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CLINICAL RESEARCH
Heart failure/cardiomyopathy

Very long-term survival and late sudden cardiac death in cardiac resynchronization therapy patients

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Aims The very long-term outcome of patients who survive the first few years after receiving cardiac resynchronization therapy (CRT) has not been well described thus far. We aimed to provide long-term outcomes, especially with regard to the occurrence of sudden cardiac death (SCD), in CRT patients without (CRT-P) and with defibrillator (CRT-D).

Methods and results A total of 1775 patients, with ischaemic or non-ischaemic dilated cardiomyopathy, who were alive 5 years after CRT implantation, were enrolled in this multicentre European observational cohort study. Overall long-term mortality rates and specific causes of death were assessed, with a focus on late SCD. Over a mean follow-up of 30 months (interquartile range 10–42 months) beyond the first 5 years, we observed 473 deaths. The annual age-standardized mortality rates of CRT-D and CRT-P patients were 40.4 [95% confidence interval (CI) 35.3–45.5] and 97.2 (95% CI 85.5–109.9) per 1000 patient-years, respectively. The adjusted hazard ratio (HR) for all-cause mortality was 0.99 (95% CI 0.79–1.22). Twenty-nine patients in total died of late SCD (14 with CRT-P, 15 with CRT-D), corresponding to 6.1% of all causes of death in both device groups. Specific annual SCD rates were 8.5 and 5.8 per 1000 patient-years in CRT-P and CRT-D patients, respectively, with no significant difference between groups (adjusted HR 1.0, 95% CI 0.45–2.44). Death due to progressive heart failure represented the principal cause of death (42.8% in CRT-P patients and 52.6% among CRT-D recipients), whereas approximately one-third of deaths in both device groups were due to non-cardiovascular death.

Conclusion In this first description of very long-term outcomes among CRT recipients, progressive heart failure death still represented the most frequent cause of death in patients surviving the first 5 years after CRT implant. In contrast, SCD represents a very low proportion of late mortality irrespective of the presence of a defibrillator.

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Keywords Cardiac resynchronization therapy • Implantable cardioverter-defibrillator • Cause of death • Sudden cardiac death • Heart failure

Introduction

Cardiac resynchronization therapy (CRT) devices have revolutionized the treatment of heart failure patients with severe left ventricular (LV) systolic dysfunction and prolonged QRS duration. Randomized data have shown that CRT can decrease mortality through a reduction in both heart failure and sudden cardiac death (SCD).[1] These benefits are seen soon after implantation but appear to persist during longer follow-up.[2] Responders, especially super-responders to CRT, are at relatively low risk of long-term cardiac mortality.[3] Whether the primary prevention implantable cardioverter-defibrillator (ICD) improves outcomes over and above CRT is a matter of ongoing debate,[4–7] with the recent CeRtiTuDe cohort study revealing that the majority of the excess mortality among CRT-pacemaker (CRT-P) subjects at 2-year follow-up is related to an increase in non-SCD.[8]

Although a progressively diminishing risk of SCD among heart failure patients in general has been recently reported,[9] there are no data specifically on very late causes of death among patients who have survived the initial period following CRT implantation. It is plausible that these patients may represent a lower risk group not only for death in general but specifically SCD. The continued analysis of the MADIT-CRT study, which enrolled patients in New York Heart Association (NYHA) Class I–II, showed that CRT was associated with continuing benefit over long-term follow-up in patients with mild heart failure and left bundle branch block,[10] but whether this benefit extends to *real-life* patients with more advanced heart failure is unclear.

In this context, a better comprehension of the relative contribution of late SCD as opposed to other competing causes of late mortality in the CRT population, similar to what has been previously assessed in the CeRtiTuDe cohort study for a shorter duration of follow-up, may provide valuable insight on the relative usefulness of CRT-defibrillator (CRT-D) and CRT-P in this population. In this large European multicentre study, we assessed the very long-term outcome and late causes of death among CRT patients who survived the first 5 years post-implantation, with a particular focus on late SCD.

