

Atrial fibrillation in cardiac resynchronization therapy



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Patients with atrial fibrillation (AF) were largely excluded from the major clinical trials of cardiac resynchronization therapy (CRT), despite the presence of AF in up to 40% of patients receiving CRT in clinical practice. AF appears to attenuate the response to CRT, by the combination of a reduction in biventricular pacing and the loss of atrioventricular synchrony. In addition, remodeling secondary to CRT may influence the progression of AF. Management options for patients with AF and CRT include rate control, with drugs or atrioventricular node ablation, or rhythm control, with electrical cardioversion and antiarrhythmic therapy, or AF catheter ablation. The evidence for these therapies in patients with CRT is largely limited to observational studies or inferred from randomized studies in the general heart failure population. In this review, we explore

the complex interaction between AF, heart failure, and CRT and discuss the evidence for the treatment options in this difficult patient cohort.

KEYWORDS Atrial fibrillation; Cardiac resynchronization therapy; Rate control; Rhythm control; AV node ablation; AF ablation; Pulmonary vein isolation

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Introduction

Heart failure is a major cause of morbidity and mortality worldwide, with an estimated prevalence in developed countries of 1%–2% of the general adult population.¹ Atrial fibrillation (AF) is a common and complex problem in patients with heart failure, with an average prevalence of 25%.² AF and heart failure form a complex synergistic interaction, with each influencing progression of the other. Chronically elevated left atrial pressures caused by left ventricular (LV) dysfunction induces structural and electrical atrial remodeling, creating the substrate for AF. The prevalence of AF rises with increasing heart failure severity, from 10% in New York Heart Association (NYHA) class II to 50% in NYHA class IV.³ In turn, AF can reduce cardiac output owing to loss of atrial systole and rapid irregular LV filling times, and is associated with poorer outcomes in patients with existing heart failure.² The relationship is further complicated by associated pro-inflammatory comorbidities, such as diabetes, obesity, and hypertension, and complex neurohormonal interactions.²

Approximately a third of patients with heart failure are indicated for cardiac resynchronization therapy (CRT).⁴ The presence of AF in these patients brings additional challenges, with reduction in biventricular pacing owing to rapid

intrinsic activation of the ventricles, and loss of atrioventricular (AV) resynchronization. Patients with AF were largely excluded from the major randomized controlled trials of CRT; however, up to 40% of patients receiving CRT in clinical practice have AF at the time of implantation,⁵ and new-onset AF has been reported in between 20% and 24% of patients after implantation.^{6,7} AF appears to attenuate the response to CRT, and patients with AF have a higher long-term mortality after CRT implant compared to those in sinus rhythm.^{8,9} The delivery of CRT may also alter the natural progression of AF in patients with heart failure. In this article we review the evidence for CRT in patient with AF, explore the relationship between AF and CRT delivery, and discuss the treatment options available in this patient cohort.

The evidence for cardiac resynchronization therapy in patients with atrial fibrillation

There is limited evidence from randomized trials on the use of CRT in patients with AF. In a sub-study of the Resynchronization/Defibrillation for Ambulatory Heart Failure Trial (RAFT) trial, 229 patients with permanent AF and dyssynchronous heart failure (NYHA class II–III, LV ejection fraction $\leq 30\%$, and QRS duration ≥ 120 ms) were randomized to either implantable cardioverter-defibrillator (ICD) or CRT-defibrillator.¹⁰ No difference in mortality was found between groups, though there was a borderline significant trend towards fewer heart failure hospitalizations in those who

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KEY FINDINGS

- Atrial fibrillation (AF) attenuates the response to cardiac resynchronization therapy (CRT) in patients with heart failure and electrical dyssynchrony owing to a combination of reduced biventricular pacing and loss of atrioventricular (AV) synchrony.
- AV node ablation increases biventricular pacing and has been shown to improve mortality after CRT in large observational studies.
- AF ablation in patients with CRT is feasible, and may provide a benefit over AV node ablation by restoring AV synchrony, but randomized trials are needed to determine if this theoretical benefit translates into improved clinical outcomes.
- CRT device programming in patients with AF is challenging, and multiple vendor-specific algorithms are available to try to optimize CRT delivery, achieve rate response, and potentially reduce AF burden.

received a CRT-defibrillator (hazard ratio [HR] 0.58; 95% confidence interval [CI] 0.38–1.01; $P = .052$). It should be noted, however, that only 1 patient received an AV node ablation and satisfactory biventricular pacing (>95%) in the 6-month follow-up period was achieved in only 34% of patients. The effect of paroxysmal AF, including new-onset in-trial AF, on CRT outcomes has been examined in several sub-analyses of key randomized trials. In a sub-study of the MADIT-CRT trial, previous or in-trial intermittent atrial tachyarrhythmias did not attenuate the reduction in heart failure events or death seen with CRT-defibrillators vs ICD.¹¹ Similarly, in the sub-analysis of the RAFT trial, new-onset atrial arrhythmias (which remained paroxysmal in 69.5% of cases) did not affect the primary trial combined endpoint of death or heart failure hospitalization, though an increased risk of heart failure hospitalizations alone was reported.¹² In contrast, a sub-analysis of the COMPANION trial showed that in patients with a prior history of intermittent AF or atrial flutter, CRT did not reduce death or hospitalizations over optimal medical therapy.¹³ The discrepancy between these sub-analyses may be related to the AF burden and effect on biventricular pacing. In the RAFT and MADIT-CRT sub-studies, in-trial atrial arrhythmias did not reduce biventricular pacing percentage compared to patients who remained in sinus rhythm. The effect of atrial arrhythmias on biventricular pacing percentage was not reported in the COMPANION sub-study. Notably, the atrial arrhythmia cohort in the COMPANION study had more advanced heart failure at baseline, with all included patients in NYHA functional class III or IV, whereas the majority of patients in the MADIT-CRT and RAFT studies were in NYHA class II. Furthermore, only 52% of patients with atrial arrhythmias in the COMPANION study were on a beta-blocker at baseline, vs 88% in MADIT-CRT and 84.7% in RAFT. It is therefore possible that the

