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ORIGINAL ARTICLE

Patient-specific modifiers of survival benefit in cardiac resynchronization therapy - A multicentre interaction analysis

Bert Vandenberk[1,2]*, Marius Brusselmans[3], Gabor Voros[1,2], Pieter Martens[4], Sebastian Ingelaere[2], Pascal Betschart[5], Jens-Uwe Voigt[1,2], Matthias Dupont[4], Alexander Breitenstein[5], Jan Steffel[5], Rik Willems[1,2], Frank Ruschitzka[5], Wilfried Mullens[4,6], Sander Trenson[1,2,5,7] and Stephan Winnik[5]

[1]*Department of Cardiology, UZ Leuven, Leuven, Belgium;* [2]*Department of Cardiovascular Sciences, KU Leuven, Leuven, Belgium;* [3]*Department of Clinical and Epidemiological Virology, KU Leuven, Leuven, Belgium;* [4]*Department of Cardiology, Ziekenhuis Oost-Limburg, Genk, Belgium;* [5]*Department of Cardiology, University Hospital Zurich, Zurich, Switzerland;* [6]*Department of Life Sciences, Hasselt University, Hasselt, Belgium; and* [7]*Department of Cardiology, Sint-Jan Hospital Bruges, Bruges, Belgium*

Abstract

Background Cardiac resynchronization therapy (CRT) is a key intervention for patients with heart failure. The choice between a CRT with defibrillator therapy (CRT-D) and a CRT with pacemaker (CRT-P) is influenced by individual clinical characteristics. This study explores the interaction between these clinical variables and the benefit of CRT-D versus CRT-P on all-cause mortality.

Methods All patients who underwent CRT implantation in three European centres were included in a multicentre, retrospective registry. The impact of clinical variables on all-cause mortality was analysed using interaction tests within multivariable Cox proportional hazard models. Significant interactions were explored to assess how patient characteristics modify the effect of CRT-D compared with CRT-P.

Results A total of 2271 patients with CRT implantation were included. CRT-D was associated with a 35% reduction in all-cause mortality compared with CRT-P [hazard ratio (HR) 0.65; 95% confidence interval (CI) 0.53–0.80]. Significant interactions were observed for left bundle branch block (LBBB) morphology (P = 0.028), left ventricular ejection fraction (LVEF, P = 0.025) and renal function (P = 0.019). The survival benefit of CRT-D was pronounced in patients with LBBB (HR 0.57; 95% CI 0.44–0.73) but was not significant in those without LBBB (HR 0.81; 95% CI 0.59–1.10). For LVEF at implant, CRT-D provided benefit between 17.9% and 37.6%. Similarly, CRT-D improved outcomes in patients with an estimated glomerular filtration rate >31.8 mL/min but not in those with more advanced renal impairment. No interaction was observed with age at implant (P = 0.286).

Conclusions This study provides insights into the benefits of CRT-D over CRT-P, identifying LBBB morphology, LVEF and renal function as key covariates associated with implantable cardioverter–defibrillator (ICD) therapy's benefit.

Keywords cardiac resynchronization therapy; heart failure; implantable cardioverter–defibrillator; pacemaker

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**Correspondence to: Bert Vandenberk, Department of Cardiology, UZ Leuven, Leuven, Belgium. Email:; bert.vandenberk@kuleuven.be*
Bert Vandenberk, Marius Brusselmans and Gabor Voros shared first authorship.
Sander Trenson and Stephan Winnik shared senior authorship.

Introduction

In the past decades, cardiac resynchronization therapy (CRT) has emerged as a cornerstone in the management of heart failure (HF) with reduced ejection fraction (HFrEF).[1,2] The benefit of CRT lies in its ability to synchronize ventricular contraction through biventricular pacing, thereby ameliorating the effects of interventricular and intraventricular dyssynchrony. By restoring synchrony and the associated improvement in left ventricular (LV) function and remodelling,

CRT has been shown to improve HF symptoms, reduce HF hospitalizations and improve survival.[1]

In selecting patients for CRT, the decision-making process also involves the choice between an implantable cardioverter–defibrillator (ICD) function and only pacing, that is, CRT-D versus CRT-P.[1] In addition to the benefits of CRT, a CRT-D combines resynchronization therapy with the capability of delivering anti-tachycardia pacing or defibrillation therapy in case of potentially life-threatening ventricular arrhythmias. On the other hand, CRT-P provides resynchronization without defibrillation capabilities and therefore primarily targets improvement in HF symptoms and quality of life. In the COMPANION trial, a CRT-D was associated with a significant 36% decrease in the risk of all-cause mortality, while for CRT-P, the observed 24% decrease did not reach statistical significance (P = 0.059).[3] The choice between CRT-D and CRT-P depends on the interplay of individual patient characteristics, underlying cardiac pathology, comorbidities, risk of ventricular arrhythmias and patient preferences. As such, patients receiving a CRT-D differ from those receiving a CRT-P, which in meta-analyses results in significant heterogeneity and challenging interpretation of the results of a direct comparison between CRT-D and CRT-P.[4] This statistical hurdle can be overcome by interaction analyses on patient-level data.

