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Causes-of-death analysis of patients with cardiac resynchronization therapy: an analysis of the CeRtiTuDe cohort study

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Aims The choice of resynchronization therapy between with (CRT-D) and without (CRT-P) a defibrillator remains a contentious issue. Cause-of-death analysis among CRT-P, compared with CRT-D, patients could help evaluate the extent to which CRT-P patients would have additionally benefited from a defibrillator in a daily clinical practice.

Methods and results A total of 1705 consecutive patients implanted with a CRT (CRT-P: 535 and CRT-D: 1170) between 2008 and 2010 were enrolled in CeRtiTuDe, a multicentric prospective follow-up cohort study, with specific adjudication for causes of death at 2 years. Patients with CRT-P compared with CRT-D were older ($P < 0.0001$), less often male ($P < 0.0001$), more symptomatic ($P = 0.0005$), with less coronary artery disease ($P = 0.003$), wider QRS ($P = 0.002$), more atrial fibrillation ($P < 0.0001$), and more co-morbidities ($P = 0.04$). At 2-year follow-up, the annual overall mortality rate was 83.80 [95% confidence interval (CI) 73.41–94.19] per 1000 person-years. The crude mortality rate among CRT-P patients was double compared with CRT-D (relative risk 2.01, 95% CI 1.56–2.58). In a Cox proportional hazards regression analysis, CRT-P remained associated with increased mortality (hazard ratio 1.54, 95% CI 1.07–2.21, $P = 0.0209$), although other potential confounders may persist. By cause-of-death analysis, 95% of the excess mortality among CRT-P subjects was related to an increase in non-sudden death.

Conclusion When compared with CRT-D patients, excess mortality in CRT-P recipients was mainly due to non-sudden death. Our findings suggest that CRT-P patients, as currently selected in routine clinical practice, would not potentially benefit with the addition of a defibrillator.

Keywords Heart failure • Sudden death • Cardioverter defibrillator • Competing risk • Cardiac resynchronization

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Introduction

Patients with congestive heart failure (HF) are at high risk of dying from its progression as well from sudden cardiac death related to ventricular tachyarrhythmia.[1] Over the last decade, cardiac resynchronization therapy (CRT) and implantable cardioverter defibrillators (ICDs) have markedly improved the prognosis of HF patients, with prolongation of survival over and above that conferred by medical therapy alone.[2–5] It has been well established in trials that in patients with severe left ventricular (LV) systolic dysfunction, New York Heart Association (NYHA) class III/IV symptoms, and wide QRS, CRT improves symptoms/quality of life and also reduces mortality.[3,6] Additionally, more recent trials have shown beneficial reverse LV remodelling even in patients with milder symptoms.[5,7–11] This has resulted in a class I recommendation for CRT in appropriately selected candidates in guidelines framed on both sides of the Atlantic.[12,13]

Since most patients who are candidates for CRT will have a LV ejection fraction (EF) of ≤35%, this 'automatically' makes them candidates for an ICD as well by the current guidelines, which makes the assumption that there is universally significant excess mortality due to sudden cardiac death (SCD) among CRT-P patients who can therefore definitively benefit from the added defibrillator.[13] However, concrete evidence for such a premise in a contemporary CRT-P population is lacking and in any population of this kind; competing risks for mortality need to be carefully considered. A few studies have attempted to directly compare outcomes between CRT-P vs. CRT-D subjects.[14,15] Furthermore, such outcome comparisons based on observational studies have methodological limitations and may be biased. Current guidelines do not make firm recommendations in terms of the choice between CRT-P vs. CRT-D, leaving room for physician discretion. This has resulted in wide variation in the rates of implantation worldwide. For instance, the proportion of CRT implantations, which are CRT-D, reaches >90% in most practices in the USA,[16] whereas it is relatively lesser across Europe.[17] The use of CRT-D or CRT-P in clinical practice is an important question with significant implications in terms of costs,[18] as well as device-related complications.[19,20]

In this context, a better understanding of the relative contribution of SCD as opposed to other competing causes of mortality in the CRT population can be very informative. A cause-of-death analysis among CRT-P vs. CRT-D patients, may represent a novel approach to this problem. Using a large, multicentre study with prospective follow-up, we evaluated the characteristics of CRT-P vs. CRT-D patients in a real-world scenario and analysed to what extent CRT-P subjects, as currently chosen in clinical practice, would have potentially additionally benefited from the presence of a back-up defibrillator.