patients in the COMPANION sub-study had a higher AF burden, related to more advanced heart failure at baseline, and poorer rate control, with a resultant worsening of CRT delivery.

Wilton and colleagues⁸ performed a meta-analysis of observational trials incorporating 7495 patients and found that patients with AF had a higher risk of clinical non-response and all-cause mortality after CRT implant compared to those in sinus rhythm. A more recent meta-analysis of observational studies, which included 83,571 patients, also demonstrated a significantly higher mortality rate after CRT implant in patients with AF, compared to those in sinus rhythm.⁹ In addition, patients with heart failure and AF were not found to have a significant reduction in mortality or in a composite endpoint of mortality or heart failure hospitalization after CRT, when compared to either ICD or medical therapy. Importantly, in the sub-group of patients with AF who received an AV node ablation, mortality was significantly lower, and equivalent to patients with sinus rhythm, as discussed later in this article. These meta-analyses did not examine the different effects of permanent, persistent, or paroxysmal AF on CRT outcomes. Current guidelines have a class IIa recommendation for CRT for patients with AF and LV ejection fraction $\leq 35\%$ who meet CRT criteria, provided a strategy to ensure biventricular capture is in place.^{14,15}

More recently, conduction system pacing techniques (His bundle pacing and left bundle branch pacing) have emerged as novel methods of delivering CRT.¹⁶ Conduction system pacing in patients with AF is feasible, and has predominantly been reported as a means of delivering physiological pacing in nondyssynchronous patients with high-degree AV block or after AV node ablation.^{17,18} The use of conduction system pacing for ventricular resynchronization in patients with AF, heart failure, and electrical dyssynchrony has been demonstrated in small observational studies, with symptomatic and LV remodeling benefits, but randomized trials to compare against conventional biventricular pacing are lacking.^{19,20} Further study is required to assess the benefit of conduction system pacing in this patient cohort.

The deleterious effects of atrial fibrillation on cardiac resynchronization therapy

Suboptimal biventricular pacing

Rapid and irregular intrinsic activation of the ventricles in AF can reduce the delivery of biventricular pacing during CRT. In an observational study of over 32,000 patients with CRT devices, atrial arrhythmias were the most common reason for patients having a biventricular pacing percentage of less than 95% (Figure 1).²¹ Furthermore, ventricular rate during AF has a strong inverse correlation with biventricular pacing percentage²² and suboptimal biventricular pacing has been reported in up to 60% of patients with persistent or permanent AF.²³ Suboptimal biventricular pacing is associated with a higher risk of mortality. This was most elegantly demonstrated by Hayes and colleagues²⁴ in a large registry study

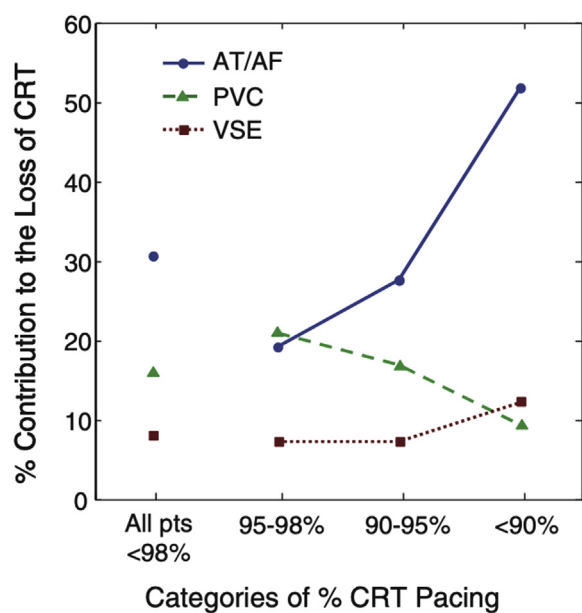


Figure 1 Atrial fibrillation (AF) / atrial tachycardia (AT) is the most common etiology for loss of effective cardiac resynchronization therapy (CRT) pacing. As the percentage of CRT pacing decreases, the contribution of AT/AF to the loss increases. PVC = premature ventricular contraction; VSE = ventricular sensing episodes. Reproduced with permission from Cheng et al (2012).