This study aims to explore the interaction between clinical variables and the benefit of ICD on all-cause mortality in patients who underwent CRT implantation.

Methods

Study population

This international, multicentre, retrospective registry encompasses all patients aged 18 years and above with ischaemic or non-ischaemic cardiomyopathies who underwent CRT implantation, either de novo or an upgrade from a pacemaker or ICD, across three tertiary care centres: UZ Leuven (Leuven, Belgium), Ziekenhuis Oost-Limburg (Genk, Belgium) and University Hospital Zurich (Zurich, Switzerland). The specifics and initial analysis of this registry have been previously published.[2,5] In brief, the criteria for CRT adhered to the guidelines outlined by the European Society of Cardiology (ESC) at the time of the procedure. CRT programming, guideline-directed medical therapy and clinical follow-up were conducted based on institutional protocols. Ethical approval was obtained from the respective institutional ethics committees (Leuven: S64276; Genk: b371201627103; and Zurich: KEK-ZH-NR: 2011-0304), and the requirement for written informed consent was waived due to the retrospective nature of the study.

Retrospective registries and endpoints

Data were collected separately in each centre, and registries were subsequently merged under the supervision of two investigators (B.V. and S.T.). The procedural timeline spanned from 30 November 2000 to 31 December 2019. Patient demographics, clinical characteristics, medication profiles, and biochemical and electrocardiographic data immediately prior to CRT implantation were retrospectively gathered from electronic medical records. Ischaemic cardiomyopathy was defined as patients where the underlying aetiology of the cardiomyopathy was most likely due to coronary artery disease. LV ejection fraction (LVEF) prior to CRT implantation was collected from either cardiac magnetic resonance imaging or two-dimensional echocardiography (modified Simpson's biplane method in the apical two- and four-chamber view or visual assessment) depending on availability. For this study, only variables in common were used for further analysis.

The endpoint of the analysis was all-cause mortality, which could be reliably ascertained in all three centres. Patient's follow-up was censored at heart transplantation, implantation of a ventricular assist device or last follow-up available. All endpoints were collected with the respective date.

Statistical analysis

Categorical variables were presented as number and percentages. As all continuous variables showed non-normal distribution using the Kolmogorov–Smirnov test for normality, these were presented as median with inter-quartile range [Q1–Q3]. Comparison of parameters between groups was performed using Mann–Whitney U testing and χ^2 testing, as appropriate. All-cause mortality was analysed using time-to-event analyses, including Kaplan–Meier analysis with log-rank testing and Cox proportional hazard regression modelling. First, a baseline multivariable Cox proportional hazard regression model was constructed to identify all variables of interest for interaction analysis. All variables with a P value <0.100 in univariable regression were included in a stepwise multivariable model with forward parameter selection (entry $P < 0.050$). The final model was assessed using proportional hazard plots and the Schoenfeld residuals test for the proportional hazard assumptions and covariance matrices for multicollinearity. Given the violation of the proportional hazard assumptions, stratification was applied. Subsequently, the interaction between the clinical variables of interest and ICD therapy was evaluated. For each covariate, a model was fitted with main and interaction effects for ICD therapy and the covariate in question. Significance of the interaction was evaluated by comparing the full model to a main effects-only model. If this interaction test is significant, there is reason to believe that the effect of ICD therapy depends on the covariate. All tests performed were likelihood ratio tests.

The effect of ICD on patient outcome was quantified using hazard ratios (HRs), as estimated by the interaction effect models. These were graphed as a function of the value of the covariate for both categorical (forest plot) and continuous (hazard plots) covariates. To further explore the relationship between clinical characteristics, echocardiographic CRT response and all-cause mortality, the proportion of patients with an echocardiographic response as well as the incidence of all-cause mortality was compared across key subgroups. Echocardiographic response to CRT was defined as an increase in LVEF $\geq$ 5% and was compared using χ^2 statistics. The incidence of all-cause mortality across subgroups was compared using log-rank testing. An overview of data availability is presented in Data S1; missing values were handled by listwise deletion. Significance was defined as a P value $<$0.05. Statistical analyses were performed using R statistical software Version 4.2.3 (R Core Team 2021), Stata (StataCorp LLC, TX, USA) and GraphPad Prism Version 6.00 (GraphPad Software, La Jolla, CA, USA).

