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Cardiac resynchronization therapy in heart failure patients: An update

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Abstract

Heart failure continues to be a major public health problem with high morbidity and mortality rates, despite the advances in medical treatment. Advanced heart failure patients have severe persistent symptoms and a poor quality of life. Cardiac resynchronization therapy (CRT), an invasive therapy which involves synchronized pacing of both right and left ventricles, improves ventricular conduction delay and left ventricular performance. Several clinical trials of CRT in medically refractory heart failure patients with wide QRS (> 120 ms), left ventricular ejection fraction ≤ 35% and New York Heart Association (NYHA) class III and IV have shown improved quality of life, NYHA class, left ventricular ejection fraction and reduced mortality. About 30% of heart failure patients who receive CRT do not respond to treatment. Mechanical dyssynchrony may play a role in identifying patients who may respond better to CRT treatment. However, recent large scale clinical trials PROSPECT and RethinQ have challenged this concept. The role of CRT in heart failure patients with narrow QRS (< 120 ms), NYHA class I and II, atrioventricular nodal ablation in patients with atrial fibrillation and triple site pacing are evolving. Our review discusses the current evidence, indications, upcoming trials and future directions. (Cardiol J 2009; 16, 3: 197–209)

Key words: cardiac resynchronization therapy, heart failure, review

Introduction

Despite advances in medical management, heart failure continues to be a significant health problem in the United States. With a high incidence of 550,000/year and a prevalence of 5 million, heart failure causes about 287,000 deaths in the US each year [1, 2]. Hospitalizations due to heart failure are increasing [1, 3, 4] and this is especially true for the aging population [3, 5]. In 2006 the estimated direct cost for heart failure in the US was $29.6 billion dollars [1, 2].

Mortality in patients with heart failure is mostly due to progressive heart failure or sudden death related to arrhythmias [6, 7]. Even though medications such as beta-blockers, angiotensin converting enzyme inhibitors and angiotensin receptor blockers have been shown to decrease morbidity and mortality [8–13], the prognosis in these patients remains poor [14, 15]. A significant number of heart failure patients have electromechanical dyssynchrony which increases their mortality [16]. The commonly described types of electromechanical dyssynchrony are atrioventricular delay, intraventricular delay, interventricular delay and intramural delay [17].

Cardiac resynchronization therapy (CRT) is a recent advance in managing heart failure patients with New York Heart Association (NYHA) class III and IV symptoms despite optimal medical management.

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Conceptual and mechanistic principles

Several studies have shown significant improvements in cardiac function in heart failure patients when treated with CRT [18–25]. CRT involves synchronized stimulation of both right and left ventricles so that they contract simultaneously, thereby correcting interventricular conduction delay and improving left ventricular (LV) contractility [14, 17].

Cardiac resynchronization therapy involves placing an LV lead via the coronary sinus to achieve LV pacing [14]. This is commonly done using a transvenous approach, which involves initial cannulation of the coronary sinus using a specially designed sheath. Once cannulation of the coronary sinus is achieved, retrograde venography is performed to identify the coronary sinus anatomy. A left ventricular lead is then positioned in one of the side branches such as marginal, posterior or posterolateral vein and adjusted to achieve adequate pacing, stability and freedom from phrenic nerve or diaphragmatic stimulation [14].

Cardiac resynchronization therapy decreases the atrioventricular mechanical asynchrony by optimizing the atrioventricular interval and thereby decreases the late diastolic ventriculoatrial gradient [17, 26]. Another significant benefit of pacing from the LV lateral wall is early activation of LV papillary muscles which decreases the severity of mitral regurgitation [27]. A combination of these functions optimizes LV loading, improves myocardial contractility and even has a modest effect in improving diastolic dysfunction [28].

Role of cardiac resynhronization therapy in heart failure patients with wide QRS

Clinical studies with cardiac resynchronization therapy and implantable pacemaker

Early clinical studies have shown that biventricular pacing in heart failure patients with wide QRS (> 120 ms) improves LV hemodynamics [29––31], prompting subsequent randomized clinical trials. In patients with wide QRS, CRT using biventricular pacing has been shown to facilitate reverse modeling of the left ventricle leading to increased LV ejection fraction (LVEF), reduced mitral regurgitation and reduced heart size [6].

The baseline characteristics and primary outcomes of major trials comparing the role of CRT to optimal medical management are shown in Tables 1 and 2 respectively. One of the earliest randomized clinical trials was MUSTIC (Multisite Stimulation

Table 1. Characteristics of trials in heart failure patients with wide QRS.

Baseline characteristics	CARE HF [24]		COMPANION [23]		MIRACLE [20, 32]		MUSTIC [18]		MUSTIC AF [19]	
	Medical Rx	CRT	Medical Rx	CRT	Medical Rx	CRT	First study group	Second study group	UniRV––BiV	BiV––UniRV
Randomization	Yes		Yes		Yes		Yes		Yes	
Follow up	24.9 months		12 months		6 months		6 months		6 months	
Number	404	409	308	617	225	228	29	29	18	25
Mean QRS	160*	160*	158*	160*	165 ± 20	167 ± 21	172 ± 22	175 ± 19	209 ± 18	209 ± 21
Age	66*	67*	68*	67*	64 ± 11	64 ± 10.7	64 ± 11	64 ± 8	66 ± 9	65 ± 9
Men (%)	73	74	69	67	68	68	65.5	82.7	77	84
Ischemic (%)	40	36	59	54	58	50	37.3	37.3	143	13
NYHA III (%)	93	94	82	87	91	90	100	100	100	100
QoL	NA	NA	39	40	59 ± 21	59 ± 20	48 ± 19	46 ± 25	50 ± 20	40 ± 23
6 MWD	NA	NA	244*	274*	291 ± 101	305 ± 85	354 ± 110	346 ± 111	317 ± 71	338 ± 95
LVEF	25*	25*	22*	20*	21.6 ± 6.2	21.8 ± 6.3	23 ± 7	23 ± 7	30 ± 12	23 ± 7
Diuretics (%)	44	43	94	94	93	94	94	94	100	100
ACEI or ARB (%)	95	95	89	89	90	93	96	96	100	100
Beta-blockers (%)	74	70	66	68	55	62	28	28	23	23
Spirinolactone (%)	59	54	53	53	NA	NA	22	22	16	16
Digoxin (%)	45	40	NA	NA	79	78	48	48	58	58

