Modalities of ventricular pacing for cardiac resynchronization therapy in patients with heart failure: a meta-analysis and systematic review

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Abstract

Introduction: This meta-analysis evaluated 14 studies which compared clinical and functional outcomes after different cardiac resynchronization therapy (CRT) modalities.
Material and methods: Relevant studies were selected from the Medline, PubMed, Cochrane, and Google Scholar databases until June 27th, 2016. We analyzed and compared the clinical outcomes (peak O_2 consumption and LVEF) and functional outcomes (6-min walk distance and quality of life (SF-36)) of HF patients who received different CRT modalities with outcomes in patients who received conventional univentricular therapy.
Results: There was no significant difference in post-treatment 6-min walking distance between the biventricular (BiV) and left/right univentricular (LUV/RUV) groups (standardized difference in means = 0.049, 95% CI: –0.119 to 0.217, p = 0.566), or between the BiV and triventricular (TriV) groups (standardized difference in means = 0.035, 95% CI: –0.270 to 0.340, p = 0.822). Peak O_2 consumption was comparable between BiV and LUV/RUV groups (standardized difference in means = 0.306, 95% CI: –0.002 to 0.614, p = 0.052). Patients in the TriV group had a significant improvement in LVEF compared to the BiV group (standardized difference in means = 0.647, 95% CI: 0.313 to 0.982, p < 0.001).
Conclusions: TriV CRT is an attractive alternative to univentricular or BiV pacing for heart failure patients. It is necessary to conduct further large randomized trials to validate our present data.

Key words: heart failure, cardiac resynchronization therapy, biventricular, triventricular, left ventricular ejection fraction.

Introduction

Cardiovascular disease is the leading cause of mortality in the world, with more than 22 million people suffering from heart failure (HF) [1]. The New York Heart Association (NYHA) classification system categorizes HF patients into class I–IV based on the degree of effort needed to elicit symptoms [2].

A number of cardiac devices are used to achieve hemodynamic improvement in HF patients. Patients who require pacing for atrioventric-

ular block or bradycardia after coronary artery bypass grafting (CABG) are now routinely treated with right univentricular (RUV) pacing. However, RUV has been shown to result in dyssynchrony between the two ventricles, arrhythmias, and HF [3, 4]. Cardiac resynchronization therapy (CRT) achieves coordinated pacing of the left and right ventricles by addition of a left ventricular (LV) pacing lead to a pacemaker or defibrillator system which includes a right ventricular (RV) and possibly a right atrial lead [5]. Targeted resynchronization therapy in the early period after cardiac surgery was shown to reduce morbidity and mortality in HF patients [6], and CRT is currently the recommended therapy for selected patients who have refractory HF with systolic dysfunction and a QRS duration ≥ 120 ms on optimal medical therapy [7].

The three major CRT modalities are: 1) simultaneous biventricular (BiV) pacing, 2) sequential BiV pacing where the timing of RV and LV stimulation is programmed to allow one ventricle to be activated before the other, and 3) LV pacing. A number of studies have compared outcomes of different CRT modalities. Left univentricular pacing (LUV) was shown to significantly improve peak oxygen consumption, 6-minute walk distance and the quality of life in chronic HF patients who had LV systolic dysfunction and QRS interval > 150 ms [8]. Patients who received RUV pacing showed more pronounced progression of heart failure symptoms compared to patients who received BiV pacing [9, 10], and BiV has been shown to prevent adverse remodeling induced by RUV pacing [11]. BiV, when used as adjunctive therapy to pharmacologic strategies, reduced the risk of sudden cardiac death, and reduced hospitalization rates in patients classified as NYHA class III or IV, who had an ejection fraction of 35% or less [12, 13]. Increased heart rate was recently shown to be significantly associated with enhanced contractility in patients receiving BiV pacing compared to those receiving single-site RUV or LUV stimulation [14], and the rise in contractility with increasing stimulation rates was higher for BiV compared to univentricular pacing [15]. The BiV was associated with a significant clinical benefit and lower mortality compared to isolated left ventricular pacing [16].

In contrast, other studies reported no significant difference in clinical benefits between LUV pacing and BiV pacing [17, 18]. Left univentricular pacing pacing was also non-inferior to BiV with respect to improvement in NYHA class and reverse remodeling [19–21]. Additionally, it was recently reported that LV electrical delay, which is a predictor of the acute hemodynamic response to CRT, was independent of the pacing strategy [22]. Studies have also reported that tri-ventricular CRT configurations (TriV) using two RV leads and one LV lead [23] or one RV lead and two LV leads [24] were shown to be safe, effective, and provided a benefit in ventricular remodeling compared to conventional CRT.

In this study, we analyzed the findings from 14 different studies which compared the clinical outcomes (peak O_2 consumption and LVEF) and functional outcomes (6-min walk distance and quality of life (SF-36)) of HF patients who received different CRT modalities with outcomes in patients who received conventional univentricular therapy.

Material and methods

This meta-analysis analyzed data from 14 studies which compared clinical outcomes and functional outcomes in congestive heart failure (CHF) patients who received biventricular with those who received univentricular (either left or right ventricular) stimulation for CRT. Studies that compared bi-ventricular versus tri-ventricular pacing were also included. The Medline, PubMed, Cochrane, and Google Scholar databases were searched (until June 27th, 2016) using the keywords heart failure, atrial fibrillation, cardiac resynchronization therapy, biventricular, quality of life, and functional status. Reference lists of relevant studies were hand-searched.