Results

Baseline clinical characteristics

A total of 2271 patients were included in the analysis, as four patients were excluded due to unavailable ICD status. Of these, 819 (36.1%) received CRT-P, while 1452 (63.9%) received CRT-D. Significant differences in baseline characteristics were observed between the CRT-P and CRT-D groups (*Table* 1). CRT-D recipients were younger (median age 67.0 [58.9–73.1] vs. 76.7 [70.2–81.1] years, $P < 0.001$) and predominantly male (78.3% vs. 65.4%, $P < 0.001$). CRT-D patients had a lower median LVEF (25.0% [20.0–30.0] vs. 30.0% [25.0–40.0], $P < 0.001$), higher prevalence of ischaemic cardiomyopathy (46.3% vs. 36.7%, $P < 0.001$) and fewer comorbidities, such as arterial hypertension (62.0% vs. 78.5%, $P < 0.001$), reflecting different medication profiles.

All-cause mortality

Over a median follow-up period of 2.98 years [1.80–4.99], 589 deaths (26.2%) were recorded. Kaplan–Meier survival analysis demonstrated significantly better survival in CRT-D recipients compared with CRT-P recipients (log-rank $P < 0.001$; *Figure* 1). *Table* 2 summarizes the incidence rates and cumulative event rates at 1, 3, 5 and 10 years of follow-up. The incidence of all-cause mortality was significantly higher in CRT-P recipients at 8.9% per year, compared with 6.3% per year in CRT-D recipients.

In multivariable Cox proportional hazard analysis, CRT-D therapy was associated with a 35% reduction in the risk of all-cause mortality compared with CRT-P [HR 0.65; 95% confidence interval (CI) 0.53–0.80]. Independent associations with higher all-cause mortality included older age, male sex, ischaemic cardiomyopathy, a history of stroke, diabetes mellitus, non-left bundle branch block (LBBB) QRS morphology, a QRS duration $\leq$130 ms, lower LVEF and worse renal function. In contrast, the use of angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers or angiotensin receptor–neprilysin inhibitors was associated with improved survival (*Table* 3).

Interaction tests for all-cause mortality

The forest plot in *Figure* 2 highlights significant interactions for categorical variables, including ICD therapy with LBBB morphology (P = 0.028) and the use of ACE inhibitors, angiotensin receptor blockers or angiotensin receptor–neprilysin inhibitors (P = 0.037). Compared with CRT-P, the choice for CRT-D implantation was associated with a significantly lower risk of all-cause mortality in patients with LBBB (HR 0.57; 95% CI 0.44–0.73), whereas this benefit was not observed in the 33.1% of patients without LBBB (HR 0.81; 95% CI 0.59–1.10). Similarly, the benefit of CRT-D was not apparent in the 13.8% of patients not receiving ACE inhibitors, angiotensin receptor blockers or angiotensin receptor–neprilysin inhibitors, to be noted with a wide 95% CI (HR 0.93; 95% CI 0.60–1.45).

For continuous variables, we observed significant interactions between ICD therapy and both LVEF (P = 0.025) and renal function (P = 0.019), but not for age at implant (P = 0.286). The hazard plot in *Figure* 3B illustrates the benefit of ICD therapy on top of CRT across the range of LVEF. In multivariable analysis, there was a significant survival benefit of CRT-D for patients with an LVEF at implant between 17.9% and 37.6%, compared with CRT-P. Similarly, the reduction in risk of all-cause mortality in recipients selected for CRT-D when compared with CRT-P was lost in those with an estimated glomerular filtration rate (eGFR) lower than 31.8 mL/min.

Among 1939 patients with follow-up echocardiographic data, 66.4% met the criteria for CRT response. Results of the interaction analysis by echocardiographic response are presented in *Table* 4. When stratified by device type, CRT-D patients had a lower incidence of all-cause mortality compared with CRT-P patients across most subgroups, particularly in those with LBBB, preserved renal function and LVEF range of 17.9%–37.6%. The highest rates of response and lowest incidence of all-cause mortality were observed in CRT-D patients with LBBB and preserved renal function. These findings further support the interaction between clinical characteristics and the benefit derived from CRT-D, emphasizing the importance of individualized device selection.

Table 1 Baseline demographics and clinical characteristics.

