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The Benefit of Atrioventricular Junction Ablation for Permanent Atrial Fibrillation and Heart Failure Patients Receiving Cardiac Resynchronization Therapy: An Updated Systematic Review and Meta-analysis

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ABSTRACT

Background: Atrial fibrillation (AF) is correlated with a poor biventricular pacing and inadequate response to cardiac resynchronization therapy (CRT). Biventricular pacing improvement can be achieved by conducting the atrioventricular junction ablation (AVJA). We aimed to investigate the benefit of AVJA for permanent AF and heart failure with reduced ejection fraction (HFrEF) patients receiving CRT.
Methods: In August 2020, a systematic review and meta-analysis study comparing CRT plus AVJA versus CRT for permanent AF and HFrEF patients was conducted. Relevant articles were identified through the electronic scientific database such as ClinicalTrials.gov, ProQuest, ScienceDirect, PubMed, and Cochrane. The pooled risk ratio (RR) and pooled mean difference (MD) were estimated.
Results: A total of 3199 patients from 14 cohort studies were involved in this study. Additional AVJA reduced cardiovascular mortality (RR = 0.75, 95% confidence interval [CI] = 0.61 to 0.93, P < 0.01) in permanent AF and HFrEF patients receiving CRT. Biventricular pacing rate was higher in CRT plus AVJA group (MD = 8.65%, 95% CI = 5.62 to 11.67, P < 0.01) than in CRT alone group. The reverse remodeling characterized by the reduction of left ventricular end-diastolic diameter (LVEDD) was greater in the CRT plus AVJA group (MD = −2.11 mm, 95% CI = −3.79 to −0.42, P = 0.01).
Conclusion: In permanent AF and HFrEF patients receiving CRT, AVJA effectively increased the biventricular pacing rate. Adequate biventricular pacing rate provided a better response to the CRT marked by the greater ventricular reverse remodeling and survival from cardiovascular mortality.

1. Introduction

Both heart failure (HF) and atrial fibrillation (AF) are well known as the “perfect partner in crime.” About 15% to 50% of HF patients also suffer from AF [1]. The presence of AF is correlated with increased HF severity, cardiovascular death, and rehospitalization due to the worsening of HF [2,3]. Heart failure with reduced ejection fraction (HFrEF) patients have a poor prognosis, despite being treated using an optimal medical treatment (OMT). Several guidelines strongly recommend cardiac resynchronization therapy (CRT) for HFrEF patients with New York Heart Association (NYHA) functional class II to IV despite OMT, left ventricular ejection fraction (LVEF) ≤35%, sinus rhythm, QRS duration ≥130 msec, and left bundle branch block (LBBB) morphology [4,5]. However, for patients with HFrEF and AF, the current guidelines give the lower class of recommendation because several randomized controlled trials (RCTs) for CRT excluded patients with AF [4–8].

In HFrEF patients, AF is correlated with a high risk of death, poor biventricular pacing, and inadequate response to CRT [9–11]. The previous studies revealed that consistent and effective delivery of biventricular pacing significantly contributed to the successful CRT [10–13]. For patients with AF and HFrEF receiving CRT, atrioventricular junction ablation (AVJA) could be the therapeutic choice for heart rate control and biventricular pacing improvement by creating a complete atrioventricular (AV) block [14–16]. However, the AVJA procedure has been limited by its permanent character

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and the need for long-life ventricular pacing [17]. It has not been answered whether AVJA is a procedure that must be done in conjunction with CRT implantation or is a procedure that can be conducted if pharmacologic therapy has been unable to control heart rate. Therefore, we performed a systematic review and meta-analysis to investigate the benefit of AVJA for permanent AF and HFrEF patients receiving CRT.

2. Methods

2.1. Design

This systematic review and meta-analysis study had been conducted based on the guidance from Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) [18]. We looked for and identified relevant articles published in the electronic scientific database such as ClinicalTrials.gov, ProQuest, ScienceDirect, PubMed, and Cochrane. Articles that met the eligibility criteria were included in the study quality assessment and data extraction process. The pooled effect was determined using risk ratio (RR) or mean difference (MD) for categorical data or continuous data, respectively.

2.2. Search strategy

Up to August 2020, relevant articles about the comparison between CRT plus AVJA and CRT for permanent AF and HFrEF patients were collected from the electronic scientific database such as ClinicalTrials.gov, ProQuest, ScienceDirect, PubMed, and Cochrane. These keywords: "atrioventricular junction ablation" OR "AVJA," AND "catheter ablation" OR “ablation,” AND "permanent atrial fibrillation" OR "permanent AF," AND “systolic heart failure” OR "heart failure" OR "HF," AND “heart failure with reduced ejection fraction” OR “HFrEF,” AND "cardiac resynchronization therapy" OR "CRT" were used to identify the relevant articles. We also identified potentially relevant information from the reference lists of all collected full-text articles.

2.3. Eligibility criteria

We involved articles that fulfill the following criteria: (1) articles compared CRT plus AVJA versus CRT in patients with HFrEF and permanent AF; (2) the shortest follow-up duration was six months; and (3) availability of data about mortality, rehospitalization, biventricular pacing rate, functional status changes, or echocardiographic parameter changes. The exclusion criteria included: (1) duplications; (2) non-English language; (3) unavailable full-text; (4) review articles; (5) editorials; (6) case reports; (7) sub-study of the included studies; (8) treatment group and control group were incomparable; or (9) outcomes of interest were not reported.

2.4. Exposure and outcomes

AVJA was the exposure in this systematic review and meta-analysis. Therefore, patients were divided into “CRT plus AVJA” and “CRT” groups. The all-cause mortality, cardiovascular mortality, and rehospitalization because of the worsening of HF were the primary outcomes of this study. The secondary outcomes included: (1) biventricular pacing rate; (2) improvement of LVEF; (3) reduction of left ventricular end-diastolic diameter (LVEDD); (4) improvement of NYHA functional class; (5) improvement of walking distance in six-minute walk test (SMWT); and (6) improvement of Minnesota living with heart failure questionnaire (MLHFQ).