Selection criteria

Inclusion criteria were: 1) randomized controlled studies, including cross-over RCTs, 2) studies reporting on heart failure (any stage) with/without atrial fibrillation (including all grades of AF), 3) intervention studies on resynchronization therapy (including CRT-D, CRT-P, etc.) which compared the efficacy of univentricular (mainly LUV), biventricular, and triventricular pacing.

Exclusion criteria were: 1) studies with no quantitative primary outcome. Prospective studies, retrospective studies, single arm studies, case control studies, cohort studies, letters, comments, editorials, case reports, proceedings, and personal communications were excluded.

Study selection and data extraction

Studies were identified by two independent reviewers. Where there was uncertainty regarding eligibility, a third reviewer was consulted. The study selection procedure is presented in Figure 1. Data extracted from the studies which met the eligibility criteria included the name of the first author, year of publication, study design, number of participants in each group, participants' age and gender, and the major outcomes.

Quality assessment

The Cochrane Collaboration's tool was used to assess the quality of the included studies. Quality assessment was based on seven criteria: random se-

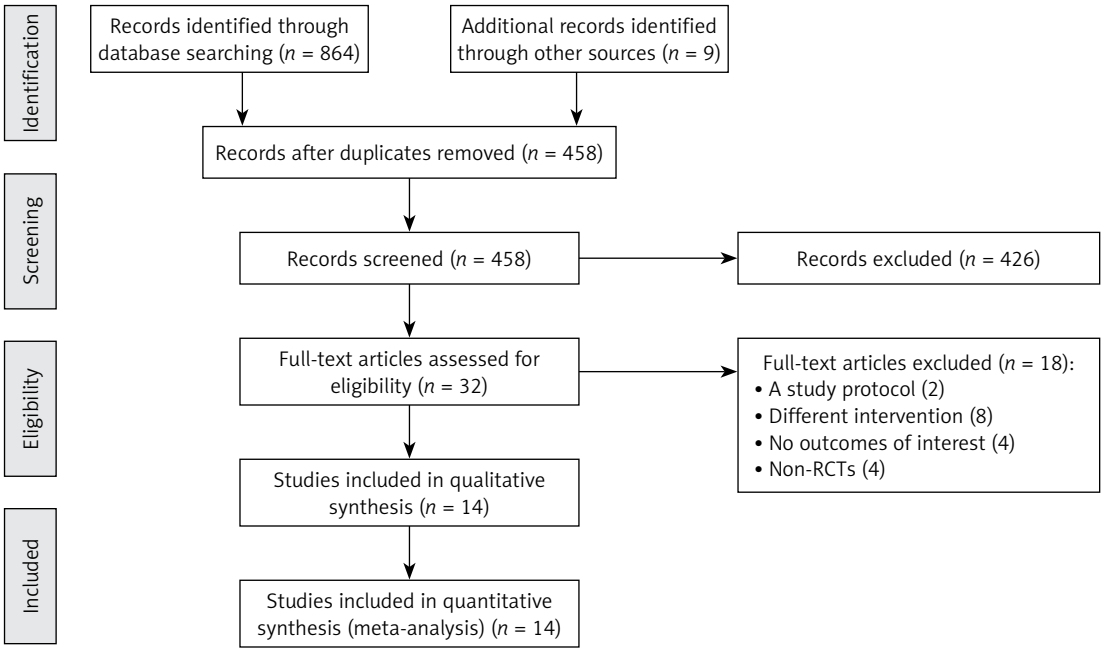


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram

quence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and intention to treat analysis [25, 26].

Outcome measures

The primary outcomes measured in this meta-analysis were the 6-min walk distance and peak VO_2 consumption of HF patients after receiving CRT. The secondary outcome was the clinical treatment response rate and improvement in quality of life. Outcomes were recorded at baseline and after intervention.

Statistical analysis

Standardized differences in the change from baseline between the treatment groups were used as the measure of effect size. Selected RCTs that compared the treatment effect of TriV with that of BiV and studies which compared the effect of BiV with that of left or right univentricular pacing (LUV/RUV) were analyzed separately. Subgroup analysis was performed for all LUV and RUV outcomes for univentricular pacing.

Study heterogeneity was presented using a χ^2-based Cochran's Q statistic and I^2. For the Q statistic, p-values < 0.10 were considered statistically significant for heterogeneity. For the I^2 statistic, heterogeneity was assessed as follows: no heterogeneity (I^2 = 0–25%), moderate heterogeneity (I^2 = 25–50%), large heterogeneity (I^2 = 50–75%), and extreme heterogeneity (I^2 = 75–100%). Pooled estimates of the standardized difference in means were determined using the DerSimonian-Laird random-effects model [24]. A two-sided p-value of < 0.05 was considered significant. Sensitivity analysis was conducted using the leave-one-out approach. Publication bias was assessed if more than 10 studies were included in the meta-analysis for each outcome [27]. All analyses were performed using the Comprehensive Meta-Analysis statistical software, version 2.0 (Biostat, Englewood, NJ, USA).

