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META-ANALYSIS

Time-trend treatment effect of cardiac resynchronization therapy with or without defibrillator on mortality: a systematic review and meta-analysis

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Aims This study aimed to investigate the impact of cardiac resynchronization therapy with a defibrillator (CRT-D) on mortality, comparing it with CRT with a pacemaker (CRT-P). Additionally, the study sought to identify subgroups, evaluate the time trend in treatment effects, and analyze patient characteristics, considering the changing indications over the past decades.

Methods and results PubMed, CENTRAL, and Embase up to October 2021 were screened for studies comparing CRT-P and CRT-D, focusing on mortality. Altogether 26 observational studies were selected comprising 128 030 CRT patients, including 55 469 with CRT-P and 72 561 with CRT-D device. Cardiac resynchronization therapy with defibrillator was able to reduce all-cause mortality by almost 20% over CRT-P [adjusted hazard ratio (HR): 0.85; 95% confidence interval (CI): 0.76–0.94; $P < 0.01$] even in propensity-matched studies (HR: 0.83; 95% CI: 0.80–0.87; $P < 0.001$) but not in those with non-ischaemic aetiology (HR: 0.95; 95% CI: 0.79–1.15; $P = 0.19$) or over 75 years (HR: 1.08; 95% CI 0.96–1.21; $P = 0.17$). When treatment effect on mortality was investigated by the median year of inclusion, there was a difference between studies released before 2015 and those thereafter. Time-trend effects could be also observed in patients' characteristics: CRT-P candidates were getting older and the prevalence of ischaemic aetiology was increasing over time.

Conclusion The results of this systematic review of observational studies, mostly retrospective with meta-analysis, suggest that patients with CRT-D had a lower risk of mortality compared with CRT-P. However, subgroups could be identified, where CRT-D was not superior such as non-ischaemic and older patients. An improved treatment effect of CRT-D on mortality could be observed between the early and late studies partly related to the changed characteristics of CRT candidates.

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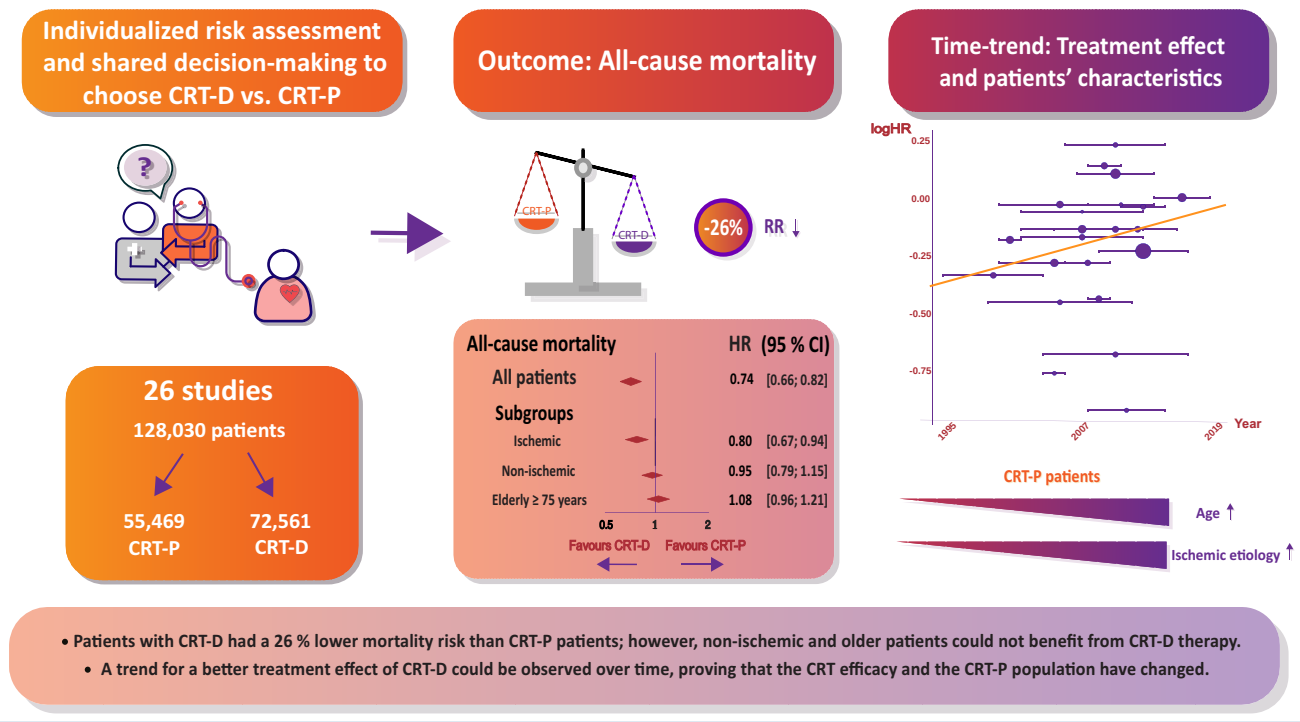
Graphical Abstract



Keywords CRT-P vs. CRT-D • Sudden cardiac death • Cardiac resynchronization therapy • Heart failure • Meta-analysis

Introduction

Cardiac resynchronization therapy with or without a defibrillator [CRT-D or CRT with a pacemaker (CRT-P)] is an effective device treatment in a selected patient population with symptomatic heart failure, heart failure with reduced left ventricular function (HFrEF), and wide QRS.[1] Choosing the optimal device type is based on individual risk assessment through measuring multiple parameters, such as aetiology, the presence of scar tissue, age, co-morbidities, and life expectancy, due to the lack of head-to-head randomized controlled trials (RCTs) comparing CRT-D with CRT-P.

While CRT-D may further improve survival over CRT-P by reducing sudden cardiac death (SCD), it also adds defibrillator-specific risks, such as inappropriate shock and lead failure, as well as higher cost.[2]

At the same time, CRT-P *per se* can decrease the risk of major ventricular arrhythmias in responder patients.[3] Moreover, the declining risk of SCD can be achieved by drug treatment alone, in which sacubitril/valsartan and sodium-glucose co-transporter-2 inhibitors (SGLT2i) seem to be effective in reducing the risk of major ventricular arrhythmias.[4,5] In this new era of heart failure drug treatment, reconsidering which patient cohort can benefit from having an implantable cardioverter-defibrillator (ICD) to CRT would be crucial.

In order to have a better understanding at the beginning of this new stage with its multiple effective drug treatments, we aimed to perform a systematic review and meta-analysis to assess the difference in outcomes using CRT-P vs. CRT-D over the last two decades, also showing the mode of death by device type and the importance of the most relevant cofactors influencing the outcome, such as ischaemic aetiology and age. Moreover, the time dependency of risk reduction in all-cause mortality was also investigated by device type.

Materials and methods

We reported our systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Supplementary material online, *Figure S3*).[6] The review protocol was registered on the PROSPERO International Prospective Register of Systematic Reviews (CRD42021281869). We did not deviate from the protocol.

Search strategy

A systematic search was performed in three scientific databases—Medline (via PubMed), Embase, and Cochrane Central Register of Controlled Trials (CENTRAL)—for studies published up to 5 December 2022. The following search key was used in all databases: (cardiac resynchronization therapy) AND (CRT-D OR ICD OR defibrillator). No restrictions (year, language, etc.) were imposed on the search.

