Device Complications with addition of Defibrillation to Cardiac Resynchronization Therapy for Primary Prevention

Short title: Device-related complications in CRT

Sérgio Barra MD[1], Rui Providência MD PhD[2], Serge Boveda MD[3], Rudolf Duehmke MD PhD[1], Kumar Narayanan MD[4,5], Anthony W. Chow MD[2], Olivier Piot MD[6], Didier Klug MD PhD[7], Pascal Defaye MD[8], Daniel Gras MD[9], Jean-Claude Deharo MD PhD[10], Paul Milliez MD PhD[11], Antoine Da Costa MD PhD[12], Pierre Mondoly MD[13], Jorge Gonzalez-Panizo MD[1], Christophe Leclercq MD PhD[14], Patrick Heck MD[1], Munmohan Virdee MD[1], Nicolas Sadoul MD PhD[15], Jean-Yves Le Heuzey MD PhD[16,17], Eloi Marijon MD PhD[5,16,17]

[1] Cardiology Department, Papworth Hospital NHS Foundation Trust, Cambridge, UK

[2] Barts Heart Centre, Barts Health NHS Trust, London, UK

[3] Cardiology Department, Clinique Pasteur, Toulouse, France

[4] Cardiology Department, MaxCure Hospitals, Hyderabad, India

[5] Paris Cardiovascular Research Center, Cardiovascular Epidemiology, Paris, France

[6] Centre Cardiologique du Nord, St Denis, France

[7] Lille University Hospital, Lille, France

[8] Grenoble University Hospital, Grenoble, France

[9] Nouvelles Cliniques Nantaises, Nantes, France

[10] La Timone University Hospital, Marseille, France

[11] Caen University Hospital, Caen, France

[12] St Etienne University Hospital, St Etienne, France

[13] Toulouse University Hospital, Toulouse, France

[14] Rennes University Hospital Rennes, France

[15] Nancy University Hospital, Nancy, France

[16] Cardiology Department, European Georges Pompidou Hospital, Paris, France

[17] Paris Descartes University, Paris, France

Corresponding author:

Sérgio Nuno Craveiro Barra

Cardiology Department, Papworth Hospital NHS Foundation Trust, Papworth Everard, Cambridge CB23 3RE, UK

E-mail address: sergioncbarra@gmail.com

Word count: 3112

ABSTRACT (WC=291)

Objective: In patients indicated for cardiac resynchronization therapy (CRT), the choice between a CRT-pacemaker (CRT-P) versus defibrillator (CRT-D) remains controversial and indications in this setting have not been well delineated. Apart from inappropriate therapies, which are inherent to the presence of a defibrillator, whether adding defibrillator to CRT in the primary prevention setting impacts risk of other acute and late device-related complications has not been well studied and may bear relevance for device selection.

Methods: Observational multicentre European cohort study of 3,008 consecutive patients with ischaemic or non-ischaemic dilated cardiomyopathy and no history of sustained ventricular arrhythmias, undergoing CRT implantation with (CRT-D, n=1,785) or without (CRT-P, n=1,223) defibrillator. Using propensity score and competing risk analyses, we assessed the risk of significant device-related complications requiring surgical re-intervention. Inappropriate shocks were not considered except those due to lead malfunction requiring lead revision.

Results: Acute complications occurred in 148 patients (4.9%), without significant difference between groups, even after considering potential confounders (OR=1.20, 95% CI 0.72-2.00, p=0.47). During a mean follow-up of 41.4±29 months, late complications occurred in 475 patients, giving an annual incidence rate of 26 (95% CI 9-43) and 15 (95% CI 6-24) per 1,000 patient-years in CRT-D and CRT-P patients, respectively. CRT-D was independently associated with increased occurrence of late complications (HR=1.68, 95%CI 1.27-2.23, p=0.001). In particular, when compared to CRT-P, CRT-D was associated with an increased risk of device-related infection (HR 2.10, 95% CI 1.18-3.45, p=0.004). Acute complications did not predict overall late complications, but predicted device-related infection (HR 2.85, 95%CI 1.71-4.56, p<0.001).

Conclusions: Compared to CRT-P, CRT-D is associated with a similar risk of periprocedural complications but increased risk of long-term complications, mainly infection. This needs to be considered in the decision of implanting CRT with or without a defibrillator.

KEY-WORDS: Implantable cardioverter-defibrillator; pacemaker; device-related complications; infection; follow-up; propensity score matching; competing risk.

LIST OF ABBREVIATIONS

CI – Confidence interval

CRT-D – Cardiac resynchronization therapy defibrillator

CRT-P – Cardiac resynchronization therapy pacemaker

DCM – Dilated cardiomyopathy

HR – Hazard Ratio

ICD – Implantable cardioverter-defibrillator

OR – Odds ratio

SCD – Sudden cardiac death

sHR – Subdistribution Hazard Ratio

KEY QUESTIONS

What is already known about this subject?

