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Comparison of survival for cardiac resynchronization therapy in atrial fibrillation patients with or without atrio-ventricular junction ablation and patients in sinus rhythm: a systematic review and network meta-analysis

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Abstract

Cardiac resynchronization therapy (CRT) has been established to improve prognosis for patients with heart failure and SR. Whether the benefit observed with CRT on survival was similar in AF patients receiving atrio-ventricular junction ablation (AVJA) or not and patients in SR remains uncertain. The primary purpose of this study was to comprehensively evaluate the impact of CRT on the outcome of survival in atrial fibrillation (AF) patients with or without AVJA and patients in sinus rhythm (SR). Medline, Embase, and the Cochrane Library were searched for inception through June 31, 2018. Two reviewers independently evaluated and extracted data from 4 studies, including a total of 7896 CRT recipients, composed of 554 AF with AVJA (CRT+AF+AVJA), 1071 AF without AVJA (CRT+AF-AVJA), and 6244 SR (CRT+SR). The benefit on survival was comparable between CRT+AF+AVJA and CRT+SR (HR = 1.00; 95% CI, 0.73–1.40). CRT+AF+AVJA and CRT+SR both were associated with significantly higher survival compared with CRT+AF-AVJA, with hazard ratio of 0.64 (95% CI, 0.46–0.91) and 0.63 (95% CI, 0.53–0.75), respectively. The survival benefit was similar for patients with CRT+AF+AVJA and CRT+SR, while it was 36–37% high as compared to CRT+AF-AVJA. Whether aggressive intervention with AVJA in AF should be routinely combined with CRT despite rate-slowing drug treatment is helpful deserves further studies.

Keywords Atrial fibrillation · Cardiac resynchronization therapy · Atrio-ventricular junction ablation · Heart failure · Survival

Introduction

The prognosis of heart failure (HF) remains poor, despite contemporary pharmacological therapy. Cardiac resynchronization therapy (CRT) has been established to improve long-term survival and recommended as class IA indication for patients in sinus rhythm (SR) with drug refractory HF, impaired ejection fraction (EF), prolonged QRS duration, and advanced New York Heart Association (NYHA) functional class [1–4]. Individuals with atrial fibrillation (AF) are virtually excluded in randomized controlled trials of CRT and considered as eligible to CRT with class IIA, since its loss of resynchronization pacing in a failing heart, despite its common co-occurrence with HF [4, 5]. Data from large registries [6, 7] indicated that effective delivery of biventricular pacing (BVP) was a prerequisite for successful CRT pacing and can be achieved with atrio-ventricular junction ablation (AVJA) in AF patients. In recent systematic reviews [8–10], CRT combined with AVJA in AF patients was associated with a substantial reduction in relative risk (RR) of long-term mortality, compared with CRT without AVJA. However, the decision to perform AVJA is still a matter of debate with several studies [11–13] that showed similar improvement on the long-term mortality in SR and AF, while the risk of pacemaker dependency and the lack of evidence from randomized trials. Furthermore, for survival

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data, it is more appropriate to use hazard ratio (HR) that provides time-to-event prognostic information, instead of relative risk (RR) with which were compiled in most conventional meta-analyses, for pooled analysis.

In view of traditional meta-analysis, methods do not allow adequate assessment of the comparative effectiveness of CRT pacing in AF with or without AVJA as well as in SR in one hand and lack of time-to-event data on another hand; we did a systematic review and network meta-analysis of existing studies to comprehensively compare the impact of CRT on the risk of survival in AF patients receiving AVJA (CRT+AF+AVJA) or not (CRT+AF-AVJA) and patients in SR (CRT+SR), with outcome that was finally pooled in HR.

Materials and methods

Search strategy and selection criteria

We searched Medline, Embase, and Cochrane Library databases, using the search terms "cardiac resynchronization therapy OR biventricular pacing" AND "atrial fibrillation" AND "atrio-ventricular junction ablation" without date restrictions up to June 31, 2018. We manually searched for additional eligible studies in reference lists of retrieved publications and relevant meta-analysis in the discipline.

Studies were included if they enrolled patients with EF ≤ 35%, and QRS width ≥ 120 ms, and at least one group investigated the impact of AVJA on mortality. No limitations on the approach to cardiac resynchronization and NYHA functional class were pre-specified. Studies without mortality outcome were excluded. Individual case reports, editorials, and review articles were excluded. Studies containing ≤ 20 patients or in any treatment group were excluded.