Selection and eligibility criteria

Search results from the three applied databases were imported into citation management software (EndNote X9, Clarivate Analytics) for selection. After automatic and manual duplicate removal, the selection was conducted in two phases by two independent review authors (B.V. and S.G.) based firstly on the title and abstract and secondly on their full texts. After each phase, the rate of agreement and Cohen's Kappa were calculated to assess the quality of selection.[7] Any disagreement over the eligibility of a particular study was resolved through discussion with a third reviewer (A.K.).

There were no restrictions on the study designs eligible for inclusion. The inclusion criteria specified any peer-reviewed studies that reported

on a comparison between CRT-D and CRT-P regarding mortality. We excluded studies only available as conference abstracts or with fewer than 10 patients.

If the number of studies was sufficient (at least three per subgroup), subgroups were formed based on ischaemic and non-ischaemic heart failure aetiology and age. To incorporate changes in the therapy of the investigated population over time, a meta-regression was performed using the start year of patient enrolment as a dependent variable if there were at least 10 studies reporting on the same outcome in a comparable manner.

Data extraction

A standardized data collection form was used to extract data from the included studies for quality assessment and evidence synthesis. Data collected for extraction included the characteristics of the study (e.g. title, name of first author, publication year, number of patients, and location), demographics of the participants (e.g. age, gender, sample size per group, and follow-up months), and outcomes (number of patients experiencing outcome in the case of dichotomous variables; mean and standard deviation or median and interquartile range in the case of continuous variables). Two authors (B.V. and S.G.) extracted data independently; discrepancies were resolved through consensus.

Risk of bias assessment

Two review authors (B.V. and S.G.) independently assessed the risk of bias in included studies using the 'Risk Of Bias In Non-randomised Studies—of Interventions' (ROBINS-I) tool (Supplementary material online, *Figure S1*).[8]

Disagreements between the review authors over the risk of bias in particular studies were resolved by third-party arbitration (A.K.).

GRADE

Two review authors (B.V. and S.G.) performed the grading of trials and all of the outcomes, and disagreements between the two authors were resolved by the third author (A. K.). The grading was performed with GRADEpro (Supplementary material online, *Figure S2*).[9]

Statistical analysis

The estimated hazard ratios (HRs) were extracted and analysed for all outcomes. Raw data from the selected studies were log transformed and pooled using random effect models. We estimated the τ^2 using the restricted maximum likelihood approach and the *Q* profile method for calculating the confidence interval (CI) of τ^2. Statistical heterogeneity across studies was assessed by means of the Cochrane *Q* test and the I^2 values. Outlier and influence analyses were carried out following the recommendations of Harrer *et al.*[10] To assess the temporal effect on all-cause mortality HRs, we first took each study's reported timespan (in years) and calculated the midpoint for each time period. These central values were later used as an explanatory variable for a meta-regression. To further investigate the evolution of outcomes in question over time, we implemented random-effect cumulative meta-analyses. These cumulative meta-analyses were visualized with rainforest plots. All statistical analyses were made with R 4.1 (R Core Team[11]) using the *meta* (Balduzzi *et al.*[12]) *dmetar* (Harrer *et al.*[10]) and metafor packages (Viechtbauer[13]).

Results

A total of 26 studies were selected for the current analysis comprising 128 030 CRT patients, including 55 469 patients implanted with CRT-P and 72 561 patients who underwent CRT-D implantation (*Figure 1*). Only one single article was a RCT, and another one, the COMPANION trial's *post hoc* analysis, was evaluated as an observational one since it was not designed for comparing CRT-D and CRT-P directly. The rest of the articles were retrospective ($n = 17$)[14–30] or prospective ($n = 8$)[31–38] observational cohort studies, two-thirds of them ($n = 15$)[14,16,19–28,30,35,37] were single centre, and one-third of them were multi-centre studies ($n = 10$)[15,18,29,31–34,36,38,39] (*Table 1*). Six studies seemed to be also eligible for the analysis, but in five studies of them, there were no reported HRs available,[41–45] and one full-text article was not found in the scientific databases[46] so we excluded them.

Baseline clinical characteristics of patients

Out of 26 studies, eight reported that the mean age was over 75 years in their cohorts, and others showed CRT recipients were approximately 65 years old, particularly younger in CRT-P groups. Overall ischaemic aetiology rate occurred at almost 60%, most frequently in CRT-D patients. The rate of male patients was nearly 75%, and the atrial fibrillation rate was around 40%. Regarding the inclusion criteria, the median left ventricular ejection fraction (LVEF) was 30%, and QRS duration ranged between 150 and 170 ms except for one study by Leish-Farkas showed 134 ms as a mean QRS duration for their cohort. Sever symptomatic patients were over-represented, as 80–90% of the investigated patients were in NYHA II–III functional class. The presence of diabetes was heterogenous; 15–54% of the patients had this condition. The optimal medical treatment was common in most of the included studies, as 70% of those with available data reported over 80% use of ACEi/ARB and around 80% use of BB treatment and 50% use of MRA treatment. At the same time, four studies described approximately only half of patients added optimal treatment, while diuretics were less frequently used between 50 and 97% (*Table 2*).

Mode of death

The selected articles all reported all-cause mortality; more than three described results for death from heart failure progression, SCD, or cardiovascular and non-cardiovascular mortality. Unfortunately, no data were available for heart failure or cardiovascular hospitalization in these articles; therefore, despite the PICO, no analyses could be conducted.

All-cause mortality

Unadjusted HRs were available in 18 studies in 62 894 patients. Pooled analysis of HR was 0.74 (95% CI: 0.66–0.82), with a moderate heterogeneity ($I^2 = 77\%$; 95% CI: 64–85%; $P < 0.01$), showing a clear benefit of CRT-D over CRT-P (*Figure 2A*). When prospective and retrospective studies were compared, no significant differences could be found between them (see Supplementary material online, *Figure S6*).

Altogether 22 studies described adjusted HRs (aHRs) reporting 73 488 patients' data using age, gender, aetiology, symptoms, atrial fibrillation, diabetes, beta-blocker administration, and Left Bundle Branch Block (LBBB) morphology as the most frequent covariates. The overall aHRs was 0.85 (95% CI: 0.76–0.94) ($I^2 = 55\%$; 95% CI: 28–72%; $P < 0.01$), also showing an almost 20% risk reduction in death from any cause in CRT-D group compared with CRT-P (*Figure 2B*).

Those eight studies, which reported propensity score matching (PSM) analysis-based HRs, were also collected and analysed with 13 220 patient pairs' data, showing a HR of 0.83 (95% CI: 0.80–0.87) with a negligible heterogeneity rate, confirming that CRT-D was superior compared with CRT-D (*Figure 2C*).