of 36,935 patients in a remote monitoring network. There was a decremental reduction in survival seen with reducing biventricular percentage, with even patients receiving less than 99.6% pacing having a higher mortality, thus demonstrating the need to obtain as close to 100% pacing as possible (Figure 2A). Interestingly, patients with AF and biventricular pacing greater than 98.5% still had a higher mortality than patients in sinus rhythm (Figure 2B). This suggests that factors other than suboptimal biventricular pacing contribute to the attenuated response to CRT caused by AF. However, it should be noted that biventricular pacing percentages provided by device interrogation may be an overestimate of true CRT delivery. In a small study of 19 patients with permanent AF and CRT, despite all patients having greater than 90% biventricular pacing on device interrogation, only 53% of patients were found to have >90% true biventricular paced beats on Holter monitoring, with responders having a higher percentage of fully paced beats than nonresponders ($86.4\% \pm 17.1\%$ vs $66.8\% \pm 19.1\%$; $P = .03$) (Figure 3).²⁵ This was due to the presence of fusion beats, which occur when a paced beat fuses with intrinsic activation of the ventricles, and pseudo-fusion beats, which occur when a pacing spike is delivered in the refractory period just after intrinsic activation, resulting in noncapture. This suggests that patients with AF who have seemingly adequate biventricular pacing on device interrogation may still be receiving suboptimal CRT. Automatic device algorithms, such as EffectivCRT™ (Medtronic), can use the morphology of the unipolar LV electrogram to determine if each paced beat was effective or ineffective and may provide a more accurate assessment of CRT delivery. In a study of 57 CRT patients,

the use of this algorithm, which was validated with Holter monitoring, demonstrated that conventional device counters significantly underestimated the percentage of effective CRT pacing ($94.8\% \pm 8\%$ vs $87.5\% \pm 23\%$; $P < .001$), with AF being the primary cause of ineffective CRT.²⁶

Loss of atrioventricular synchrony

AF removes the contribution of atrial systole to cardiac output, which is estimated to be as high as 20%–30%.²⁷ It also eliminates the benefit of AV resynchronization during CRT. Small observational studies have demonstrated acute hemodynamic benefits of optimizing AV delays during CRT.^{28–30} Although the use of echocardiography-based AV optimization was not shown to provide clinical benefit over empirical AV delays in a large randomized trial,³¹ studies using dynamic device-based algorithms to optimize AV delays have shown more promise.^{32,33} Interestingly, in a recently reported mechanistic study of 19 patients undergoing temporary His bundle pacing at the time of CRT implant, the majority of the hemodynamic benefit derived from CRT was found to be secondary to shortening of the AV delay, rather than ventricular resynchronization.³⁴ It therefore follows that the loss of AV synchrony during AF is likely to attenuate the hemodynamic benefit provided by CRT.

Inappropriate defibrillator therapies

For patients who receive a CRT-defibrillator, the presence of AF also has a significant impact on the risk of ICD shocks. Multiple observational studies have demonstrated that the presence of AF significantly increases the risk of inappropriate ICD therapies.^{35–39} AF also appears to increase the risk of appropriate therapies for ventricular arrhythmias.^{36,37} In addition to a significant effect on quality of life, inappropriate shocks have been independently associated with increased long-term mortality.^{35,37,38}

The effects of cardiac resynchronization therapy on atrial fibrillation

Conversely, CRT may alter disease progression in patients with AF and heart failure. A meta-analysis examining the effect of CRT on AF demonstrated that restoration of sinus rhythm occurred in 10.7% of patients (95% CI 6.9%–16.3%) with persistent or permanent AF after CRT implant.⁴⁰ Overall, 10 out of 12 studies demonstrated a beneficial effect of CRT on AF; however, data were predominantly limited to observational studies. This may be related to the effect of reverse LV remodeling on left atrial hemodynamics, and improved left atrial function has been demonstrated in CRT responders who are in sinus rhythm.⁴¹ Furthermore, up to 40% of patients indicated for CRT have significant functional mitral regurgitation, owing to combination of LV dyssynchrony and dilatation, and improvement in mitral regurgitation severity has been reported in 23%–49% of patients after CRT in clinical trials.⁴² Mitral regurgitation has a complex interaction with AF, and has been associated with poorer outcomes after ablation. In a retrospective study of 216

