Clinical outcomes of automatic algorithms in cardiac resynchronization therapy: Systematic review and meta-analysis

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BACKGROUND Algorithms to automatically adjust atrioventricular (AV) and interventricular (VV) intervals in cardiac resynchronization therapy (CRT) devices are common, but their clinical efficacy is unknown.

OBJECTIVE The purpose of this study was to evaluate automatic CRT algorithms in patients with heart failure for the reduction of mortality, heart failure hospitalizations, and clinical improvement.

METHODS We performed a systematic review and meta-analysis of randomized controlled trials (RCTs) in patients with CRT using automatic algorithms that change AV and VV intervals dynamically without manual input, on a beat-to-beat basis. We performed a subgroup analysis including intracardiac electrogram-based (EGM) algorithms and contractility-based algorithms.

RESULTS Nine RCTs with 8531 participants were included, of whom 4275 (50.1%) were randomized to automatic algorithm. Seven of the 9 trials used EGM-based algorithms, and 2 used contractility sensors. There was no difference in all-cause mortality (10.3% vs 11.3%; odds ratio [OR] 0.90; 95% confidence interval [CI] 0.71–1.03; $P = .13$; $I^2 = 0\%$) or heart failure hospitalizations (15.0% vs 16.1%; OR 0.924; 95% CI 0.81–1.04; $P = .194$; $I^2 = 0\%$) between the automatic algorithm group and the control group. Study-defined clinical improvement was also not significantly different between groups (66.6% vs 63.3%; risk ratio 1.01; 95% CI 0.95–1.06; $P = .82$; $I^2 = 50\%$). In the contractility-based subgroup, there was a trend toward greater clinical improvement with the use of the automatic algorithm (75% vs 68.3%; OR 1.45; 95% CI 0.97–2.18; $P = .07$; $I^2 = 40\%$), which did not reach statistical significance. The overall risk of bias was low.

CONCLUSION Automatic algorithms that change AV or VV intervals did not improve mortality, heart failure hospitalizations, or cardiovascular symptoms in patients with heart failure and CRT.

KEYWORDS Cardiac resynchronization therapy; Pacing; Heart failure; Algorithm; Optimization

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Introduction

Heart failure (HF) with reduced ejection fraction affects at least 23 million people worldwide.[1] QRS prolongation, particularly with left bundle branch block (LBBB), is an independent risk factor for hospitalization and death in patients with HF.[2,3] This is thought to be related to electromechanical dyssynchrony, decreased systolic efficiency, and mitral regurgitation, which result in left ventricular (LV) dilation and worsening systolic function.[4]

Cardiac resynchronization therapy (CRT) is a type of cardiac pacing that involves placing an extra lead in a branch of the coronary sinus with the goal of promoting epicardial pacing of the LV, causing near simultaneous biventricular activation. In patients with HF and LBBB, CRT leads to a 22% reduction in all-cause mortality, as well as reduced hospitalizations and a nearly 30% decrease in LV end-systolic volume.[5,6] Despite its effectiveness, approximately one-third of patients will not respond to CRT. Multiple predictors of nonresponsiveness have been identified, such as non-LBBB morphology, QRS <150 ms, and, most importantly, the percentage of ventricular beats that occur due to biventricular pacing, with the greatest benefit observed in those with >95% of biventricular paced beats.[7–9]

Automatic CRT algorithms that attempt to predict the optimal atrioventricular (AV) and interventricular (VV) intervals have been developed in an attempt to increase CRT pacing percentage. Implantable device companies strongly market proprietary algorithms as beneficial to patients. However, individual randomized controlled trials (RCTs) were underpowered to detect clinically meaningful differences. Thus, we aimed to perform a systematic review and meta-analysis of RCTs to evaluate the efficacy of

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KEY FINDINGS

- This was a systematic review and meta-analysis including heart failure patients with cardiac resynchronization therapy devices.
- The study compared automatic algorithms using intracardiac electrograms or intracardiac sensors vs usual care echocardiography-guided optimization.
- Automatic algorithms did not improve clinical outcomes such as mortality, heart failure hospitalization, or clinical improvement.

automatic CRT algorithms in patients with HF with reduced ejection fraction.