Variable	All patients	CRT-P	CRT-D	*P* value
N	2271 (100%)	819 (36.1%)	1452 (63.9%)	
Age at implant (years)	70.3 (61.9–76.8)	76.7 (70.2–81.1)	67.0 (58.9–73.1)	<0.001
Female	596 (26.4%)	283 (34.6%)	313 (21.7%)	<0.001
Upgrade	604 (26.6%)	199 (24.3%)	405 (27.9%)	0.063
Epicardial LV lead	121 (5.4%)	30 (3.7%)	91 (6.3%)	0.009
ICMP	962 (42.9%)	297 (36.7%)	665 (46.3%)	<0.001
Arterial hypertension	1532 (68.0%)	642 (78.5%)	890 (62.0%)	<0.001
Dyslipidaemia	1449 (64.5%)	551 (67.6%)	898 (62.7%)	0.020
History of stroke	228 (10.2%)	79 (9.7%)	149 (10.4%)	0.600
Diabetes mellitus	602 (26.7%)	232 (28.4%)	370 (25.7%)	0.171
LVEF (%)	27.0 (21.0–34.0)	30.0 (25.0–40.0)	25.0 (20.0–30.0)	<0.001
≤35	1888 (84.9%)	560 (70.1%)	1328 (93.1%)	<0.001
35–50	292 (13.1%)	200 (25.0%)	92 (6.5%)	
>50	45 (2.0%)	39 (4.9%)	6 (0.4%)	
eGFR (mL/min)	57.7 (41.1–74.6)	53.5 (37.0–72.7)	60.1 (42.8–75.6)	<0.001
CKD 1–2	1041 (47.0%)	334 (41.4%)	707 (50.3%)	<0.001
CKD 3a	488 (22.0%)	186 (23.1%)	302 (21.5%)	
CKD 3b	401 (18.1%)	151 (18.7%)	250 (17.8%)	
CKD 4–5	284 (12.8%)	136 (16.9%)	148 (10.5%)	
NYHA classification				
I	85 (3.8%)	34 (4.2%)	51 (3.6%)	0.587
II	693 (31.2%)	243 (30.2%)	450 (31.9%)	
III–IV	1441 (65.0%)	529 (65.6%)	912 (64.5%)	
Rhythm				
Sinus	1680 (75.3%)	541 (66.7%)	1139 (80.2%)	<0.001
AF	391 (17.5%)	210 (25.9%)	181 (12.8%)	
Atrial pacing	160 (7.2%)	60 (7.4%)	100 (7.0%)	
Conduction				
Normal	175 (7.8%)	72 (8.9%)	103 (7.2%)	0.066
RBBB	198 (8.9%)	83 (10.2%)	115 (8.1%)	
LBBB	1493 (66.9%)	536 (66.1%)	957 (67.3%)	
Non-specific	192 (8.6%)	56 (6.9%)	136 (9.6%)	
Ventricular pacing	175 (7.8%)	64 (7.9%)	111 (7.8%)	
QRS (ms)	158 (138–176)	158 (140–176)	158 (137–176)	0.704
≤130	420 (18.9%)	143 (17.7%)	277 (19.6%)	0.506
130–150	487 (21.9%)	176 (21.8%)	311 (22.0%)	
>150	1318 (59.2%)	490 (60.6%)	828 (58.5%)	
ACE inhibitor/ARB/ARNI	1942 (86.2%)	657 (80.4%)	1285 (89.4%)	<0.001
BB	1917 (85.1%)	646 (79.1%)	1272 (88.5%)	<0.001
MRA	1366 (60.6%)	407 (49.8%)	959 (66.8%)	<0.001
Loop diuretic	1417 (63.2%)	470 (57.5%)	947 (66.4%)	<0.001
Amiodarone	512 (22.8%)	138 (16.9%)	374 (26.1%)	<0.001

Abbreviations: ACE, angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BB, beta-blocker; CKD, chronic kidney disease; CRT-D, cardiac resynchronization therapy with defibrillator; CRT-P, cardiac resynchronization therapy with pacemaker; eGFR, estimated glomerular filtration rate; ICMP, ischaemic cardiomyopathy; LBBB, left bundle branch block; LV, left ventricular; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; RBBB, right bundle branch block.

