Review

CRT-D or CRT-P: When There Is a Dilemma and How to Solve It

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Review

CRT-D or CRT-P: When There Is a Dilemma and How to Solve It

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Abstract

Cardiac resynchronization therapy (CRT) represents a cornerstone in the management of patients with heart failure and electrical dyssynchrony, improving symptoms, reducing hospitalizations, and prolonging survival. CRT can be delivered via a pacemaker (CRT-P) or an ICD (CRT-D). Despite its widespread use, the mortality benefit of CRT-D over CRT-P remains uncertain, as no head-to-head randomized trials have been designed to directly compare the two modalities, making device selection a frequent clinical dilemma. In practice, CRT-D accounts for 70–80% of CRT implantations in developed countries, yet solid evidence demonstrating its superiority over CRT-P is lacking. Specific patient groups including those with non-ischemic cardiomyopathy, advanced age, multiple comorbidities, or limited life expectancy, may derive limited incremental benefit from CRT-D, which should be balanced against device specific risks such as lead failure and inappropriate shocks. The present review aims to provide a comprehensive comparison between CRT-D and CRT-P, focusing on the existing body of evidence, criteria for patient selection, comparative clinical outcomes, and risk-benefit considerations for clinical decision-making.

Keywords: CRT-D; CRT-P; sudden cardiac death

1. Introduction

Heart failure remains a leading cause of morbidity and mortality worldwide, affecting 1-2% of the adult population, with a rising prevalence mainly due to ageing [1–3]. Patients with heart failure and left ventricular dysfunction commonly exhibit significant intraventricular conduction delay, resulting in electrical dyssynchrony, exacerbating cardiac function [4,5]. Cardiac Resynchronization Therapy (CRT) has emerged as a cornerstone therapeutical intervention for such patients, aiming to achieve coordinated biventricular contraction and improve hemodynamic performance [6–9], raising the number of CRT implantations up to 76% from 2010 to 2019 [10]. Multiple randomized clinical trials (RCTs) have shown reduced mortality and hospitalizations as well as improvement of symptoms and quality of life in patients with heart failure and reduced left ventricular ejection fraction (LVEF) receiving a CRT device [6,7,9,11,12].

CRT can be delivered via cardiac resynchronization therapy with a pacemaker (CRT-P) and cardiac resynchronization therapy with a defibrillator (CRT-D). The mortality benefit of CRT-D compared to CRT-P remains uncertain, primarily due to the absence of head-to-head RCTs specifically designed to compare these two therapeutic modalities. Selecting the most appropriate device type requires an individualized risk assessment that takes into account multiple factors,

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including the underlying etiology, presence of myocardial scar tissue, patient age, comorbidities, and overall life expectancy. ICD-specific risks such as inappropriate shocks, lead failure and high cost should also be considered.

This review aims to provide a comprehensive comparison between CRT-D and CRT-P, focusing on the existing body of evidence, criteria for patient selection, comparative clinical outcomes, and key considerations for clinical decision-making.

2. Clinical Effectiveness of CRT

Current understanding and clinical use of CRT is based on landmark RCTs conducted since 2002. The MIRACLE trial was the first prospective study to demonstrate the effectiveness of CRT over a six-month follow-up period in patients with moderate-to-severe heart failure and intraventricular conduction delay, as compared with medical treatment [11]. Similar results were reported in CARE-HF trial, where patients at NYHA III-IV receiving CRT experienced significant improvement in quality of life and clinical outcomes as opposed to those treated with medication alone [13,14]. Along this line, patients with advanced heart failure, wide QRS interval and CRT exhibited reduced combined risk of death from any cause or hospitalization in the COMPANION trial, the only study to randomize patients to CRT-D or CRT-P, however the study was designed to assess the effectiveness of CRT compared to medical treatment [7]. Patients with mild heart failure (NYHA I-II) also benefit from CRT, as shown in MADIT-CRT [8], RAFT [9] and REVERSE [12] clinical trials. The major clinical trials of CRT are summarized in Table 1.

Table 1. Major CRT clinical trials.