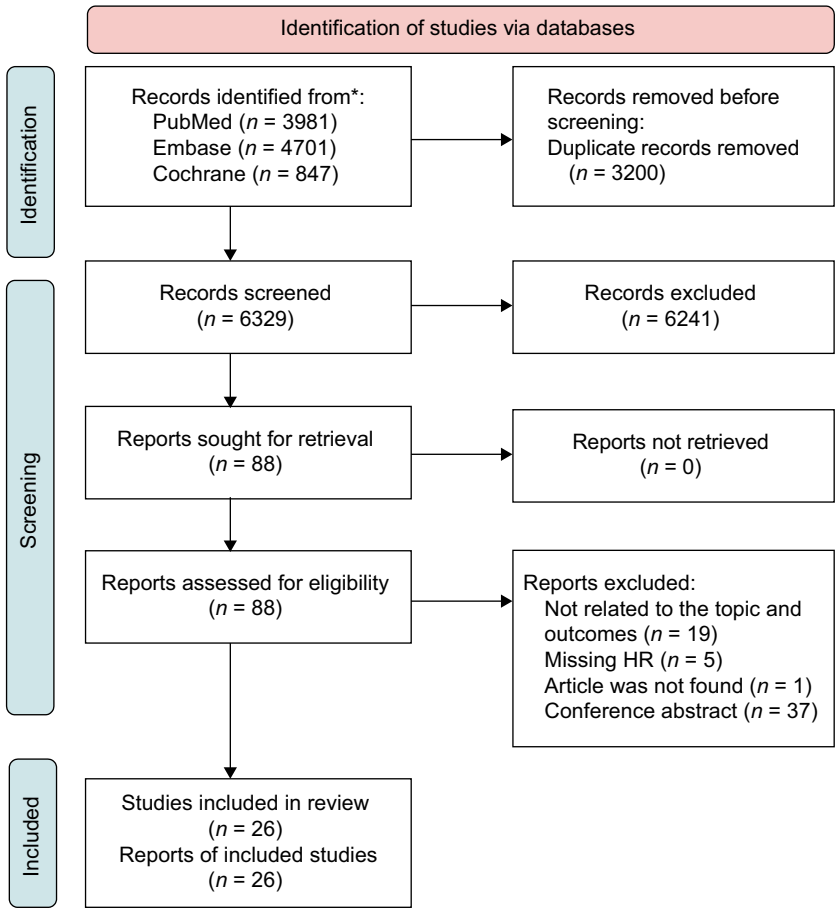


Figure 1 PRISMA flow chart of searching for publications. HR, hazard ratio.

Death from heart failure progression

Heart failure events were reported in three retrospective studies including 4723 patients. Pooled HR was 0.59 (95% CI: 0.41–0.85) with a high heterogeneity ($I^2 = 71\%$; 95% CI: 1–91%; $P = 0.03$) (*Figure 3A*).

Sudden cardiac death

From five prospective articles reported events as SCD including 6434 patients, the pooled analysis proved a 55% risk reduction in this endpoint [HR: 0.45 (95% CI: 0.32–0.62) ($I^2 = 0\%$; 95% CI: 0–79%; $P = 0.57$)], where all events were adjudicated by a previously declared independent committee (*Figure 3B*).

Cardiovascular mortality

Altogether four studies (three retrospective and one prospective) evaluated cardiovascular mortality including 49 834 patients. Pooled HR was 0.68 (95% CI: 0.49–0.94) ($I^2 = 67\%$; 95% CI: 4–89%; $P = 0.03$) showing a 32% risk reduction, also confirming a better treatment effect of CRT-D (*Figure 3C*).

Non-cardiovascular mortality

Concerning non-cardiovascular mortality, 48 770 patient's data were analysed from three articles, which showed a pooled HR: 0.58 (95% CI: 0.55–0.61) ($I^2 = 0\%$; 95% CI: 0–90%; $P = 0.86$) (see Supplementary material online, *Figure S4*).

Different subgroups by the most relevant covariates on all-cause death

Aetiology

The presence of ischaemic aetiology was reported in five studies, whereas non-ischaemic in seven studies in 4891 and 10 192 patients, respectively. In case of ischaemic aetiology, a substantial decrease in the risk of all-cause mortality could be observed by using aHRs (HR: 0.80; 95% CI: 0.67–0.94) ($I^2 = 0\%$; 95% CI: 0–79%; $P < 0.001$) (*Figure 4A*).

In non-ischaemic CRT patients, the use of CRT-D could not show an additional benefit compared to CRT-P [HR: 0.95 (95%CI 0.79–1.15) ($I^2 = 32\%$; 95% CI: 0–71%; $P = 0.19$)] in decreasing the risk of all-cause mortality (*Figure 4A*).

Age

When studies, analysed their patient cohort by age, a cut-off of 75 years was used. Altogether six studies reported aHRs from 5411 individuals. In patients over 75 years, implanting CRT-D had no additional benefit in all-cause mortality compared with CRT-P [aHR: 1.08 (95% CI: 0.96–1.21) ($I^2 = 0\%$; 95% CI: 0–75%; $P = 0.72$) (*Figure 4B*).

Time-trend differences by device type

All-cause mortality

As studies were investigated by the median year of patient inclusion times, reported aHRs for the total cohorts were comparable.

Table 1 Characteristics of enrolled studies

Author, year	Centrum numbers	Country	Study design	Enrolment	Follow-up mean ± SD or median (IQR)	Sample size	
						CRT-P	CRT-D
Auricchio, 2007[31]	4	Italy, Germany	Observational prospective	1994–2004	34 months (10–40)	572	726
Gold, 2015[32]	72	USA, Canada, Europe	Observational, prospective	2004–06	5 years (median)	74	345
Morani, 2013[34]	Multi-centre	Italy	Registry, prospective	2004–07	55 months (median)	108	266
Kutyifa, 2014[14]	1	Hungary	Registry, retrospective	2000–11	28 months (median)	693	429
Looi, 2014[17]	1	UK	Observational, retrospective	2006–10	29 months (median)	354	146
Marijon, 2015[33]	41	French	Cohort study, prospective	2008–10	6656 days (mean)	535	1170
Reitan, 2015[25]	1	Sweden	Observational retrospective	1999–12	59 months (4–165)	448	257
Munir, 2016[28]	1	USA	Observational retrospective	2002–13	40.8 months (median)	107	405
Witt, 2016[20]	1	Denmark	Observational retrospective	2000–10	4.0 years (2.4–6.3),	489	428
Laish-Farkas, 2017[37]	1	Israel	Observational prospective	2006–15	5 years (median)	142	104
Barra, 2017[38]	Multi-centre	French, British, Swedish	Observational cohort	2002–12	41.4 ± 29 months	1270	4037
Martens, 2017[16]	1	Belgium	Observational retrospective,	2008–15	38 ± 22 months	361	326
Yokoshiki, 2017[27]	1	Japan	Observational retrospective,	2011–15	21 ± 12 months	97	620
Drozd, 2016[30]	1	UK	Observational retrospective	2008–11	1072 ± 556 days	544	251
Wang, 2019[26]	1	USA	Observational retrospective	2002–13	46 months (median)	42	93
Leyva, 2018[22]	1	UK	Observational retrospective	2000–17	4.7 years (median)	999	551
Döring, 2018[21]	1	Germany	Observational retrospective,	2008–14	26 ± 19 months	80	97
Barra, 2019[15, 40]	Multi-centre	French, UK, Czech, and Swedish	Observational cohort study retrospective	2002–13	30 months (10–42)	534	1241
Liang, 2020[23]	1	China	Observational retrospective	2005–16	36 months (median)	126	219
Saba, 2019[24]	1	USA	Claims data retrospective	2007–14	5 years	1236	4359
Leyva, 2019[19]	1	UK	Observational retrospective	2009–17	2.7 years (1.3–4.8)	24 811	25 273
Huang, 2021[36]	58	China	Cohort study. prospective,	2012–13	27.7 ± 12.0 months	237	362
Gras, 2020[18]	1546	French	Longitudinal, nationwide cohort-study retrospective,	2010–17	913 ± 841 days	19 266	26 431
Doran, 2021[39]	128	USA	*Post hoc* secondary analysis of COMPANION trial	2000–02	16.5 months (median)	617	595
Schrage, 2022[35]	1	Sweden	Nationwide, registry prospective,	2000–16	2.35 years (0.92–3.00)	880	1108
Hadwiger, 2022[29]	Multi-centre	Germany	National health claim data, retrospective	2014–19	2.35 years (1.09–3.92)	847	2722

However, there was a clear difference between the results of early studies before the publication year of 2015 and those thereafter. Early studies reported an overall lower risk reduction [mean HR for studies with median patient enrolment year <2008 (released before 2015): *0.82* vs. mean HR for studies with median patient enrolment year >2008 (released after 2015): *0.73*] in mortality in CRT-D patients with a wide range of CIs. After 2015, a trend could be observed for a plateau in HRs and even narrower CIs. The meta-regression of HRs over time showed a non-significant slight increase [log (HR) $= -26.49 + 0.0131 * \text{median year}$; *P*-value = 0.28] (*Figure 5A*; see Supplementary material online, *Figure S5*) (*Graphical Abstract*).

