ESC European Society of Cardiology

European Heart Journal (2020) **41**, 1976–1984
doi:10.1093/eurheartj/ehz773

CLINICAL RESEARCH
Arrhythmia/electrophysiology

Time trends in sudden cardiac death risk in heart failure patients with cardiac resynchronization therapy: a systematic review

Sérgio Barra [1,2,3], Rui Providência[4], Kumar Narayanan [5,6], Serge Boveda [7], Rudolf Duehmke [3,8], Rodrigue Garcia [9], Francisco Leyva [10,11], Véronique Roger[12,13], Xavier Jouven[6,14,15], Sharad Agarwal[3], Wayne C. Levy [16], and Eloi Marijon [6,14,15]*

[1]Cardiology Department, Hospital da Luz Arrabida, Praceta de Henrique Moreira 150, 4400-346 V. N. Gaia, Portugal; [2]Cardiology Department, V. N. Gaia Hospital Center, Rua Conceição Fernandes 4434-502 V. N. Gaia, Portugal; [3]Cardiology Department, Royal Papworth Hospital NHS Foundation Trust, Papworth Rd, Cambridge CB2 0AY, UK; [4]Cardiology Department, Barts Heart Centre, Barts Health NHS Trust, W Smithfield, London EC1A 7BE, UK; [5]Cardiology Department, Medicover Hospitals, Hyderabad, India; [6]Paris Cardiovascular Research Center (Inserm U970), Cardiovascular Epidemiology Unit, 56 Rue Leblanc, 75015 Paris, France; [7]Cardiology Department, Clinique Pasteur, 45 Avenue de Lombez - BP 27617 - 31076 TOULOUSE, 31300 Toulouse, France; [8]Cardiology Department, James Paget University Hospital, Lowestoft Road Gorleston-on-Sea, Great Yarmouth NR31 6LA, UK; [9]Cardiology Department, Poitiers University Hospital, 2 Rue de la Milétrie, 86021 Poitiers, France; [10]Aston Medical Research Institute, Aston University Medical School, 295 Aston Express Way, Birmingham B4 7ET, UK; [11]Cardiology Department, Queen Elizabeth Hospital, Mindelsohn Way, Birmingham B15 2TH, UK; [12]Department of Cardiovascular Diseases, Mayo Clinic College of Medicine and Science, 200 1st St SW, Rochester, MN 55905, USA; [13]Department of Health Sciences Research, Mayo Clinic College of Medicine and Science, 200 1st St SW, Rochester, MN 55905, USA; [14]Cardiology Department, European Georges Pompidou Hospital, 20 Rue Leblanc, 75015 Paris, France; [15]Paris Descartes University, 12 Rue de l'École de Médecine, 75006 Paris, France; and [16]Division of Cardiology, University of Washington, Seattle, WA, USA

Received 10 March 2019; revised 7 June 2019; editorial decision 9 October 2019; accepted 25 October 2019; online publish-ahead-of-print 21 November 2019

See page 1985 for the editorial comment on this article (doi: 10.1093/eurheartj/ehz860)

Aims While data from randomized trials suggest a declining incidence of sudden cardiac death (SCD) among heart failure patients, the extent to which such a trend is present among patients with cardiac resynchronization therapy (CRT) has not been evaluated. We therefore assessed changes in SCD incidence, and associated factors, in CRT recipients over the last 20 years.

Methods and results Literature search from inception to 30 April 2018 for observational and randomized studies involving CRT patients, with or without defibrillator, providing specific cause-of-death data. Sudden cardiac death was the primary endpoint. For each study, rate of SCD per 1000 patient-years of follow-up was calculated. Trend line graphs were subsequently constructed to assess change in SCD rates over time, which were further analysed by device type, patient characteristics, and medical therapy. Fifty-three studies, comprising 22 351 patients with 60 879 patient-years of follow-up and a total of 585 SCD, were included. There was a gradual decrease in SCD rates since the early 2000s in both randomized and observational studies, with rates falling more than four-fold. The rate of decline in SCD was steeper than that of all-cause mortality, and accordingly, the proportion of deaths which were due to SCD declined over the years. The magnitude of absolute decline in SCD was more prominent among CRT-pacemaker (CRT-P) patients compared to those receiving CRT-defibrillator (CRT-D), with the difference in SCD rates between CRT-P and CRT-D decreasing considerably over time. There was a progressive increase in age, use of beta-blockers, and left ventricular ejection fraction, and conversely, a decrease in QRS duration and antiarrhythmic drug use.

Conclusion Sudden cardiac death rates have progressively declined in the CRT heart failure population over time, with the difference between CRT-D vs. CRT-P recipients narrowing considerably.

Keywords Sudden death • Cardiac resynchronization • Implantable cardioverter-defibrillator • Biventricular pacemaker • Heart failure

* Corresponding author. Tel: +33 6 62 83 38 48, Fax: +33 1 56 09 30 47, Email: eloi_marijon@yahoo.fr

Introduction

Sudden cardiac death (SCD) is a frequent mode of death in patients with heart failure and reduced ejection fraction.[1,2] However, recent data from randomized controlled trials looking at patients with heart failure and reduced ejection fraction on pharmacological treatment alone have revealed a substantial decline in the occurrence of SCD over the last two decades.[3] A previous sub-analysis of the Framingham Heart Study had already shown a gradual reduction in the risk of SCD in subjects with and without heart disease in the second half of the 20th century.[4] This decline possibly reflects increasing use of evidence-based medications on all-cause mortality in general and SCD in particular. Another possible reason for the decline in SCD among heart failure patients may be due to the effects of cardiac resynchronization therapy (CRT), offered to patients since the late 90s, given its proven benefit in the reduction of ventricular arrhythmias and SCD even in the absence of a defibrillator.[5] However, the extent to which such a declining trend in the rate of SCD is present among patients with heart failure selected for CRT has not been reported. Although a detailed analysis of causes-of-death among CRT patients has already been published,[6] a comprehensive assessment of temporal trends in the occurrence of SCD could be of particular relevance for device selection between CRT-defibrillator (CRT-D) vs. CRT-pacemaker (CRT-P), given the lack of randomized studies directly comparing these two modalities in the primary prevention setting.

The main purpose of this systematic review was to assess trends in SCD incidence and associated factors among the CRT population over the last two decades, and examine how these may differ according to the use of CRT-D vs. CRT-P.

Methods

Literature search

We searched MEDLINE (via PubMed), EMBASE, clinicaltrials.gov, and COCHRANE databases (from inception to 30 April 2018) using the following Medical Subject Headings: ('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. When needed, authors were contacted to retrieve necessary information. Longitudinal studies written in English were considered for inclusion. The population, intervention, comparison and outcome (PICO) approach was used.[7] The population of interest included patients receiving CRT with or without an implantable cardioverter-defibrillator (ICD).

Study outcomes

The primary outcome of interest was the occurrence of SCD. This was defined as any sudden unexpected death presumed to be of cardiovascular origin and fulfilling at least one of the following criteria[6]: (i) occurring within 1 h of onset of cardiac symptoms in the absence of progressive cardiac deterioration (when observed); (ii) occurring during sleep; or (iii) occurring within 24 h after last being seen alive and stable (when not observed). The secondary outcomes were all-cause, progressive heart failure, and non-cardiovascular mortalities. Progressive heart failure death was defined as any death due to progressive circulatory failure.

Eligibility criteria and study selection

Two independent reviewers selected studies of any study design and written in English, using original data and assessing the outcome of CRT patients with cause-of-death data. Observational studies, registries and randomized trials involving CRT patients were considered eligible for analysis only when providing the number of patients who died of SCD or, alternatively, if such information could be retrieved after contacting the authors. Two independent reviewers (S.B., R.D.) screened all abstracts and titles to identify potentially eligible studies. The full texts of all potentially eligible studies were subsequently assessed to determine suitability for inclusion in the systematic review. Given the objective of assessing time trends, in cases of multiple publications pertaining to the same population, we included only the first publication providing cause-of-death data, with the exception of those cases where the initial publication only included a small percentage of the population. Decisions regarding the inclusion of studies required an agreement between both reviewers. Any discordances were discussed with a third author (R.P. or E.M.).