Methods

Setting and design of the study

CeRtiTuDe, a 2-year, prospective, multicentre registry launched in January 2008 and held under the direction of the Working Group on Pacing and Arrhythmias of the French Society of Cardiology, was funded and coordinated by the French Society of Cardiology. Its primary objective was to define the baseline characteristics and clinical outcomes of French patients who undergo implantation of CRT systems. An analysis of the precise causes of death was planned at 2 years after device implantation.

The 41 medical centres participating in the study (Appendix) enrolled consecutive patients who, between 1 January 2008 and 31 December 2010, had undergone CRT device implantations. The criteria for CRT implantation were as per the 2007 guidelines of the European Society of Cardiology and European Heart Rhythm Association, updated in 2010. However, all CRT recipients were enrolled, in order for the registry to reflect 'real-world' medical practice. Each patient was then enrolled in a specific follow-up programme with clinical, ECG, echocardiographic, and device interrogation data collected every 6 months over the following 2 years (up to 1 January 2013).

The study was conducted in accordance with Good Clinical Practice, French Law, and the French data protection law. The protocol was reviewed by the Committee for the Protection of Human Subjects in Biomedical Research (CCTIRS #08-522) and the data file was reported to, and authorized by, the Commission Nationale Informatique et des Libertés (French Data Protection Committee, CNIL #909048).

Baseline characteristics at implant

Individual patient data were collected, using an electronic case report form created by the Scientific Committee to record, at each participating medical centre, the demographic and baseline clinical characteristics, and the implantation procedures and techniques. These data were regularly transferred (every 3 months) via an internet-based system to a central database created at the data management centre of the French Society of Cardiology in collaboration with the Paris Cardiovascular Research Center, European Georges Pompidou Hospital, Paris (INSERM Unit 970).

All variables recorded before device implantation were defined and classified using standard clinical terminology, including gender, age (stratified as <60, 60–74, and ≥75 years), and underlying heart disease (ischaemic vs. non-ischaemic). Renal clearance was estimated using the Cockroft and Gault's formula, and defined as severe renal insufficiency if <30 mL/min/1.73 m^2, and QRS duration was classified as ≤120, 121–149, and ≥150 ms. Left ventricular ejection fraction was measured on transthoracic echocardiograms, using Simpson's method, and recorded as a continuous variable and also stratified as ≤20, 21–35, and >35%. A history of atrial fibrillation (AF) was based on medical records, and classified as paroxysmal or permanent. In addition to AF and renal failure, other co-morbidities were systematically recorded, including cancer, chronic obstructive pulmonary disease, liver disease, diabetes mellitus, and cerebral vascular disease.

Device implant, hospital discharge, and follow-up

The type of CRT (CRT-P or CRT-D) implanted was recorded without the manufacturer's information. The complications recorded included infections, changes in capture threshold, lead dislodgement, haematomas, HF, fever, arrhythmias, pneumothorax, phrenic nerve stimulation, and death. Finally, drug regimens prescribed at the time of hospital discharge including beta-adrenergic blockers, anti-arrhythmics, digoxin, calcium antagonists, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, mineralocorticoid receptor antagonists, diuretics, and anticoagulants were recorded. Device programming was left to the discretion of the investigators at each centre, with the guiding principle being achievement of maximal biventricular pacing.

All patients were followed at 6-month intervals for 2 years by the implanting centre till the close of study on 1 January 2013. At each follow-up, the patients underwent clinical examination, ECG, transthoracic

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echocardiogram, and device interrogation. In addition, information on any intercurrent events (such as hospitalization) was also recorded in the file. The above data were systematically gathered at each follow-up visit from the date of device implantation to study closure or death or heart transplantation.

Vital status, specific causes of death, and adjudication process

The investigators at each enrolling centre recorded major clinical events, using a standardized form, and a Clinical Events Committee verified their accuracy by contacting the attending physicians or the patients as required, on a yearly basis, focusing on the vital status and on the specific modes and causes of death and on major clinical events or interventions during follow-up, including changes in drug regimens, as well as interim hospitalizations. Sources to ascertain the vital status also included registries of the patients' birthplaces, the French National Institute of Health and Medical Research (INSERM CépiDc Unit—Le Kremlin-Bicêtre, France), and the French National Institute of Statistics and Economical Studies.

