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Cardiac Resynchronization in Patients With Atrial Fibrillation

A Meta-Analysis of Prospective Cohort Studies

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Objectives This study is a meta-analysis of prospective cohort studies comparing the impact of cardiac resynchronization therapy (CRT) for patients in atrial fibrillation (AF) and sinus rhythm (SR).

Background Although close to one-third of advanced heart failure patients exhibit AF, the impact of CRT in this group remains unclear.

Methods Prospective cohort studies comparing patients in normal SR and chronic AF treated with CRT were included. All studies reported death, New York Heart Association functional class, ejection fraction, 6-min walk test, and the Minnesota score or its equivalent as outcomes. Data sources included Ovid MEDLINE In-Process & Other Non-Indexed Citations, the Cochrane Central Register of Controlled Trials, the Database of Abstracts of Reviews of Effects, and the American College of Physicians Journal Club.

Results Of 2,487 reports identified, 5 studies following a total of 1,164 patients were included. Both AF and SR patients benefited significantly from CRT. Mortality was not significantly different at 1 year (relative risk ratio: 1.57, 95% confidence interval [CI]: 0.87 to 2.81). The New York Heart Association functional class improved similarly for both groups (−0.90 for SR patients, −0.84 for AF patients). SR patients showed greater relative improvement in the 6-min walk test (11.6 m greater, 95% CI: 10.4 to 12.8 m) and the Minnesota score (3.9 points less, 95% CI: 3.4 to 4.5 points) than AF patients. AF patients, however, achieved a small but statistically significant greater change in ejection fraction (0.39% greater change in ejection fraction, 95% CI: 0.22% to 0.55%).

Conclusions Patients in AF show significant improvement after CRT, with similar or improved ejection fraction as SR patients, but smaller benefits in regard to functional outcomes. (J Am Coll Cardiol 2008;52:1239–46) © 2008 by the American College of Cardiology Foundation

Heart failure continues to be the most frequent cause of hospitalization among the elderly, with annual health care costs totaling $33.2 billion in the U.S. alone (1,2). Although advances in diagnostic and pharmacotherapeutic strategies have led to improved survival in the past 2 decades, the observed benefits have been modest and variable among diverse groups of heart failure patients (3–5).

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In recent years, the armamentarium of treatment options for heart failure patients has expanded to include new device-based interventions: specifically, atrial-synchronized biventricular cardiac pacemakers or cardiac resynchronization therapy (CRT). Targeted toward patients with left ventricular dysfunction and mechanical dyssynchrony, CRT offers additive mortality and morbidity benefits beyond medication (6,7). Large-scale randomized clinical trials evaluating CRT have validated its use for patients in sinus rhythm on stable medical therapy, symptomatically severe New York Heart Association (NYHA) heart failure, significant systolic dysfunction, and prolonged QRS duration (8–13).

Importantly, although close to one-third of patients with advanced heart failure show atrial fibrillation (AF), there is

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Abbreviations and Acronyms

6MWD = 6-min walking distance

AF = atrial fibrillation

AVJ = atrioventricular junction

CI = confidence interval

CRT = cardiac resynchronization therapy

LVEF = left ventricular ejection fraction

MLWHF = Minnesota Living With Heart Failure

NYHA = New York Heart Association

QOL = quality of life

a paucity of data regarding the impact of CRT in this subgroup (14). Previous systematic reviews of randomized clinical trials have evaluated the impact of CRT on morbidity and mortality for patients in sinus rhythm, largely excluding patients with AF (6,7,15,16). Recently reported data from smaller prospective cohort studies now make it possible to begin to assess the clinical benefit of CRT for patients with AF. Accordingly, we conducted a meta-analysis to determine the differential impact of CRT for patients in AF and sinus rhythm.

