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# Metaanalysis on effects of cardiac resynchronization therapy in heart failure patients with narrow QRS complex

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## Abstract

**Background:** *To systematically review the benefits of cardiac resynchronization therapy (CRT) in heart failure patients with narrow QRS (< 120 ms) who have baseline mechanical asynchrony.*

**Methods:** *We searched the MEDLINE, Cochrane Central Register of Controlled Trials, and reference lists of retrieved articles for relevant trials through October 2007. Studies were included if they were clinical trials in heart failure patients with narrow QRS complex, had at least 3 months of duration and measured baseline mechanical dyssynchrony. Weighted mean difference (WMD) for changes in left ventricular ejection fraction (LVEF), New York Heart Association (NYHA) class and 6 minute walk distance (6MWD) at the end of follow up period were estimated using fixed effects meta-analysis.*

**Results:** *Three relevant clinical trials (enrolling 98 patients) out of 80 identified studies were included in the final analysis. When compared to baseline, CRT in heart failure patients with narrow QRS complex significantly improved mean LVEF (WMD 7.98%, 95% CI 5.94, 10.03) and 6MWD (WMD 67 m, 95% CI 39.12, 94.98) at the end of follow up period with no significant heterogeneity between the included studies ($I^2$ < 50%). Similarly, there was a significant reduction in NYHA at the end of follow-up (WMD –0.87, 95% CI –1.01, –0.74) but there was significant heterogeneity between the included studies.*

**Conclusions:** *In patients with narrow QRS complex and baseline mechanical asynchrony, who underwent CRT after optimal medical management, there was a significant reduction in NYHA class, improvement in LVEF and increase in 6MWD during follow up. Further data from large randomized trials are warranted to explore the role of CRT in heart failure patients with narrow QRS complex.* (Cardiol J 2008; 15: 230–236)

**Key words: cardiac resynchronization therapy, heart failure, narrow QRS**

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## Introduction

About 5 million people in United States currently have heart failure [1, 2]. Each year about 550,000 patients are newly diagnosed with heart failure and about 287,000 deaths occur each year which are attributable to heart failure [1, 2]. Hospitalizations due to heart failure are increasing [1, 3, 4] and this is especially true with the aging population [3, 5]. In 2006, the estimated direct cost for heart failure in United States was $ 29.6 billion dollars [1, 2].

In patients with wide QRS (> 120 ms), cardiac resynchronization therapy (CRT) has been shown to facilitate reverse modeling of the left ventricle leading to increased left ventricular ejection fraction, reduced mitral regurgitation and reduced heart size [6]. Several trials have shown that CRT in patients with wide QRS improved quality of life, improved exercise tolerance, and 6 min walking distance [7–12]. More importantly, clinical trials [13, 14] and meta-analyses [15–18] have shown that CRT decreases mortality in heart failure patients with wide QRS complex.

However non-response rate to CRT in heart failure patients with wide QRS complex is reported up to 30% [19]. Baseline QRS duration has been found to be a poor predictor of clinical and echocardiographic responses to CRT [20]. Clinically it is often difficult to predict who will respond to the CRT. Therefore, there is a need to explore other possible factors that might play a role to get better response to CRT. Left ventricular mechanical asynchrony is one such factor which has been recently shown to predict prognosis in patients with CRT [21–23]. Recent studies have also shown that there is a high prevalence of left ventricular mechanical asynchrony in patients with narrow QRS (< 120 ms) [24]. Only few clinical trials have looked at the benefit of CRT in patients with narrow QRS [25–31]. Since there is a high prevalence of left ventricular asynchrony in heart failure patients with narrow QRS complexes, and there is a need to explore the role of CRT in these group of patients, we aimed to systematically review the benefits of CRT in heart failure patients with narrow QRS who have baseline mechanical asynchrony.

## Methods

### Search strategy

We searched MEDLINE and the Cochrane Controlled Trials Register in October 2007 for clinical trials of CRT in heart failure patients with narrow QRS complex using the appropriate terms: cardiac resynchronization therapy, heart failure, congestive heart failure, pacemaker, narrow QRS complex.

### Study selection/data extraction

Two investigators independently screened all titles and abstracts to identify the studies which looked at benefits of CRT in patients with narrow QRS complex and heart failure. One of these reviewers extracted relevant data using a standardized data extraction from the included studies. Disagreements were resolved by discussion with James P. Daubert. Both randomized and non-randomized studies with a follow-up period of at least 3 months were considered for inclusion. Changes in left ventricular ejection fraction (LVEF), NYHA class and 6 minute walk distance (6MWD) at the end of follow up period were the primary outcome measures. Studies were excluded if the effects of CRT were not reported separately from CRT with implantable cardioverter defibrillator (ICD).