The cause-of-death were classified as sudden if the patient (i) died suddenly and unexpectedly within 1 h of symptoms in the absence of progressive cardiac deterioration, (ii) died unexpectedly in sleep, or (iii) died unexpectedly within 24 h after last being seen alive and in the usual state of health. Other cardiovascular deaths included myocardial infarction, HF, acute aortic syndrome, stroke, and pulmonary embolism. Fatal arrhythmias associated with end-stage HF were classified as non-sudden cardiovascular deaths. Deaths attributable to causes, such as cancer, infectious disease, or renal or respiratory failure, were classified as non-cardiovascular. When inadequate or no data were available, the cause of death was classified as unknown or unidentifiable. We used multiple sources to assess and finally adjudicate the cause of death, which included medical data obtained by the regional investigators, pathology report, Emergency Medical Services report, as well as data from the French Center on Medical Causes of Death (INSERM CépiDc unit), which is able to provide the causes of death occurring in France.

Statistical analysis

This report was prepared in compliance with the STROBE checklist for observational studies.[21] Continuous variables are presented as mean $\pm$ standard deviation and categorical variables are presented as numbers and percentages. Comparisons between groups (patients with CRT-P vs. patients with CRT-D) were made, using the χ^2 or Fisher's exact tests for discrete variables and with unpaired *t*-tests, Wilcoxon signed-rank tests, or one-way analysis of variance for continuous variables. Factors associated with the implantation of CRT-P were identified, using a multiple variable, stepwise, logistic regression analysis.

Kaplan–Meier curves were constructed to estimate the 2-year survival, and CRT-P and CRT-D groups were compared using the log-rank test. For the cause-specific mortality, we used a competing risk analysis and estimated the cumulative incidence function. We then used Gray tests to assess the difference between the CRT-P and CRT-D groups.[22] A Cox proportional hazards regression analysis was used to identify variables independently associated with overall mortality. The proportional hazard assumptions were tested. The crude associations between mortality and different variables (listed in *Table 1*) were first quantified by univariate Cox regression. All covariates that reached a significance level of $P < 15\%$ were then included in an initial multivariate regression model. A stepwise selection was applied to obtain a final model that included covariates with $P < 5\%$. Given the observational design of the study and minimization of indication bias for device implantation, propensity score analyses were conducted. We estimated the propensity score of receiving a CRT-P therapy by fitting a logistic regression model using age, sex, AF, LVEF, aetiology of HF, NYHA, and beta-adrenergic blockers as covariates. We then matched patients who received CRT-D therapy with those who received CRT-P in an 1 : 1 ratio using a greedy matching algorithm with a maximum allowable difference of 0.05 (see Supplementary material online, *Table S1* and *Figure S1*). Patients who could not be matched using these criteria were removed from the analysis. Then, the association between device type and mortality was repeated after propensity score matching (462 patients). All data were analysed at INSERM, Unit 970, Cardiovascular Epidemiology and Sudden Death, Paris, using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

Baseline characteristics and device implantation

Overall, a total of 1705 consecutive patients were enrolled in the study and received CRT devices. The mean age of the overall population was 68.8 $\pm$ 11.1 years, 33% were >75 years of age, and 77% were men. Nearly 20% had been hospitalized for decompensated HF within the previous 6 months. The heart disease was ischaemic in 47% of patients and related to non-ischaemic dilated cardiomyopathy in 53%. Overall, 29% of patients presented with a LVEF of $\leq$20% at the time of implantation.

A CRT-D was implanted in 1170 patients (69%). Overall, 13% of the CRT-D group was implanted in the secondary prevention, following symptomatic ventricular tachycardia or sudden cardiac arrest. Patients with CRT-P compared with CRT-D were older (75.9 vs. 65.6 years, $P < 0.0001$), less often male (69.5 vs. 80.8%, $P < 0.0001$), more symptomatic (proportion of NYHA class III/IV, 87.9 vs. 80.8%, $P = 0.0005$), with less coronary artery disease (40.7 vs. 49.3%, $P = 0.003$), wider QRS (160.8 vs. 154.9 ms, $P = 0.002$), more AF (38.7 vs. 22.1%, $P < 0.0001$), and more comorbidities ($\geq$2 comorbidities, 16.9 vs. 12.9%, $P = 0.04$; *Table 1*). Independent variables associated with CRT-P (vs. CRT-D) implantation are depicted in *Table 2*.

Fatal periprocedural complications occurred in one patient, and death occurred before hospital discharge in five others (0.3%), due to severe cardiogenic shock. Overall, significant perioperative complications occurred in 133 subjects (7.8%) without significant difference between CRT-D and CRT-P (8.9 vs. 6.7%, $P = 0.20$). Pulse generator pocket haematoma (2.5%), lead dislodgment (1.6%), and phrenic nerve stimulation (1.6%) were the most frequent complications, and the need for new intervention during the same hospital stay was observed in 40 patients (2.3%).