*Continuous measures reported as median values, NA — not available, CRT — cardiac resynchronization therapy, NYHA — New York Heart Association, QoL — quality of life, LVEF — left ventricular ejection fraction, Rx — treatment, 6 MWD — six minute walk distance, ACEI — angiotensin-converting enzyme inhibitor, ARB — angiotensin II receptor blockers, BiV–UniRV — pacemaker was programmed biventricular (BiV) during first 3 months then right ventricular (UniRV) during the second cross over period, first study group — pacemaker was programmed to be active first then inactive, second study group — vice versa

Table 2. Primary outcomes after cardiac resynchronization therapy at follow up in heart failure patients with wide QRS (3 to 6 months).

	CARE HF [24]		COMPANION [23]		MIRACLE [20, 32]		MUSTIC [18]		MUSTIC AF [19]	
	Medical Rx	CRT	Medical Rx	CRT	Medical Rx	CRT	First study group	Second study group	UniRV–BiV	BiV–UniRV
NYHA	2.7 ± 0.9	2.1 ± 1.0	38[§]	61[§]	32%[¶]	52%[¶]	NA	NA	NA	NA
QoL	40 ± 22	31 ± 22	–12 ± 23[#]	–25 ± 26[#]	–9*	–18*	33.3 ± 22	25.7 ± 24	38.5 ± 21.4	34.1 ± 20.6
Improvement 6 MWD	NA	NA	9 ± 84	33 ± 99	+10*	+39*	384 ± 78.9	412.9 ± 116	341 ± 100	359 ± 121
All cause mortality	120	82	77	131	16	12	0	1[$]	0	1
Sudden death	38	29	18	48	7	5	0	1[$]	0	1
Progressive HF	56	33	34	53	10	4	0	0	0	0
HF hospitalizations	133	72	NA	NA	34	18	9[‡]	3[$]	2	1

#mean change, *median change, [¶]percent improved by one or more class, [§]percent improved in NYHA class symptoms, [$]active pacing group, [‡]inactive pacing group, Rx — treatment, QoL — quality of life, 6 MWT — six minute walk distance, HF — heart failure, NA — not available, CRT — cardiac resynchronization therapy, BiV–UniRV — pacemaker was programmed biventricular (BiV) during first 3 months then right ventricular (UniRV) during the second cross over period, first study group — pacemaker was programmed to be active first then inactive, second study group — vice versa

in Cardiomyopathies) [18, 19]. Cazeau et al. [18] studied the role of CRT in 67 patients in sinus rhythm with NYHA class III, LVEF ≤ 35%, and mean QRS > 150 ms. This was a single-blind, randomized controlled cross-over study design. The study involved a three month period of active atriobiventricular pacing and a three month period of inactive pacing (ventricular inhibited pacing at a basic rate of 40 bpm). A significant improvement in quality of life (QoL) score, and distance walked in six minutes (6 MWD) were noted (Table 2).

Leclercq et al. [19] studied 59 patients with NYHA class III with LV systolic dysfunction, and wide QRS. These patients were in atrial fibrillation. This was a single-blind, randomized cross-over study design with two three month periods of right univentricular vs. biventricular pacing. As compared with univentricular pacing, effective biventricular pacing improved peak oxygen uptake by 13% and 6 MWD by 9.3% (Table 2).

Abraham et al. [20, 32] published the results of the MIRACLE study (Multicenter InSync Randomized Clinical Evaluation) which included 453 patients with moderate to severe heart failure symptoms (NYHA III–IV), LVEF ≤ 35% and QRS duration of ≤ 130 ms. Patients were randomized to a CRT group or a control group for six months, while continuing conventional medical therapy. Significant improvement in 6 MWD, NYHA class, LVEF and QoL scores were observed (Table 2). Moreover, hospitalizations for worsening heart failure were reduced. Subsequent publications documented improvements in echocardiographic volumes and ejection fraction.

Clinical studies with cardiac resynchronization therapy and implantable cardioverter defibrillator

The CONTAK CD study [21] examined the safety and effectiveness of CRT when combined with an implantable cardioverter defibrillator (ICD). Higgins et al. [21] studied 490 patients with NYHA II–IV, LVEF ≤ 35%, QRS ≥ 120 ms and with an existing indication for ICD. Patients were implanted with a device capable of providing CRT and ICD therapy and were then randomized to CRT or no CRT. Patients were followed for up to six months. The primary end point was progression of heart failure, defined as all-cause mortality, hospitalization for heart failure, and ventricular tachycardia/ /ventricular fibrillation requiring intervention. A 15% (statistically non-significant) reduction in heart failure progression was observed. However, CRT improved peak oxygen consumption, 6 MWD and LV dimensions and function.