### Statistical analysis

Statistical analyses were performed using the Cochrane Revman software 4.2.8 and the results were expressed as weighted mean difference (WMD) for continuous outcomes, with 95% confidence intervals (95% CI) using fixed effects model. We planned to conduct sensitivity analyses if significant heterogeneity was found ($I^2$) for any one of the outcomes.

## Results

### Search results

Three relevant clinical trials (enrolling 98 patients) out of 80 studies were included in the final analysis (Fig. 1). The trials included in this meta-analysis for narrow QRS studies were reported by Yu et al. [25], Bleeker et al. [26] and Achilli et al. [28], two trials Turner et al. [29] and Gasparini et al. [31] were excluded as these studies did not measure baseline LV dyssynchrony. The baseline characteristics of the studies included in meta-analysis for narrow QRS are shown in Table 1 and 2. Primary outcomes of the studies included are shown in Table 3.

### Left ventricular ejection fraction

When compared to baseline, CRT in patients with narrow QRS complex improved mean LVEF (3 studies, 98 patients, WMD 7.98%, 95% CI 5.94, 10.03) without any significant heterogeneity between the included studies ($\chi^2 = 0.41$, $p = 0.82$, $I^2 = 0\%$) (Fig. 2).

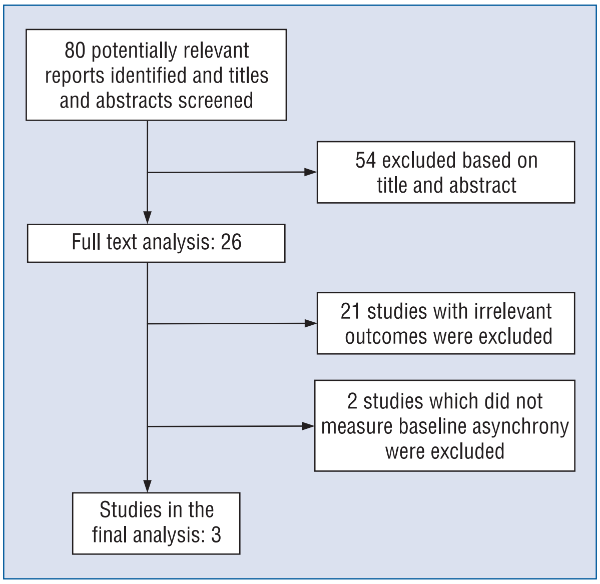


**Figure 1.** Study Selection from MEDLINE search.

## Six minute walk distance (6MWD)

In comparison to baseline, CRT in patients with narrow QRS complex increased the 6MWD significantly (3 studies, 98 patients, WMD 67 m, 95% CI 39.12, 94.98) at the end of follow up period with no heterogeneity between the included studies ($\chi^2 = 2.8$, $p = 0.24$, $I^2 = 30.3\%$) (Fig. 3).

## Change in NYHA classification

There was a significant reduction in NYHA at the end of follow-up period with CRT in patients with narrow QRS complex (3 studies, 98 patients, WMD –0.87, 95% CI –1.01, –0.74) with significant heterogeneity between the included studies ($\chi^2 = 15.18$, $p = 0.0005$, $I^2 = 86.8\%$) (Fig. 4).

## Sensitivity analysis

Heterogeneity was explored through sensitivity analyses and the exclusion of the trial by Achili et al. [28] eliminated the heterogeneity for change in NYHA. This is probably related to the smaller sample size in this study compared to the other two studies included in the analyses.

# Discussion

Our meta-analysis showed that there was a significant improvement in mean LVEF and 6MWD at the end of follow up period. Similarly, there was a significant reduction in NYHA at the end of follow-up period. These results suggest that there is a potential role of CRT in narrow QRS complex heart failure patients.

