

Association between changes in QRS width and echocardiographic responses to cardiac resynchronization therapy

A systematic review and meta-analysis

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Abstract

Background: Numerous studies have illustrated the association of QRS width with the incidence of echocardiographic response to cardiac resynchronization therapy (CRT). This study aimed to summarize the observational studies regarding the magnitude of change in QRS width between responders and nonresponders to CRT.

Methods: The PubMed, Embase, and the Cochrane Library were systematically searched for relevant studies investigating the changes of QRS width with the incidence of echocardiographic response to CRT from inception till May 2019. The pooled weighted mean difference (WMD) with 95% confidence interval (CI) was calculated through random-effects model.

Results: Five prospective and 6 retrospective studies with a total of 1524 patients were selected for final analysis. The reduction of QRS width in responders was significantly greater than nonresponders (WMD: -20.54 ms; 95% CI: -26.78 to -14.29 ; $P < .001$). Moreover, responders were associated with greater percentage reduction in QRS width when compared with nonresponders (WMD: -8.80% ; 95% CI: -13.08 to -4.52 ; $P < .001$). Finally, the mean change in QRS width between responders and nonresponders differed when stratified by country, study design, mean age, percentage male, ejection fraction, measuring time of postimplanted QRS, ischemic cardiomyopathy, atrial fibrillation, and study quality.

Conclusions: These findings indicated that shortening QRS width after CRT device implantation showed association with greater incidence of echocardiographic responses to CRT. Further prospective studies should be conducted to evaluate the prognostic values of QRS width on the incidence of echocardiographic response to CRT.

Abbreviations: CI = confidence interval, CRT = cardiac resynchronization therapy, EF = ejection fraction, LV = left ventricular, LVEF = left ventricular ejection fraction, NYHA = New York Heart Association, WMD = weighted mean difference.

Keywords: cardiac resynchronization therapy, echocardiographic, QRS

1. Introduction

Cardiac resynchronization therapy (CRT) is an established treatment strategy for patients with heart failure for improving

left ventricular function via reverse remodeling who remain symptomatic despite optimal medical therapy.^[1,2] Patients with New York Heart Association (NYHA) classes II to IV, wide QRS, and reduced left ventricular ejection fraction (LVEF) received CRT for improving the symptoms, exercise tolerance and quality of life, and reducing mortality risk.^[3,4] However, nearly one-third patients who received CRT did not yield any advantageous results because the beneficial effects correlate with strict follow-up schedules, and accurate atrioventricular and interventricular interval optimization. Therefore, potential predictors for screening of patients are required to improve the operative risk and medical costs.

Both European and American guidelines suggested QRS duration as a key indicator for selecting patients for CRT therapy.^[1,5] Previous studies have already indicated that prolongation of the QRS complex was one of the strongest predictors for response to CRT, even after taking into account bundle branch block morphology.^[6,7] The potential reason for this could be that QRS duration showed significant correlation with left ventricular (LV) mass, LV diameter, LV volumes, and LV length irrespective of the presence of bundle branch block.^[8-10] Nowadays, numerous studies have already explored the mean and percentage changes of QRS width between responders and nonresponders of CRT therapy, and also the magnitude of effect estimates regarding the association of QRS width with the incidence of echocardiographic response to CRT should be summarized. Therefore, the current systematic review and meta-analysis was conducted based on published observational studies to evaluate the association of

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changes in QRS width before and after CRT with the incidence of echocardiographic response to CRT.

2. Materials and methods

This study was a systematic review and meta-analysis so ethical approval was waived or not necessary, and informed consent cannot be obtained.

2.1. Data sources, search strategy, and selection criteria

The present study was performed and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Statement.^[11] Observational studies published in English and observational studies that investigated the changes of QRS width between responders and nonresponders of CRT therapy were eligible for inclusion in this study. We systematically searched PubMed, Embase, and the Cochrane Library to select potentially relevant studies without restriction to the publication status. The following search terms were used: “QRS duration” OR “QRS width” OR “QRS change” OR “QRS narrowing” OR “QRS shortening” OR “Electrocardiogram” OR “Electrocardiographic” AND “cardiac resynchronization therapy” AND “response.” Moreover, the references from the retrieved studies were also reviewed by manual search to identify for any new eligible studies.