The MIRACLE ICD trial [22] examined the efficacy and safety of combined CRT and ICD therapy in heart failure patients with NYHA class III or IV despite optimal medical management and who had LVEF ≤ 35% and QRS ≥ 130 ms. Three hundred and sixty nine patients received a device with combined capability of CRT and ICD and in

the control group the CRT was off. At the six month follow up, patients in the CRT group achieved significant improvement in their QoL score, peak oxygen consumption and functional capacity. However, there was no significant improvement in 6 MWD, heart failure hospitalization and LV size or function.

Major clinical trials with morbidity and mortality as primary endpoints

Two major subsequent trials assessed morbidity and mortality benefits, while the previously mentioned studies looked at improvements in symptoms and LV performance measures. The COMPANION trial [23] (Comparison of Medical Therapy, Pacing and defibrillation in Heart Failure) randomized 1,520 patients with NYHA class III or IV, QRS ≥ 120 ms in a 1:2:2 ratio to receive optimal medical therapy alone or in combination with either CRT with a pacemaker or CRT with a pacemaker-defibrillator. The primary composite end point was the time to death from, or hospitalization for, any cause. When compared to optimal medical therapy alone, CRT with pacemaker decreased the risk of primary end point by 19% (hazard ratio, 0.81; $p = 0.014$), and CRT with a pacemaker-defibrillator decreased the risk of primary end point by 20% (hazard ratio, 0.80; $p = 0.01$). However there was only a nonsignificant decrease in secondary end point of all cause mortality in the CRT pacemaker group while there was a significant reduction in all cause mortality in the CRT pacemaker-defibrillator group (Table 2, Fig. 1).

The CARE-HF study (Cardiac Resynchronization in Heart Failure) [24] included 813 patients with NYHA III or IV heart failure, LVEF ≤ 35%, a LV end-diastolic dimension of at least 55 mm and QRS duration of at least 120 ms on the electrocardiogram. The primary end point was time to death from any cause, or unplanned hospitalization from a major cardiovascular event. Significant differences were noted in the primary end point between the CRT group vs. the medical therapy group (39% *vs*. 55%) (Table 2, Fig. 2).

Cardiac resynchronization therapy and mortality benefit

Four meta-analyses have studied the mortality benefits of CRT in heart failure patients. CRT in heart failure patients with wide QRS has been shown to decrease mortality from progressive heart failure [33, 34] and also decrease all cause mortality [34–36].

From the above clinical trials and meta-analysis, it is clear that CRT reduces heart failure symptoms, and furthermore decreases mortality in medically refractory heart failure patients with prolonged QRS and low ejection fraction.

Current indications

For the ranking of level of evidence and classes of recommendations by ACC/AHA/HRS guidelines [37] writing committee, please see Appendices I and II.

The most recent ACC/AHA/HRS guidelines [37] published in 2008 gives a class I indication for treatment with CRT (with or without an ICD) in patients who have LVEF ≤ 35%, a QRS duration ≥ 120 ms, and sinus rhythm, for the treatment of NYHA functional class III or ambulatory class IV heart failure symptoms with optimal recommended medical therapy (Level of evidence A).

Class IIa recommendations include:

— (a) treatment with CRT with or without an ICD is considered reasonable in patients who have LVEF ≤ 35%, a QRS duration ≥ 120 ms, and atrial fibrillation, for the treatment of NYHA functional class III or ambulatory class IV heart failure symptoms on optimal recommended medical therapy (Level of evidence B);

— (b) treatment with CRT is considered reasonable in patients with LVEF ≤ 35% with NYHA functional class III or ambulatory class IV symptoms who are receiving optimal recommended medical therapy and who have frequent dependence on ventricular pacing (Level of evidence C).

Class IIb recommendations were given for treatment with CRT in patients with LVEF ≤ 35% with NYHA functional class I or II symptoms who are receiving optimal recommended medical therapy and who are undergoing implantation of a permanent pacemaker and/or ICD with anticipated frequent ventricular pacing (Level of evidence C).

Class III recommendations include:

— (a) treatment with CRT is not indicated for asymptomatic patients with reduced LVEF in the absence of other indications for pacing (Level of evidence B);

— (b) treatment with CRT is not indicated for patients whose functional status and life expectancy are limited predominantly by chronic non-cardiac conditions (Level of evidence C).

Non-response to cardiac resynchronization therapy in wide QRS heart failure patients

Despite the established role of CRT in heart failure patients with a wide QRS, there is a high