The magnitude of incremental benefit of the primary prevention defibrillator in patients receiving cardiac resynchronization therapy (CRT) is a matter of some debate. Except for few studies involving limited number of CRT-Pacemaker patients followed for a relatively short duration, there has not been any large study comparing CRT-Defibrillator with CRT-Pacemaker regarding the acute and late risk of device-related complication.

What does this study add?

Our findings suggest that, in a large contemporary cohort of patients receiving CRT, the addition of a defibrillator is associated with a higher rate of late device-related complications compared to a conventional biventricular pacemaker. The difference is mostly accounted for by an increase in the risk of late lead- and generator-related complications as well as device-related infections, while the risk of acute complications is similar.

How might this impact on clinical practice?

Physicians should prescribe CRT-Defibrillator whenever the patient is deemed to be at high risk of sudden cardiac death. However, in groups where the benefit-risk ratio is less certain, prescription of CRT-Defibrillator instead of CRT-Pacemaker should be carefully weighed, as the lower infection and overall complication risks of CRT-Pacemaker may outweigh the benefit of the defibrillator in a low-sudden cardiac death risk setting.

INTRODUCTION

Cardiac resynchronisation therapy (CRT) is associated with improved survival in heart failure patients with ischaemic or non-ischaemic dilated cardiomyopathy (DCM), prolonged QRS duration and severe left ventricular (LV) systolic dysfunction.(1) Current guidelines recommend an implantable cardioverter-defibrillator (ICD) for the prevention of sudden cardiac death (SCD) in symptomatic patients with an LV ejection fraction of ≤35% (2) and thus most patients undergoing CRT get a CRT-Defibrillator (CRT-D). However, the magnitude of incremental benefit of the primary prevention defibrillator in this setting is a matter of some debate. Furthermore, the addition of a defibrillator lead and the bulkier device may potentially increase the risk of device-related complications. Previous investigators have assessed the acute and short- to mid-term risk of device-related complications amongst large cohorts of ICD and CRT-D patients.(3, 4) Nevertheless, except for few studies involving limited number of CRT-Pacemaker (CRT-P) patients followed for a relatively short duration,(5–7) there has not been any large study comparing CRT-D with CRT-P regarding the acute and late risk of device-related complication.

Although inappropriate therapies as a complication would obviously be restricted to the CRT-D population, this can be reasonably assessed only in the context of potential lives saved by appropriate therapies or any mortality reduction vis-à-vis CRT-D versus CRT-P, which is the subject matter of a separate ongoing debate.(8, 9) However, whether other complications differ significantly between CRT-D versus CRT-P has not been well studied in adequate numbers of patients and is an important issue to consider in decision-making. In this large observational multicentre study, we aimed to compare the outcome of CRT-D vs. CRT-P patients with respect to the risk of acute and late device-related complications.

METHODS

Study design and setting

Data obtained from a large European consortium totalling 3,008 patients with ischaemic or non-ischaemic DCM without history of sustained ventricular arrhythmia receiving CRT-D or CRT-P between 2006 and 2013.(9–11) Indications were as per the *European Society of Cardiology* and *European Heart Rhythm Association* guidelines (12) for patients treated in France and the *National Institute for Health and Care Excellence* (NICE) guidelines [https://www.nice.org.uk/guidance/ta120] for British patients.

Using proportional hazards regression and propensity score analysis,(13, 14) we compared the outcome of CRT-D vs. CRT-P patients with regards to acute and late risk of device-related complications, taking the competing risk of death into consideration.

The CeRtiTuDe cohort study protocol was approved by the French Ethics and Data Protection National Committees. Data analysis in the remaining Hospitals was approved by the individual sites' institutional review boards.

Patient eligibility criteria and sample characterization

Of the 3,008 patients, 1,785 (59.3%) received a CRT-D while the remaining 1,223 (40.7%) received a CRT-P. All procedures were new implants or upgrades from a standard pacemaker. Patients with a cardiomyopathy other than ischaemic or non-ischaemic DCM or a previous history of sustained ventricular arrhythmia were not included. Data collected: demographics, aetiology, renal dysfunction (glomerular filtration rate <30 ml/min), atrial fibrillation (AF), chronic obstructive pulmonary disease, cerebrovascular event, diabetes mellitus, cancer, type of device, *de novo* implantation vs. upgrade, LV function, NYHA class, and medication including beta-blocker, angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blockers (ARBs), aldosterone antagonists, antiplatelet and

anticoagulant drugs. Device programming was left to the discretion of the investigators at each centre, with the guiding principle being achievement of maximal biventricular pacing.