Two reviewers conducted the literature search and study selection processes independently, and any discrepancy was settled by discussion with each other by referring to the original article until a consensus was reached. The inclusion criteria of this study are listed as follows:

1. patients status: patients belonging to NYHA classes II to IV, with QRS > 120 ms, with LVEF < 40.0%, and received CRT;
2. case and control: responders and nonresponders to CRT;
3. outcomes: mean change or percentage change in QRS between responders and nonresponders; and
4. study design: studies design as observational, irrespective of prospective or retrospective study.

2.2. Data collection and quality assessment

The data items of this study including the first authors' surname; publication year; country; study design; sample size; mean age; percentage male; NYHA class; ejection fraction (EF); QRS duration; measuring time of postimplanted QRS; definition of response, percentage of ischemic cardiomyopathy, and atrial fibrillation; LVEF; Left ventricular end-diastolic dimension (LVEDD); CRT pacemaker/defibrillator; percentage of ACEI/ARB, beta blocker, and diuretic uses; and investigated outcomes were collected. The quality of enrolled studies was assessed using the Newcastle-Ottawa Scale based on selection (4 items: 4 stars), comparability (1 item: 2 stars), and outcome (3 items: 3 stars).^[12] The data abstraction and quality evaluation were assessed by 2 reviewers, and any inconsistencies between the 2 reviewers were resolved by an additional reviewer by reviewing the full text of the included studies.

2.3. Statistical analysis

The mean or percentage changes in QRS width between responders and nonresponders were examined based on mean, standard deviation, and sample size in responders and nonresponders

groups in each study. After this, the summary weighted mean differences (WMDs) with 95% confidence intervals (CIs) were calculated using the random-effects model, considering that the true underlying effect varies among the included trials.^[13,14] Heterogeneity among the included studies was assessed by Cochrane Q statistic and I^2 , and $P < .10$ indicated significant heterogeneity.^[15,16] Sensitivity analysis was performed to evaluate the stability of pooled conclusion.^[17] Subgroup analyses for mean change of QRS width between responders and nonresponders were conducted based on country, study design, mean age, percentage male, EF, measuring time of postimplanted QRS, ischemic cardiomyopathy, atrial fibrillation, LVEF, LVEDD, and study quality, and P values between the subgroups were calculated by interaction test.^[18] Publication biases were evaluated using Funnel plots, Egger,^[19] and Begg tests.^[20] The inspection level for pooled results was 2-sided, and $P < .05$ was considered to be statistically significant. All analyses in this study were carried out using Stata 10 (version 10.0, Stata Corporation, College Station, TX).

3. Results

3.1. Literature search

Electronic searches from PubMed, Embase, and the Cochrane Library yielded 1181 records after excluding duplicate articles. Of these, 1146 were excluded due to irrelevant topics. The remaining 35 articles were retrieved for further evaluations, and 24 articles of these were excluded due to the following reasons: no sufficient data ($n=12$), study reported clinical response to CRT ($n=8$), and review ($n=4$). Manual searching of the references of included articles did not yield any new eligible study. Finally, 11 studies were selected for the final quantitative analysis,^[20-30] and the details of study selection process are displayed in Figure 1.

3.2. Study characteristics

Baseline characteristics of recruited patients and enrolled studies are summarized in Table 1 and Supplemental Digital Content (Table S1, <http://links.lww.com/MD/D575>). Of the 11 included

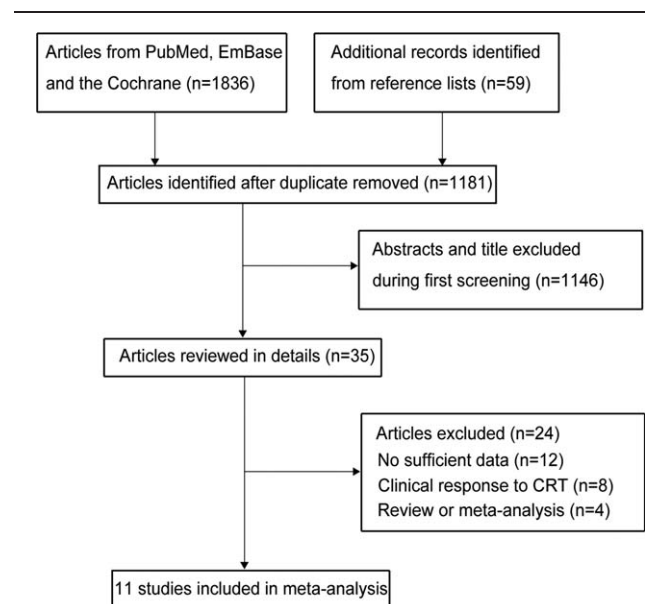


Figure 1. Flow diagram of literature search and studies selection process.

