Cause-of-death analysis in patients with cardiac resynchronization therapy with or without a defibrillator: a systematic review and proportional meta-analysis

Sergio Barra[1], Rui Providencia[2], Rudolf Duehmke[1], Serge Boveda[3], David Begley[1], Andrew Grace[1], Kumar Narayanan[4], Anthony Tang[5], Eloi Marijon[6,7,8], Sharad Agarwal[1]

[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] MaxCure Hospitals, Hyderabad, India

[5] University of Western Ontario, London, Ontario, Canada

[6] Paris Cardiovascular Research Center, Cardiovascular Epidemiology Unit, Paris, France

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

[8] Paris Descartes University, Paris, France

Corresponding author:

Sérgio Nuno Craveiro Barra

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

E-mail address: sergioncbarra@gmail.com

Telephone number: 0044 1480 830541

Word count: 3731

ABSTRACT

Background: The additional benefit of a defibrillator in cardiac resynchronization therapy (CRT) patients is a matter of debate. Cause-of-death analysis in a CRT population has been recently proposed as a useful approach to gain insight into this problem.

Methods and Results: We performed a systematic review and meta-analysis looking at cause of death in studies involving CRT subjects with (CRT-D) or without (CRT-P) a defibrillator. Literature search performed from inception to March 31, 2016 for relevant studies. Proportional and conventional meta-analyses were performed to obtain and compare causes of death in CRT-D versus CRT-P patients, including sudden cardiac death (SCD), all-cause mortality, heart failure, cardiovascular and non-cardiovascular mortalities.

The systematic review included a total of 44 studies and 18,874 patients (13,248 receiving CRT-D and 5,626 receiving CRT-P), representing 48,504 patient-years of follow-up. CRT-D recipients were younger, more often male, had lower NYHA class, less atrial fibrillation, more ischemic heart disease and were more often on beta-blockers than those receiving CRT-P. There were an additional 42 deaths per 1,000 patient-years in the CRT-P group compared with CRT-D (97±9, 95%CI 79-115 vs. 55±5, 95%CI 44-65, respectively), of which 35.7% were due to SCD (20±2, 95%CI 15-24 vs. 5±1, 95%CI 3-6) and the remaining 64.3% due to non-SCD. Of all deaths reported in CRT-D and CRT-P patients, 9.1% and 20.6% were due to SCD, respectively. The extent of SCD in CRT-P patients significantly increased in studies with higher percentage of males, ischemic cardiomyopathy and NYHA class 3.

Conclusions: Overall, compared to CRT-D patients, unadjusted mortality rate was almost two-fold higher in CRT-P recipients, with SCD representing one third of the excess mortality. Rate of SCD was significantly higher in certain subgroups (males, ischemic cardiomyopathy, NYHA class 3), where a CRT-D may be of more pronounced benefit; this deserves further focused investigation.

Key-words: Cardiac resynchronization therapy; implantable cardioverter-defibrillator; cause of death; sudden death; heart failure; mortality; competing risk

CONDENSED ABSTRACT

Systematic review on causes of death in CRT subjects. There were an additional 42 deaths per 1,000 patient-years in CRT-P patients compared with CRT-D, of which 35.7% due to SCD. Of all deaths in CRT-D and CRT-P patients, 9.1% and 20.6% were due to SCD, respectively. The extent of SCD in CRT-P patients was higher in males with ischemic cardiomyopathy and NYHA class 3.

WHAT'S NEW?

- Compared with CRT-D, CRT-P patients have an almost two-fold higher unadjusted risk of all-cause mortality. In general, SCD accounts for roughly a third of the excess unadjusted mortality, while non-SCD accounts for two-thirds, although these percentages vary as per the patients' underlying characteristics.
- In the setting of primary prevention and CRT, the ICD may be more cost-effective in young male patients with ischemic cardiomyopathy who are on stable NYHA class III despite optimal medical treatment and have few comorbidities.
- In a "best case scenario" where every additional SCD noted in the CRT-P population would be prevented by the presence of an ICD and, furthermore, this gain would not be offset by the competing risk of non-SCD, we calculated a patient-based NNT of 13.5 per battery life (assuming a median CRT-D battery life of 5 years), or an annual NNT of 67.5. These represent the number of CRT patients who would need an ICD for one SCD to be prevented during the battery-life or a 12-month period, respectively.

INTRODUCTION

The implantable cardioverter-defibrillator (ICD) is a widely accepted treatment for the prevention of sudden cardiac death (SCD) in heart failure patients[1]. However, the additional benefit of the ICD in patients receiving cardiac resynchronization therapy (CRT) has not been as extensively studied as in patients without CRT.

There has not been any specifically designed randomized study comparing CRT-defibrillator (CRT-D) versus CRT-pacemaker (CRT-P). The CeRtiTuDe cohort study has recently shown that only a very small proportion of the increased mortality seen in CRT-P patients, compared with CRT-D, was actually related to SCD[3]. CRT-D patients have lower all-cause mortality rates, which could be related to differences in patient characteristics and/or the presence of the ICD[4]. A detailed cause-of-death analysis in a large cohort of patients receiving CRT, with and without an ICD, would allow us to gain a better insight into the relative contribution of SCD in these populations and thus the potential added interest of a defibrillator. This in turn would help select the patients who are more likely to benefit from this therapy.

We therefore performed a systematic review and proportional meta-analysis of the causes of death among CRT recipients with (CRT-D) or without (CRT-P) a defibrillator across multiple studies. Using pooled data on cause-of-death, we evaluated the extent to which the addition of the ICD may contribute to reduced risk of SCD.

METHODS

Data Sources and Study Selection

We searched MEDLINE (via PubMED), EMBASE, clinicaltrials.gov and COCHRANE databases (from inception to March 31, 2016) using the following search strings: “cardiac

resynchronization therapy" OR "CRT-D" OR "CRT-P" OR "biventricular pacemaker" OR "biventricular defibrillator" OR "implantable cardioverter-defibrillator" AND "mode of death" OR "cause of death" OR "sudden cardiac death" OR "sudden death" OR "sudden arrhythmic death" OR "cardiovascular death". Reference lists of all accessed full-text articles were searched for sources of potentially relevant information and experts in the field were contacted about further potentially eligible studies. Authors of full-text papers were also contacted by email to retrieve additional information when required.

Only longitudinal studies performed in humans and written in English were considered for inclusion. The population, intervention, comparison and outcome (PICO) approach was used[5]. The population of interest included patients with guideline indication for CRT, with or without an ICD. The intervention was CRT implantation and the comparison was CRT-D vs. CRT-P.

