

Role of AV Nodal Ablation in Cardiac Resynchronization in Patients With Coexistent Atrial Fibrillation and Heart Failure

A Systematic Review

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Objectives	The aim of this study was to systematically review the medical literature to evaluate the impact of AV nodal ablation in patients with heart failure and coexistent atrial fibrillation (AF) receiving cardiac resynchronization therapy (CRT).
Background	CRT has a substantial evidence base in patients in sinus rhythm with significant systolic dysfunction, symptomatic heart failure, and prolonged QRS duration. The role of CRT is less well established in AF patients with coexistent heart failure. AV nodal ablation has recently been suggested to improve outcomes in this group.
Methods	Electronic databases and reference lists through September 15, 2010, were searched. Two reviewers independently evaluated citation titles, abstracts, and articles. Studies reporting the outcomes after AV nodal ablation in patients with AF undergoing CRT for symptomatic heart failure and left ventricular dyssynchrony were selected. Data were extracted from 6 studies, including 768 CRT-AF patients, composed of 339 patients who underwent AV nodal ablation and 429 treated with medical therapy aimed at rate control alone.
Results	AV nodal ablation in CRT-AF patients was associated with significant reductions in all-cause mortality (risk ratio: 0.42 [95% confidence interval: 0.26 to 0.68]), cardiovascular mortality (risk ratio: 0.44 [95% confidence interval: 0.24 to 0.81]), and improvement in mean New York Heart Association functional class (risk ratio: -0.52 [95% confidence interval: -0.87 to -0.17]).
Conclusions	AV nodal ablation was associated with a substantial reduction in all-cause mortality and cardiovascular mortality and with improvements in New York Heart Association functional class compared with medical therapy in CRT-AF patients. Randomized controlled trials are warranted to confirm the efficacy and safety of AV nodal ablation in this patient population. (J Am Coll Cardiol 2012;59:719-26) © 2012 by the American College of Cardiology Foundation

Atrial fibrillation (AF) and heart failure (HF) are common and linked clinical conditions. The development of AF in patients with HF may significantly affect HF outcomes. Population data from Framingham suggest that new-onset

AF after a HF diagnosis conferred a hazard ratio for death of 1.6 in men and 2.7 in women (1).

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Cardiac resynchronization therapy (CRT) has become established as an important therapy for HF patients in sinus rhythm (SR) with left ventricular ejection fraction (LVEF) $\leq 35\%$, ventricular dyssynchrony (assessed by QRS duration ≥ 120 ms), and advanced New York Heart Association (NYHA) functional class (\geq III to IV) (2-4). The role of CRT in patients with coexistent HF and AF is considered to be less well defined (5). In AF patients, the evidence base for CRT has been predominantly derived from observational case series (6-14), with only limited randomized controlled trial data in studies enrolling CRT-AF patients (15,16). Two recent meta-analyses have evaluated CRT out-

**Abbreviations
and Acronyms**

AF = atrial fibrillation
AVNA = AV nodal ablation
BVP = biventricular pacing
CI = confidence interval
CRT = cardiac resynchronization therapy
HF = heart failure
LVEF = left ventricular ejection fraction
NYHA = New York Heart Association
RR = risk ratio

comes in HF patients in AF (CRT-AF) compared with those in SR (CRT-SR) (17,18). When considered as a group, CRT-AF patients have experienced, at best, mixed results for mortality and functional capacity, with higher rates of nonresponse, compared with CRT-SR patients (17,18). Despite this relatively limited supporting evidence, CRT has gained increasing acceptance as a useful therapeutic adjunct in patients with coexistent HF and AF. A recent 140-center European survey, for example, identified that

23% of patients receiving CRT implants had coexistent AF (19). Current guidelines from the American College of Cardiology/American Heart Association/Heart Rhythm Society and the European Society of Cardiology (Class IIa, Level of Evidence: B) endorse the use of CRT in AF patients with LVEF $\leq 35\%$ and ventricular dyssynchrony. However, both guidelines advise that AV nodal ablation (AVNA) may be required to ensure complete biventricular capture in patients with AF (2,3).