Follow-up, overall mortality, and specific causes of death

The 1705 consecutive patients enrolled in the study were followed for a mean of 665.6 $\pm$ 173.8 days (1.0–730.5 days). At 2-year follow-up (completed in 94.5% of subjects), 267 patients died, giving an overall annual mortality rate of 83.8% (95% CI 73.4–94.2) per 1000 person-years, with a higher rate among CRT-P, compared with CRT-D, patients [130.8 vs. 65.1 per 1000 year, respectively, relative risk (RR) 2.01, 95% CI 1.56–2.58, $P < 0.0001$; *Figure 1A*].

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Table 1 Characteristics of the entire registry sample and of the CRT-P vs. CRT-D recipients

	Total (*N* = 1705)	CRT-D (*N* = 1170)	CRT-P (*N* = 535)	*P*-value
Age (years)	68.8 ± 11.1	65.6 ± 10.4	75.9 ± 9.0	<0.0001
Men	1317 (77.2)	945 (80.8)	372 (69.5)	<0.0001
Heart disease				
Ischaemic	724 (47.0)	556 (49.3)	168 (40.7)	0.0026
Non-ischaemic	816 (53.0)	571 (50.7)	245 (59.3)	
QRS duration				
Mean (ms)	157.7 ± 27.1	155.0 ± 26.2	160.8 ± 29.0	0.0018
Left ventricular ejection fraction				
Median, %	25.5 (10.0)	25.5 (10.0)	25.5 (10.0)	0.084
≤20%	484 (29.3)	333 (29.2)	151 (29.6)	<0.0001
21–35%	1078 (65.3)	764 (67.1)	314 (61.5)	
>35%	88 (5.3)	42 (3.7)	46 (9.0)	
New York Heart Association functional class				
I	16 (1.0)	14 (1.3)	2 (0.4)	<0.0001
II	250 (16.0)	194 (18.0)	56 (11.7)	
III	1188 (76.2)	824 (76.2)	364 (76.0)	
IV	106 (6.8)	49 (4.5)	57 (11.9)	
History of:				
Atrial fibrillation	445 (27.3)	248 (22.1)	197 (38.7)	<0.0001
Renal insufficiency	211 (14.4)	138 (13.0)	73 (18.2)	0.0128
COPD	264 (18.1)	198 (18.7)	66 (16.4)	0.3120
Cancer	122 (8.4)	88 (8.3)	34 (8.5)	0.9272
Miscellaneous disorders	266 (18.2)	174 (16.4)	92 (22.9)	0.0043
Drug therapy at the time of implantation				
Diuretics	1045 (66.2)	752 (69.2)	293 (59.6)	0.0002
ACE inhibitors/ARB	1057 (66.9)	792 (72.9)	265 (53.9)	<0.0001
MRA	404 (25.6)	331 (30.5)	73 (14.8)	<0.0001
Beta-adrenergic blockers	945 (59.9)	732 (67.3)	213 (43.3)	<0.0001
Oral anticoagulant agent	658 (41.7)	438 (40.3)	220 (44.7)	0.0989
Antiplatelet agents	693 (43.9)	512 (47.1)	181 (36.8)	0.0001

Values are means ± SD, median (IQR), or numbers (%) of observations.
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; MRA, mineralocorticoid receptor antagonist; CRT-D: cardiac resynchronization therapy with defibrillator; CRT-P: cardiac resynchronization therapy without defibrillator.

The incidence of SCD was not statistically higher in the CRT-P group compared with CRT-D (RR 1.57, 95% CI 0.71–3.46, $P = 0.42$) (*Figure 1B*). The rate of hospitalization for HF was not different between the CRT-D vs. CRT-P groups (19.6 vs. 22.0%, $P = 0.28$).

After considering potential confounding factors in a Cox proportional hazards regression analysis, CRT-P remained associated with increased mortality [hazard ratio (HR) 1.54, 95% CI 1.07–2.21, $P = 0.0209$], as well as the presence of co-morbidities (HR 1.98, 95% CI 1.34–2.92, $P = 0.0006$) and functional NYHA class IV (HR 1.85, 95% CI 1.10–3.11, $P = 0.0207$). Using the propensity-matched cohort, CRT-P was associated with increased mortality (RR 2.0, 95% CI 1.22–3.28, $P = 0.01$). Cardiac resynchronization therapy without defibrillator was not associated with a higher incidence of SCD (RR 1.21, 95% CI 0.45–3.29, $P = 0.70$). Forest plots showing hazard ratios of CRT-P vs. CRT-D for mortality by different subgroups were represented in *Figure 2*.