**Table 1.** Baseline characteristics of studies included in the meta-analysis.

| Study | Objective | Study duration (months)/ /No. of patients | Outcomes analyzed | Findings |
|---|---|---|---|---|
| Bleeker et al. [26] | Role of CRT in HF patients with narrow QRS (<120 ms) and echocardiographic evidence of baseline asychrony | 6/33 | 1. Reduction in NYHA class<br>2. Improvement in 6MWD<br>3. Improvement in LVEF (%)<br>4. Improvement in QoL<br>5. Reduction in LVESV<br>6. Reduction in LVEDV | Significant improvement of NYHA functional class, improvement in 6MWD, improvement in LVESV |
| Yu et al. [25] | Effects of CRT in HF patients with narrow QRS (< 120 ms) and evidence of baseline asynchrony on tissue Doppler imaging | 3/51 | 1. Reduction in NYHA class<br>2. Improvement in 6MWD<br>3. Improvement in LVEF (%)<br>4. Improvement in QoL<br>5. Reduction in LVESD<br>6. Reduction in LVEDD | Significant improvement of NYHA functional class, improvement in 6MWD, improvement in LVESD, Reduction in mitral regurgitation area |
| Achilli et al. [28] | Effects of CRT in refractory HF patients with narrow QRS (< 120 ms) and evidence of baseline asynchrony on echocardiography | 6/14 | 1. Reduction in NYHA class<br>2. Improvement in 6MWD<br>3. Improvement in LVEF (%)<br>4. Reduction in LVESD<br>5. Reduction in LVEDD | Significant improvement of NYHA functional class, improvement in 6MWD, improvement in LVESD, reduction in mitral regurgitation area |

CRT — cardiac resynchronization therapy; HF — heart failure; NYHA — New York Heart Association heart failure class; QoL — quality of life; 6MWD — 6 min 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

**Table 2.** Characteristics of trials included in meta-analysis.

| Baseline characteristics | Bleeker et al. [26] | Yu et al. [25] | Achilli et al. [28] |
|---|---|---|---|
| Mean QRS | 110 ± 8 | 103 ± 13 | NA |
| Age (mean ± SD) | 63 ± 11 | 63 ± 11 | 68.3 ± 8 |
| Men | 85% | 78.4% | 71% |
| Ischemic | 70% | 49% | 29% |
| NYHA | 3.1 ± 0.3 | 2.84 ± 0.46 | 3.4 ± 0.5 |
| QoL | 39 ± 18 | 28 ± 14 | NA |
| 6MWD [m] | 274 ± 133 | 333 ± 96 | 276.4 ± 88.9 |
| LVEF (%) | 22 ± 6 | 27.8 ± 7 | 24.6 ± 5.0 |
| LVEDV[1] [cc]/LVEDD[2] [mm] | 216 ± 78[1] | 167 ± 47[1] | 71.8 ± 9.2[2] |
| LVESV[1] [cc]/LVESD[2] [mm] | 174 ± 75[1] | 122 ± 42[1] | 61.4 ± 8.4[2] |
| Left ventricular dyssynchrony | 102 ± 32 | 35.9 ± 14.0 | NA |
| Diuretics | 82% | 96% | 100% |
| ACEI | 88% | 92% | 90%* |
| Beta-blocker | 76% | 67% | 60% |

NA — not available; NYHA — New York Heart Association heart failure class; QoL — quality of life; 6MWD — 6 min 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; ACEI — angiotensin converting enzyme inhibitor; *including angiotensin receptor blockers

**Table 3.** Primary outcomes after cardiac resynchronization therapy at 6 months.

| | Bleeker et al. [26] | Yu et al. [25] | Achilli et al. [28] |
|---|---|---|---|
| Reduction in NYHA | 0.9 ± 0.6 | 0.73 ± 0.4 | 1.6 ± 0.1 |
| Reduction in QoL | 13 ± 16 | 8 ± 19 | NA |
| Improvement 6MWD | 89 ± 107 | 46 ± 88 | 93.5 ± 18.7 |
| Improvement in LVEF (%) | 8 ± 8 | 7.3 ± 6.3 | 9 ± 0.9 |
| Reduction in LVEDV[1] [cc]/LVEDD[2] [mm] | 26 ± 32[1] | 8.6 ± 14[1] | 6.2 ± 0.7[2] |
| Reduction in LVESV[1] [cc]/LVESD[2] [mm] | 39 ± 34[1] | 17.1 ± 18.6[1] | 5.8 ± 0.2[2] |
| All cause mortality | 9 | NA | 3/14 |
| Sudden death | 0 | NA | 1 |
| Progressive heart failure deaths | 8 | NA | 2 |
| Noncardiac deaths | NA | NA | 0 |
| Hospitalizations | 6 | NA | NA |

NA — not available; NYHA — New York Heart Association heart failure class; QoL — quality of life; 6MWD — 6 min 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

Although the role of CRT in heart failure patients with wide QRS (> 120 ms) is established, about 30 to 40% of patients do not respond to treatment [19]. The usefulness of QRS duration as a selection criterion among these patients has been questioned. There is a need to identify other factors that might help improve outcomes among patients with CRT. Left ventricular asynchrony is an important factor which predicts prognosis in patients with CRT [21–23]. Some of the other reported predictors of non-response to CRT include ischemic heart disease, severe MR and LVEDD ≥ ≥ 75 mm [32]. Incidence of left ventricular dyssynchrony in heart failure patients vary between 27% to 56% and one study which specifically looked at narrow QRS complex heart failure patients reported 33% of left ventricular dyssynchrony [33].