The effectiveness of biventricular capture during AF has been suggested as an important limitation to CRT in AF patients, with a recent 12-lead Holter study suggesting a high prevalence of fusion and pseudo-fusion beats in this group (20). In this context, a role for AVNA has been advocated to ensure complete synchronized biventricular capture (7,11,14,17,21,22). Acceptance of this approach has been limited, however, perhaps because AVNA results in permanent pacemaker dependency (14). To determine the role of adjunctive AVNA in AF patients with LVEF $\leq 35\%$ and QRS duration ≥ 120 ms receiving CRT for HF, we performed a systematic review of the literature. Our goal was to evaluate the impact of adjunctive AVNA in this setting on mortality, left ventricular function, and functional capacity in this group of patients.

Methods

We searched PubMed, Scopus, Embase, Database of Abstracts of Reviews of Effects, and Cochrane Database of Systematic Reviews, using the search terms “cardiac resynchronization OR biventricular AND atrial fibrillation.” This search was supplemented by hand-searching of bibliographies of published studies, as well as reviews of AF and HF. Citations were included if they involved patients with coexistent HF and AF patients undergoing CRT, and reported outcomes for medically treated AF patients separate from those treated with AVNA. No pre-specified limitation was placed on the approach to cardiac resynchronization. Studies were accepted if they included patients with left ventricular systolic dysfunction, defined as LVEF

$\leq 35\%$, and QRS width ≥ 120 ms. No limitation on NYHA functional class was pre-specified. Individual case reports, editorials, and review articles were excluded. Studies containing ≤ 10 patients or in any treatment group were excluded. The search was conducted on September 15, 2010. Citations were appraised by independent reviewers (A.G.B. and A.N.G.), with differences resolved by consensus. Citations from journals in languages other than English were not included. Selected publications were analyzed for the following outcomes: all-cause mortality; cardiovascular mortality; changes in LVEF assessed by objective criteria; and changes in functional capacity assessed by using objective criteria such as the 6-min walk test. Mortality data clarification was obtained for 1 study from the authors (10). Figure 1 shows the number and reasons for exclusion of publications from the originally retrieved group of citations. **Statistical analysis.** Studies reporting outcomes with homogenous characteristics were grouped for analysis. When ≥ 2 unique studies reported outcomes with homogenous characteristics, meta-analysis was performed. Mean differ-

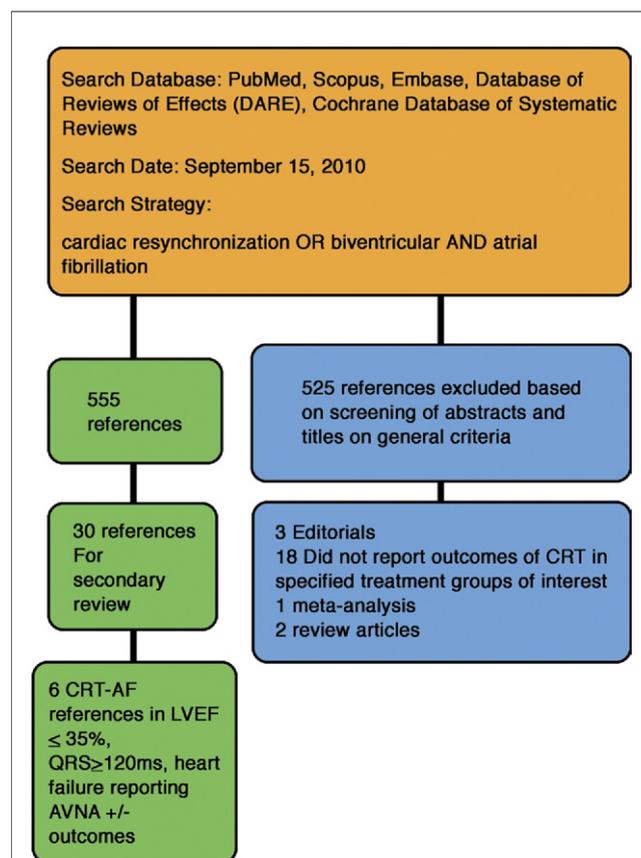


Figure 1 Search Flow Diagram for Studies Included in This Systematic Review

From a total of 555 citations identified by the preliminary search, 6 studies were selected for inclusion in this review. AF = atrial fibrillation; AVNA+ = AF patients undergoing CRT for heart failure who had undergone AVNA; AVNA- = AF patients who did not have AVNA; CRT = cardiac resynchronization therapy; LVEF = left ventricular ejection fraction.