Results

Characteristics of selected RCTs

A total of 864 studies were identified, of which 32 full text articles were finally assessed for eligibility. Of these, 4 studies were not RCTs, 4 studies did not report outcomes of interest, 8 studies had different interventions, and 2 studies were excluded for being a study protocol (Figure 1). Of the 14 RCTs which were included in the final analysis, six were cross-over trials [19, 21, 28–31]. Three RCTs compared the effect of TriV to that of BiV [23, 29, 30], and the sample size ranged from 18 to 306 patients. The mean or median age ranged from 59 to 73 years, and the studies had a majority of male participants. Three of the studies reported that diabetes mellitus (DM) and hypertension were the most prevalent co-morbidities among the study patients. The duration over which outcomes were measured ranged from 12 weeks to 3 years after the intervention (Table I).

Primary outcome measures

There was no heterogeneity across studies which reported 6-min walk distance, regardless of wheth-

Table I. Summary of basic characteristics of selected RCTs for meta-analysis

Author (year)	Study design	Trial name/no.	Intervention	No. of patients	Mean age [years]	Male (%)	Ischemic heart disease (%)	Co-morbidity	Max LV d*P*/d*t* [mm Hg/s]	Time point of outcome measured
Anselme (2015)	RCT	NCT00887237	TriV	20	68.9	82.9	42.9			12 months
			BiV	20	69.9	61.0	43.9			
Stockburger (2014)	RCT	Prevent-HF	BiV	25	73	76.0	38.0	Hypertension: 86%		12 months
			RUV	31	70	84.0	42.0	Hypertension: 81%		
Taborsky (2013)	Cross-over RCT	TUGENDHAT	BiV	46	Median: 72.0	62.7		DM: 23.9% Hypertension: 4.3% Hypo/hyperthyroidism: 10.9% Other: 4.3%	0 (0, 1400)[a]	12 months
			RUV	56				DM: 23.2% Hypertension: 3.6% Hypo/hyperthyroidism: 8.9% Other: 3.6%	0.00 (0.00, 1550.00)[a]	
Rogers (2012)	Cross-over RCT		TriV (simultaneous)	37	66.7	81.4	62.8			12 months
			BiV (simultaneous)							
Thibault (2011)	Cross-over RCT	NCT00901212	BiV (simultaneous)	61	60.9	75.2	51.2	Hypertension: 52.1% DM: 33.9% COPD: 16.5%		
			LUV	60						6 + 6 months (cross-over design)
Albertsen (2011)	RCT	NCT00228241	BiV	25	Median: 76	68.0				3 years
			RUV	25	Median: 76	68.0				
Boriani (2010)	RCT	B-LEFT HF	BiV	90	66	76.0	53.0			6 months
			LUV	86	66	73.0	51.0			

Table I. Cont.

Sedlacek (2010)	RCT		BiV	16	59.6	56.3			12 months
			LUV	17	62.1	64.7			
Leclercq (2008)	Cross-over RCT	TRIP-HF	TRiV	26	70	100.0	27.0		Combined 6 and 9 months
			BiV						
Valzania (2008)	RCT		BiV	11	Median: 66	72.7			3 months
			LUV	11	Median: 61	81.8			
Sirker (2007)	Cross-over RCT	LOLA ROSE	BiV (sequential)	18	72.2	89.0	78.0		8 + 8 weeks (cross-over design)
			LUV						
Rao (2007)	RCT	DECREASE-HF	BiV (sequential)	104	66.6	67.0	67.0	182 ±207[b]	6 months
			BiV (simultaneous)	101	66.2	68.0	57.0	291 ±271[b]	
			LUV	101	67.4	65.0	66.0	106 ±192[b]	
Gasparini (2006)	RCT	BELIEVE	BiV	33	66.9	94.4			12 months
			LUV	36	66.5	87.9			
Auricchio (2002)	Cross-over RCT		BiV	24	59	45.8	42.0	17.0 ±15.8[b]	12 weeks
			LUV	17	60	58.8	6.0	18.4 ±16.6[b]	

[a]Presented as median (5th–95th percentile). [b]Presented as mean ± standard deviation.

er the study compared BiV vs. LUV/RUV (I^2 = 0%, p = 0.530) or TriV vs. BiV (I^2 = 0%, p = 0.373). Patients who received BiV showed no significant improvement in the 6-min walk distance compared to patients treated with univentricular pacing (standardized difference in means = 0.049, 95% CI: –0.119 to 0.217, p = 0.566). Similarly, patients treated with TriV showed no significant improvement in 6-min walk distance compared to patients treated with BiV (standardized difference in means = 0.035, 95% CI: –0.270 to 0.340, p = 0.822) (Figure 2 A).

Patients in the BiV group had a greater change in peak VO_2 compared to patients in the LUV/RUV group, although this was not statistically significant (standardized difference in means = 0.306, 95% CI: –0.002 to 0.614, p = 0.052). Comparison of the change in peak VO_2 between the TriV and BiV groups was only performed in one RCT, and there was no significant difference between the two groups (Figure 2 B).

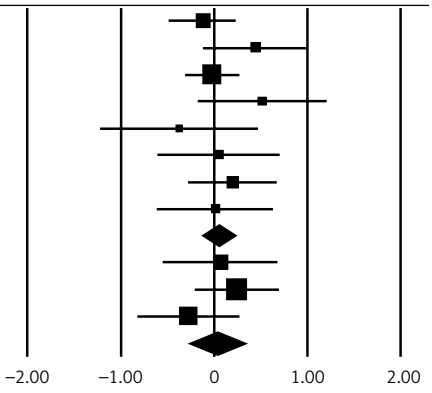
Secondary outcome measures

There was only mild heterogeneity across the three trials which compared left ventricular ejection fraction (LVEF) in the TriV and BiV groups (I^2 = 11.2%, p = 0.324). On the other hand, there was moderate heterogeneity across eight trials which compared LVEF in the BiV and the LUV/RUV groups (I^2 = 38.6%, p = 0.122). The LVEF in BiV-treated patients was similar to that of LUV/RUV-treated patients (standardized difference in means = 0.147, 95% CI: –0.041 to 0.335, p = 0.125). However, patients in the TriV group had a significantly higher LVEF compared to patients in the BiV group (standardized difference in means = 0.647, 95% CI: 0.313 to 0.982, p < 0.001) (Figure 3 A).