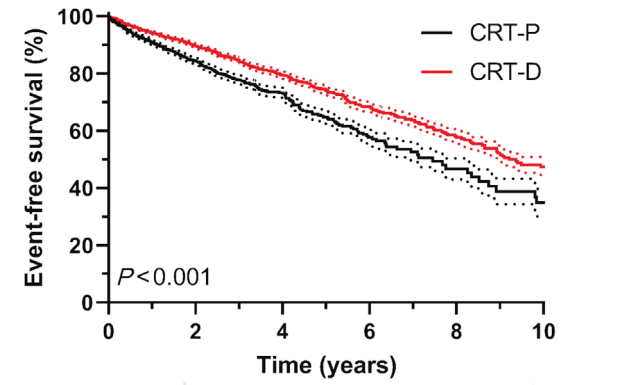
Discussion

In this multicentre registry, the choice of CRT-D over CRT-P was associated with a 35% reduction in all-cause mortality. The interaction analyses revealed that LBBB morphology, LVEF and renal function were key modifiers of the benefit of ICD therapy. CRT-D showed only benefits across a range of LVEF and renal function values, with thresholds identified where CRT-D's advantage lost significance (LVEF $< 17.9\%$ and eGFR < 31.8 mL/min). Importantly, these findings do not necessarily implicate a lack of clinical benefit from an HF perspective but rather identify subgroups with a lack of benefit from ICD therapy on top of CRT due to a high intrinsic mortality risk.

Interaction analyses are underutilized in cardiovascular research, while they may add both statistical and clinical understanding to the nuanced effects of an intervention.[6] Statistically, interaction analysis can identify subgroups where the effect of ICD therapy diverges, highlighting patient-specific factors that modify the efficacy of treatment. The strengths of this study include the robustness of the multicentre dataset with high data completeness (Data S1) and the extended follow-up duration with sufficient clinical events (53.5 events per variable included in the final model). This results in a robust model with Harrell's *C* index of 0.691 and clinically acceptable CIs for several key variables, such as LVEF and renal function. Clinically, interaction analysis bridges towards individualized care by delineating which patients de-

rive the most benefit from CRT-D. The identification of clinically meaningful thresholds for LVEF and eGFR function further strengthens the application of these findings, as these provide detailed insights for patient selection in a real-world scenario, ensuring that the risks and costs of CRT-D are directed towards those most likely to experience meaningful survival benefits. However, it is important to recognize that the observed mortality difference between CRT-P and CRT-D patients reflects both the preselection survival benefit based on evidence from randomized clinical trials and the additional protective effect of defibrillator therapy.

Figure 1 Kaplan–Meier survival analysis by implantable cardioverter–defibrillator status. CRT-D, cardiac resynchronization therapy with defibrillator; CRT-P, cardiac resynchronization therapy with pacemaker.



At risk						
CRT-P	819	548	232	106	35	18
CRT-D	1452	1024	538	274	135	65

The observed reduction in all-cause mortality in patients with CRT-D compared with CRT-P aligns with recent findings. The study by Leyva et al. included 1046 patients with a median follow-up of 3.7 years and showed a survival benefit for CRT-D of 33% when compared with CRT-P (HR 0.67; 95% CI 0.53–0.84).[7] Further, a recent propensity score matching analysis by Schrage et al. found an all-cause mortality difference of 24% at 1 year, while this was 28% in our study.[8] It is intuitive to state that the observed difference in survival can at least in part be attributed to ventricular arrhythmias and sudden cardiac death, as a meta-analysis by Barra et al. showed that sudden cardiac death represented one third of excess mortality in CRT-P patients.[9] However, the choice between CRT-D and CRT-P by the clinician is guided by demographic and clinical characteristics that may

Table 2 Endpoint analysis.

	Events, *n* (%)	Incidence rate, % per year (95% CI)	Cumulative event rate (%)			
			1 year	3 years	5 years	10 years
All-cause mortality	589 (26.2%)	7.2% (6.6–7.8)	7.1%	18.0%	30.3%	56.5%
CRT-P	239 (29.5%)	8.9% (7.8–10.1)	9.4%	22.6%	35.5%	65.3%
CRT-D	350 (24.4%)	6.3% (5.7–7.0)	6.7%	15.3%	26.0%	52.6%

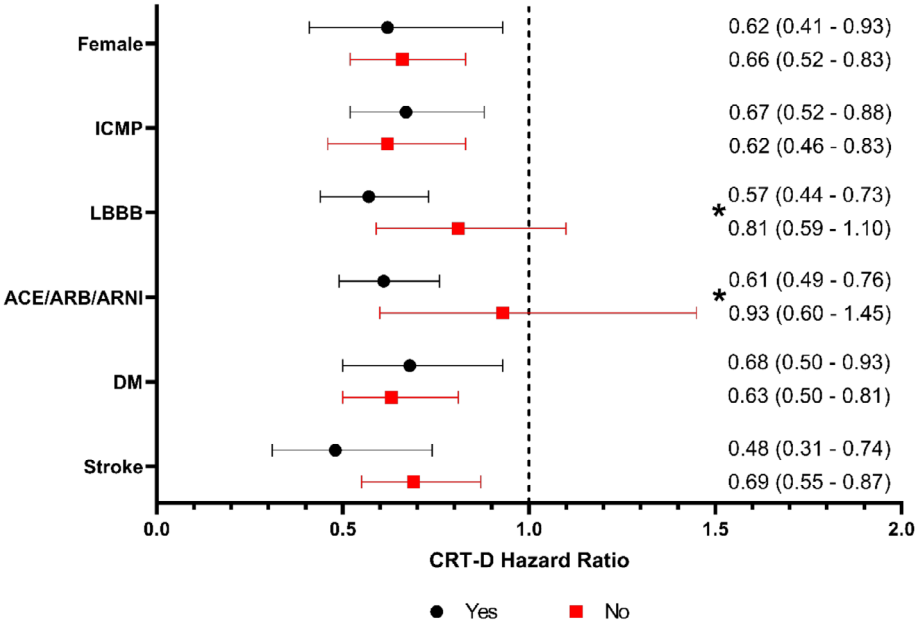
Abbreviations: CI, confidence interval; CRT-D, cardiac resynchronization therapy with defibrillator; CRT-P, cardiac resynchronization therapy with pacemaker.