Table 1
Baseline characteristics of included patients and studies in the systematic review and meta-analysis.

Study	Publication year	Country	Study design	Sample size	Mean age (yr)	Percentage male (%)	NYHA class	Ejection fraction (%)	QRS duration (ms)	Measuring time of postimplanted QRS	Definition of response	NOS
Boriani et al ^[21]	2006	Italy	Pro	20	62.0	75.0	III or IV	<40.0	157.0	During follow-up	A reduction $\geq 15\%$ of LVESV	6
Bonakdar et al ^[22]	2009	Iran	Pro	82	56.0	74.4	III or IV	<35.0	153.0	Immediately after CRT	Alive without cardiac decompensation and experienced $\geq 15\%$ decrease in LVESV	8
Kamireddy et al ^[23]	2009	United States	Pro	113	69.3	70.0	NA	NA	155.3	During follow-up	A relative increase of $\geq 15\%$ in LVEF after CRT	8
Rickard et al ^[24]	2011	United States	Retro	218	64.5	NA	II–IV	<40.0	165.6	Immediately after CRT	A reduction in LVESV $\geq 10\%$ from baseline	7
Rickard et al ^[25]	2012	United States	Retro	507	66.4	69.2	NA	<40.0	164.1	Immediately after CRT	No deterioration in LV function (deterioration was defined as an absolute decrease of 5% or greater in EF from baseline)	7
Rickard et al ^[26]	2013	United States	Retro	112	69.3	70.5	NA	<35.0	187.8	Immediately after CRT	A reduction in LVESV $\geq 15\%$ from baseline	6
Yang et al ^[27]	2014	China	Pro	74	61.0	65.0	II–IV	<35.0	163.0	Immediately after CRT	An absolute improvement in LVEF by $\geq 10\%$ from baseline	7
Zhang et al ^[28]	2015	China	Pro	30	57.1	73.3	II or III	<35.0	156.0	Immediately after CRT	Those patients exhibiting ≥ 5 mm reduction in LVED after 6 mo of CRT	7
Niebauer ^[29]	2016	United States	Retro	182	64.3	56.6	II or III	<35.0	160.6	Immediately after CRT	A $\geq 15\%$ reduction in LV end-diastolic volume	6
Karaca et al ^[29]	2016	Turkey	Retro	125	63.5	64.0	II–IV	<35.0	156.7	During follow-up	A reduction in LVESV $\geq 15\%$	7
Chen et al ^[30]	2017	China	Retro	61	74.0	41.0	III or IV	<35.0	160.0	During follow-up	A reduction in LVESV $\geq 15\%$	6

CRT = cardiac resynchronization therapy, EF = ejection fraction, LV = left ventricular, LVED = Left ventricular end diastolic, LVEF = left ventricular ejection fraction, LVESV = left ventricular end-systolic volume, NA = not available, NOS = Newcastle-Ottawa Scale, NYHA = New York Heart Association, Pro = prospective, Retro = retrospective.

studies (for a total of 1524 participants), 5 were prospective cohort studies and 6 were retrospective cohort studies. These studies were published between 2006 and 2017, and 20 to 507 patients were included in each study. Six studies were conducted in the United States or Europe, and the remaining 5 studies were conducted in Asia. The mean age of patients included ranged from 56.0 to 69.3 years, and the baseline QRS duration ranged from 153.0 to 187.8 ms. Four studies measured QRS during the follow-up, and the remaining 7 studies measured QRS duration

after undergoing CRT immediately. Study quality was assessed using the Newcastle-Ottawa Scale, where studies with 7 stars or more were regarded as high quality. Two studies had 8 stars, 5 studies had 7 stars, and the remaining 4 studies had 6 stars.