Two independent reviewers (Yangjing Xue and Jinsheng Wang) performed the search, and a third reviewer (Kangting Ji) resolved any discrepancies.

Data extraction

Two investigators (Yangjing Xue and Jinsheng Wang) independently reviewed the main reports and supplementary materials and extracted information into an electronic database: study and patient characteristics, study design, interventions, the number of events of death in each group, and the duration of follow-up. Any discrepancies regarding the extraction of data were resolved by an additional investigator (Kangting Ji).

Data analysis

We initially did a pairwise meta-analysis to calculate the HR and appropriate 95% confidence interval (CI) from original studies with methods described by Tierney and colleagues [14]. We pooled summary estimate using the DerSimonian-Laird random-effect method [15], which recognizes and anchors studies as a sample of all potential studies. The I^2 statistic was calculated as a measure of the proportion of the overall variation that is attributable to between-study heterogeneity.

For indirect and mixed comparisons, we used network meta-analysis to compare the relative effect of CRT+AF+AVJA, CRT+AF-AVJA, and CRT+SR on survival, within a

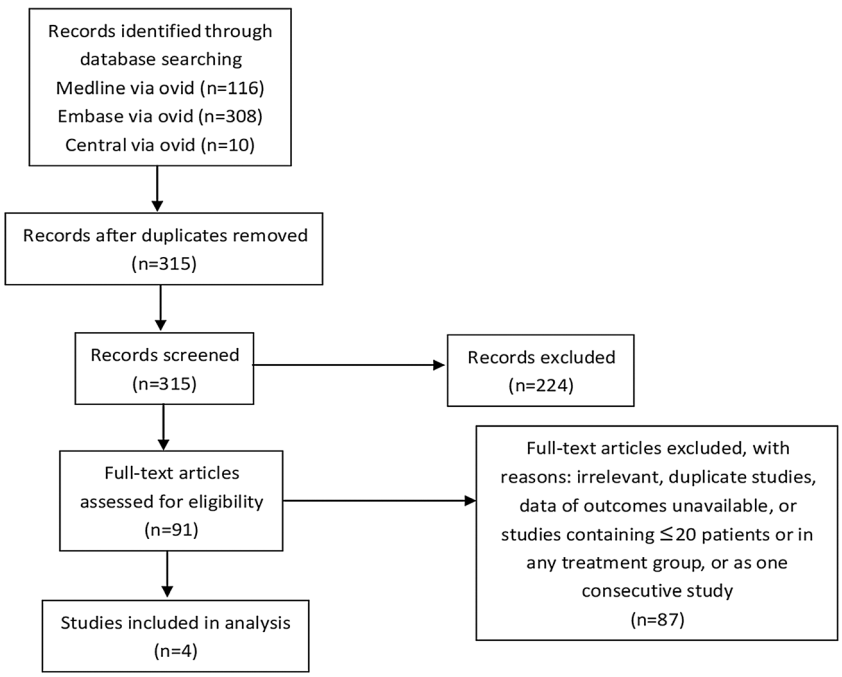

Fig. 1 Flowchart of studies considered for inclusion

Table 1 Study and patient characteristics

First author, year	Study type	Inclusion criteria	Intervention groups	Number	Age (years)	Male (%)	AF characteristics	Follow-up	CRT-D (%)	BVP (%)	Ischemic cardiomyopathy (%)	LVEF (%)	QRS (ms)
Ferreira, 2008	Retrospective single--center cohort	Drug-refractory NYHA II–IV HF, LVEF ≤ 35%, QRS duration ≥ 120 ms	AF+AVJA+ CRT	26	67 ± 9	92	NA	Mean follow-up 29 ± 18 months	77	98 ± 6	58	24 ± 9	NA
			AF-AVJA+ CRT	27	70 ± 8	96			85	87 ± 19	48	26 ± 9	NA
			SR+CRT	78	66 ± 10	74			76	95 ± 13	53	26 ± 9	NA
Dong, 2010	Retrospective single--center cohort	Heart failure symptoms despite medical therapy, LVEF ≤ 35%, QRS duration ≥ 120 ms	AF+ AVNA+ CRT	45	72 ± 9	84	88% permanent AF	Median follow-up 2.1 years (interquartile 1.4–3.0 years)	100	99.00	51	25.5 ± 8.1	161.2 ± 35.0
			AF+CRT	109	68 ± 11	87			100	96.50	61	22.6 ± 6.4	174.6 ± 34.6
Gasparini, 2006 and 2013*	Prospective multicenter observa-tional cohort	Systolic HF in NYHA III–IV (or II in recent HF hospitalization), despite maximum tolerated pharmacologic therapy for at least 2 months, LVEF ≤ 35%, QRS duration ≥ 120 ms	AF+AVJA+ CRT	443	68.4 ± 9.1	84.2	100% permanent AF	Median follow-up 37 months (interquartile 14–58 months)	68.2	96 ± 6	41	27.0 ± 6.6	159.2 (37.9)
			AF+CRT	895	69.7 ± 9.3	85.4			70.9	87 ± 14	36.4	25.9 ± 6.9	155.4 (33.5)
			SR+CRT	6046	66.4 ± 10.3	78			80.9	92 ± 13	47	25.9 ± 6.5	157.6 (31.9)