Table 3 Multivariable Cox proportional hazard regression model for all-cause mortality.

	Cox regression			Interaction *P* value	
Variable	Hazard ratio	95% CI	Multivariable *P* value	Univariable	Multivariable
Age (per year)	1.02	1.01–1.03	0.004	0.354	0.286
LVEF (per %)	0.98	0.97–0.99	0.002	0.285	0.025
eGFR (per 10 mL/min)	0.85	0.81–0.89	<0.001	0.003	0.019
Female	0.68	0.55–0.86	0.001	0.953	0.823
CRT-D	0.65	0.53–0.80	<0.001		
ICMP	1.38	1.14–1.65	0.001	0.715	0.621
LBBB	0.76	0.64–0.92	0.004	0.312	0.028
ACE inhibitor/ARB/ARNI	0.58	0.46–0.74	<0.001	0.002	0.037
Diabetes mellitus	1.33	1.11–1.59	0.002	0.927	0.705
History of stroke	1.27	1.00–1.61	0.046	0.011	0.113
QRS duration (ms)					
≤130	Reference			0.595	0.488
130–150	0.65	0.49–0.86	0.002		
>150	0.70	0.56–0.88	0.002		

Note: The model was stratified by implanting centre and use of loop diuretics due to violation of the Schoenfeld residuals. Global Schoenfeld residuals test of the final model: $P = 0.216$. Harrell's C index of the final model = 0.691.
Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; CI, confidence interval; CRT-D, cardiac resynchronization therapy with defibrillator; eGFR, estimated glomerular filtration rate; ICMP, ischaemic cardiomyopathy; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction.

Figure 2 Forest plot for multivariate interaction analysis of categorical variables. Significant interactions are marked with an asterisk (*). ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; CRT-D, cardiac resynchronization therapy with defibrillator; DM, diabetes mellitus; ICMP, ischaemic cardiomyopathy; LBBB, left bundle branch block.



not be included in the multivariable model yet could have affected clinical decision-making. Together with a known underutilization of CRT, this may result in residual confounding explaining the remaining difference in survival.[10–12]

An important but unaddressed confounder in our study is the occurrence of ventricular arrhythmias and the impact of ICD therapies on patient outcomes. Several prior studies suggest a complex interplay between arrhythmic events, defibrillator interventions and mortality. The MADIT-RIT trial demonstrated that both appropriate and inappropriate ICD shocks were independently associated with increased mortality, underscoring the potential harm of device therapy in certain settings, especially when triggered by inappropriate detection or delivered via suboptimal programming strategies.[13] Similarly, the OBSERVO-ICD registry reported that CRT-D patients experienced significantly lower rates of electrical storm compared with ICD-only recipients, particularly among CRT responders, suggesting that the benefits of defibrillator therapy may depend on underlying resynchronization response.[14] In contrast, data from CRT-P cohorts, such as the study by Bortnik et al., showed that in selected patients, the incidence of ventricular arrhythmias was low and that CRT-P alone may be well tolerated during long-term follow-up.[15] Unfortunately, due to the retrospective and multicentre nature of our registry, we were unable to collect uniform or reliable data on appropriate ICD interventions or arrhythmia burden across all participating centres. As a result, we cannot assess the extent to which ventricular arrhythmia incidence or ICD therapy mediates the observed mortality differences.