Data extraction and statistical analysis

Data extraction and presentation for the preparation of this manuscript followed the recommendations of the PRISMA group. Data extracted, whenever available, included age, sex, type of device (CRT-D or CRT-P), left ventricular ejection fraction, New York Heart Association (NYHA) class, QRS duration, aetiology (ischaemic or non-ischaemic dilated cardiomyopathy), history of atrial fibrillation, treatment with beta-blockers, aldosterone antagonists, angiotensin-converting-enzyme inhibitors (ACEi) or angiotensin type-2 receptor blockers (ARB) and antiarrhythmic medication, and follow-up duration.

For each study, we obtained the total length of follow-up in patient-years and the number of SCD and then calculated the rate of SCD per 1000 patient-years of follow-up. The association between year of publication and SCD rates was assessed through linear regression modelling using weighted least squares, such that larger studies were given greater weight in determining the regression coefficients. This analysis was performed using SPSS v.24. Trend line graphs were subsequently constructed in Microsoft Excel 2013 to illustrate the change in SCD rates over time, according to year of study publication. A similar analysis was performed for the secondary outcomes. A supplementary meta-regression analysis (using the Comprehensive Meta-analysis software v2) was performed for studying the association of the year of publication with the differences in SCD rates between both treatment arms (CRT-D and CRT-P). Potential time trends in baseline characteristics such as medication, age, sex, aetiology, left ventricular ejection fraction, QRS duration, and NYHA class were also sought.

Subgroup analyses

Although this study focused on CRT patients overall, separate analyses were performed for patients receiving CRT-D or CRT-P. A subgroup analysis according to study design (randomized vs. observational) was also performed. Finally, given the possible heterogeneity in SCD definitions/ascertainment, we conducted a sensitivity analysis including only those studies which either provided a formal definition of SCD or had an independent events committee for the adjudication of cause-of-death data.

Quality assessment

Quality assessment was performed using the Delphi Consensus criteria for randomized controlled trials and a modified Newcastle–Ottawa

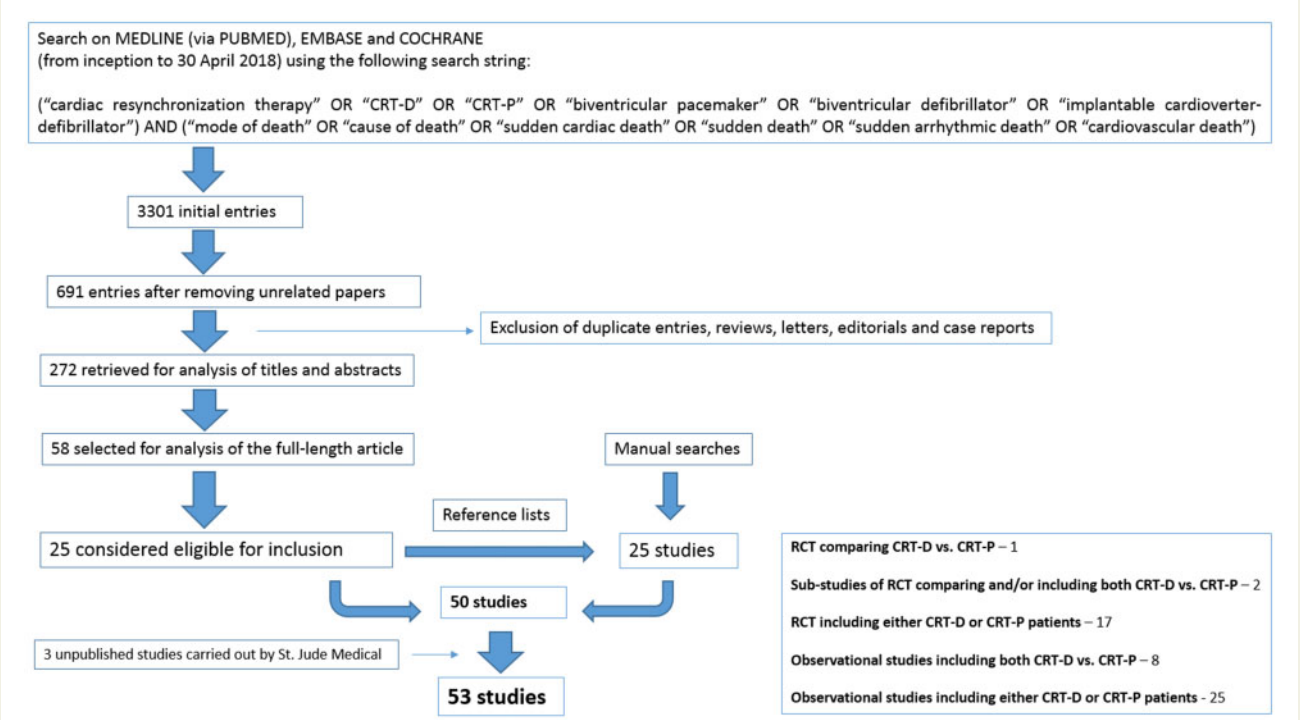


Figure 1 Study selection.

Quality Assessment Scale for Cohort Studies by two authors (S.B. and R.D.).[8,9]

Results

Search results and patients' characteristics

Out of a total of 3301 initial entries, 691 remained after eliminating papers unrelated to the subject. Of these, 272 were retrieved for analysis of titles and abstracts and 58 of these were selected for further analysis of the full-length article. Twenty-five were considered eligible for inclusion.[5,6,10–32] A further 25 published studies were retrieved after reviewing their reference lists and following manual searches.[33–57] Three additional randomized studies carried out by *St Jude Medical* (unpublished in peer-reviewed journals, but available online) were also considered following manual searches (the VecToR and RHYTHM ICD studies and the RHYTHM ICD QuickSite Lead Clinical Investigation).[58,59] The systematic review finally included a total of 53 studies. *Figure 1* illustrates the study selection process.

The design of included studies and baseline data are summarized in *Table 1* and Supplementary material online, *Table S1*. Nineteen studies were randomized controlled trials or *post hoc* analyses of randomized trials,[5,16,33,34,36,39,43,44,46,51,52,54,58–63] although randomization for CRT-D vs. CRT-P was only performed in one.[33] The remaining studies were observational (including prospective registries). Quality assessment of the included studies is shown in Supplementary material online, *Table S2*.

The final population included 22 351 patients (15 245 receiving CRT-D and 7106 receiving CRT-P), representing 60 879 patient-years of follow-up: 40 948 in patients receiving CRT-D and 19 931 in those receiving CRT-P. A total of 585 SCD were reported among these patients. As commonly observed in CRT studies, patients receiving CRT-P were in general older and had more advanced heart failure and comorbidities.

Sudden cardiac death and other mortality rates over time

In the general population of CRT patients, all-cause mortality occurred at a rate of 68.1 per 1000 patient-years of follow-up: 60.9 in CRT-D patients and 97.9 in CRT-P recipients. The overall rate of SCD was 9.6 per 1000 patient-years of follow-up, corresponding to approximately 14.1% of all deaths. The rates of death attributed to progressive heart failure, cardiovascular (including heart failure), and non-cardiovascular conditions were 34.5, 48.8, and 19.3 per 1000 patient-years, respectively.

Among CRT-D patients, SCD rate was 5.5 per 1000 patient-years, corresponding to 9.0% of all deaths, whereas the rates of death due to heart failure and non-cardiovascular death were 29.8 and 16.1 per 1000 patient-years, respectively. Conversely, SCD occurred at a rate of 18.1 events per 1000 patient-years in CRT-P patients, corresponding to 18.5% of all deaths in this group. Rates of death due to heart failure and non-cardiovascular death in the CRT-P group were 44.7 and 27.5 per 1000 patient-years, respectively.