Jedrzejczyk-Patej, 2014	Prospective single--center registry cohort	Drug refractory symptomatic HF in NYHA III–IV, LVEF ≤ 35%, QRS duration> 120 ms	AF + AVJA + CRT	40	62 (57–69)	77.5	52.5% permanent AF	Median follow-up 36.1 (24.3–-54.6) months	NA	≥ 95	47.5	23.5 (20–27.5)	160 (140–190)
			AF + CRT	40	57 (49–66)	77.5			NA	≥ 95	45	24 (20–29)	177 (160–200)
			SR + CRT	120	59 (53–67)	73.3			NA	≥ 95	47.5	24 (21–28)	169.5 (155–185)

NYHA New York Heart Association, *HF* heart failure, *LVEF* left ventricular ejection fraction, *AF* atrial fibrillation, *CRT* cardiac resynchronization therapy, *AVJA* atrio-ventricular junction ablation, *SR* sinus rhythm, *BVP* biventricular pacing

*Study published in 2006 and 2013 was considered as one consecutive study

Bayesian framework, and the results were summarized using HR and their CI.

Ranking probabilities for all treatments on survival outcome were estimated to obtain a treatment hierarchy using the mean ranks. A loop-specific approach was used to evaluate the presence of inconsistency locally in network meta-analysis models, that is, if the information of both sources of evidence (direct and in direct estimations) is similar enough to be combined. Inconsistency was defined as disagreement between direct and indirect evidence with a 95% CI that excluded 1.

Analyses were conducted using STATA 13 and R software (version 3.5.1).

Results

Study characteristics

There were six observational studies [16–21] that reported the outcome of survival, of which two studies belong to Gasparini and colleagues [18, 19]. After e-mail contact with Professor Gasparini M., we affirmed that the CERTIFY (Cardiac Resynchronization Therapy in Atrial Fibrillation Patients Multinational Registry) study [19] encompasses a part of population in the study [18] they published in 2008. Meanwhile, Gasparini et al. claimed that the study [22] published in 2006 could be considered as an extension of the study [18] they published in 2008. Therefore, we considered these three studies as one consecutive study and enrolled the CERTIFY study [19] as for extraction of survival data. We excluded Kuznetsov's study [21] with its results has remained to be in an abstract format (orally presented in 2014). Overall, four observational studies met the eligibility criteria and were included in the network meta-analysis. The flowchart of the literature search is shown in Fig. 1.

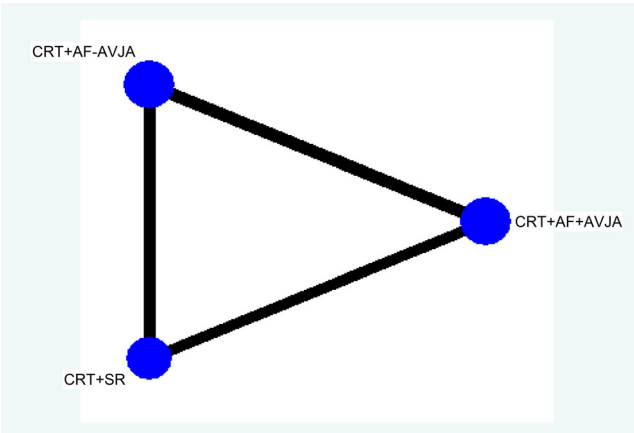

Fig. 2 Evidence structure of eligible comparisons on survival. The numbers along the link lines indicate the number of studies or pairs of study arms. Lines connect the interventions that have been studied in head-to-head (direct) comparisons in the eligible studies. The width of the lines represents the cumulative number of studies for each pairwise comparison. The size of every node is proportional to the number of participants. CRT cardiac resynchronization therapy, AF atrial fibrillation, AVJA atrio-ventricular junction ablation