The primary outcome of interest was SCD, while secondary outcomes included all-cause mortality, heart failure death, cardiovascular mortality and non-cardiovascular mortality, evaluated at the longest follow-up available. SCD was defined as any sudden unexpected death presumed to be of cardiovascular origin and fulfilling at least one of the following criteria[3]: **i)** occurring within 1 h of the initiation of cardiac symptoms in the absence of progressive cardiac deterioration; **ii)** occurring in bed during sleep; or **iii)** occurring within 24 h after last being seen alive and stable. Progressive heart failure death was defined as any death due to progressive circulatory failure. Cardiovascular death was defined as any death due to a cardiac or vascular cause, including SCD, heart failure death, deaths due to coronary, cerebrovascular, aortic events and thromboembolism.

A meta-analysis of proportions was conducted to obtain average incidence rates per patient-year (and 95 percent confidence intervals [CI]) of the different endpoints in both groups. In addition, a conventional meta-analysis was also performed to provide a

comparison between patients receiving CRT-D vs. CRT-P in studies reporting causes of death in both groups. The majority of meta-analyses aim to establish the effects of interventions by getting a pooled estimate of effect size (for example, relative risk, odds ratio, risk difference). However, meta-analyses can also be useful to get a more precise estimate of disease frequency, such as disease incidence rates and prevalence proportions.

In order to be eligible, studies needed to report information on the direct cause of death of patients receiving CRT. **Incidence or number of SCD, the primary endpoint, had to be reported, or provided by the authors, for a study to be included.** Registries, observational studies and randomized trials were considered eligible for analysis. The methods sections of evaluated studies were reviewed to confirm the suitability and composition of the reported endpoint. Studies reporting causes of death of CRT patients but without specification of device type (CRT-P or CRT-D) were excluded unless the authors could provide such information. Studies comprising only patients implanted either with CRT-P or CRT-D but providing information on cause of death were included in the proportional meta-analysis but not the conventional meta-analysis.

Two independent reviewers (SB, RD) screened all abstracts and titles to identify potentially eligible studies. The full text of all potentially eligible studies was then evaluated to determine the eligibility of the study for inclusion in the systematic review.

Data Extraction and Quality Assessment

Data extraction and presentation for the preparation of this manuscript followed the recommendations of the PRISMA group. The following data were extracted for characterizing each patient sample in the selected studies, whenever available: demographics and sample characterization, LV ejection fraction (EF), New York Heart Association (NYHA) class, QRS duration, etiology (ischemic or non-ischemic dilated cardiomyopathy), history of

atrial fibrillation, treatment with beta-blockers, angiotensin-converting-enzyme inhibitors or angiotensin type-2 receptor blockers and antiarrhythmic medication, and follow-up duration.

Quality Assessment was performed using the Delphi Consensus criteria for randomized controlled trials and a modified Newcastle–Ottawa Quality Assessment Scale for Cohort Studies by three reviewers (SB, RP and RD).

Data Synthesis and Statistical Analysis

A random-effects model was used to calculate a pooled estimate of the incidence rate from the combined studies. We summarized the incidence rate of each of the study endpoints at the study level and produced an average incidence rate for each outcome. Comparisons of the two device groups were performed using the raw mean difference of the incidence of SCD and respective 95% CIs. For the conventional meta-analysis, the rate ratio (RR) with respective 95% CI was used as measurement of treatment effect.

Sensitivity analyses were performed to assess potential differences in mortality rates between CRT-D and CRT-P depending on study design (randomized vs. non-randomized; single vs. multicenter), date of publication (studies published before vs. from 2008) and in specific scenarios (primary prevention only; prevalence of ischemic cardiomyopathy >50% vs. ≤50%; percentage of patients in NYHA class >2 ≥75% vs. <75%; percentage of patients on beta-blockers >75% vs. ≤75%; percentage of patients on ACEI/ARA-II >90% vs. ≤90%; these cut-offs took into consideration the means in the study group).

For the conventional meta-analysis, statistical heterogeneity on each outcome of interest was quantified using the I^2 statistic, which describes the percentage of total variation across studies due to true heterogeneity rather than chance. Values of <25%, 25-50% and >50% are by convention classified as low, moderate, and high degrees of heterogeneity, respectively[8].

Funnel plots and meta-regression analyses were obtained using Comprehensive Meta-Analysis software (Version 2). Funnel plots were used for evaluating the presence of publication bias and traced for comparisons including more than 10 studies. A meta-regression (using the Unrestricted ML method) was performed for assessing the possible association of moderator variables with the effect estimate or incidence rates.

RESULTS

Search Results and Patients' Characteristics

A total of **656** entries were obtained from the initial literature search. Two-hundred and thirty-seven were retrieved for analysis of titles and abstracts and 49 of these were selected for further analysis of the full-length article. Eighteen were considered eligible for inclusion[3,9–25]. A further 26 studies were retrieved after reviewing their reference lists and following manual searches[2,26–50]. Eleven additional studies containing data on cause of death were found, yet they did not fulfill inclusion criteria (details in supplementary file). The systematic review finally included a total of **44 studies**. **Figure 1** illustrates the study selection process.

The design of selected trials and baseline data are summarized in **table 1 and supplementary table 1**. Sixteen studies were randomized controlled trials[2,10,26,29,31,33,36,37,39,40,45,47,49,51,52], although randomization for CRT-D vs. CRT-P was only performed in one[2]. The remaining studies were observational. Twenty studies were multi-centre[2,3,9,10,26,29–33,36,37,39,40,45,47,49,52,53] . Quality assessment of the included studies is shown in **supplementary table 2**. All but one[2] of the randomized controlled studies had <6 Delphi criteria and thirteen cohort studies had a Newcastle-Ottawa score of ≥7.

The final population for the proportional meta-analysis included 18,874 patients (13,248 receiving CRT-D and 5,626 receiving CRT-P), representing 48,504 patient-years of follow-up: 33,928 in patients receiving CRT-D and 14,576 in those receiving CRT-P. The

conventional meta-analysis included 8,143 patients (4,947 receiving CRT-D and 3,196 receiving CRT-P) with 20,775 patient-years of follow-up: 12,556 in CRT-D patients and 8,219 in CRT-P patients.

The CRT-D and CRT-P groups had significant differences in characteristics (**Tables 1-2**). Patients receiving CRT-D had a mean age in their 60s in all studies, while the mean age of CRT-P patients was in their 70s in eight studies[3,14,27,30,33,37,38,50]. Overall, those receiving CRT-D were younger (65 years vs. 68.2) , more often males (80.3% vs. 72%), had lower NYHA class (60% in NYHA class 2 vs. 88.6%), lower prevalence of atrial fibrillation (21% vs. 24.6%), higher prevalence of ischaemic heart disease (55.3% vs. 45.5%) and were on beta-blockers (78.2% vs. 63.3%) and class III anti-arrhythmic drugs (23.5% vs. 15.2%) more often than those receiving CRT-P (**Table 2**).