Methods

Search strategy. We performed an electronic literature search of MEDLINE (1950 to May 2007), MEDLINE In-Process & Other Non-Indexed Citations, Cumulative Index to Nursing & Allied Health Literature, the Cochrane Database of Systematic Reviews (Second Quarter, 2007), the American College of Physicians Journal Club (1991 to May/June 2007), Database of Abstracts of Reviews of Effects, and the Cochrane Central Register of Controlled Trials using the following search terms: heart, cardiac, biventricular pacing, biventricular pacemaker, cardiac resynchronization therapy, resynchronization therapy, or cardiac resynchronization. We conducted additional searches based on 9 trial acronyms that are frequently cited in narrative reviews of cardiac resynchronization. We also hand searched the bibliographies of all review articles published in the past 5 years regarding the role of CRT or cardiac resynchronization and patients with AF.

Studies reporting the impact of CRT on mortality, echocardiographic data (e.g., ejection fraction), and functional outcomes (e.g., NYHA functional class, 6-min walk test, and quality of life [QOL] as measured by the Minnesota Living with Heart Failure (MLWHF) questionnaire) in patients with sinus rhythm and chronic AF were selected. We included both published data from subgroups in randomized trials and published prospective cohort studies. Reports in which the majority of AF patients developed AF after enrollment or had primarily intermittent or paroxysmal AF were excluded, as were studies with a total number of <25 participants and those that did not present original research data (e.g., letters, commentaries, reviews, or study design articles).

Data extraction. Two investigators (G.A.U. and J.P.S.) independently extracted data on patient and study characteristics, outcomes, and study quality for each trial using a standardized protocol and reporting form. Disagreements were resolved by consensus.

Data analysis. We calculated relative risks for dichotomous outcomes (e.g., mortality) using the DerSimonian and Laird random effects models. For continuous outcomes, weighted mean differences were calculated using Mantel-Haenszel fixed-effects models. Only outcomes in which 3 or more studies reported on results were combined in our weighted mean difference calculations. Heterogeneity was quantified using the I^2 statistic (17). Statistical analyses were conducted using Review Manager 4.3 (The Cochrane Collaboration, Copenhagen, Denmark), and 95% confidence intervals (CIs) were reported for all results. For trials that reported results at multiple time points, we used 6- or 12-month follow-up data to ensure comparability between studies. In the case of Linde et al. (18), results used were those documented for patients who had completed the randomization crossover periods.

Results

Search results. The initial search yielded 2,487 results, of which 5 (4 prospective cohort studies [19–22] and a subgroup of 1 randomized clinical trial [18]) met our inclusion criteria (Fig. 1). The studies included a total of 1,164 patients, of whom 797 were in sinus rhythm and 367 were in AF. Table 1 summarizes the baseline characteristics for patients enrolled in each study. Taken together, the weighted average age of patients was 66 years, with patients in AF being 1.6 years older on average ($p = 0.005$). Most patients (78%, weighted average) were men. More AF patients had NYHA functional class III to IV heart failure than those in sinus rhythm (99.6% and 89.0%, respectively). Among 841 patients in whom the cause of heart failure was reported, 42% were identified as having ischemic cardiomyopathy (18,19,21).

The quality of the studies included is limited in that the majority are prospective cohort studies rather than randomized trials. The inclusion criteria for enrollment were similar across studies and were consistent with the generally accepted criteria for the large-scale randomized trials validating CRT, however, including: electrocardiographic evidence of conduction delay (QRS duration ≥120 ms or QRS ≥200 ms for paced patients), severe symptomatic heart failure (NYHA functional class III to IV patients), and significant systolic dysfunction (left ventricular ejection fraction [LVEF] ≤35%). Exceptions included the enrollment of a minority of NYHA functional class II heart failure patients in 2 studies (21,22) and the use of a longer QRS interval (QRS ≥150 ms) for entry in 1 trial (18). All patients were on a stable combination of medical therapy for heart failure before enrollment including beta-blockade, angiotensin inhibition, and use of diuretics.