The four studies were published or presented in the years ranged from 2006 to 2014 and included a total of 7896 CRT recipients, of whom including 554 AF with AVJA (AF+AVJA), 1071 AF without AVJA (AF-AVJA), and 6244 SR.

Study inclusion criteria were generally similar across all studies, including patients with LVEF ≤ 35%, QRS duartion ≥ 120 ms, and advanced NYHA functional class (Table 1). Patients were generally undergoing accepted medical therapy for HF, including use of beta blockers, angiotensin-converting enzyme inhibitors, aldosterone antagonists, and diuretics.

Among patients with AF+AVJA, AF-AVJA, and SR, the mean age was 67.35, 66.18, and 63.80 years; the mean proportion of males was 84.43%, 86.48%, and 75.10%; and the mean use of CRT-D was 81.73%, 85.30%, and 78.45%, respectively. Mean follow-up was 31.83 months among the three groups.

Prevalence of ischemic cardiomyopathy was 49.38%, 47.85%, and 49.17% while the averaged left ventricular ejection fraction (LVEF) was 25.00%, 24.63%, and 25.3%, separately, in patients with AF+AVJA, AF-AVJA, and SR.

The mean QRS duration ranged from 155 to 162 ms in patients with AF+AVJA, from 155.4 to 177 ms in those with AF-AVJA, and from 169.5 to 170 ms in those with SR. The majority of patients had a mean QRS duration > 150 ms, in accordance with the recommendations made by various societies for CRT therapy.

Effectiveness of ventricular rate control was only considered by Dong et al., not available in any other retrieved studies. However, in multivariate analysis, neither Holter nor electrocardiogram monitored heart rates were statistically significant survival predictors in this study. Not all patients had left bundle branch block (LBBB), and percentage of LBBB was only considered by Gasparini et al.

Effectiveness of biventricular capture was nearly complete in AF+AVJA and SR patients. In AF-AVJA patients, BVP (%) varied from 87 to 96.5%.

Study quality was limited in that the four included studies were observational design with no randomized controlled trial data available. To further assess study quality, we classified study method by using a composite of features derived from the Newcastle–Ottawa Scale [23], which has been used to assess quality in nonrandomzied studies. Detailed data are presented in Appendix.

Device implantation and reasons for AVJA

Conventional right ventricular lead or defibrillation electrode was usually positioned in the apex or the interventricular septum. Left ventricular lead placement was prioritized as lateral

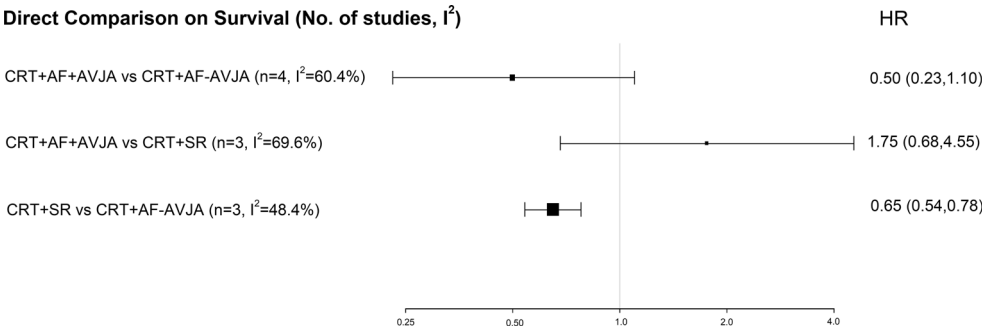

Fig. 3 Effect of three regimens on survival by direct pairwise meta-analysis. CRT cardiac resynchronization therapy, AF atrial fibrillation, AVJA atrio-ventricular junction ablation

or posterolateral through the coronary sinus. Implantation of atrial lead into a right atrial appendage in patients with paroxysmal/persistent AF was inconsistent across the four studies. Transvenous, venogram-guided technique was the routine approach undertaking for device implantation, in case of one study [17, 19, 22] that stated that epicardial screw-in or steroid-eluting passive lead through limited thoracotomy was used for failure or technical difficulty cases. For patients with preserved SR, the CRT device was programmed in atrial-synchronous sequential pacing (DDD mode), while in patients with AF, a biventricular rate adaptive response was activated (VVIR mode).