Annual Incidence Rates of Specific Causes of Death

The pooled data of studies revealed that CRT-D patients had significantly lower incidence rates of all-cause mortality (55±5 per 1000 patient-years, 95%CI 44-65, vs. 97±9, 95%CI 79-115, p<0.001), SCD (5±1, 95%CI 3-6 vs. 20±2, 95%CI 15-24, p<0.001), progressive heart failure death (27±3, 95%CI 21-33 vs. 41±5, 95%CI 30-51, p<0.001) and non-cardiovascular death (13±1, 95%CI 10-15 vs. 20±3, 95%CI 15-25, p<0.001) compared to CRT-P recipients. Of all deaths reported in CRT-D patients, 9.1% were SCD, 49.1% due to progressive heart failure, 23.6% represented non-cardiovascular mortality and the remaining consisted of deaths due to cardiovascular causes other than SCD and progressive heart failure death. The distribution of causes of death was different amongst CRT-P patients: 20.6% were SCD, 42.3% due to progressive heart failure, 20.6% represented non-cardiovascular mortality, while the remaining consisted of deaths due to other cardiovascular causes. In the proportional meta-analysis, there were an additional 42 deaths per 1,000 patient-years in the

CRT-P group compared with CRT-D, of which 35.7% were due to SCD and the remaining 64.3% due to non-SCD. The forest-plots in **Figures 2 to 5** illustrate the incidence rates of all-cause mortality and SCD (per patient-years) in CRT-D and CRT-P patients across studies included in the proportional meta-analysis.

The pooled data of studies included in the conventional meta-analysis revealed that CRT-D patients had a significantly lower risk of all-cause mortality (RR=0.65, 95%CI 0.52-0.80; p<0.001; I^2=65%) (**supplementary figure 1**), SCD (RR=0.34, 95%CI 0.24-0.47; p<0.001; I^2=12%) (**supplementary figure 2**) and cardiovascular mortality (RR=0.60, 95%CI 0.44-0.81; p=0.001; I^2=66%) compared with those receiving CRT-P. There was also a trend towards lower risk of non-cardiovascular mortality (RR=0.74, 95%CI 0.54-1.02; p=0.063; I^2=25%). No difference was observed regarding the risk of progressive heart failure mortality (RR=0.83, 95%CI 0.56-1.23; p=0.35; I^2=75%). The observed I^2 values revealed mild heterogeneity for the analysis on SCD, but marked heterogeneity for the analysis on the risk of all-cause mortality, cardiovascular and progressive heart failure mortality. Funnel plots for the different endpoints revealed the presence of a publication bias.

Sensitivity Analyses and Meta-Regression

Sensitivity analyses and meta-regression were performed in our proportional meta-analysis for the endpoint of SCD, while meta-regression was also performed in the conventional meta-analysis. **Table 3** shows the results of our sensitivity analyses. As shown, the incidence rate of SCD in studies where less than 75% of patients were in NYHA class >2 was 7 per 1,000 patient-years in CRT-P patients vs. 4 in CRT-D patients.

The incidence rate of SCD was higher in randomized trials compared with observational studies for both CRT-D and CRT-P patients. For CRT-P patients, but not CRT-D, SCD was more frequent in multicentre vs. single-centre studies, and in studies where

percentage of patients with ischemic cardiomyopathy was higher than 50% vs. <50%. In both device groups, SCD was much more frequent in studies published before 2008 compared to studies published after 2008. The incidence rate of SCD was similar in CRT-D studies including PP patients only vs. studies including both PP and SP patients. **Table 3** describes these results.

The meta-regression (**supplementary table 3**) revealed that the risk of SCD in CRT-P patients increased in studies with higher prevalence of males, ischaemic cardiomyopathy and NYHA class 3. The incidence rate of SCD decreased in studies with older patients, higher prevalence of atrial fibrillation and higher LV ejection fraction. Likewise, SCD decreased in more recent studies compared with older studies, presumably a result of improved heart failure management. In our conventional meta-analysis, the benefit of the ICD in decreasing the risk of SCD was more pronounced with increasing QRS duration (**supplementary table 4**). No other associations were seen in both meta-analyses.

DISCUSSION

This study has shown that, compared to CRT-D, CRT-P patients have an almost two-fold higher unadjusted risk of all-cause mortality; SCD accounts for roughly a third of the excess mortality, while non-SCD and non-cardiovascular mortality account for two-thirds. Given the significant differences in population characteristics between the two groups and the significant competing 8.4% annual non-SCD risk in CRT-P patients, the extent of mortality reduction contributed by the presence of the ICD is difficult to infer. However, our results suggest that the ICD may be more cost-effective in primary prevention in young male CRT patients with ischemic cardiomyopathy who are on stable NYHA class III despite optimal medical treatment and have few comorbidities, while the cost-effectiveness ratio of routine CRT-D implantation (compared with CRT-P) in elderly patients or those with mild heart

failure may be less attractive. Considering that CRT-D associates with a higher risk of complications[44,55,56] and a significantly higher cost compared with CRT-P, our results reinforce the importance of selecting the right patient for the procedure and suggest that providing every CRT candidate with an ICD is unlikely to be clinically beneficial or cost-effective.

It is also useful to look at the presumptive magnitude of mortality benefit which could be conferred by the ICD. Assuming a median CRT-D battery life of 5 years[6] and an incidence rate of 5 SCD per 1,000 patient-years in CRT-D and 20 in CRT-P, after computing the cumulative incidence of the event we calculated a patient-based NNT of 13.5 per battery life, or an annual NNT of 67.5. These represent the number of CRT patients who would need an ICD for one SCD to be prevented during the battery-life or a 12-month period, respectively. However, it needs to be borne in mind that this represents a "best case scenario" where every additional SCD noted in the CRT-P population would be prevented by the presence of an ICD and, furthermore, this gain would not be offset by the competing risk of non-SCD. However, the ICD does not prevent all cases of SCD. In SCD-HeFT, the ICD was able to prevent approximately 60% of all SCDs compared with placebo[1], a similar reduction to what we have seen. Furthermore, almost one tenth of all deaths in CRT-D patients are still due to SCD[1,19,62]. Therefore, it seems logical that, to be cost-effective, candidates for CRT-D have to be carefully chosen where there is a significant additional risk from SCD and a lower competing risk of non-SCD. The results from our cumulative data suggest that this could be the case in selected subgroups such as younger patients, males, those with ischemic cardiomyopathy and in stable NYHA class 3. This can be informative in planning targeted RCTs to evaluate this question further.