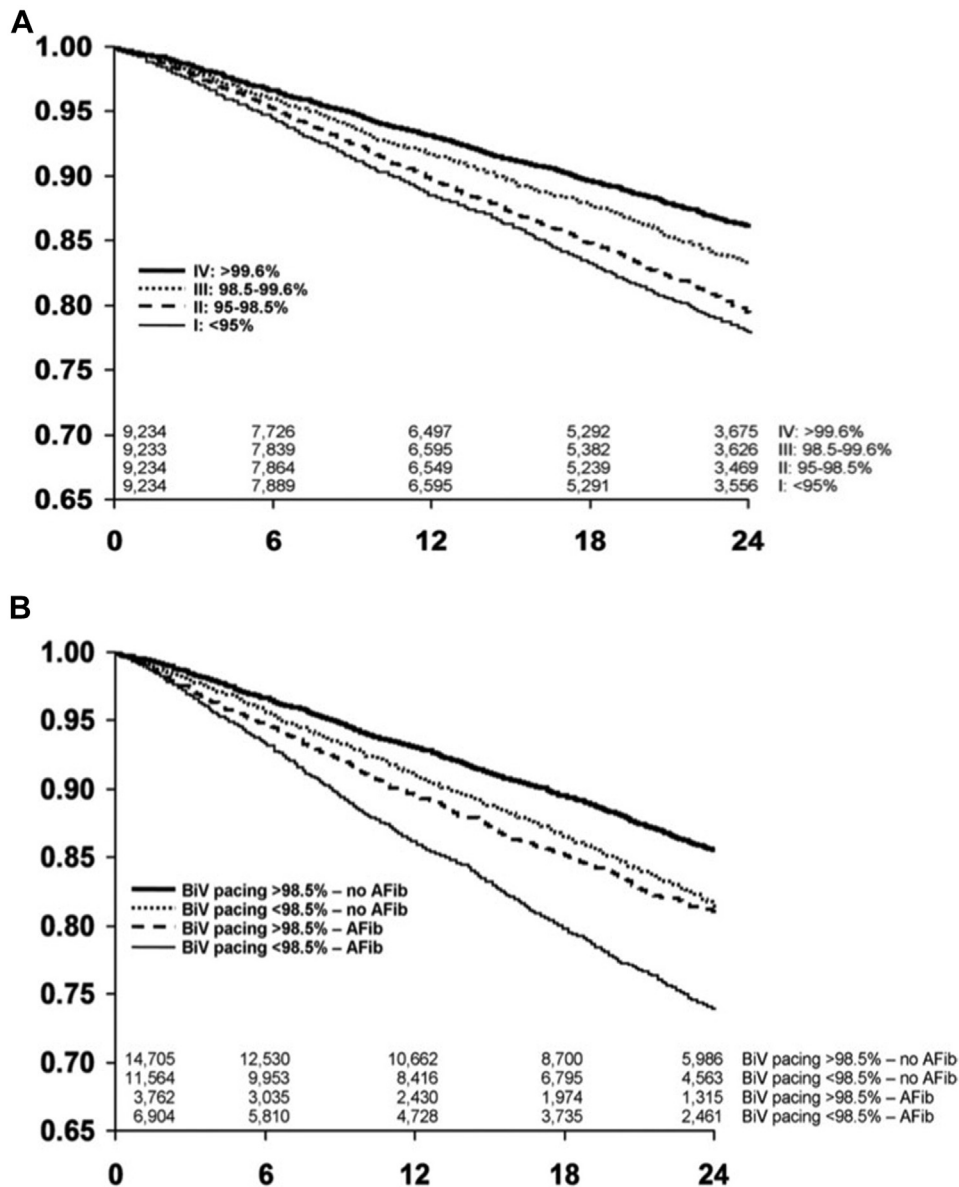


Figure 2 Survival decreases with reducing biventricular (BiV) pacing in an observational analysis of 36,935 patients with cardiac resynchronization therapy defibrillators. **A:** Survival analysis by biventricular pacing percentage. **B:** Survival analysis by biventricular pacing percentage and by the presence of significant atrial fibrillation (AFib), defined as average daily burden >0.5%. Reproduced with permission from Hayes et al 2011.

patients with longstanding persistent AF who underwent ablation, mitral regurgitation was an independent predictor of atrial tachyarrhythmia recurrence.⁴³ Furthermore, the rate of recurrence increased with the grade of mitral regurgitation severity.

There is also evidence that CRT reduces the elevated sympathetic activity associated with heart failure. In a study of 36 patients who received CRT for heart failure, average skin sympathetic nerve activity was significantly reduced in CRT responders (defined by improvement in LV ejection fraction $\geq 5\%$), but not in nonresponders.⁴⁴ AF ablation may also affect the autonomic nervous system, owing to coincidental modification of ganglionated plexi during pulmonary vein isolation, and elevated sympathetic tone has been shown to predict AF

recurrence after ablation.⁴⁵ It could therefore be postulated that CRT may help restore and maintain sinus rhythm in patients with AF, owing to a combination of reverse LV remodeling, reduction in mitral regurgitation, and a potential reduction in sympathetic nerve activity.

Management of atrial fibrillation in patients with cardiac resynchronization therapy

Rate control

Rate control strategies minimize the rapid, irregular ventricular activation that can occur in AF. This can be achieved with pharmacological AV nodal blocking agents such as beta-blockers and digoxin, or by performing an AV node