The reasons for performing AVJA in AF patients included poor heart rate control with rate-slowing drugs and insufficient biventricular pacing or inappropriate implantable cardioverter defibrillator shocks.

Effects of CRT+AF+AVJA, CRT+AF-AVJA, and CRT+SR on survival

Network evidence on survival is shown in Fig. 2. Three treatments were analyzed, including CRT+AF+AVJA, CRT+AF-AVJA, and CRT+SR. Three trials were three-arm studies that included data on CRT+AF+AVJA, CRT+AF-AVJA, as well as CRT+SR, and one was two-arm study reported data for comparing CRT+AF+AVJA with CRT+AF-AVJA.

Figure 3 shows the effect of CRT+AF+AVJA, CRT+AF-AVJA, and CRT+SR on survival from pairwise meta-analyses (direct meta-analyses). CRT+AF+AVJA did not indicate statistical significance on survival compared with CRT+AF-AVJA (HR = 0.50; 95% CI, 0.23–1.10, I^2 = 60.4%) and CRT+SR (HR = 1.75; 95% CI, 0.68–4.55, I^2 = 69.6%). CRT+SR was associated with decreased mortality compared with CRT+AF-AVJA (HR = 0.65; 95% CI, 0.54–0.78, I^2 = 48.4%).

The result of network meta-analysis on survival is shown in Fig. 4. The HR of CRT+AF+AVJA on survival was comparable with CRT+SR (HR = 1.00; 95%CI, 0.73–1.40), whereas CRT+AF+AVJA was associated with significantly higher survival compared with CRT+AF-AVJA (HR = 0.64; 95% CI, 0.46–0.91). In addition, CRT+SR was associated with increased survival compared with CRT+AF-AVJA (HR = 0.63; 95% CI, 0.53–0.75).

Figure 5 shows the ranking probability of each treatment on overall survival. According to rank probability, CRT+SR ranked first on survival benefit among the three treatments with a probability of 56.2%. CRT+AF+AVJA and CRT+AF-AVJA separately had 43.8% and 0% probability with the second and third on survival benefit.

As shown in Fig. 6, the loop was consistent because their 95% CI included one according to the inconsistency plots. The inconsistency test failed to detect any significant inconsistency (P = 0.318), which meant the direct estimation of the summary effect did not differentiate from the indirect estimation. The summary estimations of network meta-analysis were relatively robust.

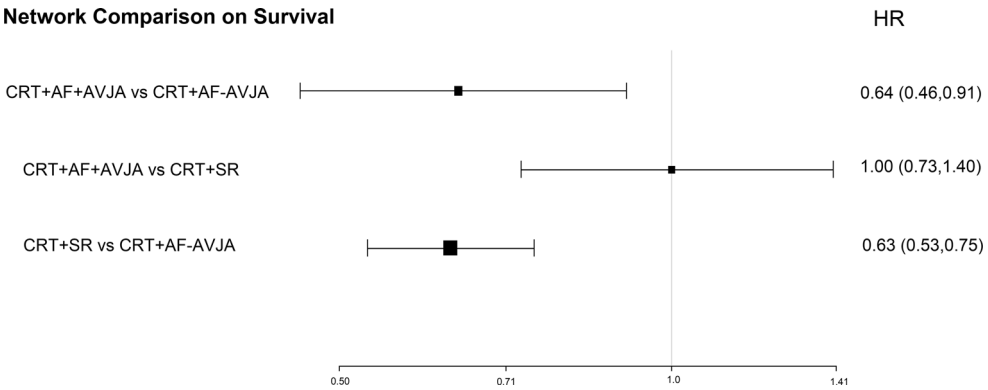

Fig. 4 Network meta-analysis of three regimens for survival. CRT cardiac resynchronization therapy, AF atrial fibrillation, AVJA atrio-ventricular junction ablation