The differences in patient characteristics explain the higher risk of non-SCD among CRT-P subjects. Patients receiving CRT-P are in general older, more often of female sex, have

more advanced heart failure and comorbidity and are less often on beta-blockers and class III antiarrhythmic drugs. In the CeRtiTuDe cohort study, the higher all-cause mortality rate in CRT-P patients (mean age 75 years) was almost entirely due to much higher number of progressive heart failure related- or non-cardiac deaths, while SCD was only slightly more frequent[3]. The CeRtiTuDe findings illustrate that the benefit of the ICD may dramatically decrease with increasing number of comorbidities to a point where patients may cease to benefit from it[63,64]. It is noteworthy that the mean pooled age of our CRT-P group was relatively low when compared with more recent studies such as CeRtiTuDe, possibly leading to a greater difference in observed SCD incidence rates[3]. The extent of the benefit of adding the ICD will be lower as the population receiving CRT gets older. Moreover, male patients and those with ischemic cardiomyopathy have been shown to obtain a more pronounced benefit from the ICD compared with females[4,65] and those with non-ischemic cardiomyopathy, respectively[4]. The lower use of beta-blockers and class III antiarrhythmic drugs amongst CRT-P patients may also help explain their higher risk of SCD. Differences in the use of these drugs may be a reflection of the higher prevalence of sustained or non-sustained arrhythmias amongst CRT-D patients (in fact, as our CRT-P patients did not have a secondary prevention indication for the ICD, we can assume that poorly tolerated sustained VT had not occurred in this group) and the lower age and degree of comorbidity of the CRT-D group and therefore better tolerance to these drugs.

Response to CRT leads not only to improved LV systolic function and heart failure symptoms but also to a decrease in the risk of potentially life-threatening arrhythmias[57–60]. CRT alone decreases the risk of SCD even in the absence of an ICD[10]. However, approximately one third of all deaths among CRT-P patients in CARE-HF were sudden (equivalent to 7% of all CRT patients)[61], a rate similar to that observed among CRT-P patients in COMPANION[2]. As such, the addition of the ICD may in theory provide incremental

protection. Nevertheless, this comes at the expense of an increased risk of device-related complications[44,55,56] and significantly higher cost; therefore this question merits careful scrutiny.

In summary, given the marked differences in characteristics between patients receiving CRT-D and CRT-P, and the fact that both devices have slightly different objectives, with the former focusing on both quality and duration of life while the latter focuses especially (but not exclusively) on quality of life, some arguments can be put forth. Patients for CRT-D have to be carefully selected, taking into account the competing risk of non-SCD and using well described risk stratification scores to determine the probability of obtaining a benefit from the ICD[66,67]. The decision-making has to be individualized, with role for patient empowerment and informed-decision making, discussing the specific objectives of the two types of devices. A thorough discussion with the patient and his/her family on the benefits and risks of each device would be useful, explaining that the addition of the ICD will allow a small number of patients to live longer at the expense of potentially increased comorbidity and a higher likelihood of death due to heart failure, infection or malignancy. In their Editorial on the CeRtiTuDe cohort study, Upadhyay and Singh emphasized the need for an individualized, patient-centric decision-making model, and a prospectively constructed risk scoring system to identify patients more likely to benefit from the addition of the defibrillator[68]. An experienced physician should consider not only the results of their mortality and SCD risk stratification but also the expectations of the patient, the risk of device-related complications and the cost-effectiveness of the proposed treatment.

Limitations

Several limitations should be taken into account when interpreting the results of our meta-analyses. Firstly, the overall study quality is limited by the fact that, with the exception of the

COMPANION trial, no study randomized patients for CRT-D vs. CRT-P. This limitation cannot be overcome and should be accepted. The very recently published *Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure* (DANISH) randomized controlled trial, which has not been included in the present meta-analysis, suggested that the lack of benefit of the ICD in patients with non-ischaemic cardiomyopathy was independent of CRT status[69].

Secondly, the cause-of-death definition and classification across studies were based on criteria specified by each group of authors. Although the definition of SCD was relatively uniform between studies, cause-of-death analysis is always a challenging task even when data is prospectively adjudicated, such as in the CeRtiTuDe cohort study. Most studies included in this meta-analysis did not use an adjudication process with predefined definitions of the different causes of death. However, the extent to which those differences in the adjudication process may significantly alter the main message of the paper is unclear. The SCD rate in CRT-P patients and therefore the potential benefit of the ICD was higher in randomized and multicentre studies, partly because of the more rigorous cause-of-death collection and adjudication which lead to fewer SCD being misspecified. Furthermore, it should be kept in mind that, although the defibrillator aims to prevent sudden arrhythmia death, in some cases it may prevent death due to heart failure of infection by treating a life-threatening arrhythmia and allowing time for the underlying condition to be overcome.

Thirdly, when interpreting the outcomes of CRT patients and the results of our cause-of-death analyses, the reader should always take into account the very significant differences in baseline characteristics between CRT-D and CRT-P patients. It is likely that many unmeasured factors may differ as well.

Finally, the inclusion of both primary and secondary prevention patients adds some heterogeneity to the analysis. However, **i)** none of the CRT-P patients included in the meta-

analysis had a secondary prevention indication for an ICD; **ii)** only three studies on CRT-D recipients included a majority (>50%) of SP patients; **iii)** there was no difference in SCD risk between studies including PP patients only and those including both PP and SP.

CONCLUSION

SCD represents approximately twenty per cent of all deaths in patients receiving CRT-P and one third of all excess mortality in this group compared with CRT-D patients. The cost-effectiveness of CRT-D implantation in patients otherwise eligible for CRT-P is highly dependent on the baseline risk of SCD, competing risks of non-sudden mortality and device battery longevity. Amongst patients with CRT indication, those of male gender, with ischemic cardiomyopathy and in stable NYHA class 3 may be more likely to benefit from the addition of the ICD, while in some sub-groups of patients, such as those with mild heart failure, the cost-effectiveness ratio may be much less favorable, emphasizing the need to evolve a tailored strategy for device selection in individual patients.

Acknowledgments: none

Financial Support: none

Disclosures: none

REFERENCES

1. Bardy GH,Lee KL,Mark DB,Poole JE,Packer DL,Boineau R et al;Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) Investigators. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005;352:225–37.