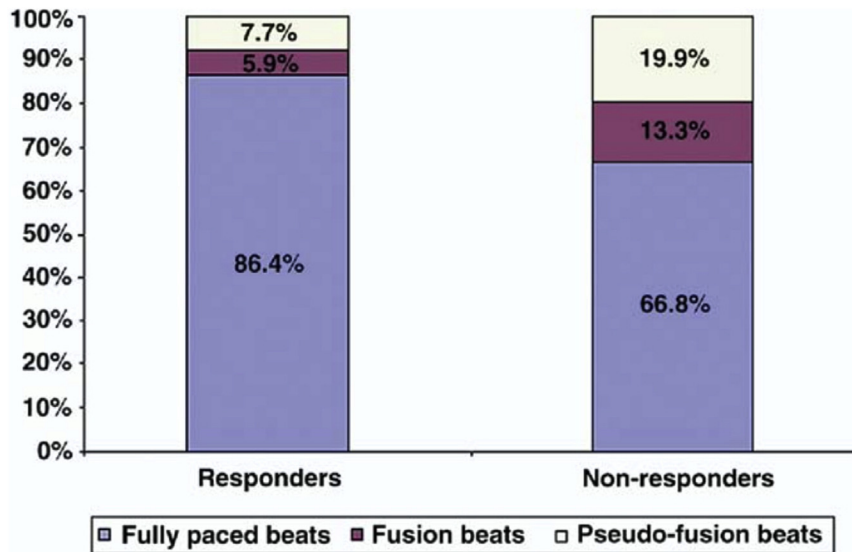


Figure 3 Nonresponders have a low percentage of effective cardiac resynchronization therapy paced beats on Holter monitoring despite high (>90%) biventricular pacing percentage on device interrogation. Reproduced with permission from Kamath et al 2009.

ablation. In contrast to medical therapy, AV node ablation completely eliminates AV conduction, thus rendering the patient dependent on pacing from the CRT device. This can often achieve biventricular pacing of close to 100%, though it should be noted that the presence of ventricular arrhythmias or ectopy can still result in suboptimal CRT delivery. Although no randomized studies have been performed to compare AV node ablation with medical rate control, observational studies have consistently shown superior CRT response and improved long-term mortality after AV node ablation in patients with AF and CRT (Table 1).^{8,46–50} This was most notably demonstrated in a large prospective multicenter trial of 7384 patients undergoing CRT (CERTIFY Study), where patients with AF who were treated with medical rate control alone had a higher all-cause mortality compared to those who received AV node ablation (HR 1.52; 95% CI 1.28–1.82; $P < .001$), as shown in Figure 4.⁴⁷ Indeed, patients with AF who had an AV node ablation had comparable mortality to patients in sinus rhythm (HR 0.93; 95% CI 0.74–1.67), a finding that has also been demonstrated in a recent meta-analysis of over 80,000 patients.⁹ This is reflected in current European guidelines, where AV node ablation after CRT in the case of incomplete biventricular pacing has a class IIa indication.¹⁴ AV node ablation has also been shown to significantly reduce the incidence of both inappropriate and appropriate ICD shocks in patients with AF and CRT-defibrillators.⁴⁹

Rhythm control

Restoration of sinus rhythm can be achieved with electrical cardioversion and/or antiarrhythmic drug therapy. However, long-term success likely requires invasive catheter-based left atrial ablation, comprising pulmonary vein isolation with or without additional lesions. Small studies of non-ablation-based strategies have shown variable benefit for rhythm control in patients with CRT (Table 2). In a nonrandomized study

of patients with permanent AF, 28 patients were scheduled for internal electrical cardioversion 3 months after CRT implant (group A), though cardioversion was not performed in 6 patients owing to the presence of left atrial appendage thrombus.⁵¹ Outcomes were compared with a control group of 27 patients (group B). After 12 months, 58% of the patients in group A (and 78% of those who actually underwent cardioversion) were in sinus rhythm, compared to 4% of patients in group B. AV node ablation was performed at 3 months if biventricular pacing was <90%, which occurred in 1 patient in group A and 2 patients in group B. Although improvements in LV ejection fraction were observed in both groups, a significant reduction in LV end-systolic volume was only found in group A. In a subsequent randomized study of 52 patients with heart failure, persistent AF, and left bundle branch block, all patients underwent CRT implantation, AV node ablation, and cardioversion.⁵² Patients randomized to rhythm control were discharged in sinus rhythm (with or without the initiation of antiarrhythmic drugs), while those in the rate control group had AF reinduced by rapid atrial pacing. At 1 year there was no difference between groups in a variety of echocardiographic and symptom-based endpoints, despite excluding patients in whom rhythm control was not achieved from the analysis. Notably, patients in the rhythm control group had a significantly higher number of hospital encounters, owing to the requirement for repeat cardioversions and the initiation and monitoring of antiarrhythmic drugs. More recently, the PilotCRAFT study randomized 43 patients with CRT and persistent or permanent AF to a rate control or rhythm control (via external electrical cardioversion).⁵³ Both groups received amiodarone therapy. At 12 months, both groups had similar improvements in biventricular pacing percentage. In a per-protocol analysis (only 19 of 22 patients in the rhythm control group underwent electrical cardioversion), LV ejection fraction was higher in the rhythm control group than the rate control group at follow-up

Table 1 Summary of studies comparing atrioventricular node ablation with medical therapy in patients with atrial fibrillation and cardiac resynchronization therapy