ences were calculated for continuous variables, and risk ratios (RRs) were calculated for dichotomous variables. For each mean difference and risk difference, 95% confidence intervals (CIs) were evaluated. Pooled estimates were of differences and RRs were combined with random-effects models. Homogeneity was assessed with the I^2 statistic. Statistical analysis was performed with Comprehensive Meta-Analysis software, version 2 (Biostat, Englewood, New Jersey).

Results

Search and synthesis of literature. There were 555 unique citations identified after the initial literature search was combined with supplementary hand-searches; 525 were excluded on general criteria, and 30 were selected for secondary review (Fig. 1). From this group, 6 studies were selected that separately reported outcome data for AF patients undergoing CRT for HF who had undergone AVNA (AVNA+), compared with those who had not (AVNA-) (Fig. 1, Table 1) (6,7,10,11,13,14). Five of the 6 studies included data on CRT-SR patients as well as CRT-AF patients (6,7,10,11,13). One of the 6 studies solely reported outcome data for CRT-AF patients (14). For the purpose of this systematic review, we extracted the data on CRT-AF patients.

Included studies were published in the years 2004 through 2010. With the exception of the MILOS Registry (11) and the SPARE (Spanish Atrial Fibrillation and Resynchronization) study (13), which were multicenter observational series, all included studies were cohorts recruited from 1 or 2 centers only (Table 1) (6,7,10,14). The studies included 768 AF patients, including 339 who underwent additional AVNA and 429 patients who were treated with rate-controlling medication alone. Study size varied considerably, from small (Molhoek et al. [6], 30 CRT-AF patients) to much larger studies (Gasparini et al. [11], 243 CRT-AF patients) (Table 1). Three studies consisted solely of permanent AF patients (7,11,13). One study included persistent AF lasting >3 months (6). One study did not report the breakdown according to AF subtype (10).

Study quality was limited in that 4 of the included studies were retrospective with only 2 prospective cohort studies. No randomized controlled trial data were available. Study inclusion criteria were generally similar across all studies, including patients with LVEF $\leq 35\%$, ventricular dyssynchrony (assessed by QRS duration ≥ 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 (6,7,10,11,13,14).

To further assess study quality, we classified study method by using a composite of features derived from the Newcastle-Ottawa Scale, which has been used to assess quality in nonrandomized studies (23). Detailed data are presented in

the Appendix. Case definition was mostly performed by individual treating clinicians in study centers, with the majority of studies reporting consecutive recruitment. Significant differences were noted in baseline characteristics in 3 studies (11,13,14). Outcome data were limited in that the majority of studies involved nonblinded clinical follow-up, with limited descriptions of the completeness of follow-up. **Selection of CRT-AF patients for AVNA.** The method of selection of patients for AVNA varied between the studies. In 4 studies, AVNA was undertaken in patients who did not have adequate rate control with medical therapy, but detailed information regarding decision making for AVNA was generally not reported (6,10,13,14). In the other 2 studies, a systematic selection process was applied to select patients for AVNA. Patients with AF were evaluated for percentage of biventricular pacing (BVP%) after the implantation of their CRT device (7,11). If BVP% was $\leq 85\%$, it was recommended that the patient undergo AVNA.

Effectiveness of ventricular rate control in patients treated with medical therapy. We attempted to extract data for effectiveness of ventricular rate control in AVNA+ and AVNA- patients, but this was not available in any of the retrieved studies. The only study to consider the issue of ventricular rate control was that of Dong et al. (14), who considered heart rate parameters as variables in a univariate model. Neither electrocardiogram nor Holter average heart rates were statistically important predictors of survival in this study.

Effectiveness of biventricular capture. Effectiveness of biventricular capture was described in all studies according to the percentage of biventricular capture from device diagnostics. In AVNA+ patients, biventricular capture was near to complete. In AVNA- patients, BVP% varied from 82% (6) to 96.5% (14) (Table 1). Only 1 study reported the use of ventricular rate regularization as a routine part of device programming to enhance biventricular capture in CRT-AF patients (7). The use of this algorithm was not reported in the other studies.