However, when considering the specific cause-of-death analysis (*Table 3*), the increase in mortality among CRT-P patients was not related to that in SCD, though SCD incidence was higher in the CRT-P group: 11.8 per 1000 among CRT-P vs. 7.5 per 1000 among CRT-D recipients ($P = 0.26$). The main reasons for the almost twice-higher risk of death in the CRT-P group were an increase in non-SCD cardiovascular mortality, mainly comprising progressive HF (RR 2.27, 95% CI 1.62–3.18) as well as other cardiovascular mortality (RR 4.40, 95% CI 1.29–15.03). Overall, 95% of the excess mortality among CRT-P recipients was not related to SCD.

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Table 2 Independent variables associated with CRT-P (vs. CRT-D) implantation

Variables	OR	95% CI	*P*-value
Age	1.17	1.14–1.19	<0.0001
Female	1.78	1.24–2.55	0.0018
Dilated non-ischaemic cardiomyopathy	1.75	1.28–2.40	0.0005
Atrial fibrillation	1.58	1.14–2.20	0.0062
LVEF <25%	1.05	1.02–1.07	0.0001
NYHA IV	2.82	1.61–4.92	0.0003
No beta-adrenergic blockers	2.40	1.76–3.26	<0.0001

LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; CRT-D: cardiac resynchronization therapy with defibrillator; CRT-P: cardiac resynchronization therapy without defibrillator.

Discussion

To the best of our knowledge, our study provides the first cause-of-death analysis comparing CRT-P with CRT-D patients in a real-world population. We demonstrate that CRT-P patients, as chosen in routine clinical practice, were older, more likely to be female, with less ischaemic heart disease, more advanced HF, and greater co-morbidity burden compared with CRT-D patients. These characteristics of the CRT-P patients are in agreement with previous reports.[14,19] At 2 years, the overall mortality in the CRT-P group was greater than that in the CRT-D group. However, importantly, this difference in mortality was mostly accounted for by an increase in non-SCD. Since SCD did not significantly contribute to the excess mortality in the CRT-P group, it suggests that the presence of a back-up defibrillator would probably not have been beneficial in terms of improving survival for these patients. The rates of HF hospitalization were greater in the CRT-P group, which is in line with the greater HF mortality in this group. This is likely related to a sicker population with more co-morbidity, older age, and potentially more severe HF and serves to highlight that progressive HF rather than SCD may be the main driver of morbidity as well as mortality in the CRT-P population. These results from a large, prospective cohort with robust cause-of-death adjudication need careful consideration in the context of the current controversy in the selection of CRT-P vs. CRT-D. Our study is not intended as a direct comparison of outcomes between CRT-D and CRT-P, and subgroup analyses should be interpreted with caution. While direct comparisons in observational studies may reveal differences in death rates, knowledge of what makes up this difference takes our understanding an important step further. Cause-of-death analysis, while being technically challenging to perform in a large population, represents an innovative, alternate approach to this problem. It also helps bring to the forefront the issue of competing risks for mortality in any population of this nature.

With the exception of patients with AF, where the evidence-base is admittedly weaker,[20] CRT represents an important therapeutic option for a growing segment of the HF population. Though the guidelines presently do not make definitive recommendations for CRT-D vs. CRT-P, in practice, many physicians may feel compelled to use CRT-D, as a defibrillator is considered 'necessary' in the presence of low LVEF. The effect of this choice may be even greater in light of the fact that many centres are exploring broader indications for CRT in patients with milder symptoms and narrow QRS.[23] This has important economic implications in that the incremental cost of CRT-D over CRT-P is significantly greater when compared with the cost over optimal medical therapy and this difference is even steeper in the older age group.[24] The addition of a defibrillator lead can also contribute to additional adverse events and need for repeat procedures.[25] Thus, there is a fairly urgent need for more data such as from the present study to tease out the putative benefits of an added defibrillator over CRT-P,[25] and to better define optimal criteria to select CRT-P or CRT-D. Since the CRT-P group had a greater proportion of non-ischaemic cardiomyopathy where the benefit from primary preventive ICD is lower, this could influence results as well.[6] In the absence of proven superiority by trials and the small survival benefit, the 2013 European Society of Cardiology Task Force was of the opinion that no strict recommendations can be made, and has preferred to merely offer guidance regarding the selection of patients for CRT-D or CRT-P,[13] based on overall clinical condition, device-related complications, and cost; factors favouring CRT-P being advanced HF, co-morbidities, including frailty and cachexia. In contrast, factors favouring CRT-D implantation are life expectancy >1 year, stable HF, moderate functional status, ischaemic heart disease, and lack of comorbidities being in favour of CRT-D implantation, and the French practice appears to be in agreement with this.