Trial Name	Year	Population	Sample size	Comparison	Endpoints
PATH-CHF[15]	1999	NYHA III-IV	42	Univentricular pacing vs. BiVP	Trends for improvement regarding $\dot{V}O2$max and 6MWT
MUSTIC[16]	2002	NYHA III LVEF <35% QRS>150ms	67	BiVP vs. no pacing (sinus) BiVP vs. Univentricular (patients with Af)	6MWT +20% $VO2$ max +10% LVEF +5% Mitral regurgitation improved by 45–50%
MIRACLE[11]	2002	NYHA III-IV LVEF ≤35% QRS >130 ms,	453	OMT vs CRT	Improved quality of life, 6MWT, NYHA class, LVEF
MIRACLE-ICD[17]	2003	NYHA III-IV LVEF ≤35% QRS >130 ms	369	BiVP+ICD vs. ICD	BiVP favorably affected quality of life, functional status, and exercise capacity No significant difference in LV function or survival
CONTAK-CD[18]	2003	NYHA) II -IV LVEF ≤35%	490	BiVP+ICD vs. ICD	6MWT +20 m $VO2$max +0.8

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		QRS ≥120 ms			mL/kg/min LVEF +2.3%
COMPANION[7]	2004	NYHA III-IV LVEF ≤35% QRS ≥120 ms	1520	OMT vs CRT/CRT-D	CRT-D reduced all-cause mortality by 36% CRT-P by 24%
CARE-HF[13]	2005	NYHA III-IV LVEF≤35% QRS ≥120 ms	813	OMT vs CRT	CRT-P reduced mortality and HF hospitalization
HOBIPACE[19]	2006	LVEF ≤40% Symptomatic bradycardia and impaired AV conduction	33	BiVP vs. Univentricular pacing	Favorable effects of BiVP on LV dimensions, LVEF, NT-proBNP levels, and functional status
MADIT-CRT[8]	2009	NYHA I-II LVEF ≤30% QRS ≥130 ms,	1820	CRT-D vs ICD	Reduced HF events and improved LV function, especially in LBBB
REVERSE[12]	2008	NYHA I-II LVEF ≤40% QRS ≥120 ms	610	OMT vs CRT	CRT-P improved LV function and reduced HF progression
RAFT[9]	2010	NYHA II-III LVEF ≤30% QRS ≥120 ms	1798	CRT-D vs ICD	CRT-D reduced mortality and HF hospitalizations
RESET-CRT[20]	2023	NYHA II-IV LVEF ≤35% QRS ≥120 ms	3569	CRT-P vs CRT-D	Non-inferior mortality with CRT-P vs CRT-D

Abbreviations: NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; HF, heart failure; MWT, minute walking distance; OMT, optimal medical treatment; CRT, cardiac resynchronization

3. CRT Indications

CRT is recommended in selected patients with heart failure who remain symptomatic despite optimal guideline-directed medical therapy (OGMT). According to the 2021 ESC Guidelines on cardiac pacing and resynchronization therapy, CRT-D is indicated in patients with left ventricular ejection fraction (LVEF) ≤ 35%, sinus rhythm, and a widened QRS complex, particularly with left bundle branch block (LBBB) morphology [21]. The greatest benefit is observed among those with QRS duration ≥ 150 ms. Additionally, patients with atrial fibrillation (AF) may be candidates for CRT, given that adequate biventricular pacing can be ensured, either with medical treatment or following AV nodal ablation [21]. Patients who have received a conventional ICD and who subsequently develop symptomatic HF with LVEF≤ 35% despite OGMT, and who have a significant proportion of RV pacing, should be considered for CRT upgrade [22,23].

4. CRT-D or CRT-P

Should all patients with a CRT indication receive a defibrillator lead? The choice between the two is a frequent clinical dilemma. Recent survey studies have shown that CRT-D devices account

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for over 70–80% of all CRT implantations in developed countries [24–26]. However, this widespread use of CRT-D is not supported by solid evidence demonstrating its superiority over CRT-P.