There was no significant heterogeneity across the studies which compared the quality of life in the BiV and LUV/RUV groups (I^2 = 0%, p = 0.689), or the studies which compared quality of life in the TriV and BiV groups (I^2 = 0%, p = 0.649). There was no difference in the change of quality of life between the BiV and LUV/RUV groups (standardized difference in means = 0.004, 95% CI: –0.167 to 0.174, p = 0.966) or between the TriV and BiV groups (standardized difference in means = –0.133, 95% CI: –0.438 to 0.172, p = 0.392) (Figure 3 B).

A

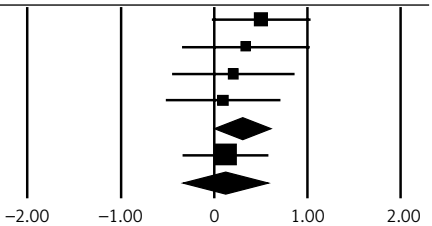
Group by	Study name	Std diff in means	Standard error	Lower limit	Upper limit	*Z*-value	*P*-value
BiV vs. LUV/RUV	Thibault (2011)	–0.120	0.182	–0.477	0.237	–0.659	0.510
	Albertsen (2011)	0.443	0.286	–0.118	1.004	1.548	0.122
	Boriani (2010)	–0.025	0.151	–0.321	0.270	–0.169	0.866
	Sedlacek (2010)	0.514	0.354	–0.180	1.208	1.452	0.146
	Valzania (2008)	–0.373	0.430	–1.216	0.470	–0.867	0.386
	Sirker (2007)	0.051	0.333	–0.603	0.704	0.153	0.879
	Gasparini (2006)	0.197	0.242	–0.277	0.670	0.814	0.416
	Auricchio (2002)	0.010	0.317	–0.611	0.632	0.033	0.974
	Total	0.049	0.086	–0.119	0.217	0.573	0.566
TriV vs. BiV	Anselme (2015)	0.066	0.316	–0.554	0.685	0.207	0.836
	Rogers (2012)	0.235	0.233	–0.222	0.692	1.007	0.314
	Leclercq (2008)	–0.274	0.279	–0.820	0.272	–0.984	0.325
	Total	0.035	0.156	–0.270	0.340	0.224	0.822



Heterogeneity test: BiV vs. LUV/RUV: I^2 = 0%, p = 0.530
TriV vs. BiV: I^2 = 0%, p = 0.373

B

Group by	Study name	Std diff in means	Standard error	Lower limit	Upper limit	*Z*-value	*P*-value
BiV vs. LUV/RUV	Stockburger (2014)	0.506	0.273	–0.029	1.041	1.854	0.064
	Sedlacek (2010)	0.341	0.351	–0.347	1.028	0.971	0.332
	Sirker (2007)	0.208	0.334	–0.448	0.863	0.621	0.535
	Auricchio (2002)	0.097	0.317	–0.525	0.718	0.305	0.761
	Total	0.306	0.157	–0.002	0.614	1.947	0.052
TriV vs. BiV	Rogers (2012)	0.124	0.233	–0.332	0.580	0.533	0.594
	Total	0.124	0.233	–0.332	0.580	0.533	0.594



Heterogeneity test: BiV vs. LUV/RUV: I^2 = 0%, p = 0.784
TriV vs. BiV: I^2 = 0%, p = 1.000

Figure 2. Forest plots for comparison of treatment effect of biventricular versus univentricular or triventricular CRT in patients with HF. **A** – 6-min walk distance, **B** – peak VO_2

Sensitivity analysis

Results from the leave-one-out sensitivity analysis showed that the statistical significance and direction of association did not change when each study was removed one at a time for the comparison of BiV vs. LUV/RUV for walk distance (Figure 4 A). The direction of association changed when the Rogers *et al.* [30] study was removed for the comparison of TriV vs. BiV for walk distance (Figure 4 B). Figure 4 C shows that Auricchio *et al.* [31] had an impact on peak VO_2 consumption across four studies.