2.5. Study quality assessment and data extraction

The Newcastle-Ottawa Scale (NOS) was used to evaluate the study quality in this systematic review and meta-analysis [19,20]. The quality of studies was considered as good (NOS $\geq$7), moderate (NOS 5 to 6), and poor (NOS $\leq$4) [21]. The important information about: (1) the first author name; (2) year of publication; (3) study design; (4) center involved; (5) CRT implantation criteria (6) indications for AVJA; (7) duration of the follow-up period; (8) sample size; (9) age; (10) gender; (11) LVEF; (12) etiology of HF; (13) chronic AF and HF medications such as diuretic, angiotensin-converting enzyme inhibitor (ACEI), mineralocorticoid receptor antagonist (MRA), angiotensin receptor blocker (ARB), β-blocker, digoxin, and negative chronotropic drugs; (14) cardiac resynchronization therapy defibrillator (CRT-D); (15) all-cause mortality; (16) cardiovascular mortality; (17) rehospitalization because of worsening HF; (18) biventricular pacing rate; (19) improvement of LVEF; (20) reduction of LVEDD; (21) improvement of NYHA functional class; (22) improvement of walking distance in SMWT; and (23) improvement of MLHFQ were extracted from each article. Numeric data were shown using mean and standard deviation (SD), while categorical data were shown using number and percentage. The mean and SD could also be calculated from the median and interquartile range (IQR) using the Tiejun Tong group formula [22–24].

2.6. Statistical analysis

The statistical analysis process was conducted based on the standard guideline [25]. Before final conclusion determination, data were evaluated for heterogeneity and publication bias. The Q test was used to identify heterogeneity. We used P for heterogeneity (PHet) of 0.1 as the cut-off point. The random-effect analysis model was used in the presence of heterogeneity (PHet $<$ 0.1). On the contrary, the fixed-effect analysis model was used in the absence of heterogeneity (PHet $\geq$ 0.1) [26]. The assessment of publication bias was conducted using a combination of the Egger test and the funnel plot analysis. The P Egger (pE) $<$ 0.05 and/or the asymmetric funnel plot indicates the presence of publication bias [27]. For continuous data, the inverse variance statistical method was used to determine the pooled MD and its 95% confidence interval (CI). For categorical data, the pooled RR and its 95% CI were estimated using the Mantel-Haenszel statistical method. Statistically significant was considered if a p-value $<$ 0.05. The data analysis process was conducted using Review Manager Version 5.3 (Cochrane, Copenhagen, Denmark) and Comprehensive Meta-Analysis version 3.0 (CMA, New Jersey, US).

3. Results

3.1. Eligible articles

Through ClinicalTrials.gov, ProQuest, ScienceDirect, PubMed, and Cochrane, we successfully obtained 356 records. From the reference lists of the accessed full-text article, we identified four articles. A total of 297 records were excluded due to duplications. In the initial screening, we excluded a total 36 articles because of: (1) written in non-English language (n = 2); (2) unavailable full text (n = 2); (3) review articles (n = 13); (4) editorials (n = 2); and (5) case reports (n = 17). In further screening and assessment, 13 articles were excluded due to: (1) treatment group and control group were incomparable (n = 6); (2) outcomes of interest were not reported (n = 4); and (3) sub-study of the included studies (n = 3). Finally, 14 studies were involved in this systematic review and meta-analysis [28–41]. Fig. 1 shows the flow diagram of the study selection process.

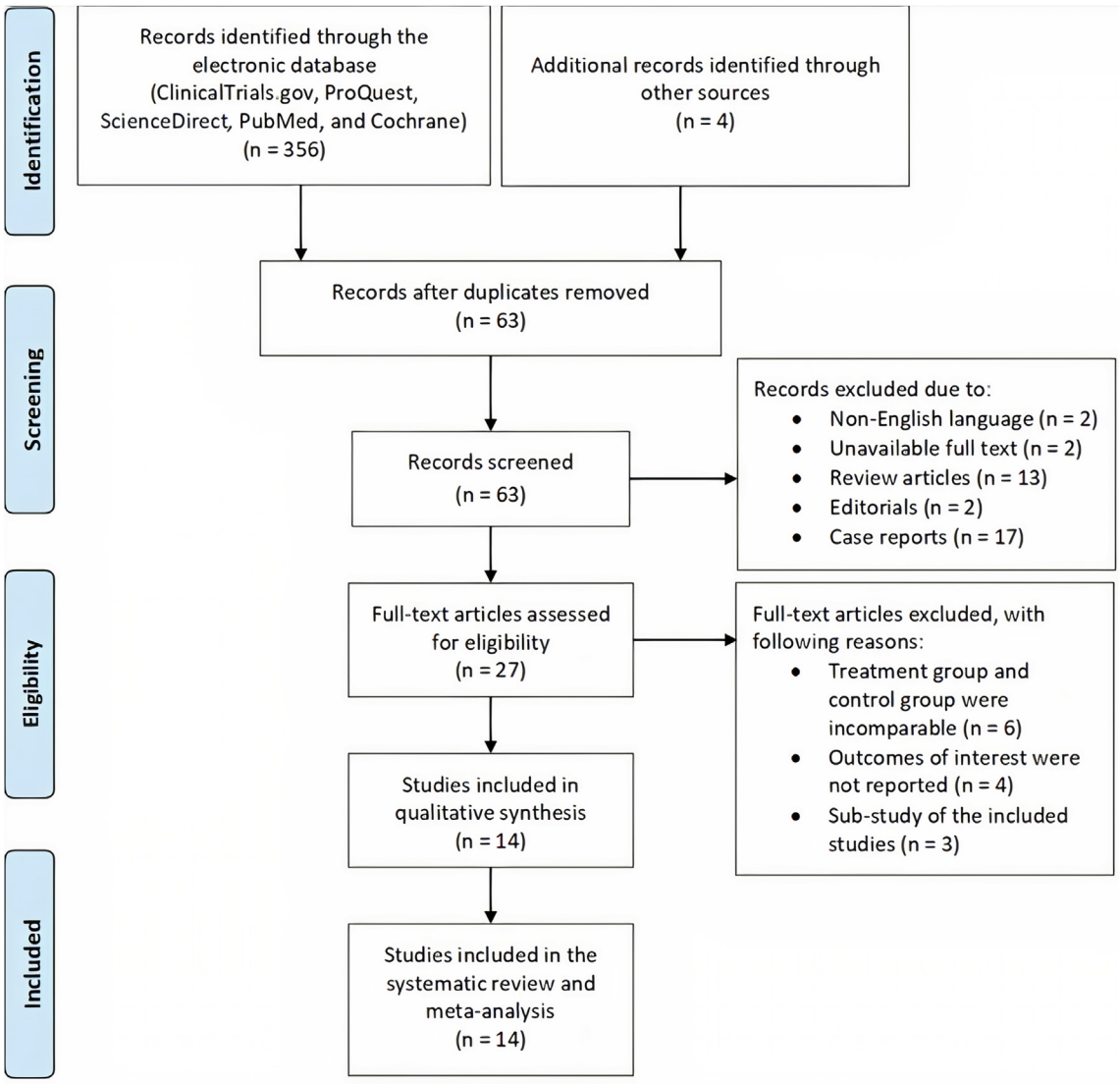

Fig. 1. Flowchart of the study selection process.