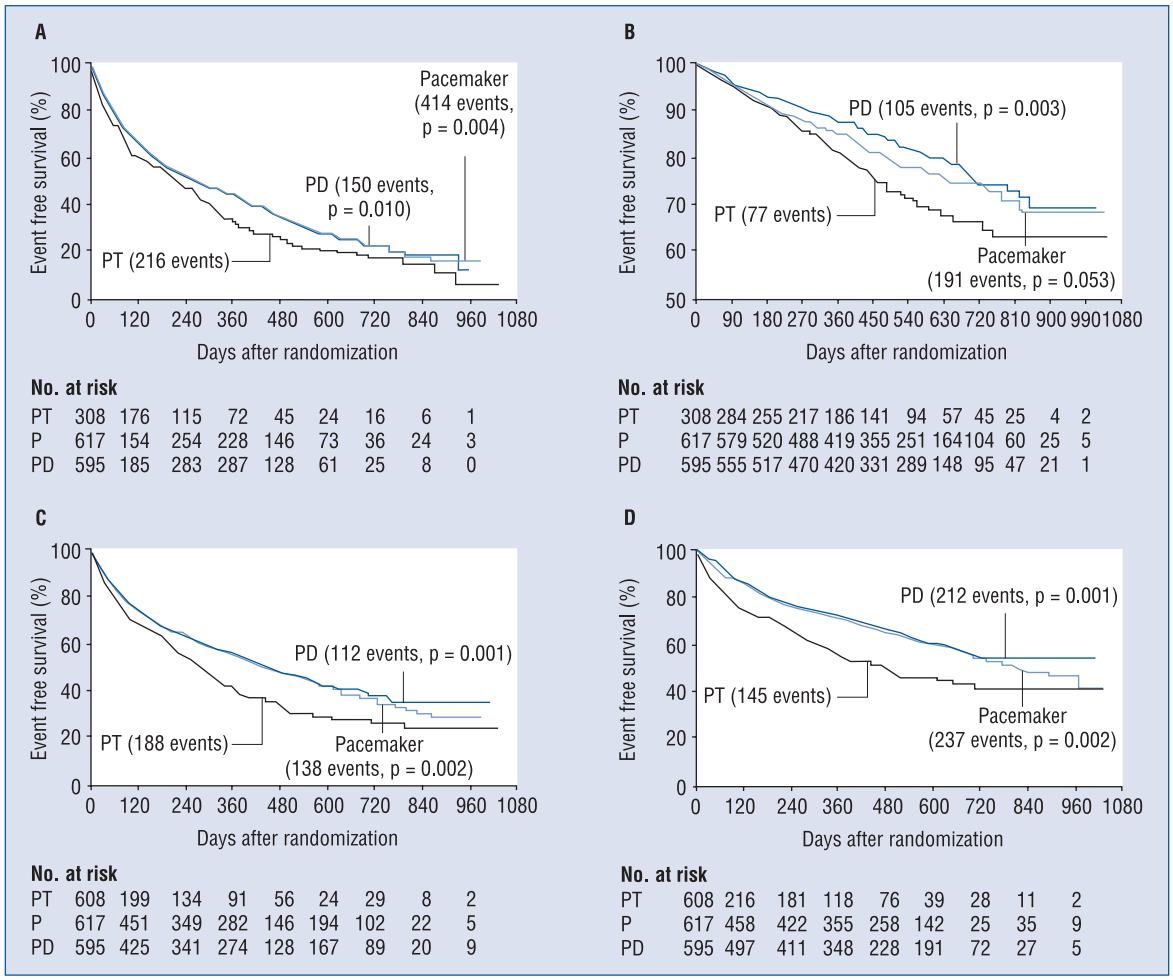

Figure 1. Kaplan-Meier estimates from COMPANION trial [23]. **A.** The differences in the primary end point — 12-month rates of death from or hospitalization for any cause (68% in the pharmacologic-therapy group *vs*. 56% in the group that received a pacemaker as part of cardiac-resynchronization therapy, *vs*. 56% in the group that received a pacemaker-defibrillator as part of cardiac-resynchronization therapy); **B.** The differences in secondary end point — the 12-month rates of death from any cause (19% in the pharmacologic-therapy group, 15% in the pacemaker group, and 12% in the pacemaker-defibrillator group); **C.** The differences in 12-month rates of death from or hospitalization for cardiovascular causes (60% in the pharmacologic-therapy group *vs*. 45% in the pacemaker group *vs*. 44% in the pacemaker-defibrillator group); **D.** The difference in the 12-month rates of death from or hospitalization for heart failure (45% in the pharmacologic-therapy group *vs*. 31% in the pacemaker group *vs*. 29% in the pacemaker--defibrillator group). P values are for the comparison with optimal pharmacologic therapy. Reproduced with permission from the publishing division of Massachusetts Medical Society (MMS Reference Number: PS-2009-0630); PT — pharmacologic therapy; P — pacemaker; PD — pacemaker defibrillator.

rate of non-response to CRT in these patients [38]. Baseline QRS duration alone has been found to be a poor predictor of clinical and echocardiographic responses to CRT [39]. Clinically, it is often difficult to predict who will respond to CRT. Therefore, there is a need to explore other possible factors that might play a role to provide a higher response rate to CRT. LV dyssynchrony is one such factor recently shown to predict prognosis in patients with CRT [40–42]. The incidence of LV dyssynchrony in heart failure patients varies between 27% and 56% [43]. On the other hand, reported predictors of non-response to CRT include ischemic heart disease, severe mitral regurgitation, LV end-diastolic diameter ≥ 75 mm, pre-implantation apical wall motion abnormality and posterolateral ventricular scar [44, 45].

Next, we describe the role of CRT in narrow QRS heart failure patients, upcoming clinical trials and future directions.

