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# Cardiac resynchronization therapy with or without defibrillator in patients with heart failure

**Benedikt Schrage[1,2], Lars H. Lund[1,3], Michael Melin[1,3], Lina Benson[1], Alicia Uijl[1,4], Ulf Dahlström[5,6], Frieder Braunschweig[1,3], Cecilia Linde [1,3], and Gianluigi Savarese [1,3]***

[1]Division of Cardiology, Department of Medicine, Karolinska Institutet, SE-17176 Stockholm, Sweden; [2]Department of Cardiology, University Heart and Vascular Center Hamburg, Hamburg, Germany & German Center for Cardiovascular Research, partner site Hamburg/Kiel/Lübeck, Hamburg, Germany; [3]Heart and Vascular Theme, Karolinska University Hospital, Stockholm, Sweden; [4]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, The Netherlands; [5]Department of Cardiology, Linkoping University, Linkoping, Sweden; and [6]Department of Health, Medicine and Caring Sciences, Linkoping University, Linkoping, Sweden

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**Aims** Randomized data on the efficacy/safety of cardiac resynchronization therapy with vs. without defibrillator (CRT-D,-P) in heart failure with reduced ejection fraction (HFrEF) are scarce. We aimed to evaluate survival associated with use of CRT-D vs. CRT-P in a contemporary cohort with HFrEF.

**Methods and results** Patients from Swedish HF Registry treated with CRT-D/CRT-P and fulfilling criteria for primary prevention defibrillator use were included. Logistic regression was used to evaluate predictors of CRT-D non-use. All-cause mortality was compared in CRT-D vs. CRT-P by Cox regression in a 1:1 propensity-score-matched cohort. Of 1988 patients with CRT, 1108 (56%) had CRT-D and 880 (44%) CRT-P. Older age, higher ejection fraction (EF), female sex, and the lack of referral to HF nurse-led outpatient clinic were major determinants of CRT-D non-use. After matching, 645 CRT-D patients were compared with 645 with CRT-P. The CRT-D use was associated with lower 1- and 3-year all-cause mortality [hazard ratio (HR):0.76, 95% confidence interval (CI):0.58–0.98; HR: 0.82, 95% CI: 0.68–0.99, respectively]. Results were consistent in all pre-specified subgroups except for CRT-D use being associated with lower 3-year mortality in patients with an EF < 30% but not in those with an EF ≥ 30% (HR: 0.73, 95% CI: 0.59–0.89 and HR: 1.24, 95% CI: 0.83–1.85, respectively; *P*-interaction = 0.02).

**Conclusion** In a contemporary HFrEF cohort, CRT-D was associated with lower mortality compared with CRT-P. The CRT-D use was less likely in older patients, females, and in patients not referred to HF nurse-led outpatient clinic. Our findings support the use of CRT-D vs. CRT-P in HFrEF, in particular with severely reduced EF.

**Keywords** Heart failure • Heart failure with reduced ejection fraction • Implantable cardioverter-defibrillator • Cardiac resynchronization therapy • Primary prevention • Swedish Heart Failure Registry

## Introduction

Cardiac resynchronization therapy (CRT) improves quality of life and survival in selected patients with heart failure (HF) with reduced ejection fraction (HFrEF) by resynchronizing intraventricular conduction/contraction and fostering favourable reverse remodelling.[1–5] CRT is therefore recommended by current guidelines in HFrEF patients who are symptomatic, have prolonged QRS, and ejection fraction (EF) ≤ 35% despite optimal medical treatment.[6]

* Corresponding author. Tel: +46 72-596 83 40. *E-mail address*: gianluigi.savarese@ki.se

## What's new?

- In a contemporary heart failure with reduced ejection fraction cohort, cardiac resynchronization therapy-defibrillator (CRT-D) was associated with lower mortality as compared with CRT-pacemaker.
- This association was observed in those with an ejection fraction (EF) <30%, but not in those with an EF ≥30%.
- CRT-D use was less likely in older patients, females, and in patients not referred for specific heart failure follow-up care.

Improvements in HF pharmacotherapy over the past 20 years have impacted the risk profile of patients with HFrEF, decreasing the risk of sudden cardiac death (SCD) by 44%.[7] It has also been hypothesized that reverse remodelling linked with CRT use might reduce the risk of ventricular arrhythmias and thus contribute to the observed reduction in risk of SCD.[8] Therefore, the need of an implantable cardioverter-defibrillator (ICD) in HFrEF patients meeting the criteria for primary prevention of SCD but also eligible for CRT is often questioned. Notably, ICD is currently recommended in patients with HF, EF ≤35%, and symptoms despite optimal medical therapy, and thus many patients have simultaneous indication for CRT and ICD.[6]

Contemporary, randomized data directly assessing the efficacy of ICD in patients with CRT, i.e. head-to-head comparison of CRT-defibrillator (CRT-D) vs. CRT-pacemaker (CRT-P), are scarce.[6] Subgroup analysis from a previous study from the Swedish HF Registry (SwedeHF) suggested that primary prevention ICD use might be associated with lower mortality irrespective of CRT use, but was not designed to address this specific question.[9]

Therefore, we aimed to compare survival in patients treated with CRT-D vs. CRT-P in a large and contemporary cohort of patients with HFrEF, focusing also on relevant pre-specified subgroups who may report particularly large or perhaps no benefit associated with the use of these devices.

# Methods

## Study protocol and setting

The SwedeHF registry (www.SwedeHF.se) has been previously described.[10] Briefly, it is a nationwide, prospective registry enrolling patient with clinician-judged HF since May 2000. It records approximately 80 variables at discharge from hospital (for inpatients) or after an outpatient visit. Enrolment in SwedeHF does not require individual patient consent, but patients are informed about the enrolment and may decide to opt out.[10]

To obtain data on additional baseline comorbidities, SwedeHF was linked to the National Patient Registry. Furthermore, the Cause of Death registry provided date and cause of death; Statistics Sweden provided data on education level and income. Both the National Patient Registry and the Cause of Death registry are administered by the Swedish Board of Health and Welfare.