Methods

Eligibility criteria

Inclusion in this meta-analysis was restricted to studies that met all the following eligibility criteria: (1) RCTs; (2) compared automatic computerized algorithms with usual care or echocardiography-guided CRT optimization; (3) performed in patients with CRT and a history of HF; and (4) reported any of the outcomes of interest. We excluded studies with (1) no control group; (2) nonautomatic CRT optimization techniques such as electrocardiography-guided; and (3) persistent atrial fibrillation.

Search strategy and data extraction

The research presented in this systematic review and meta-analysis followed PRISMA guidelines.[10] We systematically searched PubMed, Scopus, and Cochrane Central Register of Controlled Trials in September 2022 using the following medical subject heading terms: *cardiac resynchronization therapy*, *pacing*, *algorithm, optimization, cardiac pacemaker, randomized controlled trial*. We also subsequently searched for abstracts presented in cardiovascular conferences and references from the included studies through August 2023. Two authors (LK, BW) independently performed a literature search and extracted the data after predefined search criteria and quality assessment. Disagreements were resolved by consensus and with senior author (ML) input.

Endpoints and subgroup analyses

The primary outcomes of interest were mortality, HF hospitalizations, and study-defined clinical improvement. We aimed to perform a subgroup analysis of purely intracardiac electrogram (EGM)-based algorithms and intracardiac contractility sensor-based algorithms, which use intracardiac accelerometer-based adjustment of AV and VV intervals.

Quality assessment

Quality assessment was performed with the Risk of Bias 2 (RoB2) tool,[11] recommended by the Cochrane Collaboration for assessing bias in randomized trials.[12] Studies are scored as unclear, high, or low risk of bias in 5 domains: selection, performance, detection, attrition, and reporting. A funnel plot was used to interrogate for publication bias.

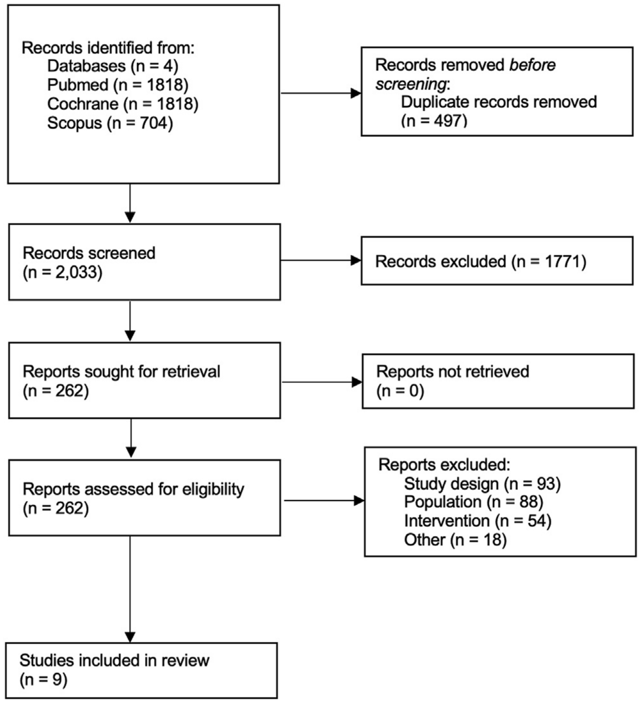

Figure 1 PRISMA flow diagram of study selection.

Statistical analysis

The systematic review and meta-analysis were performed in accordance with recommendations from the Cochrane Collaboration and the Updated Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement.[10,13] Pooled treatment effects for binary endpoints were compared using odds ratio (OR) with 95% confidence interval (CI), or risk ratio (RR) if event rates were >20%. Heterogeneity was examined with the I^2 statistic. The DerSimonian random effects model was used. Review Manager 5.4.1 (Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) was used for statistical analysis.

Results

Study selection and characteristics

The initial search yielded 2534 results. After removal of duplicate records, 2034 results remained (Figure 1). After unrelated studies were excluded, 263 were fully reviewed for the inclusion criteria. Of those studies, 9 RCTs were included in the qualitative and quantitative review.[14–22] A total of 8531 participants were included. CRT algorithms were used in 4275 patients (50.1%). Seven studies used EGM-based algorithms, and 2 used intracardiac contractility sensor-based algorithms.