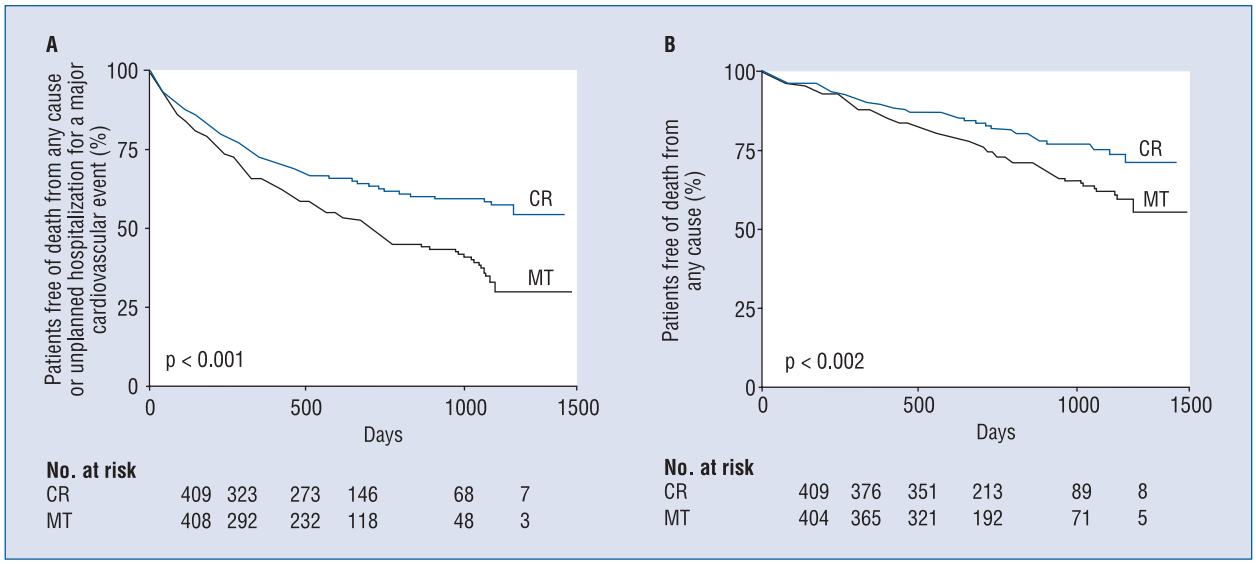

Figure 2. Kaplan-Meier Estimates from CARE-HF study [24]. **A.** The differences in the primary outcome — death from any cause or an unplanned hospitalization for a major cardiovascular event; **B.** The differences in secondary outcome — death from any cause. Reproduced with permission from the publishing division of Massachusetts Medical Society (MMS Reference Number: PS-2009-0684); CR — cardiac resynchronization; MT — medical therapy.

Role of cardiac resynchronization therapy in narrow QRS heart failure patients

In addition to the benefit of CRT in patients with wide QRS, recent studies have looked at the benefit of CRT in patients with narrow QRS duration (≤ 120 ms) [46–53]. CRT has been shown to improve hemodynamics in heart failure patients with narrow QRS [53]. High prevalence of LV asynchrony has been noted in heart failure patients despite a narrow QRS complex [40].

The baseline characteristics and primary outcomes of trials in narrow QRS complex heart failure patients are shown in Tables 3 and 4 respectively. Achilli et al. [46] studied the role of CRT in 52 patients with refractory heart failure. Patients were eligible if there was echocardiographic evidence of interventricular and intraventricular asynchrony regardless of the QRS duration. The patient population was divided into two groups: one with QRS duration ≤ 120 ms and the other with > 120 ms. Significant improvement in NYHA functional class, LVEF, left ventricular end diastolic and systolic diameter and mitral regurgitation area was observed in a similar magnitude in both groups (Tables 3, 4).

Another study from the Netherlands by Bleeker et al. [47] looked at 33 consecutive narrow QRS complex (QRS duration ≤ 120 ms) heart failure patients and compared the benefits of CRT to 33 consecutive heart failure patients having a wide QRS > 120 ms. All patients had inclusion criteria of LV dyssynchrony ≥ 65 ms on tissue doppler imaging (TDI), NYHA class III or IV and LVEF ≤ 35%. Significant improvement in clinical symptoms and LV reverse modeling was observed in the narrow QRS group and was comparable to the benefits in wide QRS heart failure patients (Tables 3, 4).

Yu et al. [48] studied the role of CRT in 51 wide QRS patients and 51 narrow QRS patients who had NYHA class III or IV symptoms and baseline systolic asynchrony. At three month follow up, there was significant reduction of LV end-systolic volume in both groups. Improvement in NYHA class, maximal exercise capacity, 6 MWD and LVEF were observed in both groups (Tables 3, 4).

A larger study of 376 heart failure patients who were not pre-selected by baseline mechanical dyssynchrony was done by Gasparini et al. [49]. Similar benefits of improvement in 6 MWD, NYHA class, LV end-systolic volume were seen in both narrow QRS complex and wide QRS heart failure patients with CRT. The long term death rate was lower in the narrow QRS group compared to the wide QRS group. This probably reflected the underlying pre-existing mortality risks between the two groups. An important finding of this study is that the improvement in LV function persisted for a long duration follow up (three years).

A systematic review of the role of CRT in narrow QRS (< 120 ms) heart failure patients by our

Table 3. Characteristics of trials in heart failure patients with narrow QRS.

Baseline characteristics	Bleekar et al. [47]		Yu et al. [48]		Achilli et al. [46]		Gasparini et al. [49]	
	< 120 ms	> 120 ms	< 120 ms	> 120 ms	< 120 ms	> 120 ms	< 120 ms*	> 120 ms
Randomization	No (consecutive)		No		No		No	
Baseline LVD + normal QRS	Yes		Yes		Yes		No	
Mortality data	NA		NA		Yes		Yes	
Follow up	6 months		3 months		6 months		28 months	
Number	33	33	51	51	14	38	45	331
Mean QRS	110 ± 8	175 ± 22	103 ± 13	163 ± 24	NA	NA	109 ± 8	174 ± 26
Age	63 ± 11	67 ± 9	63 ± 11	66 ± 12	68.3 ± 8	70.1 ± 9	67.8 ± 9.1	66.3 ± 9.5
Male (%)	85	76	78.4	72.5	71	55	84.4	78.8
Female (%)	15	24	21.5	27.4	NA	NA	NA	NA
Ischemic (%)	70	64	49	43.1	29	45	60	46
NYHA III	29 (88%)	29 (88%)	2.84 ± 0.46	3.24 ± 0.4	3.4 ± 0.5	3.6 ± 0.4	5 (11%)*	43 (13.8%)*
QoL	39 ± 18	42 ± 15	28 ± 14	37 ± 25	NA	NA	36 ± 11	46 ± 14
6 MWD	274 ± 133	253 ± 124	333 ± 96	298 ± 99	276.4 ± 88.9	256 ± 65.4	308 ±114	316± 115
LVEF (%)	22 ± 6	21 ± 6	27.8 ± 7	25.2 ± 9.2	24.6 ± 5.0	22.6 ± 4.6	29.4± 4.3	28.9± 6.3
LVEDV[1] (cc)/ /LVEDD[2] [mm]	216 ± 78[1]	238 ± 72[1]	167 ± 47[1]	194 ± 82[1]	71.8 ± 9.22[2]	77.4 ± 10.62[2]	NA	NA
LVESV[1] (cc)/ /LVESD[2] [mm]	174 ± 75[1]	189 ± 60[1]	122 ± 42[1]	148 ± 74[1]	61.4 ± 8.42[2]	64.8 ± 10.22[2]	127.4 ± 29	144 ± 56
LVD	102 ± 32	113 ± 30	35.9 ± 14.0	38.3 ± 12.7	NA	NA	NA	NA
Diuretics (%)	82	91	96	98	100	100	91.1	86.1
ACEI (%)	88	85	92	94	90	92	84.4	87.5
Beta-blockers (%)	76	79	67	71	60	64	84.4	78.8