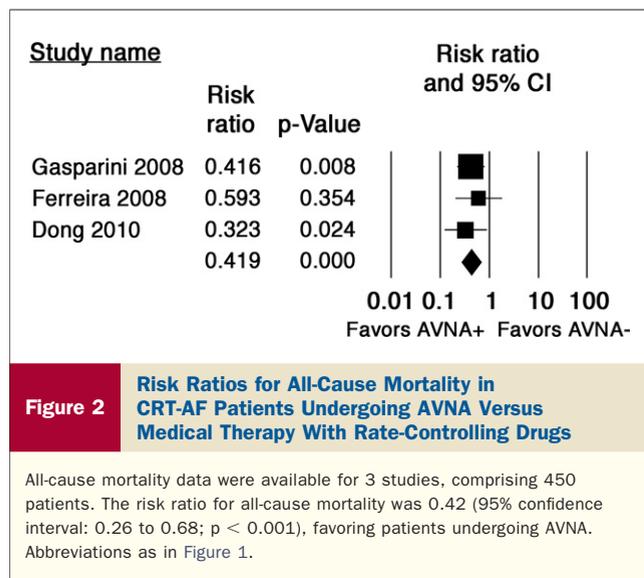
Impact of AV nodal ablation on mortality in CRT-AF patients. Overall, 3 studies reported mortality data comparing CRT-AF patients undergoing AVNA with those with pharmacological rate control (10,11,14). All-cause mortality data in CRT-AF patients undergoing AVNA compared with those receiving medical therapy were available for 3 studies (Fig. 2) (10,11,14). Eighty-six deaths were reported from 450 CRT-AF patients in these studies (11,14). RRs were calculated using numbers of deaths for AVNA+ and AVNA- patients, respectively. The RR for all-cause mortality in AF patients undergoing AVNA was 0.42 (95% CI: 0.26 to 0.68; $p < 0.001$) (Fig. 2). Between-study heterogeneity for all-cause mortality was low ($I^2 = 0.00$). Cardiovascular mortality was reported in Gasparini et al. (11) and Ferreira et al. (10). The RR for cardiovascular mortality for CRT-AF patients undergoing AVNA was 0.44 (95% CI: 0.24 to 0.81; $p < 0.01$) (Fig. 3). Between-

Table 1 Six Studies Reporting Outcome Data for AF Patients Undergoing CRT for HF

First Author, Year	Study Type	n	Inclusion Criteria	Comparator Intervention Groups	n	Age (yrs)	Male (%)	AF Characteristics	Follow-Up	%BVP
Molhoek, 2004	Prospective single-center cohort	60	Drug-refractory NYHA III–IV heart failure, LVEF \leq 35%, QRS duration \geq 120 ms	CRT-SR	30	68 \pm 8	80	100% long-standing persistent AF (>3 months)	6 months	Not reported
				CRT-AF-AVNA+	17	63 \pm 10*	90			100%
				CRT-AF-AVNA–	13					82%
Gasparini, 2006	Prospective 2-center cohort	673	Drug-refractory NYHA \geq II heart failure, LVEF \leq 35%, QRS duration \geq 120 ms	CRT-SR	511	66*	85	100% permanent AF	25.2 \pm 18 months	98.5 \pm 1.8%
				CRT-AF-AVNA+	114					98.4 \pm 2.1%
				CRT-AF-AVNA–	48					88.2 \pm 3.1%
Ferreira, 2008	Retrospective single-center cohort	131	Drug-refractory NYHA II–IV heart failure, LVEF \leq 35%, QRS duration \geq 120 ms	CRT-SR	78	66 \pm 10	74	Not listed for each subgroup	6 months	95 \pm 13%
				CRT-AF-AVNA+	26	67 \pm 9	92			98 \pm 6%
				CRT-AF-AVNA–	27	70 \pm 8	96			87 \pm 19%
Gasparini, 2008	Retrospective multicenter registry cohort	1,285	Not pre-specified	CRT-SR	1,042	63 \pm 10	75	100% permanent AF	Median follow-up 34 months	Not reported
				CRT-AF-AVNA+	118	66 \pm 9	78			98.7 \pm 1.8%
				CRT-AF-AVNA–	125	67 \pm 9	84			89.4 \pm 2.4%
Tolosana, 2008	Retrospective multicenter cohort	470	Drug-refractory NYHA III–IV heart failure, LVEF \leq 35%, QRS duration \geq 120 ms	CRT-SR	344	67 \pm 9	76	100% permanent AF	12 months	Not reported
				CRT-AF-AVNA+	19	70 \pm 7	81			100%
				CRT-AF-AVNA–	107	68 \pm 10				92 \pm 7%
Dong, 2010	Retrospective single-center cohort	154	Heart failure symptoms despite medical therapy, LVEF \leq 35%, QRS duration \geq 120 ms	CRT-AF-AVNA+	45	72 \pm 9	84	88% permanent AF	Median follow-up 274 days	99.0% (95% CI: 95%–100%)
				CRT-AF-AVNA–	109	68 \pm 11	87		Median follow-up 222 days†	96.5% (95% CI: 85.5%–99%)