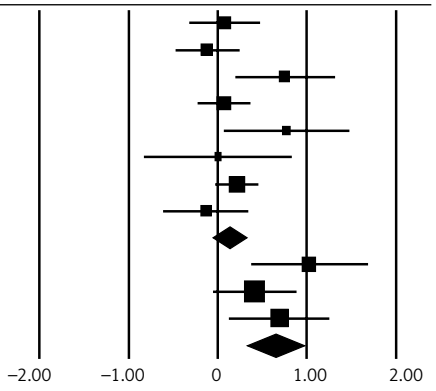
Subgroup analysis

Our subgroup analysis showed no significant difference in 6-min walk distance in four studies which compared the BiV and LUV groups (standardized difference in means = 0.010, 95% CI: –0.166 to 0.187, p = 0.909) and one study which compared the BiV and RUV groups (standardized difference in means = 0.443, 95% CI: –0.118 to 1.004, p = 0.122) (Figure 5 A). Our analysis showed no significant difference in peak VO_2 in two studies which compared the BiV and LUV groups (standardized difference in means = 0.207, 95% CI: –0.170 to 0.584, p = 0.283) and one study which compared the BiV and RUV groups (standardized difference in means = 0.506, 95% CI: –0.029 to 1.041, p = 0.064) (Figure 5 B). We found no significant difference in the pooled estimate for LVEF in three studies which compared the BiV and LUV groups (standardized difference in means = 0.095, 95% CI: –0.089 to 0.280, p = 0.310), and two studies which compared the BiV and RUV groups (standardized difference in means = 0.384, 95% CI: –0.283 to 1.050, p = 0.259) (Figure 5 C). Furthermore, we found no significant association between BiV or LUV treatment and quality of life (standardized difference in means = –0.014, 95% CI: –0.204 to 0.176, p = 0.885) (Figure 5 D).

A

Group by	Study name	Std diff in means	Standard error	Lower limit	Upper limit	*Z*-value	*P*-value
BiV vs. LUV/RUV	Taborsky (2013)	0.076	0.199	–0.314	0.466	0.380	0.704
	Thibault (2011)	–0.111	0.182	–0.468	0.246	–0.610	0.542
	Albertsen (2011)	0.759	0.293	0.185	1.333	2.593	0.010
	Boriani (2010)	0.071	0.151	–0.224	0.367	0.472	0.637
	Sedlacek (2010)	0.773	0.361	0.065	1.481	2.141	0.032
	Valzania (2008)	0.000	0.426	–0.836	0.836	0.000	1.000
	Rao (2007)	0.208	0.122	–0.031	0.447	1.708	0.088
	Gasparini (2006)	–0.127	0.241	–0.600	0.345	–0.528	0.597
	Total	0.147	0.096	–0.041	0.335	1.534	0.125
TriV vs. BiV	Anselme (2015)	1.025	0.336	0.366	1.684	3.048	0.002
	Rogers (2012)	0.416	0.235	–0.045	0.877	1.770	0.077
	Leclercq (2008)	0.691	0.286	0.132	1.251	2.421	0.015
	Total	0.647	0.171	0.313	0.982	3.794	0.000

Heterogeneity test: BiV vs. LUV/RUV: I^2 = 38.6%, p = 0.122
TriV vs. BiV: I^2 = 11.2%, p = 0.324



B

Group by	Study name	Std diff in means	Standard error	Lower limit	Upper limit	*Z*-value	*P*-value
BiV vs. LUV/RUV	Taborsky (2013)	0.078	0.199	–0.312	0.469	0.394	0.694
	Thibault (2011)	–0.106	0.182	–0.463	0.250	–0.584	0.559
	Boriani (2010)	0.000	0.151	–0.296	0.296	0.000	1.000
	Sedlacek (2010)	0.317	0.350	–0.370	1.004	0.904	0.366
	Valzania (2008)	–0.479	0.432	–1.327	0.368	–1.109	0.268
	Sirker (2007)	0.360	0.336	–0.299	1.018	1.070	0.285
	Auricchio (2002)	–0.149	0.317	–0.771	0.473	–0.470	0.638
	Total	0.004	0.087	–0.167	0.174	0.042	0.966
TriV vs. BiV	Anselme (2015)	–0.048	0.316	–0.668	0.572	–0.152	0.879
	Rogers (2012)	–0.292	0.234	–0.751	0.166	–1.251	0.211
	Leclercq (2008)	0.026	0.277	–0.518	0.569	0.093	0.926
	Total	–0.133	0.156	–0.438	0.172	–0.855	0.392

Heterogeneity test: BiV vs. LUV/RUV: I^2 = 0%, p = 0.689
TriV vs. BiV: I^2 = 0%, p = 0.649

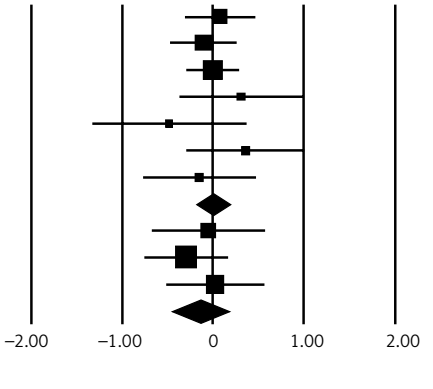


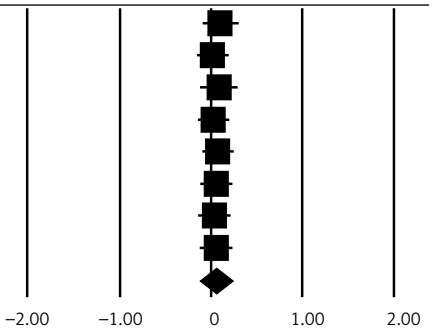
Figure 3. Forest plots for comparison of treatment effect of biventricular versus univentricular or triventricular CRT in patients with HF. **A** – Left ventricular ejection fraction, **B** – quality of life