## Patients

The study population consisted of in and outpatients treated with CRT-D or CRT-P and registered in SwedeHF between 11 May 2000 and 31 December 2016. Inclusion criteria were defined according to the recommendations from the 2016 European Society of Cardiology HF guidelines on ICD use for primary prevention of SCD, which were adapted according to SwedeHF data as follows: EF <40% (EF is categorized in SwedeHF as <30%, 30–39%, 40–49%, and ≥50%), HF duration ≥3 months, and New York Heart Association (NYHA) class ≥II.[6] Patients who died during the hospitalization/visit linked to the registration in SwedeHF were excluded. In case of multiple eligible registrations for the same patient, the first one was selected. The index date was defined as the day of hospital discharge or outpatient visit when patients were registered in SwedeHF. The end of follow-up was 31 December 2016.

## Statistical analyses

Missing data for variables of interest were handled by chained equations multiple imputation (R-package *mice*; 10 imputed datasets generated). *Table 1* reports the variables which were used for the multiple imputation models and the proportion of missing data for each variable.

To evaluate patient characteristics which were independently associated with CRT-D non-use/CRT-P use, a multivariable logistic regression model was fitted, with CRT-D non-use/CRT-P use as dependent variable and the baseline characteristics reported in *Figure 1* as covariates. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for each potential predictor.

Propensity scores (PS) for CRT-D use were calculated in each imputed dataset for each patient by a logistic regression model including 35 potential confounders (marked with superscript a in *Table 1*), and then averaged across the 10 imputed datasets.[11] Based on their PS, CRT-D recipients were matched 1:1 to CRT-P recipients by the nearest neighbour method with a calliper of 0.15 and no replacement. The balance in potential confounders between the CRT-D and the CRT-P group was considered achieved whether the absolute standard difference was below 0.10.

Primary outcomes in this analysis were 1-year and 3-year all-cause mortality. Secondary outcomes were 1-year and 3-year cardiovascular (CV) mortality (with censoring for non-CV death). The Kaplan–Meier method was used to estimate survival functions in patients treated with CRT-D vs. CRT-P in the PS-matched cohort (i.e. adjusting for confounders). Finally, as a negative control outcome analysis, Cox regression models with 1-year and 3-year risk of non-CV hospitalization as endpoints were fitted in the PS-matched cohort to investigate the presence of residual confounding, since neither CRT-D nor CRT-P (i.e. the exposures) are expected to affect this outcome. The proportional-hazards assumption was assessed based on Schoenfeld residuals.

As for subgroup analysis, Cox proportional hazard models including the interaction between CRT-D/CRT-P use and the variables representing the pre-specified subgroups of interest were fitted in the matched cohort. The following subgroups were investigated: females vs. males, age >70 vs. ≤70 years, NYHA class II vs. III/IV, EF 30–39% vs. <30%, history vs. no history of ischaemic heart disease, date of enrolment 2000–12 vs. 2013–16, follow-up referral to specialty vs. primary care, referral vs. no referral to follow-up in nurse-led HF clinic.

Supplementary material online, *Table S1* reports the definition of the variables used in this study. All statistical analyses were performed by R 3.5.3. A *P*-value <0.05 (two-tailed) was considered statistically significant.

## Ethical considerations

This study was conducted in accordance with the declaration of Helsinki. The establishment of SwedeHF and this analysis with linkage to other governmental registries was approved by a national ethics committee.

