study focused on patients who received successful CRT upgrade in the context of pacing-induced cardiomyopathy, which was defined as the gradual decline in LV systolic function in the context of chronic RV pacing in patients who had normal LV systolic function when they received their first pacemaker and where no other plausible cause for the deterioration was found. Exclusion criteria included any history of known genetic cardiomyopathy (n=4), complex congenital heart disease (n=4) or structural heart disease other than pacing-induced cardiomyopathy (n=3), sustained ventricular arrhythmia (n=4), low percentage of RV pacing (n=10), dual RV pacing after failed LV lead implantation (n=3), history of myocardial infarction or ischaemic cardiomyopathy before CRT upgrade (n=27) or LV ejection fraction <50% at the time of initial pacemaker implantation (n=11). At the time of CRT implant, all patients had a paced QRS duration >120 ms, a LV ejection fraction ≤45% and were on NYHA functional class ≥2 and maximally tolerated medical therapy. This study assessed patients with significant percentages of RV pacing -defined as percent RV pacing >40% given the results of the Dual-Chamber and VVI Implantable Defibrillator (DAVID) trial (1), which has shown this to represent the best cutoff for predicting endpoints. However, median percent RV pacing was 100, as the majority of patients had received their initial pacemaker due to complete heart block. **The final study cohort thus included 104 patients.** All participants had previously undergone coronary

angiography. None of the 104 patients included in this study had a secondary prevention indication for an ICD or a history of unexplained syncope or well tolerated sustained VT and none had had a previous myocardial infarction. Likewise, none had severe organic valvular disease at the time of first pacemaker implantation or any comorbidity thought to limit survival for 12 months at the time of CRT upgrade. **Figure 1** illustrates patient selection.

In all 104 patients included in the study group, the diagnosis of pacing-induced cardiomyopathy was based on the preserved/normal LV function and absence of heart failure symptoms at the time of initial pacemaker implantation and the gradual deterioration of heart failure symptoms and LV systolic function over a period of months to a few years after chronic RV pacing without any other plausible explanation.

The decision to implant a CRT-P rather than CRT-D in those without previous arrhythmic events had several justifications. Firstly, it was our understanding that these cases represented predominantly pacing-induced cardiomyopathy and therefore a potentially reversible cause of LV systolic dysfunction. Secondly, in the United Kingdom ICD therapy for the primary prevention of sudden cardiac death in CRT patients was only recommended in late 2007 by National Institute of Clinical Excellence (NICE) guidelines (almost two years after our study started) (14). Thirdly, NICE guidelines in place at the time the whole study was performed recommended CRT-P rather than CRT-D in patients with non-ischaemic dilated cardiomyopathy (14). Fourth, none of the trials assessing the role of the ICD in primary prevention heart failure patients addressed individuals with pacing-induced cardiomyopathy and therefore there are no guidelines supporting or opposing the use of the defibrillator in this specific patient population. Finally, implanting a CRT-D device associates with higher risk of follow-up complications compared with CRT-P, mostly a result of a higher risk of lead-related complications (15,16).

Devices were routinely upgraded using standard transvenous techniques. In seven cases, CRT upgrade was not possible using a transvenous approach. Four of these patients received a surgical epicardial LV lead within a few weeks and their follow-up started at the time of surgical LV lead implantation. The remaining three received dual RV leads and, as previously mentioned, were excluded from the study. Follow-up visits were performed at 1 and 3 months after CRT upgrade and, in general, every 6 months thereafter. Patients were censored at the time of last-follow-up or death.

The control group consisted of 95 patients included in the DAI-PP study (*Defibrillateur Automatique Implantable Prevention Primaire;* NCT01992458). Briefly, this was a registry on 5,539 patients implanted with an ICD (with or without CRT) in the setting of primary prevention in 12 French centers (13). Our control group included all patients with no history of coronary artery disease or any underlying cardiomyopathy who had an upgrade of pacemaker to CRT-D due to LV systolic function deterioration deemed to be the result of chronic RV pacing. Of the 103 patients who fulfilled these criteria, eight were lost to follow-up and were therefore excluded. None of the patients in the control group had a history of sustained ventricular arrhythmias.

Data Collection

The following data were collected in the study group: demographic characteristics, medical history, indication for original pacemaker implantation, echocardiogram results prior to original pacemaker implantation and prior to CRT upgrade, blood test results at the time of upgrade, medication, CRT responsiveness (defined as a reduction in NYHA class in the first year following upgrade), occurrence of sustained or non-sustained ventricular arrhythmias during follow-up and mortality data including immediate cause of death.