Study Endpoints and Follow-Up

The primary endpoint of the study was the occurrence of a complication related to the implanting procedure or the device itself which required surgical re-intervention. Complications were divided into **i) acute**, defined as a complication occurring during the implanting procedure or diagnosed prior to hospital discharge, and **ii) late**, defined as a complication occurring or diagnosed following hospital discharge, and which had not been seen to occur during the index hospitalisation. Complications which were managed conservatively and did not require surgical intervention were not included in our analysis, except for pocket haematoma requiring transfusion and venous thrombosis requiring anticoagulation. Inappropriate shocks, which can occur only in the CRT-D group, were not considered except when it was due to lead malfunction requiring lead revision. This was done for the reasons outlined in the introduction earlier; **essentially we did an unbiased comparison of those complications which would have a possibility to occur in either group.** Complications were further classified into four categories:(15)

- ***Access-related***: Any complication which occurred while gaining access to the vasculature or which was vessel-related, including **i)** pneumothorax or haemothorax requiring chest drain insertion or surgery, and **ii)** venous thrombosis and/or occlusion requiring anticoagulation.
- ***Lead-related***: Any complication related directly to the positioning of the lead or the lead itself requiring lead replacement or repositioning, including **i)** lead dysfunction (due to fracture or insulation defect), **ii)** lead displacement, **iii)** phrenic nerve stimulation without macro- lead displacement, **iv)** loose set screw; **v)** coronary sinus

dissection causing cardiac tamponade and/or preventing completion of the implant, and **vi)** lead perforation.

- ***Generator-related***: Any complication other than infection related directly to the generator itself or its pocket, including **i)** premature device failure requiring generator replacement, **ii)** pocket haematoma requiring surgical drainage and/or blood transfusion, **iii)** chronic pain or threatened erosion requiring pocket revision.
- ***Infection***: Any device-related infection requiring surgical intervention, either extraction or pocket/wound revision, but not causing the death of the patient.
- ***Device-related death:*** Any death directly caused by a device-related complication (such as systemic infection) or complication during the implanting procedure, or when these were considered to have contributed to the death of the patient. This sub-group included all cases of periprocedural death, defined as death during the same hospital admission.

When definite data on the type of complication were unavailable, these were labeled as "unclassified".

Patients were followed at 6-month intervals. Additional unscheduled visits or remote ICD interrogations were performed in CRT-D patients receiving ICD shocks. The investigators at each centre recorded major clinical events and the accuracy of the data was verified, on an yearly basis, by crosschecking of clinical notes from hospital admissions, procedural reports, information provided by treating physicians and electronic medical records, focusing on the vital status, specific modes/causes of death, major clinical events, interventions as well as interim hospitalizations during follow-up.

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 Chi-square test, Student's t-test and non-parametric equivalent tests were used when appropriate. P values <0.05 (two-sided) were considered statistically significant. Missing data were assumed to be random and were treated with multiple imputation by chained equations. However, the results of an analysis restricted to complete cases are also presented.

The outcome of CRT-D vs. CRT-P patients with regards to the occurrence of **i)** any acute complication, **ii)** any late complication and **iii)** infection was compared using logistic regression (for acute complications) or proportional hazards regression (for late complications) with adjustment on the propensity score and all predictors of complications in univariate analysis. The time to complication was of primary interest, but the occurrence of death (the competing event) would preclude its occurrence. Therefore, we calculated yearly cause-specific incidence rates using the method described by Wolbers et al,(16) and performed competing risk regression using the Fine-Gray model for obtaining subdistribution hazard ratios (sHR). Similar analysis was performed for the endpoint infection, as death would also be a competing event.

The analysis was complemented with propensity score matching. Greedy nearest-neighbour matching within a specified caliper width (0.01), without replacement, was used for forming pairs of CRT-D and CRT-P patients matched on the propensity score.(17) In order to assess the balance on the newly created PS-matched sample, we compared standardized differences in the means of continuous and binary covariates between treatment groups.(13) After the matched sample was created, comparison between device groups was performed taking into account the matched nature of the data (logistic regression estimated

using a generalised estimating equation for acute complications and cox regression stratified on matched pairs for late complications). The proportional hazards assumption was tested with time by covariate interaction. For obtaining the propensity score, we included all baseline covariates that were shown to associate with the occurrence of complications or the competing risk of mortality.(18)

Assuming a 10.5% 3-year rate of "unanticipated events" requiring system revision amongst CRT-D patients,(19) and 6-month risk of major complications of 11% for CRT-D patients and 6.7% for those receiving CRT-P,(5) we estimated that a sample size of 2,374 patients (1,187 per group) followed for approximately 3 years would provide 95% power to detect a similar difference in complication risk at a two-tailed alpha level of 0.05.