**Table 1 Baseline characteristics of the unmatched and the propensity score-matched cohort**

| Variable | Unmatched cohort | | | | PS-matched cohort | | |
|---|---|---|---|---|---|---|---|
| | CRT-P (*N* = 880, 44%) | CRT-D (*N* = 1108, 56%) | *P*-value | % missing | CRT-P (*N* = 645, 50%) | CRT-D (*N* = 645, 50%) | ASD |
| Demographics | | | | | | | |
| Age (years), mean (SD) | 74.3 (9.3) | 67.6 (9.8) | <0.01 | 0 | 72.9 (10.0) | 70.3 (9.4) | 0.27 |
| Age ≥70 years[a] (%) | 639 (72.6) | 479 (43.2) | <0.01 | | 410 (63.6) | 399 (61.9) | 0.04 |
| Sex, female[a] (%) | 188 (21.4) | 175 (15.8) | <0.01 | 0 | 124 (19.2) | 118 (18.3) | 0.02 |
| Outpatient[a] (%) | 511 (58.1) | 688 (62.1) | 0.08 | 0 | 379 (58.9) | 374 (58.1) | 0.02 |
| Year of registration[a] | | | <0.01 | 0 | | | 0.02 |
| 2000–12 (%) | 549 (62.4) | 473 (42.7) | | | 340 (52.7) | 345 (53.5) | |
| 2013–16 (%) | 331 (37.6) | 635 (57.3) | | | 305 (47.3) | 300 (46.5) | |
| Clinical | | | | | | | |
| HF duration ≥6 months[a] (%) | 842 (95.7) | 1048 (94.6) | 0.31 | 0 | 616 (95.5) | 616 (95.5) | <0.01 |
| Ejection fraction[a] | | | <0.01 | 0 | | | 0.02 |
| 30–39 (%) | 293 (33.3) | 289 (26.1) | | | 190 (29.5) | 184 (28.5) | |
| <30 (%) | 587 (66.7) | 819 (73.9) | | | 455 (70.5) | 461 (71.5) | |
| NYHA class[a] | | | 0.09 | 0 | | | 0.07 |
| II (%) | 310 (35.2) | 438 (39.5) | | | 243 (37.7) | 235 (36.4) | |
| III (%) | 515 (58.5) | 594 (53.6) | | | 361 (56.0) | 358 (55.5) | |
| IV (%) | 55 (6.2) | 76 (6.9) | | | 41 (6.4) | 52 (8.1) | |
| Heart rate (b.p.m.), mean (SD) | 72.1 (11.0) | 71.6 (11.7) | 0.39 | 0.5 | 71.9 (11.2) | 71.6 (12.0) | 0.03 |
| ≥70 b.p.m.[a] (%) | 511 (62.2) | 647 (60.1) | 0.38 | | 365 (60.5) | 373 (59.7) | 0.02 |
| MAP (mmHg), mean (SD) | 85.5 (12.3) | 85.1 (12.1) | 0.58 | 0.2 | 85.5 (12.4) | 84.7 (11.5) | 0.06 |
| ≥90 mmHg[a] (%) | 311 (36.0) | 382 (35.3) | 0.78 | | 219 (34.6) | 209 (33.1) | 0.03 |
| NT-proBNP (pg/L), median (IQR) | 3190 (1528, 7124) | 2543 (1050, 5205) | <0.01 | 48.8 | 3245 (1433, 6906) | 3070 (1310, 5986) | 0.11 |
| >Median[a] (%) | 234 (55.7) | 274 (45.9) | <0.01 | | 178 (54.6) | 177 (53.8) | 0.02 |
| BMI (kg/m$^2$), mean (SD) | 26.60 (4.9) | 27.8 (4.9) | <0.01 | 33.7 | 26.8 (5.0) | 27.3 (4.7) | 0.10 |
| >30 kg/m$^{2a}$ (%) | 136 (23.7) | 213 (28.6) | 0.06 | | 106 (24.4) | 112 (26.2) | 0.04 |
| eGFR (mL/min/1.73 m$^2$), mean (SD) | 53.1 (21.5) | 59.6 (21.9) | <0.01 | 0.3 | 55.2 (22.1) | 55.5 (21.2) | 0.02 |
| <60 mL/min/1.73m$^{2a}$ (%) | 563 (65.2) | 563 (52.6) | <0.01 | | 386 (61.1) | 388 (62.2) | 0.02 |
| Treatments | | | | | | | |
| Beta-blocker[a] (%) | 819 (93.3) | 1072 (96.9) | <0.01 | 0.02 | 615 (95.6) | 615 (95.6) | <0.01 |
| RASI[a] (%) | 801 (91.2) | 1039 (94.0) | 0.02 | 0.03 | 596 (92.7) | 598 (93.1) | 0.02 |
| MRA[a] (%) | 450 (51.3) | 660 (60.1) | <0.01 | 0.06 | 350 (54.5) | 352 (55.3) | 0.02 |
| Diuretics[a] (%) | 766 (87.0) | 936 (84.5) | 0.12 | 0 | 557 (86.4) | 552 (85.6) | 0.02 |
| Digoxin[a] (%) | 197 (22.5) | 198 (17.9) | 0.01 | 0.03 | 136 (21.2) | 130 (20.2) | 0.02 |
| Oral anticoagulant[a] (%) | 517 (59.0) | 706 (63.9) | 0.03 | 0.04 | 405 (63.0) | 410 (64.0) | 0.02 |
| Platelet inhibitor[a] (%) | 317 (36.5) | 407 (37.3) | 0.74 | 0.1 | 222 (35.0) | 235 (36.8) | 0.04 |
| Nitrate[a] (%) | 168 (19.2) | 158 (14.3) | <0.01 | 0.03 | 110 (17.1) | 121 (18.8) | 0.04 |
| Statin[a] (%) | 504 (57.4) | 711 (64.5) | <0.01 | 0.04 | 390 (60.6) | 411 (64.0) | 0.07 |
| Follow-up referral specialty[a] | | | <0.01 | 3.4 | | | 0.07 |
| Specialty care (%) | 717 (85.8) | 995 (91.7) | | | 539 (88.1) | 566 (90.1) | |
| Primary care (%) | 119 (13.5) | 90 (8.1) | | | 73 (11.3) | 62 (9.6) | |
| Follow-up in nurse-led HF clinic[a] | | | <0.01 | 5.0 | | | <0.01 |
| Yes (%) | 411 (49.7) | 682 (64.2) | | | 339 (55.9) | 342 (55.6) | |
| No (%) | 416 (47.3) | 380 (34.3) | | | 267 (41.4) | 273 (42.3) | |
| Comorbidities | | | | | | | |
| Ischaemic heart disease[a] (%) | 644 (73.2) | 813 (73.4) | 0.96 | 0 | 474 (73.5) | 482 (74.7) | 0.03 |
| Prior coronary revascularization[a] (%) | 409 (46.5) | 577 (52.1) | 0.02 | 0 | 323 (50.1) | 337 (52.2) | 0.04 |
| Current smoking[a] (%) | 60 (8.3) | 82 (9.4) | 0.54 | 19.8 | 44 (8.5) | 35 (6.9) | 0.06 |
| Atrial Fibrillation[a] (%) | 596 (67.7) | 681 (61.5) | <0.01 | 0 | 425 (65.9) | 428 (66.4) | 0.01 |
| Anaemia[a] (%) | 336 (39.2) | 368 (35.0) | 0.06 | 0.4 | 238 (38.0) | 222 (36.3) | 0.04 |

*Continued*

**Table 1** *Continued*

| Variable | Unmatched cohort | | | | PS-matched cohort | | |
|---|---|---|---|---|---|---|---|
| | CRT-P (*N* = 880, 44%) | CRT-D (*N* = 1108, 56%) | *P*-value | % missing | CRT-P (*N* = 645, 50%) | CRT-D (*N* = 645, 50%) | ASD |
| Diabetes mellitus[a] (%) | 316 (35.9) | 406 (36.6) | 0.77 | 0 | 231 (35.8) | 236 (36.6) | 0.02 |
| Arterial hypertension[a] (%) | 539 (61.3) | 684 (61.7) | 0.86 | 0 | 401 (62.2) | 402 (62.3) | <0.01 |
| Valvular heart disease[a] (%) | 324 (36.8) | 341 (30.8) | <0.01 | 0 | 227 (35.2) | 226 (35.0) | <0.01 |
| Peripheral vascular disease[a] (%) | 135 (15.3) | 126 (11.4) | 0.01 | 0 | 90 (14.0) | 94 (14.6) | 0.02 |
| COPD[a] (%) | 134 (15.2) | 157 (14.2) | 0.55 | 0 | 97 (15.0) | 98 (15.2) | <0.01 |
| Cancer within the last 3 years[a] (%) | 92 (10.5) | 90 (8.1) | 0.09 | 0 | 64 (9.9) | 57 (8.8) | 0.04 |
| Stroke/transient ischaemic attack[a] (%) | 162 (18.4) | 166 (15.0) | 0.05 | 0 | 114 (17.7) | 117 (18.1) | 0.01 |

Continuous variables are presented as mean (SD) if normally distributed and median (IQR) if non-normally distributed, categorical variables as frequency (percentage). The *t*-test was used to compare patients treated with CRT-D vs. CRT-P for normally distributed and Man–Whitney *U* test for non-normally distributed continuous variables, Fisher's exact test for categorical variables. Absolute standardized differences (ASD) are defined as the difference in means, proportions, or ranks divided by the mutual standard deviation; values below 0.1 were considered as not significant.

[a]Variables marked with () were included in the multiple imputation model (together with the outcome 3-year all-cause death and CRT-D use) and were also used for the calculation of propensity scores. In these models, NYHA class was categorized as NYHA II vs. NYHA III–IV.

BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRT-D/-P, cardiac resynchronization therapy with defibrillator/pacemaker; eGFR, estimated glomerular filtration rate (calculated by Chronic Kidney Disease Epidemiology Collaboration formula); IQR, inter-quartile range; MAP, mean arterial pressure; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; RASI, renin–angiotensin-system inhibitor; SD, standard deviation.

# Results

## Study cohort

Between 11 May 2000 and 31 December 2016, SwedeHF included 130 420 registrations from 76 506 unique patients. After applying the inclusion criteria for this study, 1988 patients were analysed. Of these, 1108 (56%) patients were treated with CRT-D and 880 patients (44%) with CRT-P. After PS-matching, the study cohort consisted of 1290 patients, 645 (50%) treated with CRT-D vs. 645 (50%) treated with CRT-P (see Supplementary material online, *Figure S1*).

## Baseline characteristics

In the unmatched cohort, mean age was 71 ± 10 years and 18% of the patients were female. Most of the baseline characteristics were differently distributed in patients treated with CRT-D vs. CRT-P. The CRT-D recipients were younger, more likely male, had lower N-terminal pro-B-type natriuretic peptide levels, lower EF, and fewer comorbidities. Use of beta-blockers and mineralocorticoid receptor antagonists was overall high but more likely in patients with CRT-D vs. CRT-P (*Table 1*).

In the PS-matched cohort, CRT-D vs. CRT-P patients were comparable for all the potential confounders considered in our analysis.

## Independent predictors of cardiac resynchronization therapy-defibrillator non-use/cardiac resynchronization therapy-pacemaker use

Differences in baseline characteristics shown in *Table 1* are unadjusted. Therefore, in the overall (i.e. unmatched) cohort, a multivariable logistic regression model was fitted to identify patient characteristics independently associated with CRT-D non-use/CRT-P use. The CRT-D use was less likely in older patients, in females, and in patients with a history of stroke or transient ischaemic attack, whereas it was more likely in patients registered in 2013 or later, in those with prior coronary revascularization, receiving beta-blockers, or anticoagulants, and with planned referral to HF nurse-led outpatient clinic. Variables reflecting HF severity, such as N-terminal pro-B-type natriuretic peptide and NYHA class, but also most of the comorbidities did not explain the use of CRT-D vs. CRT-P. Finally, CRT-D was more likely used in patients with lower EF, which reflects the current guideline recommendations where an EF < 35% is required (*Figure 1*).

## Outcome analysis

### Primary outcome: all-cause mortality

In the overall cohort, over a median follow-up of 2.35 [inter-quartile range (IQR) 0.92–3.00] years, 677 deaths (51.6%) occurred. Crude 1-year risk of all-cause death in patients treated with CRT-D vs. CRT-P was 14.7% (95% CI: 12.5–16.9%) vs. 20.5% (95% CI: 17.7–23.2%; $P < 0.01$), whereas 3-year risk was 35.7% (95% CI: 32.4–38.8%) vs. 44.8% (95% CI: 41.2.48.2%; $P < 0.01$), respectively. Corresponding unadjusted hazard ratios (HR) and 95% CI were 0.68 (0.55–0.85) at 1 year and 0.73 (0.63–0.85) at 3 years (*Figure 2*).

In the matched cohort, 460 deaths (35.7%) occurred over a median follow-up of 2.24 (IQR: 0.87–3.00) years. One-year mortality risk was 16.9% (95% CI: 13.9–19.9%) vs. 21.6% (95% CI: 18.3–24.8%; $P = 0.03$) in patients treated with CRT-D vs. CRT-P, with a 4.7% absolute risk reduction (ARR) and HR = 0.76 (95% CI: 0.58–0.98; *Figure 3*). Three-year all-cause mortality risk was 38.4% (95% CI: 34.1–42.4%) vs. 43.9% (95% CI: 39.9–47.9%; $P = 0.04$) in patients treated with CRT-D vs. CRT-P, with a 5.5% ARR and HR = 0.82 (95% CI: 0.68–0.99; *Figure 3*).