In a post-hoc analysis of the COMPANION study, CRT-D was associated with 36% mortality risk reduction as compared to CRT-P and regarding the cause of death, CRT-D rather than CRT-P significantly reduced sudden cardiac death (SCD) [(HR 0.44, 95% CI 0.23 - 0.86; P = 0.02) and (HR 1.21, 95% CI 0.7-2.07; P = 0.50) respectively] [7]. Importantly though, the COMPANION trial was underpowered to detect a survival benefit from CRT-D. A network meta-analysis of 13 randomized clinical trials including >12.000 patients found that CRT-D reduced total mortality by 19% (95% CI 1-33%, unadjusted) compared with CRT-P [27]. Similar results were reported in a propensity-matched cohort, where CRT-D was associated with a significantly lower all-cause mortality than CRT-P in patients with heart failure of ischemic etiology and in patients with non-ischemic heart failure below 75 years of age [28]. Accordingly, recently published meta-analysis of 26 observational studies including 55.469 CRT-P patients and 72.561 CRT-D patients, showed that patients with CRT-D had 26% lower risk of all-cause mortality compared with CRT-P. However, patients aged > 75 years old and those with non-ischemic heart failure were less-likely to benefit from a CRT-D [29]. Along this line, a previous meta-analysis focused on non-ischemic cardiomyopathy (NICM) reported that the addition of a defibrillator was not significantly associated with a reduction in all-cause mortality in CRT-eligible patients [30]. The DANISH trial had similarly reported no significant difference in mortality risk in patients with NICM between the ICD and no-ICD arm, irrespective of CRT [31]. Likewise, data from observational studies from Kutyifa *et al*. and Barra *et al*. suggest substantial (24–30%) mortality benefit from CRT-D only in patients with ischemic cardiomyopathy [32,33]. Contradictory though results were reported in another meta-analysis assessing the effect of CRT-P versus CRT-D on mortality in patients with NICM, where CRT-D was associated with significantly lower all-cause mortality (log HR − 0.169, SE 0.055; $p = 0.002$) as compared to CRT-P [34]. CRT with pacing only was reported to be non-inferior to CRT-D in the retrospective observational RESET-CRT study, in an overall population of 3.569 patients with both ischemic and non-ischemic heart failure [20].

Although CRT-D may offer additional survival benefit over CRT-P reducing sudden cardiac death (SCD) risk [7], there is data that CRT-P alone could confer SCD risk reduction. In particular, in the CARE HF extended study CRT-P reduced SCD risk by 5.6% [35]. Accumulating data from subgroup analyses from RCTs suggest that SCD risk is related to the extent of reverse LV remodeling with CRT, thus CRT responders are at lower risk for malignant ventricular arrhythmias and SCD than non-responders [36,37]. Women are shown to be better responders with higher percentage of biventricular pacing, improved rates of death and fewer hospitalizations, as compared to male counterparts, although they are underrepresented in CRT trials and less likely to receive CRT-D [38]. Current medical treatment may mitigate ventricular arrhythmia risk, particularly the use of sacubitril/valsartan and sodium-glucose co-transporter-2 inhibitors (SGLT2i) [39,40]. Increasing comorbidities on the other hand are associated with a mortality risk that competes with sudden arrhythmic death. The incremental benefit of an ICD is questioned in certain clinical settings. High comorbidity burden such as advanced age, chronic kidney disease, diabetes and peripheral vascular disease, is significant predictor of mortality in CRT-D recipients, attenuating survival benefit of ICD therapy [41–44]. Data from observational studies suggest that the addition of ICD has no impact on survival in elderly patients undergoing implantation of a CRT device [45,46]. Adding ICD to CRT seems a better option for the younger patients with good survival prognosis. Contrast-enhanced CMR-guided scar adds valuable information concerning the risk of ventricular arrhythmia. According to Gaudi CRT study, the presence of myocardial scar independently can predict appropriate ICD therapies and SCD in CRT patients [47]. Similarly, patients with NICM and left ventricular midwall fibrosis in CMR benefit from CRT-D than CRT-P [48].

As no head-to-head RCTs directly comparing CRT-D to CRT-P have been developed, the mortality benefit of CRT-D is not established. Defibrillator-specific complications, including inappropriate shocks, lead failures, and increased procedural costs are important issues to be

 doi:10.20944/preprints202508.1754.v1

considered [21]. It is crucial thus to reassess and refine patient selection criteria in order to identify which individuals will truly benefit from the addition of a defibrillator component. Tables 2 and 3 summarizes existing studies and meta-analyses respectively on the effect of CRT on mortality in patients with ischemic and non-ischemic cardiomyopathy.

Table 2. RCTS and observational on the effect of CRT on mortality.