A significant limitation of many previous analyses lies in the tendency to dichotomize or categorize continuous variables when developing clinical risk scores. While this approach simplifies interpretation and implementation in clinical practice, it fails to capture the true nature of risk, which often behaves as a continuum. By analysing continuous variables without artificial categorization, our study better reflects the nuanced relationship between ICD therapy and LVEF and renal function, respectively. Previous research has shown that patients with chronic kidney disease (CKD) stage 4 still benefit from CRT with improved clinical outcome and improvement in eGFR, albeit to a lesser extent than patients with CKD stages 1–3.[16,17] However, the benefits of ICD therapy were lost in CKD stage 4, which corresponds to the eGFR cut-off of 31.8 mL/min reported in our analysis.[17,18] A meta-analysis of 26 studies (n = 119 263) showed that patients with CKD stage 4/5 had a 2.7 (95% CI 1.93–3.80) times higher risk of all-cause mortality compared with patients with CKD stage 3.[19] This can be attributed to the competing risk of non-arrhythmic mortality due to the higher incidence of asystole and pulseless electrical activity, as well as higher complication rates such as infections, in patients with more advanced CKD.[17,18]

The interaction analysis between ICD therapy and LVEF showed a window of benefit between 17.9% and 37.6%. In MADIT-CRT, the clinical benefit of CRT was independent of baseline LVEF, including patients with LVEF $\leq$ 25% and those with LVEF $>$ 30%.[20] However, echocardiographic response decreased with lower LVEF.[20,21] The relationship between

Figure 3 Hazard plots for multivariate interaction analysis of continuous variables. (A) Age at implant. (B) Left ventricular ejection fraction. (C) Renal function. Hazard plots with 95% confidence intervals for multivariable interaction analysis of (A) age at implant, (B) left ventricular ejection fraction and (C) renal function assessed using estimated glomerular filtration rates. The cut-offs are indicated as dotted lines on the *X* axis, respectively, where the 95% confidence intervals or hazard ratios cross the baseline of 1.0. The violin plot shows the availability of data in the registry. ICD, implantable cardioverter–defibrillator.

CRT-D benefit and LVEF has traditionally been evaluated using categorical thresholds. A meta-analysis of the placebo arms of four randomized trials (n = 2828) showed a U-shaped

Table 4 Echocardiographic response and all-cause mortality in CRT-D versus CRT-P patients stratified by clinical subgroups.

	CRT-D				CRT-P			
	Lower bound	Benefit	Upper bound	*P* value	Lower bound	Benefit	Upper bound	*P* value
LVEF	<17.9%	17.9%–37.6%	>37.6%		<17.9%	17.9%–37.6%	>37.6%	
ACM incidence (% per year)	8.3 (6.4–10.6)	6.0 (5.3–6.7)	7.0 (4.3–11.2)	0.099	12.6 (7.9–20.3)	9.5 (8.2–11.1)	6.7 (5.1–9.0)	0.046
LVEF increase ≥5%	131 (77.5%)	642 (62.5%)	33 (45.2%)	<0.001	21 (77.8%)	357 (80.2%)	99 (50.0%)	<0.001
eGFR	<31.8 mL/min	≥31.8 mL/min	Not applicable		<31.8 mL/min	≥31.8 mL/min	Not applicable	
ACM incidence (% per year)	16.5 (13.1–20.7)	5.4 (4.8–6.0)		<0.001	19.0 (14.9–24.3)	7.3 (6.3–8.5)		<0.001
LVEF increase ≥5%	80 (58.8%)	710 (63.9%)		0.251	85 (69.7%)	387 (71.5%)		0.682
LBBB morphology	Absent	Present	Not applicable		Absent	Present	Not applicable	
ACM incidence (% per year)	9.4 (8.0–11.1)	5.2 (4.5–6.0)		<0.001	11.7 (9.5–14.3)	7.6 (6.5–9.0)		0.001
LVEF increase ≥5%	224 (55.6%)	577 (67.1%)		<0.001	133 (58.9%)	344 (77.8%)		<0.001
ACE inhibitor/ARB/ARNI	Absent	Present	Not applicable		Absent	Present	Not applicable	
ACM incidence (% per year)	13.8 (10.4–18.2)	5.8 (5.2–6.5)		<0.001	10.3 (7.7–13.8)	8.6 (7.5–9.9)		0.283
LVEF increase ≥5%	69 (57.5%)	737 (64.1%)		0.150	80 (63.5%)	397 (73.0)		0.034

Abbreviations: ACE, angiotensin-converting enzyme; ACM, all-cause mortality; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; CRT-D, cardiac resynchronization therapy with defibrillator; CRT-P, cardiac resynchronization therapy with pacemaker; eGFR, estimated glomerular filtration rate; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction.