3.2. Baseline characteristics

Only good-quality studies were involved in this systematic review and meta-analysis. Ten prospective cohort studies [28,31–37,40,41] and four retrospective cohort studies [29,30,38,39] were included in this study. Eight studies were single-center studies [28–30,35–38,41], while six studies were multi-center studies [31–34,39,40]. Generally, the main indications of CRT implantation included the presence of HF symptoms despite OMT, severe left ventricular systolic dysfunction, and long QRS duration [28,30,31,33–41]. In most studies, the main indication to perform AVJA was inadequate biventricular pacing [31–36,38,40] and/or poor heart rate control [28,39,41]. The shortest follow-up period was six months [28–41]. Baseline characteristics of the involved studies are summarized in Table 1.

A total of 3199 patients, including 1207 patients in CRT plus AVJA group and 1992 patients in CRT group, were involved in this systematic review and meta-analysis study. The mean age ranged from 57.1 to 71.5 years old [28–37,39–41]. About 54% to 96% of the included participants were male [28–34,36,37,40,41]. The mean LVEF varied from 20% to 28% [28–37,39–41]. Ischemic heart disease was the etiology for HF in 10% to 72.1% of the included patients [28–36,39–41]. β-blocker, digoxin, and/or other negative chronotropic were the pharmacologic treatment of choice for rate control [28–36,38–41]. In 10 studies, CRT-D was implanted in 40.7% to 100% patients, but the indication of the CRT-D implantation was not explicitly described [28-34,39-41]. The summary of baseline characteristics of the included patients is shown in Table 2.

3.3. Heterogeneity and publication bias

Heterogeneity was found during performing meta-analysis of all-cause mortality, biventricular pacing rate, improvement of LVEF, reduction of LVEDD, and improvement of NYHA functional class. Therefore, effect estimation was determined using a random-effect model. The other outcomes did not reveal any heterogeneity. Therefore, the effect estimation was determined using the fixed-effect model (Figs. 2, 3 and 4). We found the publication bias only in the all-cause mortality analysis. It was identified by the PE = 0.04 (Table 3) and the asymmetric funnel plot (Fig. 5). Tables 3 and 4 demonstrate the summary of heterogeneity and publication bias assessment.

Table 1
Baseline characteristics of the involved studies.

Study	Design	Center	CRT implantation criteria	Indications for AVJA	Follow up	NOS
Dong, 2010 [28]	Prospective cohort	Single-center	• HF symptoms despite optimal medical therapy • LVEF <35% • QRS duration ≥120 ms	Poor rate control	• 274 (193 - 427) days in CRT + AVJA group • 222 (111 -501) days in CRT group	8
Eisen, 2013 [29]	Retrospective cohort	Single-center	NA	NA	2 years	9
Ferreira, 2008 [30]	Retrospective cohort	Single-center	• Symptomatic HF (NYHA functional class II - IV) • Severe LV systolic dysfunction (LVEF ≤35%) • QRS duration >120 ms	NA	29 ± 18 months	8
Gasparini, 2006 [31]	Prospective cohort	Multicenter	• LVEF ≤35% • Ventricular conduction delay (QRS duration ≥120 ms) • NYHA functional class ≥II despite optimal drug therapy, including β-blockers, ACEIs or ARBs, diuretics, and spironolactone.	Biventricular pacing ≤85%	48 months	8
Gasparini, 2008 [32]	Prospective cohort	Multicenter	NA	Biventricular pacing ≤85%	34 (10 - 40) months	7
Gasparini, 2013 [33]	Prospective cohort	Multicenter	• Systolic HF in NYHA functional class III or ambulatory IV (or II in the case of a recent HF hospitalization) • LVEF ≤35% • QRS ≥120 ms • Maximum tolerated pharmacologic therapy with ACEIs or ARBs, β-blockers, diuretics, and spironolactone for at least 2 months.	Clinical improvement and/or adequate biventricular pacing percentage did not occur with rate slowing drugs within 3 months	37 (14 - 58) months	7
Gasparini, 2018 [34]	Prospective cohort	Multicenter	• Systolic HF in NYHA functional class III or ambulatory IV (or II in the case of recent HF hospitalization) • LVEF ≤35% • QRS ≥120 ms • Maximum tolerated pharmacological therapy and had at least 3-month follow-up.	Adequate biventricular pacing percentage (>95%) did not occur with rate-slowing drugs within 3 months	18 (12–18) months	8
Himmel, 2012 [35]	Prospective cohort	Single-center	• Drug-refractory HF (NYHA functional class III - IV), LVEF ≤35% • QRS duration ≥120 ms • LBBB morphology	Biventricular pacing ≤80%	12 ± 3 months	7
Jędrzejczyk-Patej, 2014 [36]	Prospective cohort	Single-center	• Refractory symptomatic HF (NYHA functional class III - IV) • LVEF ≤35% • QRS duration >120 ms	Biventricular pacing <95%	6 months	7
Molhoek, 2004 [37]	Prospective cohort	Single-center	• Drug-refractory HF (NYHA functional class III - IV) • LVEF <35% • QRS duration >120 ms or >200 ms for a paced QRS • LBBB morphology	NA	6 months	7
Schütte, 2009 [38]	Retrospective cohort	Single-center	• Drug-refractory HF (NYHA functional class III - IV) • LVEF <35% • QRS duration >120 ms • LBBB morphology	Biventricular pacing <90%	11 ± 0.34 months	7
Tolosana, 2008 [39]	Retrospective cohort	Multicenter	• Symptomatic HF (NYHA functional class ≥ III) despite optimal drug therapy, with LVEF ≤35%, and QRS duration >120 ms. OR • Symptomatic HF (NYHA functional class ≥II) with LVEF ≤35% who received a defibrillator or pacemaker and needed permanent pacing regardless of QRS duration.	Poor rate control despite negative chronotropic therapy	12 months	8
Tolosana, 2012 [40]	Prospective cohort	Multicenter	• Symptomatic HF (NYHA functional class ≥ III) despite optimal drug therapy, with LVEF ≤35%, and QRS duration >120 ms. OR • Symptomatic HF with LVEF ≤35% who received a pacemaker or defibrillator and were in NYHA functional class ≥II, regardless of QRS duration.	Biventricular pacing ≤85%	12 months	9
Tolosana, 2013 [41]	Prospective cohort	Single-center	• Symptomatic HF (NYHA functional class ≥III) despite optimal drug therapy, as well as LVEF ≤35% and QRS duration >120 ms. OR • Symptomatic HF with LVEF ≤35% who received a device, required continuous ventricular pacing due to severe bradycardia, and were in functional class ≥II were also included regardless of QRS duration.	Poor rate control	30 (13 - 51) months	8