There was a progressive decline in SCD rates since the early 2000s, with SCD rates falling by an average of 1.5 events per 1000

Table 1 Selected studies for the systematic review

Author	Trial name (if applicable)	Year	Study design	Sample size (patients)			Mean follow-up (months)
				Total	CRT-D	CRT-P	
Linde *et al.*	MUSTIC	2002	Multi-centre, RCT	75	0	75	12
Abraham *et al.*	MIRACLE	2002	Multi-centre, RCT	228	0	228	6
Leclercq *et al.*	MUSTIC-AF	2002	Multi-centre, RCT	25	0	25	3
Auricchio *et al.*	PATH-CHF	2002	Single-centre, RCT	24	0	24	1
Pappone *et al.*	—	2003	Single-centre, observational	135	88	47	28
Young *et al.*	MIRACLE ICD I	2003	Multi-centre, RCT	187	187	0	6
Higgins *et al.*	CONTAK CD	2003	Multi-centre, RCT	581[a]	248	0	4
Bristow and Carson *et al.*	COMPANION	2005	Multi-centre, RCT	1520[a]	595	617	16
Bax *et al.*	—	2004	Observational	85	0	85	12
Abraham *et al.*	MIRACLE ICD II	2004	Multi-centre, RCT	85	85	0	6
Molhoek *et al.*	—	2004	Single-centre, observational	60	28	32	22
Yu *et al.*	—	2005	Dual-centre, observational	141	0	141	23.2
RHYTHM ICD	—	2005	Multi-centre, RCT	183	183	0	12.1
RHYTHM ICD (QuickSite Clinical Lead Investigation)	—	2005	Multi-centre, RCT	153	153	0	12.1
VECTOR study	—	2005	Multi-centre, RCT	51	0	51	6
Wang *et al.*	—	2005	Single-centre, observational	25	0	25	20.9
Doshi *et al.*	PAVE	2005	Multi-centre, RCT	103	0	103	36
Cleland *et al.*	CARE-HF	2006	Multi-centre, RCT	409	0	409	36.4
Auricchio *et al.*	—	2007	Multi-centre, observational	1298	726	572	34
Leclercq *et al.*	RD-CHF	2007	Multi-centre, RCT	44	0	44	6
Khadjooi *et al.*	—	2008	Single-centre, observational	295	0	295	23
Di Biase *et al.*	—	2008	Multi-centre, observational	398	398	0	23
Ferreira *et al.*	—	2008	Single-centre, observational	131	102	29	29
Rolink *et al.*	—	2009	Single-centre, observational	119	26	93	18
Boveda *et al.*	MONA LISA	2009	Multi-centre, observational	198	0	198	9.8
Ypenburg *et al.*	—	2009	Single-centre, observational	302	302	0	22
Moss *et al.*	MADIT-CRT	2009	Multi-centre, RCT	1820[a]	1089	0	28.8
Soliman *et al.*	—	2010	Single-centre, observational	169	169	0	21.8
Suzuki *et al.*	—	2010	Single-centre, observational	62	0	62	35
Tang *et al.*	RAFT	2010	Multi-centre, RCT	894	894	0	40
Boriani *et al.*	B-LEFT HF	2010	Multi-centre, RCT	90	90	0	6
Van Bommel *et al.*	—	2010	Single-centre, observational	716	660	56	25
Prochnau *et al.*	—	2011	Single-centre, observational	143	0	143	19
Theuns *et al.*	—	2011	Dual-centre, observational	463	463	0	30.5
Thijssen *et al.*	—	2012	Single-centre, observational	1189	1189	0	40.8
Verbrugge *et al.*	—	2013	Single-centre, observational	220	92	128	20
Jastrzebski *et al.*	—	2013	Single-centre, observational	262	190	172	24.7
Gold *et al.*	REVERSE	2013	Multi-centre, RCT	419	345	74	60
Schuchert *et al.*	MASCOT	2013	Multi-centre, RCT	402	228	174	12
Frigerio *et al.*	—	2014	Single-centre, observational	330	190	140	54.5
Bortnik *et al.*	—	2014	Single-centre, observational	84	0	84	29
Marijon *et al.*	CeRtiTuDe	2015	Multi-centre, observational	1705	1170	535	24
Roubicek *et al.*	—	2015	Single-centre, observational	329	250	79	39.6
Palmisano *et al.*	—	2015	Dual-centre, observational	138	138	0	46
Reitan *et al.*	—	2015	Single-centre, observational	705	257	448	59
Providencia *et al.*	DAI-PP	2016	Multi-centre, observational	2952	2952	0	33.1
Trucco *et al.*	—	2016	Single-centre, observational	42	0	42	60
Barra *et al.*	—	2016	Single-centre, observational	638	224	414	63
Leyva *et al.*	—	2016	Single-centre, observational	556	0	556	54.2

Continued

Table 1 *Continued*

Author	Trial name (if applicable)	Year	Study design	Sample size (patients)			Mean follow-up (months)
				Total	CRT-D	CRT-P	
Leyva *et al.*	—	2017	Single-centre, observational	847	436	411	38.4
Martens *et al.*	—	2017	Single-centre, observational	687	326	361	38
Ioannou *et al.*	—	2017	Single-centre, observational	695	521	174	60.4
Acosta *et al.*	—	2018	Single-centre, observational	217	154	63	35.5

[a]The study also included patients who did not receive cardiac resynchronization therapy.

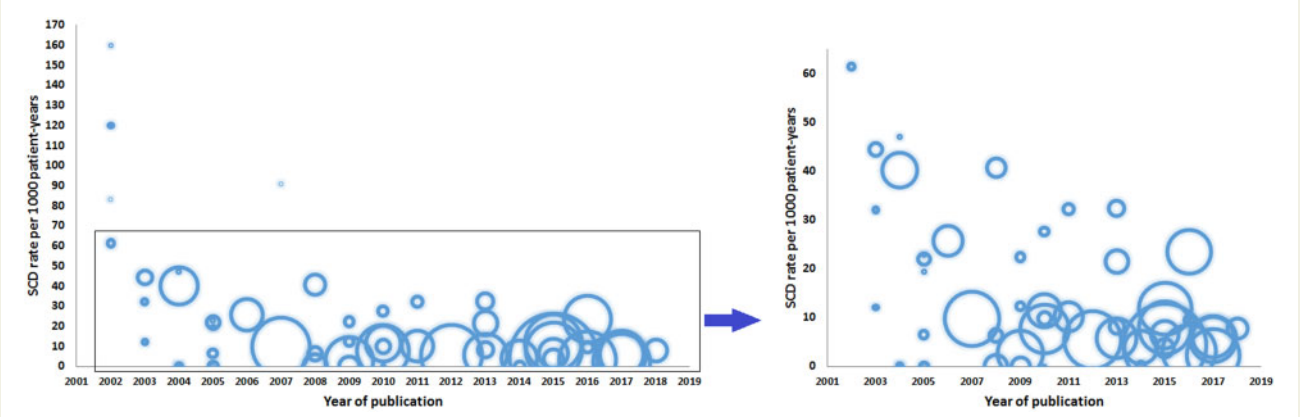


Figure 2 Trend line graphs illustrating the time-trend variation of sudden cardiac death rates among cardiac resynchronization therapy recipients. The area of each circle represents the size of each study (assessed by the number of patient-years of follow-up).

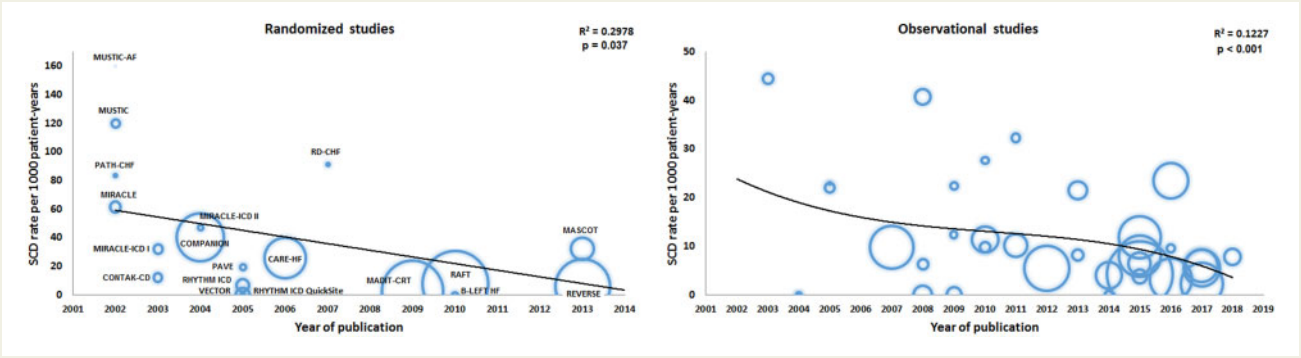
patient-years every year. Over the duration of this study, SCD rates fell to less than one-fourth the rate seen in the early 2000s (*Figure 2*), from approximately 40.6 per 1000 patient-years in 2002–2004 to 8.5 in 2008–2010 and 6.9 in 2014–2016, with the average annual risk of SCD stabilizing below 1% over the last decade. The greatest reduction was seen in the early 2000s. Despite higher rates of SCD being observed in randomized trials compared to observational studies (15.3 vs. 8.2 per 1000 patient-years, respectively, $P = 0.012$), the decrease in SCD rates occurred in both randomized and observational studies (*Take home figure*). The assessment of potential moderator variables through meta-regression revealed a significant association between an increasing year of publication and a decreasing difference of SCD rates between CRT-D and CRT-P patients, corroborating the results of the previous analyses (Supplementary material online, *Figure S1*).