Study (year)	Study design	Inclusion criteria	Comparator groups	N	F/U (mo)	Baseline characteristics	Outcome	
Gasparini et al (2006)	Multicenter prospective observational	CRT for -LVEF \leq 35% -NYHA class \geq 2 -QRSd \geq 120 ms	Perm AF + AVNA* Perm AF + drugs	48 114	24.6	Age Sex (% M) LVEF (%) QRSd (ms) NYHA class (% III-IV)	66.0 (8.3) 85.8 26.3 (6.7) 165.0 (35.5) 96.9	AVNA group superior in: -CRT response (68% vs 18%; $P = .001$) -LVEF ($P < .001$) -LVESV ($P < .001$) -NYHA class ($P < .001$) -Functional capacity score ($P < .001$) Higher mortality in AF + drugs group (OR 11.1; 95% CI 4.03-25.35; $P < .001$)
			*Performed if BiVp% \leq 85% at 2 months					
Gasparini et al (2008)	Multicenter prospective observational	All patients who received CRT	Perm AF + AVNA* Perm AF + drugs	118 125	34	Age Sex (% M) LVEF QRSd NYHA class	66.2 (8.9) 81.9 26.0 (8.0) 161 (32) 3.12	Lower mortality in AF + AVNA group (HR 0.31; 95% CI 0.1-0.99; $P = .048$)
			*Performed if BiVp% \leq 85% at 2 months					
Dong et al (2010)	Single-center prospective observational	CRT-D for -LVEF \leq 35% -QRSd \geq 120 ms	AF + AVNA AF + drugs	45 109	25.2	Age Sex (% M) LVEF (%) QRSd (ms) NYHA class	70.5 (9.8) 86.3 23.4 (7.0) 170.7 (35.1) 3.0 (0.4)	AVNA group superior in: -BiVp% (99 vs 96; $P = .05$) -NYHA improvement (0.8 vs 0.4; $P = .04$) AVNA independently associated with survival (HR 0.13; 95% CI 0.03-0.58; $P = .008$) and freedom from death, transplant, and LVAD (HR 0.19; 95% CI 0.06-0.62; $P = .006$) No difference in LVEF, LVEDD, HFH
CERTIFY (2013)	Multicenter prospective observational	CRT for -LVEF \leq 35% -NYHA class III-IV (or II if recent HFH) -QRSd \geq 120 ms	AF + AVNA AF + drugs	443 895	37	Age Sex (% M) LVEF (%) QRSd (ms) NYHA class (% III-IV)	69.3 (9.3) 85.1 26.3 (6.8) 156.7 (35.0) 79.2	Lower all-cause mortality in AF + AVNA group (HR 0.67; 95% CI 0.52-0.85; $P = .001$) Lower cardiac mortality in AF + AVNA group (HR 0.63; 95% CI 0.46-0.86; $P = .003$)
Gasparini et al (2018)	Multicenter prospective observational	CRT-D for -LVEF \leq 35% -QRSd \geq 120 ms -NYHA class III-IV (or II if recent HFH)	Perm AF + AVNA* Perm AF + drugs	262 402	18	Age Sex (% M) LVEF (%) QRSd (ms) NYHA class (% III-IV)	69 (9.4) 86.0 27.4 (5.6) 142.4 (30.2) 71.6	Lower annual rates of all-cause ICD shocks (IRR 0.18; 95% CI 0.10-0.32; $P < .001$) and all-cause hospitalizations (IRR 0.57; 95% CI 0.41-0.79; $P < .001$) in AF + AVNA group Both inappropriate and appropriate ICD shock rates lower in AVNA group
		(pooled analysis from 2 RCTs and 1 observational trial)	*Performed if BiVp% $<$ 95% at 2 months					

Continuous baseline characteristics expressed as mean (standard deviation).

AF = atrial fibrillation; AVNA = atrioventricular node ablation; BiVp% = biventricular pacing percentage; CI = confidence interval; CRT = cardiac resynchronization therapy; F/U = mean follow-up; HFH = heart failure hospitalization; HR = hazard ratio; ICD = implantable cardioverter-defibrillator; IRR = incidence rate ratio; LVAD = left ventricular assist device; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; NYHA = New York Heart Association; OR = odds ratio; perm AF = permanent atrial fibrillation; QRSd = QRS duration; RCT = randomized controlled trial.

(36.8% vs 29.9%; $P = .039$). It should be noted, however, that only 1 patient in the rate control group received an AV node ablation, and no patients in the rhythm control group underwent AF ablation.