Study characteristics are given in Table 1. Mean age was 65 years. Most patients were male and had New York Heart

Table 1 Characteristics of included studies

Study name or author	Interventions	Year	N	Age (y)	Male (%)	NYHA functional class III (%)	LVEF (mean [%])	PR duration (mean)	QRS duration (mean)	LBBB (%)	AF (%)	Definition of clinical improvement	Follow-up (mo)
ADAPTRESPONSE	AdaptivCRT vs standard CRT	2023	3618	64	57	51	25.5	172	162	96	13	Clinical composite score	59
FREEDOM QUICK	QuickOpt vs echo	2016	1647	66	73	NA	NA	NA	NA	NA	0	NYHA w/o hospitalization	12
ADAPTIV CRT	AdaptivCRT vs echo	2012	522	65	69	95	24	NA	155	77	18	Clinical composite score	6
SMART-AV	SmartDelay vs fixed 120 ms AV delay + echo	2010	1014	66	68	95	24	NA	153	79	13	NYHA	6
Zhang	QuickOpt vs echo + ECG	2019	124	59	60	NA	31	NA	143	100	0	NYHA	48
Jensen	QuickOpt vs echo	2011	48	65	81	39	20	NA	146	100	14	NYHA	12
RESPOND CRT	SonR contractility sensor vs echo	2017	967	67	68	96	NA. 32% of patients had LVEF <25%	188	160	86	16	Alive, without HF events, with improvement in NYHA class	24
CLEAR	SonR contractility sensor vs echo	2012	199	73	63	NA, mean NYHA was III	26	NA	160	NA	0	Death, HF hospitalization, NYHA, quality of life	12
QUICK OPT	QuickOpt vs echo	2018	392	60	73	0	30	NA	153	62	2	NYHA	12

AF = atrial fibrillation; ECG = electrocardiography; echo = echocardiography; LBBB = left bundle branch block. LVEF = left ventricular ejection fraction; NA = not available; NYHA: New York Heart Association.

Association (NYHA) functional class III (>90%) functional capacity, except for the QuickOpt Chronic study, in which >98% were NYHA functional class IV.[21] NYHA class was also commonly used as a metric for clinical improvement in individual studies. Mean QRS duration was >150 ms in most studies, and mean prevalence of LBBB was 90%. Most studies had echocardiography-based optimization or a conventional CRT approach in which the AV intervals are fixed and not adaptive, and always biventricular-paced (and not LV-only).

Pooled analysis of all studies

There was no difference in all-cause mortality (10.3% vs 11.3%; OR 0.90; 95% CI 0.78–1.03; P = .13; I^2 = 0%) (Figure 2) or HF hospitalizations (15.0% vs 16.1%; OR 0.92; 95% CI 0.81–1.04; P = .19; I^2 = 0%) (Figure 3) between patients vs without automatic CRT algorithms. Study-defined clinical improvement was also not significantly different between groups (66.6% vs 63.3%; RR 1.01; 95% CI 0.95–1.06; P = .82; I^2 = 50%) (Figure 4).

Subgroup analyses

In the intracardiac contractility sensor-based algorithm subgroup, there was a trend toward greater clinical improvement (75% vs 68.3%; OR 1.45; 95% CI 0.97–2.18; P = .07; I^2 = 40%), which did not reach statistical significance. There was no difference in all-cause mortality (6% vs 7.4%; OR 0.86; 95% CI 0.53–1.39; P = .54; I^2 = 0%) or HF hospitalization (9.8% vs 13.1%; OR 0.78; 95% CI 0.54–1.14; P = .20; I^2 = 0%). In the EGM subgroup, there was also no difference in all-cause mortality (11.2% vs 11.7%; OR 0.90; 95% CI 0.78–1.04; P = .16; I^2 = 0%), HF hospitalizations (16.1% vs 16.5%; OR 0.94; 95% CI 0.82–1.07; P = .35; I^2 = 0%), or study-defined clinical improvement (64.8% vs 62.7%; RR 0.98; 95% CI 0.94–1.01 P = .15; I^2 = 2%) between patients vs without automatic CRT algorithms.