Study (Year)	Population	Study Period	Follow-up	CRT-P (n)	CRT-D (n)	Outcomes
RCTs						
Køber (2016)	NICM	2008-2014	67months (median)	323	322	No difference in all-cause mortality between patients who received CRT and patients who did not.
Doran (2021)	ICM and NICM	2000–2002	16.5months (median)	617	595	The unadjusted and adjusted HRs for CRT-D versus CRT-P were both 0.84 (95% CI: 0.65-1.09) for all-cause mortality. NICM (n = 555): CRT-D reduced all-cause mortality compared to CRT-P (aHR: 0.54; 95% CI: 0.34-0.86) ICM (n = 657): CRT-D did not reduce all-cause mortality (aHR: 1.05; 95% CI: 0.77-1.44).
Observational studies						
Auricchio (2007)	ICM and NICM	1994–2004	34months (median)	572	726	CRT-D Non-significant decrease in mortality by 20% (HR 0.83, 95% CI 0.58-1.17, p = 0.284) Significant decrease of sudden cardiac death (HR 0.04, 95% CI 0.04-0.28, p <0.002).
Morani (2013)	ICM and NICM	2004–2007	55months (median)	108	266	CRT-D significantly reduced all-cause mortality compared to CRT-P (73 CRT-D and 44 CRT-P patients died, rate 6.6 vs. 10.4%/year; log-rank test, P = 0.020).
Kutyifa (2014)	ICM and NICM	2000–2011	28months (median)	693	429	No mortality benefit in patients with CRT-D compared with CRT-P in the total cohort (HR 0.98, 95% CI 0.73-1.32, P = 0.884). ICM: CRT-D was associated with 30% risk reduction in all-cause mortality

 doi:10.20944/preprints202508.1754.v1

						compared with CRT-P (HR 0.70, 95% CI 0.51-0.97, P = 0.03). NICM: No mortality benefit of CRT-D over CRT-P (HR 0.98, 95% CI 0.73-1.32, P = 0.894).
Looi (2014)	ICM and NICM	2006–10	29months (mean)	354	146	CRT-D did not offer additional survival advantage over CRT-P
Gold (2015)	ICM and NICM	2004–06	60months (median)	74	345	10% mortality among CRT-D patients and 11.8% among CRT-P patients. CRT-ON was predicted to increase survival 22.8% (CRT-ON 52.5% vs. CRT-OFF 29.7%; HR 0.45; p = 0.21), leading to expected survival of 9.76 years (CRT-ON) versus 7.5 years (CRT-OFF).
Marijon (2015)	ICM and NICM	2008–10	222months (mean)	535	1,170	Increased mortality rate among CRT-P patients compared with CRT-D (relative risk 2.01, 95% CI 1.56–2.58). 95% of the excess mortality among CRT-P subjects was related to an increase in non-sudden death.
Reitan (2015)	ICM and NICM	1999–12	59months (median)	448	257	Annual mortality differed between CRT-D and CRT-P (5.3% and 11.8%, respectively) After adjustment for covariates, CRT-D treatment (vs CRT-P) was not associated with better long-term survival.
Munir (2016)	ICM and NICM	2002–13	40.8months (median)	107	405	CRT-P patients had higher unadjusted mortality compared to CRT-D (HR = 1.54, 95% CI 1.15–2.08, P = 0.004). After adjustment (age at implant, sex, prior myocardial infarction, Charlson index, pre-implant LVEF, QRS morphology, drugs) this effect lost statistical significance (HR 1.18, 95% CI 0.78–1.77, P = 0.435)
Witt (2016)	ICM and NICM	2000–10	48months (median)	489	428	CRT-D reduced all-cause mortality in ICM (aHR 0.74, 95% CI, 0.56–0.97; *P* = 0.03) but not in NICM (aHR 0.96, 95% CI, 0.60–1.51; *P* = 0.85)
Drozd (2016)	ICM and NICM	2008–12	36months (mean)	544	251	No survival benefit in CRT-D patients compared with CRT-P (HR 1.09, 95% CI 0.84-1.41, P = 0.51).