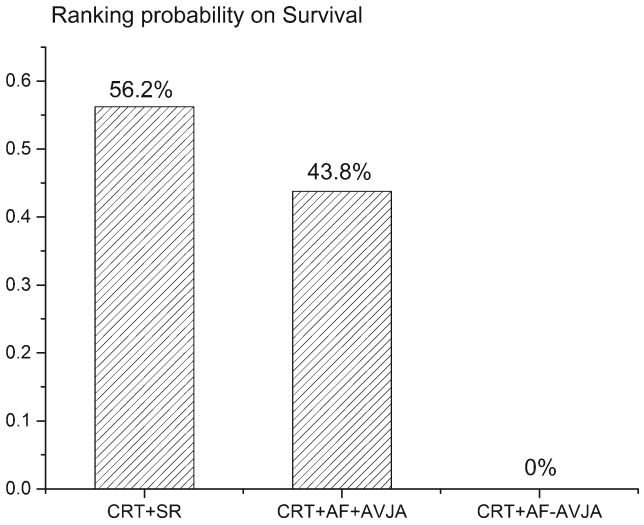

Fig. 5 Ranking probability of each regimen on benefit of survival. CRT cardiac resynchronization therapy, AF atrial fibrillation, AVJA atrio-ventricular junction ablation

Discussion

In the present network meta-analysis, data on the strong end point of survival show clear benefit on CRT+AF+AVJA and CRT+SR. The hazard risk of survival was similar in patients with CRT+SR and CRT+AF+AVJA. In contrast, CRT+AF+AVJA and CRT+SR conferred significant lower risk of mortality with HR of 0.64 and 0.63, respectively, as compared with CRT+AF-AVJA. The finding was consistent across the four studies.

Management of permanent AF in the setting of HF undergoing CRT is challenging, since the percentage of effectively CRT delivery is markedly reduced as compared to patients in SR. In a recent meta-analysis of 23 observational studies that included data of 7495 CRT recipients, Wilton [24] found a lower all-cause mortality and favor CRT response in patients with CRT+SR than CRT+AF. The role of AVJA in combination with CRT in patients with AF was evaluated by a series of observational studies [16–22] and has been demonstrated to be useful for optimizing CRT delivery in AF with robust outcome. Two meta-analysis [8, 10] had specifically compared CRT+AF patient outcome according to AVJA, demonstrating that patients with AVJA was associated with almost 50% reduction in all-cause mortality. In the present network meta-analysis, the outcome on long-term survival after CRT in AF patients with AVJA was similar to patients in SR, while it was almost 36–37% as high in AF patients without AVJA.

The survival benefit of CRT was believed to be majorly determined by the effective delivery of biventricular pacing. In large retrospective studies, Koplan [6] and Hayes [7] found that the greatest reduction of total mortality was observed with a biventricular pacing achieved in excess of 92% and 98.47% respectively. The work of Hayes also enrolled more than