*Represents mean age of CRT-AF patients as a group. †24% lost to follow-up.

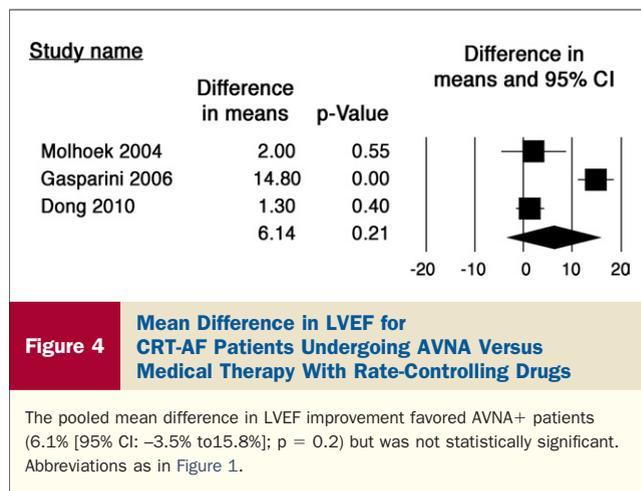
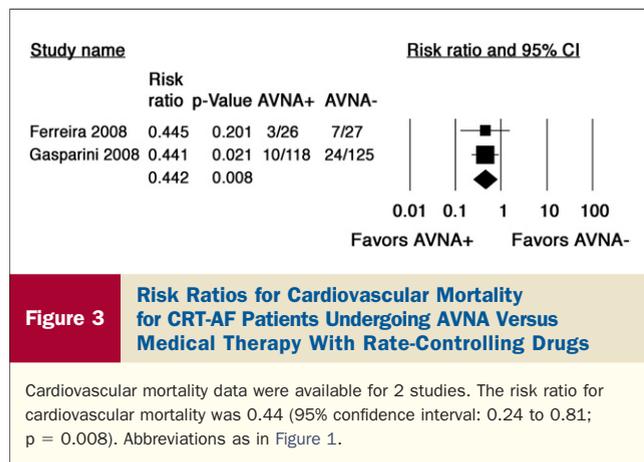
AF = atrial fibrillation; AVNA+ = patients who had undergone AV nodal ablation; AVNA– = patients who did not undergo AV nodal ablation; BVP% = percentage biventricular pacing; CI = confidence interval; CRT = cardiac resynchronization therapy; HF = heart failure; NYHA = New York Heart Association; LVEF = left ventricular ejection fraction; SR = sinus rhythm.



study heterogeneity for cardiovascular mortality was also low ($I^2 = 0.00$).

Impact of AV nodal ablation on LVEF in CRT-AF patients. We identified 3 studies that evaluated the impact of AVNA on LVEF in 346 CRT-AF patients (Fig. 4) (6,7,14). In these studies, LVEF increased in both CRT-AF AVNA+ and AVNA- patients after CRT. The mean increase in LVEF was 4.2% (95% CI: -1.2% to 9.6%) in AVNA- patients and 10.3% (95% CI: 6.4% to 14.2%) in AVNA+ patients. The pooled mean difference in LVEF improvement favored AVNA+ patients (6.1% [95% CI: -3.5% to 15.8%]; $p = 0.2$) but was not statistically significant (Fig. 4). There was significant heterogeneity for this outcome ($I^2 = 0.94$).