Device implantation and use of atrioventricular junction (AVJ) ablation. The implantation site of the left ventricular lead in all studies was in a tributary of the coronary sinus, usually in a lateral or posterolateral cardiac vein. The venography-guided, transvenous approach was the preferred

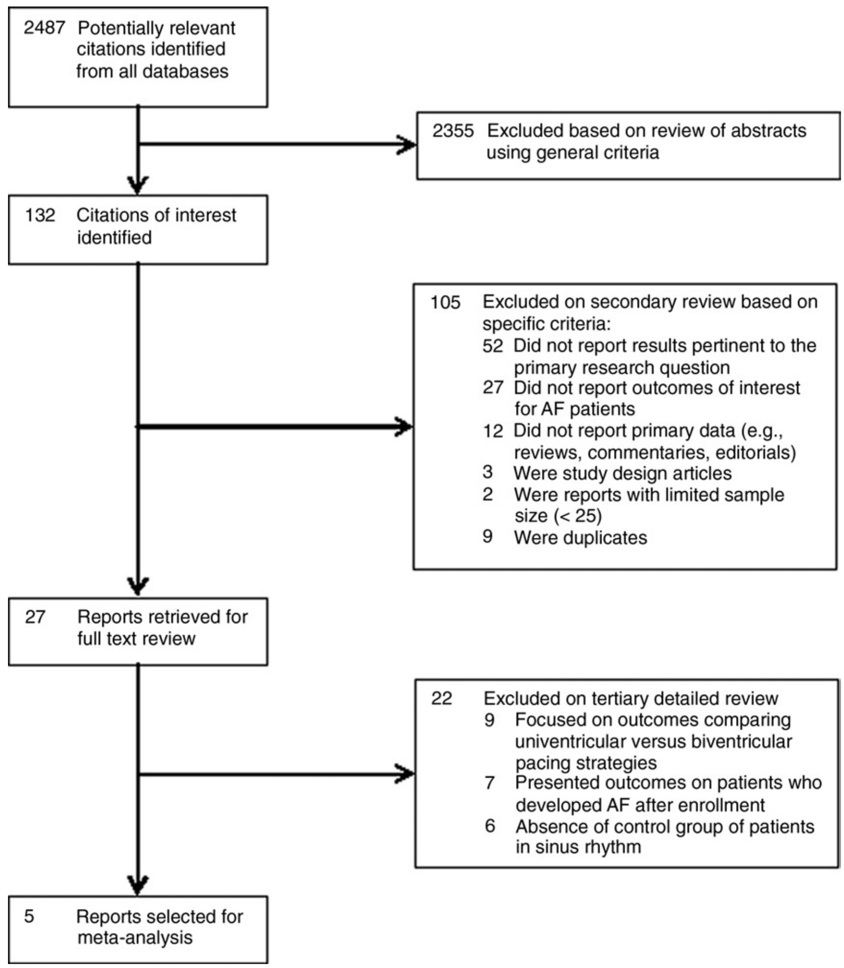

Figure 1 **Search Flow Diagram For Reports Included in the Meta-Analysis**

AF = atrial fibrillation.

modality of placement used, although an epicardial approach via limited thoracotomy was used in 1 study for a handful of technically difficult cases (21). Two studies implanted combination CRT and defibrillation (i.e., CRT-D) devices where necessary along with conventional CRT devices (20,21). Patients with preserved sinus rhythm were programmed to receive atrial-synchronous sequential pacing (DDD), and the majority of AF patients were paced in a biventricular rate adaptive (VVIR) mode. Four of 33 AF patients in the MUSTIC (MUltisite STimulation In Cardiomyopathy) trial (18), however, preferred right ventricular VVIR pacing after the crossover period, and were programmed accordingly.