RESULTS

Study population

Baseline characteristics of the entire population are reported in **table 1.** CRT-P patients were older, more often female and had more advanced heart failure and comorbidity. Ischaemic cardiomyopathy was more frequent in CRT-D patients, and they were more often treated with standard heart failure medication. Overall, during a mean follow-up of 41.4±29 months (36.2±27.2 in CRT-D patients vs. 43.7±29.2 in those receiving CRT-P), 923 patients died (436 CRT-D patients and 487 CRT-P recipients) and 475 patients experienced complications, 303 among CRT-D and 172 among CRT-P (**table 2**). While acute complication data were obtained for the whole study group, data on late complications were available for 2,754 patients (91.6%) of the cohort, without significant difference between the two groups.

Acute complications

Overall, acute complication occurred in 148 patients (4.9%). Lead displacement was the most frequent acute complication (n=43, 1.4%), followed by pocket haematoma (n=23, 0.8%) and pneumothorax (n=20, 0.7%). Acute complications occurred in 88 CRT-D (4.9%) and 60 CRT-P patients (4.9%) respectively, with a similar pattern with respect to the details of complications (**table 2**). Implantation of a CRT-D device was not associated with an increased risk of acute complications (OR=1.16, 95%CI 0.71-1.89, p=0.56) when adjusted for age, sex, aetiology, upgrade vs. de novo implantation and the propensity score. After multivariate adjustment and multiple imputation for missing data, the type of device was not associated with occurrence of acute complications (OR=1.2, 95%CI 0.72-2.0, p=0.47). In addition, after propensity-score matching (n=1,404; 702 per group), and after confirming that groups were well balanced (**supplementary table 1**), the risk of acute complications did not significantly differ between the two groups (5.4% in CRT-D patients vs. 4.3% with CRT-P; OR=1.29, 95%CI 0.81-2.05, p=0.29).

Late complications

Late complications were reported in 285 patients (10.4%). Device-related infection (n=79) was the most frequent, followed by lead displacement (n=76) and lead dysfunction (n=73). The mean annual cause-specific incidence rate of late complications was 26 (95%CI 9-43) and 15 (95%CI 6-24) per 1,000 patient-years in CRT-D and CRT-P patients. **Figure 1** illustrates annual cause-specific incidence rates of complications in both device groups, while **table 3** shows the number and type of late complications. Patients receiving CRT-D experienced a significantly higher rate of late complications (11.4% vs. 8.9%; sHR=1.68, 95%CI 1.27-2.23, p=0.001). Late complications were more frequent in patients receiving an upgrade to a CRT device (sHR=1.88±0.13, p<0.001), and less frequent in those with ischaemic cardiomyopathy (sHR=0.76±0.14, p=0.042), male patients (sHR=0.75±0.16,

p=0.066) and older individuals (sHR=0.99±0.007, p=0.088). **Figure 2** illustrates the cumulative risk of complications over time when taking the competing risk of mortality into consideration. After propensity-score matching (n=1404; 702 per group), CRT-D was still associated with increased risk of late complications (12.9% vs. 9.1%; sHR=1.73, 95%CI 1.11-2.68, p=0.013). Patients younger than 65 years and receiving upgrade to CRT-D were at particularly high risk of late complications (22.0%).

The mean annual cause-specific incidence of infection was 9 (95%CI 3-14) and 5 (95%CI 1-9) per 1000 patient-years in CRT-D and CRT-P patients, respectively. After considering potential confounders, CRT-D was significantly associated with device-related infection compared with CRT-P (4.3% vs. 2.7%; sHR=2.1, 95%CI 1.18-3.45, p=0.004). Other factors associated with late infection included upgrade to CRT (sHR=2.46±0.21, p<0.001) and the occurrence of a previous acute complication (sHR=2.85±0.28, p<0.001). **Figure 3** illustrates the cumulative risk of infection over time when considering the competing risk of mortality. In the propensity score-matched cohort, infection was more frequent in CRT-D patients (4.9% vs. 2.3%; sHR=2.58, 95%CI 1.36-5.1, p=0.009). Infection occurred during the first 12-months of follow-up in 56.7% of cases. Patients younger than 65 years and receiving upgrade to CRT-D were at particularly high risk of infection (10.7%).

Without imputed data, CRT-D implantation remained associated with an increased risk of late complications (sHR=1.61, 95%CI 1.14-2.31, p=0.001) when adjusted for age, sex, aetiology, upgrade vs. de novo implantation, the propensity score and the occurrence of an acute complication at time of implantation, and an increased infection risk (sHR=1.9, 95%CI 1.25-3.52, p=0.002).

Supplementary table 2 compares CRT-D vs. CRT-P patients with respect to frequently recognised risk factors for infection.