Impact of AVNA on functional outcomes in CRT-AF patients. Three studies reported the effect of AVNA on NYHA functional class in 346 CRT-AF patients (Fig. 5) (6,7,14). NYHA functional class improved in both AVNA- (pooled change -0.45 [95% CI: -0.65 to -0.25]) and AVNA+ patients (pooled change -0.81 [95% CI: -0.99 to -0.63]) (Table 2). However, NYHA functional class im-



proved more in AVNA+ than in AVNA- patients, with a mean difference of -0.34 (95% CI: -0.56 to -0.13; $p = 0.002$) (Table 2, Fig. 5). The I^2 statistic for this outcome was 0.59.

Six-min walk test times were reported in 2 studies (Table 2). Molhoek et al. (6) reported a significant increase in 6-min walking distance, from 229 ± 125 m to 388 ± 172 m in AVNA+ patients ($p < 0.05$) (Table 2). In contrast, Tolosana et al. (13) did not find a significant change in 6-min walking distance in AVNA+ patients compared with AVNA- patients.

Discussion

The most important finding of this study was the decisive all-cause mortality and cardiovascular mortality advantage of AVNA in CRT-AF patients. In the 3 studies reporting mortality data, AVNA conferred an RR for overall mortality of 0.42; for cardiovascular mortality, the RR was 0.44. The studies reporting mortality data were the largest, containing a minimum of 20 patients in each study arm (Table 1) (10,11,14). Furthermore, the finding seemed to be consis-

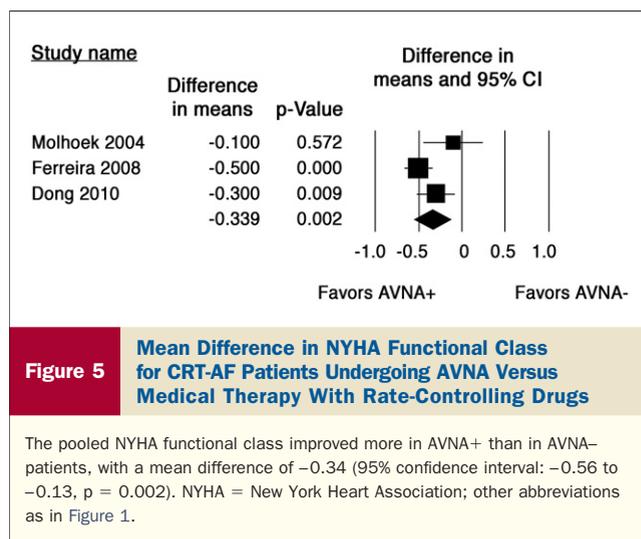


Table 2
Results for Patients Included in This Systematic Review

First Author, Year	Comparator Intervention Groups	n	All-Cause Mortality	Cardiovascular Mortality	NYHA Functional Class		LVEF (%)		Functional Capacity/ 6-Min Walking Distance (m)		QOL Score	
					Pre	Post	Pre	Post	Pre	Post	Pre	Post
Molhoek, 2004	AVNA+ AVNA-	17 13	— —	— —	3.1 ± 0.3 3.2 ± 0.4	2.2 ± 0.5 2.4 ± 0.7	21 ± 7 19 ± 9	30 ± 12 26 ± 10	229 ± 125 224 ± 101	388 ± 172 310 ± 134	42 ± 19* 44 ± 13	28 ± 21 37 ± 22
Gasparini, 2006	AVNA+ AVNA-	114 48	— —	— —	96% NYHA III 100% NYHA III	19%† NYHA III 59% NYHA III	27 ± 7 25 ± 6	37 ± 13 24 ± 11	31.7 ± 7.1 24.6 ± 3.5	44.2 ± 8.0‡ 27.5 ± 4.8	— —	— —
Ferreira, 2008	AVNA+ AVNA-	26 27	4 7	3 7	3.1 ± 0.5 2.9 ± 0.4	2.2 ± 0.7 2.1 ± 0.5	— —	— —	— —	— —	85%§ 52%	— —
Gasparini, 2008	AVNA+ AVNA-	118 125	11 28	10 24	— —	— —	— —	— —	— —	— —	— —	— —
Tolosana, 2008	AVNA+ AVNA-	19 107	— —	— —	— —	— —	+6 ± 9 +7 ± 10	— —	+99 ± 220¶ +75 ± 140	— —	-17 ± 31# -13 ± 31	— —
Dong, 2010	AVNA+ AVNA-	45 109	4 30	— —	2.9 ± 0.5 3.0 ± 0.4	2.3 ± 0.8 2.7 ± 0.8	26 ± 8 23 ± 6	33 ± 10 29 ± 11	— —	— —	— —	— —