The use of AVJ ablation was variable across AF patients, between 22% in Delnoy et al. (22) to 100% in Leclerq et al. (19), with an overall rate of 56% across patients in this analysis (Table 2). Gasparini et al. (21) prospectively determined that all AF patients who achieved ≤85% biventricular pacing would undergo AVJ ablation. In Delnoy et al. (22), AVJ ablation was performed in only 2 patients after pacemaker implantation. All other use of AVJ ablation in AF patients across all studies had been performed before study initiation, and indication for ablation was not specified. Global biventricular capture rates for AF patients after CRT were reported in 2 studies: 75% in Gasparini et al. (21) and 82% in Molhoek et al. (20). These 2 investigators also reported results of subsets of their patients who underwent AVJ ablation. Results reported here, however, represent all AF patients, inclusive of both AVJ ablated and nonablated patients. Delnoy et al. (22) did not report global biventricular capture rates, but did observe that 90% of patients in AF achieved a biventricular pacing percentage of >90%, 6% achieved 50% to 90% biventricular pacing, and 4% were biventricularly paced <50% despite medication adjustments, thus necessitating AVJ ablation.

All-cause mortality. A total of 85 deaths were reported across the included studies at 1 year (41 among AF patients and 44 in sinus rhythm patients). Although there was

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Table 1 Baseline Characteristics of Patients Included in Meta-Analysis

	Delnoy et al. (22) 2007		Gasparini et al. (21) 2006		Molhoek et al. (20) 2004		Linde et al. (18) 2002 (MUSTIC)		Leclercq et al. (19) 2000	
	SR	AF	SR	AF	SR	AF	SR	AF	SR	AF
Number of patients	167	96	511	162	30	30	67	64	22	15
Age, mean ± SD (yrs)	72 ± 9	73 ± 8	63.4 ± 10	66 ± 8.3	68 ± 8	63 ± 10	63 ± 10	65 ± 9	67 ± 8	68 ± 6
Male gender (%)	68.3	75	77.3	85.8	80	90	75	81	91.9*	
Ischemic HF (%)	NA	NA	47.2	37.1	NA	NA	37	27	45.5	26.7
QRS duration, mean (ms)	171	171	165.3	165	NA	NA	176	206	178	186
LVEDD, mean (mm)	NA	NA	67	66	74	76	73	68	NA	NA
Peak Vo_2, mean ± SD (ml/min/kg)	NA	NA	13.1 ± 2.8	12.1 ± 2.2	NA	NA	13.6 ± 3.8	12.7 ± 3.9	13.4 ± 4.3	11.2 ± 3.2
EF, mean (%)	22	25	26	26.3	23	20	22	26	22	24
6MWD, mean ± SD (m)	238 ± 124	262 ± 129	332 ± 117	311 ± 107	262 ± 97	227 ± 113	320 ± 97	328 ± 80	NA	NA
MLWHF score, mean ± SD	35 ± 17	32 ± 15	NA	NA	43 ± 13	43 ± 17	47 ± 23	45 ± 23	NA	NA
NYHA functional class III to IV (%)	78.8	76.9	89.7	96.9	100	100	100	100	100	100

*Trial did not report separate percent male proportions for SR versus AF patients.
6MWD = 6-min walking distance; AF = atrial fibrillation; EF = ejection fraction; HF = heart failure; LVEDD = left-ventricular end-diastolic diameter; MLWHF = Minnesota Living with Heart Failure questionnaire score; NA = not available; NYHA = New York Heart Association; Peak Vo_2 = peak symptom-limited oxygen consumption; SR = sinus rhythm.

increased mortality in patients with AF, the calculation of risk did not reach statistical significance (risk ratio: 1.57, 95% CI: 0.87 to 2.81, p = 0.13) (Fig. 2). There was no significant heterogeneity between studies (I^2 = 47.5%). Among 4 studies that reported cause of death, approximately 79% (weighted average) were from cardiovascular causes, including stroke (18–20,22).

Ejection fraction. The LVEF improved significantly across all studies for both patients in sinus rhythm and patients in AF. Average LVEF increased from 25.3% to 35.2% in patients with AF and from 24.6% to 33.8% for those in sinus rhythm. Although patients in AF had slightly higher LVEF at baseline, they also showed a slightly greater change in LVEF (0.39% greater change in LVEF vs. those in sinus rhythm, 95% CI: 0.22 to 0.55, p < 0.0001) (Fig. 3). There was a significant degree of heterogeneity for this outcome (I^2 = 97.1%). Notably, the method of calculating LVEF was not reported in standard fashion and could not be compared between studies.