 doi:10.20944/preprints202508.1754.v1

Laish-Farkas (2017)	Elderly with ICM and NICM	2006–15	60months (median)	142	104	In octogenarians CRT-P is associated with similar morbidity and mortality outcomes as CRT-D.
Barra (2017)	ICM and NICM	2002–12	41.4months (mean)	1,270	4,037	ICM: better survival with CRT-D vs CRT-P (HR 0.76; 95% CI: 0.62-0.92, P = 0.005) NICM: no such difference was observed (HR: 0.92; 95% CI: 0.73-1.16, P = 0.49).
Martens (2017)	ICM and NICM	2008–15	38months (mean)	361	326	All-cause mortality was higher in patients with CRT-P versus CRT-D (21% vs 12%, p=0.003), even after adjusting for baseline characteristics (HR 2.5; 95% CI 1.36-4.60, P=0.003). Predominant non-cardiac mode of death in CRT-P recipients (n=47 (71%) vs n=13 (38%) in CRT-D, P=0.002).
Yokoshiki (2017)	ICM and NICM	2011–15	21months (mean)	97	620	All-cause death or heart failure hospitalization diverged between the CRT-D and CRT-P groups with a rate of 22% vs. 42%, respectively, at 24 months (P=0.0011). However, this apparent benefit of CRT-D over CRT-P was no longer significant after adjustment for covariates.
Leyva (2018)	ICM and NICM	2000–17	56.4months (median)	999	551	CRT-D was associated with a lower total mortality (HR 0.72) ICM: CRT-D was associated with a lower total mortality (HR 0.62), total mortality or HF hospitalization (HR 0.63), and total mortality or hospitalization for MACE (HR 0.59) (all P < 0.001) NICM: No differences in outcomes between CRT-D and CRT-P
Döring (2018)	Elderly with ICM and NICM	2008–14	26months (mean)	80	97	No significant difference in mortality between the two groups (P= 0.562)
Wang (2019)	NICM	2002–13	46months (median)	42	93	CRT-P recipients had similar unadjusted mortality compared to CRT-D recipients (HR 1.04, 95% CI 0.56-1.93) Unchanged after adjusting for unbalanced covariates (HR 0.95, 95% CI 0.47-1.89) (LVEF, drugs, comorbidities)

 doi:10.20944/preprints202508.1754.v1

Saba (2019)	NICM	2007–14	60months	1,236	4,359	No difference between matched CRT-P and CRT-D recipients regarding the time to all-cause mortality (HR 0.90; 95% CI 0.74-1.09), any hospitalization (HR 1.13; 95% CI 0.98-1.30), and cardiac hospitalization (HR 0.98; 95% CI 0.83-1.17). CRT-P recipients had significantly lower medical costs at 12 and 24 months.
Barra (2019)	ICM and NICM	2002–13	30months (mean)	534	1,241	ICM: better survival with CRT-D vs CRT-P (HR for mortality adjusted on propensity score and all mortality predictors: 0.76; 95% CI: 0.62 to 0.92; p = 0.005) NICM: no such difference was observed (HR: 0.92; 95% CI: 0.73 to 1.16; p = 0.49).
Leyva (2019)		2009–17	32.4months (median)	24,811	25,273	Excess mortality was lower after CRT-D than after CRT-P in all patients (aHR 0.80, 95% CI 0.76-0.84] in subgroups with (aHR 0.79, 95% CI 0.74-0.84) or without (aHR 0.82, 95% CI 0.74-0.91) ICM
Liang (2020)	ICM and NICM	2005–16	36 months (median)	126	219	No significant difference in the risk of mortality between CRT-D and CRT-P groups (HR 0.99, 95% CI 0.70-1.40, P= 0.95]. No significant difference between CRT-D and CRT-P in reducing mortality was observed in any pre-specified subgroups.
Gras (2020)	ICM and NICM	2010–17	913 ± 841 days	19,266	26,431	Higher all-cause mortality in CRT-P (11.6%) than CRT-D patients (6.8%) (HR 1.70, 95% CI 1.63-1.76, P < 0.001). No difference in mortality in NICM patients >75 years old with CRT-P and CRT-D (HR 0.93, 95% CI 0.80-1.09, P = 0.39). Higher mortality in NICM CRT-P patients <75 years old (HR 1.22, 95% CI 1.03-1.45, P = 0.02). Higher mortality with CRT-P than with CRT-D irrespectively of age in patients with ICM (<75 years old: HR 1.22, 95% CI 1.08-1.37, P = 0.01; ≥75 years old: HR 1.13, 95% CI 1.04-1.22, P = 0.003).

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Huang (2021)	ICM and NICM	2012–13	27.7months (mean)	237	362	SCD rate was 8.0% in CRT-P group and 3.3% in CRT-D group No significant differences in all-cause death rate between the CRT-D and CRT-P groups (CRT-D vs. CRT-P, 20.4% vs. 19.4%, P = 0.840).
Schrage (2022)	ICM and NICM	2000–16	28.2months (median)	880	1,108	CRT-D was associated with lower 1- and 3-year all-cause mortality (HR:0.76, 95% CI:0.58-0.98; HR: 0.82, 95% CI: 0.68-0.99, respectively).
Hadwiger (2022)	ICM and NICM	2014–19	28.2months (median)	847	2,722	CRT-P treatment was not associated with inferior survival compared with CRT-D.
Farouq (2023)	NICM	2005-2020	51.6months (median)	2334	1693	CRT-D was associated with higher 5-year survival (HR 0.72 95% CI 0.61–0.85, P < 0.001). CRT-P was associated with higher mortality in age groups <60 years and 70–79 years.