3.3. Meta-analysis

After pooling all the included studies, a mean reduction of QRS width in responders group was significantly greater than

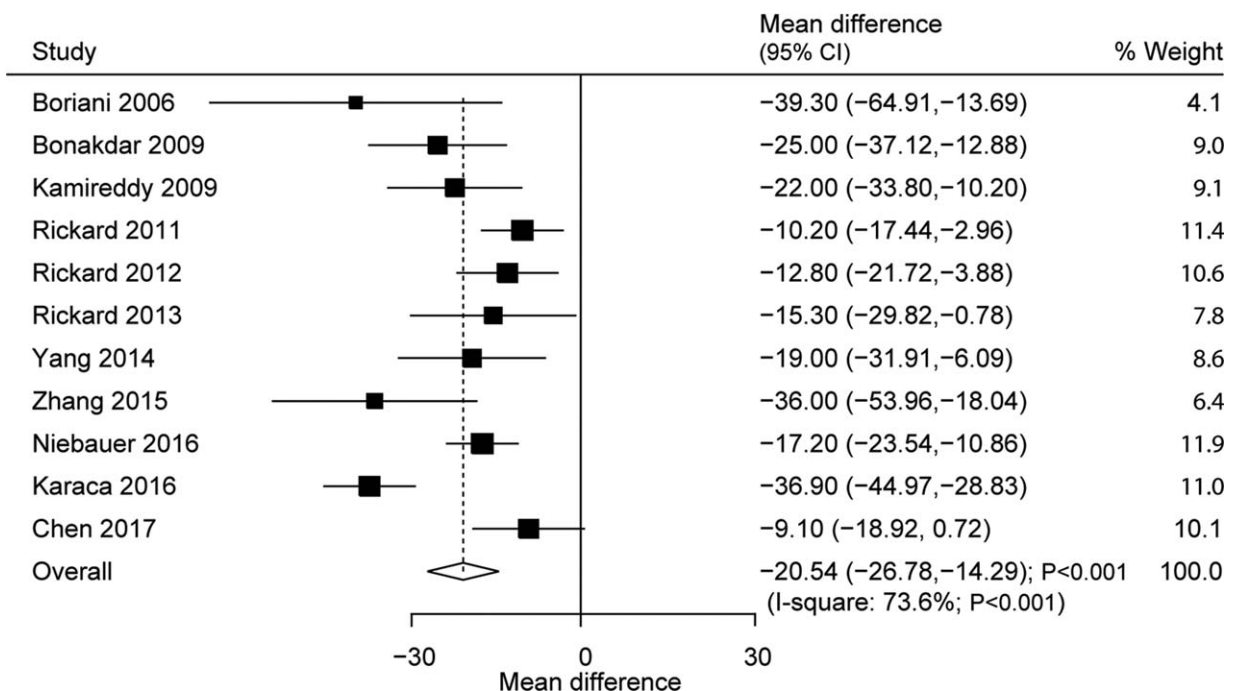


Figure 2. The mean change of QRS width between responders and nonresponders.