Data on the occurrence of ventricular arrhythmias was obtained from stored intracardiac electrograms. Sustained ventricular tachycardia (VT) was defined as any ventricular arrhythmia lasting for more than 30 seconds, while non-sustained VT (NSVT) was defined as any ventricular arrhythmia lasting between 3 beats and 30 seconds. Bipolar sensing was preferred and devices were routinely programmed to store any spontaneous ventricular rhythm > 160 bpm. Ventricular tachycardia events in the control group were defined as any ICD therapy (antitachycardia pacing or shock) delivered to treat VT or ventricular fibrillation.

Mortality data, including the direct cause of death, were collected through the analysis of death certificates and necropsy results, clinical notes and information provided by the patients' General Practitioners. The latter was important in those cases where the information provided by the death certificate could not unequivocally elucidate on the immediate cause of death. This included all cases where the immediate cause of death in the certificate was reported as "Heart Failure" – in these cases the reported cause of death would have to be corroborated by the clinical history revealing a gradual deterioration of heart failure symptoms and signs over the preceding days or weeks. All patients who had a presumed sudden death had a post-mortem examination which helped elucidate on the immediate cause of death. Information regarding clinical outcome in the study group was collected by two different investigators who were not blind to the purpose of the study or patient data (SB/RD). However, any discordance between these two investigators was discussed with a third investigator who was blind to all patient data and the purpose of the study (PH). Sudden cardiac death was defined as any unexpected death due to cardiac causes which occurred within one hour from the start or acute deterioration of any cardiac-related symptoms. Sudden arrhythmic death was defined as any sudden cardiac death

presumably resulting from a primary ventricular arrhythmia where any other plausible structural cause for sudden death was reliably excluded by the post-mortem examination and clinical history. 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. As mentioned, for heart failure death to be established as the immediate cause of death, a concordance between the information provided by the death certificate and that reported by hospital admission notes and the patient's General Practitioner was necessary. 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.

Study Endpoints

The primary endpoint of this study was the occurrence of a presumed primary sudden arrhythmic death. Secondary endpoints included a composite endpoint of all-cause mortality or cardiac transplantation, the occurrence of sustained or non-sustained ventricular arrhythmias and device-related complications during follow-up. These were defined as any complications reported after the first 24 hours post-procedure which required surgical intervention. These included device-related infection requiring extraction, lead displacement or dysfunction requiring repositioning or replacement and painful pocket or threatened erosion requiring wound revision. Analysis was performed according to the intention-to-treat principle.

Statistical Analysis

Statistical analysis was done using *IBM SPSS Statistics*, v.22. When needed, baseline characteristics are 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. Cox regression analysis was performed to assess the impact of gender on mortality rates over time. Survival curves were performed to illustrate cumulative survival and cumulative survival free of sudden arrhythmic death when adjusted for the risk of non-sudden death. P values <0.05 (two-sided) were considered statistically significant.

RESULTS

Baseline characteristics

Patients' characteristics at the time of CRT upgrade in both study and control groups are described in **table 1**. As expected, patients in the study group were older, had more advanced heart failure and higher degree of comorbidity than those in the control group, reflecting the recognised trend towards ICD implantation in younger and fitter patients.

In the study cohort, mean follow-up for surviving patients was 66±24 months, while the 40 patients who died during follow-up lived for an average of 39±25 months after CRT upgrade. Mean age at the time of the procedure was 72±9.5 years and patients received CRT 5.4±4.7 years following their initial pacemaker implantation. Left ventricular ejection fraction had gradually reduced from a mean 59±6% at the time of initial pacemaker implantation to 30±9% at the time of CRT upgrade.