The only randomized trial to have CRT-P as well as CRT-D arms—the COMPANION trial did not show a significant benefit of CRT-D over CRT-P for the primary endpoint.[6] However, the study was not powered to compare these two treatments. Non-randomized studies, which have compared outcomes for these two modalities, have yielded conflicting results. Using registry-based data, Morani *et al.*[14] showed that among patients with an European Society of Cardiology Class IA indication for CRT, CRT-D was associated with better survival than CRT-P. Similar findings were reported from a US-based registry, which concluded that 'CRT-D should be recommended to most congestive HF patients with indications for biventricular pacing'.[27] However, recent experience with reasonable numbers of patients emphasized the higher risk of mortality among CRT-P patients compared with CRT-D, indicating that long-term benefit of an additional defibrillator may be restricted to a selected subgroup.[15,19] Furthermore, logistic regression models which are relied on in comparative studies to draw conclusions, may not adequately overcome the limitations in comparing heterogeneous groups.[28] A Bayesian network meta-analysis in 2007 concluded that evidence from randomized trials is insufficient to prove the superiority of CRT-D over CRT-P.[29]

Whether CRT-P by itself reduces risk of arrhythmia is still a matter of some debate. Long-term data from CARE-HF show reduction in SCD rates by CRT.[30] A mechanistic link is supported by the fact that SCD is reduced in subjects with systolic HF and ventricular dyssynchrony.[31] Recent analysis from the MADIT-CRT trial showed that risk of ventricular arrhythmias was significantly reduced in CRT patients with normalization of LVEF. Importantly, risk of inappropriate ICD therapy was unchanged, suggesting that these

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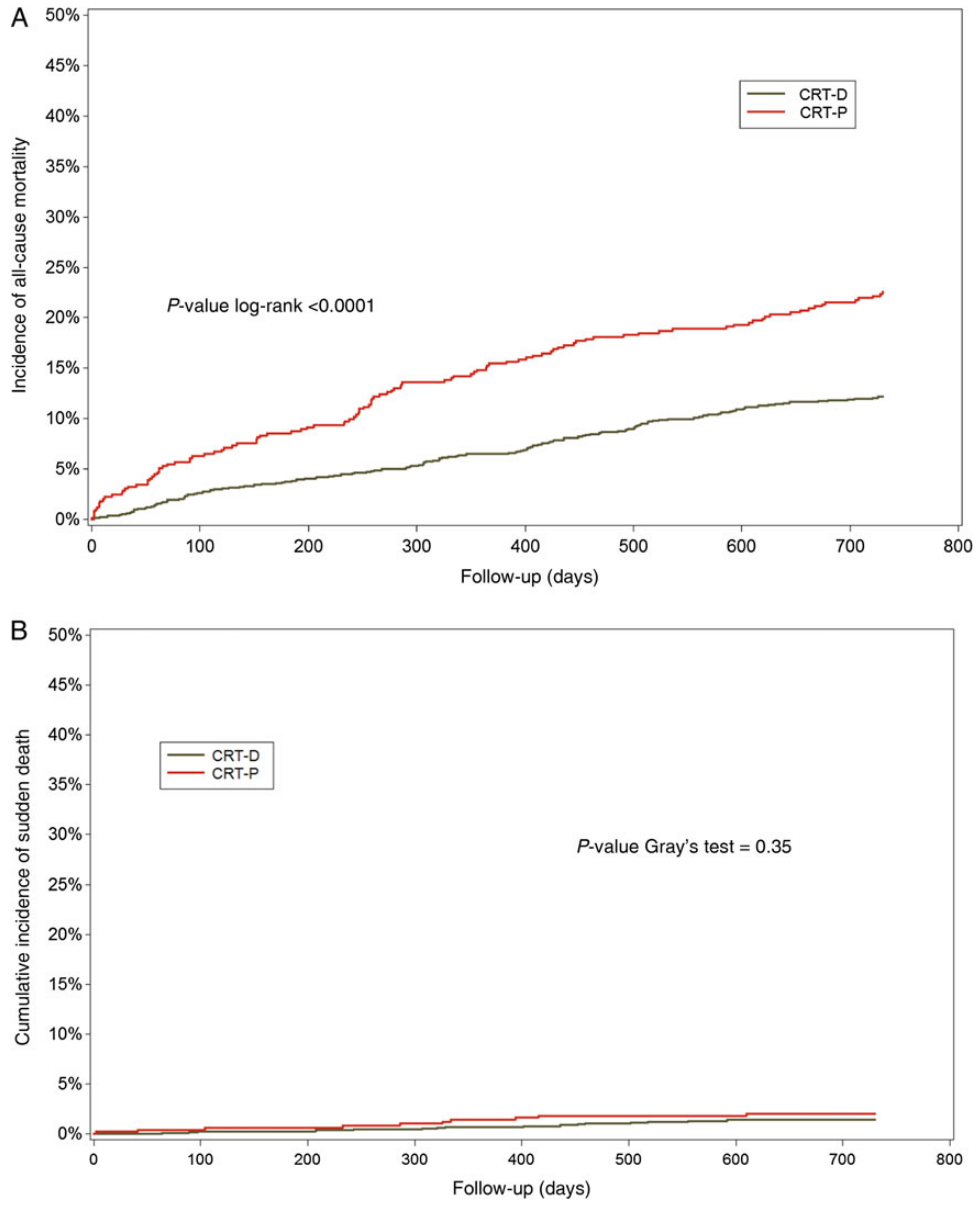