AVJA = atrioventricular junction ablation; CRT = cardiac resynchronization therapy; HF = heart failure; LBBB = left bundle branch block; LV = left ventricle; LVEF = left ventricular ejection fraction; NA = not available; NOS = Newcastle-Ottawa scale; NYHA = New York Heart Association.

Table 2
Baseline characteristics of the included patients.

Study	Arm	Size, n	Age (years old)	Male, %	LVEF (%)	Ischemic etiology, %	β - blocker, %	ACEI or ARB, %	MRA, %	Diuretic, %	Digoxin, %	Negative chronotropic, %	CRT-D
Dong, 2010 [28]	CRT + AVJA	45	68.1 ± 10.5	84	25.5 ± 8.1	56	60	82	NA	NA	64	9	100
	CRT	109	71.5 ± 9.4	87	22.6 ± 6.4	63	80	88	NA	NA	63	20	100
Eisen, 2013 [29]	CRT + AVJA	10	69.5 ± 12.7	78.8	23.5 ± 11	72.1	80.3	83.3	47	NA	35.4	NA	48.5
	CRT	56											
Ferreira, 2008 [30]	CRT + AVJA	26	67 ± 9	92	24 ± 9	58	50	96	46	100	54	54	77
	CRT	27	70 ± 8	96	26 ± 9	48	67	100	30	100	63	33	85
Gasparini, 2006 [31]	CRT + AVJA	114	66.8 ± 9.0	86.8	26.8 ± 7.1	36	83.3	93.8	52.5	91.4	NA	98.7	48.8
	CRT	48	64.1 ± 6.3	83.3	25.1 ± 5.7	39.6							
Gasparini, 2008 [32]	CRT + AVJA	118	66.5 ± 9.2	86.4	27 ± 12	41.5	78	94.1	61.9	89.8	66.9	96.6	40.7
	CRT	125	65.9 ± 8.6	77.6	24.8 ± 7.6	38.4	81.6	93.5	49.6	96.6	73.6	98.4	55.2
Gasparini, 2013 [33]	CRT + AVJA	443	68.4 ± 9.1	84.2	27.0 ± 6.6	41	76.3	87.3	47.6	89.6	17.8	26	68.2
	CRT	895	69.7 ± 9.3	85.4	25.9 ± 6.9	36.4	74.8	84	47.8	93.2	25.8	31.7	70.9
Gasparini, 2018 [34]	CRT + AVJA	262	69 ± 10	83.8	28 ± 5	43	71.2	73.1	NA	87.4	33.9	19.4	100
	CRT	402	69 ± 9	87.3	27 ± 6	44.1	69.8	72.2	NA	86	30.9	23.3	100
Himmel, 2012 [35]	CRT + AVJA	15	70 ± 7	NA	23.7 ± 6.9	60	87	87	40	100	47	20	NA
	CRT	31	69 ± 9	NA	23.6 ± 6.2	65	97	94	42	77	58	45	NA
Jędrzejczyk-Patej, 2014 [36]	CRT + AVJA	40	62.2 ± 2.8	77.5	23.6 ± 1.7	47.5	97.5	92.5	90	97.5	52.5	25	NA
	CRT	40	57.1 ± 3.9	77.5	24.1 ± 2.1	45	95	90	87.5	95	22.5	37.5	NA
Molhoek, 2004 [37]	CRT + AVJA	17	63 ± 10	90	20 ± 11	NA	NA	NA	NA	NA	NA	NA	NA
	CRT	13											
Schütte, 2009 [38]	CRT + AVJA	9	NA	NA	NA	NA	97	94	33	75	53	36	NA
	CRT	27											
Tolosana, 2008 [39]	CRT + AVJA	19	69.7 ± 7	NA	26 ± 8	10	32	73	49	100	68	0	52
	CRT	107	68.2 ± 10	NA	27 ± 12	35	54	73	42	91	63	30	
Tolosana, 2012 [40]	CRT + AVJA	13	68 ± 10	84	24 ± 5	31	54	69	31	NA	69	NA	61
	CRT	33	67 ± 9	67	25 ± 7	33	70	88	57	NA	57	NA	76
Tolosana, 2013 [41]	CRT + AVJA	76	69.7 ± 7.5	82	23.7 ± 6.3	32	64	84	47	NA	45	31	49
	CRT	79	68 ± 8.3	81	25.3 ± 7.5	39	76	91	57	NA	45	25	62

ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; AVJA = atrioventricular junction ablation; CRT = cardiac resynchronization therapy; CRT-D = cardiac resynchronization therapy - defibrillator; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NA = not available.

3.4. Outcome

The meta-analysis of seven studies revealed that the AVJA reduced all-cause mortality in permanent AF and HFrEF patients receiving CRT (RR = 0.71, 95% CI = 0.52 to 0.96, P = 0.03). Through the meta-analysis of four studies, we found that the AVJA also reduced cardiovascular mortality (RR = 0.75, 95% CI = 0.61 to 0.93, P < 0.01). However, from the meta-analysis of three studies, AVJA did not significantly reduce the HF rehospitalization (RR = 0.73, 95% CI = 0.48 to 1.12, P = 0.15). The forest plot of the primary outcomes is shown in Fig. 2, and the summary of the primary outcomes is summarized in Table 3.