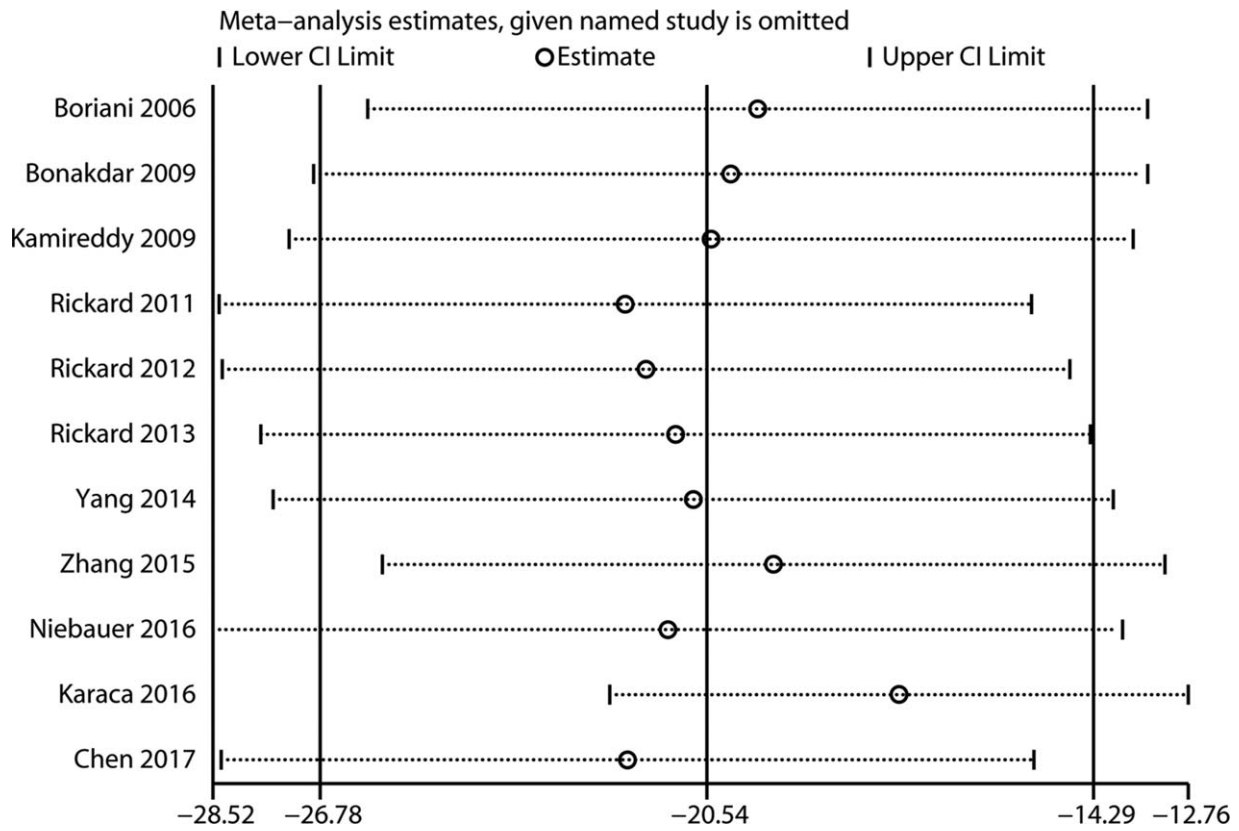


Figure 3. Sensitivity analysis for the mean change of QRS width.

nonresponders (WMD: -20.54 ms; 95% CI: -26.78 to -14.29; $P < .001$; Fig. 2), and significant heterogeneity was observed among the included studies. The results of sensitivity analysis indicated that the pooled conclusion was stable and were not altered by excluding any particular study (Fig. 3).

Four studies reported the percentage change in QRS width between responders and nonresponders to CRT. The summary of WMD indicated that the percentage reduction of QRS width in responders group was significantly greater than nonresponders (WMD: -8.80%; 95% CI: -13.08 to -4.52; $P < .001$; Fig. 4), and

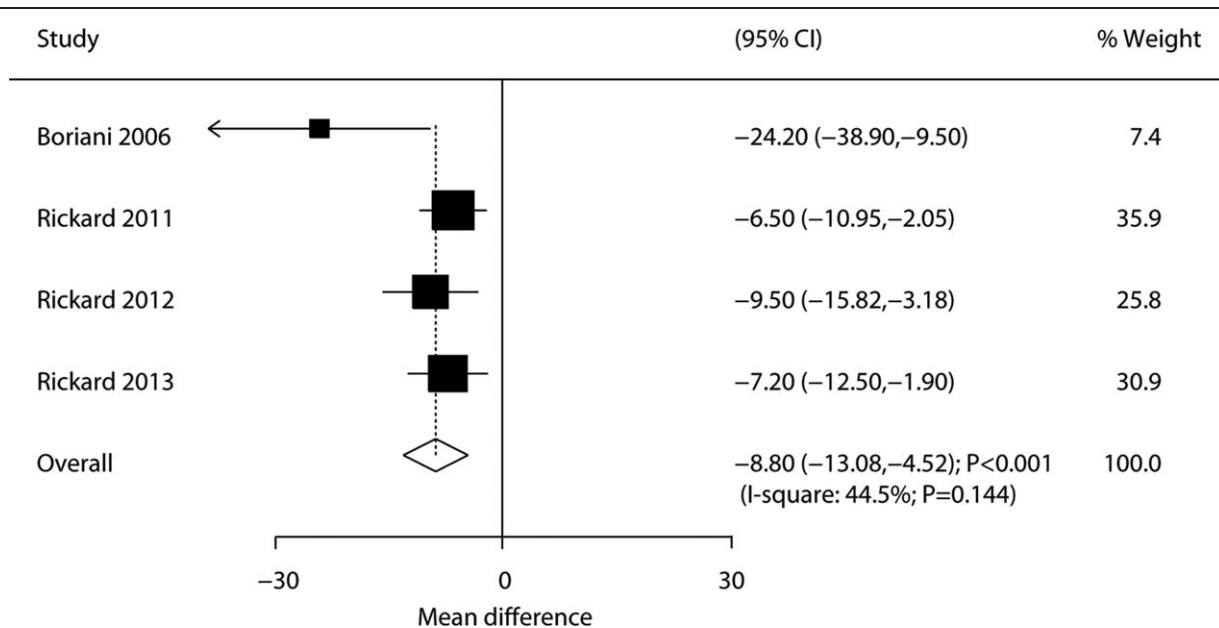


Figure 4. The percentage change of QRS width between responders and nonresponders.