DISCUSSION

Our findings suggest that the addition of the defibrillator in patients receiving CRT associates with a higher risk of device-related complications compared to CRT alone. The difference is mostly accounted for by an increase in the risk of late complications, in particular infection, while the risk of acute complications is similar.

The indications for the ICD and CRT often overlap. However, there has never been any randomized trial specifically comparing CRT-D vs. CRT-P in heart failure patients. Recent registry and observational data suggest that CRT alone may still be appropriate in the primary prevention setting in specific groups of patients,(8, 9) but this is an area of ongoing debate.(8, 9, 20–23) Studies have strongly suggested that additional ICD likely reduces mortality in men and in ischaemic cardiomyopathy,(8) while in other sub-groups such as the elderly, women and patients with non-ischaemic DCM, the evidence for a putative additional benefit over and above CRT appears questionable.(24) In these patients, the risk/benefit ratio may also depend on whether the addition of the ICD associates with increased risk of device-related comorbidity and complications.

Although several studies have assessed the risk of complications in patients receiving ICD or CRT-D,(3, 4, 25) no large study has thus far compared the outcome of CRT-D versus CRT-P with regard to the adjusted risk of device-related complications. It is known that CRT-D devices are associated with a higher risk of short- and long-term device-related events than single- or dual-chamber ICDs.(3, 25) A previous study revealed an increased risk of complications in patients receiving dual-chamber ICD or CRT-D compared with pacemakers or CRT-P.(5) However, this study included a small number of CRT-P patients followed for 6 months only. An additional small study observed a nearly three-fold higher 12-month risk of lead dysfunction in CRT-D compared with CRT-P patients, while the rate of system-related infections was similar in both groups.(23) In the European CRT survey, the

unadjusted risk of perioperative complications was not significantly different between CRT-D and CRT-P patients.(26) To the best of our knowledge, we provide the first assessment and comparison of both acute and late complications among patients receiving CRT-D vs. CRT-P taking into account the competing risk of death as well as the well-recognised treatment selection bias by performing propensity score analysis. We observed that perioperative complications occur similarly in both device groups, as seen in the European CRT survey,(26) and the increased follow-up complication risk amongst CRT-D patients is accounted for by a greater incidence of lead- and generator-related complications, and, quite importantly, infection. The increased risk of overall complications in CRT-D recipients is possibly explained by the increased device/lead complexity.

However, the increased risk of infection has not been well acknowledged before. An unadjusted analysis by Sohail et al reported a similar infection rate between those receiving CRT-D and CRT-P,(27) while Unsworth and colleagues reported that late infection rate in patients with cardiac electronic devices is mostly driven by increased CRT-D infection.(28) It seems plausible that CRT-D patients may be at increased risk of infection. Compared with CRT-P recipients, those receiving CRT-D are not only more likely to require anticipated generator replacement due to shorter battery life, but also unanticipated re-intervention due to lead dysfunction and wound issues, as we have shown. Surgical re-intervention is undoubtedly one of the most important predictors of infection amongst cardiac electronic device recipients.(29) In our study, the occurrence of a previous acute complication requiring surgical intervention predicted a higher risk of infection, as expected. Also, CRT-D patients have a higher mean number of leads given their lower incidence of AF but also the fact patients having upgrade from pacemaker to CRT-D receive two new leads, while upgrade to CRT-P requires one new lead only. The extra number of leads in CRT-D patients may have also contributed to the increased infection risk. Furthermore, CRT-D recipients are more

often men and younger compared to CRT-P patients. These factors have been shown to associate with an increased risk of infection.(30) However, the higher infection risk amid CRT-D recipients in our study was seen to be independent of sex and age.

In patients at lower risk of SCD, the addition of the ICD should be carefully weighed, as the lower complication risk of a biventricular pacemaker may outweigh the small benefit of the ICD in a low-SCD risk setting. Device-related infection may result in a substantial increase in both hospital admissions and long-term mortality.(27) The future development of smaller devices with thinner leads to reduce pocket bulk and longer battery-lives thus reducing the need for re-intervention may have a favorable impact on the CRT-D risk-benefit ratio. Also, a lower threshold for sub-pectoral implants and antibacterial envelope usage may be justifiable amongst CRT-D recipients.

Limitations of this study

The non-randomized nature of this study is its main limitation. Propensity score analysis can only account for measured variables. In particular, the absence of data regarding operator and center experience should be considered when interpreting our results. It is possible that late complications may be less frequent in centers with greater experience with device follow-up; however, all centres involved in this study were high volume, academic centres and centre-specific differences would not be expected to be large.

Inappropriate shocks which did not result in surgical re-intervention were not considered in this study, as we aimed to compare complications common to both CRT-D and CRT-P patients. However, inappropriate shocks may represent additional morbidity and distress among CRT-D patients. In our study, inappropriate shocks were reported in 4.9% of patients receiving CRT-D.