Methods

Study design and setting

Data obtained from a large European CRT consortium comprising French, UK, Czech, and Swedish patients who received CRT implantation/upgrade between 2002 and 2013 in the context of ischaemic or non-ischaemic dilated cardiomyopathy, and who completed at least 5 years of follow-up.[8,11–15] The indications for CRT, with or without a defibrillator, were as per the *European Society of Cardiology* and *European Heart Rhythm Association* guidelines[16] for those treated in French, Czech, and Swedish Hospitals and the *National Institute for Health and Care Excellence* (NICE) guidelines (https://www.nice.org.uk/guidance/ta120, 11 April 2019) for British patients. We assessed the very long-term outcome of these patients and their causes of death in an intention-to-treat fashion, with a focus on late SCD. The 5-year cut-off was chosen for two reasons: firstly, it represents the median CRT-D battery-life[17]—the longevity of CRT-D devices is still sub-optimal and significantly overestimated by industry-published product performance reports,[18] with almost half of implanted devices requiring replacement due to battery depletion within 5 years[17]; secondly, including only patients having elective CRT generator replacement (rather than a pre-specified cut-off) would result in a wide range of follow-up durations within the study population, considering the much longer battery life of CRT-P compared with CRT-D, and therefore comprise patients at varying stages of their post-CRT clinical course and with varying degrees of cumulative CRT exposure. Essentially, the pre-specified cut-off was used to reduce heterogeneity in the study population.

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 5782 consecutive patients with ischaemic or non-ischaemic dilated cardiomyopathy who received CRT implantation or upgrade between January 2002 and February 2013, 1775 completed at least 5 years of follow-up [1241 with CRT-D (69.9%) and 534 with CRT-P (30.1%)]. Data collected: age, sex, aetiology of cardiomyopathy (ischaemic vs. non-ischaemic dilated cardiomyopathy), glomerular filtration rate estimated by The Modification of Diet in Renal Disease (MDRD) Study equation, history of atrial fibrillation, chronic obstructive pulmonary disease (COPD), cerebrovascular event, diabetes mellitus, cancer, type of device (CRT-D or CRT-P), *de novo* implantation vs. upgrade, indication for the ICD (primary vs. secondary prevention), LV ejection fraction, medications including beta-blocker, angiotensin-converting enzyme inhibitor (ACEi), or angiotensin II receptor blocker (ARB-II) and aldosterone antagonist, clinical CRT response (positive response defined as improvement in NYHA class), and a history of ICD therapy.

Study endpoints and follow-up

The primary endpoints of this study were all-cause mortality and late SCD. Late SCD was defined as an unexpected sudden death occurring due to cardiac causes within 1 h from the start or acute deterioration of any cardiac-related symptoms, or that which occurred within 24 h of the patient last being seen alive and stable, with no other plausible (non-cardiac) cause for a sudden death found during autopsy or reported in the death certificates.

The methods used for collecting cause-of-death data have been described elsewhere.[7,12,14] In the DAI-PP registry,[12] vital status data were obtained from the hospital or general practitioner and systematically controlled through the National Institute of Statistics Economical Studies, whereas causes of death were obtained by the investigators and/or by the French Center on Medical Causes of Death and adjudicated after consideration of all the available information including medical data obtained by the regional investigators, pathology reports and Emergency Medical Services reports. Cause-of-death data for UK and Czech patients were collected by the investigators through analysis of death certificates and necropsy results, clinical notes from hospital admissions and information provided by the patients' General Practitioners, with an agreement

between at least two different investigators required for allocating deaths into a specific cause. Data for Swedish patients were gathered from the Swedish National Patient registry and the Swedish pacemaker registry and crosschecked with manual assessment of electronic medical records, while causes of death were retrieved from the Swedish Cause of Death Register. Deaths were categorized into four major groups: *SCD*, previously defined; progressive *heart failure death*, defined as death due to progressive circulatory failure over a period of weeks or months without any precipitating acute event; *other cardiovascular death*, defined as any mortality due to a cardiovascular cause which did not fulfil the criteria for SCD or heart failure death; *non-cardiovascular death*. When insufficient information was available to make a reasonable assumption of the cause of death, the death was classified as unidentifiable.

Follow-up visits were performed in general every 6 months, although additional visits or remote ICD interrogations were also performed in CRT-D patients receiving ICD shocks.

Statistical analysis

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 χ^2 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, assumed to be random, were treated with multiple imputation by chained equations.