Looking at the influence of underlying substrate, SCD rates declined both in studies with majority (>50%) of patients with ischaemic cardiomyopathy ($P = 0.012$), and also in studies with higher prevalence of non-ischaemic dilated cardiomyopathy ($P = 0.001$), although the decline was more pronounced in the latter.

There was a non-significant trend for decline in cardiovascular death over time (average annual reduction of 2.4 events per 1000 patient-years, $P = 0.07$), whereas no significant decline was seen for progressive heart failure mortality (annual reduction of 0.5 events per 1000 patient-years, $P = 0.54$), and non-cardiovascular mortality (annual reduction of 0.6 events per 1000 patient-years, $P = 0.20$) (*Figure 3*). Overall, all-cause mortality incidence rates significantly decreased over the last 17 years ($P = 0.023$) (*Figure 3*). However, the rate of decline in SCD was higher than that of all-cause mortality, and the percentage of fatalities related to SCD declined by an average of 1.3% every year ($P < 0.001$) (Supplementary material online, *Table S3* and *Figure 4*).

As the rate of decline in SCD and all-cause mortality seemed much steeper in the first period of the evaluation, a sensitivity analysis was performed after excluding all studies published between 2002 and 2004: a weaker, but still significant correlation was observed between year of publication and SCD rate ($P = 0.015$, Supplementary material online, *Figure S2*), but not all-cause mortality ($P = 0.44$). Except for the COMPANION trial, all the main randomized trials on CRT patients were published after 2004 (CARE-HF, MADIT-CRT, RAFT, and REVERSE).

An additional sensitivity analysis was performed including only those studies which either (i) provided a standardized definition of SCD, or (ii) had cause of death data adjudicated by an independent events committee (Supplementary material online, *Table S4*). Study selection was performed by three different



Take home figure Trend line graphs illustrating the time-trend variation of sudden cardiac death rates among cardiac resynchronization therapy recipients according to study design (randomized vs. observational studies). The area of each circle represents the size of each study.

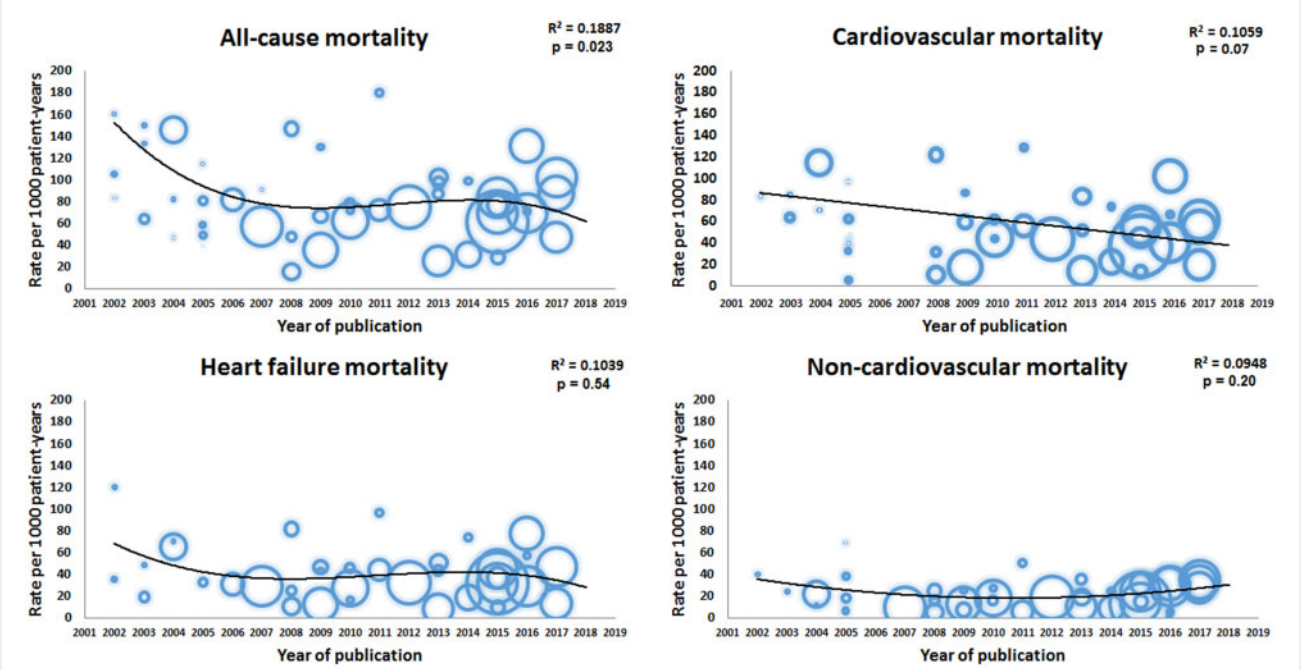


Figure 3 Trend line graphs illustrating the time-trend variation of all-cause mortality, heart failure, cardiovascular, and non-cardiovascular mortalities among cardiac resynchronization therapy recipients. The area of each circle represents the size of each study.

investigators (S.B., R.D., and R.G.), with disagreements discussed with a fourth (R.P.). This analysis, including 22 studies,[5,6,10–12,15,17,18,20,23,26,29,33,37,42,43,45,49,50,52,62,63] had similar results to those seen in the main analysis, confirming a gradual decline in SCD rates over time (Supplementary material online, *Figure S3*).

Sudden cardiac death trends according to device type

Sudden cardiac death rates declined progressively in both CRT-D and CRT-P recipients over the years (*Figure 5*), regardless of study design. There was a similar relative decline in both groups, although the absolute decline in SCD rates was more pronounced in the CRT-P group. The incidence rate of SCD among CRT-P patients fell from approximately 58.7 cases per 1000 patient-years in 2002–2004 to 30 in 2008–2010 and 13.7 in 2014–2016. The annual risk of SCD among CRT-P patients was consistently below 2% in the second half of this study. Among CRT-D patients, the SCD rate fell from 22.1 cases per 1000 patient-years in 2002–2004 to 5.5 in 2008–2010 and 4.1 in 2014–2016. Hence in terms of actual incidence, the difference in SCD rates between CRT-P and CRT-D decreased over time. Thus, in the period between 2002 and 2004, there was one additional case of SCD per year for every 28 CRT-P patients compared with an identical number of CRT-D patients, whereas in 2014–2016 this number changed to 105.

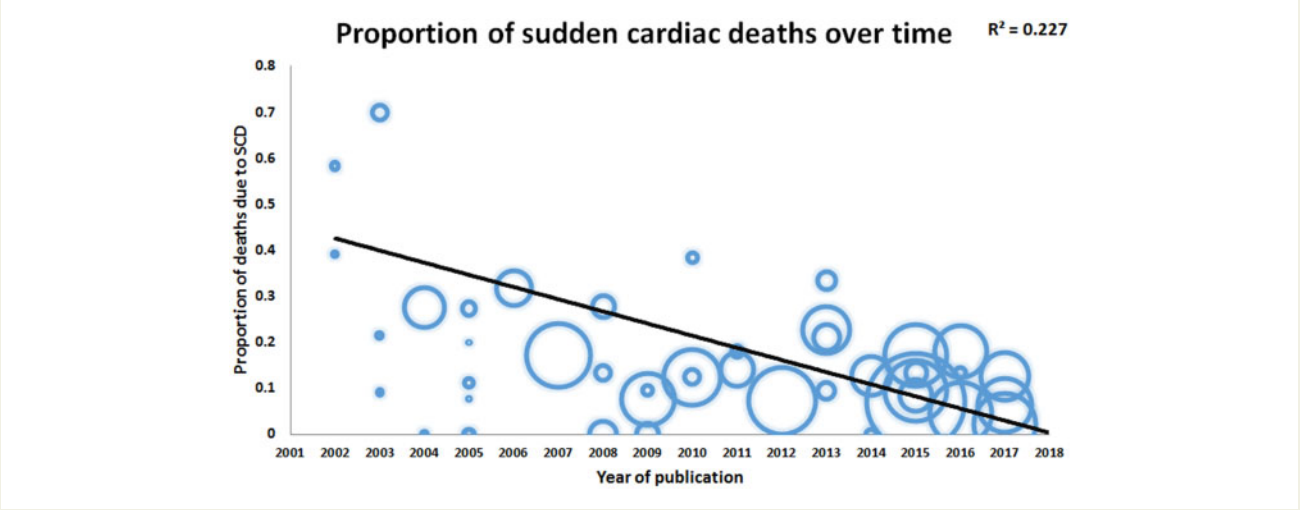


Figure 4 Trend line graphs illustrating the time-trend variation of the proportion of deaths due to sudden cardiac death. The area of each circle represents the size of each study.