*Molhoek 2004: QOL score assessed by using the Minnesota Living With Heart Failure questionnaire. Significant improvement in score noted in the AVNA+ group ($p < 0.05$) but not in the AVNA- group ($p = NS$). †Gasparini 2006: NYHA functional class expressed as percentage of patients in NYHA class III; significant improvement in the AVNA+ group compared with the AVNA- group ($p < 0.001$). ‡Gasparini 2006: Functional capacity score determined from composite results of patients tested with 6-min walk test or symptom-limited peak oxygen consumption. Results showed significant improvement in AVNA+ patients versus AVNA- patients ($p < 0.001$). §Ferreira 2008: Significant difference in percentage of responders between AVNA+ and AVNA- patients ($p = 0.008$). ¶Tolosana 2008: results are reported as mean change in LVEF. No significant difference between AVNA+ and AVNA- patients. ††Tolosana 2008: mean change in 6-min walking test distance. No significant difference between AVNA+ and AVNA- patients. †††Tolosana 2008: mean change in QOL score. No significant difference between AVNA+ and AVNA- patients. NYHA = New York Heart Association; QOL = quality of life; other abbreviations as in Table 1.

tent across the studies reporting this outcome (Fig. 2). Heterogeneity was low for this outcome. The mortality findings are particularly striking, when considered in the context of the all-cause mortality benefit in CRT-SR patients. In a meta-analysis of SR patients, the all-cause mortality RR with CRT was 0.78 (95% CI: 0.67 to 0.91) (4).

AVNA was also associated with a significant improvement in NYHA functional class in studies reporting this outcome. The mean difference in NYHA functional class was -0.34 , which favored AVNA+ patients (Fig. 5). Other studies used different measures of functional capacity, with the majority of studies favoring AVNA+ patients. Six-minute walking distance was reported in 2 studies. Molhoek et al. (6) found a statistically significant increase in AVNA+ patients compared with AVNA- patients (Table 2). Tolosana et al. (13) identified an increase of 99 ± 220 m in 6-min walking distance in AVNA+ patients compared with -13 ± 31 m in AVNA- patients, but statistical significance was not reported (Table 2). Significantly larger improvements in functional capacity measures were noted in two-thirds of studies reporting these outcomes (Table 2) (6,7). Ferreira et al. (10) reported functional outcomes in terms of the percentage of “responders” to CRT, defined as the percentage of patients surviving with an improvement of ≥ 1 NYHA functional class at 6 months. AVNA+ patients had a significantly higher percentage of responders (85% vs. 62%) than AVNA- patients (10). Gasparini et al. (7) also reported a higher percentage of responders, defined here as the percentage of patients showing a $\geq 10\%$ reduction in left ventricular end-systolic volume, among AVNA+ patients compared with AVNA- patients.

Interestingly, the improvements in mortality and functional capacity with AVNA were not accompanied by a significant LVEF improvement, with a nonsignificant increase in LVEF among AVNA+ patients compared with AVNA- patients. There was significant heterogeneity for this outcome ($I^2 = 0.94$). The study heterogeneity seemed to be driven by the study of Gasparini et al. (7), which showed a sharp increase in LVEF in CRT-AF patients receiving AVNA, a finding that was not observed in the other 2 studies reporting LVEF (6,14). Interestingly, these 2 studies revealed findings favoring AVNA with respect to functional (6,14) and mortality (14) outcomes. The explanation for the observed functional and mortality improvements without concomitant definitive LVEF improvement is unclear, but possible explanations include selective LVEF echocardiographic assessment on adequately resynchronized beats or interobserver variability in the published studies.