Aetiology

Upon scrutinizing the articles included in the analysis, it was found that the CRT-P group had a more pronounced increase in the total number of patients with an ischaemic aetiology compared to the CRT-D subgroup (*Figure 5B*).

Age

In both subgroups, the mean age of the patients has increased over time, but the rise was more noticeable in the CRT-P group (*Figure 5C*).

Risk of bias assessment and GRADE

After assessing risk of bias in the enrolled studies, all of the studies showed moderate risk of bias (see Supplementary material online, *Figure S1*). Using

Table 2 Baseline clinical characteristics of the cohorts from enrolled studies

Author, year	Age		Male		Ischaemic aetiology		NYHA III-IV		Atrial fibrillation		Diabetes		QRS duration		LVEF (%)		ACE inhibitor or ARB		Beta-blocker		MRA		diuretics	
	CRT-P	CRT-D	CRT-P (%)	CRT-D (%)	CRT-P (%)	CRT-D (%)	CRT-P (%)	CRT-D (%)	CRT-P (%)	CRT-D (%)	CRT-P (%)	CRT-D (%)	CRT-P	CRT-D	CRT-P	CRT-D	CRT-P (%)	CRT-D (%)	CRT-P (%)	CRT-D (%)	CRT-P (%)	CRT-D (%)	CRT-P (%)	CRT-D (%)
Auricchio, 2007[31]	64.0 ± 10.0	64.0 ± 9.0	66.0	83.0	27.0	55.0	95.0	93.0	18.0	17.0	—	—	—	—	25.0 ± 7.0	25.0 ± 7.0	—	—	—	—	—	—	—	—
Gold, 2015[32]	63.6 ± 10.6	62.7 ± 10.7	71.6	79.4	45.9	58.6	—	—	—	—	16.2	22.9	157.0 ± 20.0	152.0 ± 21.0	30.0 ± 6.5	26.1 ± 7.0	98.6	95.9	91.9	96.5	—	—	—	—
Moriani, 2013[34]	74.0 ± 9.0	67.0 ± 9.0	68.0	85.0	41.0	62.0	80.0	75.0	—	—	31.0	30.0	175.0 + 29.0	165.0 + 32.0	27.0 ± 5.0	27.0 ± 5.0	79.0	88.0	70.0	75.0	21	29	70.0	76.0
Kutyifa, 2014[14]	66.3 ± 10.5	63.9 ± 10.9	71.0	84.0	34.0	51.0	—	—	28.0	22.0	35.0	31.0	165.5 ± 27.8	158.2 ± 27.1	28.2 ± 7.4	27.6 ± 6.4	84.0	86.0	84.0	88.0	53	61	75.0	77.0
Looi, 2014[17]	70 ± 9.9	67 ± 9.3	72.6	91.1	48.3	65.8	94.1	87.7	20	14.4	16.1	13.7	159 ± 25.4	161.0 ± 30.0	25.3 ± 7.7	23.9 ± 7.1	90.1	91.2	69.5	76.9	63	56	92.2	89.3
Marijon, 2015[33]	75.9 ± 9.0	65.6 ± 10.4	69.5	80.8	40.7	49.3	87.9	80.7	38.7	22.1	—	—	160.8 + 29.0	155.0 + 26.2	25.5 ± 10.0	25.5 ± 10.0	53.9	72.9	43.3	67.3	15	31	59.6	69.2
Reitan, 2015[25]	72.1 ± 9.7	65.3 ± 9.8	83.0	84.4	60.0	51.6	85.5	65.0	50.0	42.2	34.2	27.6	170.0 ± 27.9	164.0 ± 27.5	25 0.0 ± 7.0	25.0 ± 7.0	89.9	93.1	78.7	89.1	—	—	89.1	83.9
Munir, 2016[28]	83.0 (79.0–86.0)	81.0 (78.0–83.0)	63.6	72.8	29.9	57.3	—	—	—	—	29.0	27.7	154.0 (132.0–178.0)	154.0. (140.0–172.0)	28.0 (23.0–33.0)	23.0 (20.0–28.0)	48.6	85.4	77.6	76.8	11	15	72.0	78.3
Witt, 2016[20]	—	—	75.0	85.5	37.6	71.5	84.4	67.8	43.1	36.4	26	24	—	—	—	—	90	89	75	78	55	52	85	79
Laish-Farkas, 2017[37]	84.5 ± 3.0	82.3 ± 2.4	65.0	86.0	71.0	87.0	—	—	45.0	38.0	32.0	44.0	134.0 ± 32.4	133.8 ± 30.4	—	—	70.0	74.0	79.0	77.0	—	—	—	—
Barra, 2017[38]	73.0 10.1	65.2 10.7	57.6	84.6	46.3	51.9	83.1	69.9	35.0	35.7	18.9	22.4	—	—	27.1 9.1	25.5 7.7	77.5	84.5	62.0	81.2	40.1	40.3	—	—
Martens, 2017[16]	75.7 ± 9.1	68.6 ± 10.5	58.6	77.3	35.7	52.8	62.4	58.9	41.5	32.5	26.4	26.4	155.0 ± 30.0	153.0 ± 29.0	32.9 ± 10.4	26.7 ± 7.8	80.5	90.1	75.5	92.6	50	75	47.5	51.2
Yokoshiki, 2017[27]	77.0 ± 10.2	66.8 ± 11.2	60.8	76.8	21.6	27.9	75.2	72.2	12.4	13.2	28.9	31.5	157.9 ± 24.7	153.5 ± 30.7	33.0 ± 11.1	26.5 ± 9.0	56.7	66.6	61.9	76.9	30	45	76.3	80.5
Drozd, 2016[30]	75.1 10.3	69.3 10.0	74.0	93.0	54.0	90.0	63.0	60.0	35.0	23.0	24.0	27.0	156.4 ± 27.0	150.0 ± 24.4	—	—	84.0	92.0	74.0	88.0	—	—	—	—
Wang, 2019[26]	81.6 ± 5.3	80.7 ± 3.5	—	—	0	0	—	—	85.7	76.3	19	26.9	152.0 ± 34.8	159.0 ± 24.9	28.0 ± 5.50	24.1 ± 6.42	52.4	87.1	73.8	78.5	5	14	—	—
Leyva, 2018[22]	73.1 ± 11	70.1 ± 9	70.8	79.7	43.7	75.3	91.3	80.9	36.2	28.0	20.1	25.4	155.1 ± 21	150.8 ± 21	—	—	87.4	92.9	60.7	77.3	39	51	95.1	98.3
Döring 2018[21]	82.6 ± 4.5	77.8 ± 1.9	56.3	75.5	50.0	53.1	83.7	83.5	23.8	20.4	—	—	150.0 ± 19	158.0 ± 18	29.6 ± 5.9	27.4 ± 6.0	86.3	93.8	80.0	90.7	29	59	92.5	86.8
Barra, 2019[15,40]	69.8 ± 10.2	63.8 ± 10.4	69.7	80.4	47.8	52.5	82.0	68.3	42.7	47.1	28.1	26.7	—	—	26.8 ± 7.6	25.5 ± 6.3	91.4	83.5	74.2	79.1	43	32	—	—
Liang, 2020[23]	62.4 ± 10.4	59.8 ± 12.0	64.3	75.3	7.1	7.8	—	—	15.1	15.1	19.8	16.9	161.28 ± 30.91	157.96 ± 31.53	;	;	91.3	94.5	84.9	90	14	21	91.3	89.5
Saba, 2019[24]	77.9 ± 8.4	72.6 ± 9.2	60.1	64.9	22.7	29.6	—	—	68.4	45.1	53.8	54.5	—	—	—	—	—	—	—	—	—	—	—	—
Leyva, 2019[19]	74.3 ± 11.3	68.1 ± 11.1	68.9	80.8	56.0	67.2	—	—	—	—	24.4	27.3	—	—	—	—	—	—	—	—	—	—	—	—
Huang, 2021[36]	60.3 ± 11.5	60.0 ± 12.1	55.3	74.6	19.8	28.2	77.6	84.2	12.7	10.2	16.9	13.8	163.6 ± 24.9	157.8 ± 27.0	28.1 ± 5.4	27.3 ± 5.2	82.8	80.7.4	87.3	87.3	79	77	83.5	83.7
Gras, 2020[18]	78.4 ± 9	67.5 ± 10	64.6	77.4	57.6	65.5	—	—	68.8	52.1	31.7	36.9	—	—	—	—	—	—	—	—	—	—	—	—
Doran, 2021[39]	67.0	66.0	67.0	67.0	54.0	55.0	—	—	—	—	39.0	41.0	160.0	160.0	—	—	89.0	90.0	68.0	68.0	53	55	94.0	97.0
Schrage, 2022[35]	74.3 ± 9.3	67.6 ± 9.8	78.6	84.2	73.2	73.4	64.7	60.5	67.7	61.5	—	—	—	—	—	—	91.2	94.0	93.3	96.9	51	60	87.0	84.5
Hadwiger, 2022[29]	76.7 (8.89)	69.9 (9.57)	52.0	65.0	73.0	75.0	85.0	85.0	59.0	41.0	32.0	36.0	—	—	—	—	—	—	—	—	—	—	—	—