QoL — quality of life, 6 MWD — six minute walk distance, LVD — left ventricular dyssynchrony, LVEF — left ventricular ejection fraction, LVEDV — left ventricular end-diastolic volume, LVEDD — left ventricular end-diastolic diameter, LVESV — left ventricular end-systolic volume, LVESD — left ventricular end-systolic diameter, HF — heart failure, NYHA — New York Heart Association, ACEI — angiotensin-converting enzyme inhibitor

group done before the results of RethinQ were published showed significant improvement in LVEF, NYHA class and 6 MWD [54]. However, the studies in this meta-analysis were pre and post CRT studies without a medically managed control group. Therefore the results need to be validated by large scale clinical trials.

Recent clinical trials and ongoing studies of cardiac resynchronization therapy in narrow QRS heart failure patients

While all the studies mentioned above were non-randomized studies without a placebo controlled arm, ReThinQ [55] study (Cardiac Resynchronization Therapy in Patients with Heart Failure and Narrow QRS) was the first randomized controlled study. Patients who had a standard indication for ICD (ischemic or non-ischemic cardiomyopathy with LVEF ≤ 35%), NYHA class III symptoms, a QRS duration of ≤ 130 ms and who had evidence of mechanical dyssynchrony measured on echocardiography, were included in the study. The primary end point was increase in peak oxygen consumption during cardiopulmonary exercise testing at six month follow up. The study showed that CRT in heart failure patients with narrow QRS complex did not improve peak oxygen consumption, Minnesota Living With Heart Failure (MLWHF) score, 6 MWD and LV volume or EF at six months.

Another protocol for a large scale multi-center prospective randomized EchoCRT (Echocardiography guided Cardiac Resynchronization Therapy) [55] trial in heart failure patients with narrow QRS complex patients was announced by the University of Zurich in 2007 [56]. This trial is designed to evaluate the role of CRT in heart failure patients with narrow QRS duration and who show mechanical dyssynchrony as assessed by echocardiography. More than 1,000 patients will be randomized to receive CRT or no CRT with ICD. The primary end point is reduction of combined endpoint of all cause mortality or hospitalization for cardiovascular events.

From Gasparini's trial [49] we know that the CRT benefits in heart failure patients with narrow

Table 4. Primary outcomes after cardiac resynchronization therapy at follow up in heart failure patients with narrow QRS.

	Bleeker et al. [47]		Yu et al. [48]		Achilli et al. [46]		Gasparini et al. [49]	
	< 120 ms	> 120 ms	< 120 ms	> 120 ms	< 120 ms	> 120 ms	< 120 ms	> 120 ms
Reduction in NYHA	0.9 ± 0.6	1.1 ± 0.6	0.73 ± 0.49	0.81 ± 0.68	1.6 ± 0.1	1.7	NA	NA
Reduction in QoL	13 ± 16	17 ± 12	8 ± 19	18 ± 20	NA	NA	NA	NA
Improvement 6 MWD	89 ± 107	130 ± 95	46 ± 88	53 ± 61	93.5 ± 18.7	138.2 ± 27	182	128
Improvement in LVEF (%)	8 ± 8	9 ± 7	7.3 ± 6.3	8.3 ± 7.6	9 ± 0.9	10.6 ± 0.8	14	9
Reduction in LVEDV[1] (cc)/ /LVEDD[2] [mm]	26 ± 32[1]	35 ± 51[1]	8.6 ± 14[1]	16.1 ± 17.6[1]	65.6 ± 8.52[2]	71.6 ± 10.72[2]	NA	NA
Reduction in LVESV[1] (cc)/ /LVESD[2] [mm]	39 ± 34[1]	44 ± 46[1]	17.1 ± 18.6[1]	24.2 ± 21[1]	55.6 ± 8.22[2]	57.9 ± 112[2]	71.8	55.3
All cause mortality	9	14	NA	NA	3	7	3	51
Sudden death	0	2	NA	NA	1	4	1	5
Progressive HF	8	11	NA	NA	2	2	0	35

*Differences between baseline and 12 months, QoL — quality of life, 6 MWT — six minute walk distance, LVEF — left ventricular ejection fraction, LVEDV — left ventricular end-diastolic volume, LVEDD — left ventricular end-diastolic diameter, LVESV — left ventricular end-systolic volume, LVESD — left ventricular end-systolic diameter, HF — heart failure

QRS duration may not become evident without a longer duration of follow up. The results of Echo-CRT trial [56] and perhaps results from ReThinQ [55] after a longer duration of follow up (if conducted) would help us understand the role of CRT in narrow QRS heart failure patients.