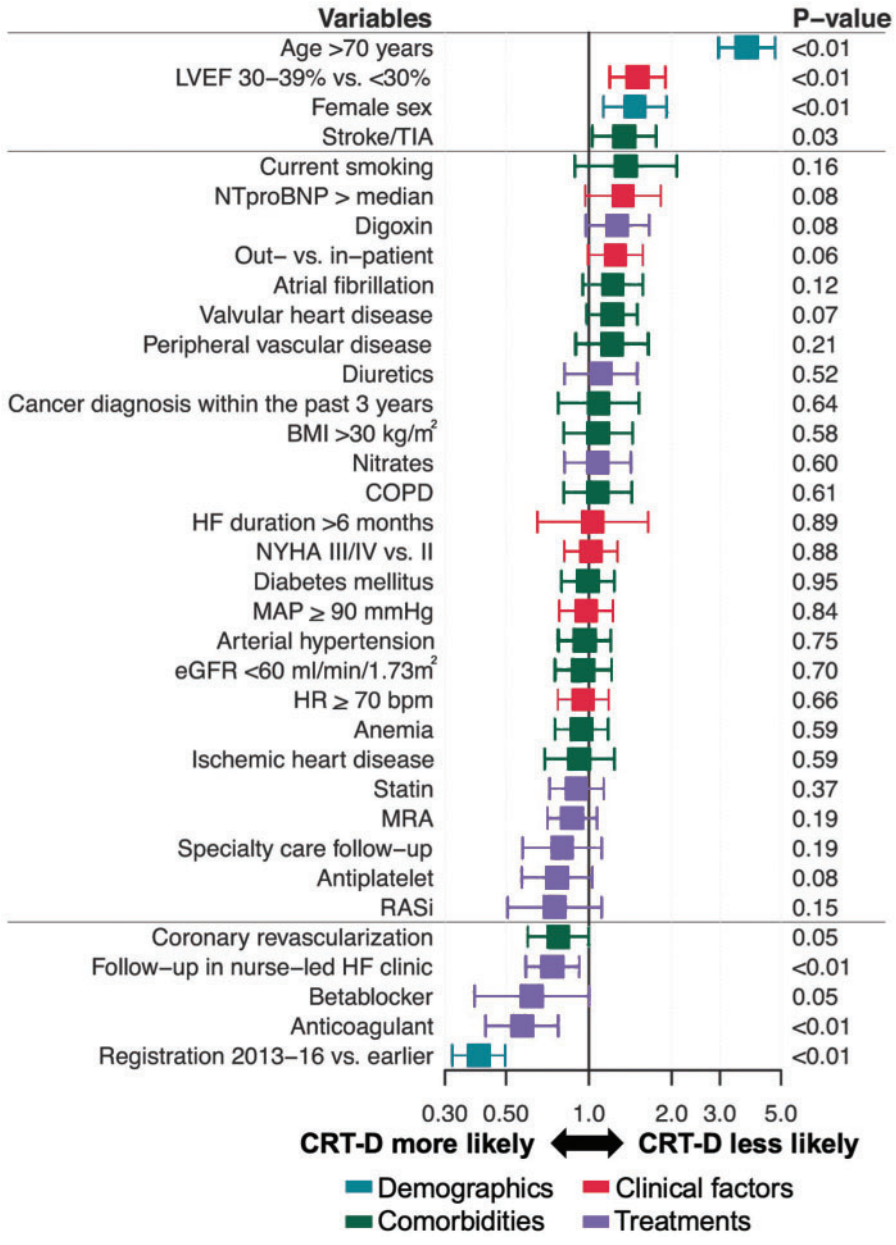


**Figure 1** Patient characteristics independently associated with defibrillator use among patients with heart failure and cardiac resynchronization therapy. BMI, body mass index; CRT-D/-P, cardiac resynchronization therapy with defibrillator/pacemaker; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, heart rate; MAP, mean arterial pressure; MRA, mineralocorticoid receptor antagonist; NTproBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; RASi, renin–angiotensin-system inhibitor; TIA, transient ischaemic attack.

### Secondary outcome: cardiovascular mortality

In the overall cohort, 529 (26.6%) CV deaths occurred. Crude 1-year risk of CV death was 11.8% (95% CI: 9.8–13.8%) in CRT-D vs. 17.6% (95% CI: 15.0–20.2%; $P < 0.01$) in CRT-P patients, whereas 3-year risk was 28.4% (95% CI: 25.3–31.4%) vs. 37.3% (95% CI: 33.7–40.8%; $P < 0.01$), respectively. Corresponding unadjusted HRs and 95% CI were 0.64 (0.50–0.81) at 1 year and 0.70 (0.59–0.83) at 3 years (*Figure 2*).

In the matched cohort, 365 CV deaths (28.3%) occurred. One-year CV mortality risk was 13.8% (95% CI: 11.0–16.5%) in CRT-D vs. 18.7% (95% CI: 15.5–21.8%; $P = 0.02$) in CRT-P patients, with a 4.9% ARR and HR = 0.72 (95% CI: 0.54–0.95; *Figure 3*). Three-year risk was 31.7% (95% CI: 27.5–35.6%) vs. 36.3% (95% CI: 32.0–40.4%; $P = 0.06$), respectively, leading to a HR = 0.82 (95% CI: 0.67–1.01; *Figure 3*).

## Negative control analysis

In the matched cohort, 1 and 3-year risk of non-CV hospitalization was 40.2% (95% CI: 36.0–44.1%) vs. 37.9% (95% CI: 33.8–41.8%; $P = 0.39$) and 67.2% (95% CI: 62.6–71.3%) vs. 65.0% (95% CI: 60.1–

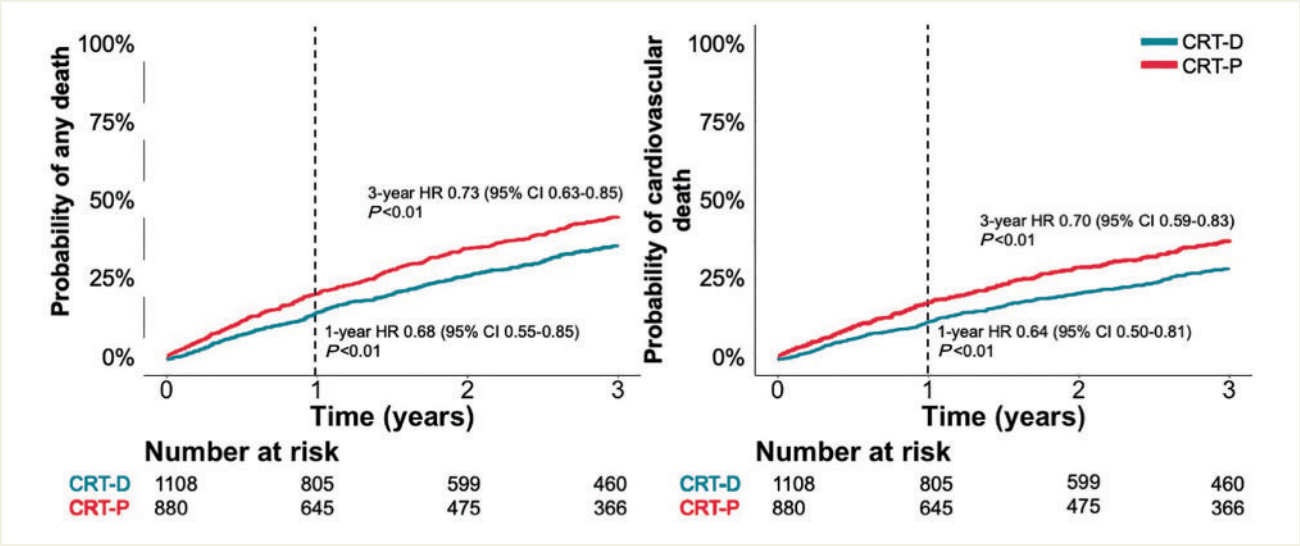


**Figure 2** Kaplan–Meier curves for all-cause and cardiovascular mortality in patients treated with cardiac resynchronization therapy with defibrillator vs. cardiac resynchronization therapy with pacemaker in the overall cohort. Vertical-dashed line marks the 1-year endpoint. CI, confidence interval; CRT-D/-P, cardiac resynchronization therapy with defibrillator/pacemaker; HR, hazard ratio.