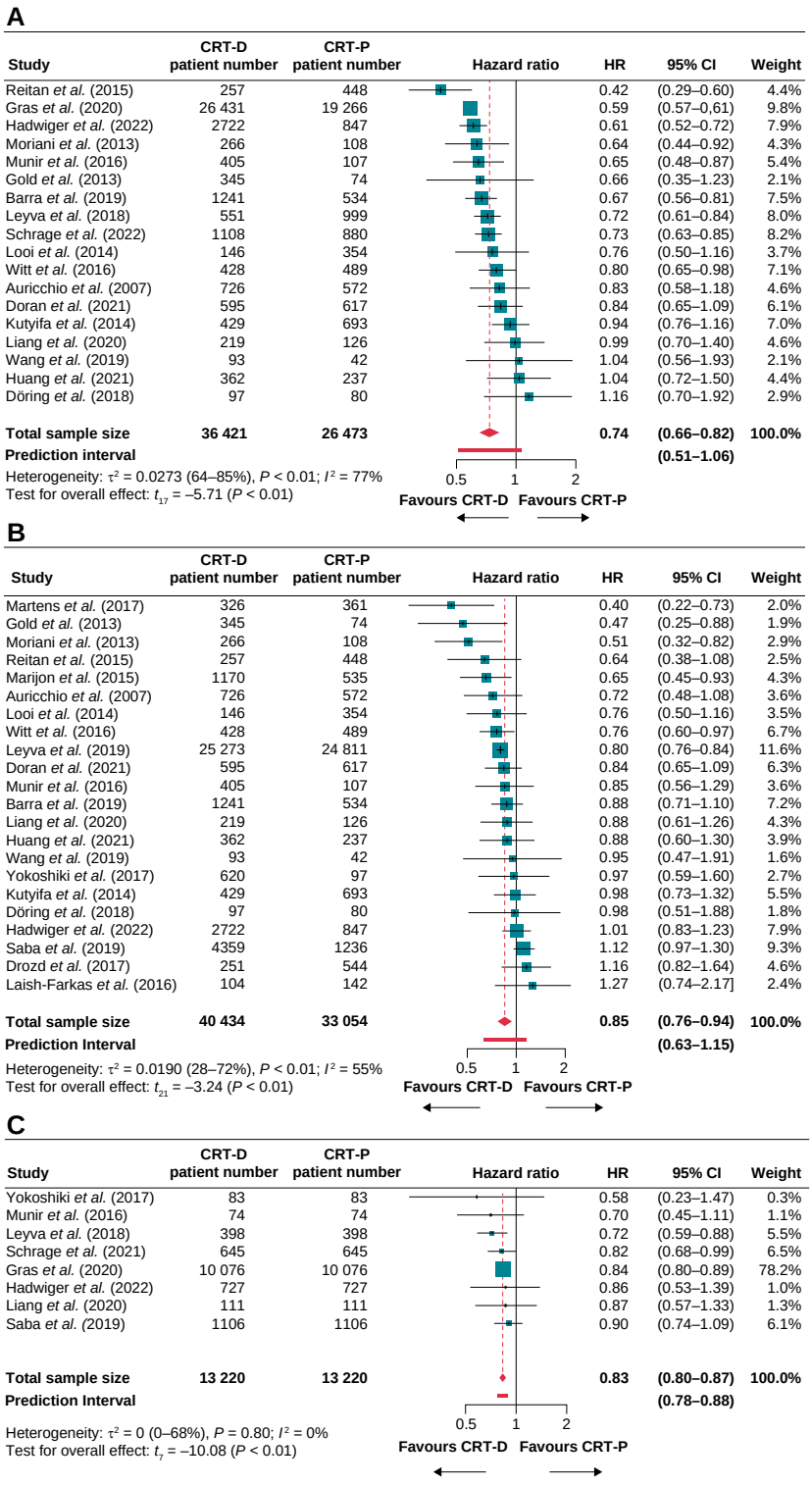
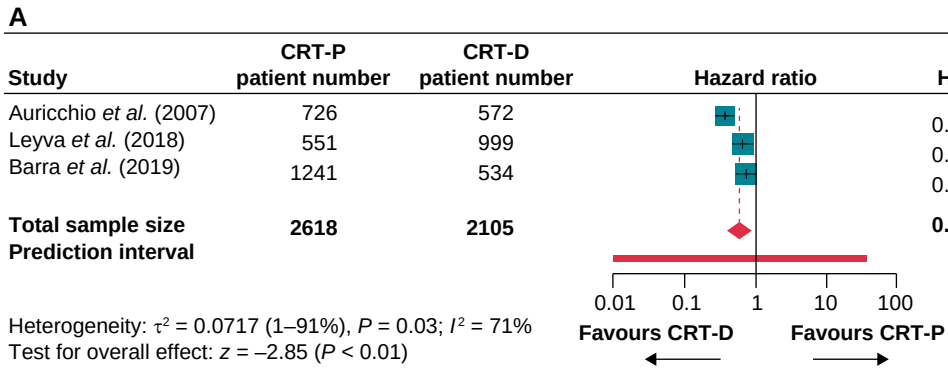
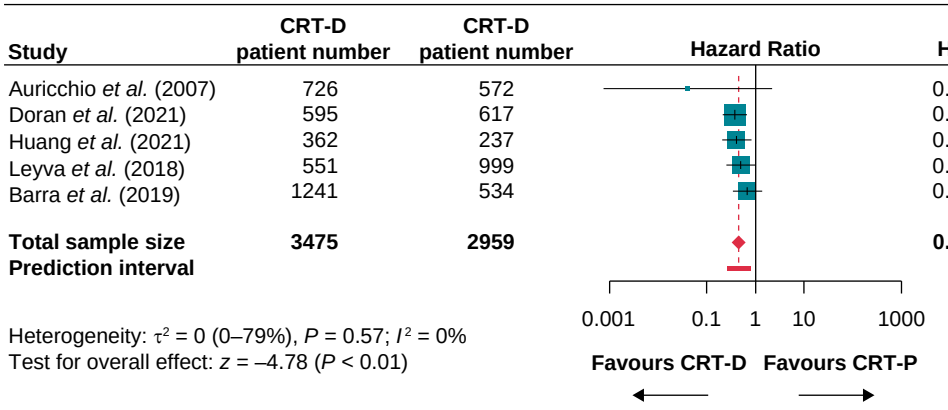