Table 2 Use of AVJ Ablation in AF Patients

Study	Total AF Patients	No. of Received AVJ Ablation	% Received AVJ Ablation
	AF Patients		
Delnoy et al. (22), 2007	96	21	22%
Gasparini et al. (21), 2006	162	114	70%
Molhoek et al. (20), 2004	30	17	57%
Linde et al. (18), 2002	64	40	63%
Leclercq et al. (19), 2000	15	15	100%

AVJ = atrioventricular junction; other abbreviations as in Table 1.

Change in NYHA functional class. Four studies reported data on NYHA functional class (18–20,22). At baseline, patients in AF had slightly more severe NYHA functional class heart failure than those in sinus rhythm (3.0 vs. 2.9, p = 0.03). Overall, both groups improved by approximately 1 functional class, although patients in AF showed slightly less improvement on average (−0.84 average change, 95% CI: −0.96 to −0.73 for AF patients; −0.90, 95% CI: −1.0 to −0.8 for sinus rhythm patients; weighted mean difference of change in NYHA functional class was 0.06, 95% CI: 0.04 to 0.08, p < 0.0001) (Fig. 4).

Functional outcomes. Three studies reported the impact of CRT on 6-min walking distance (6MWD) and the MLWHF questionnaire (18,20,22). Both AF and sinus rhythm patients showed significant improvements in 6MWD; however, patients in sinus rhythm achieved a greater relative improvement in 6MWD than their counterparts in AF, walking 11.6 m further on average (95% CI: 10.4 to 12.8 m, p < 0.0001) (Fig. 5A). Quality of life improvement, as measured by the MLWHF questionnaire, also favored patients in sinus rhythm (where lower scores indicate an improved self-perceived QOL). At baseline, QOL scores were similar across both groups (2.33 points higher for patients in sinus rhythm, p = 0.17). Although both groups showed improvements in MLWHF scores (13.2 points lower for sinus rhythm patients and 9.7 points lower for AF patients), patients in sinus rhythm achieved greater relative improvement (3.94 points weighted mean difference, 95% CI: 3.35 to 4.54 points, p < 0.0001) (Fig. 5B).

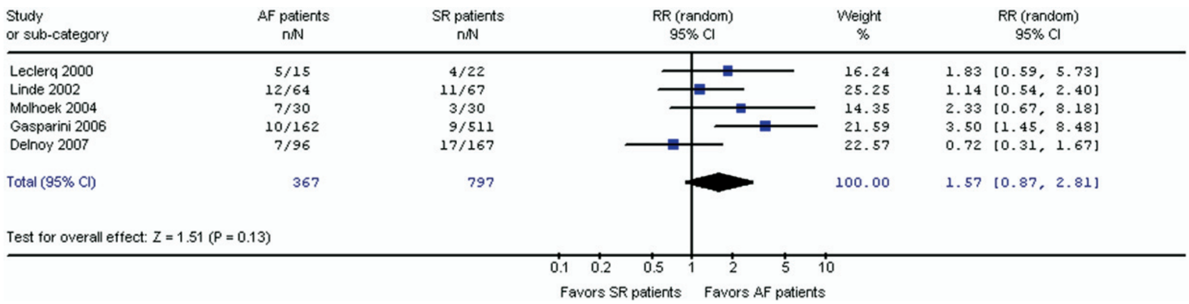

Figure 2 **All-Cause Mortality for Patients in SR Versus AF**

AF = atrial fibrillation; CI = confidence interval; RR = relative risk; SR = sinus rhythm.

Discussion

In this meta-analysis of prospective studies comparing CRT in patients with AF and sinus rhythm, we find that patients with AF have similar or slightly greater improvements in LVEF than patients in sinus rhythm but have smaller functional benefits as measured by NYHA functional class, 6MWD, and the MLWHF score. There were no significant mortality differences from CRT in patients in AF and sinus rhythm at 1 year, although the CIs around this estimate were wide, and thus we cannot exclude small mortality differences between patients with AF and sinus rhythm.