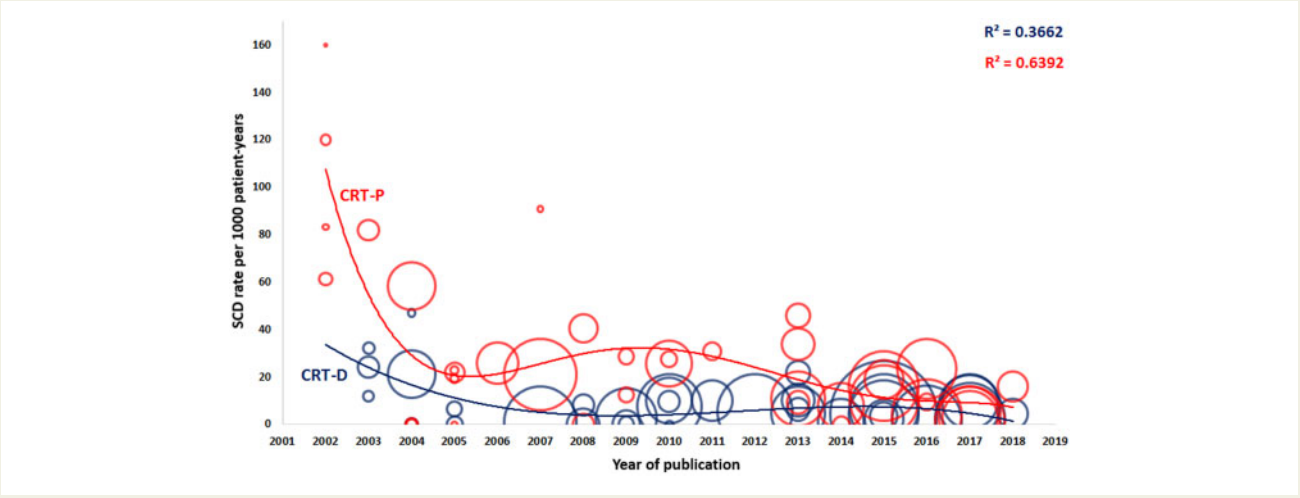


Figure 5 Trend line graphs illustrating the time-trend variation of sudden cardiac death rates among cardiac resynchronization therapy defibrillator and cardiac resynchronization therapy pacemaker recipients. The area of each circle represents the size of each study. CRT-D, cardiac resynchronization therapy defibrillator; CRT-P, cardiac resynchronization therapy pacemaker; SCD, sudden cardiac death.

Change in patients' characteristics over time

Over the same time period, there was a progressive increase in usage of beta-blockers ($P = 0.002$), patient age ($P = 0.041$), and left ventricular ejection fraction ($P < 0.001$), with, conversely, a decrease in baseline pre-CRT QRS duration ($P = 0.026$) and antiarrhythmic drug usage ($P = 0.008$) (*Figure 6* and Supplementary material online, *Figure S4*). On the other hand, NYHA class, sex, aetiology, atrial fibrillation prevalence, and use of ACEi/ARB and aldosterone antagonists remained relatively stable.

Discussion

Three important observations can be made from our findings. First, we demonstrate that SCD rates have declined significantly among patients receiving CRT since the early 2000s. This trend was noted not only in observational but also in randomized controlled studies, and in both CRT-D and CRT-P patients. Moreover, although the most significant decline was seen in the earlier 2000s, even after excluding the earlier studies there was still a gradual decline in SCD, albeit of lower magnitude. Importantly, not only have absolute SCD rates declined, but also the proportion of deaths related to SCD

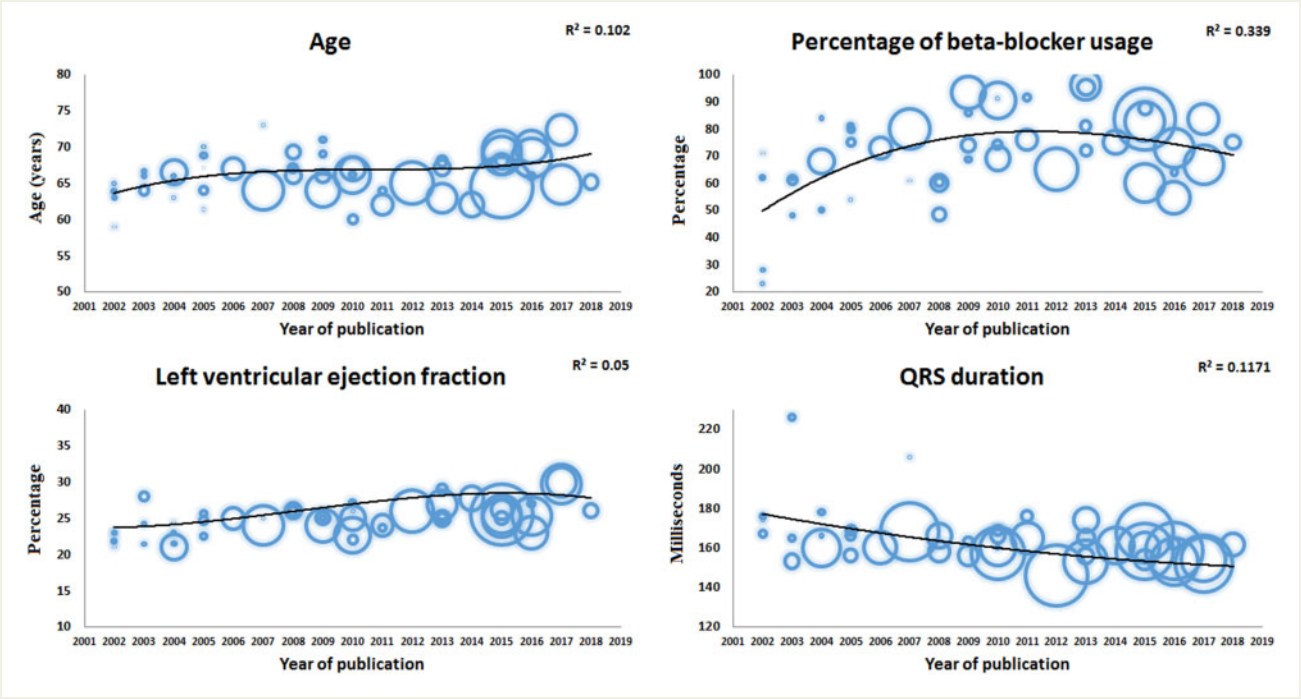


Figure 6 Trend line graphs illustrating the time-trend variation of baseline characteristics (age, beta-blocker usage, left ventricular ejection fraction, and QRS duration) among CRT recipients. The area of each circle represents the size of each study.

diminished over the years. Second, with a larger absolute decline in SCD rates among CRT-P patients, the difference in SCD has narrowed considerably between CRT-P and CRT-D recipients in the later periods. Finally, the decline in SCD rates paralleled improved medical therapy and changes in patients' baseline characteristics, which possibly contributed to the observed decline in SCD risk.

Cardiac resynchronization therapy by itself has been shown to be associated with a decrease in SCD via multiple mechanisms, including improvement in left ventricular ejection fraction and positive left ventricular remodelling. In the CARE-HF trial, CRT reduced the risk of sudden death even in the absence of defibrillator,[5] confirming its independent effect on prevention of arrhythmic death. Progressive improvements in CRT technology and delivery as well as patient selection and better adherence to guideline-recommended therapies, such as beta-blockers, are also likely vital in contributing to the decline in SCD rates. Indeed, this study confirmed that beta-blocker usage has progressively increased among CRT patients over the last 15–20 years, and this probably had a significant impact in the reduction of SCD risk. Likewise, changes in patients' baseline characteristics may have also had an impact on SCD rates over time. Shen *et al.*[3] had shown that, in heart failure patients with reduced ejection fraction, the rate of SCD had almost halved over a period of 19 years, which the authors associated with improvements in optimal medical therapies over time. The decline in SCD rates seen in our study was even more pronounced. Furthermore, contrary to non-CRT patients where the falling rates of SCD are proportionate to the downward trend in the overall death rates,[3] in the context of CRT, the decline in SCD is steeper than that of all-cause mortality. This is in line with the specific benefits of CRT for SCD reduction through favourable left ventricular remodelling.