Figure 2 (*A*) Risk of all-cause mortality based on hazard ratio in CRT-D vs. CRT-P patients. Forest plot of studies with data on all-cause mortality using hazard ratios. The analysis included 18 studies comparing 36 421 CRT-D patients with 26 473 CRT-P patients. The HR was 0.74 (95% CI: 0.66–0.82). (*B*) Risk of all-cause mortality based on adjusted hazard ratio in CRT-D vs. CRT-P patients. Forest plot of studies with data on all-cause mortality using adjusted hazard ratios. The analysis included 22 studies comparing 40 434 CRT-D patients with 33 054 CRT-P patients. The aHR was 0.85 (95% CI: 0.76–0.94). (*C*) Risk of all-cause mortality based on PSM in CRT-D vs. CRT-P patients. Forest plot of studies with data on all-cause mortality using PSM. The analysis included eight studies comparing 13 220 CRT-D patients with 13 220 CRT-P patients. The HR was 0.83 (95% CI: 0.80–0.87). aHR, adjusted hazard ratio; CI, confidence interval; CRT-D, cardiac resynchronization therapy with defibrillator; CRT-P, cardiac resynchronization therapy with pacemaker.





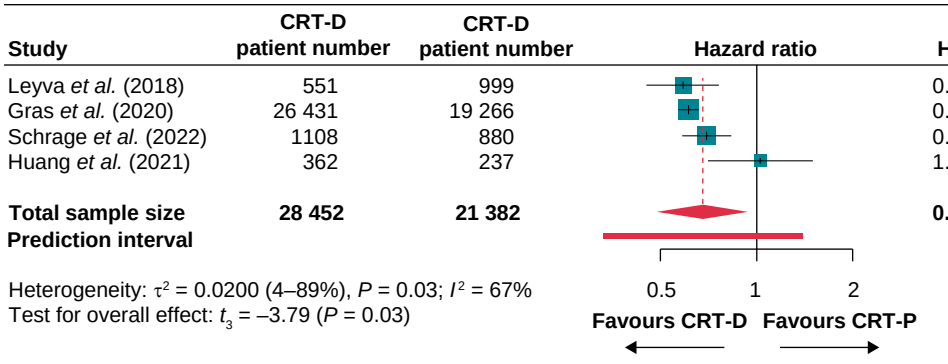


Figure 3 (*A*) Risk of mortality from progressions of heart failure. Forest plot of studies with data on heart failure mortality using hazard ratios. The analysis included three studies comparing 2618 CRT-D patients with 2105 CRT-P patients. The HR was 0.59 (95% CI: 0.41–0.85). (*B*) Risk of mortality from sudden cardiac death. Forest plot of studies with data on sudden cardiac death using hazard ratios. The analysis included five studies comparing 3475 CRT-D patients with 2959 CRT-P patients. The HR was 0.45 (95% CI: 0.32–0.62). (*C*) Risk of mortality from cardiovascular mortality. Forest plot of studies with data on cardiovascular mortality using hazard ratios. The analysis included four studies comparing 28 452 CRT-D patients with 21 382 CRT-P patients. The HR was 0.68 (95% CI: 0.49–0.94). CI, confidence interval; CRT-D, cardiac resynchronization therapy with defibrillator; CRT-P, cardiac resynchronization therapy with pacemaker; HR, hazard ratio.

the GRADE approach to grade the evidence in systematic reviews, low and very low certainty were established, probably due to the observational nature of the enrolled articles (see Supplementary material, *Figure S2*).

Discussion

In this systematic review and meta-analysis, the following results were found: in observational studies that directly compared CRT-P with CRT-D, CRT-D was superior in death from any cause, i.e. death due to heart failure progression, SCD, and non-cardiovascular death. Assessing those papers reporting results with advanced statistical methods (aHRs or propensity score matched cohorts), CRT-D still showed a better treatment effect compared with CRT-P in all-cause mortality.

When patients were further analysed, certain subgroups could be identified that did not show a significant risk reduction from a CRT-D over CRT-P, namely those with non-ischaemic aetiology or those aged over 75 years.