Data on late complications were not available for 8.7% of patients. However, this group was not significantly different from the remaining 91.3% with complete data. This suggests missing data occurred at random and would be unlikely to significant influence the main findings of our study.

CONCLUSIONS

In patients receiving CRT, the addition of an ICD is associated with an increased risk of complications during follow-up, particularly infection. Treating physicians should factor in the potential added risk of complications into their discussion with the patient and the decision making process.

Financial support: None

Conflicts of interest

Rui Providencia received training grant from Boston Scientific, and Sorin Group and a Research Grant from Medtronic. Serge Boveda received consulting fees from Medtronic, Boston Scientific, and Sorin Group. Olivier Piot received travel support and consulting fees from Abbott, Boston Scientific, LivaNova and Medtronic. Didier Klug received consultant fees from St. Jude Medical, Medtronic, Sorin Group, Boston Scientific, and Biotronik. Pascal Defaye received consulting fees from Boston Scientific, Medtronic, St Jude Medical and LivaNova. Daniel Gras receiving consulting fees from Boston scientific, Medtronic, Biotronik, Abbot. Paul Milliez received consulting fees from Biotronik, Boston Scientific and St Jude Medical. Nicolas Sadoul received consulting fees from Biotronik, Boston Scientific, Medtronic, Sorin Group and St. Jude Medical. Jean-Yves Le Heuzey received consulting fees from Astra Zeneca, Bayer, BMS/Pfizer, Boehringer Ingelheim, Daiichi Sankyo, Meda,

Novartis , Sanofi, Servier. All other authors have reported that they have no relationships relevant to the contents of this article to disclose.

REFERENCES

1. Cleland JGF, Daubert J-C, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N. Engl. J. Med. 2005;352:1539–49.

2. Priori SG, Blomström-Lundqvist C, Mazzanti A, et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the Europe. Eur Heart J. 2015 Nov 1;36(41):2793-867.

3. Landolina M, Gasparini M, Lunati M, et al. Long-term complications related to biventricular defibrillator implantation: Rate of surgical revisions and impact on survival: Insights from the italian clinicalservice database. Circulation 2011;123:2526–2535.

4. Ranasinghe I, Parzynski CS, Freeman J V., et al. Long-Term Risk for Device-Related Complications and Reoperations After Implantable Cardioverter-Defibrillator Implantation. Ann. Intern. Med. 2016;165:20.

5. Kirkfeldt RE, Johansen JB, Nohr EA, et al. Complications after cardiac implantable electronic device implantations: an analysis of a complete, nationwide cohort in Denmark. Eur. Heart J. 2014;35:1186–1194.

6. Schuchert A, Muto C, Maounis T, et al. Lead complications, device infections, and clinical outcomes in the first year after implantation of cardiac resynchronization therapy-defibrillator and cardiac resynchronization therapy-pacemaker. Europace 2013;15:71–76.

7. Romeyer-Bouchard C, Da Costa A, Dauphinot V, et al. Prevalence and risk factors related to infections of cardiac resynchronization therapy devices. Eur. Heart J. 2010;31:203–10.

8. Barra S, Boveda S, Providência R, et al. Adding Defibrillation Therapy to Cardiac Resynchronization on the Basis of the Myocardial Substrate. J. Am. Coll. Cardiol. 2017;69:1669–1678.

9. Marijon E, Leclercq C, Narayanan K, et al. Causes-of-death analysis of patients with cardiac resynchronization therapy: an analysis of the CeRtiTuDe cohort study. Eur Heart J. 2015 Nov 1;36(41):2767-76.

10. Barra S, Looi K-L, Gajendragadkar PR, et al. Applicability of a risk score for prediction of the long-term benefit of the implantable cardioverter defibrillator in patients receiving cardiac resynchronization therapy. Europace. 2016 Aug;18(8):1187-93.

11. Ioannou A, Papageorgiou N, Barber H, et al. Impact of an Age-Adjusted Co-morbidity Index on Survival of Patients With Heart Failure Implanted With Cardiac Resynchronization Therapy Devices. Am J Cardiol. 2017 Oct 1;120(7):1158-1165.

12. Brignole M, Auricchio A, Baron-Esquivias G, et al; ESC Committee for Practice Guidelines (CPG WC. 2013 ESC guidelines on cardiac pacing and cardiac resynchronization therapy: the task force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association. EHJ 2013;34:2281–32.

13. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. Multivariate Behav. Res. 2011;46:399–424.

14. Kurth T, Walker AM, Glynn RJ, et al. Results of multivariable logistic regression, propensity matching, propensity adjustment, and propensity-based weighting under conditions of nonuniform effect. Am. J. Epidemiol. 2006;163:262–70.