We assessed the overall effect of additional AVJA for permanent AF and HFrEF patients receiving CRT on biventricular pacing rate and echocardiographic parameters, including LVEF and LVEDD (Fig. 3). Data from meta-analysis of six studies revealed that biventricular pacing rate was higher in CRT plus AVJA group (MD = 8.65%, 95% CI = 5.62 to 11.67, P < 0.01). Through the meta-analysis of eight studies, we found the comparable improvement of LVEF between both groups (MD = 1.43%, 95% CI = −4.88 to 7.74, P = 0.66). However, a meta-analysis of four studies revealed that the reduction of LVEDD was greater in the CRT plus AVJA group (MD = −2.11 mm, 95% CI = −3.79 to −0.42, P = 0.01). The additional AVJA for permanent AF and HFrEF patients receiving CRT did not give a significant improvement on the several clinical or functional parameters including: (1) NYHA functional class (MD = −0.12, 95% CI = −0.41 to 0.17, P = 0.43); (2) walking distance in SMWT (MD = 32.95 m, 95% CI = −0.46 to 66.37, P = 0.05); and (3) MLHFQ (MD = −1.82 mm, 95% CI = −8.5 to 4.87, P = 0.59) (Fig. 4). The summary of the secondary outcomes is summarized in Table 4.

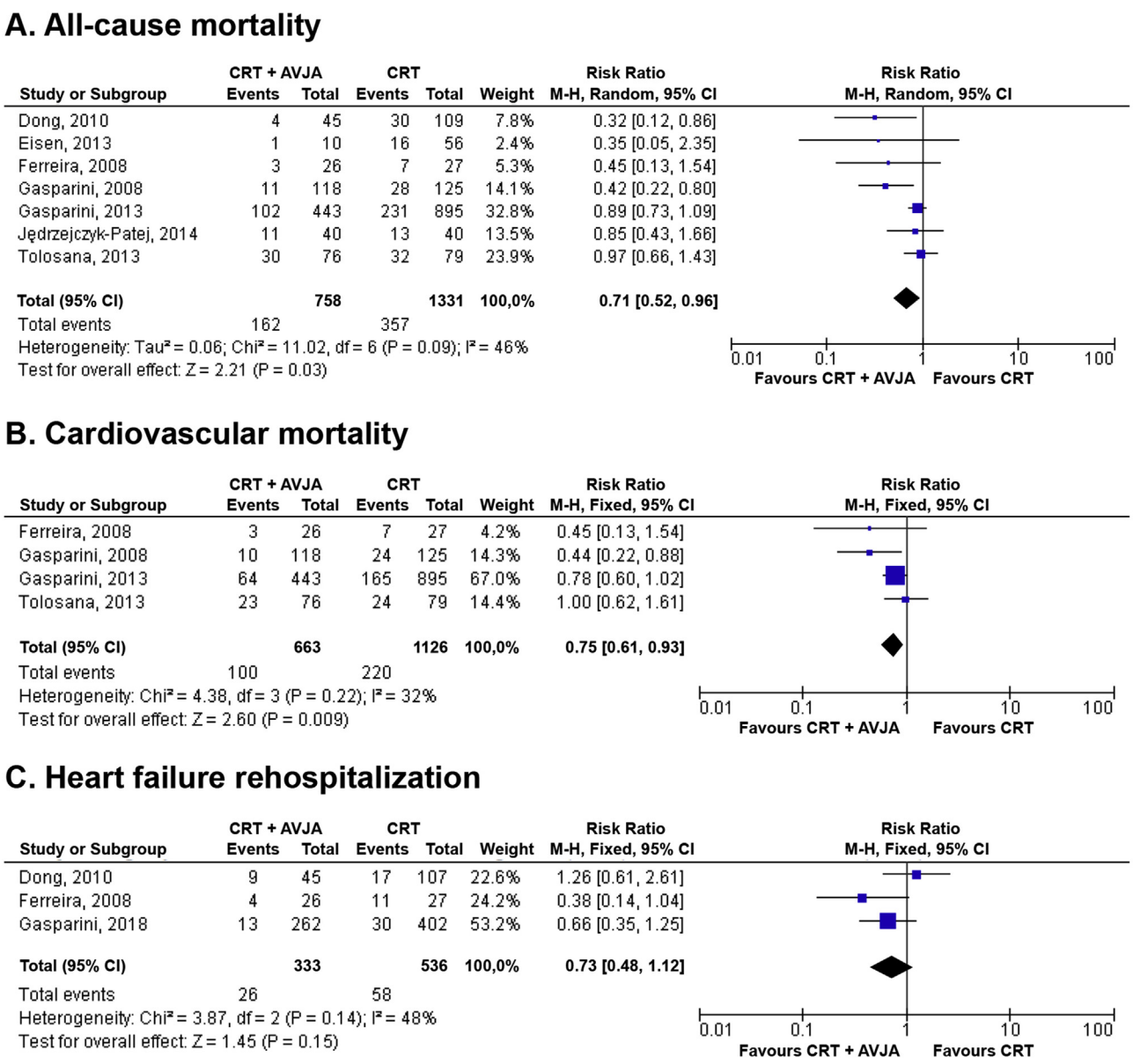

Fig. 2. Forest plot of primary outcomes: (A) all-cause mortality; (B) cardiovascular mortality; and (C) heart failure rehospitalization. AVJA = atrioventricular junction ablation; CI = confidence interval; CRT = cardiac resynchronization therapy; M-H = Mantel-Haenszel.

4. Discussion

4.1. Atrioventricular junction ablation for rate control strategy in atrial fibrillation

The prevention of thromboembolism, rate control, and rhythm control are the current AF treatment strategies [16,42] The decision to adopt a rate control or rhythm control strategy is very important for patients with AF and HFrEF. The Atrial Fibrillation and Congestive Heart Failure trial revealed that compared to the rate control strategy, the routine rhythm control strategy did not decrease cardiovascular mortality in patients who suffered from AF and HF with LVEF ≤35% [43]. The Resynchronization for Ambulatory Heart Failure Trial (RAFT), which included 114 patients with CRT-D, provided important lessons for us that even though rate control strategy was achieved, the biventricular pacing rate ≥95% could be achieved in 34.3% of patients. In contrast, a biventricular pacing rate of ≥90% could be achieved in 47.1% of patients [44]. For AF patients with LVEF <40%, digoxin and/or β-blockers are recommended for rate control strategy [16].