Our analysis was limited in that of the 5 eligible studies yielded from our literature search, 4 were prospective observational cohort studies. Particularly in light of an aging patient population in whom the rate of AF is increasing annually, the need for a randomized controlled trial assessing the impact of CRT in this important subgroup is clear. These limitations notwithstanding, the results across the selected studies uniformly suggest that AF patients may benefit from CRT. Patients with AF had improvements in ejection fraction (weighted mean improvement 8.6%, 95% CI: 7.1% to 10.1%, $p < 0.0001$) (18–22), NYHA functional class (weighted mean improvement of 0.8, 95% CI: 0.7 to 1.0, $p < 0.0001$) (18–20,22), 6MWD (11.6 m > baseline, 95% CI: 13.51 to 19.59 m, $p = 0.005$) (18,20,22), and a better self-perceived QOL (MLWHF reduction of 9.4 points, 95% CI: −13.38 to −5.37 points, $p < 0.0001$) (18,20,22).

Frequently comorbid with heart failure, the prevalence of AF increases with severity of heart failure, affecting 5% to 20% of patients in NYHA functional classes I to II and as high as 50% of NYHA class IV patients (23,24). Although some data suggest that CRT might reduce the incidence of AF (25,26), recent data from large trials indicate that AF occurs similarly in CRT-treated patients versus those controlled with pharmacotherapy alone, at a rate of 16% per year (27,28). Indeed, even in CRT trials requiring normal sinus rhythm for enrollment, paroxysmal AF had been present in up to 20% of patients in the year before entry (28). Our results suggest, however, that CRT may still be associated with continued improvement in these patients.

Echocardiographic improvement, in particular, seems similar for patients in AF versus those in sinus rhythm, whereas functional benefits seem to lag. Potential con-

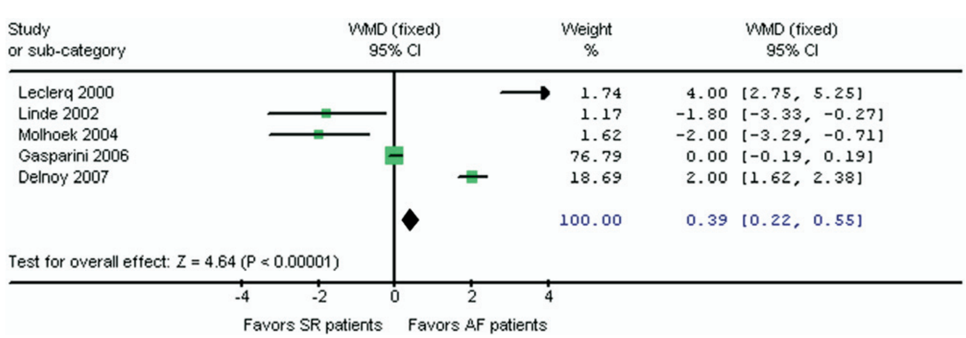

Figure 3 **WMD in Change of Ejection Fraction for Patients in SR Versus AF**

WMD = weighted mean difference; other abbreviations as in Figure 2.

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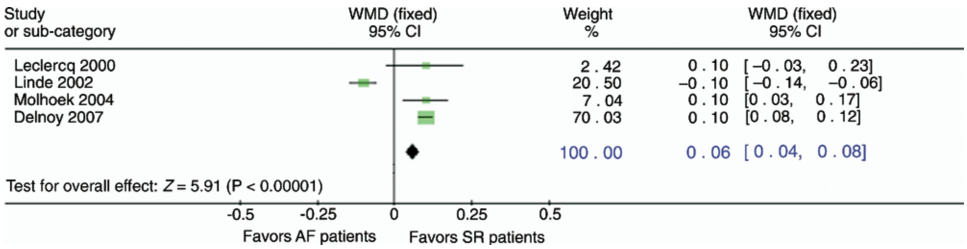