Quality assessment

The RCT appraisal using the RoB2 tool is shown in Figure 5. Patients and investigators were blinded in all RCTs except for CLEAR (Clinical Evaluation on Advanced Resynchronization),[22] and the studies by Jensen et al[19] and Zhang et al.[20]

Study or Subgroup	Algorithm Events	Algorithm Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.5.1 EGM-based						
AdaptivCRT	35	318	19	160	5.6%	0.92 [0.51, 1.66]
AdaptResponse	282	1810	320	1807	67.2%	0.86 [0.72, 1.02]
FREEDOM	44	816	42	828	9.8%	1.07 [0.69, 1.65]
Jensen	0	24	0	22		Not estimable
QUICKOPT CHRONIC	21	198	14	196	3.1%	1.54 [0.76, 3.13]
SMART AV	7	332	21	648	3.5%	0.64 [0.27, 1.53]
Zhang	7	28	25	92	2.2%	0.89 [0.34, 2.36]
Subtotal (95% CI)		**3526**		**3753**	**91.3%**	**0.90 [0.78, 1.04]**
Total events	396		441			
Heterogeneity: Chi^2 = 3.69, df = 5 (P = 0.59); I^2 = 0%						
Test for overall effect: Z = 1.39 (P = 0.16)						
1.5.2 Contractility-based						
CLEAR	9	100	12	99	2.7%	0.72 [0.29, 1.79]
RESPOND-CRT	36	649	19	318	6.0%	0.92 [0.52, 1.64]
Subtotal (95% CI)		**749**		**417**	**8.7%**	**0.86 [0.53, 1.39]**
Total events	45		31			
Heterogeneity: Chi^2 = 0.21, df = 1 (P = 0.64); I^2 = 0%						
Test for overall effect: Z = 0.62 (P = 0.54)						
Total (95% CI)		**4275**		**4170**	**100.0%**	**0.90 [0.78, 1.03]**
Total events	441		472			
Heterogeneity: Chi^2 = 3.93, df = 7 (P = 0.79); I^2 = 0%						
Test for overall effect: Z = 1.51 (P = 0.13)						
Test for subgroup differences: Chi^2 = 0.03, df = 1 (P = 0.86), I^2 = 0%						

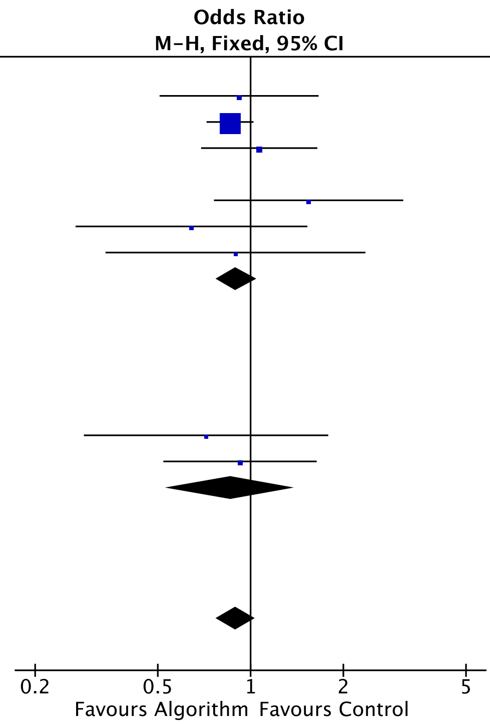

Figure 2 Forest plot of all-cause mortality. CI = confidence interval; EGM = electrogram.

Overall, studies were considered at low risk of bias. The funnel plot analysis of all-cause mortality showed a symmetric distribution of study weights relative to the efficacy estimate. Therefore, there was no evidence of publication bias (Supplemental Figure 1).

Discussion

In this systematic review of 8 RCTs and 4913 patients, automatic algorithms did not improve all-cause mortality, HF hospitalizations, or clinical status compared with usual care after median follow-up of 12 months. There was also

Study or Subgroup	Algorithm Events	Algorithm Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
1.7.1 EGM-based						
AdaptivCRT	46	318	21	160	4.9%	1.12 [0.64, 1.95]
AdaptResponse	239	1810	262	1807	42.3%	0.90 [0.74, 1.08]
FREEDOM	250	816	261	828	34.6%	0.96 [0.78, 1.18]
Jensen	0	24	0	22		Not estimable
QUICKOPT CHRONIC	0	198	1	196	0.1%	0.33 [0.01, 8.11]
SMART AV	31	332	60	648	7.3%	1.01 [0.64, 1.59]
Subtotal (95% CI)		**3498**		**3661**	**89.3%**	**0.94 [0.82, 1.07]**
Total events	566		605			
Heterogeneity: Tau^2 = 0.00; Chi^2 = 1.16, df = 4 (P = 0.88); I^2 = 0%						
Test for overall effect: Z = 0.94 (P = 0.35)						
1.7.2 Contractility-based						
CLEAR	18	100	18	99	2.9%	0.99 [0.48, 2.03]
RESPOND-CRT	56	649	37	318	7.8%	0.72 [0.46, 1.11]
Subtotal (95% CI)		**749**		**417**	**10.7%**	**0.78 [0.54, 1.14]**
Total events	74		55			
Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.55, df = 1 (P = 0.46); I^2 = 0%						
Test for overall effect: Z = 1.29 (P = 0.20)						
Total (95% CI)		**4247**		**4078**	**100.0%**	**0.92 [0.81, 1.04]**
Total events	640		660			
Heterogeneity: Tau^2 = 0.00; Chi^2 = 2.53, df = 6 (P = 0.86); I^2 = 0%						
Test for overall effect: Z = 1.31 (P = 0.19)						
Test for subgroup differences: Chi^2 = 0.82, df = 1 (P = 0.36), I^2 = 0%						