Lack of consensus regarding quantification and role of mechanical dyssynchrony

Potential differences in the results between the ReThinQ study and prior narrow QRS complex studies could be the method of measurement of mechanical dyssynchrony. Beshai et al. [55] used the opposite wall delay method to measure mechanical dyssynchrony by using both TDI and M-mode echocardiography. TDI was used to measure the mechanical delay in the septal-to-lateral and anteroseptal-to-posterior walls and M-mode echocardiography measured the mechanical delay in the septal-to-posterior wall (obtained by M-mode in the parasternal long-axis view) [55]. Yu et al. [48] used a dyssynchrony index to measure mechanical dyssynchrony by calculating the standard deviation of time to peak velocity in ejection phase of 12 LV segments.

LV dyssynchrony was defined as the maximum delay between peak systolic velocities among the four walls within the left ventricle using TDI by Bleeker et al. [47]. Evaluation of asynchrony by Achilli et al. [46] involved both intraventricular and interventricular asynchrony. Interventricular asynchrony was defined as interventricular delay > 20 ms, whereas intraventricular asynchrony was identified when Q-LW > Q-E (Q-LW represents the posterolateral LV wall activation delay and Q-E represents the QRS onset-beginning of transmitral filling interval) and Q-LW > 9.9 corrected units (c.u. = = measured interval in ms/√ R-R interval) [46].

The Predictors Of Response to CRT (PROSPECT) [57] study tested the performance of 12 echocardiographic parameters in 498 patients with standard CRT indications. M-mode, pulsed Doppler mode and TDI echocardiographic methods were used. There was a high level of quality control, all 53 centers having undergone training on image acquisition and assessment with oversight and monitoring by a blinded core laboratory. The sensitivity and specificity of 12 echocardiographic parameters to predict clinical composite score (combined score for improvement in all-cause mortality, heart failure hospitalization, NYHA class, and patient global assessment) varied widely, with sensitivity ranging from 6% to 74% and specificity ranging from 35% to 91%. The ability for predicting LV end-systolic volume response also varied widely, with sensitivity ranging from 9% to 77% and

specificity from 31% to 93%. The study could not settle upon any single echocardiographic measure of dyssynchrony which would predict a better response to CRT. However, several small single center studies using TDI have shown that mechanical dyssynchrony may play a significant role in predicting response to CRT [58–60].

The most significant challenge with regard to measuring mechanical dyssynchrony is the lack of consensus in favor of a single methodology. Apart from the differences in the parameters used, the differences in technical and interpretive challenges make it even more difficult. Abraham et al. [60], in their review, highlighted the importance of continuing to study the role of mechanical dyssynchrony in patients undergoing CRT. Since there is significant room for improvement in TDI and strain imaging techniques, and therefore in the evaluation of their role in predicting response to CRT, it may be imprecise to conclude that CRT is not effective in patients with narrow QRS heart failure and that there is no significant role in echocardiographic measurement of mechanical dyssynchrony [60]. As outlined by Abraham et al. [60], perhaps a multifactor dyssynchrony score which would factor in clinical factors, QRS duration and multiple imaging parameters might predict response to CRT.

Upcoming clinical trials and future directions

Role of cardiac resynchronization therapy in NYHA class I or II heart failure patients

Most clinical trials [18–20, 23, 24], studied the role of CRT in heart failure patients with NYHA class III or IV. An observational registry analysis from InSync/InSync ICD [61] compared the effects of CRT in patients in NYHA class II with those in class III or IV. CRT in heart failure patients with NYHA class II showed similar improvements in LV end-systolic and end-diastolic diameter, a similar improvement in ejection fraction but no significant improvement in NYHA class when compared to heart failure patients with class III or IV.

Two large scale randomized clinical trials are assessing the role of CRT in heart failure patients with less severe NYHA classes. MADIT CRT [62] is designed to evaluate whether cardiac resynchronization therapy with defibrillator (CRT-D) will reduce the risk of mortality and heart failure events in subjects with ischemic (NYHA class I–II) and non-ischemic (NYHA class II) cardiomyopathy, LV dysfunction (EF ≤ 30%), and prolonged intraventricular conduction (QRS duration ≥ 130 ms). The Resynchronization Reverses Remodeling in Systolic LV Dysfunction (REVERSE) [63] study is an ongoing randomized controlled trial assessing the safety and efficacy of CRT in heart failure patients in NYHA class II (82.3%) or asymptomatic (NYHA class I) LV dysfunction with previous symptoms (17.7%). The preliminary results from REVERSE [63] presented at ACC 08 showed that CRT in asymptomatic and mildly symptomatic heart failure patients on optimal medical therapy reverses LV remodeling. However, there was no statistically significant difference in primary end point of all-cause mortality [64].

Epicardial versus transvenous left ventricular lead placement

CRT requires placement of right and LV leads to have synchronous ventricular contraction which augments LV output. The postero-lateral wall of the left ventricle appears to be a preferred area of LV lead placement [65, 66]. Currently, there are two approaches to place the LV lead in the postero--lateral wall [66]. One is to place the LV lead by catheter based access via coronary sinus and coronary venous tree. The other approach is to do open surgical access via a left lateral mini-thoracotomy.

Catheter based transvenous implantation is the much more commonly adopted method. However, the success rate of LV lead placement through transvenous implantation depends upon operator skill and experience, difficult coronary venous anatomy and myocardial scar formation. These difficulties can easily prolong the procedure time and fluoroscopy time, and increase the required amount of potentially nephrotoxic contrast dye. Open surgical epicardial LV lead placement is an alternative method, and one which is attractive especially following the development of minimally invasive techniques [66, 67].