Figure 4 **WMD in Change of NYHA Functional Class for Patients in SR Versus AF**

NYHA = New York Heart Association; other abbreviations as in Figures 2 and 3.

founders that may explain the differential performance between AF and sinus rhythm patients include the calculation of LVEF (which was not described in standard fashion across studies), heterogeneity in lead placement across both patients and studies, and age of selected patients (which was 1.6 years greater for AF patients). Prior investigations in univentricular pacing devices postulated that tachycardia-induced cardiomyopathy may also drive poor outcomes for AF patients (29,30). This last rationale seems unlikely in the 5 selected studies for this analysis, because ventricular rates for AF patients were kept in a narrow range (usually 70 to 90 beats/min). It is notable, however, that to maximally deliver CRT, AF patients are often programmed to a higher ventricular rate than their counterparts in sinus rhythm. They may therefore see detriment from greater diastolic dysfunction rather than rapid ventricular response.

Perhaps more important than rate control, insufficient biventricular capture has been suggested by some investigators as the primary barrier to achieving optimal clinical response after CRT for patients in AF. Erratic native activity and electrical penetrance of the AV node may override the CRT device and interrupt ventricular synchrony, particularly in situations of increased myocardial demand (e.g., during stress or exercise). Gasparini et al. (21) also report that the occurrence of fusion or pseudofusion beats between intrinsic conducted and paced beats tends to overestimate percentage of biventricular stimulation time, and thus the true effective time of CRT delivery. In our

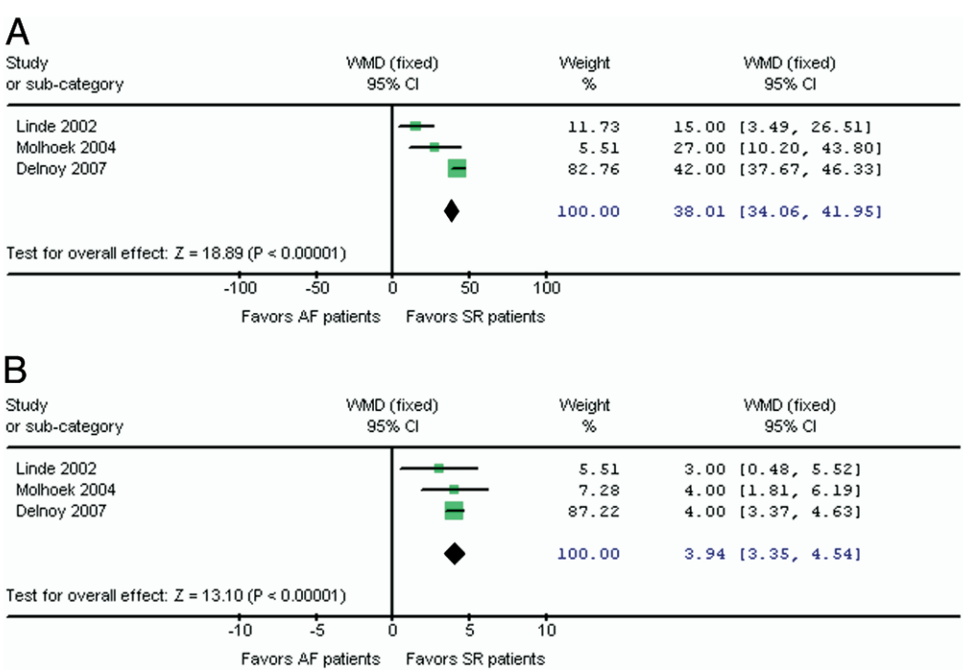

Figure 5 **WMD in Change of 6MWD and Change of MLWH Score for Patients in SR Versus AF**

(A) Weighted mean difference (WMD) in change of 6-min walk distance (6MWD) for patients in SR versus AF.
(B) Weighted mean difference in change of Minnesota Living With Heart Failure (MLWH) score for patients in SR versus AF. Abbreviations as in Figure 2.

study, only limited data from Gasparini et al. (21) and Molhoek et al. (20) were available to confirm this hypothesis, who reported that reduced mean global biventricular capture rates (75% and 82%, respectively) were present in AF patients treated with CRT.