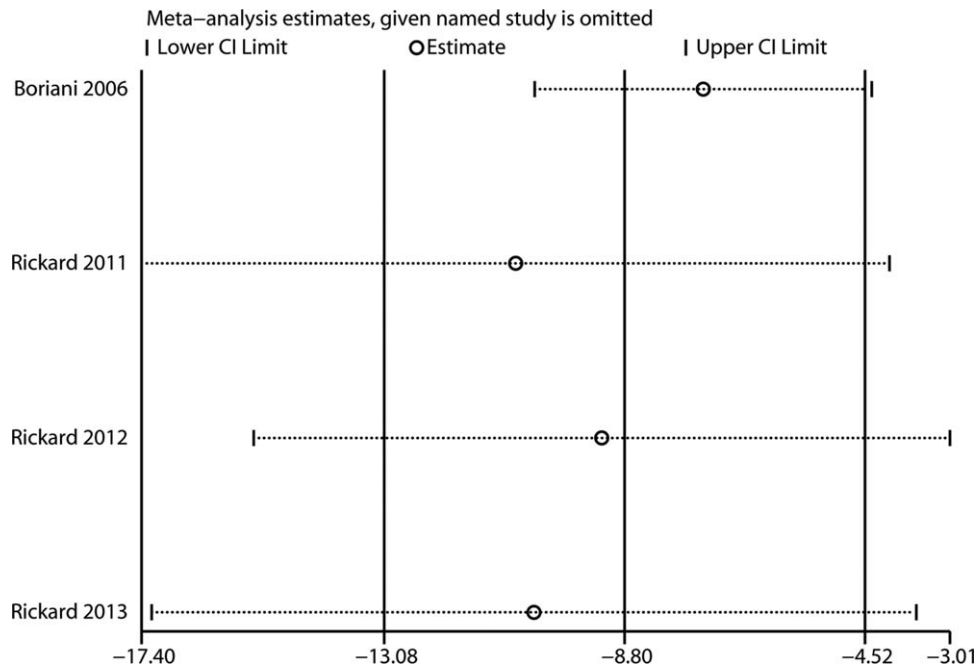


Figure 5. Sensitivity analysis for the percentage change of QRS width.

moderate heterogeneity was detected across the included studies. This conclusion was stable and unchanged after sequential exclusion of included studies (Fig. 5).

3.4. Subgroup analysis

Subgroup analyses for mean change of QRS width between responders and nonresponders were conducted and the

results are summarized in Table 2. The mean changes of QRS width between responders and nonresponders showed statistically significant association in all the subsets, whereas the extent of mean changes was affected by country, study design, mean age, percentage male, EF, measuring time of postimplanted QRS, ischemic cardiomyopathy, atrial fibrillation, and study quality.

Table 2

Subgroup analyses for the association of mean changes in QRS width with the incidence of echocardiographic response to cardiac resynchronization therapy.