Doll et al. [66] randomized 80 consecutive patients with standard indications for CRT to receive transvenous or epicardial LV lead placement. The transvenous group had a shorter Intensive Care Unit stay, and shorter ventilation time but had prolonged exposure time to radiation and contrast medium. At six months follow up no significant differences in LV lead pacing, sensing and impedance were noted. Similar benefits have been shown for surgical epicardial placement method in other studies [68, 69]. With this limited data, the surgical approach for LV lead placement appears to be an alternative method in patients with difficult transvenous implantation conditions. More data is needed to assess its long term safety and efficacy.

Benefits of cardiac resynchronization therapy in atrial fibrillation patients and role of atrioventricular junction ablation

Most clinical studies have evaluated only the short term benefits of CRT in heart failure patients with atrial fibrillation (AF) [70–72]. The role of CRT in heart failure patients with AF is still evolving and the ACC/AHA/HRS guideline [37] committee had given a class IIa recommendation for treatment of heart failure patients in AF with CRT. In the MUSTIC trial [71] the ejection fraction improved by 4% in patients with AF compared to a 5% increase in patients with sinus rhythm at 12 months follow up. Mitral regurgitation decreased by 50% in patients with AF compared to 45% in patients with sinus rhythm [71].

Molhoek et al. [72] studied the role of CRT in 30 patients who had a underlying rhythm of AF with baseline NYHA class III or IV symptoms, LVEF < 35% and QRS > 120 ms and a left bundle branch block and compared them to 30 patients in sinus rhythm with similar baseline parameters. Significant improvement was observed in both groups in NYHA class symptoms, Minnesota QoL score and 6 MWD. However the number of non--responders was higher in the patients with AF. Another recent study showed a similar observation that new onset AF was associated with failure to CRT [73].

In patients with permanent AF, adequate rate control to relieve symptoms with pharmacological therapy alone is sometimes difficult. These patients can develop rapidly conducted AF despite maximally tolerated pharmacological treatment, and eventually develop heart failure. In these situations atrioventricular junction ablation is performed and pacing is done to achieve relief of symptoms and increase exercise tolerance. Gasparini et al. [74] studied the long-term effects of atrioventricular junction ablation on ventricular function, reverse modeling and exercise tolerance in patients with AF and compared to patients in whom adequate heart rate was achieved with pharmacological agents. The study showed that sustained long term improvement of LV function and functional capacity was achieved in CRT patients with AF only if atrioventricular junction ablation was performed.

However, it should be noted that the patient population who underwent atrioventricular junction ablation in this study were much younger and the reason for atrioventricular junction ablation was not drug refractory control of ventricular rate during AF, but for suboptimal biventricular pacing. Also the mean ventricular rate was 80 beats/min, which is much lower than the usual population referred for atrioventricular junction ablation. Nevertheless, this is an important concept which deserves further study.

Three site pacing *vs.* dual site pacing

Apart from the conventional LV lateral wall pacing site, placing leads in additional pacing sites has generated significant interest recently. It is conceivable that additional pacing in different ventricular sites might lead to multiple waves of electrical activation and thereby reduce dyssynchrony [75].

Triple Resynchronization In Paced Heart Failure Patients (TRIP-HF) by Leclercq et al. [76] is the first study to compare triple site stimulation (two epicardial transvenous leads placed on the anterior and lateral or posterolateral LV wall and one RV lead) with conventional biventricular pacing. It showed that triple site stimulation pacing achieved more LV reverse modeling compared to conventional biventricular pacing. Triple site pacing patients achieved a higher ejection fraction and smaller LV end-systolic volume compared to biventricular pacing.

As noted in the editorial by Auricchio et al. [75], TRIP-HF was performed in patients with a slow ventricular rate during AF in need of antibradycardia pacing. The benefits of triple site pacing need to be studied in a more common group of heart failure patients with sinus rhythm and ventricular conduction disturbances [75].

Conclusions

Cardiac resynchronization therapy has been shown to have significant benefit in terms of symptomatic relief and LV reverse remodeling and mortality in heart failure patients with wide QRS complex. Non-response to CRT in these patients remains an important concern. Other unresolved issues include the role of CRT in heart failure patients with narrow QRS complex, AF and atrioventricular nodal ablation, NYHA class I and II, the method of LV lead placement, and triple site pacing.

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Appendix I. Ranking of level of evidence by ACC/AHA/HRS guidelines writing committee [37].

Level A	Level of evidence A means the data were derived from multiple randomized clinical trials that involved a large number of individuals
Level B	Level of evidence B means that the data were derived either from a limited number of trials that involved a comparatively small number of patients, or that the data was derived from well-designed data analyses of non-randomized studies or observational data registries
Level C	Level of evidence C means that only consensus of experts was the primary source of the recommendation

Appendix II. Classes of recommendations used by ACC/AHA/HRS writing committee [37].

Class I	Class I recommendation means that the benefit greatly outweighs the risk and that the procedure or treatment should be performed or administered
Class IIa	Class IIa recommendation means that the benefit outweighs the risk but additional studies with focused objectives are needed. Class IIa recommendation means that it is reasonable to per form the procedure or treatment
Class IIb	Class IIb recommendation means that the benefit is equal to or greater than the risk but additional studies with broad objectives are needed and additional registry data would be helpful. Class IIb recommendation means that the procedure or treatment may be considered
Class III	Class III recommendation means that the risk outweighs the benefit and that the procedure or treatment should not be performed

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