2. Bristow MR,Saxon LA,Boehmer J,Krueger S,Kass DA,De Marco T et al;Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Investigators. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004;350:2140–50.
3. Marijon E,Leclercq C,Narayanan K,Boveda S,Klug D,Lacaze-Gadonneix J et al; CeRtiTuDe Investigators.Causes-of-death analysis of patients with cardiac resynchronization therapy: an analysis of the CeRtiTuDe cohort study. *Eur Heart J* 2015; 36(41):2767-76.
4. Barra S,Providencia R,Tang A,Heck P,Virdee M,Agarwal S. Importance of Implantable Cardioverter-Defibrillator Back-Up in Cardiac Resynchronization Therapy Recipients: A Systematic Review and Meta-Analysis. *J Am Heart Assoc* 2015;4(11).
5. Menzies D. Systematic reviews and meta-analyses. *Int J Tuberc Lung Dis*. 2011;15:582–93.
6. Landolina M,Curnis A,Morani G,Vado A,Ammendola E,D'onofrio A et al. Longevity of implantable cardioverter-defibrillators for cardiac resynchronization therapy in current clinical practice: an analysis according to influencing factors, device generation, and manufacturer. *Europace* 2015;17:1251–8.
7. Suissa D,Brassard P,Smiechowski B,Suissa S. Number needed to treat is incorrect without proper time-related considerations. *J Clin Epidemiol* 2012;65:42–6.
8. Higgins JPT,Thompson SG,Deeks JJ,Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557–60.
9. Auricchio A,Metra M,Gasparini M,Lamp B,Klersy C,Curnis A et al;Multicenter Longitudinal Observational Study (MILOS) Group. Long-term survival of patients with heart failure and ventricular conduction delay treated with cardiac resynchronization therapy. *Am J Cardiol*. 2007;99:232–238.
10. Cleland JG,Daubert JC,Erdmann E,Freemantle N,Gras D,Kappenberger L et al. Longer-term effects of cardiac resynchronization therapy on mortality in heart failure [the CArdiac REsynchronization-Heart Failure (CARE-HF) trial extension phase]. *Eur Heart J* 2006;27:1928–32.
11. Jastrzebski M,Wilinski J,Fijorek K,Sondej T,Czarnecka D. Mortality and morbidity in cardiac resynchronization patients: impact of lead position, paced left ventricular QRS morphology and other characteristics on long-term outcome. *Europace*. 2013;15:258–265.
12. Khadjooi K,Foley PW,Chalil S,Anthony J,Smith RE,Frenneaux MP et al. Long-term effects of cardiac resynchronisation therapy in patients with atrial fibrillation. *Heart* 2008;94:879–883.
13. Prochnau D,Kuehnert H,Heinke M,Figulla HR,Surber R. Left ventricular lead position and nonspecific conduction delay are predictors of mortality in patients during cardiac resynchronization therapy. *Can J Cardiol* 2011;27:363–368.
14. Reitan C,Chaudhry U,Bakos Z,Brandt J,Wang L,Platonov PG et al. Long-Term Results of Cardiac Resynchronization Therapy: A Comparison between CRT-Pacemakers versus Primary Prophylactic CRT-Defibrillators. *Pacing Clin Electrophysiol* 2015; 38(6):758-67.
15. Rolink M,Verheugt FW,Bosker H a. Cardiac resynchronisation therapy: results from daily practice in Rijnstate Hospital, Arnhem. *Neth Hear J* 2009;17:6–8.

16. Roubicek T,Wichterle D,Kucera P,Nedbal P,Kupec J,Sedlakova J et al. Left Ventricular Lead Electrical Delay Is a Predictor of Mortality in Patients with Cardiac Resynchronization Therapy. *Circ Arrhythm Electrophysiol* 2015;8:1113–21.
17. Soliman OI, Theuns DA,van Dalen BM,Vletter WB,Nemes A,Jordaens LJ et al. Prediction of appropriate defibrillator therapy in heart failure patients treated with cardiac resynchronization therapy. *Am J Cardiol* 2010;105:105–111.
18. Suzuki H,Shimano M,Yoshida Y,Inden Y,Muramatsu T,Tsuji Y et al. Maximum derivative of left ventricular pressure predicts cardiac mortality after cardiac resynchronization therapy. *Clin Cardiol*. 2010;33:18–23.
19. Thijssen J,van Rees JB,Venlet J,Borleffs CJ,Höke U,Putter H et al. The mode of death in implantable cardioverter-defibrillator and cardiac resynchronization therapy with defibrillator patients: results from routine clinical practice. *Heart Rhythm* 2012;9:1605–12.
20. Tolosana J. Predictors of mortality in cardiac resynchronization therapy. Which patients benefit less from the therapy? *Europace*. 2011;vol./is. 1:1099–5129.
21. Trucco E,Tolosana JM,Castel MÁ,Batlle M,Borràs R,Sitges M et al. Plasma tissue inhibitor of matrix metalloproteinase-1 a predictor of long-term mortality in patients treated with cardiac resynchronization therapy. *Europace* 2016;18:232–7.
22. van Bommel RJ,Borleffs CJ,Ypenburg C,Marsan NA,Delgado V,Bertini M et al. Morbidity and mortality in heart failure patients treated with cardiac resynchronization therapy: Influence of pre-implantation characteristics on long-term outcome. *Eur Heart J*. 2010;31:2783–2790.
23. Verbrugge FH,Dupont M,De Vusser P,Rivero-Ayerza M,Van Herendael H,Vercammen J et al. Response to cardiac resynchronization therapy in elderly patients (>70 years) and octogenarians. *Eur J Heart Fail*. 2013;15:203–210.
24. Wang D. The long-term effects of single- or dual-chamble pacemakers upgraded biventricular pacing in patients with heart failure. *Circulation*. 2010;vol./is. 1:0009–7322.
25. Yu CM,Bleeker GB,Fung JW,Schalij MJ,Zhang Q,van der Wall EE et al. Left Ventricular Reverse Remodeling but Not Clinical Improvement Predicts Long-Term Survival After Cardiac Resynchronization Therapy. *Circulation* 2005;112:1580–1586.
26. Abraham WT,Fisher WG,Smith AL,Delurgio DB,Leon AR,Loh E et al;MIRACLE Study Group. Multicenter InSync Randomized Clinical Evaluation. Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002;346:1845–53.
27. Barra S,Duehmke R,Providencia R,Marijon E,Boveda S,Virdee M et al. Patients upgraded to cardiac resynchronization therapy due to pacing-induced cardiomyopathy are at low risk of life-threatening ventricular arrhythmias: a long-term cause-of-death analysis. *Europace* 2016. (in press)
28. Bax JJ,Bleeker GB,Marwick TH,Molhoek SG,Boersma E,Steendijk P et al. Left ventricular dyssynchrony predicts response and prognosis after cardiac resynchronization therapy. *J Am Coll Cardiol*. 2004;44:1834–1840.
29. Boriani G,Kranig W,Donal E,Calo L,Casella M,Delarche N et al;B-LEFT HF study group. A randomized double-blind comparison of biventricular versus left ventricular stimulation for cardiac resynchronization therapy: The Biventricular versus Left Univentricular Pacing with ICD Back-up in Heart Failure Patients (B-LEFT HF) trial. *Am Heart J* 2010;159:1052–1058.e1.