A variety of hypotheses may be postulated to explain the mortality and functional benefits with AVNA in CRT-AF patients. AVNA is believed to improve cardiac systolic function not only by lowering the ventricular rate and regularizing the ventricular rhythm (24,25) but also by improving the quality of resynchronization by diminishing the burden of conducted and fused ventricular beats (22). In our study, benefits seem to have occurred despite reasonably

effective rate control in AVNA– patients. The minimum mean BVP% in the medical rate control CRT-AF patients in the 6 studies was 82% (Table 1). It should be noted, however, that details of device-programming algorithms used to enhance biventricular capture were not generally reported.

Recent findings using 12-lead Holter monitoring of CRT-AF patients suggest that the biventricular paced percentage from device diagnostics may significantly overestimate the efficacy of truly “clean” biventricular paced beats in this group (20). The findings of our study would correlate with this finding, by suggesting that achieving near to complete resynchronization with AVNA is highly important.

Other reports have documented a favorable relationship between an increased BVP% and improved clinical outcomes in CRT patients. Hayes et al. (26) reported HF outcomes in >30,000 patients with the LATITUDE remote monitoring system. Patients paced 100% had a 27% reduction in mortality compared with all other groups, whereas patients paced <95% had a 35% increase in mortality. Koplan et al. (27) analyzed HF outcomes in 1,812 predominantly CRT-SR patients from the CRT RENEWAL and REFLEX trials. In subgroup analysis of patients with a history of atrial arrhythmia, subjects with $\geq 92\%$ BVP% had a hazard ratio of HF events or all-cause mortality of 0.44 compared with subjects receiving <92% BVP%. No increment, however, was found with increased percentage of pacing beyond 92%. Most recently, Santini et al. (28) examined HF outcomes in 1,193 real-world patients implanted with CRT defibrillation devices. Device-detected atrial tachycardia/fibrillation episodes lasting >10 min were strongly associated with a 2-fold increase in the composite death/HF hospitalization endpoint.

AVNA is a long-established therapy for the maintenance of ventricular rate control in AF patients. One possible reason why AVNA has not been more widely adopted in the CRT-AF cohort is a perceived fear of pacemaker dependency. However, in the CRT setting, the presence of the additional left ventricular lead (especially bipolar left ventricular leads) should reduce the risk associated with loss of ventricular capture. Furthermore, complications associated with AVNA due to loss of pacemaker function are very rare and were not reported in the current studies.

Study limitations. The results of this report were compiled using meta-analysis of primarily observational data, which for the most part was retrospectively collected, rather than randomized controlled trial data. Significant differences in baseline characteristics were noted between AVNA– and AVNA+ patients in a number of studies. The majority of studies involved nonblinded recruitment and assessment of study outcomes, and limited documentation of completeness of follow-up. Nonetheless, the technique of meta-analysis is accepted in the literature to aggregate results from observational data to facilitate rapid synthesis of available evidence and generation of new hypotheses. The data

available were compiled from a limited number of usable but relatively small studies. In addition, the limitation of including data only from published studies may lead to a risk of publication or “file drawer” bias. In particular, all-cause mortality or cardiovascular mortality data were available in only 3 studies. The small number of studies also reduced the opportunity for more detailed subgroup analyses to explore for sources of heterogeneity. Nonetheless, a consistent trend toward clinically significant reductions in all-cause mortality and cardiovascular mortality with AVNA was observed in the available studies. Furthermore, improved functional capacity with AVNA was observed among the majority of studies included, suggesting that AVNA in CRT-AF patients is worthy of investigation in a randomized controlled trial.

Conclusions

AVNA in CRT-AF patients was associated with reductions in all-cause mortality and cardiovascular mortality and improvements in NYHA functional class. To confirm these data, prospective evaluation of AVNA in CRT-AF patients by randomized controlled trial is warranted.

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Key Words: atrial fibrillation ■ biventricular pacing ■ cardiac resynchronization ■ heart failure ■ systematic review.

 **APPENDIX**

For a supplementary table on the quality assessment of included studies, please see the online version of this article.