The declining SCD rates in heart failure patients in general and CRT patients in particular, combined with recent evidence suggesting that CRT-D is associated with higher risk of device-related complications compared with CRT-P,[64] highlights the need in the current era to carefully identify those CRT candidates who would still derive a significant benefit from added defibrillator function. Our group had previously shown that men and patients with ischaemic cardiomyopathy may be more likely to benefit from the addition of the ICD.[65,66] The *Danish Study to Assess the Efficacy of ICDs in Patients with Non-*ischaemic *Systolic Heart Failure on Mortality (DANISH)* also found that non-ischaemic cardiomyopathy patients on optimal medical therapy (including CRT when indicated) do not seem to benefit from the ICD.[67] The present findings are in line with this, showing that the decline in SCD rates since the early 2000s has been more marked in studies with higher prevalence of non-ischaemic patients. It is generally accepted that non-ischaemic dilated cardiomyopathy patients are more likely to have favourable response to CRT, which in turn may lead to a more significant reduction in the risk of ventricular arrhythmias.

However, it is noteworthy that the decline in SCD rates among CRT recipients does not simply reflect a gradual increase in the prevalence of non-ischaemic cardiomyopathy and female sex (which are known to associate with lower risk of SCD), as these parameters did not change significantly over time. Likewise, although we could speculate that the ageing of CRT recipients could contribute to a reduction in the relative contribution of SCD in a competing risk fashion, we note that our data is not well suited to evaluate the effect of

age on time trends in SCD rate, as we only had access to mean patient age rather than individual patient data and the span in mean age is limited between studies.

Nevertheless, the present study does demonstrate certain time trends in patient characteristics which are likely the result of less strict, or more liberal, criteria for selecting patients for CRT implantation. In fact, in more recent studies, CRT has been offered to older patients with less prolonged QRS duration and less severe left ventricular systolic dysfunction. This is likely a result of continuously improving operator/centre experience, increasing procedural success, decreasing complication rates and cost, and widespread use of this therapy, as increasing evidence for benefit accumulates from a large number of randomized trials and registries. The publication of studies such as MADIT-CRT, RAFT, and REVERSE, which enrolled patients with less advanced heart failure, indeed expanded CRT indications to include 'less sick' patients, which also likely contributed to the decline on the incidence rate of SCD.

The decline in the risk of SCD, with very low rates in more recent studies, is undoubtedly reassuring and reinforces the notion that not all primary prevention CRT candidates on optimal medical therapy, including a beta-blocker, require added defibrillator, particularly in the context of non-ischaemic myocardial substrate. This is an area in need for further research focusing on those subgroups of patients whose risk of SCD is already low or very low in the absence of the defibrillator, and/or when the competing risk of non-SCD is deemed high.

Some limitations should be acknowledged when interpreting the findings of this study. First, most of the observational studies did not have an adjudication process with pre-specified definitions of the causes of death. It is plausible that some cases of SCD in observational studies may have been misclassified, and such heterogeneity of SCD definitions may have played a role in the secular trends. However, although we recognized *a priori* that many studies, particularly older ones, with an endpoint of sudden death or SCD would not have provided a formal definition, it is important to state that the definition of SCD has been relatively static throughout the years. Furthermore, when restricting the analysis to randomized trials, where cause-of-death data was more robust and usually centrally adjudicated, there was still a significant decline in SCD rates. In the study by Shen *et al.*,[3] the lack of a standardized definition of sudden death did not explain its falling rate over time. Second, the main limitation of randomized clinical trials is their external validation. The extent to which the trends noted in randomized studies reflect the 'real world' population of patients with heart failure receiving CRT has been a matter of discussion. Third, the ideal methods to calculate specific cumulative mortality rates (e.g. SCD) include the non-parametric cumulative incidence function of Fine and Gray, which takes the competing risk of non-SCD into consideration, and the use of standardized incidence rates rather than crude rates. However, this would require individual patient-level data for all studies which would be impracticable. Fourth, inferences were made about individuals based on aggregate data for a group (e.g. population mean age rather than individual data). To determine whether hypotheses obtained through group-level analyses apply to individuals, individual-level data would be required. Fifth, one might argue that the year of publication is a single point in time and does not reflect the entire period of study enrolment. However, as shown in Supplementary material online, *Figure S5*, while there is some overlap, the enrolment periods also move forward in a similar manner as the publication dates, as observed by the parallel linear time trends for year of publication, start dates, and end dates for the various studies. Therefore, using year of publication provides a reasonable method of assessing time trends. Finally, data on delivery of ICD therapies in the CRT-D population were not consistently available and any potential decline in the number of ICD therapies could also reflect recent changes in ICD programming (high-rate and delayed detection) rather than a true decline in the incidence of sustained ventricular arrhythmias.

Conclusions

This systematic review demonstrates a significant decline in the rates of SCD over the last two decades amongst CRT studies, with a diminishing gap in SCD rates between CRT-P vs. CRT-D recipients. Progressive improvements in medical therapy and CRT device technology and changes in patients' baseline characteristics may possibly result in further reductions in SCD rates among heart failure patients with CRT, irrespective of the use of additional defibrillator, which treating physicians should carefully consider in choice of device type.

Supplementary material

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

Conflict of interest: Serge Boveda is a consultant for Medtronic, Boston Scientific, Microport and Zoll. Eloi Marijon is part of the Paris-SDEC with activities supported by the Institut National de la Santé et de la Recherche Médicale (INSERM), University of Paris, Assistance Publique – Hôpitaux de Paris, Fondation Coeur et Artères, Global Heart Watch, Fédération Française de Cardiologie, Société Française de Cardiologie, Fondation Recherche Medicale, as well as unrestricted grants from industrial partners (Medtronic, St Jude Medical, Boston Scientific, MicroPort, Biotronik, and Zoll). Eloi Marijon is a consultant for Boston Scientific, Medtronic and Zoll. Levy C. Wayne: COI are the following: Clinical Endpoint Committee Member; SOLVE CRT - EBR Systems Inc; CHAMPION - CardioMEMS - Abbott/St Jude/CardioMEMS; GUIDE-HF - CardioMEMS - Baim Institute; Steering Committee Member; CARILLON - Cardiac Dimensions Inc; Remede FDA Post Approval Registry - Respircardia; ADMIRE ICD - GE Healthcare; Consultant for Amgen, Medtronic, Evalve, PharmaIN, Impuse Dynamics, Stock Options. No COI to declare for other coauthors of this paper.

References

1. SOLVD Investigators, Yusuf S, Pitt B, Davis CE, Hood WB, Cohn JN. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991;**325**:293–302.
2. Effect of metoprolol CR/XL in chronic heart failure: metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* 1999;**353**:2001–2007.
3. Shen L, Jhund PS, Petrie MC, Claggett BL, Barlera S, Cleland JGF, Dargie HJ, Granger CB, Kjekshus J, Køber L, Latini R, Maggioni AP, Packer M, Pitt B, Solomon SD, Swedberg K, Tavazzi L, Wikstrand J, Zannad F, Zile MR, McMurray J. Declining risk of sudden death in heart failure. *N Engl J Med* 2017;**377**:41–51.
4. Fox CS, Evans JC, Larson MG, Kannel WB, Levy D. Temporal trends in coronary heart disease mortality and sudden cardiac death from 1950 to 1999: the Framingham Heart study. *Circulation* 2004;**110**:522–527.