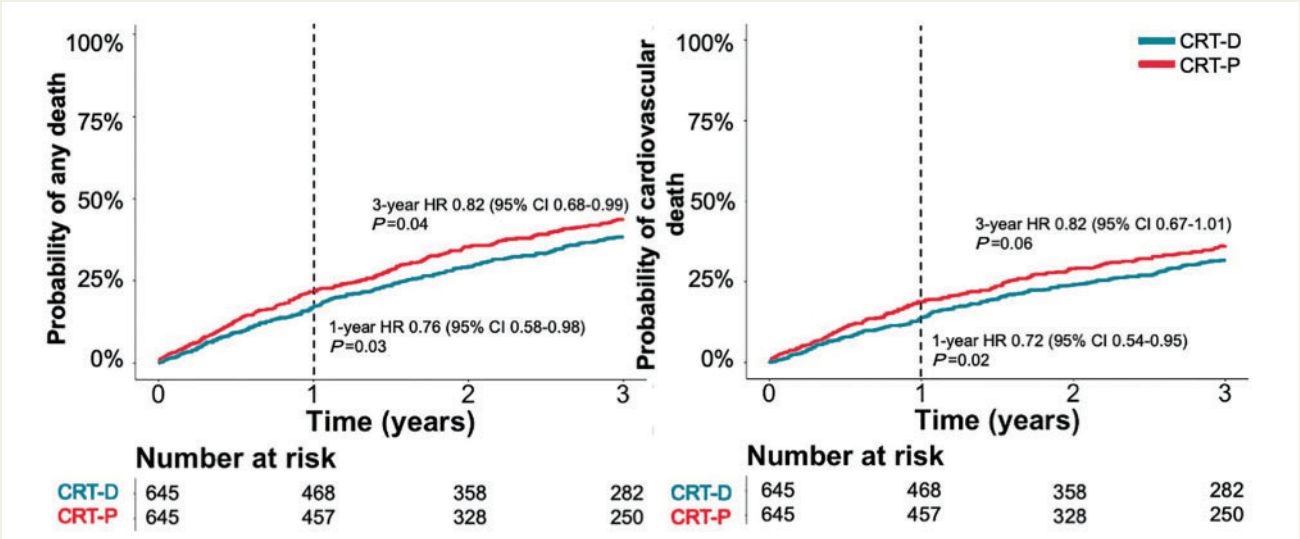


**Figure 3** Kaplan–Meier curves for all-cause and cardiovascular mortality in patients treated with cardiac resynchronization therapy with defibrillator vs. cardiac resynchronization therapy with pacemaker in the propensity score-matched cohort. Vertical-dashed line marks the 1-year endpoint. CI, confidence interval; CRT-D/-P, cardiac resynchronization therapy with defibrillator/pacemaker; HR, hazard ratio.

69.3%; $P = 0.31$), respectively, in CRT-D vs. CRT-P receivers. There was no statistically significant difference in risk of the negative control outcome between the study arms [1-year HR = 1.08 (95% CI: 0.90–1.30); 3-year HR = 1.08 (95% CI: 0.93–1.26; *Figure 4*)].

## Subgroup analysis

*Figure 5* shows the association between CRT-D vs. CRT-P use and 1- and 3-year risk of all-cause death in pre-specified subgroups. There was no significant interaction between CRT-D/CRT-P use and each of the variables defining the subgroups of interest for 1-year all-cause mortality. Similar results were reported for 3-year mortality, except for the EF subgroup analysis, where CRT-D vs. CRT-P use was significantly associated with lower risk of outcome in patients with EF <30%, but not in those with EF 30–39%.

# Discussion

In this PS-matched analysis of SwedeHF including a contemporary HFrEF population treated with CRT and with an indication for ICD

use for primary prevention of SCD, CRT-D use was associated with a 24% lower 1-year and an 18% lower 3-year risk of all-cause mortality compared with CRT-P. One-year but not 3-year risk of CV death was significantly lower in CRT-D vs. CRT-P arm. Notably, the finding of a lower risk of any death associated with the use of CRT-D was consistent across all the explored subgroups at 1 year, but not at 3 years where a higher survival was observed in patients with EF <30% but not in those with EF = 30–39%.

## Cardiac resynchronization therapy-defibrillator vs. cardiac resynchronization therapy-pacemaker use in contemporary patients with heart failure with reduced ejection fraction

Following the publication of the DANISH trial, showing no effect of primary prevention ICD use on all-cause mortality in non-ischaemic HF,[12] the role of ICD in primary prevention of SCD in HFrEF has been debated. Further concerns have been linked with the observation of a declining incidence of SCD in HF patients over the past two decades,[7] which might be explained by the use of new pharmacotherapies and of CRT-P decreasing not only the risk of HF-related death but also risk of SCD.[7] Additionally, recent studies have shown that the excess mortality in HFrEF patients treated with CRT-P mainly stems from non-sudden deaths, which cannot be prevented by an ICD.[13,14] Therefore, it has been speculated that the combination of contemporary HF pharmacotherapy and CRT use might obviate the need for primary prevention ICD use in patients with HFrEF treated by CRT-P, and thus CRT-P use might be preferred to CRT-D.

In a real-world HF cohort receiving contemporary care including CRT, we showed that use of ICD, i.e. CRT-D vs. CRT-P, was associated with a lower risk of all-cause and CV mortality. This finding strengthens the evidence from a previous SwedeHF analysis showing a lower short-term/long-term risk of all-cause mortality and lower short-term risk of CV mortality associated with primary prevention use of ICD use regardless of concomitant CRT use.[9] In the subgroup analysis of the same study, CRT-D was associated with higher survival compared with CRT-P.[9] However, based on the exploratory characteristics of subgroup analyses, there was no matching of CRT-D vs. CRT-P patients and therefore the control for confounders was limited.[9]

Consistent findings were previously observed in the COMPANION trial, which enrolled HFrEF patients in sinus rhythm with NYHA class III/IV.[4] When compared with optimal medical therapy alone, CRT-D use led to a statistically significant survival benefit, whereas the 24% relative risk reduction in mortality associated with CRT-P only approximated statistical significance.[4] However, there was no pre-specified analysis for an head-to-head comparison between CRT-D and CRT-P, which precluded any direct comparison for efficacy between the two CRT strategies.[4] Finally, the COMPANION trial enrolled patients almost 20 years ago and, therefore, the patient characteristics (e.g. younger age) and medical therapy (less use of renin–angiotensin-system inhibitors and beta-blockers) of this trial cohort might not reflect those of contemporary HFrEF populations which have reported a reduced risk of SCD compared with previous studies.[7] Furthermore, a *post hoc* analysis of the