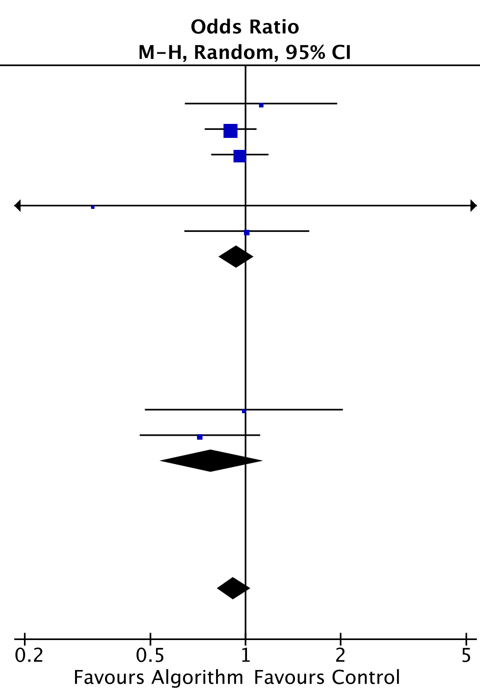

Figure 3 Forest plot of heart failure hospitalization. CI = confidence interval; EGM = electrogram.

Study or Subgroup	Algorithm Events	Algorithm Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 EGM-based						
AdaptivCRT	234	318	116	160	12.3%	1.01 [0.90, 1.14]
AdaptResponse	1250	1810	1290	1807	25.5%	0.97 [0.93, 1.01]
FREEDOM	551	816	559	828	20.5%	1.00 [0.94, 1.07]
Jensen	21	24	16	22	2.8%	1.20 [0.89, 1.62]
QUICKOPT CHRONIC	135	198	147	196	11.2%	0.91 [0.80, 1.03]
SMART AV	76	332	169	648	4.3%	0.88 [0.69, 1.11]
Subtotal (95% CI)		**3498**		**3661**	**76.7%**	**0.98 [0.94, 1.01]**
Total events	2267		2297			
Heterogeneity: Tau² = 0.00; Chi² = 5.08, df = 5 (P = 0.41); I² = 2%						
Test for overall effect: Z = 1.45 (P = 0.15)						
1.4.2 Sensor-based						
CLEAR	76	100	61	99	6.1%	1.23 [1.02, 1.49]
RESPOND-CRT	487	649	224	318	17.2%	1.07 [0.98, 1.16]
Subtotal (95% CI)		**749**		**417**	**23.3%**	**1.12 [0.98, 1.28]**
Total events	563		285			
Heterogeneity: Tau² = 0.01; Chi² = 1.91, df = 1 (P = 0.17); I² = 48%						
Test for overall effect: Z = 1.61 (P = 0.11)						
Total (95% CI)		**4247**		**4078**	**100.0%**	**1.01 [0.95, 1.06]**
Total events	2830		2582			
Heterogeneity: Tau² = 0.00; Chi² = 13.92, df = 7 (P = 0.05); I² = 50%						
Test for overall effect: Z = 0.23 (P = 0.82)						
Test for subgroup differences: Chi² = 3.67, df = 1 (P = 0.06), I² = 72.7%						