Since 1982, intentional devastation of the atrioventricular (AV) junction to establish the total AV block has been used as a rate control strategy for AF [45]. In the correctly selected patient, it is a simple approach that can relieve symptoms and may also improve left ventricular systolic function [14]. Moreover, for patients with permanent AF and HFrEF receiving CRT, AVJA ensures the regular ventricular rhythm. In the studies involved in this meta-analysis, the decision to conduct AVJA was based on the patient's poor heart rate control, with a cut-off point of biventricular pacing rate ranged from 80% to 95% . The retrospective analysis of 2 RCTs for CRT showed that the >92% biventricular pacing rate was associated with a significant clinical benefit [13]. The LATITUDE study provided us a valuable lesson in which the most significant impact of the reduction in mortality was observed with a biventricular pacing

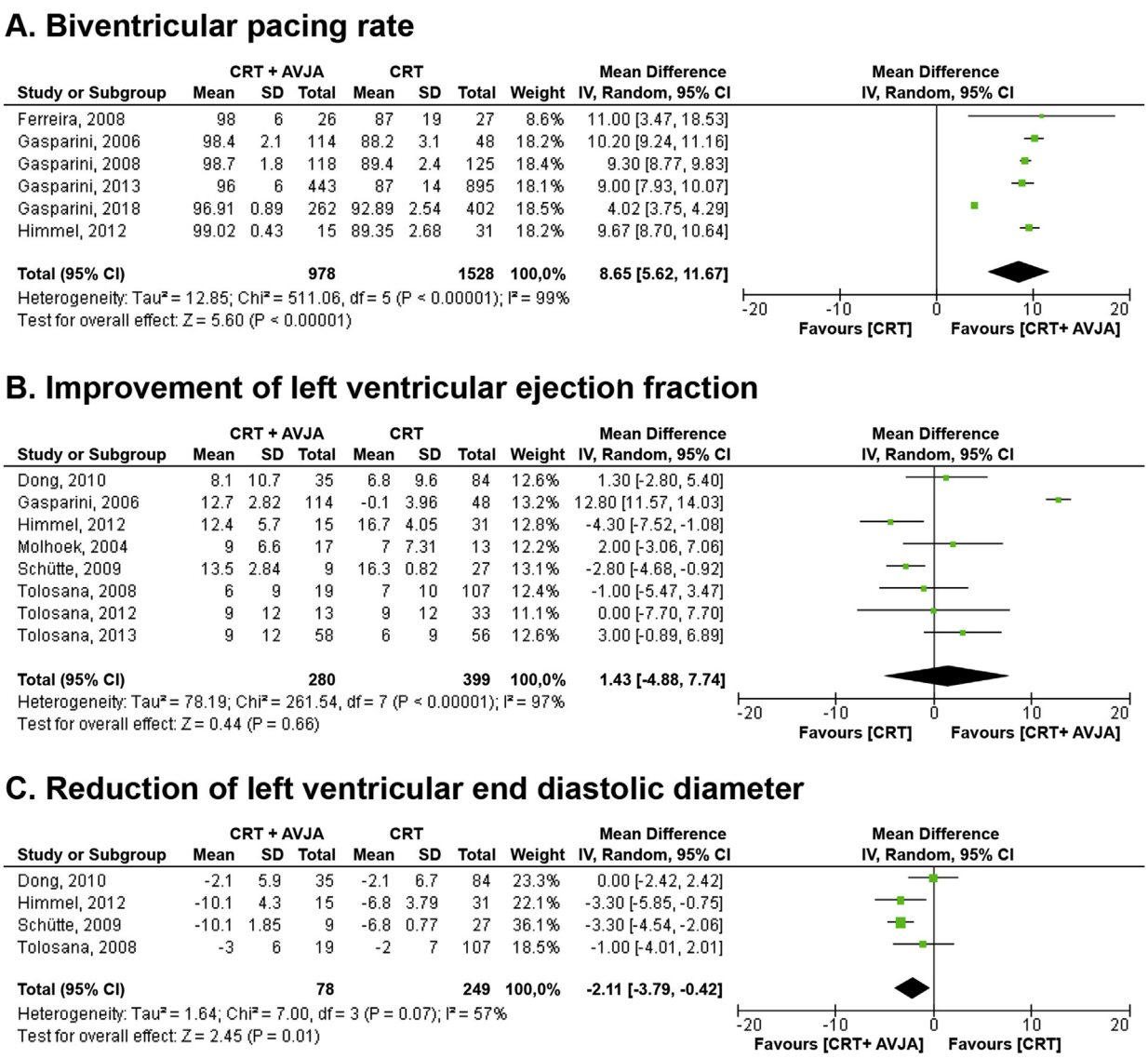

Fig. 3. Forest plot of secondary outcomes: (A) biventricular pacing rate; (B) improvement of left ventricular ejection fraction; and (C) reduction of left ventricular end diastolic diameter. AVJA = atrioventricular junction ablation; CI = confidence interval; CRT = cardiac resynchronization therapy; IV = inverse variance; SD = standard deviation.

rate reaching more than 98% of all ventricular beats [10]. However, according to the current guideline from the European Society of Cardiology (ESC), AVJA should be added to incomplete biventricular pacing (Class of recommendation IIa; Level of evidence B). AVJA can be conducted during the CRT implantation or several weeks later [15].

4.2. Primary outcomes and comparison with the previous studies

Through this meta-analysis of 14 studies with the follow-up period ranged from 6 to 48 months, we directly compared CRT plus AVJA versus CRT alone in AF and HFrEF patients. We found that AVJA effectively reduced all-cause mortality in permanent AF and HFrEF patients receiving CRT. For the all-cause mortality outcome, our result supported the previous meta-analysis study from Ganesan et al. [46] and Yin et al. [47]. A study from Xue et al. revealed that AVJA was correlated with a a higher survival rate in permanent AF and HFrEF patients receiving CRT [48]. However, we found the publication bias in the analysis of all-cause mortality. The possible explanation for this bias might be due to: (1) old aged patients (mean age 63 to 72 years old); (2) risk of bleeding because of the effect of the long-term anticoagulant treatment as the consequences of rate control strategy; and (3) inadequate data about the comorbid condition.