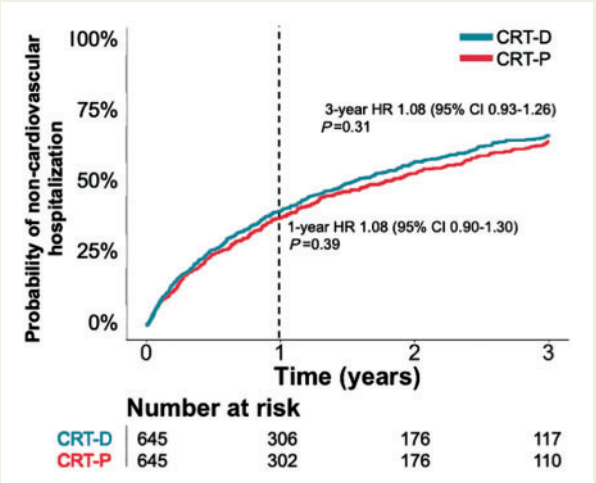


**Figure 4** Kaplan–Meier curves for non-cardiovascular hospitalization in patients treated with cardiac resynchronization therapy with defibrillator vs. cardiac resynchronization therapy with pacemaker in the propensity score-matched cohort. Vertical-dashed line marks the 1-year endpoint. CI, confidence interval; CRT-D/-P, cardiac resynchronization therapy with defibrillator/pacemaker; HR, hazard ratio.

REVERSE study, which randomized mildly symptomatic HF patients to CRT on vs. CRT off on top of standard medical therapy, reported a 65% reduction in 5-year mortality with CRT-D vs. CRT-P.[15] Finally, our findings are also consistent with an individual patient data network meta-analysis showing a 19% reduction in mortality with CRT-D vs. CRT-P,[16] and with reports from other registries.[17] Overall, our analysis supports previous studies suggesting survival benefits in CRT-D vs. CRT-P, but in a contemporary HFrEF population characterized by higher use HF drug therapy, older age, and high comorbidity burden (such as atrial fibrillation).

## Cardiac resynchronization therapy-defibrillator vs. cardiac resynchronization therapy-pacemaker in ejection fraction ≤30% vs. 30–39%

In our subgroup analysis, CRT-D use was associated with a lower long-term mortality (i.e. at 3 years) risk in patients with an EF <30% but not in those with an EF of 30–39%, whereas there was no interaction between exposure and EF regarding short-term mortality (i.e. at 1 year). This might be driven by the inverse relationship between risk of SCD and EF in HF, i.e. higher incidence of SCD with lower EF,[18] and, therefore, time-dependent improvement in EF could slightly reduce the need for an ICD in patients with EF 30–39%. This hypothesis might be further supported by a previous study where EF ≤35% predicted appropriate ICD therapy but, at the same time, the risk of appropriate ICD therapy was still significant in patients with EF > 35% (5% vs. 12% per year, respectively).[19] Additionally, programming and device capabilities have also improved over the last years, which might have led to benefit even with a slightly higher EF at baseline.[20,21] Finally, in our analysis we did not consider that CRT-P could have

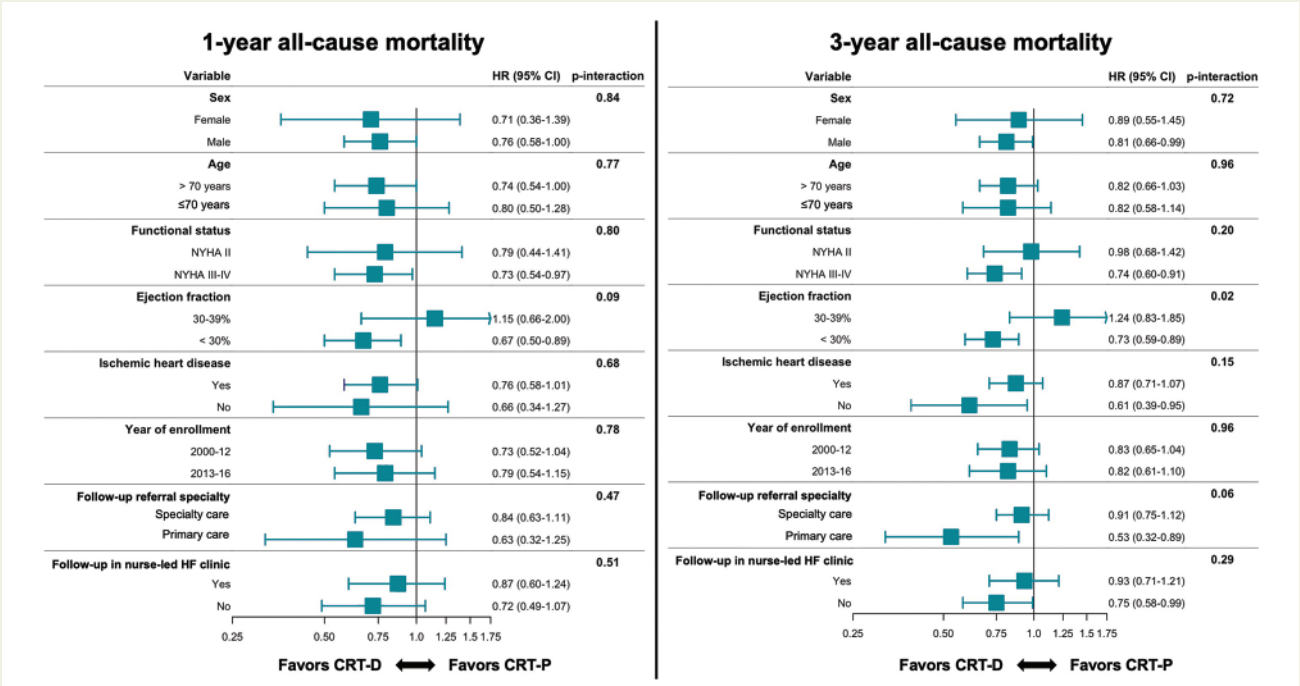


**Figure 5** Association between use of cardiac resynchronization therapy with defibrillator, 1 and 3-year all-cause mortality risk in pre-specified subgroups. CI, confidence interval; CRT-D/-P, cardiac resynchronization therapy with defibrillator/pacemaker; HR, hazard ratio; NYHA, New York Heart Association.

been upgraded to CRT-D in some patients who experienced a reduction in EF over the 3-year follow-up, which might further explain why we did observe a lower mortality risk linked with CRT-D use for the EF = 30–39% group in the shorter (i.e. at 1 year) but not in the longer term (i.e. at 3 years).