Only few studies have looked at the potential role of CRT in patients with narrow QRS [25–31]. CRT has been shown to improve hemodynamics in CHF patients with narrow QRS [34]. Similarly, our systematic review shows significant improvement in clinical and functional parameters in narrow QRS complex patients who had CRT when compared to their baseline.

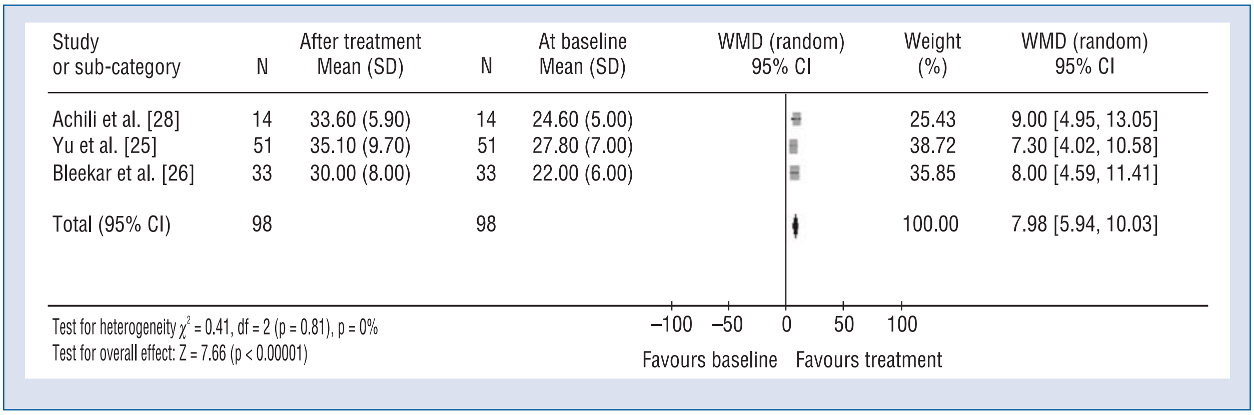


**Figure 2.** Improvement in left ventricular ejection fraction in heart failure patients with narrow QRS and baseline asynchrony at follow up compared to baseline.

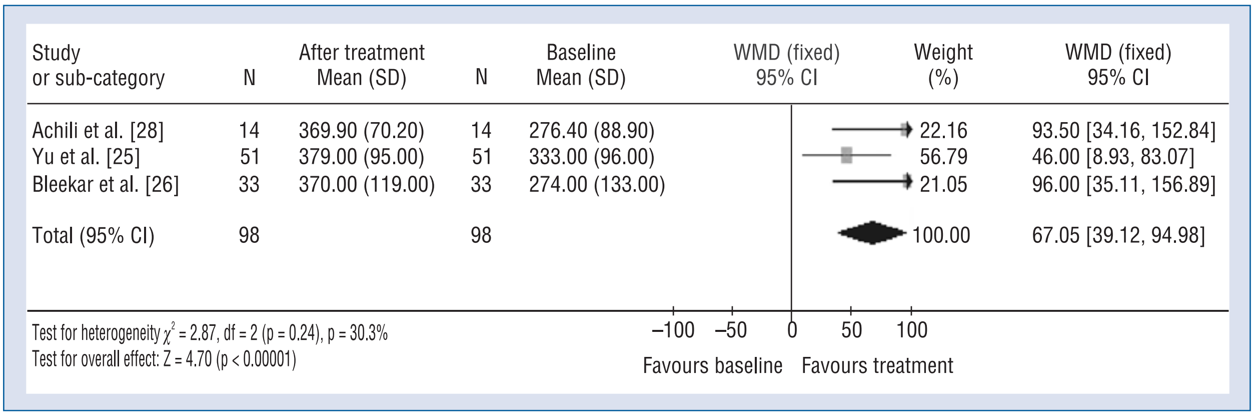


**Figure 3.** Improvement in 6 minute walk distance in heart failure patients with narrow QRS and baseline asynchrony at follow up compared to baseline.