We compared the mortality rates of the study population with that of the original cohort from which our patients were retrieved to test the hypothesis that patients who survive at least 5 years of follow-up represent a lower risk group for death in general. Having completed 5 years of follow-up, the study group is on average 5 years older than the original population of patients implanted with CRT. As such, we used the 1976 European Standard Population as reference for calculating annual age-standardized mortality rates.[19] In brief, mortality and population data in our study group and the original CRT cohort were organized into 5-year age groups, up to 85+ years, to correspond with the age categories used in the European Standard Population. Age-specific crude rates were calculated, and we then estimated age-standardized rates per 1000 patient-years with 95% confidence intervals (CIs) using the direct method, based on the age-specific crude rates in each population and the age-structure of the European Standard Population. Finally, the number of deaths per 1000 patient-years were divided by the mean number of years of follow-up in each group to obtain the annual age-standardized mortality rates.

Predictors of late all-cause mortality and late SCD were sought using multivariate analysis with adjustment on the conditional probability of receiving CRT-D rather than CRT-P (the propensity score, estimated with logistic regression). For obtaining the propensity score, we included all baseline covariates that were shown to affect the outcome in our patients (in univariate analysis).[20] The following parameters were included: age, NYHA class, renal function, upgrade vs. *de novo* implantation, aetiology (ischaemic vs. dilated non-ischaemic), history of atrial fibrillation, cancer, stroke, COPD or diabetes, LV ejection fraction, use of beta-blockers, and site (country) of implantation. All variables were collected at baseline. Further variables which did not help outcome prediction were not included in the model. Proportional hazards regression was used for identifying predictors of all-cause mortality, while the analysis on late SCD was performed using the Fine–Gray model for obtaining subdistribution hazard ratios (sHRs), thereby taking the competing risk of non-SCD into consideration.

An additional analysis using propensity score matching was also performed. The methods used, as well as results, are described in the Supplementary material online, *Material* section.

Results

Beyond the first 5 years post-implant, which all patients included in the present analysis completed, the median additional follow-up amongst survivors was 23 months (interquartile range 10–42 months). *Table 1* depicts the baseline characteristics of the study patients at the time of CRT implantation or upgrade. As expected, patients receiving CRT-D were significantly younger, more often men and had less advanced heart failure and comorbidity. Upgrade to CRT was less common (as opposed to *de novo* implantation) compared with CRT-P patients, with greater proportion of ischaemic cardiomyopathy in the CRT-D group. During the time period described in this analysis, only five CRT-P patients (out of 534) were upgraded to CRT-D.

A total of 473 deaths occurred after the first 5 years post-implant, corresponding to unadjusted mortality rates of 94.7 and 139 per 1000 patient-years for CRT-D and CRT-P patients, respectively. The annual age-standardized mortality rates of our CRT-D and CRT-P patients were 40.4 (95% CI 35.3–45.5) and 97.2 (95% CI 85.5–109.9) per 1000 patient-years, respectively. Moreover, the annual age-standardized mortality rates of our study group were lower than those of the original cohort from which our patients were retrieved—62.4 deaths per 1000 patient-years (95% CI 56.7–68.0) in the former vs. 85.4 deaths per 1000 patient-years (95% CI 80.7–90.2) in the latter.

When considering the cause-of-death analysis (*Table 2* and *Take home figure*), 29 patients in total (1.6%) died of SCD—15 (1.2%) with CRT-D and 14 (2.6%) with CRT-P. This corresponded to 6.1% of all deaths in both device groups and an annual SCD rate of 7 per 1000 patient-years (5.8 in CRT-D patients and 8.5 in CRT-P patients). Death due to progressive heart failure represented the principal cause of death in both groups, corresponding to 52.6% and 42.8% of known causes in the CRT-D and CRT-P groups, respectively. Approximately one-third of deaths was due to a non-cardiovascular cause—33.1% of CRT-D and 33.3% of CRT-P patients. The risk of SCD in each device group in the propensity score-matched sample, as well as the percentage of deaths due to SCD, were very similar to those seen in the main analysis (Supplementary material online).

Among the 250 secondary prevention CRT-D patients, only two late SCD were reported, while heart failure death was by far the most frequent (54.1% of known causes of death).