30. Boveda S,Marijon E,Jacob S,Defaye P,Winter JB,Bulava A et al;MonaLisa Study Group. Incidence and prognostic significance of sustained ventricular tachycardias in heart failure patients implanted with biventricular pacemakers without a back-up defibrillator: results from the prospective, multicentre, Mona Lisa cohort study. *Eur Heart J* 2009;30:1237–44.
31. Carson P,Anand I,O'Connor C,Jaski B,Steinberg J,Lwin A et al. Mode of death in advanced heart failure: The Comparison of Medical, Pacing, and Defibrillation Therapies in Heart Failure (COMPANION) trial. *J Am Coll Cardiol*. 2005;46:2329–2334.
32. Di Biase L,Gasparini M,Lunati M,Santini M,Landolina M,Boriani G et al;InSync/InSync ICD Italian Registry Investigators.Antiarrhythmic Effect of Reverse Ventricular Remodeling Induced by Cardiac Resynchronization Therapy. The InSync ICD Italian Registry. *J Am Coll Cardiol*. 2008;52:1442–1449.
33. Doshi RN,Daoud EG,Fellows C,Turk K,Duran A,Hamdan MH et al;PAVE Study Group. Left ventricular-based cardiac stimulation post AV nodal ablation evaluation (The PAVE study). *J Cardiovasc Electrophysiol*. 2005;16:1160–1165.
34. Ferreira AM,Adragão P,Cavaco DM,Candeias R,Morgado FB,Santos KR et al. Benefit of cardiac resynchronization therapy in atrial fibrillation patients vs. patients in sinus rhythm: The role of atrioventricular junction ablation. *Europace*. 2008;10:809–815.
35. Frigerio M,Lunati M,Pasqualucci D,Vargiu S,Foti G,Pedretti S et al. Left ventricular ejection fraction overcrossing 35% after one year of cardiac resynchronization therapy predicts long term survival and freedom from sudden cardiac death: Single center observational experience. *Int J Cardiol*. 2014;172:64–71.
36. Gold MR,Daubert JC,Abraham WT,Hassager C,Dinerman JL,Hudnall JH et al. Implantable defibrillators improve survival in patients with mildly symptomatic heart failure receiving cardiac resynchronization therapy analysis of the long-term follow-up of remodeling in systolic left ventricular dysfunction (reverse). *Circ Arrhythmia Electrophysiol*. 2013;6:1163–1168.
37. Leclercq C,Cazeau S,Lellouche D,Fossati F,Anselme F,Davy JM et al. Upgrading from single chamber right ventricular to biventricular pacing in permanently paced patients with worsening heart failure: The RD-CHF study. *PACE - Pacing Clin Electrophysiol*. 2007;30:23–30.
38. Leyva F,Umar F,Taylor R,Steeds RP,Frenneaux MP. The clinical outcome of cardiac resynchronization therapy in post-surgical valvular cardiomyopathy. *Europace* 2016; 18(5):732-8.
39. Linde C,Leclercq C,Cazeau S,Kappenberger L,Sutton R,Bailleul C et al. Reverse mechanical remodeling by biventricular pacing in congestive heart failure: one-year results from patients in atrial fibrillation in the MUSTIC study. *J Am Coll Cardiol*. 2002;39:124.
40. Marta GM,Aigner C,Klepetko W. Clinical Summary. *Chest*. 2005;221–223.
41. Molhoek SG,Bax JJ,Bleeker GB,Boersma E,van Erven L,Steendijk P et al. Comparison of response to cardiac resynchronization therapy in patients with sinus rhythm versus chronic atrial fibrillation. *Am J Cardiol* 2004;94:1506–9.
42. Palmisano P,Accogli M,Pisanò EC,Zaccaria M,De Blasi S,Ponzetta MA et al. Reduced long-term overall mortality in heart failure patients with prolonged QRS treated with CRT combined with ICD vs. heart failure patients with narrow QRS treated with ICD only. *Europace* 2015 Nov 26. pii: euv347.

43. Pappone C,Vicedomini G,Augello G,Mazzone P,Nardi S,Rosanio S. Combining electrical therapies for advanced heart failure: The Milan experience with biventricular pacing-defibrillation backup combination for primary prevention of sudden cardiac death. *Am J Cardiol*. 2003;91.
44. Schuchert A,Muto C,Maounis T,Frank R,Boulogne E,Polauck A et al;MASCOT study group. 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.
45. Summary C. Contak cd. Accessed from https://www.bostonscientific.com/content/dam/Manuals/us/current-rev-en/358487-006_US_S.pdf
46. Theuns DA,Schaer BA,Soliman OI,Altmann D,Sticherling C,Geleijnse ML et al. The prognosis of implantable defibrillator patients treated with cardiac resynchronization therapy: Comorbidity burden as predictor of mortality. *Europace*. 2011;13:62–69.
47. Young JB,Abraham WT,Smith AL,Leon AR,Lieberman R,Wilkoff B et al;Multicenter InSync ICD Randomized Clinical Evaluation (MIRACLE ICD) Trial Investigators.Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure:the MIRACLE ICD Trial. *JAMA* 2003;289:2685–94.
48. Ypenburg C,van Bommel RJ,Borleffs CJ,Bleeker GB,Boersma E,Schalij MJ et al. Long-Term Prognosis After Cardiac Resynchronization Therapy Is Related to the Extent of Left Ventricular Reverse Remodeling at Midterm Follow-Up. *J Am Coll Cardiol*. 2009;53:483–490.
49. Expanded Indications for Medtronic CRT-D Based on REVERSE & RAFT Studies.2011; accessed from http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM282274.pdf
50. Bortnik M,Degiovanni A,Dell'era G,Cavallino C,Occhetta E,Marino P. Prevalence of ventricular arrhythmias in patients with cardiac resynchronization therapy without back-up ICD: a single-center experience. *J Cardiovasc Med* 2014;15:301–6.
51. Piepoli MF,Villani GQ,Corrà U,Aschieri D,Rusticali G. Time course of effects of cardiac resynchronization therapy in chronic heart failure: benefits in patients with preserved exercise capacity. *Pacing Clin Electrophysiol* 2008;31:701–8.
52. Schuchert A,Muto C,Maounis T,Frank R,Ella RO,Polauck A et al;MASCOT Study Group. Gender-related safety and efficacy of cardiac resynchronization therapy. *Clin Cardiol*. 2013;36:683–690.
53. Providência R,Marijon E,Lambiase PD,Bouzeman A,Defaye P,Klug D et al. Primary Prevention Implantable Cardioverter Defibrillator (ICD) Therapy in Women-Data From a Multicenter French Registry. *J Am Heart Assoc* 2016;5.
54. Feldman AM,de Lissovoy G,Bristow MR,Saxon LA,De Marco T,Kass DA et al. Cost effectiveness of cardiac resynchronization therapy in the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial. *J Am Coll Cardiol* 2005;46:2311–21.
55. Kirkfeldt RE,Johansen JB,Nohr EA,Jørgensen OD,Nielsen JC. Complications after cardiac implantable electronic device implantations: an analysis of a complete, nationwide cohort in Denmark. *Eur Heart J* 2014;35:1186–94.