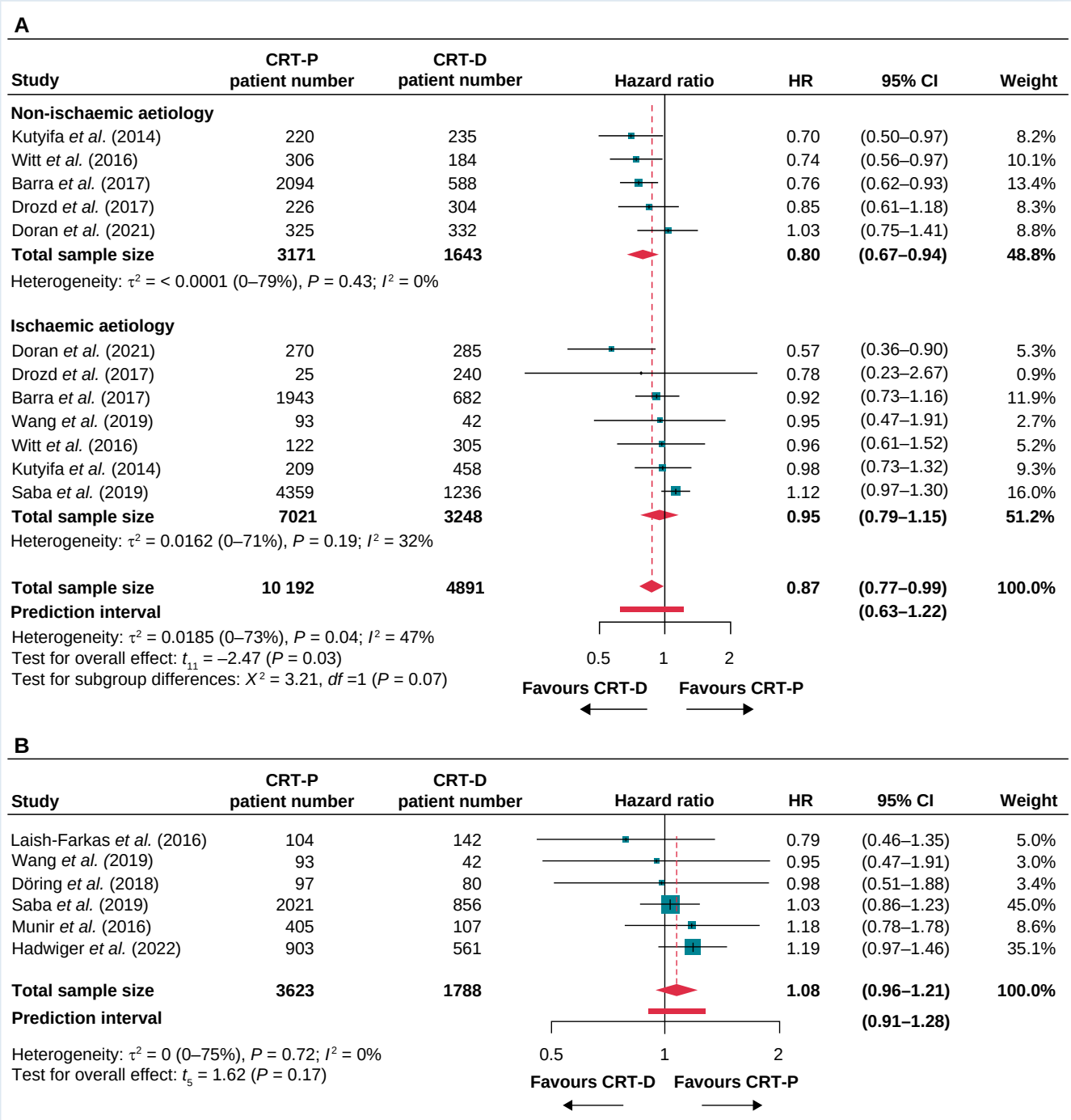


Figure 4 (*A*) Risk of mortality by aetiology in CRT-D vs. CRT-P patients, Forest plot of studies with data on all-cause mortality by ischaemic and non-ischaemic aetiology using hazard ratios. The ischaemic analysis included five studies comparing 3171 CRT-D patients with 1643 CRT-P patients. The HR was 0.80 (95% CI:0.67–0.94). The non-ischaemic analysis included seven studies comparing 7021 CRT-D patients with 3248 CRT-P patients. The HR was 0.95 (95% CI: 0.79–1.15), but there was no mortality difference between CRT-D and CRT-P patients. (*B*) Risk of mortality over 75 years in CRT-D vs. CRT-P patients. Forest plot of studies with data on all-cause mortality by age. Only patients above 75 years were included. The analysis included six studies comparing 3623 CRT-D patients with 1788 CRT-P patients. The HR was 1.08 (95% CI: 0.96–1.21) There was no mortality difference between CRT-D and CRT-P patients. CI, confidence interval; CRT-D, cardiac resynchronization therapy with defibrillator; CRT-P, cardiac resynchronization therapy with pacemaker; HR, hazard ratio.

Time-trend analysis of all-cause mortality was also performed, which proved that the difference in risk reduction by device type was stable over time. There was a clear improvement in the treatment effect of CRT-D on mortality rates between studies released before 2015 and thereafter. Nevertheless, the reduction in overall mortality risk was similar between CRT-D and CRT-P groups, despite changes in the

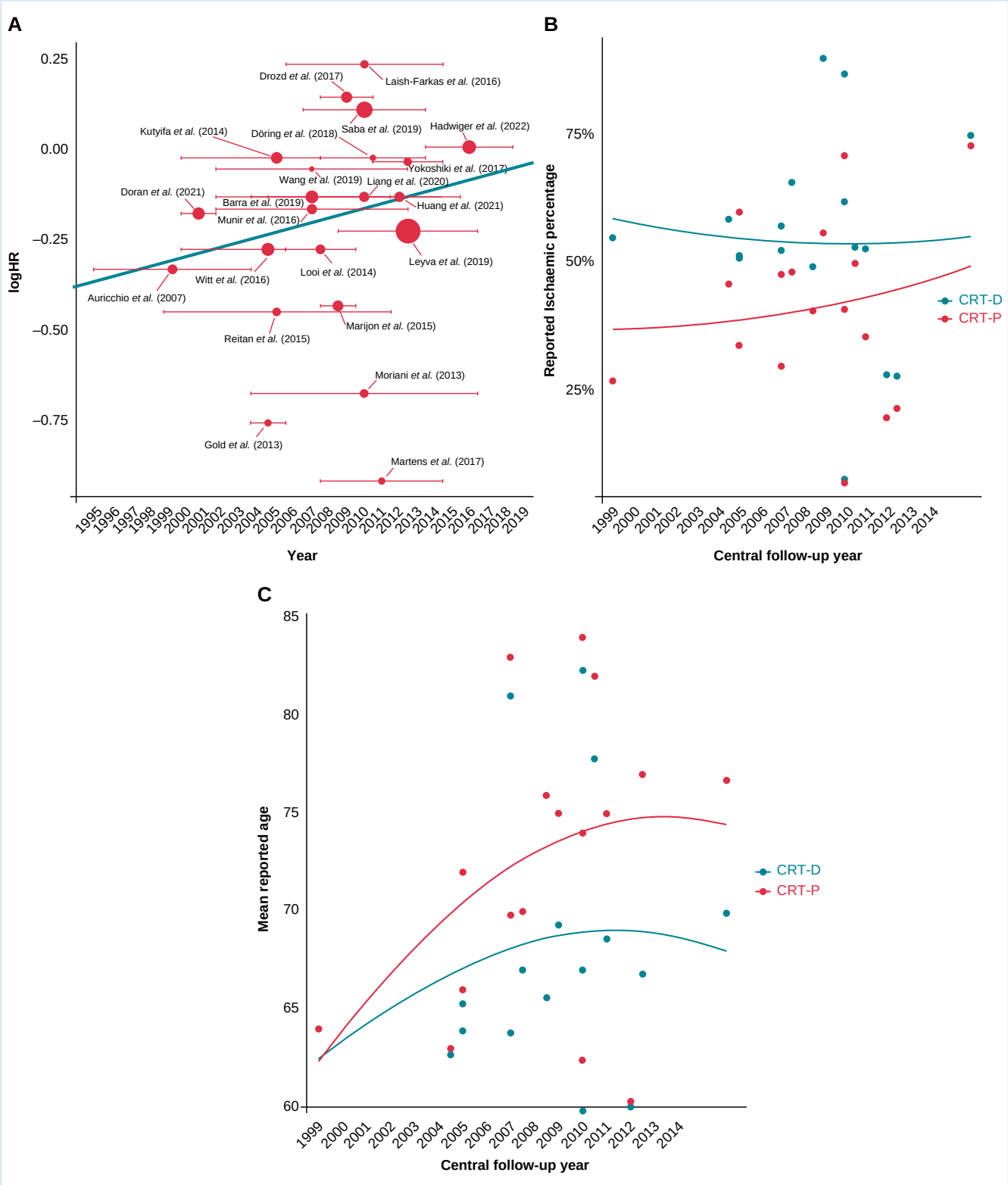


Figure 5 (*A*) Time-trend variation of all-cause mortality by device type. To assess the temporal effect on all-cause mortality HRs, we first took each study's reported timespan (in years) and calculated the midpoint for each time period. These central values were used in a meta-regression. Hazard ratios were slightly decreased, and CRT-D showed a better treatment effect of CRT-D on mortality could be observed over the years. (*B*) Time-trend variation of ischaemic aetiology. The percentage of ischaemic patients was shown over time. A trend could be observed for a higher prevalence of ischaemic patients among CRT-P candidates. (*C*) Time-trend variation of reported mean age. A time trend in age was shown, and the mean age of CRT-P patients increased, which was not such pronounced in the CRT-D cohorts. CRT-D, cardiac resynchronization therapy with defibrillator; CRT-P, cardiac resynchronization therapy with pacemaker; HR, hazard ratio.

population composition. Specifically, the mean age in the CRT-P group showed a trend towards increasing, and there was an increasing prevalence of ischaemic aetiology in this group over the years.