Abbreviations: ICM, ischemic cardiomyopathy; NICM, non-ischemic cardiomyopathy; SCD, sudden cardiac death; HF, heart failure; MACE, major adverse cardiac events; aHR, adjusted hazard ratio; CI, confidence interval

Table 3. Meta-analyses on the effect of CRT on mortality.

Meta-analysis (year)	No of studies included	Population (n)	CRT-P (n)	CRT-D (n)	Outcomes
Ischemic and non-ischemic cardiomyopathy					
Veres (2023)	26 observational studies	128.030	55.469	72.561	CRT-D reduced all-cause mortality by 20% over CRT-P (aHR: 0.85; 95% CI: 0.76–0.94; P < 0.01] Not in NICM (HR: 0.95; 95% CI: 0.79–1.15; P = 0.19) Not in patients >75 years (HR: 1.08; 95% CI 0.96–1.21; P = 0.17).
Non-ischemic cardiomyopathy					
Patel (2021)	7 observational studies	9.944	3.079	6.865	CRT-D was not significantly associated with a reduction in all-cause mortality in CRT-eligible patients with NICM (aHR 0.92, 95% CI, 0.83–1.03)
Al Sadawi (2023)	13 observational and 2 RCTs	22.763	9.596	13.167	CRT-D was associated with lower all-cause mortality (log HR − 0.169, SE 0.055; P = 0.002) as compared to CRT-P.
Liu (2023)	9 observational and 2 RCTs	28.768	11.980	16.788	CRT-D was associated with a modest but statistically significant survival benefit compared to CRT-P (aHR 0.90 95% CI, 0.81–0.99)

 doi:10.20944/preprints202508.1754.v1

Neto (2024)	11 observational and 2 RCTs	61.326	7.338	9.108	CRT-D was associated with a significantly lower risk of all-cause mortality compared to CRT-P (pooled HR 0.74; 95% CI: 0.62-0.88; I2=84%). No statistically significant difference in mortality risk for patients > 75 years old (pooled HR 0.96; 95% CI: 0.811-1.15; I^2 = 39%, P<0.001).

Abbreviations: RCTs, randomized clinical trials; ICM, ischemic cardiomyopathy; NICM, non-ischemic cardiomyopathy; aHR, adjusted hazard ratio; CI, confidence interval

5. Our 2-Step Approach

A two-step, multifactorial, electrophysiology (EP)-guided approach was proposed for risk stratification and management of post-myocardial infarction patients [49]. According to current guidelines ICD is suggested in patients with LVEF<35% for primary prevention. However, the PRESERVE EF study revealed a high-risk subpopulation among those with preserved LVEF, who received an ICD following inducible sustained monomorphic ventricular tachycardia during PVS. The authors propose a stepwise approach, involving the assessment of non-invasive risk factors (NIRFs) such as LVEF, late potentials, ventricular premature beats, non-sustained ventricular tachycardia, heart rate variability, T wave alternans, QT prolongation, deceleration capacity and heart rate turbulence [49,50]. The presence of at least one NIRF leads to subsequent programmed ventricular stimulation (PVS), and according to inducibility of sustained monomorphic ventricular tachycardia (SMVT), to ICD implantation. Risk stratification for SCD in NICM is also traditionally based on LVEF, although LVEF as sole criterion cannot accurately identify truly high-risk individuals [51]. The results from the DANISH trial questioned the utility of ICDs in NICM and low LVEF [31], while at the same time a considerable SCD risks exists among those with mildly reduced and preserved LVEF [52,53]. Similar to ICM two-step EP-guided risk stratification approach has been suggested for patients with NICM and preserved ejection fraction, with pending results [54,55]. Unexplained syncope and LGE presence have been added in the risk stratification algorithm of the ReCONSIDER study [54,56]. A recently published comparative analysis of ICD efficacy in patients with ICM and NICM showed clear benefit in ICM whereas no significant reduction in mortality or ventricular arrhythmias was shown in ICM [57]. Thus, patients with a CRT-D indication who are questionable whether they will benefit from a defibrillator lead, such as the elderly, or patients with multiple comorbidities, or patients with NICM, could be subjected to this multifactorial strategy, in order to assess SCD risk, facilitating decision making. Likewise, patients with a pacemaker who become eligible for CRT upgrade could be subjected to non-invasive programmed stimulation (NIPS) via the device in order to assess arrhythmic risk and proceed to CRT-D implantation [58].