Performing AF ablation in patients with CRT is feasible. In a small observational study by Fink and colleagues,⁵⁴ 38 patients with AF and nonresponse to CRT (defined as at least 1 of the following: <95% biventricular pacing, <1 point improvement in NYHA class, or <5% improvement in LV ejection fraction) underwent AF ablation. Significant improvements in biventricular pacing percentage, LV ejection fraction, and NYHA class were demonstrated and 67% of patients were free from AF at 24 months, though 45.9% of patients required at least 1 redo ablation and 16.2% of patients underwent AV node ablation during follow-up. Randomized studies of AF ablation in patients with CRT and AF are lacking, though evidence may be inferred from studies in the general heart failure population. In the PABA-CHF study, 81 patients with AF and heart failure (LV ejection fraction $\leq 40\%$) were randomized to either AF ablation or AV node ablation + CRT implantation, with superior improvements in LV ejection fraction, heart failure symptoms, and 6-minute walk test performance demonstrated in the AF ablation group.⁵⁵ However, it should be noted that this patient cohort did not have electrical dyssynchrony at baseline (QRS duration of 91 ± 9.5 ms), and thus differs from the population of patients who receive CRT for dyssynchronous heart failure. Therefore, while this suggests a potential benefit for a rhythm control strategy, the AV node ablation + CRT group here may have experienced the negative impact of electrical dyssynchrony induced by CRT in patients with underlying narrow QRS.^{56,57} Further small randomized studies have also demonstrated that AF catheter ablation improves LV ejection fraction^{58–60} and exercise capacity⁶¹ compared to medical rate control in patients with heart failure. The multicenter AATAC study randomized 203 patients with persistent AF and LV impairment to either AF ablation or amiodarone.⁶² In addition to a significant reduction in the primary endpoint of AF recurrence in the ablation arm, significant reductions in the predefined secondary endpoints of hospitalization and all-cause mortality were also demonstrated. While all patients enrolled in the AATAC study had an existing ICD or CRT-defibrillator, the proportion of patients with CRT were not reported, nor were specific outcomes in this subgroup. In the CASTLE-AF study, 398 patients with severe LV impairment and symptomatic paroxysmal or persistent AF were randomized to either AF ablation or medical therapy.⁶³ There was a significant reduction in the primary composite endpoint of death or heart failure hospitalization in the ablation group (HR 0.62; 95% CI 0.43–0.87; $P = .007$) and 63% of patients were free from AF on device interrogation after 60 months of follow-up. 27.5% of patients had a CRT-defibrillator and there was a nonsignificant trend towards a lower primary endpoint event rate in the AF ablation arm compared to medical therapy in this subgroup (HR 0.54; 95% CI 0.28–1.04). There was also no significant interaction found between the primary

endpoint and the presence of CRT-defibrillator (vs ICD) on Cox logistic regression analysis ($P = .60$). However, all patients required a device manufactured by Biotronik to be included, and overall only 13% of patients screened for the study were deemed eligible for inclusion, which has raised questions about the real-world applicability of the findings.

Rate vs rhythm control

Previous studies attempting to compare rate vs rhythm control in patients with CRT have produced variable results and had significant limitations, as previously discussed.^{51–53} Importantly, these studies focused on nonablation techniques for rhythm control. While there is evidence that both AV node ablation and AF ablation are beneficial in patients with AF and CRT, the question of which treatment is superior remains unanswered, and randomized studies are greatly needed. Patients with heart failure and AF are a heterogeneous cohort, and there are multiple factors that may determine the optimal treatment strategy. As with any patient with AF, CRT patients with symptomatic, paroxysmal AF are likely to benefit from a rhythm control strategy, while those with longstanding “permanent” AF are more likely to benefit from rate control. There does, however, remain a significant proportion of patients with CRT who have persistent AF, or paroxysmal AF with sufficiently high AF burden to significantly reduce biventricular pacing, in whom the optimal treatment strategy remains unclear. Although AV node ablation will undoubtedly achieve close to 100% biventricular pacing, and has been shown to improve mortality, the additional benefit gained by restoring atrial systole and AV resynchronization with rhythm control remains unclear.

Though AF ablation may offer the additional benefits of AV synchrony over AV node ablation, a significant proportion of patients are likely to require multiple procedures, with associated expense and risk, and AF recurrence at some stage in the disease process is almost inevitable. AF ablation success rates from randomized studies in heart failure vary between 50% and 88%,⁶⁴ and an international multicenter registry has demonstrated that the presence of heart failure significantly reduces success rates for catheter ablation in patients with persistent AF (57.3% vs 75.8%), though there was no significant difference for patients with paroxysmal AF (78.7% vs 85.7%).⁶⁵ Prediction of which patients are likely to respond to AF ablation with a low risk of recurrence is therefore important, with a multitude of factors requiring consideration, including age, duration of AF, the presence of clinical comorbidities, and structural and electrical left atrial remodeling.⁶⁴ Careful patient selection is likely to be key in determining the optimal treatment strategy in this challenging cohort. A flow diagram with a proposed clinical approach to patients with AF and CRT is shown in [Figure 5](#).

Device programming

AF brings additional challenges in device programming, and various strategies and algorithms have been developed to