## Cardiac resynchronization therapy-defibrillator vs. cardiac resynchronization therapy-pacemaker in patients with vs. without ischaemic heart disease

Differences in disease modification by the use of CRT in patients with ischaemic vs. non-ischaemic HFrEF might alter the risk of SCD and therefore limit the efficacy/usefulness of the defibrillator on top of the CRT. Current evidence on this topic is conflicting. A large European cohort study could only identify an association between CRT-D use and lower mortality in patients with ischaemic cardiomyopathy, but not in those with dilated cardiomyopathy.[22] Additionally, although the COMPANION trial suggested that CRT-D use might reduce mortality only in non-ischaemic HFrEF, which might be also somehow supported by the more recent DANISH trial, registry studies have shown the opposite.[4,12,23] Our analysis, including an HFrEF population characterized by a more implemented use of HF treatments as compared with previous studies, suggest CRT-D being beneficial in terms of lower mortality compared with CRT-P in HFrEF patients with and without history of ischaemic heart disease. Notably, we could only stratify our population based on presence or absence of history of ischaemic heart disease rather than on the underlying ischaemic/non-ischaemic aetiology, which was not fully available in our cohort. This might contribute to explain the differences between our findings on those of a large European cohort study.[22] However, whether our subgroup of patients with history of ischaemic heart disease might also include patients who developed ischaemic heart disease on top of a primary-dilated cardiomyopathy, the diagnosis of non-ischaemic-dilated cardiomyopathy is very likely in those HFrEF patients without history of ischaemic heart disease. As there was no significant interaction in the respective subgroup analyses, the main findings of our analysis might be particularly generalizable to patients with non-ischaemic HFrEF, and presumably also to those with ischaemic HFrEF. Although history of ischaemic heart disease might be a good surrogate for ischaemic cardiomyopathy HF aetiology, further research on the role of CRT-D in patients with ischaemic vs. non-ischaemic HFrEF is still needed.

## Cardiac resynchronization therapy-defibrillator vs. cardiac resynchronization therapy-pacemaker in females vs. males and younger vs. older patients

Lower short- and long-term mortality risk with CRT-D vs. CRT-P was consistent in females vs. males and older vs. younger patients. However, females and older patients were less likely to be treated with CRT-D vs. CRT-P. This finding might be at least partially explained by concerns regarding the efficacy of primary prevention

ICD use in these subgroups, with older patients expected to benefit less of ICD due to the high risk of competing non-arrhythmic events. However, in the COMPANION trial, there was no interaction between sex or age and treatment effect of CRT-P or CRT-D vs. pharmacotherapy, which might somehow support our finding.[4] More, although contrasting, evidence is available for sex- and age-related differences in outcome associated with ICD use for primary prevention.[9,12,24,25] The limited female participation in trials, as well as the different cut-off for age used for defining the older subgroup, might contribute to these inconsistencies.

## Limitations

The main limitation of this study is linked with its observational design. Although we matched CRT-D vs. CRT-P by PS which was calculated by considering an extensive number of potential confounders, residual and unmeasured confounding cannot be ruled out. We had limited data on QRS length and morphology which was not missing at random and thus could not be used for multiple imputation models. Therefore, these variables were not considered in the study to avoid further reductions in sample size. However, this limitation is not expected to impact our findings as all patients implanted with a CRT are expected to have a QRS length and morphology meeting the guideline recommendations. Due to the design of SwedeHF where EF was collected as a categorical variable, <40% was used as EF cut-off for assessing the presence of an indication for CRT rather than <35% as recommended by the guidelines. As EF measurements have a high variability and as EF may change over time, this is unlikely to have a substantial impact on our findings, although this cannot ultimately be completely ruled out. Data on HF aetiology were limited and therefore we considered history of ischaemic heart disease as a surrogate. Data on the use of antiarrhythmic drugs, delivery of ICD therapy, as well as SCD which would have been a key outcome, were not available. Therefore, we can only speculate that the observed lower risk in all-cause/CV mortality in the CRT-D vs. CRT-P group was explained by a lower occurrence of SCD. Furthermore, some patients in this analysis might have received CRT-D for secondary prevention purposes. Lastly, cross-over, i.e. CRT-P might be upgraded to CRT-D later due to a reduction in EF, as well as the limited sample size in the matched cohort, might have prevented to observe statistically significant differences in outcomes in particular in the subgroup analyses.

# Conclusions

In a contemporary real-world cohort of patients with HFrEF treated with CRT and with an indication for primary prevention ICD, CRT-D was associated with significantly lower short-term and long-term all-cause mortality compared with CRT-P. Lower long-term mortality risk (i.e. at 3 years but not at 1 year) linked with CRT-D vs. CRT-P use was observed in patients with EF < 30% but not in those with EF = 30–39%. The association between CRT-D use and lower mortality risk was consistent regardless of sex, age, and follow-up referral, although older age, female sex, and the lack of referral to HF nurse-led outpatient clinic were major determinants of CRT-D non-use. Overall, these findings support the use of CRT-D in contemporary HFrEF patients, in particular in those with more severely reduced EF.

# Supplementary material

Supplementary material is available at *Europace* online.

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**Conflict of interest:** B.S. reports personal fees from AstraZeneca and Abiomed. G.S. reports grants and personal fees from Vifor, grants and non-financial support from Boehringer Ingelheim, personal fees from Societá Prodotti Antibiotici, grants from MSD, grants and personal fees from AstraZeneca, personal fees from Roche, personal fees from Servier, grants from Novartis, grants from personal fees from GENESIS, personal fees from Cytokinetics, personal fees from Medtronic, outside the submitted work. L.H.L. reports personal fees from Merck, personal fees from Sanofi, grants and personal fees from Vifor-Fresenius, grants and personal fees from AstraZeneca, grants and personal fees from Relypsa, personal fees from Bayer, grants from Boston Scientific, personal fees from Pharmacosmos, personal fees from Abbott, grants and personal fees from Mundipharma, personal fees from Medscape, personal fees from Myokardia, grants and personal fees from Boehringer Ingelheim, grants and personal fees from Novartis, outside the submitted work. U.D. reports grants and personal fees from AstraZeneca, personal fees from Novartis and Amgen and grants from Boehringer Ingelheim, Pfizer, Boston Scientific, Vifor, and Roche Diagnostics. The other authors did not report a conflict of interest.

## Data availability

The data that support the findings of this study are available from the agencies that administrate the registries, provided it is approved by the appropriate ethics committees and administrating agencies and that data sharing are permitted by European Union General Data Protection Regulation.

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