Refinement of patient selection criteria is particularly warranted in NICM, where adjunctive tools such as CMR and genetic testing are gaining ground and together with EPS provide valuable guidance for risk stratification and clinical decision-making [59,60]. CMR provides reliable information about biventricular function and myocardial substrate through late gadolinium enhancement (LGE) and advanced tissue mapping techniques. The extent and distribution of myocardial scar, especially in ischemic cardiomyopathy, are closely linked to the risk of ventricular arrhythmias and sudden cardiac death; in such patients, the addition of defibrillator therapy may be justified. In NICM, mid-wall fibrosis detected by LGE or diffuse fibrosis identified by T1 mapping has also been associated with increased arrhythmic risk, potentially favoring CRT-D over CRT-P. A range of CMR parameters have been associated with SCD, including presence and extent of LGE, T1 relaxation times, and myocardial strain [61,62]. For example, 252 patients with NICM and CRT, of whom 68 had LGE, were prospectively followed and what was observed was that CRT-D was associated with significantly higher survival than CRT-P only in patients with LGE. In patients without LGE, with their low arrhythmic risk, CRT-D offered no benefit compared with CRT-P [10].

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Parallel advances in cardiogenetics have improved our understanding of the complex genetic architecture of dilated cardiomyopathy [63]. Identifying a causative gene variant in a patient with DCM improves prognostic accuracy regarding disease progression and may contribute to the indications for device implantation. In specific, variants in genes such as *LMNA, RBM20, PLN,* and *BAG3* are consistently associated with a worse prognosis and are recognized as risk modifiers for the primary prevention of sudden cardiac death [64,65]. Similarly, pathogenic or likely pathogenic variants in *FLNC* or desmosomal genes (e.g., *DSP, DES*) confer an increased susceptibility to ventricular arrhythmias and/or progression to heart failure [66]. Of note, previously published guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death, proposed PVS as a risk factor along with syncope, LGE in CMR and pathogenic mutations in certain genes, in the suggested SCD risk stratification algorithm [67]. Currently, artificial intelligence (AI) is emerging as a complementary tool to imaging and genomics in cardiomyopathies [63,68]. By integrating multimodal data, AI may provide new insight advancing our understanding of cardiomyopathies and potentially refining the choice between CRT-D and CRT-P. Although early in clinical use, AI offers a promising path toward precision medicine.

6. CRT Non-Responders

Non-responders to CRT comprise a rather non negligeable amount of CRT receivers and nonresponse to CRT has been related to right ventricular dysfunction. Approximately 30% of patients fail to exhibit clinical or echocardiographic improvement with CRT [69], partly attributed to the non-physiologic electrical resynchronization between an epicardial wavefront from the CS lead and the RV endocardium, suboptimal lead position, presence of LV scar, and latency due to localized conduction delay [70]. Moreover, in 5-7% of the case CS lead implantation may be unsuccessful, because of anatomic challenges, high pacing thresholds, or phrenic nerve stimulation [71]. Several approaches have been proposed to address this issue, including direct pacing of the conduction system (His bundle or left bundle branch pacing), pacing the left ventricle from multiple sites within the coronary sinus (multipoint pacing), or preferential LV pacing [72–74].

It is noteworthy that biventricular pacing may be complicated by ventricular proarrhythmia in the early post implantation period, a rare but clinically significant phenomenon [75–79]. For example, VT storm occurred in 4% of the 191 patients included in a prospective study examining the incidence of VT storm after CRT-D implantation [77]. Similarly, 5 of 145 consecutive patients (3.4%) receiving a CRT device over a 4-year period experienced ventricular tachyarrhythmia after initiation of biventricular pacing, in a case series study [80]. The causes of the proarrhythmogenicity are multiple. The reversal of the direction of the activation of the LV wall, from the epicardium to the endocardium, results in prolongation of repolarization that may trigger polymorphic VT. Secondarily, pacing close to or within myocardial scar and regions of slow conduction may increase the likelihood of VT. CRT responders though are less likely to experience ventricular proarrhythmia, compared to non-responders [81]. Data suggest a modest effect of biventricular pacing on the incidence of new-onset atrial fibrillation as well [75]. Conduction system pacing through more physiological pacing and more effective resynchronization promotes remodeling providing a less arrhythmogenic substrate compared with biventricular pacing.