As there have been no randomized head-to-head controlled trials comparing the effect of CRT-D over CRT-P, the current recommendations have to refer to observational studies and registries, suggesting an individual patient risk assessment during the optimal device selection.[2,47] The ongoing Re-evaluation of Optimal Re-synchronization Therapy in Patients with Chronic Heart Failure (RESET-CRT) trial, hypothesizing that CRT-P is non-inferior to CRT-D for all-cause mortality, will address the answer to this question.[48]

The most important factors to assess are the ischaemic aetiology and the presence of scar tissue, gender, and age in addition to the co-morbidities to predict the outcome and the risk of mortality.[2] At the same time, adverse outcomes should be also measured when using an ICD lead and device (such as higher risk for infection, lead dislocation or fracture, and inappropriate shocks).[2]

Based on CRT trials, CRT itself can decrease the risk of SCD by reverse remodelling.[3,49,50] Additionally, major arrhythmias have halved during the last two decades due to modern heart failure therapies (heart failure medication such as sacubitril/valsartan or SGLT2 inhibitors) and technical improvements [e.g. quadripolar leads or remote monitoring (RM) systems].[40,51] It is essential to re-evaluate the question of who can experience mortality risk reduction with CRT-D over CRT-P.

Evaluating all-cause mortality risk reduction in this advanced heart failure population is a complex question influenced by several factors. The selection bias of candidates receiving CRT-D or CRT-P in everyday clinical practice is one, as those with CRT-D are younger, with fewer co-morbidities and better conditions compared with CRT-P patients.[2] Studies with no adjustments for these covariates therefore show a better outcome for those with CRT-D, with a wide range of mortality risk reduction of up to 58%. At the same time, data using advanced statistical methods, e.g. aHRs or propensity score-matching, are less pronounced,[15] but our current analysis has still proved that CRT-D has a substantially better treatment effect over CRT-P. Wood *et al*., in their meta-analysis, also observed a similar distinction between CRT-D and CRT-P therapy. However, it is important to note that their study employed a network analysis approach and encompassed a broader focus beyond the direct comparison of these two therapies. Our specific aim, on the other hand, was to evaluate the direct comparison between CRT-D and CRT-P therapies.[52]

On the other hand, the relatively high heterogeneity also proves that besides the characteristics of the investigated patients, the timeframe of the enrolment period and the date of inclusion also influence the final results. However, our systematic review has demonstrated that although the difference in mortality risk between CRT-D and CRT-P has been relatively stable, studies after 2015 show a better treatment effect. Based on Barra *et al*.,[40] the all-cause mortality and the SCD rate have decreased over the years due to improved drug treatment and technological changes. Leyva *et al*.[53] also clarified that survival of patients improved and HF hospitalizations decreased after CRT implantation over the past decade. Moreover, in a retrospective, observational database, those with a RM system and a CRT-D or ICD device had a substantially lower all-cause mortality at 4 years compared with those with no RM, which may further improve the outcome of patients with a device.[54] This would imply that the difference between the two therapies is getting even narrower. However, the characteristics of CRT patients have also changed as the RCTs—such as MADIT and RAFT trials—have been extended to CRT candidates.[1,49] Moreover, due to the aging population, the number of CRT candidates among the elderly is increasing.[55] At the same time, the recommendations and guidelines have also clarified additional previous questions, resulting in a more precise selection of patients for the optimal treatment.[2] Therefore, the appropriate choice for those who may benefit from adding an ICD remains essential.

Time-trend effects were also analysed in different subgroups. Cardiac resynchronization therapy with pacemaker cohorts are getting older by an average of 10 years, displaying a growing proportion of patients with ischaemic cardiomyopathy over the years. These results are in line with our pooled subgroup analysis. In patients over 75 years or with non-ischaemic aetiology, no further risk reduction in all-cause mortality could be observed by adding an ICD. As the DANISH trial revealed, those with non-ischaemic aetiology and >59 years have no additional mortality benefit from adding an ICD, investigating HFrEF patients with or without a CRT.[56] As our previous observational study and one from Barra *et al*. have shown, only patients with ischaemic cardiomyopathy have a substantial (24–30%) mortality benefit from CRT-D, while this current analysis showed a 20% risk reduction.[14,38]

Beyond all-cause death, the risk reduction of SCD was the most prominent, showing an overall 55% reduction in CRT-D compared with CRT-P. From the five studies that reported detailed SCD data, Auricchio *et al*.[31] described the largest treatment effect of CRT-D on SCD. This was the only study in which the enrolment period was between 1995 and 2000—before the new drug era—showing the ICD effect alone. Only a moderate difference could be observed thereafter between the two device types, which may justify the relevance of optimal HF pharmacological treatments.

In mortality from cardiovascular causes, heart failure progression, and even in non-cardiovascular death, CRT-D was superior to CRT-P. In such an advanced-stage HFrEF population, the leading cause of death is cardiovascular and SCD within, reflecting the robust treatment effect of ICD.[57] At the same time, heart failure death can occur less frequently once a CRT induces reverse remodelling. Moreover, according to the findings of Leyva *et al*., the duration between the initial hospitalization for heart failure and the implantation of CRT had a direct impact on long-term clinical outcomes. Once the patient had experienced HF hospitalization, the overall prognosis worsened despite a subsequent CRT implantation. The research highlighted that the most favourable clinical outcomes were observed in two specific groups: patients with no prior hospitalization for heart failure and individuals who underwent CRT implantation during their initial hospitalization for heart failure.[58] Non-cardiovascular causes may reflect the selection bias as they were seen in all-cause deaths as well.

Our systematic review with meta-analysis is based on observational studies, mainly retrospective. Within these limits, the results suggest that CRT-D is an effective therapy, showing substantial risk reduction in mortality (death from any cause and cardiovascular) and death from heart failure progression. However, there were certain subgroups that did not show any benefit from CRT-D compared with CRT-P, such as non-ischaemic patients and those over 75 years. Similar questions have been addressed in several previous meta-analyses as well.[59] When time trends were assessed, a trend for the better treatment effect of CRT-D could be observed between the early and late studies, proving that the efficacy and the CRT population have changed.

Limitations

Our meta-analysis has certain limitations. First, only observational studies could be included, mainly with retrospective nature, since no head-to-head randomized trials have been conducted in this field. Therefore, the overall results may be affected by selection bias. On one hand, these studies are lacking the endpoint adjudications; on the other hand, these populations are similar to the real-world data. Second, regarding cardiovascular death and non-cardiovascular death analyses, a limited number of studies could be included; thus, large-scale studies had a huge impact on the pooled results. Unfortunately, except for elderly patients (those over 75 years), patient-level data were missing. At the same time, not only age but also LVEF and body mass index (BMI) as mortality and SCD predictors would be valuable to analyse. Third, the uses of new drugs such as sacubitril/valsartan and SGLT2i

that have shown to improve outcomes were not represented in these studies at the time of inclusion.

Supplementary material

Supplementary material is available at *Europace* online.

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Data availability

The data are available on request from the corresponding author.

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