A

Study name	Std diff in means	Standard error	Lower limit	Upper limit	*Z*-value	*P*-value
Thibault (2011)	0.098	0.097	–0.093	0.288	1.003	0.316
Albertsen (2011)	0.010	0.090	–0.166	0.187	0.115	0.909
Boriani (2010)	0.085	0.104	–0.120	0.289	0.814	0.415
Sedlacek (2010)	0.020	0.088	–0.153	0.194	0.228	0.819
Valzania (2008)	0.067	0.088	–0.105	0.238	0.762	0.446
Sirker (2007)	0.050	0.090	–0.126	0.226	0.559	0.576
Gasparini (2006)	0.028	0.092	–0.152	0.208	0.304	0.761
Auricchio (2002)	0.053	0.090	–0.123	0.229	0.592	0.554
Total	0.049	0.086	–0.119	0.217	0.573	0.566

Statistics with study removed

Std diff in means and 95% CI with study removed

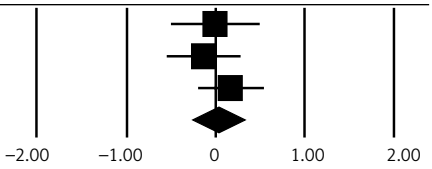


B

Study name	Std diff in means	Standard error	Lower limit	Upper limit	*Z*-value	*P*-value
Anselme (2015)	0.003	0.253	–0.494	0.500	0.013	0.990
Rogers (2012)	–0.126	0.209	–0.536	0.284	–0.601	0.548
Leclercq (2008)	0.175	0.188	–0.193	0.543	0.933	0.351
Total	0.035	0.156	–0.270	0.340	0.224	0.822

Statistics with study removed

Std diff in means and 95% CI with study removed



C

Study name	Std diff in means	Standard error	Lower limit	Upper limit	*Z*-value	*P*-value
Stockburger (2014)	0.207	0.192	–0.170	0.584	1.075	0.283
Sedlacek (2010)	0.297	0.176	–0.047	0.642	1.691	0.091
Sirker (2007)	0.334	0.178	–0.015	0.684	1.875	0.061
Auricchio (2002)	0.374	0.181	0.019	0.729	2.068	0.039
Total	0.306	0.157	–0.002	0.614	1.947	0.052

Statistics with study removed

Std diff in means and 95% CI with study removed

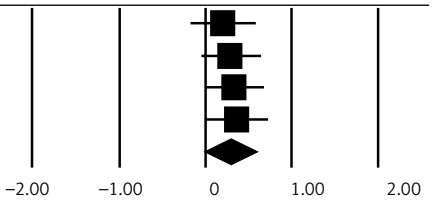


Figure 4. Sensitivity analysis for treatment effect of biventricular versus univentricular or triventricular CRT in patients with HF. **A** – 6-min walk distance (BiV vs. LUV/RUV), **B** – 6-min walk distance (TriV vs. BiV), and **C** – peak VO_2 (BiV vs. LUV/RUV)

Publication bias

Publication bias was not assessed since less than 10 studies were included in the meta-analysis for each outcome.

Quality assessment

Quality assessment was performed for all 14 included studies (Figure 6). Most of the studies had an unclear bias for allocation concealment (Figure 6 A), except for the Boriani *et al.* and the Leclercq *et al.* studies [20, 29]. For treatment therapies such as those included in this analysis, it is difficult, and unethical, to achieve allocation concealment since the physicians need to assess the different treatments based on the condition of individual patients.

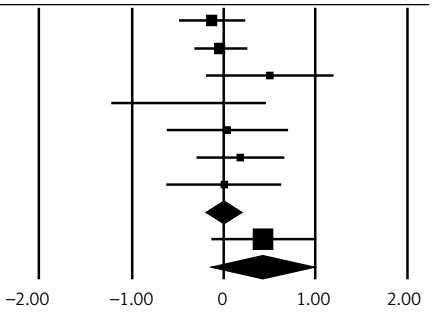
All the studies except for Rogers *et al.* [30] had an unclear or high risk of performance bias. Complete blinding of participants and personnel for interventional treatments was difficult due to ethical reasons and the health conditions of individual patients. In general, Figure 6 A shows that over half of the studies had a low risk of bias in terms of random sequencing, attrition, reporting bias and intention-to-treat analysis, suggesting that the quality of our analysis was adequate.

Discussion

This meta-analysis compared the clinical and functional outcomes of CRT in 14 studies which used univentricular, biventricular, or triventricular pacing to treat HF patients. There was no signif-

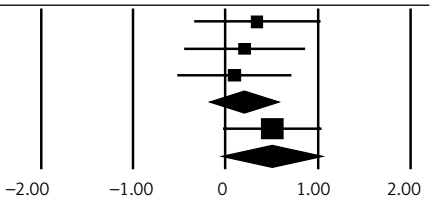
A

Group by	Study name	Statistics for each study					
		Std diff in means	Standard error	Lower limit	Upper limit	*Z*-value	*P*-value
BiV vs. LUV	Thibault (2011)	–0.120	0.182	–0.477	0.237	–0.659	0.510
	Boriani (2010)	–0.025	0.151	–0.321	0.270	–0.169	0.866
	Sedlacek (2010)	0.514	0.354	–0.180	1.208	1.452	0.146
	Valzania (2008)	–0.373	0.430	–1.216	0.470	–0.867	0.386
	Sirker (2007)	0.051	0.333	–0.603	0.704	0.153	0.879
	Gasparini (2006)	0.197	0.242	–0.277	0.670	0.814	0.416
	Auricchio (2002)	0.010	0.317	–0.611	0.632	0.033	0.974
	Total	0.010	0.090	–0.166	0.187	0.115	0.909
BiV vs. RUV	Albertsen (2011)	0.443	0.286	–0.118	1.004	1.548	0.122
	Total	0.443	0.286	–0.118	1.004	1.548	0.122