Factors	Groups	WMD and 95% CI	P value	Heterogeneity (%)	P value for heterogeneity	P value between subgroups
Country	United States or Europe	-15.77 (-20.63 to -10.90)	<.001	30.2	.209	.001
	Asia	-24.85 (-36.55 to -13.16)	<.001	80.6	<.001	
Study design	Prospective	-24.93 (-31.31 to -18.56)	<.001	0.0	.446	.042
	Retrospective	-17.07 (-25.68 to -8.47)	<.001	83.4	<.001	
Mean age (yr)	≥65.0	-13.93 (-19.29 to -8.58)	<.001	0.0	.420	.023
	<65.0	-24.47 (-33.41 to -15.54)	<.001	80.0	<.001	
Percentage male (%)	≥70.0	-24.72 (-31.83 to -17.61)	<.001	12.6	.333	.014
	<70.0	-19.15 (-28.98 to -9.32)	<.001	83.9	<.001	
EF (%)	<35.0	-22.26 (-30.56 to -13.96)	<.001	76.5	<.001	.020
	<40.0	-14.70 (-24.43 to -4.96)	.003	56.5	.100	
Measuring time of postimplanted QRS	During follow-up	-25.60 (-40.83 to -10.38)	.001	84.9	<.001	.005
	Immediately after CRT	-17.14 (-22.19 to -12.09)	<.001	41.1	.117	
Ischemic cardiomyopathy (%)	≥50.0	-15.07 (-19.08 to -11.06)	<.001	22.5	.258	<.001
	<50.0	-31.92 (-41.88 to -21.96)	<.001	47.8	.125	
Atrial fibrillation (%)	≥50.0	-11.76 (-17.00 to -6.52)	<.001	0.0	.795	.001
	<50.0	-24.85 (-36.55 to -13.16)	<.001	80.6	<.001	
LVEF (%)	≥25.0	-30.79 (-42.77 to -18.82)	<.001	63.5	.064	<.001
	<25.0	-15.94 (-20.14 to -11.74)	<.001	19.3	.287	
LVEDD (mm)	≥70.0	-26.31 (-42.80 to -9.81)	.002	55.9	.132	.537
	<70.0	-18.98 (-26.64 to -11.32)	<.001	33.6	.222	
Study quality	High	-22.49 (-31.32 to -13.67)	<.001	79.9	<.001	.095
	Low	-16.09 (-23.70 to -8.48)	<.001	42.5	.157	

CI=confidence interval, CRT=cardiac resynchronization therapy, EF=ejection fraction, LVEDD=Left ventricular end-diastolic dimension, LVEF=left ventricular ejection fraction, WMD=weighted mean difference.

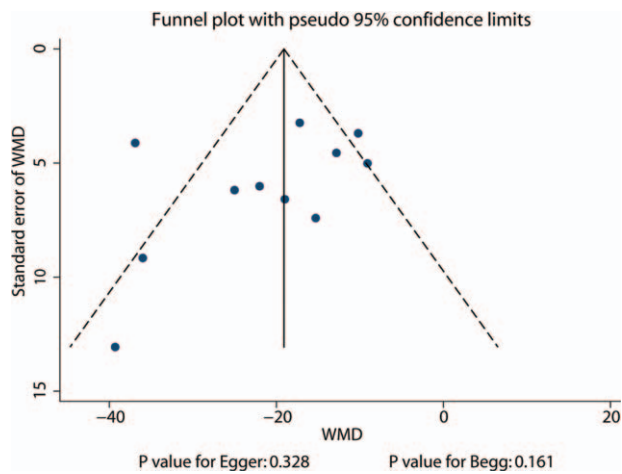


Figure 6. Publication bias for the mean change of QRS width.

3.5. Publication bias

Funnel plots could not rule out the publication biases for mean or percentage changes in QRS duration between responders and nonresponders (Figs. 6 and 7). The results showed no significant publication bias for mean change in QRS duration (P value for Egger: .328; P value for Begg: .161), whereas a potential publication bias for percentage change in QRS duration was observed (P value for Egger: .005; P value for Begg: .089). This conclusion was not altered after adjustment using the trim and fill method.^[31]

4. Discussion

This systematic review and meta-analysis was conducted based on observational studies to calculate the magnitude of changes in QRS width with the incidence of echocardiographic response to CRT. This study recruited 1524 patients from 5 prospective and 6 retrospective studies with broad range characteristics of patients. The results of this study indicated that responders versus nonresponders to CRT were associated with greater mean or percentage changes in QRS width, and these conclusions are robust. Subgroup analyses indicated that the mean reduction of QRS width in responders is significantly greater than non-

responders to CRT if pooled studies are conducted in Asia, study designed as prospective cohort studies, mean age of the patients was <65.0 years, percentage male $\geq 70.0\%$, baseline EF $< 35.0\%$ as selection criteria, measuring time of QRS during follow-up, percentage of ischemic cardiomyopathy of $<50.0\%$, atrial fibrillation of $<50.0\%$, LVEF $\geq 25.0\%$, LVEDD $\geq 70.0\%$, and high-quality studies.