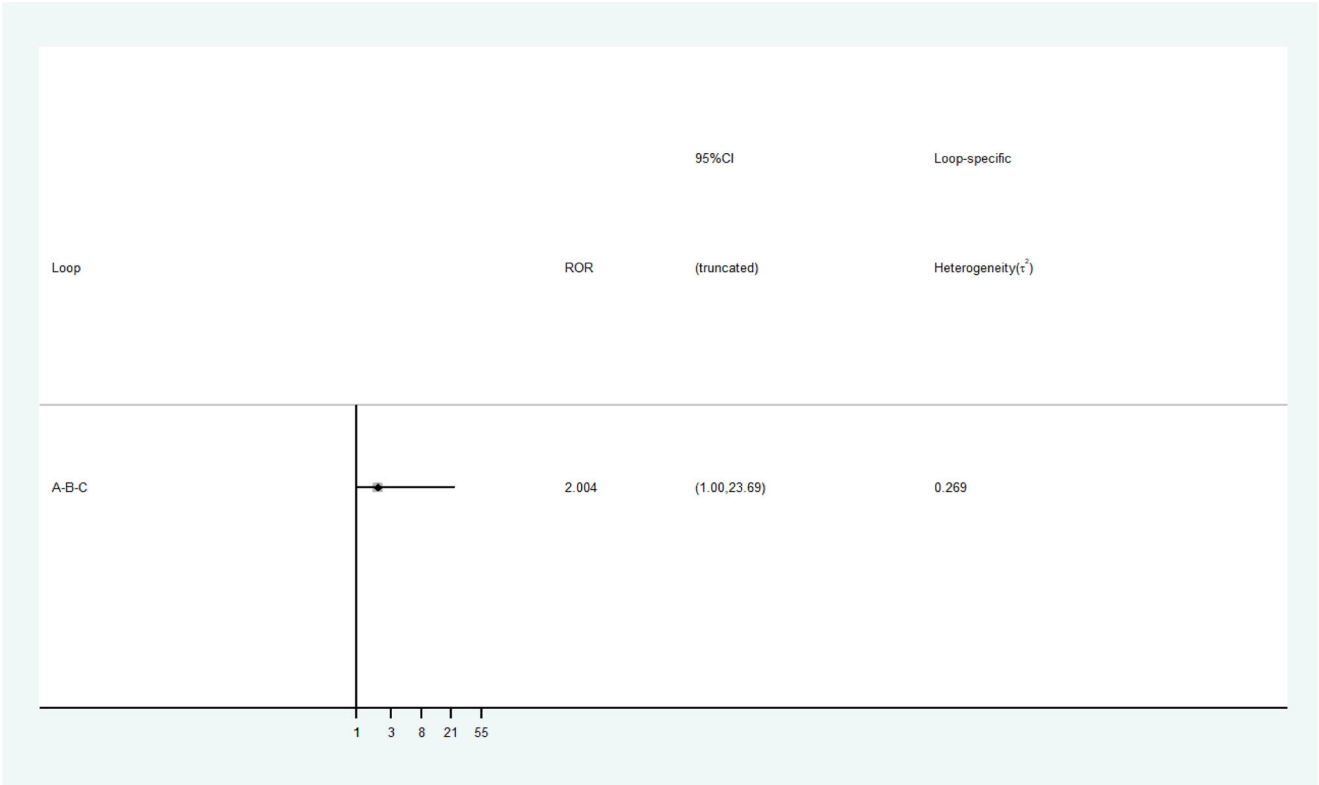

Fig. 6 Inconsistence check for closed loop in network. CRT cardiac resynchronization therapy, AF atrial fibrillation, AVJA atrio-ventricular junction ablation

10,000 AF patients, and a biventricular pacing exceeding 98.5% in CRT+AF demonstrated a survival rate equivalent to their counterpart in CRT+SR. Of the four studies included in the present study, effectiveness of biventricular capture was near complete in patients of CRT+AF with AVJA and CRT+SR while lower in CRT+AF without AVJA.

The consistent relationship between high percentage biventricular pacing and improved CRT responding and benefit on survival in our and other studies supporting interventions with CRT+AF with AVJA and CRT+SR was superior to CRT+AF without AVJA. In current guidelines [1–4], CRT is not an indication to carry out AVJA in AF patients except in cases when ventricular rate remains poorly controlled by pharmacological treatment. Indeed, AVJA can not only improve biventricular pacing delivery by lowering the ventricular rate but also improve the quality of resynchronization by diminishing the competing AF rhythm of spontaneous, fusion, or pseudo-fusion ventricular beats [4, 19, 25, 26]. Creation of complete heart block by AVJA needs to be balanced with the risk of pacemaker dependency [26]. Besides becoming pacemaker dependent, there is a slight increase in the incidence of sudden death that can be minimized by pacing at relatively high rates for 2 months following AVJA [27]. However, it must be noted that in the dual pacing setting offered by CRT, loss of ventricular pacing is low. In addition, complications related to AVJA are rare and were not reported in the available studies. For these reasons, the pursuit of aggressive intervention with AVJA in AF should routinely accompany CRT despite rate-slowing drug control, which may be switched to a higher indication equal to CRT+SR.

Several limitations were worthy of mention. Above all, only observational studies are available; this review was limited by the potential for residual confounding in the component studies. Second, we just selected studies reporting mortality outcome, which may lead to potential publication bias and selection bias. Finally, the finding was the result of direct and indirect comparisons and should be validated in large randomized controlled studies.

Conclusions

HF patients with AF combined with AVJA and patients in SR had significant positive impact on survival benefit conveyed by CRT. The time of death after CRT in AF patients without AVJA was almost 36–37% high. These findings should be prospective evaluations by randomized controlled trial.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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