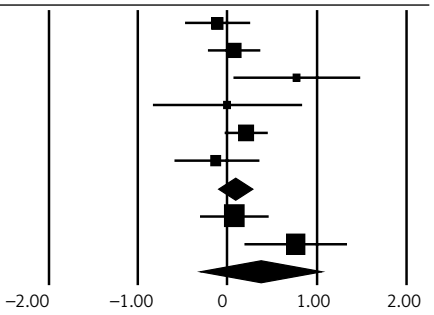
B

Group by	Study name	Statistics for each study					
		Std diff in means	Standard error	Lower limit	Upper limit	*Z*-value	*P*-value
BiV vs. LUV	Sedlacek (2010)	0.341	0.351	–0.347	1.208	0.971	0.332
	Sirker (2007)	0.208	0.334	–0.448	0.863	0.621	0.535
	Auricchio (2002)	0.097	0.317	–0.525	0.718	0.305	0.761
	Total	0.207	0.192	–0.170	0.584	1.075	0.283
BiV vs. RUV	Stockburger (2014)	0.506	0.276	–0.029	1.041	1.854	0.064
	Total	0.506	0.273	–0.029	1.041	1.854	0.064



C

Group by	Study name	Statistics for each study					
		Std diff in means	Standard error	Lower limit	Upper limit	*Z*-value	*P*-value
BiV vs. LUV	Thibault (2011)	–0.111	0.182	–0.468	0.246	–0.610	0.542
	Boriani (2010)	0.071	0.151	–0.224	0.367	0.472	0.637
	Sedlacek (2010)	0.773	0.361	0.065	1.481	2.141	0.032
	Valzania (2008)	0.000	0.426	–0.836	0.836	0.000	1.000
	Rao (2007)	–0.208	0.122	–0.447	0.031	–1.708	0.088
	Gasparini (2006)	–0.127	0.241	–0.600	0.345	–0.528	0.597
	Total	0.095	0.094	–0.089	0.280	1.015	0.310
BiV vs. RUV	Taborsky (2013)	0.076	0.199	–0.314	0.466	0.380	0.704
	Albertsen (2011)	0.759	0.293	0.185	1.333	2.593	0.010
	Total	0.384	0.340	–0.283	1.050	1.128	0.259



D

Group by	Study name	Statistics for each study					
		Std diff in means	Standard error	Lower limit	Upper limit	*Z*-value	*P*-value
BiV vs. LUV	Thibault (2011)	–0.106	0.182	–0.463	0.250	–0.584	0.559
	Boriani (2010)	0.000	0.151	–0.296	0.296	0.000	1.000
	Sedlacek (2010)	0.317	0.350	–0.370	1.004	0.904	0.366
	Valzania (2008)	–0.479	0.432	–1.327	0.368	–0.109	0.268
	Sirker (2007)	0.360	0.336	–0.299	1.018	1.070	0.285
	Auricchio (2002)	–0.149	0.317	–0.771	0.473	–0.470	0.638
	Total	–0.014	0.097	–0.204	0.176	–0.145	0.885
BiV vs. RUV	Taborsky (2013)	0.078	0.199	–0.312	0.469	0.394	0.694
	Total	0.078	0.199	–0.312	0.469	0.394	0.694

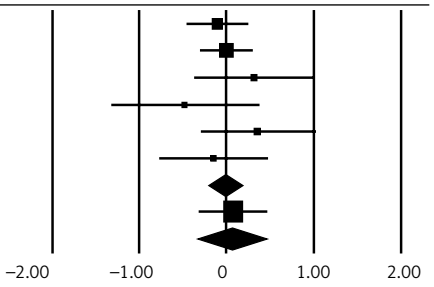


Figure 5. Subgroup analysis for treatment effect of biventricular versus univentricular CRT in patients with HF. **A** – 6-min walk distance, **B** – peak VO_2, **C** – left ventricular ejection fraction, **D** – quality of life