Long-term outcome and cause-of-death analysis in the study and control group

During a long-term follow-up of the study group, 40 patients died and none had cardiac transplantation (38.5% of the cohort reached the combined outcome), equivalent to an incidence of 83.4 deaths per 1000 patient-years of follow-up or one death per 12 patient-years of follow-up. Of those who died, three had presumed sudden arrhythmic death (7.5% of all deaths), corresponding to an approximate incidence of 6.2 sudden arrhythmic deaths per 1000 patient-years of follow-up or one sudden arrhythmic death per 160 patient-years of follow-up. A total of ten patients (9.6%) had a sudden death: three with primary arrhythmic death (previously mentioned), one with an acute myocardial infarction, three with ruptured aortic aneurysm, two with intracerebral haemorrhage and one with perforated abdominal viscus and gastrointestinal bleeding. Twenty-one patients (20.2% of study cohort) died of a cardiovascular cause while 19 (18.3%) died of a non-cardiovascular cause. **Table 2** lists all causes of death in the study group. It is noteworthy that two of the three patients who had a presumed sudden arrhythmic death were among the 26 who had a LV ejection fraction 36-45% at the time of CRT upgrade (45% and 38%, respectively). There were no significant differences in any of the study endpoints between patients with a LV ejection fraction ≤35% vs. 36-45%.

A sensitivity analysis for gender is illustrated in **Figure 2**, which reveals significantly lower mortality rates for women compared with men. Female gender was a predictor of survival in cox regression analysis when adjusted for age, NYHA class, LV ejection fraction, history of atrial fibrillation, stroke and lung disease and medical treatment (HR for mortality 0.232, p=0.048). For each 2.4 women upgraded to CRT-P due to pacing-induced cardiomyopathy there was one less death compared with men receiving the same treatment.

In the control group, 14 patients died and 4 required cardiac transplantation - 18 reached the combined outcome, 18.9% of the cohort, equivalent to 64.5 deaths or cardiac transplants per 1000 patient-years of follow-up or one death/cardiac transplantation per 15.5 patient-years of follow-up. Of the 14 deaths reported in the control group, 6 were due to heart failure and 6 were non-cardiovascular. In two cases the cause of death was unknown. **Figure 3** illustrates estimates of the time to the various clinical endpoints in both study and control groups. Upgrade to CRT-D did not associate with a lower risk of all-cause mortality when adjusted for age, gender and NYHA class (HR 0.86, 95% CI 0.44-1.70, p=0.67). The NNT to prevent one sudden arrhythmic death in the first 3 years post-CRT upgrade was 53. This means that 53 patients with pacing induced cardiomyopathy would have to be upgraded to CRT-D rather than CRT-P for one sudden arrhythmic death to be prevented over a mean follow-up of 3 years.

Ventricular arrhythmias, device-related complications and CRT responsiveness

During follow-up, 42 patients of the study group (40.4%) experienced at least one episode of non-sustained VT, but there were no episodes of sustained VT. The occurrence of VT was not a predictor of mortality (HR 0.821, 95% CI 0.378-1.779, p=0.6). In the control group, 21 patients (22.3%) experienced at least one ICD therapy during follow-up.

Nine device-related complications requiring intervention were reported during follow-up in the study group, an approximate 1.6% risk per year. An additional two patients developed diaphragmatic stimulation with pacing but no surgical intervention was needed. The occurrence of a complication did not help predict higher mortality risk. However, one patient died of device-related infective endocarditis. In the control group, 18 patients experienced a complication requiring surgical revision (an approximate 6.4% risk per year).

An additional 3 patients had inappropriate ICD shocks. The number needed to harm during a mean follow-up of 3 years was 10. This means there was one additional device-related complication requiring surgical revision during a mean follow-up of 3 years for every 10 patients upgraded to CRT-D compared with the same number of CRT-P patients. **Table 3** lists all device-related complications.

Response to CRT was seen in similar number of cases in both cohorts (77.4% in the study group vs. 83.9% in the control group, p=0.33). Patients who responded to CRT were at much lower mortality risk (HR 0.185, 95% CI 0.096-0.355, p<0.001).

DISCUSSION

Main findings

In this study involving patients with no prior significant arrhythmic events upgraded from pacemaker to CRT-P in the setting of pacing-induced cardiomyopathy, we have found that the annual risk of sudden arrhythmic death or sustained VT is very low, and similar to a control group implanted with CRT-D. The small difference in mortality between CRT-P and CRT-D was mostly accounted for by an increase in non-sudden death. These results suggest that an upgrade to CRT-D in patients with presumed pacing-induced cardiomyopathy may convey no additional benefit when compared with upgrade to CRT-P, and the cost-effectiveness ratio of such approach would be well above generally accepted benchmarks for therapeutic interventions. This is a particularly important issue if we consider the higher risk of device-related complications with CRT-D compared with CRT-P. At the best of our knowledge, this study presents the first long-term cause-of-death analysis and assessment of the risk of sudden arrhythmic death in this specific population of patients with heart failure. The validation of our findings in larger cohorts of patients may have a significant

impact on recommendations regarding the choice of device in the context of pacing-induced cardiomyopathy.