On multivariate analysis with adjustment on the propensity score, age [hazard ratio (HR) = 1.06, 95% CI 1.04–1.08, $P < 0.001$], CRT response (HR = 0.72, 95% CI 0.55–0.95, $P = 0.021$), history of cancer (HR = 1.70, 95% CI 1.19–2.44, $P = 0.005$), COPD (HR = 1.68, 95% CI 1.20–2.36, $P = 0.003$), diabetes mellitus (HR = 1.29, 95% CI 1.03–1.61, $P = 0.030$), and marginally, a lower LV ejection fraction (HR = 0.98, 95% CI 0.97–1.0, $P = 0.08$) were associated with overall mortality, whereas the type of device was not (HR for CRT-D 0.88, 95% CI 0.70–1.09, $P = 0.24$) (*Figure 1*). There was no significant device-by sex or aetiology interaction. Results obtained after propensity score matching were very similar (Supplementary material

Table 1 Baseline characteristics at the time of CRT implantation or upgrade

Variables	CRT-D (*n* = 1241)	CRT-P (*n* = 534)	*P*-value
Age (years)[a]	63.8 ± 10.4[a]	69.8 ± 10.2[a]	<0.001
Male sex	80.4% (998)	69.7% (372)	<0.001
Left ventricular ejection fraction (%)	25.5 ± 6.3	26.8 ± 7.6	<0.001
NYHA class ≥3	68.3% (847)	82% (438)	<0.001
QRS duration			
<120 ms	7.7% (95)	3.4% (18)	<0.001
120–150 ms	33.8% (420)	24.9% (133)	
>150 ms	58.6% (727)	71.7% (383)	
Ischaemic aetiology	52.5% (652)	47.8% (255)	0.072
Upgrade to CRT	14.2% (176)	23.6% (126)	<0.001
History of atrial fibrillation	47.1% (584)	42.7% (228)	0.091
History of stroke or transient ischaemic attack	7.5% (93)	11.6% (62)	0.004
History of chronic obstructive pulmonary disease	11% (137)	9.9% (53)	0.4
History of diabetes mellitus	26.7% (331)	28.1% (150)	0.3
History of cancer	8.9% (111)	9.9% (53)	0.5
Glomerular filtration rate			
≥60 mL/min	56.7% (704)	43.1% (230)	<0.001
30–59 mL/min	38.2% (474)	52.2% (279)	
<30 mL/min	5.1% (63)	4.7% (25)	
On beta-blockers	79.1% (982)	74.2% (396)	0.06
On ACEI/ARA-II	83.5% (1036)	91.4% (488)	0.005
On aldosterone antagonists	32.4% (402)	43.3% (231)	<0.001
Secondary prevention	20.1% (250)	—	—
Clinical responder to CRT during follow-up[b]	73.8% (717)[b]	71.4% (315)[b]	0.3
Mean follow-up in surviving patients (months)	85.5 ± 21.6	102.9 ± 33.6	<0.001

ACEI, angiotensin converting enzyme inhibitor; ARA-II, type 2 angiotensin receptor antagonist; CRT, cardiac resynchronization therapy; NYHA, New York Heart Association.
[a]Mean age of the cohort for the present study was 5 years higher.
[b]Data available for 971 CRT-D and 441 CRT-P patients.

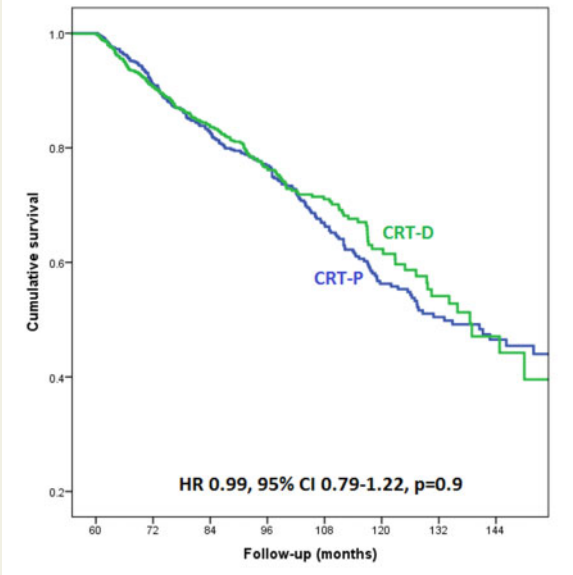
Table 2 Incidence rate of specific causes of death among CRT-D and CRT-P patients (events per 1000 patient-years), with corresponding unadjusted and adjusted hazard ratios