Figure 1 Overall mortality incidence over time according to CRT-P and CRT-D groups. (*A*) Overall mortality and (*B*) sudden cardiac death. CRT-D: cardiac resynchronization therapy with defibrillator; CRT-P: cardiac resynchronization therapy without defibrillator.

patients may be better served by a downgrade to CRT-P at device change.[32] Similarly, another study showed that based on LVEF improvement, up to one-third of CRT-D patients no longer had an ongoing indication for ICD at the time of battery change and the rate of device therapy in this group was very low.[33] By inducing favourable remodelling of the LV, CRT may reduce the substrate for ventricular arrhythmias. Some patients experience rapid reverse remodelling ('super responders'), with major improvement in EF so that they are no longer ICD candidates. Data suggest that such patients have excellent long-term prognosis.[34,35] In anticipation of rapid improvement of LVEF, it would seem logical to provide temporary protection against SCD such as using a life vest rather than implanting a defibrillator. However, although predictors of super response have been proposed,[36,37] it is still difficult to identify such super responders with a high degree of confidence; thus, more work may be needed in this regard. The rationale for an anti-arrhythmic effect of CRT is also tempered to some extent by concerns over the pro-arrhythmic effects of LV pacing.[38,39] Prospective follow-up of patients with CRT-P has shown that the incidence was overall relatively low, and that sudden cardiac death events were likely to be preceded by recorded sustained ventricular arrhythmias, emphasizing the importance of regular CRT-P device memory interrogation, as well as the potential benefit of remote monitoring in these patients, for possible urgent upgrading to CRT-D.[40] The possibility of accurate and continuous surveillance to detect life-threatening arrhythmias, with upgrading of CRT-P patients to CRT-D only after

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such objective documentation during follow-up, might represent a safe and cost-effective alternative to the practice of universal CRT-D implantation in all CRT candidates.

Our results should not be interpreted as a general lack of benefit from CRT-D vs. CRT-P or *vice versa*. Rather, we demonstrate that given currently selected CRT-P patients in the French population, addition of a defibrillator may not significantly add to survival. At least in a subset of the 'CRT eligible' HF population, competing risks of non-sudden death may diminish the incremental value of adding a defibrillator to CRT; therefore, all patients eligible for CRT cannot be 'automatically' considered as requiring a CRT-D. Thus, in a broader context, the requirement for CRT-D in similar populations needs careful consideration of the putative risks and benefits.

Relative strengths of the present study include the fact that it is prospective, multicentric with dedicated cause-of-death adjudication. However, we acknowledge some limitations. First, the study was non-randomized and therefore, selection bias may have influenced results. The clinical decision concerning device type may affect subsequent management as well lead to variations in clinical care. On the other hand, randomized trials, while being a rigorous design, have rigid selection criteria, which often do not reflect real-world scenarios. Though the results need to be interpreted with caution in view of potential confounding, it reflects actual clinical practice. Secondly, follow-up was censured at 2 years, which can influence results as device utilization is a function of time; however, there were adequate events during follow-up to draw reasonable conclusions. Thirdly, information on QRS morphology was unavailable and the extent of LBBB in the two groups may have influenced CRT outcomes. Finally, although our study suggests that mortality in this real-world CRT-P population may not be improved by upgrade to CRT-D, it does not address the question of whether, in the population implanted with a CRT-D device, CRT-P would perform just as well. Thus, this study was not intended to answer the question of whether CRT-P is comparable with CRT-D overall, but rather provides a real-world assessment of cause of death in a contemporary CRT-P vs. CRT-D population, which we believe can more meaningfully inform clinical practice. It should be borne in mind that these outcomes mainly pertain to a HF population with broad QRS.