5. Cleland JGF, Daubert J-C, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L. 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**:1928–1932.
6. Marijon E, Leclercq C, Narayanan K, Boveda S, Klug D, Lacaze-Gadonneix J, Defaye P, Jacob S, Piot O, Deharo J-C, Perier M-C, Mulak G, Hermida J-S, Milliez P, Gras D, Cesari O, Hidden-Lucet F, Anselme F, Chevalier P, Maury P, Sadoul N, Bordachar P, Cazeau S, Chauvin M, Empana J-P, Jouven X, Daubert J-C, Le Heuzey J-Y. Causes-of-death analysis of patients with cardiac resynchronization therapy: an analysis of the CeRtiTuDe cohort study. *Eur Heart J* 2015;**36**:2767–2776.
7. PICO Framework—National Library of Medicine—PubMed Health. https://www.ncbi.nlm.nih.gov/pubmedhealth/PMHT0029906/ (December 2018).
8. Ottawa Hospital Research Institute. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (December 2018).
9. Verhagen AP, de Vet HC, de Bie RA, Kessels AG, Boers M, Bouter LM, Knipschild PG. The Delphi list: a criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by Delphi consensus. *J Clin Epidemiol* 1998;**51**:1235–1241.
10. Acosta J, Fernández-Armenta J, Borràs R, Anguera I, Bisbal F, Martí-Almor J, Tolosana JM, Penela D, Andreu D, Soto-Iglesias D, Evertz R, Matiello M, Alonso C, Villuendas R, de Caralt TM, Perea RJ, Ortiz JT, Bosch X, Serra L, Planes X, Greiser A, Ekinci O, Lasalvia L, Mont L, Berruezo A. Scar characterization to predict life-threatening arrhythmic events and sudden cardiac death in patients with cardiac resynchronization therapy: the GAUDI-CRT study. *JACC Cardiovasc Imaging* 2018;**11**:561–572.
11. Auricchio A, Metra M, Gasparini M, Lamp B, Klersy C, Curnis A, Fantoni C, Gronda E, Vogt J. Long-term survival of patients with heart failure and ventricular conduction delay treated with cardiac resynchronization therapy. *Am J Cardiol* 2007;**99**:232–238.
12. Barra S, Looi K-L, Gajendragadkar PR, Khan FZ, Virdee M, Agarwal S. 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;**18**:1187–1193.
13. Ioannou A, Papageorgiou N, Barber H, Falconer D, Barra S, Babu G, Ahsan S, Rowland E, Hunter R, Lowe M, Schilling R, Lambiase P, Chow A, Providencia R. 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;**120**:1158–1165.
14. Jastrzebski M, Wiliński 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.
15. Khadjooi K, Foley PW, Chalil S, Anthony J, Smith R. A, Frenneaux MP, Leyva F. Long-term effects of cardiac resynchronisation therapy in patients with atrial fibrillation. *Heart* 2008;**94**:879–883.
16. Leclercq C, Walker S, Linde C, Clementy J, Marshall AJ, Ritter P, Djiane P, Mabo P, Levy T, Gadler F, Bailleul C, Daubert J-C. Comparative effects of permanent biventricular and right-univentricular pacing in heart failure patients with chronic atrial fibrillation. *Eur Heart J* 2002;**23**:1780–1787.
17. Leyva F, Zegard A, Qiu T, Acquaye E, Ferrante G, Walton J, Marshall H. Cardiac resynchronization therapy using quadripolar versus non-quadripolar left ventricular leads programmed to biventricular pacing with single-site left ventricular pacing: impact on survival and heart failure hospitalization. *J Am Heart Assoc* 2017;**6**:1–11.
18. Martens P, Verbrugge FH, Nijst P, Dupont M, Nuyens D, Herendael HV, Rivero-Ayerza M, Tang WH, Mullens W. Incremental benefit of cardiac resynchronisation therapy with versus without a defibrillator. *Heart* 2017;**103**:1977–1984.
19. 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.
20. Providência R, Marijon E, Lambiase PD, Bouzeman A, Defaye P, Klug D, Amet D, Perier M, Gras D, Algalarrondo V, Deharo J, Leclercq C, Fauchier L, Babuty D, Bordachar P, Sadoul N, Piot O, Boveda S, Investigators The D, Providencia R, Beganton F, Perier M. Primary prevention implantable cardioverter defibrillator (ICD) therapy in women—data from a multicenter French registry. *J Am Heart Assoc* 2016;**5**:e002756.
21. Reitan C, Chaudhry U, Bakos Z, Brandt J, Wang L, Platonov PG, Borgquist R. Long-term results of cardiac resynchronization therapy: a comparison between CRT-pacemakers versus primary prophylactic CRT-defibrillators. *Pacing Clin Electrophysiol* 2015;**38**:758–767.
22. Rolink AM, Verheugt FWA, Bosker HA. Bosker H a. Cardiac resynchronisation therapy: results from daily practice in Rijnstate Hospital, Arnhem. *Neth Hear J* 2009;**17**:6–8.
23. Roubicek T, Wichterle D, Kucera P, Nedbal P, Kupec J, Sedlakova J, Cerny J, Stros J, Kautzner J, Polasek R. Left ventricular lead electrical delay is a predictor of mortality in patients with cardiac resynchronization therapy. *Circ Arrhythm Electrophysiol* 2015;**8**:1113–1121.
24. Soliman OII, Theuns DAMJ, van Dalen BM, Vletter WB, Nemes A, Jordaens LJ, Balk AHHM, ten Cate FJ, Geleijnse ML. Prediction of appropriate defibrillator therapy in heart failure patients treated with cardiac resynchronization therapy. *Am J Cardiol* 2010;**105**:105–111.
25. Suzuki H, Shimano M, Yoshida Y, Inden Y, Muramatsu T, Tsuji Y, Tsuboi N, Hirayama H, Shibata R, Murohara T. Maximum derivative of left ventricular pressure predicts cardiac mortality after cardiac resynchronization therapy. *Clin Cardiol* 2010;**33**:E18–E23.
26. Thijssen J, van Rees JB, Venlet J, Borleffs CJW, Höke U, Putter H, van der Velde ET, van Erven L, Schalij MJ. The mode of death in implantable cardioverter-defibrillator and cardiac resynchronization therapy with defibrillator patients: results from routine clinical practice. *Heart Rhythm* 2012;**9**:1605–1612.
27. Tolosana J. Predictors of mortality in cardiac resynchronization therapy. Which patients benefit less from the therapy? *Europace* 2011;**1**:1099–5129.
28. Trucco E, Tolosana JM, Castel MÁ, Batlle M, Borràs R, Sitges M, Guash E, Matas M, Arbelo E, Berruezo A, Brugada J, Mont L. Plasma tissue inhibitor of matrix metalloproteinase-1 a predictor of long-term mortality in patients treated with cardiac resynchronization therapy. *Europace* 2016;**18**:232–237.
29. Van Bommel RJ, Borleffs CJW, Ypenburg C, Marsan NA, Delgado V, Bertini M, Van Der Wall EE, Schalij MJ, Bax JJ. 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.
30. Verbrugge FH, Dupont M, De Vusser P, Rivero-Ayerza M, Van Herendael H, Vercammen J, Jacobs L, Verhaert D, Vandervoort P, Tang WHW, Mullens W. Response to cardiac resynchronization therapy in elderly patients (>70 years) and octogenarians. *Eur J Heart Fail* 2013;**15**:203–210.
31. Wang D. The long-term effects of single- or dual-chamber pacemakers upgraded biventricular pacing in patients with heart failure. *Circulation* 2010;**1**:0009–7322.
32. Yu CM, Bleeker GB, Fung J-H, Schalij MJ, Zhang Q, van der Wall EE, Chan YS, Kong SL, Bax JJ. Left ventricular reverse remodeling but not clinical improvement predicts long-term survival after cardiac resynchronization therapy. *Circulation* 2005;**112**:1580–1586.
33. Bristow MR, Saxon L. A, Boehmer J, Krueger S, Kass D. A, De Marco T, Carson P, DiCarlo L, DeMets D, White BG, DeVries DW, Feldman AM. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004;**350**:2140–2150.
34. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, Kocovic DZ, Packer M, Clavell AL, Hayes DL, Ellestad M, Trupp RJ, Underwood J, Pickering F, Truex C, McAtee P, Messenger J. Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002;**346**:1845–1853.
35. Bax JJ, Bleeker GB, Marwick TH, Molhoek SG, Boersma E, Steendijk P, Van Der Wall EE, Schalij MJ. Left ventricular dyssynchrony predicts response and prognosis after cardiac resynchronization therapy. *J Am Coll Cardiol* 2004;**44**:1834–1840.