56. Romeyer-Bouchard C,Da Costa A,Dauphinot V,Messier M,Bisch L,Samuel B et al. Prevalence and risk factors related to infections of cardiac resynchronization therapy devices. *Eur Heart J* 2010;31:203–10.
57. Hsu JC,Solomon SD,Bourgoun M,McNitt S,Goldenberg I,Klein H et al;MADIT-CRT Executive Committee. Predictors of super-response to cardiac resynchronization therapy and associated improvement in clinical outcome: the MADIT-CRT study. *J Am Coll Cardiol* 2012;59:2366–73.
58. Schaer BA,Osswald S,Di Valentino M,Soliman OI,Sticherling C,ten Cate FJ et al. Close connection between improvement in left ventricular function by cardiac resynchronization therapy and the incidence of arrhythmias in cardiac resynchronization therapy-defibrillator patients. *Eur J Heart Fail* 2010;12:1325–32.
59. Thijssen J,Borleffs CJ,Delgado V,van Rees JB,Mooyaart EA,van Bommel RJ et al. Implantable cardioverter-defibrillator patients who are upgraded and respond to cardiac resynchronization therapy have less ventricular arrhythmias compared with nonresponders. *J Am Coll Cardiol* 2011;58:2282–9.
60. Zecchin M,Proclemer A,Magnani S,Vitali-Serdoz L,Facchin D,Muser D et al. Long-term outcome of “super-responder” patients to cardiac resynchronization therapy. *Europace* 2014;16:363–71.
61. Cleland JG,Daubert JC,Erdmann E,Freemantle N,Gras D,Kappenberger L et al;Cardiac Resynchronization-Heart Failure (CARE-HF) Study Investigators. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005;352:1539–49.
62. Packer DL,Prutkin JM,Hellkamp AS,Mitchell LB,Bernstein RC,Wood F et al. Impact of implantable cardioverter-defibrillator, amiodarone, and placebo on the mode of death in stable patients with heart failure: analysis from the sudden cardiac death in heart failure trial. *Circulation* 2009;120:2170–6.
63. Goldenberg I,Vyas AK,Hall WJ,Moss AJ,Wang H,He H et al;MADIT-II Investigators. Risk stratification for primary implantation of a cardioverter-defibrillator in patients with ischemic left ventricular dysfunction. *J Am Coll Cardiol* 2008;51:288–96.
64. Steinberg BA,Al-Khatib SM,Edwards R,Han J,Bardy GH,Bigger JT et al. Outcomes of implantable cardioverter-defibrillator use in patients with comorbidities:results from a combined analysis of 4 randomized clinical trials. *JACC Heart Fail* 2014;2:623–9.
65. Santangeli P,Pelargonio G,Dello Russo A,Casella M,Bisceglia C,Bartoletti S et al. Gender differences in clinical outcome and primary prevention defibrillator benefit in patients with severe left ventricular dysfunction: a systematic review and meta-analysis. *Heart Rhythm* 2010;7:876–82.
66. Goldenberg I,Gillespie J,Moss AJ,Hall WJ,Klein H,McNitt S et al;Executive Committee of the Multicenter Automatic Defibrillator Implantation Trial II. Long-term benefit of primary prevention with an implantable cardioverter-defibrillator:an extended 8-year follow-up study of the Multicenter Automatic Defibrillator Implantation Trial II. *Circulation* 2010;122:1265–71.
67. Providência R,Boveda S,Lambiase P,Defaye P,Algalarrondo V,Sadoul N et al. Prediction of Nonarrhythmic Mortality in Primary Prevention Implantable Cardioverter-Defibrillator Patients With Ischemic and Nonischemic Cardiomyopathy. *JACC Clin Electrophysiol* 2015;1:29–37.

68. Upadhyay GA, Singh JP. Cause of death and CRT device selection: striving for certitude? Eur Heart J. 2015 Nov 1;36(41):2777-9.
69. Køber L,Thune JJ,Nielsen JC,Haarbo J,Videbæk L,Korup E et al;DANISH Investigators. Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure. N Engl J Med. 2016;375(13):1221-30.

TABLE 1 - Selected studies for the systematic review

Author	Trial name (if applicable)	Year	Study design	Sample size (pts)			Mean follow-up (months)	Age (years)	Male gender (%)
				Total	CRT-D	CRT-P			
Abraham et al	MIRACLE	2002	Multi-centre, RCT	228	0	228	6	63.9	68
Linde et al	MUSTIC	2002	Multi-centre, RCT	75	0	75	12	64	77.9
Auricchio et al	PATH-CHF	2002	Single-centre, RCT	24	0	24	1	59	45.8
Young et al	MIRACLE ICD I	2003	Multi-centre, RCT	187	187	0	6	66.6	75.9
Pappone et al	-	2003	Single-centre, observational	135	88	47	28	CRT-D- 64 CRT-P- 63	CRT-D- 75 CRT-P- 77
Higgins et al	CONTAK CD	2003	Multi-centre, RCT	581*	248	0	4	66	84.7
Abraham et al	MIRACLE ICD II	2004	Multi-centre, RCT	85	85	0	6	63	88.2
Molhoek et al	-	2004	Single-centre, observational	60	28	32	22	NP	NP
Bristow and Carson et al	COMPANION	2005	Multi-centre, RCT	1520*	595	617	16	CRT-D- 66 CRT-P- 67	CRT-D – 67 CRT-P- 67
Doshi et al	PAVE	2005	Multi-centre, RCT	103	0	103	36	70	63
Yu et al	-	2005	Dual-centre, observational	141	0	141	23.2	64	73
Wang et al	-	2005	Single-centre, observational	25	0	25	20.9	61.4	72
Cleland et al	CARE-HF	2006	Multi-centre, RCT	409	0	409	36.4	67	74
Leclercq et al	RD-CHF	2007	Multi-centre, RCT	44	0	44	6	73	91
Auricchio et al	-	2007	Multi-centre, observational	1298	726	572	34	CRT-D- 64 CRT-P- 64	CRT-D- 83 CRT-P- 66
Di Biase et al	-	2008	Multi-centre, observational	398	398	0	23	66	88
Ferreira et al	-	2008	Single-centre, observational	131	102	29	29	NP	NP
Khadjooi et al	-	2008	Single-centre, observational	295	0	295	23	69.3	79.6
Moss et al	MADIT-CRT	2009	Multi-centre, RCT	1820*	1089	0	28.8	65	74.7
Boveda et al	MONA LISA	2009	Multi-centre, observational	198	0	198	9.8	71	67.5