Pacemaker-dependent heart failure patients requiring CRT: do they also need defibrillator back-up?

Almost one third of CRT implants in the European CRT survey were upgrades from previously implanted pacemakers (12). It is accepted that chronic RV pacing may have deleterious effects on cardiac structure and function, presumably due to inter- and intraventricular dyssynchrony. An upgrade to CRT can potentially prevent the reverse remodeling associated with chronic RV pacing. However, it remains unknown whether these patients are at high risk of life-threatening ventricular arrhythmias thus requiring defibrillator back-up. Responders and super-responders to CRT have annual appropriate device therapy incidences of 1.7% to 5.4%, with most studies reporting incidences <2.4%/year (17–21). In the Mona Lisa cohort study, a 4.3% risk of sustained VT in the first 12 months of follow-up was seen in chronic heart failure patients implanted with CRT-P (9). A recent study has shown that pacemaker-dependent patients with no prior documented ventricular arrhythmias or history of CAD upgraded from pacemaker to CRT-D have a very low risk of appropriate ICD therapies (10). Our results corroborate these findings.

Appropriate ICD therapies or VT episodes are not very accurate surrogate markers for arrhythmic mortality. Some of these ventricular arrhythmia episodes receiving appropriate ICD therapies would terminate by themselves and could therefore be labelled as “unnecessary therapies”. The number of appropriate ICD shocks in primary and secondary prevention trials have consistently outnumbered the rate of sudden cardiac deaths in control groups by a factor of 2 to 3 (22). Cause-of-death analysis can therefore

provide superior insight into the true risk of arrhythmic death. In the CERTITUDE cohort study, 95% of the excess mortality among CRT-P subjects, compared with those receiving CRT-D, was related to an increase in non-sudden death (23). Again, our results corroborate those findings. There were only two presumed sudden cardiac deaths over a period of one year in the 198 CRT-P patients naïve to cardiac pacing included in the Mona Lisa study (9). A different study reported a 1.9% risk of sudden cardiac death per year in CRT-P patients previously naïve to cardiac pacing (24). Our study provides the longest-term cause-of-death analysis based on post-mortem examinations and death certificates. Our results suggest that this specific group of patients is at low risk of life-threatening ventricular arrhythmias and sudden arrhythmic death and therefore would not derive a significant survival benefit from the defibrillator while being exposed to a higher risk of complications. The possibility of accurately and continuously detecting severe arrhythmias, with upgrading of CRT-P patients to CRT-D only after objective sustained VT monitoring during follow-up, may remain a safe and cost-effective alternative to systematic CRT-D implantation in these patients.

Main strengths and limitations of this study

The long-term follow-up and cause-of-death analysis based on death certificates and post-mortem examinations are the main strengths of this paper. In addition, this is the largest study on this specific patient population, reflecting the fact that pacing-induced cardiomyopathy requiring upgrade to CRT is relatively rare. For example, out of 262 CRT procedures performed in Papworth Hospital in 2013 only 15 fulfilled our inclusion criteria.

However, some limitations or considerations should be taken into account when interpreting our findings. Firstly, this constitutes non-randomized data and therefore the

two patient groups were not homogeneous. Nevertheless, despite CRT-P patients being older and having higher degree of comorbidity, their all-cause mortality and sudden death rates were similar to those of CRT-D patients, which lends further weight to our conclusions.

Secondly, although this is the largest study on this specific patient population, our findings must be confirmed in larger cohorts of patients with pacing-induced cardiomyopathy before any definite recommendations can be made. However, two important considerations must be made: **i)** as no previous studies on the causes of death of patients with this condition have ever been performed, we cannot make any assumption on the estimated risk of sudden cardiac death and the potential risk reduction with an ICD and therefore a power analysis would be difficult; **ii)** based on the very low risk of sudden cardiac death in patients with pacing-induced cardiomyopathy treated with CRT, an impractically large sample of CRT patients would be required to show any clinically meaningful effect of the ICD.

Thirdly, our study patients received CRT upgrade in the UK while our control group was derived from a French registry. As a result, there may be some differences in how patients were identified as having pacing-induced cardiomyopathy. Our results must be validated in cohorts of patients from different sources.