15. Ezzat VA, Lee V, Ahsan S, et al. A systematic review of ICD complications in randomised controlled trials versus registries: is our "real-world" data an underestimation? Open Hear. 2015;2:e000198.

16. Wolbers M, Koller MT, Stel VS, et al. Competing risks analyses: Objectives and approaches. Eur. Heart J. 2014;35:2936–2941.

17. Austin PC. A comparison of 12 algorithms for matching on the propensity score. Stat. Med. 2014;33:1057–69.

18. Austin PC. Propensity-score matching in the cardiovascular surgery literature from 2004 to 2006: a systematic review and suggestions for improvement. J. Thorac. Cardiovasc. Surg. 2007;134:1128–35.

19. Landolina M, Gasparini M, Lunati M, et al. Long-term complications related to biventricular defibrillator implantation: rate of surgical revisions and impact on survival: insights from the Italian Clinical Service Database. Circulation 2011;123:2526–35.

20. Barra S, Providencia R, Duehmke R, et al. Cause-of-death analysis in patients with cardiac resynchronization therapy with or without a defibrillator: a systematic review and proportional meta-analysis. Europace. 2017 Jun 28. doi: 10.1093/europace/eux094. [Epub ahead of print]

21. Barra S, Providência R, Duehmke R, et al. Sex-specific outcomes with addition of defibrillation to resynchronisation therapy in patients with heart failure. Heart 2017;103:753–760.

22. Barra S, Providência R, Tang A, et al. Importance of Implantable Cardioverter-Defibrillator Back-Up in Cardiac Resynchronization Therapy Recipients: A Systematic Review and Meta-Analysis. J. Am. Heart Assoc. 2015;4.

23. Schuchert A, Muto C, Maounis T, et al. Lead complications, device infections, and clinical outcomes in the first year after implantation of cardiac resynchronization therapy-defibrillator and cardiac resynchronization therapy-pacemaker. Europace 2013;15:71–76.

24. Køber L, Thune JJ, Nielsen JC, et al. Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure. N. Engl. J. Med. 2016:NEJMoa1608029.

25. Lee DS, Krahn AD, Healey JS, et al. Evaluation of Early Complications Related to De Novo Cardioverter Defibrillator Implantation. Insights From the Ontario ICD Database. J. Am. Coll. Cardiol. 2010;55:774–782.

26. Dickstein K, Bogale N, Priori S, et al. The European cardiac resynchronization therapy survey. Eur. Heart J. 2009;30:2450–60.

27. Sohail MR, Henrikson CA, Braid-Forbes MJ, et al. Mortality and cost associated with cardiovascular implantable electronic device infections. Arch. Intern. Med. 2011;171:1821–8.

28. Unsworth JD, Zaidi A, Hargreaves MR. Increased late complex device infections are determined by cardiac resynchronization therapy-defibrillator infection. Europace 2015;17:1708–11.

29. Klug D, Balde M, Pavin D, et al. Risk Factors Related to Infections of Implanted Pacemakers and Cardioverter-Defibrillators: Results of a Large Prospective Study. Circulation 2007;116:1349–1355.

30. Nielsen JC, Gerdes JC, Varma N. Infected cardiac-implantable electronic devices: prevention, diagnosis, and treatment. Eur. Heart J. 2015;36:2484–90.

FIGURE LEGENDS

Figure 1

Forest plots illustrating cause-specific incidence rate of follow-up complications and device-related infections in both device groups

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

Figure 2

Cox regression curves illustrating cumulative risk of device-related complications

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

Figure 3

Cox regression curves illustrating cumulative risk of device-related infection

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

TABLES

Table 1 – Baseline characteristics of study group (n=3008)

	CRT-D (n=1,785)	CRT-P (n=1,223)	p-value
Age (years)	65.2±11.4	73.2±10.4	<0.001
Male gender	1437 (80.5%)	759 (62.1%)	<0.001
LV ejection fraction (%)	25.7±6.7	27.3±8.2	<0.001
NYHA class I	40 (2.2%)	11 (0.9%)	<0.001
NYHA class II	340 (19.1%)	165 (13.5%)	
NYHA class III	1287 (72.1%)	890 (72.8%)	
NYHA class IV	117 (6.6%)	157 (12.8%)	
QRS duration	153.5±28.4	158.9±27.4	<0.001
Ischaemic aetiology	907 (50.8%)	508 (41.5%)	<0.001
Upgrade	368 (20.6%)	292 (23.9%)	0.14
History of atrial fibrillation	550 (30.8%)	448 (36.6%)	0.001
History of stroke or transient ischaemic attack	114 (6.4%)	110 (9%)	0.003
History of lung disease	325 (18.2%)	204 (16.7%)	0.3
History of Diabetes Mellitus	166 (9.3%)	209 (17.1%)	<0.001
History of cancer	164 (9.2%)	119 (9.7%)	0.53
Renal dysfunction (GFR <30 ml/min)	175 (9.8%)	186 (15.2%)	<0.001
On beta-blockers	1358 (76.1%)	725 (59.3%)	<0.001
On ACEI/ARB	1601 (89.7%)	911 (74.5%)	<0.001
On aldosterone antagonists	1085 (60.8%)	505 (41.3%)	<0.001
On antiplatelet drugs	807 (45.2%)	412 (33.7%)	<0.001
On anticoagulation	721 (40.4%)	450 (36.8%)	0.11
Mean follow-up in surviving patients (months)	36.2±27.2	43.7±29.2	<0.001