Gasparini et al. (21) and Molhoek et al. (20) also reported separately on the cohorts of their AF patients who were treated with AVJ ablation. The AVJ-ablated patients showed better response from CRT than their counterparts in AF who were not ablated, as measured by LVEF and NYHA functional class. Gasparini et al. (21) and Molhoek et al. (20) suggest, therefore, that AF patients who are CRT responders are only those who have undergone AVJ ablation. Delnoy et al. (22), on the other hand, observed significant benefit in their AF cohort despite a lower use of AVJ ablation. This may have been driven by higher rates of biventricular capture in their study, in which 90% of AF patients achieved >90% biventricular capture. Delnoy et al. (22) suggest that higher rates of amiodarone prescription, which doubled from 12% to 23% for AF patients treated with CRT, may have allowed for this response. Notably, however, the final rate of amiodarone prescription in the study by Delnoy et al. (22) was comparable, but not significantly higher, than in other studies that reported on these data. In Molhoek et al. (20) and Linde et al. (18), overall amiodarone use also occurred in approximately one-quarter of patients before CRT.

Although it is uncertain whether AVJ ablation is required for AF patients to yield benefit from CRT, concern regarding its long-term safety has limited its general use. AVJ ablation has not been associated with an increase in mortality based on current nonrandomized investigations (31), though there is a theoretical risk of device failure and death in pacemaker-dependent patients. In an unpublished cohort study by Gasparini et al. (32) following up 243 patients with AF treated with CRT, however, patients treated with AVJ ablation showed improved survival (4.3% mortality in AVJ-ablated patients vs. 15.2% for patients receiving medical management). Given these data, it seems reasonable to consider AVJ ablation in patients with AF, although the extent of benefit and long-term safety of this approach still remains to be determined.

Taken together, current guidelines regarding the use of CRT in patients with AF have been cautious, suggesting that there is a lack of evidence to support the use of CRT in patients with AF, except for those with univentricular devices that are being upgraded after AVJ ablation (33,34). We find that even with variable use of AVJ ablation, however, CRT may be associated with clinical benefit for patients in AF, and its use in these patients warrants reconsideration and further investigation with randomized controlled trials.

Study limitations. Our study has several potential limitations. Although meta-analysis was first developed with application to randomized controlled trials, this analytical method is increasingly being applied to observational studies, including both cohort and case-control studies, because of its strengths of transparency and reproducibility of analysis. This approach has enabled the rapid synthesis of emerging evidence and yield results that are hypothesis-generating, thereby hastening the call for further randomized trials.

Additionally, we restricted our selection criteria to published studies, and therefore, may have been influenced by publication bias. Because we primarily explored the relative performance of CRT in patients with sinus rhythm versus those in AF, however, the extent of this bias should be similar for both groups, allowing for the analysis of difference that we have used. There was a significant degree of heterogeneity among some outcomes (e.g., LVEF), and the small number of studies restricted our ability to perform meta-regression and subgroup analysis. A more significant limitation to our analysis is that our selected studies represent small prospective observational studies and, at baseline, patients with AF show greater morbidity than patients in sinus rhythm. This may have mitigated the impact of CRT in AF patients in these cohorts, and it would be worthwhile to investigate the effect of CRT independently in patients with AF versus optimal medical management. Although our analysis is suggestive of benefit, the need for randomized control trials is clear. Finally, lack of uniformity in the reporting of data regarding final lead position, and the use of AV optimization (for sinus rhythm patients), prevented us from substratifying the impact of these variables on outcomes.

Conclusions

Patients in AF treated by CRT benefit substantially and significantly from CRT, although relative to patients in sinus rhythm, these benefits are greater in regard to echocardiographic improvement and smaller in regard to functional outcomes. There was no statistically significant difference in mortality between the 2 groups at 1 year, although the CI around this estimate is broad and we cannot exclude clinically meaningful differences.

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