Fourthly, data on cause of death was collected by two investigators who were not blind to the purpose of the study, allowing in theory the possibility of bias leading to misclassification of some causes of death.

Finally, we did not provide data on device storage information, as this is not routinely retrieved in the UK unless specifically requested. However, it is unlikely that our analysis would have changed significantly had we had access to these data. The main utility

of device storage data is to confirm or exclude arrhythmic death in patients who have sudden unexplained death.

CONCLUSION

Patients without any prior arrhythmic events who are upgraded from pacemaker to cardiac resynchronization therapy in the setting of pacing-induced cardiomyopathy are at low risk of life-threatening ventricular arrhythmias and sudden arrhythmic death and therefore may not derive any significant benefit from the addition of the defibrillator.

CONFLICTS OF INTEREST

None declared.

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TABLES

Table 1– Baseline characteristics

	STUDY GROUP N = 104	**CONTROL GROUP N = 95**	**p-value**
Age at CRT upgrade (years, mean)	72±9.5	66.2±10.8	<0.001
Male gender	77 (74%)	77 (81.1%)	0.19
Left ventricular EF at the time of CRT upgrade (mean, %)	30.5±8.7	27±6	0.002
NYHA functional class (%) - **II** - **III** - **IV (ambulatory)**	 11 (10.6%) 85 (81.7%) 8 (7.7%)	 27 (28.4%) 63 (66.3%) 5 (5.3%)	<0.001
NYHA functional class (mean)	2.85	2.72	0.065
Paced QRS duration > 150 ms	90 (86.5%)	51 (53.9%)	<0.001
History of atrial fibrillation	72 (69.2%)	45 (47.4%)	0.003
History of chronic lung disease	20 (19.2%)	11 (11.6%)	0.18
History of cerebrovascular event	16 (15.4%)	4 (4.2%)	0.016
History of chronic kidney disease *	59 (56.7%)	53 (55.8%)	0.9
Beta-blockers	63 (60.5%)	73 (76.8%)	0.025
ACEI / ARA-II	94 (90.4%)	84 (88.4%)	0.72
Spironolactone or Eplerenone	48 (46.2%)	31 (32.6%)	0.08
Class III antiarrhythmic drugs	11 (10.6%)	36 (37.8%)	<0.001
Follow-up duration (months, mean)	55.4±28	33.5±25	<0.001

Legends: ACEI- Angiotensin converting enzyme inhibitors; ARA-II- Type II angiotensin receptor antagonists; CRT- Cardiac resynchronization therapy; NYHA- New York Heart Association

* Defined as a glomerular filtration rate < 60 ml/min/1.73 m2 according to the MDRD formula

Table 2– Causes and modes of death in the CRT-pacemaker group

CAUSE OF DEATH	**N**
End-stage heart failure	11
Respiratory infection (pneumonia or bronchopneumonia, with or without sepsis)	9
Malignancy	5
Ruptured aortic aneurysm	3
Presumed sudden arrhythmic death	3
Cerebral haemorrhage	2
Respiratory failure due to chronic obstructive pulmonary disease	2
Acute myocardial infarction	1
Perforated abdominal viscus with gastrointestinal bleeding	1
Cardiac amyloidosis*	1
Sepsis due to severe peripheral vascular disease	1
Device-related infective endocarditis	1
Sudden death	10
Non-sudden death	30
Cardiac death	16
Cardiovascular death (cardiac plus vascular)	21
Non-cardiovascular death	19

* Diagnosed after CRT upgrade

Table 3– Device-related complications

COMPLICATIONS DURING FOLLOW-UP	N	
	CRT-Pacemaker	**CRT-Defibrillator**
Lead displacement or dysfunction requiring repositioning or replacement	6	9
Device-related infection requiring extraction	3 *	9
Twitching likely due to micro-dislodgement (managed without surgical revision)	2	-
Inappropriate shock	-	3

* One patient died as a result of device-related infective endocarditis.

FIGURE LEGENDS

Figure 1 – Study inclusion criteria (AV- Atrioventricular; CHD- Congenital heart disease; CRT- Cardiac resynchronization therapy; EF- Ejection fraction; LV- Left ventricular; PM- Pacemaker; RV- Right ventricular)

Figure 2 – Survival curves illustrating cumulative survival according to gender

Figure 3 – Survival curves illustrating cumulative survival (left) and cumulative survival free of sudden arrhythmic death (right)