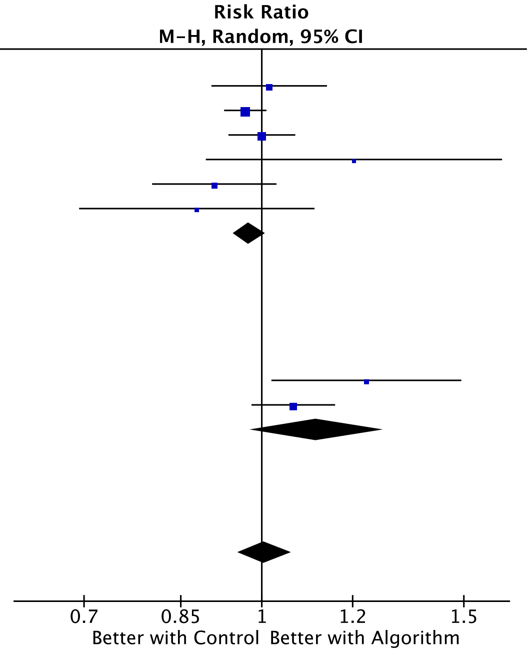

Figure 4 Forest plot of study-defined clinical improvement. CI = confidence interval; EGM = electrogram.

no difference within the contractility-based and EGM-based algorithm subgroups.

CRT algorithms have been widely adopted in the treatment of selected patients who have HF with reduced ejection fraction. Previous observational studies showed potential benefit using registry data.[23,24] However, observational evidence is plagued by biases and confounding, which are not resolved by larger datasets, hence the importance of larger trials and meta-analysis to ascertain the true effect of automatic algorithms.[25]

This meta-analysis shows that although these algorithms are safe and more convenient than echocardiography-based optimization, they do not seem to improve hard clinical outcomes. However, echocardiography-based optimization itself may not be superior to "fixed" AV and VV delay settings at device implantation. Previous meta-analyses and RCTs showed no clinical improvement with imaging-guided optimization compared with usual care, including fixed intervals or hemodynamic optimization.[26–30] Ultimately, the response to CRT may be dictated in large part by patient selection and multipoint lead positioning, leaving little to be gained in AV and VV interval titration compared to fixed settings.[31–33]

In addition, there are potential downsides of using CRT algorithms. For example, the impact of automatic algorithms on battery life is not completely known. The contractility-based algorithm can reduce CRT–defibrillator longevity by up to 1.2 years, likely due to its extra contractility sensing capabilities, and its accelerometer-sensing atrial lead has a high malfunction rate.[34] In contrast, EGM-based CRT algorithms may even improve longevity by up to 6 months, although this is still uncertain.[35]

To the best of our knowledge, this is the first meta-analysis of RCTs to compare automatic algorithms with echocardiographic or empiric optimization. Previous meta-analyses included nonrandomized studies and compared strategies using nonautomatic algorithms or pacing location.[36,37] There are subgroups of patients who may potentially benefit from CRT pacing algorithms. In a subgroup analysis of 199 patients from the AdaptivCRT (Adaptive Cardiac Resynchronization Therapy) trial, patients with LBBB >150 ms and normal AV delay potentially had greater clinical improvement.[38] These findings should be considered exploratory. In addition, other strategies to increase responsiveness are being actively investigated, such as physiological pacing.[39,40]

Study limitations

First, not all studies were double-blinded, which creates the possibility of biased results. Second, the included population consisted of HF patients without persistent or permanent atrial fibrillation; this condition represents a special population with unique challenges related to CRT and is not well represented in this meta-analysis.[41] Third, heterogeneity in study-defined clinical improvement was high, likely due to slightly different outcome definitions. Fourth, the confidence intervals were wide enough that the possibility of a small clinical benefit is not totally ruled out.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
AdaptivCRT	+	+	+	+	+	+	+
AdaptResponse	+	+	+	+	+	+	+
CLEAR	+	+	−	−	+	+	+
FREEDOM	+	+	+	+	+	+	+
Jensen	+	+	−	−	+	+	+
QUICKOPT CHRONIC	+	+	+	+	+	+	+
RESPOND-CRT	+	+	+	+	+	+	+
SMART AV	+	+	+	+	+	+	+
Zhang	+	+	−	−	+	+	+

Figure 5 Risk of bias assessment of included studies.

Conclusion

Automatic algorithms for adjustment of AV and VV intervals in CRT did not improve clinical outcomes in patients with HF. These findings indicate that these algorithms should not be implemented routinely given the lack of efficacy and the potential penalty on battery longevity.

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Authorship: All authors attest they meet the current ICMJE criteria for authorship.

Ethics Statement: The research presented in this systematic review and meta-analysis followed PRISMA guidelines.

Appendix
Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hroo.2023.09.001.

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