Our result demonstrated that conducting AVJA in permanent AF and HFrEF patients receiving CRT effectively reduced cardiovascular mortality. Our result in cardiovascular mortality was different from the prior meta-analysis study from Yin et al. which revealed that AVJA did not reduce cardiovascular mortality in these populations [47]. It was because we were able to add a study with a larger sample [33]. In our meta-analysis, AVJA did not significantly reduce the HF rehospitalization in permanent AF and HFrEF patients receiving CRT. Several factors could precipitate worsening of HF, such as acute coronary syndrome, respiratory tract infection, arrhythmia, diet non-compliance, medication non-compliance, renal failure, and uncontrolled hypertension [49], were not specifically reported [28,30,34]. To the best of our knowledge, our study is the only meta-analysis study that provide data about HF rehospitalization in this population.

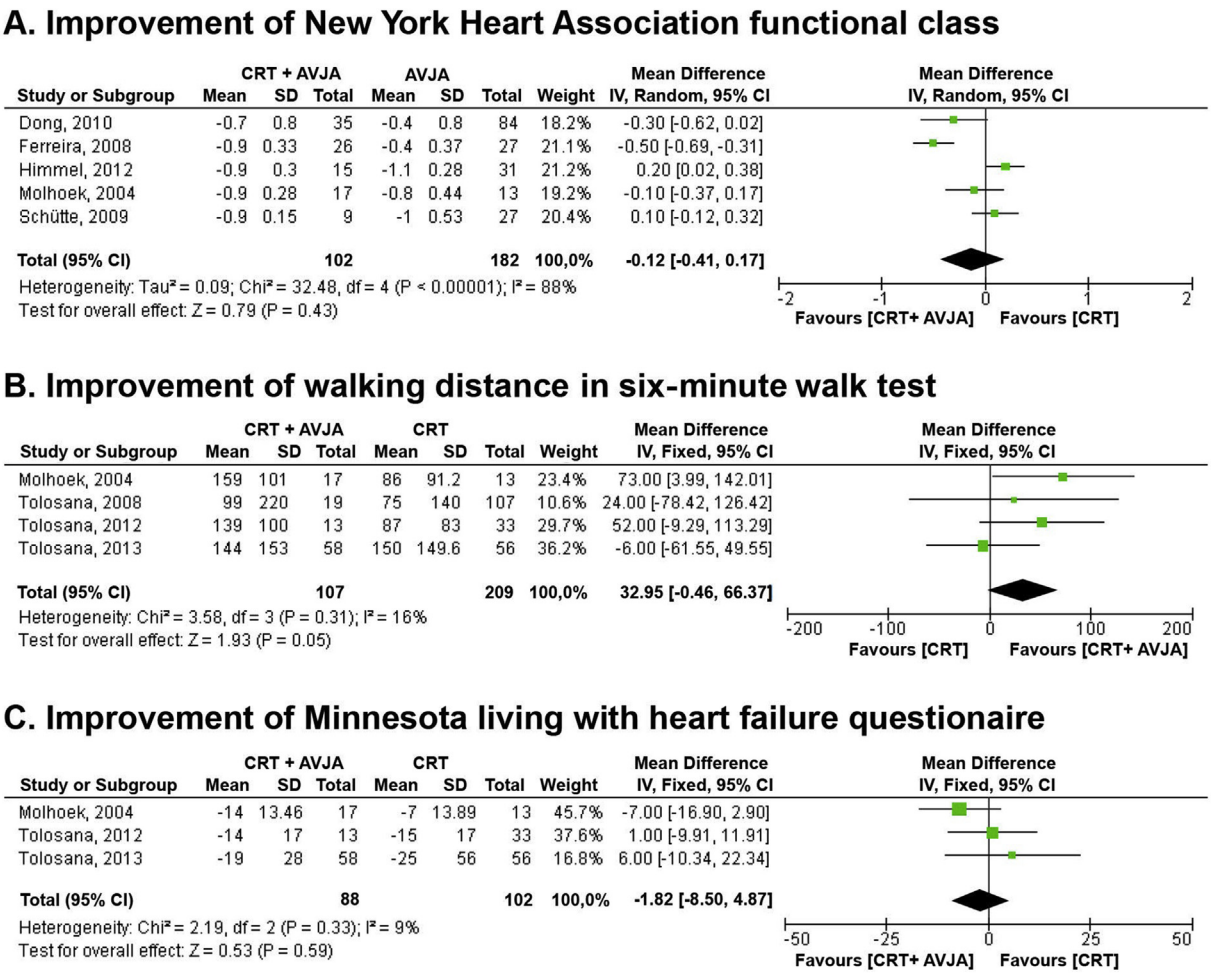

Fig. 4. Forest plot of secondary outcomes: (A) improvement of New York Heart Association functional class; (B) improvement of walking distance in six-minute walk test; and (C) improvement of Minnesota living with heart failure questionnaire. AVJA = atrioventricular junction ablation; CI = confidence interval; CRT = cardiac resynchronization therapy; IV = inverse variance; SD = standard deviation.

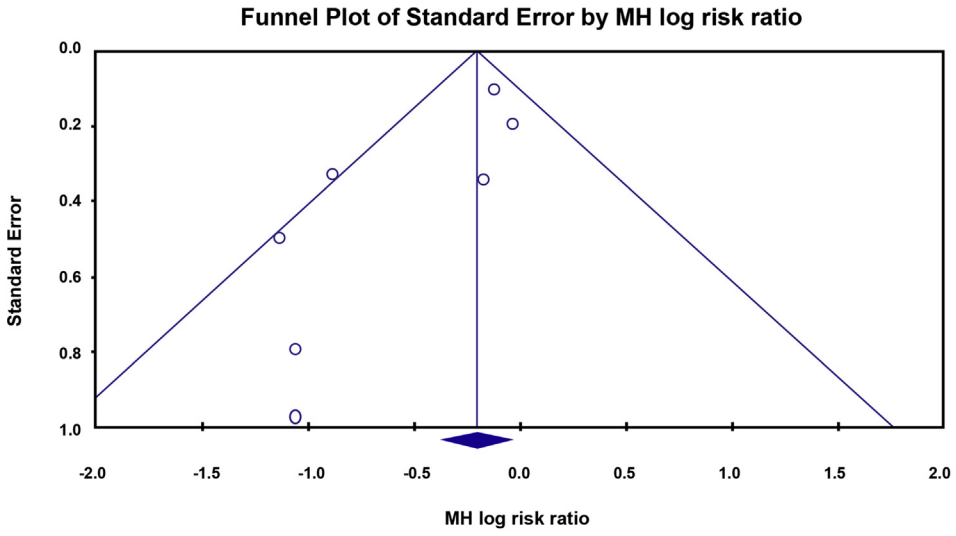

Fig. 5. Funnel plot analysis showing asymmetrical funnel plot for all-cause mortality.