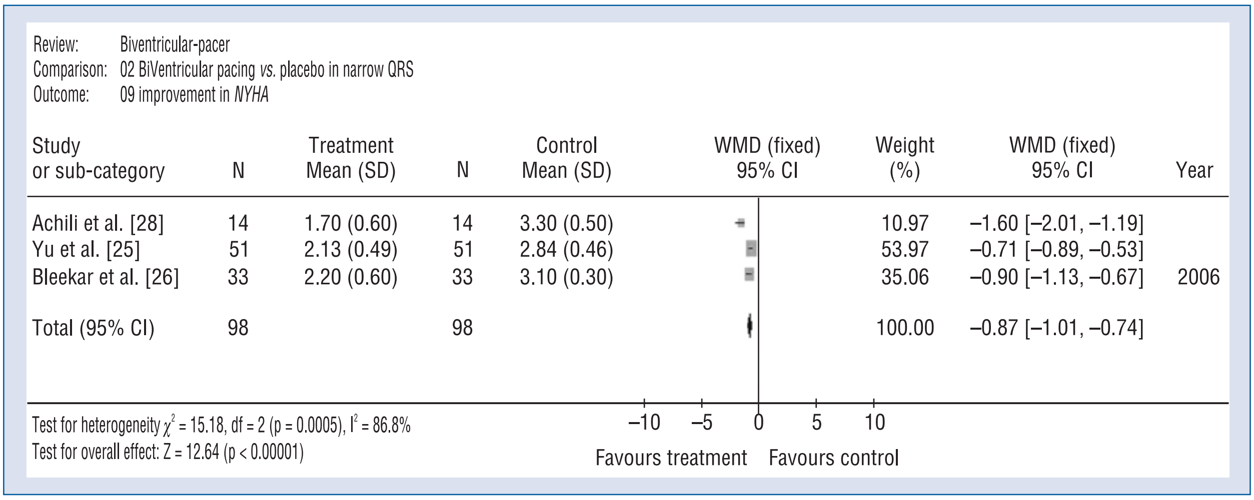


**Figure 4.** Improvement in New York Heart Association class in heart failure patients with narrow QRS and baseline asynchrony at follow up compared to baseline.

Gasparini et al. [31] studied the long term effects of CRT in heart failure patients with QRS ≤ ≤ 120 ms. Patients in this study were not pre-selected by echocardiographic presence of dyssynchrony. When we included the data at 6 months follow up from Gasparini et al. [31] to other three trials, 6MWD increased significantly (4 studies, 143 patients, WMD 63 m, 95% CI 38.85, 87.12) at the end of follow up period with no heterogeneity. Similarly LVEF increased (4 studies, 143 patients, WMD 7.73%, 95% CI 6.00, 9.47) without any significant heterogeneity. Further Gasparini et al. [31] had follow up for 36 months. When we included data at 36 months follow up there was a greater increase in 6MWD and LVEF. This shows that we need more data from long term trials which would allow adequate time for left ventricular remodeling.

### Limitations of the study

One of the major limitations of the study is that the included studies are pre and post CRT studies without any randomization and any control group. So there is a potential risk of bias. Further we were unable to analyze the potential mortality benefit of CRT in narrow QRS complex patients because the available trials did not have a control arm with optimal medical management. Thus, the results will need to be interpreted with caution.

Recently study by Beshai et al. [35] showed that CRT in heart failure patients with narrow QRS complex did not improve peak oxygen consumption, Minnesota living with heart failure scores, 6 min walk distance and left ventricular volume and ejection fraction at 6 months. Potential differences in these results could be due to the method of measurement of mechanical dyssynchrony and lack of documentation. Beshai et al. [35] used opposite wall delay method to measure mechanical dyssynchrony whereas asynchrony index was used by Yu et al. [25], maximum delay between peak systolic velocities among the 4 walls within the left ventricle using tissue Doppler imaging was used by Bleekar et al. [26] and intraventricular asynchrony was identified when Q-LW > Q-E and Q-LW > 9.9 corrected units (c.u. = measured interval in ms/√ R-R interval) by Achilli et al. [28].

Further from Gasparini's trial we know that the benefits are significantly higher with longer duration. Perhaps we need data from trials with longer duration. Another protocol for a randomized clinical trial in heart failure patients with narrow QRS complex patients has been released from University of Zurich [36]. The results of this trial along with results from ReThinQ [35] after a longer duration of follow up would help us understand the role of CRT in narrow QRS heart failure patients.

## Conclusions

In summary, CRT in heart failure patients with narrow QRS and baseline mechanical asynchrony significantly improves LVEF, 6MWD and NYHA compared to their baseline. Further larger randomized trials would be needed before we can draw definite conclusion about benefit of CRT in heart failure patients with narrow QRS complex.

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The authors do not report any conflict of interest regarding this work.

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