7. Role of Conduction System Pacing

Conduction system pacing (CSP)—whether His bundle pacing (HBP) or left bundle branch area pacing (LBBAP)—has emerged as a possible alternative to achieve cardiac resynchronization [72,82–84]. HBP has been associated with higher pacing thresholds, lower implantation success rates, and significant rates of crossover to other pacing modalities [85,86]. Recently, LBBAP has been proposed as viable and effective alternative to HBP, offering higher procedural success and lower pacing thresholds [87,88]. In LEVEL-AT, a single-center, prospective, randomized, parallel, controlled, clinical trial patients allocated to biventricular pacing or CSP (either HBP or LBBP) presented similar

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degrees of cardiac resynchronization, ventricular reverse remodeling, and clinical outcomes [72]. LBBP-CRT demonstrated greater LVEF improvement than BiVP-CRT in heart failure patients with nonischemic cardiomyopathy and LBBB in a prospective randomized trial of 40 patients [82]. Data from an observation retrospective study including 1.778 eligible patients, suggest improved clinical outcomes in those receiving LBBAP compared with BVP [89]. Along this line, findings from a systematic review and meta-analysis including 3141 patients indicate reduced mortality and hospitalizations in LBBAP receivers compared to BVP [90]. Upgrading to LBBP is feasible and effective in CRT non-responders, achieving marked cardiac function improvement and better clinical outcomes, rendering it a reasonable alternative pacing strategy [75]. Table 4 summarizes clinical trials on CSP vs CRT.

Table 4. Clinical Trials on CSP vs CRT.

Trial Name	Year	Study Type	Population	Intervention	Comparator	Key Findings
His-SYNC[83]	2017	RCT	41	HBP	BiV CRT	Similar improvements in LV function; HBP had higher crossover (48%) due to technical limitations.
His-Alternative[84]	2021	RCT	50	HBP or LBBAP	BiV CRT	CSP showed non-inferior clinical response and better electrical resynchronization.
LBBP-RESYNC[82]	2022	RCT	40	LBBAP	BiV CRT	LBBAP showed greater LVEF improvement and QRS narrowing than BiV CRT.
HOT CRT[91]	2023	RCT	160	HBP	BiV CRT	HBP superior to BiVP in LVEF; similar QRS narrowing and symptoms
LEVEL-AT[72]	2023	Prospective, non-randomized	70	LBBAP	CRT cohort	LBBAP showed better LVEF recovery and symptom improvement

 doi:10.20944/preprints202508.1754.v1

						compared to historical BiV CRT.
CONSYST CRT[92]	2025	RCT	134	CSP	BiV CRT	Non inferiority in clinical and echocardiographic response

Abbreviations: RCT, randomized clinical trial; HBP, his bundle pacing; LBBAP, left bundle brunch area pacing; BiV, biventricular; CSP, conduction system pacing; CRT, cardiac resynchronization, LVEF, left ventricular ejection fraction; LV, left ventricular

8. Conclusion

Due to lack of robust clinical evidence, the choice between CRT-D and CRT-P should be based on shared decision making and individualized risk assessment. The two step EP-guided approach could serve as a risk stratification tool. Factors that should be taken into account are age, the etiology of heart failure, life expectancy, major comorbidities, poor renal function, and of course, patient preference. Conduction system pacing is an emerging pacing modality as an alternative to CRT. Further studies are needed to identify subpopulations of patients with indications for CRT who will benefit the most from CRT-D implantation, justifying device related risks as compared to CRT-P alone.

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Abbreviations

The following abbreviations are used in this manuscript:

CRT	Cardiac Resynchronization Therapy
RCTs	Randomized clinical trials
LVEF	Left ventricular ejection fraction
LBBB	Left bundle branch block
AF	Atrial fibrillation
RV	Right ventricular
OGMT	Optimal guideline-directed medical therapy
PVS	Programmed ventricular stimulation
NIRFs	Non-invasive risk factors
NIPS	Non-invasive programmed stimulation
EP	Electrophysiology
SCD	Sudden cardiac death
SMVT	Sustained monomorphic ventricular tachycardia
CSP	Conduction system pacing
HBP	His bundle pacing
LBBAP	Left bundle branch area pacing
CMR	Cardiac magnetic resonance
NICM	Non ischemic cardiomyopathy
ICM	Ischemic cardiomyopathy

 doi:10.20944/preprints202508.1754.v1

LGE	Late gadolinium enhancement
DCM	Dilated cardiomyopathy

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