	CRT-D (*n* = 1241)	CRT-P (*n* = 534)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Total mortality	94.7 (*n* = 243)[a]	139.0 (*n* = 230)[a]	0.67 (0.56–0.81)	0.99 (0.79–1.22)
SCD	5.8 (*n* = 15)	8.5 (*n* = 14)	0.65 (0.31–1.37)	1.0 (0.45–2.44)
Heart failure	40.2 (*n* = 103)	52.0 (*n* = 86)	0.76 (0.57–1.02)	1.1 (0.81–1.58)
Other cardiovascular	5.1 (*n* = 13)	20.5 (*n* = 34)	0.25 (0.13–0.48)	0.30 (0.14–0.63)
Non-cardiovascular	25.0 (*n* = 64)	40.5 (*n* = 67)	0.62 (0.43–0.87)	1.0 (0.67–1.49)
Unidentified	19.7% of deaths (*n* = 48), 3.9% risk	12.6% of deaths (*n* = 29), 5.4% risk	1.0 (0.61–1.66)	1.5 (0.85–2.82)

[a]The annual age-standardized mortality rates of CRT-D and CRT-P patients were 40.4 (95% CI 35.3–45.5) and 97.2 (95% CI 85.5–109.9) per 1000 patient-years, respectively.

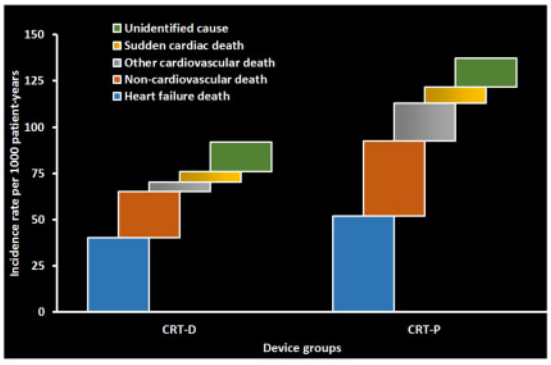
online). Conversely, only LV ejection fraction (sHR = 0.93, 95% CI 0.88–0.97, 0.038) associated with late SCD when adjusted on the propensity score and the remaining predictors of SCD in univariate analysis.

For these patients who survived the first 5 years post-implantation, the incidence of any ICD therapy in their first 5 years of follow-up was significantly higher than that reported during the time period described in the present analysis (25.5% vs. 11.3%, respectively).



N at risk	60	72	84	96	108	120	132	144
CRT-D	1241	816	509	307	179	94	54	20
CRT-P	534	405	309	232	162	108	77	50

Figure 1 Cumulative late adjusted survival in cardiac resynchronization therapy defibrillator and pacemaker patients. CI, confidence interval; CRT-D, cardiac resynchronization therapy defibrillator; CRT-P, cardiac resynchronization therapy pacemaker; HR, hazard ratio.



Take home figure Incidence rate displayed by mortality cause in cardiac resynchronization therapy defibrillator and pacemaker patients. CRT-D, cardiac resynchronization therapy defibrillator; CRT-P, cardiac resynchronization therapy pacemaker.

The occurrence of 'early' ICD therapies was not a predictor of late overall mortality or SCD.

Discussion

To the best of our knowledge, this represents the first description of very long-term outcomes of CRT recipients who survived the first few years post-implant. Our findings suggest that progressive heart failure death still represents the most frequent cause of death in these patients. In contrast, SCD occurred in less than 1% of patients every year and represented a very low proportion of late mortality irrespective of the presence of a defibrillator.

Over the last few years, CRT studies with cause-of-death analyses have provided additional insight on the issue of competing risks for mortality. In the CeRtiTude cohort study, the difference in mortality between CRT-D and CRT-P patients was mostly accounted for by an increase in the risk of non-SCD.[8] Our study followed a similar rationale and methodology as seen in the landmark CeRtiTuDe study, providing a longer-term assessment of causes of death among patients achieving long survival times following CRT implantation. Our results share some similarities with those seen in CeRtiTuDe. On the one hand, overall unadjusted mortality was significantly higher in the CRT-P group compared with CRT-D, with the different causes of death occurring more frequently in CRT-P patients. This was an expected finding, as CRT-P patients are typically older and tend to have more advanced heart failure and comorbidity. On the other hand, the excess mortality among CRT-P recipients was eventually related to SCD in an almost identical, and very small, proportion of patients. In the *Cardiac Resynchronization-Heart Failure* (CARE-HF) trial, the 2.5% annual risk of SCD in the CRT-P group was higher than that reported in our study. The differences may be partly due to the different timings of patient enrolment (2001–2003 in CARE-HF vs. 2002–2013 in the present study), the higher mean patient age in our CRT-P population, with a subsequent increase in the rate of competing non-sudden death, and the fact that our cohort of patients who survived the first 5 years post-implant may represent a healthier *lower-risk* subgroup of patients.