The association of mean changes in QRS width with the incidence of response to CRT has already been mentioned in the previous study.^[32] This study pooled the incidence of clinical and echocardiographic responses to CRT based on 12 studies, and the results of this study indicated that shortened QRS width was associated with high incidence of responses to CRT, irrespective of clinical or echocardiographic criteria. Moreover, they found that the mean change of QRS width is more pronounced if the follow-up duration of studies was <6.0 months. The reason for this could be acute QRS shortening after device implantation immediately could predict clinical and echocardiographic response to CRT.^[22] However, the results of subgroup analyses regarding previous meta-analysis contained both clinical and echocardiographic responses to CRT, which might bias the results of subgroup analyses according to other factors. Therefore, the current systematic review and meta-analysis was conducted to update the magnitude of mean or percentage changes in QRS width between responders and nonresponders to CRT.

The results of this study were consistent with the previous meta-analysis studies, and nearly all the included studies reported similar conclusion. However, the study conducted by Chen et al^[30] reported that the average change in QRS width between responders and nonresponders showed association with marginal 95% CI. However, the shortest and the longest changes in QRS with better prognostic value regarding the incidence of response to CRT were observed.^[30] Moreover, the percentage change in QRS width in responders group was significantly pronounced than nonresponders group. The potential reason for this could be that QRS shortening is significantly correlated with improved left ventricular contractile function induced by switching from right ventricular apical pacing to biventricular pacing.^[33]

Subgroup analyses indicated that the changes in QRS width between responders and nonresponders differ when stratified by country, study design, mean age, percentage male, EF, measuring time of postimplanted QRS, ischemic cardiomyopathy, atrial fibrillation, and study quality. There are several reasons for interpreting the above results:

1. the number of studies in several subsets was smaller, affecting the comparability of subgroups;
2. uncontrolled confounders in retrospective studies were inevitable, and the results might be overestimated;
3. the severity of the disease showed significant correlation with mean age, EF, and percentage of other comorbidity, and the response to CRT could be affected by these factors;
4. the lifestyle between men and women is different, which might affect the response and clinical endpoints to CRT; and
5. the reliability of abstract data from the included studies could be affected by study quality as it depends on selection, comparability, and outcome.

However, there are several important limitations that recommend the conclusion of this meta-analysis. First, studies with retrospective design and uncontrolled confounders might bias the incidence of echocardiographic responses of CRT.

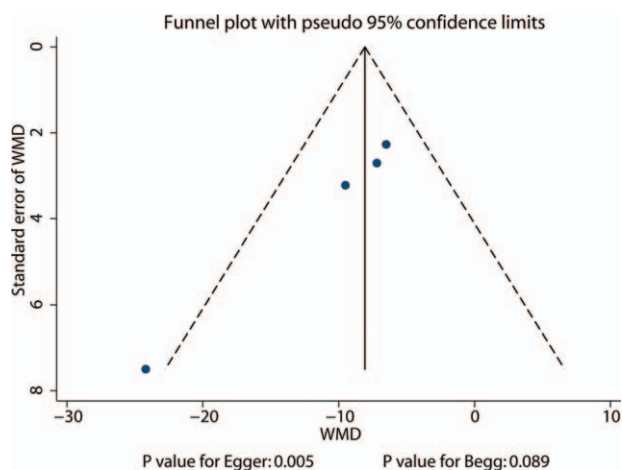


Figure 7. Publication bias for the percentage change of QRS width.

Second, the abstract data categories by responders and non-responders, and the prognostic value of the change in QRS width regarding the incidence of echocardiographic responses to CRT could not be calculated. Third, the definition of response among included studies is variable, which could affect the magnitude of change in QRS width between responders and nonresponders to CRT. Fourth, the analysis based on published data, and unpublished data were not available, which might induce potential selection as well as publication biases. Finally, the analysis of this study was conducted based on pooled data, stratified analyses could not be conducted based on specific status, and current analysis was based on average status of the patients' characteristics.

In conclusion, the greater reduction in QRS width showed significant association with the incidence of echocardiographic response of CRT. The present study provides the results regarding the association of change in QRS width between responders and nonresponders to CRT, which could identify patients at high risk to failed about CRT. Moreover, subgroup analyses were conducted to explore the association of change in QRS width with response to CRT in patients with specific characteristics. Further large-scale prospective studies are needed to evaluate the prognostic values of QRS width on the incidence of echocardiographic responses to CRT.

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Project administration: Ming Chen, Lianghua Xia.

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Writing – original draft: Jing Ma, Yi Liu, Yun Dong.

Writing – review & editing: Yi Liu.

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