Table 3
Summary of the primary outcomes.

Primary outcomes	Number of studies	CRT + AVJA		CRT		Model	RR	95% CI		PHet	PE	P
		Event, n (%)	Total, n	Event, n (%)	Total, n			Lower limit	Upper limit			
All-cause mortality	7	162 (21.4)	758	357 (26.8)	1331	Random	0.71	0.52	0.96	0.09	0.04	0.03
Cardiovascular mortality	4	100 (15.1)	663	220 (19.5)	1126	Fixed	0.75	0.61	0.93	0.22	0.42	< 0.01
HF rehospitalization	3	26 (7.8)	333	58 (10.8)	536	Fixed	0.73	0.48	1.12	0.14	0.67	0.15

AVJA = atrioventricular junction ablation; CRT = cardiac resynchronization therapy; CI = confidence interval; HF = heart failure; PE = P Egger; PHet = P for heterogeneity, RR = risk ratio.

Table 4
Summary of the secondary outcomes.

Secondary outcomes	Number of studies	CRT + AVJA, n	CRT, n	Model	Mean difference	95% CI		PHet	PE	P
						Lower limit	Upper limit			
Biventricular pacing rate	6	978	1528	Random	8.65	5.62	11.67	<0.01	0.19	<0.01
Improvement of LVEF	8	280	399	Random	1.43	-4.88	7.74	< 0.01	0.49	0.66
Reduction of LVEDD	4	78	249	Random	-2.11	-3.79	-0.42	0.07	0.25	0.01
Improvement of NYHA functional class	5	102	182	Random	-0.12	-0.41	0.17	< 0.01	0.97	0.43
Improvement of walking distance in SMWT	4	107	209	Fixed	32.95	-0.46	66.37	0.31	0.63	0.05
Improvement of MLHFQ	3	88	102	Fixed	-1.82	-8.5	4.87	0.33	0.37	0.59

AVJA = atrioventricular junction ablation; CRT = cardiac resynchronization therapy; CI = confidence interval; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; MLHFQ = Minnesota living with heart failure questionnaire; NYHA = New York Heart Association; SMWT = six-minute wak test; PE = P Egger; PHet = P for heterogeneity.

4.3. Secondary outcomes and comparison with the previous studies

We did not assess the CRT response because the definition of responders was not available in 8 studies [28,29,32–36,38]. Moreover, the definition of responders in each study was not the same [30,31,37,39–41]. We proved that AVJA could effectively increase the biventricular pacing rate in permanent AF and HFrEF patients receiving CRT through this meta-analysis. In our meta-analysis, the mean biventricular pacing rate was ranged from 96% to 99% in the CRT plus AVJA group (Fig. 3). We thought that the patients with permanent AF and HFrEF receiving CRT could get more benefit from AVJA because the previous study revealed that the >92% biventricular pacing rate was associated with a significant clinical benefit [13].

In our meta-analysis, the reduction in all-cause and cardiovascular mortality with AVJA were not accompanied by a significant improvement of LVEF. Both groups shared a similar improvement in LVEF. Our result supported the previous meta-analysis study from Ganesan et al. [46] The explanation for the mortality reduction without concomitant significant LVEF improvement is still not clear. However, the possible explanation was the diversity in: (1) LVEF assessment modalities; (2) LVEF measurement method; and (3) interobserver variability. Our result showed that the additional AVJA in permanent AF and HFrEF patients receiving CRT provided the more significant reverse remodeling on the left ventricle. Our work supported the previous study from Ruwald et al. which revealed an improvement of biventricular pacing rate (≥97%) was correlated with an increased ventricular reverse remodeling [50].

Our study results proved that AVJA in permanent AF and HFrEF patients receiving CRT did not offer any benefit in improving the functional parameters of patients consisting of: (1) improvement of NYHA functional class; (2) improvement of walking distance in SMWT, and (3) improvement of MLHFQ. Our results did not support the previous meta-analysis study from Ganesan et al. which stated that AVJA in permanent AF and HFrEF patients receiving CRT was associated with the improvement of NYHA functional class. Compared to the meta-analysis by Ganesan et al. [46], we were able to add two new studies to our meta-analysis [35,38]. As far as we are concerned, our study was the only meta-analysis that provided data about the impact of AVJA on the improvement of SMWT and MLHFQ in permanent AF and HFrEF patients receiving CRT. There were several possible explanations for the failure of AVJA to improve functional parameters in permanent AF and HFrEF patients receiving CRT. First, several studies did not exclude patients who had comorbidities that could influence those parameters. Second, patients with permanent AF are at high risk for stroke, which may worsen functional parameters [28,30,35,37–41].

4.4. Strengths and limitations

Our study had several strengths. First, to the best of our knowledge, our study represents the biggest pooled analysis of cohort studies of the benefit of AVJA for patients with permanent AF and HFrEF receiving CRT. Second, we provided the data about HF rehospitalization, improvement of walking distance in SMWT, and improvement of MLHFQ data that were not available in the prior meta-analysis studies [46–48]. Apart from the strengths mentioned above, our study also had some drawbacks. First, all studies involved in this systematic review and meta-analysis were cohort studies, causing unwanted referral bias or selection bias. Second, publication bias was also unavoidable. However, we had anticipated that situation by conducting a strict publication bias assessment using the combination of Egger test and funnel plot analysis. We found the publication bias only in the meta-analysis of all-cause mortality. Third, the complete data could not be extracted for several parameters, such as CRT implantation criteria, CRT programming, indication for performing AVJA, the method for assessing LVEF, and interobserver variability. Fourth, the inability to access the individual patient-level data limited our ability to evaluate patient-level real effects on our outcomes.

5. Conclusion

Our study revealed that in permanent AF and HFrEF patients receiving CRT, AVJA reduced cardiovascular mortality, decreased LVEDD, and increased the biventricular pacing rate. The possible association among those parameters improvement was AVJA increased biventricular pacing rate. Adequate biventricular pacing

rate improved the response to the CRT marked by the greater ventricular reverse remodeling and survival from cardiovascular mortality. Prospective evaluation of AVJA in permanent AF and HFrEF patients receiving CRT by a large size and well-designed RCT is required.

Declaration of competing interest

All authors declare that there is no conflict of interest regarding the publication of this manuscript.

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