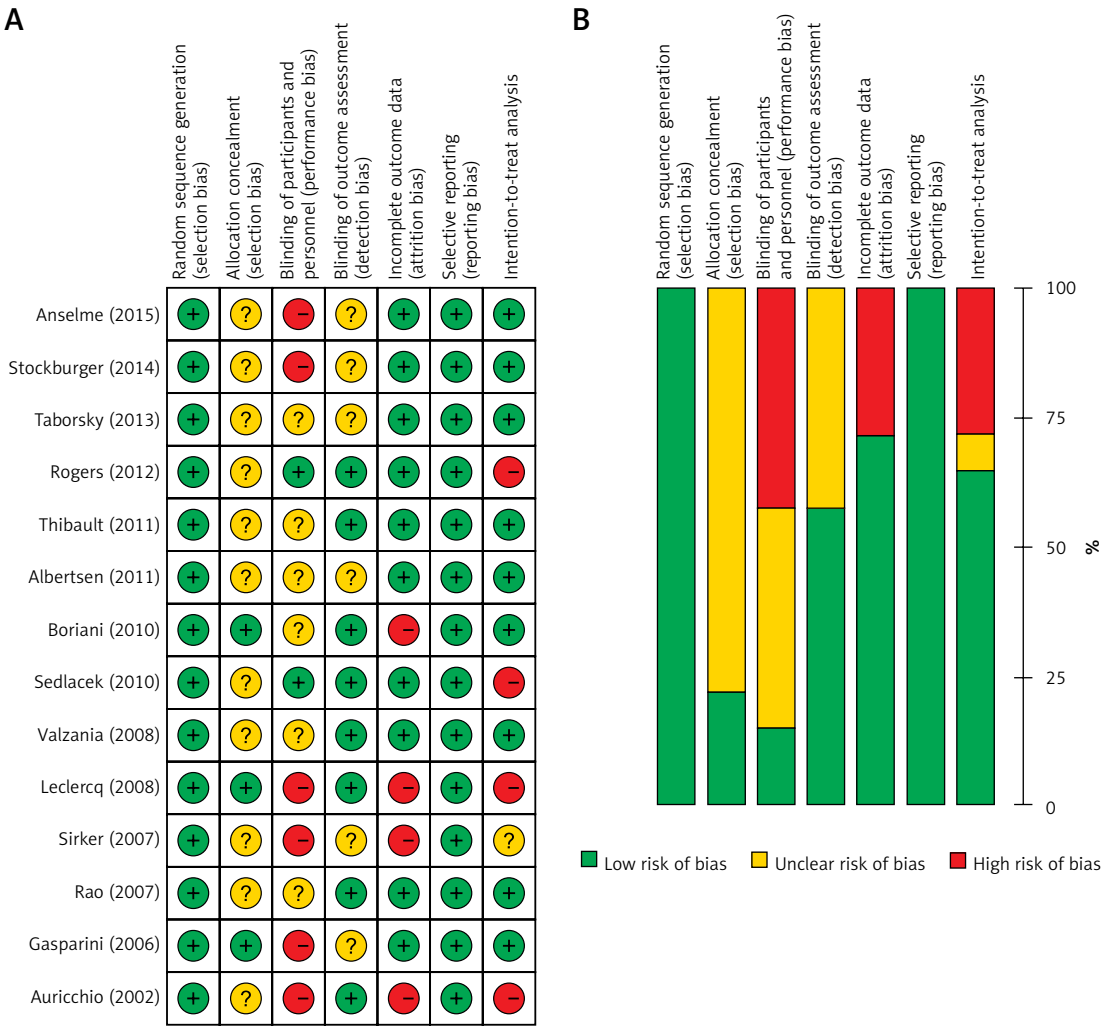


Figure 6. Quality assessment on (**A**) risk of bias for individual studies, and (**B**) summary of included studies

icant differences in the 6-min walking distance, change in peak VO_2 consumption or quality of life between patients who received univentricular, biventricular, or triventricular pacing. However, patients who received triventricular CRT had a significant improvement in LVEF compared to patients who received biventricular pacing.

Although a number of studies demonstrated that BiV pacing was associated with superior outcomes compared to conventional CRT [32], LUV pacing [33], and RUV pacing in patients without advanced HF [34], other studies reported no significant difference in improvement in NYHA scores and reverse remodeling between patients who received BiV pacing and those who received LUV pacing [20, 21], as well as between those who received BiV pacing and those who received RUV pacing [28]. Additionally, patients who failed to respond to BiV pacing responded to LUV pacing [19]. Inconsistencies in comparisons between LUV and BiV pacing modalities have been attributed to differences in the LV activation pattern, which could be differentially affected by the atrioventricular (AV) programming or atrial pacing [35].

TriV pacing is a relatively novel technique that may provide a benefit in ventricular remodeling compared to conventional CRT. TriV was recently shown to result in a higher proportion of patients with a gain in LVEF of more than 5%, 10% and 15% compared to conventional CRT [23]. These data were consistent with previous studies showing that TriV resulted in significantly higher 6-minute walk distance, LV end-systolic volume, and ejection fraction [30] and significantly more LV reverse remodeling [29] compared to the BiV modality.

Our study pooled data from only RCTs to minimize potential bias for a more robust result. Our sensitivity analysis using the leave-one-out approach showed that exclusion of one study did not change our results significantly. Subgroup analysis by stratification of the LUV and RUV univentricular pacing groups was performed, and showed no significant difference in the assessed outcomes between the RUV and BiV groups or between the

LUV and BiV groups. To the best of our knowledge, ours is the first meta-analysis that compared the clinical and functional efficacy of CRT using different pacing methods. Further studies are necessary to validate these conclusions.

Our meta-analysis had a number of limitations. Firstly, our pooled data set was small, since only a limited number of studies fit our inclusion criteria. Some outcomes were analyzed with only one or two studies, which could lead to a high probability of bias. Secondly, there was high heterogeneity for the secondary outcomes. This may also be caused by differences in the etiology of HF between studies. Subgroup analysis based on etiology of HF was not performed due to insufficient information for individual patients. Large differences in follow-up time (ranging from 12 weeks to 3 years) may also be a potential reason for heterogeneity, since HF is a chronic disease. Future studies are necessary to assess the efficacy of TriV pacing with respect to survival and long-term complications. A systematic comparison of the efficacy of CRT with medical therapy is clinically significant for optimizing treatment for HF in patients who fail to respond or are intolerant to conventional treatment.

In conclusion, our meta-analysis suggested that TriV CRT is an attractive alternative to univentricular or BiV pacing for the improvement of LVEF. It is necessary to conduct further large randomized trials to validate our present data.

Acknowledgments

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Conflict of interest

The authors declare no conflict of interest.

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