Ypenburg et al	-	2009	Single-centre, observational	302	302	0	22	66	83.8
Rolink et al	-	2009	Single-centre, observational	119	26	93	18	NP	NP
Tang et al	RAFT	2010	Multi-centre, RCT	894	894	0	40	66.1	84.8
Boriani et al	B-LEFT HF	2010	Multi-centre, RCT	90	90	0	6	66	76
Soliman et al	-	2010	Single-centre, observational	169	169	0	21.8	60	74
Suzuki et al	-	2010	Single-centre, observational	62	0	62	35	66.2	58.8
Van Bommel et al	-	2010	Single-centre, observational	716	660	56	25	NP	NP
Prochnau et al	-	2011	Single-centre, observational	143	0	143	19	63.9	84.6
Theuns et al	-	2011	Dual-centre, observational	463	463	0	30.5	62	75
Thijssen et al	-	2012	Single-centre, observational	1189	1189	0	40.8	65	77
Gold et al	REVERSE	2013	Multi-centre, RCT	419	345	74	60	62.7	79.4
Schuchert et al	MASCOT	2013	Multi-centre, RCT	402	228	174	12	CRT-D- 68 CRT-P- 68	CRT-D- 86 CRT-P- 70
Verbrugge et al	-	2013	Single-centre, observational	220	92	128	20	NP	NP
Jastrzebski et al	-	2013	Single-centre, observational	262	190	172	24.7	NP	NP
Frigerio et al	-	2014	Single-centre, observational	330	190	140	54.5	NP	NP
Bortnik et al	-	2014	Single-centre, observational	84	0	84	29	74	65.5
Marijon et al	CeRtiTuDe	2015	Multi-centre, observational	1705	1170	535	24	CRT-D- 65.6 CRT-P- 75.9	CRT-D- 80.8 CRT-P- 69.5
Roubicek et al	-	2015	Single-centre, observational	329	250	79	39.6	NP	NP
Palmisano et al	-	2015	Dual-centre, observational	138	138	0	46	68.2	83.7
Reitan et al	-	2015	Single-centre, observational	705	257	448	59	CRT-D- 65.3 CRT-P- 72.1	CRT-D- 84.4 CRT-P- 83
Providencia et al	DAI-PP	2016	Multi-centre, observational	2952	2952	0	33.1	64.6	82.9
Leyva et al	-	2016	Single-centre, observational	556	0	556	54.2	70	79
Trucco et al	-	2016	Single-centre, observational	42	0	42	60	66	83

Barra et al	-	2016	Single-centre, observational	104	0	104	66	72	74

* The study also included patients who did not receive cardiac resynchronization therapy

TABLE 2 – Overall baseline characteristics of CRT-D and CRT-P patients

	Baseline characteristics	
	CRT-D	**CRT-P**
Age (mean, years)	65	68.2
Male gender (%)	80.3	72
NYHA class >2 (%)	60	88.6
Left ventricular ejection fraction (%)	24.8	24.7
QRS duration (ms)	158	160.6
Ischemic cardiomyopathy (%)	55.3	45.5
History of atrial fibrillation (%)	21	24.6
Beta-blockers (%)	78.2	63.3
ACEI or ARA-II (%)	86.5	84.8
Class III anti-arrhythmics (%)	23.5	15.6
Mean follow-up (months)	29.3	29.8

ACEi- Angiotensin converting enzyme inhibitor; ARA- Angiotensin receptor antagonist; CRT-D- Cardiac resynchronization therapy defibrillator; CRT-P- Cardiac resynchronization therapy pacemaker; NYHA- New York Heart Association Class

TABLE 3 – Sensitivity analyses on incidence rates of SCD per 1000 patient-years of follow-up

	CRT-P				CRT-D			
Condition	**Number of studies**	**Incidence rate**	**95% CI**	**P value**	**Number of studies**	**Incidence rate**	**95% CI**	**P value**
Randomized trials	10	29	17-41	<0.001	10	7	4-10	<0.001
Observational studies	20	16	12-21	<0.001	17	4	3-6	<0.001
Multi-centre studies	13	25	17-34	<0.001	16	5	3-7	<0.001
Single-centre studies	17	16	11-22	<0.001	11	5	2-7	<0.001
Publication date ≥2008	19	16	11-20	<0.001	20	4	3-6	<0.001
Publication date <2008	11	30	19-42	<0.001	7	16	3-29	0.014
>50% patients with ischemic CM	11	23	14-32	<0.001	17	5	3-7	<0.001
≤50% patients with ischemic CM	19	17	12-23	<0.001	10	5	2-7	<0.001
≥75% patients in NYHA class >2	22	22	16-28	<0.001	14	7	4-9	<0.001
<75% patients in NYHA class >2	6	7	3-11	<0.001	12	4	3-6	<0.001
≥75% patients on beta-blockers	9	16	13-19	<0.001	12	4	2-6	<0.001
<75% patients on beta-blockers	21	22	15-29	<0.001	15	7	4-9	<0.001
>90% patients on ACE-i/ARB-II	12	28	16-40	<0.001	14	6	3-8	<0.001
≤90 patients on ACE-i/ARB-II	15	17	12-22	<0.001	12	4	2-6	<0.001
Exclusively primary prevention ICD patients	-	-	-	-	6	5	2-7	<0.001
Both primary and secondary prevention ICD patients	-	-	-	-	9	5	2-7	<0.001
Exclusively/Mainly secondary prevention ICD patients	-	-	-	-	3	10	0-21	0.071

ACEi- Angiotensin converting enzyme inhibitor; ARA- Angiotensin receptor antagonist; CM- Cardiomyopathy; CRT-D- Cardiac resynchronization therapy defibrillator; CRT-P- Cardiac resynchronization therapy pacemaker; ICD- Implantable cardioverter-defibrillator; NYHA- New York Heart Association Class

FIGURE LEGENDS

Figure 1: Study selection process (Legends: RCT- randomized controlled trial)

Figure 2: Forest-plots illustrating the incidence rate of all-cause mortality (per patient-years) in CRT-D patients

Figure 3: Forest-plots illustrating the incidence rate of SCD (per patient-years) in CRT-D patients

Figure 4: Forest-plots illustrating the incidence rate of all-cause mortality (per patient-years) in CRT-P patients

Figure 5: Forest-plots illustrating the incidence rate of SCD (per patient-years) in CRT-P patients