36. Boriani G, Kranig W, Donal E, Calo L, Casella M, Delarche N, Lozano IF, Ansalone G, Biffi M, Boulogne E, Leclercq C. 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.
37. Boveda S, Marijon E, Jacob S, Defaye P, Winter JB, Bulava A, Gras D, Albenque JP, Combes N, Pavin D, Delarche N, Teubl A, Lambiez M, Chevalier P. 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**:1237–1244.
38. Carson P, Anand I, O'Connor C, Jaski B, Steinberg J, Lwin A, Lindenfeld J, Ghali J, Barnet JH, Feldman AM, Bristow MR. 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.
39. Doshi RN, Daoud EG, Fellows C, Turk K, Duran A, Hamdan MH, Pires LA. Left ventricular-based cardiac stimulation post AV nodal ablation evaluation (The PAVE study). *J Cardiovasc Electrophysiol* 2005;**16**:1160–1165.
40. Di Biase L, Gasparini M, Lunati M, Santini M, Landolina M, Boriani G, Curnis A, Bocchiardo M, Vincenti A, Denaro A, Valsecchi S, Natale A, Padeletti L. Antiarrhythmic effect of reverse ventricular remodeling induced by cardiac resynchronization therapy: the InSync ICD (Implantable Cardioverter-Defibrillator) Italian Registry. *J Am Coll Cardiol* 2008;**52**:1442–1449.
41. Ferreira AM, Adragão P, Cavaco DM, Candeias R, Morgado FB, Santos KR, Santos E, Silva J. A. 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.
42. Frigerio M, Lunati M, Pasqualucci D, Vargiu S, Foti G, Pedretti S, Vittori C, Cattafi G, Magenta G, Campo C, Bisetti S, Mercuro G. 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.
43. Gold MR, Daubert JC, Abraham WT, Hassager C, Dinerman JL, Hudnall JH, Cerkvenik J, Linde C. 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.
44. Leclercq C, Cazeau S, Lellouche D, Fossati F, Anselme F, Davy JM, Sadoul N, Klug D, Mollo L, Daubert JC. Upgrading from single chamber right ventricular to biventricular pacing in permanently paced patients with worsening heart failure: the RD-CHF study. *Pacing Clin Electrophysiol* 2007;**30**:23–30.
45. 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**:732–738.
46. Linde C, Leclercq C, Cazeau S, Kappenberger L, Sutton R, Bailleul C, Daubert J-C. Reverse mechanical remodeling by biventricular pacing in congestive heart failure: one-year results from patients in atrial fibrillation in the MUSTIC (MUltisite STimulation in Cardiomyopathy) study. *J Am Coll Cardiol* 2002;**39**:124.
47. Marta GM, Aigner C, Klepetko W. Clinical summary. *Chest* 2005;221–223.
48. Molhoek SG, Bax JJ, Bleeker GB, Boersma E, van Erven L, Steendijk P, van der Wall EE, Schalij MJ. Comparison of response to cardiac resynchronization therapy in patients with sinus rhythm versus chronic atrial fibrillation. *Am J Cardiol* 2004;**94**:1506–1509.
49. Palmisano P, Accogli M, Pisanò ECL, Zaccaria M, De Blasi S, Ponzetta MA, Valsecchi S, Milanese G, Lauretti M, Magliari F. 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* 2016;**18**:1374–1382.
50. 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**:74F–80F.
51. Schuchert A, Muto C, Maounis T, Frank R, Boulogne E, Polauck A, Padeletti L. 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.
52. Summary C. Contak cd. https://www.bostonscientific.com/content/dam/Manuals/us/current-rev-en/358487-006_US_S.pdf (December 2018).
53. Theuns D. A M, Schaer B. A, Soliman OII, Altmann D, Sticherling C, Geleijnse ML, Osswald S, Jordaens L. The prognosis of implantable defibrillator patients treated with cardiac resynchronization therapy: comorbidity burden as predictor of mortality. *Europace* 2011;**13**:62–69.
54. Young JB, Abraham WT, Smith AL, Leon AR, Lieberman R, Wilkoff B, Canby RC, Schroeder JS, Liem LB, Hall S, Wheelan K. Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE ICD trial. *JAMA* 2003;**289**:2685–2694.
55. Ypenburg C, van Bommel RJ, Borleffs CJW, Bleeker GB, Boersma E, Schalij MJ, Bax JJ. 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.
56. 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 (Hagerstown)* 2014;**15**:301–306.
57. Expanded Indications for Medtronic CRT-D Based on REVERSE & RAFT Studies. 2011. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM282274.pdf (December 2018).
58. U.S. Food and Drug Administration. Summary of safety and effectiveness data. RHYTHM ICD, 2005. www.accessdata.fda.gov/cdrh_docs/pdf3/P030054b.pdf (December 2018).
59. U.S. Food and Drug Administration. St Jude Frontier cardiac resynchronization therapy pacing system. P030035/S3. Summary of safety and effectiveness [VecTOR], 2005. www.accessdata.fda.gov/cdrh_docs/pdf3/P030035S003b.pdf (December 2018).
60. Abraham WT, Young JB, León AR, Adler S, Bank AJ, Hall SA, Lieberman R, Liem LB, O'Connell JB, Schroeder JS, Wheelan KR; Multicenter InSync ICD II Study Group. Effects of cardiac resynchronization on disease progression in patients with left ventricular systolic dysfunction, an indication for an implantable cardioverter-defibrillator, and mildly symptomatic chronic heart failure. *Circulation* 2004;**110**:2864–2868.
61. Auricchio A, Stellbrink C, Sack S, Block M, Vogt J, Bakker P, Huth C, Schöndube F, Wolfhard U, Böcker D, Krahnefeld O, Kirkels H; Pacing Therapies in Congestive Heart Failure (PATH-CHF) Study Group. Long-term clinical effect of hemodynamically optimized cardiac resynchronization therapy in patients with heart failure and ventricular conduction delay. *J Am Coll Cardiol* 2002;**39**:2026–2033.
62. Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, Estes NAM, Foster E, Greenberg H, Higgins SL, Pfeffer MA, Solomon SD, Wilber D, Zareba W. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med* 2009;**361**:1329–1338.
63. Tang ASL, Wells GA, Talajic M, Arnold MO, Sheldon R, Connolly S, Hohnloser SH, Nichol G, Birnie DH, Sapp JL, Yee R, Healey JS, Rouleau JL. Cardiac-resynchronization therapy for mild-to-moderate heart failure. *N Engl J Med* 2010;**363**:2385–2395.
64. Barra S, Providência R, Boveda S, Duehmke R, Narayanan K, Chow AW, Piot O, Klug D, Defaye P, Gras D, Deharo J-C, Milliez P, Da Costa A, Mondoly P, Gonzalez-Panizo J, Leclercq C, Heck P, Virdee M, Sadoul N, Le Heuzey J-Y, Marijon E. Device complications with addition of defibrillation to cardiac resynchronisation therapy for primary prevention. *Heart* 2018;**104**:1529.
65. Barra S, Providência R, Duehmke R, Boveda S, Marijon E, Reitan C, Borgquist R, Klug D, Defaye P, Sadoul N, Deharo J-C, Sadien I, Patel K, Looi K-L, Begley D, Chow AW, Le Heuzey J-Y, Agarwal S. Sex-specific outcomes with addition of defibrillation to resynchronisation therapy in patients with heart failure. *Heart* 2017;**103**:753–760.
66. Barra S, Boveda S, Providência R, Sadoul N, Duehmke R, Reitan C, Borgquist R, Narayanan K, Hidden-Lucet F, Klug D, Defaye P, Gras D, Anselme F, Leclercq C, Hermida J-S, Deharo J-C, Looi K-L, Chow AW, Virdee M, Fynn S, Le Heuzey J-Y, Marijon E, Agarwal S. Adding defibrillation therapy to cardiac resynchronization on the basis of the myocardial substrate. *J Am Coll Cardiol* 2017;**69**:1669–1678.
67. Køber L, Thune JJ, Nielsen JC, Haarbo J, Videbæk L, Korup E, Jensen G, Hildebrandt P, Steffensen FH, Bruun NE, Eiskjær H, Brandes A, Thøgersen AM, Gustafsson F, Egstrup K, Videbæk R, Hassager C, Svendsen JH, Høfsten DE, Torp-Pedersen C, Pehrson S. Defibrillator implantation in patients with nonischemic systolic heart failure. *N Engl J Med* 2016;**375**:1221–1230.