relationship between LVEF and benefit of ICD therapy.[22] While the number needed to treat for an ICD to prevent one arrhythmic death was lowest when the LVEF was between 16% and 20%, this doubled for LVEF $\leq$ 15%.[22] Furthermore, among patients with LVEF $\leq$ 10%, all observed deaths were non-arrhythmic, illustrating the competing risk in patients with very low LVEF.[22] On the other hand, the observed upper limit of ICD benefit in CRT therapy falls in between the conventional LVEF cut-offs of 35% and 40% in pivotal clinical trials. For example, data from the Digitalis Investigation Group trial showed a linear inverse relation between all-cause mortality and LVEF, yet mortality rates stabilized once LVEF $\geq$ 40%.[23]

The results confirm that LBBB morphology is a critical factor in maximizing the benefit of CRT-D, as our results showed no additional benefit of CRT-D when compared with CRT-P in patients with non-LBBB. Interestingly, the prevalence of non-LBBB was balanced between the CRT-P and CRT-D groups and constituted approximately one third of patients. Because the analysis plan of the COMPANION trial did not include a prespecified CRT-P versus CRT-D analysis, there is a lack of randomized data to provide further insights in this finding.[3] Albeit the small number of patients, the subgroup analysis of COMPANION did not show a significant difference in all-cause mortality in patients with non-LBBB between CRT-D and pharmacological therapy.[3] Furthermore, a small propensity score-matched analysis including a total of 345 patients showed a similar significant interaction for QRS morphology between CRT-D and CRT-P.[24] The use of ACE inhibitors, angiotensin receptor blockers or angiotensin receptor–neprilysin inhibitors was associated with better survival, taking in mind that withdrawal of these therapies might indicate more advanced disease, symptomatic hypotension or more severe comorbidities as kidney failure and therefore explaining a higher mortality in the population selected for CRT-P based on clinical judgement. Due to the low prevalence of patients not receiving ACE inhibitors, angiotensin receptor blockers or angiotensin receptor–neprilysin inhibitors, and the resulting wide CIs in the interaction analysis, we recognize the limited interpretability and reliability of these findings.

Limitations

This study has several limitations that must be acknowledged. First, the retrospective design limits the ability to establish causal relationships between ICD therapy and observed outcomes due to selection bias. The data were collected across three centres with potential variability in institutional protocols, clinical practices and patient management strategies, which could have influenced the findings. Only variables available for each centre were included in this analysis. While efforts were made to minimize this impact by standardizing the datasets and performing multivariable analysis with stratification by centre, unmeasured confounders cannot be excluded. Additionally, data on appropriate ICD therapies, ventricular arrhythmias and clinical response to CRT were not uniformly available across all centres, limiting our ability to assess the relationship between arrhythmic events, device therapy and clinical outcomes. Echocardiographic response was assessed using LVEF improvement $\geq$5% as a surrogate, as more detailed parameters such as changes in LV volumes were not consistently recorded. Second, the study population spanned nearly two decades, during which advancements in guideline-directed medical therapy and device technology have occurred. These temporal changes, such as the emerging use of neprilysin inhibitors and the introduction of sodium–glucose cotransporter-2 (SGLT2) inhibitors, may have influenced patient outcomes and limited the generalizability of the findings to contemporary practice. Third, although the data completeness was consistently >97.5% (Data S1), the use of listwise deletion for handling missing data may have led to the exclusion of potentially informative cases.

Conclusions

This multicentre study highlights the nuanced relationship between patient-specific factors and the benefit of CRT-D therapy compared with CRT-P by performing detailed interaction analyses. The survival benefit of CRT-D was absent in patients with very low LVEF (<17.9%), advanced CKD (eGFR < 31.8 mL/min) and non-LBBB. This real-world evidence may guide the shared decision-making process when deciding between a CRT-D and a CRT-P and emphasizes the need for individual risk assessment.

Conflict of interest statement

Sander Trenson is an advisory board member of Medtronic, Vifor Pharma, AstraZeneca and Novartis and reports speaker fees from AstraZeneca, Bayer, Boehringer Ingelheim and Novartis. Jan Steffel reports consulting and/or speaker fees from Abbott, Alexion, AstraZeneca, Bayer, Berlin-Chemie, Biosense Webster, Biotronik, Boehringer Ingelheim, Boston Scientific, BMS, Daiichi Sankyo, Medscape, Medtronic, Menarini, Merck/MSD, Organon, Pfizer, Saja, Servier and WebMD and ownership of Swiss EP and CorXL. Stephan Winnik reports educational grant support and/or travel support and/or consulting/speaker fees from Abbott, Bayer, Biotronik, Boehringer Ingelheim, Boston Scientific, Cardinal Health, Daiichi Sankyo, Fehling Instruments, Medtronic and Servier. Rik Willems reports research funding from Abbott, Biotronik, Boston Scientific and Medtronic and speaker and consulting fees from Medtronic, Boston Scientific, Biotronik

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Data S1. Supporting information.

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