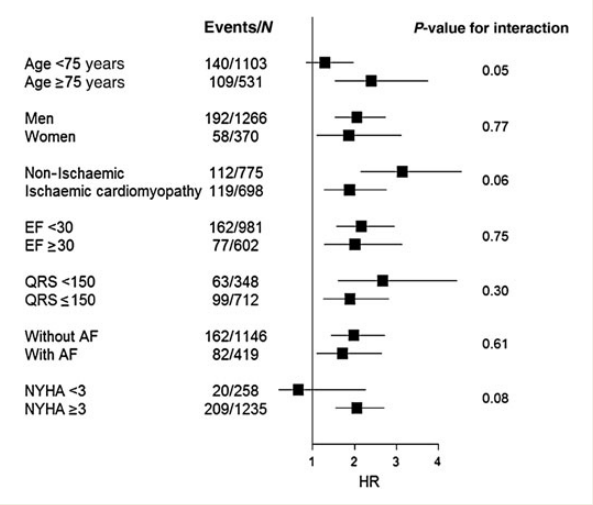

Figure 2 Forest plots showing unadjusted hazard ratios of CRT-P vs. CRT-D for mortality by different subgroups. CRT-D: cardiac resynchronization therapy with defibrillator; CRT-P: cardiac resynchronization therapy without defibrillator.

Conclusion

In this prospective, multicentre cohort study, CRT-P patients were older, with more advanced HF, and co-morbidities when compared with CRT-D recipients. At 2-year follow-up, CRT-P patients had 2-fold higher mortality than CRT-D. By cause-of-death analysis, the excess mortality among CRT-P subjects was almost entirely related to non-SCD. Our results indicate that CRT-P patients, as currently selected in routine clinical practice, would potentially not benefit from addition of a defibrillator, emphasizing that there is still considerable room for CRT-P in the present day HF treatment.

Authors' contributions

E.M., S.J., M.-C.P., J.-P.E., and X.J.: performed statistical analysis; J.-Y.L.H.: handled funding and supervision; E.M., J.L.-G., M.-C.P., and G.M.: acquired the data; E.M., C.L., M.C., G.M., J.-C.D., and J.-Y.L.H.: conceived and designed the research; C.L., K.N., S.B., D.K., P.D., and O.P.: drafted the manuscript; J.-C.D., J.-S.H., P.M., D.G., O.C., F.H.-L., F.A., P.C., and P.M.: made critical revision of the manuscript for key intellectual content.

Table 3 Incidence of specific causes of death among CRT-P and CRT-D recipients

Incidences (per 1000 patient-years)	CRT-P (*N* = 535)	CRT-D (*N* = 1170)	Unadjusted risk ratio (95% CI)
Total mortality	130.8	65.1	2.01 (1.56–2.58)
Cardiovascular			
Heart failure	75.4	33.3	2.27 (1.62–3.18)
Sudden death	11.8	7.5	1.57 (0.71–3.46)
Others	8.3	1.9	4.40 (1.29–15.03)
Device-related	1.2	2.8	0.42 (0.05–3.48)
Non-cardiovascular	31.8	19.7	1.62 (1.00–2.62)

CRT-D: cardiac resynchronization therapy with defibrillator; CRT-P: cardiac resynchronization therapy without defibrillator.

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Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Conflict of interest: S.B. is a consultant for Medtronic, Inc., Boston Scientific, and Sorin Group. P.D. is a consultant for Medtronic, Boston Scientific. and Sorin Group. D.G. is a consultant for Medtronic, Boston Scientific, Saint Jude Medical, and Biotronik. C.L. received lectures and honorarium from Medtronic, Inc., Boston Scientific, St. Jude Medical, Biotronik, and Sorin Group. P.M. received lectures and honorarium from Boston Scientific, Biotronik, and Sorin Group. O.P. received lectures and honorarium from Medtronic, Inc., St. Jude Medical, Biotronik, and Sorin Group. F.H.-L. is a consultant for Medtronic, Inc., and Biotronik. S.C. is a consultant for Medtronic and Sorin Group.

Appendix

The following investigators and institutions participated in the conception of the registry, and in the organization, collection, storage, and analysis of the data.

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