The low absolute risk of SCD among CRT patients has been recently suggested by large observational studies.[5,7] Certainly, responders to CRT are at significantly lower risk of ventricular arrhythmias,[21–25] particularly if their LV function normalizes after CRT implantation, and CRT alone has been shown to reduce the risk of SCD.[1] Furthermore, the risk of SCD among heart failure patients in general has been progressively decreasing over the last few decades.[9] Even if SCD in the CRT context may be more frequent in certain subgroups such as men and those with ischaemic cardiomyopathy,[5,7] this cause of death is strikingly less common than death due to heart failure or a non-cardiovascular cause. Our study showed that heart failure and non-cardiovascular death represent the majority of deaths among CRT patients in the very long-term (*Take home figure*).

In the present study, there was no device-by-sex or device-by-aetiology interaction with regards to mortality benefit, although these interactions have been recently proposed.[5,7,26] There are several plausible explanations for this. Firstly, we focused on a selected 'healthier' cohort of CRT patients who survived the first 5 years of follow-up. The age-standardized mortality rate of our study group was lower than that calculated for the original cohort who received CRT, which may suggest that patients surviving the first 5 years post-implant have a more benign prognosis, although this could also be the result of continuous improvements in medical therapy. Secondly, it is possible that the benefit of the ICD in the CRT context is most prominent in the first few years post-implantation. In fact, survival curves for CRT-D and CRT-P converged after only 9 months of follow-up in the COMPANION trial. It has been suggested that the lifespan gain from CRT rises nonlinearly with time, with higher-risk patients exhibiting more gain early on, while lower-risk patients

benefit the most later on.[27] Finally, our cohort had completed 5 years of follow-up post-CRT implant at the time of enrolment for this study, and the increasing patient age results in a higher percentage of deaths due to competing risk of non-SCD.

Like CeRtiTuDe, our study was not primarily intended as a direct comparison of outcomes between CRT-D and CRT-P patients, as it does not address the question of whether CRT-P would have performed just as well in the group of patients with CRT-D. Some subgroups of patients receiving CRT may have a lower mortality with an additional defibrillator, although definite data is still lacking.[28] However, our main goal was to assess the risk of very-late all-cause mortality and SCD in *real-world* patients who survived the initial 5 years post-CRT implantation. In these patients, the risk of late SCD is very low even in the absence of the defibrillator, and our results, in concert with those of recent studies,[5,7] add to the idea that the main benefit of the defibrillator may be seen early after implantation. The higher incidence of ICD therapies in the first 5 years post-CRT implantation compared with those occurred after that time period, as seen in our study, may support this theory, although this may also be the result of less aggressive ICD programming and global improvement in heart failure pharmacological treatments. The development of new DF4 adaptors to allow downgrade to CRT-P at the time of elective generator replacement without the need for an additional lead could be potentially advantageous for elderly primary prevention CRT-D patients who are thought to be at relatively higher risk of non-SCD, particularly given the recent findings of greater risk of device-related complications among CRT-D patients.[29] Nevertheless, given that SCD remains a possible, albeit uncommon cause of death in the very long-term, even in a cohort of *lower-risk* CRT patients who survived the first 5 years of follow-up, a decision to downgrade a CRT-D device to CRT-P should be taken cautiously and after thorough discussion with the patient.

The main strengths of this study include its multicentric nature and the very large size of the cohort. However, some limitations should be acknowledged. *First*, as a non-randomized study, there was some residual selection bias between device groups even after propensity score adjustment. However, this study was not designed to directly compare the outcomes of CRT-D and CRT-P patients, rather to assess their late causes of death. *Second*, despite the fact that methods for collecting cause-of-death data were robust, the mechanism of death may be occasionally difficult to determine with certainty. Access to device electrograms could have facilitated the process, but this data was not consistently available. It is possible that some cases of SCD may have been misclassified, but patients dying of unidentified cause were not comparatively more frequent in either device group. *Third*, baseline characteristics were collected at the time of device implantation. Updated values at 5 years of follow-up were not available for a significant percentage of patients and some parameters (including LV ejection fraction). However, clinical response to CRT was seen in an almost identical percentage of CRT-D and CRT-P patients, suggesting (but not excluding) that an echocardiographic response was not comparatively more frequent in either group.

Conclusions

Progressive heart failure death still represents the most frequent cause of death in patients surviving the first 5 years after CRT implant. In contrast, SCD represents a very low proportion of late mortality irrespective of the presence of a defibrillator.

Supplementary material

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

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