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

Table 2 – List of complications reported in our study group

		CRT-D (n=1,785)	CRT-P (n=1,223)	Total (n=3,008)
Access-related	**Pneumothorax**	9 (0.5%)	11 (0.9%)	20 (0.7%)
	Haemothorax	3 (0.2%)	1 (0.08%)	4 (0.1%)
	Venous thrombosis	0	1 (0.08%)	1 (0.03%)
	Total	12 (0.7%)	13 (1.1%)	25 (0.8%)
Lead-related	**Lead displacement**	78 (4.4%)	51 (4.2%)	129 (4.3%)
	Lead dysfunction	46 (2.6%)	27 (2.2%)	73 (2.4%)
	Diaphragmatic pacing without macro-displacement	22 (1.2%)	14 (1.1%)	36 (1.2%)
	Coronary sinus dissection	3 (0.2%)	4 (0.3%)	7 (0.2%)
	Perforation with tamponade	5 (0.3%)	0	5 (0.2%)
	Loose set screw	1 (0.06%)	1 (0.08%)	2 (0.06%)
	Total	155 (8.7%)	97 (7.9%)	252 (8.4%)
Generator-related	**Pocket haematoma**	18 (1%)	8 (0.7%)	26 (0.9%)
	Chronic pain or threatened erosion	12 (0.7%)	3 (0.2%)	15 (0.5%)
	Premature device failure	1 (0.06%)	0	1 (0.03%)
	Total	31 (1.7%)	11 (0.9%)	42 (1.4%)
Infection	**Total**	55 (3.1%)	24 (1.9%)	79 (2.6%)
Device-related death	**Heart failure**	7 (0.4%)	10 (0.8%)	17 (0.6%)
	Infection	3 (0.2%)	2 (0.2%)	5 (0.2%)
	Haemothorax	1 (0.06%)	0	11 (0.03%)
	Total	11 (0.6%)	12 (1%)	23 (0.8%)
Unclassified	**Total**	39 (2.2%)	15 (1.2%)	54 (1.8%)
	TOTAL	303 (17%)	172 (14%)	475 (15.8%)

CRT- Cardiac resynchronization therapy (D- defibrillator; P- pacemaker)

NOTE: A total of 148 and 285 patients had acute and late complications, respectively. Twelve patients had both acute and late complications. When considering the 54 unclassified events, the total number of patients with complications reached 475.

Table 3 – List of late complications according to device group

		CRT-D (n=1,618)*	CRT-P (n=1,136)*	Total (n=2,754)*
Lead-related	**Lead displacement**	50 (3.1%)	26 (2.3%)	76 (2.8%)
	Lead dysfunction	46 (2.8%)	27 (2.4%)	73 (2.7%)
	Diaphragmatic pacing without macro-displacement	9 (0.6%)	9 (0.8%)	18 (0.7%)
	Perforation with tamponade	2 (0.1%)	0	2 (0.07%)
	Total	107 (6.6%)	62 (5.5%)	169 (6.1%)
Generator-related	**Pocket haematoma**	1 (0.05%)	1 (0.08%)	2 (0.07%)
	Chronic pain or threatened erosion	12 (0.7%)	3 (0.3%)	15 (0.5%)
	Premature device failure	1 (0.05%)	0	1 (0.03%)
	Total	14 (0.9%)	4 (0.3%)	18 (0.7%)
Infection	**Total**	55 (3.4%)	24 (2.1%)	79 (2.9%)
Device-related death	**Infection**	2 (0.1%)	1 (0.08%)	3 (0.1%)
	Total	2 (0.1%)	1 (0.1%)	3 (0.1%)
Unclassified	**Total**	13 (0.8%)	3 (0.3%)	16 (0.6%)
	TOTAL	191 (11.8%)	94 (8.3%)	285 (10.3%)

CRT- Cardiac resynchronization therapy (D- defibrillator; P- pacemaker)

* Number of patients for whom data on late complications was available