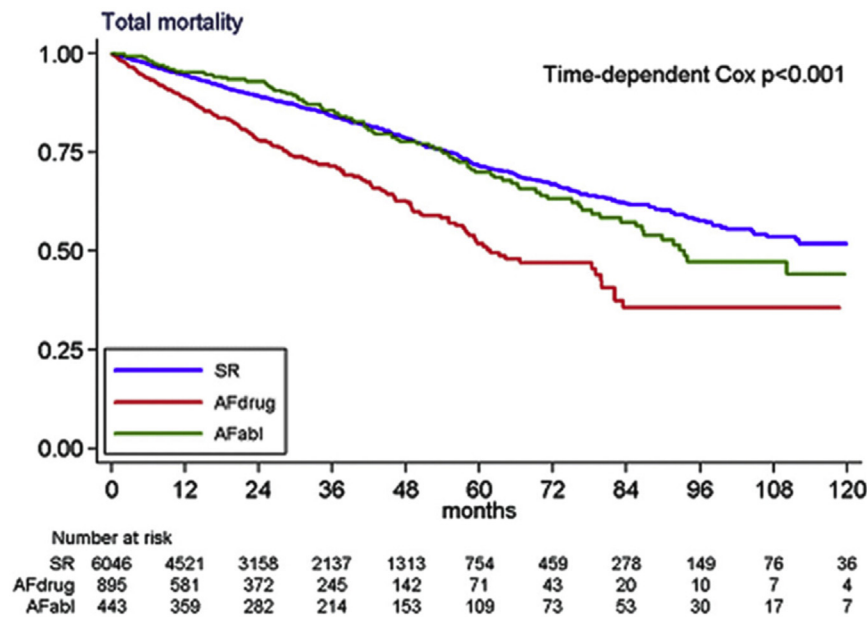


Figure 4 Atrioventricular node ablation improves mortality in patients with atrial fibrillation and cardiac resynchronization therapy in a prospective observational study (CERTIFY trial). AFabl = patients with atrial fibrillation treated with atrioventricular node ablation; AFdrug = patients with atrial fibrillation treated with drugs alone; SR = patients in sinus rhythm. Reproduced with permission from Gasparini et al 2013.

overcome these and optimize CRT delivery. The use of atrial pacing has also been proposed as a potential method of preventing AF. As discussed previously in this article, conventional device counters can overestimate CRT delivery in patients with AF, owing to fusion or pseudo-fusion beats. Algorithms such as EffectivCRT (Medtronic) can use the morphology of the LV electrogram to determine effective CRT delivery, and may provide a more accurate assessment than conventional counters. Irregular R-R intervals during AF lead to intermittent intrinsic ventricular activation. Most CRT devices feature an algorithm to trigger LV pacing in response to an intrinsically conducted right ventricular-sensed beat. This aims to increase biventricular pacing in AF, though many of these beats are likely to be fusion beats, as slow LV activation across the interventricular septum may have already commenced. No randomized trials have assessed the benefits of LV triggered pacing on CRT outcomes in patients with AF; however, there is evidence for hemodynamic benefit in a small echocardiographic-based observational study of patients in sinus rhythm.⁶⁶ Furthermore, there have been concerns about the pro-arrhythmic risk of LV trigger pacing owing to R-on-T phenomenon.⁶⁷

Several vendors also feature algorithms to automatically adjust the pacing rate to increase CRT delivery in response to ventricular-sensed events. Examples include Ventricular Rate Regulation (Boston Scientific) and Conducted AF Response (Medtronic). However, the benefit of these algorithms has not been assessed in clinical studies. The EffectivCRT during AF algorithm (Medtronic) uses the LV lead electrogram morphology to adjust pacing rate, thus allowing the system to detect ineffective fusion or pseudo-fusion beats and increase pacing rate accordingly. The use of this algorithm in a crossover randomized trial of 54 patients with

CRT, AF and intact AV conduction, resulted in a significant increase in the percentage of effective CRT ($87.7\% \pm 7.8\%$ vs $80.8\% \pm 14.3\%$; $P < .001$).⁶⁸

Another important consideration in device programming for patients with AF is the use of activity sensors to achieve rate response. Whereas patients in sinus rhythm can track the atrial activity to vary their biventricular pacing rate in response to exercise, this is not achievable in patients with AF, particularly in those who have undergone AV node ablation. The use and optimization of rate response algorithms are therefore important in this group. Various rate response algorithms are available, including minute ventilation systems and accelerometers. A full discussion of rate response programming is beyond the scope of this article, and is discussed in detail elsewhere.⁶⁹

The delivery of atrial overdrive pacing or atrial antitachycardia pacing (ATP) has been proposed as a potential method of preventing AF in patients with cardiac devices. Atrial overdrive pacing algorithms deliver pacing in response to atrial sensed events, but their use has not been shown to reduce frequency or duration of AF.⁷⁰ Device algorithms can also be used to deliver atrial pacing after long sinus pauses (Atrial Rhythm Stabilization; Medtronic) or after termination of an AF episode (Post Mode-Switch Overdrive Pacing; Medtronic) in an attempt to prevent induction of atrial arrhythmias. Atrial ATP has been theorized to terminate atrial tachycardia re-entry circuits and prevent deterioration into AF. Early trials demonstrated that, while atrial ATP can terminate atrial tachycardia episodes in some cases, there was no overall effect on AF burden.⁷⁰ More recently, a newer generation of “reactive ATP,” which delivers therapy timed to changes in the atrial arrhythmia cycle length or regularity, has been shown to reduce the incidence of persistent or

Table 2 Summary of studies of rhythm control in patients with atrial fibrillation and cardiac resynchronization therapy

Study (year)	Study design	Inclusion criteria	Comparator groups	N	F/U (mo)	Baseline characteristics	Outcome
Non-ablation strategies							
Turco et al (2012)	Multicenter prospective observational	Permanent AF CRT for- NYHA III-IV - QRSd \geq 120 ms - LBBB - LVEF \leq 35%	Rhythm control (group A)* Standard care (group B) *DCCV via ICD + amiodarone NB groups from different centers	28 27	12	Age Sex (% M) LVEF (%) QRSd (ms) NYHA class (% IV)	70.5 (10.0) 80 24 (5.5) 132 (16.3) 5.5 No difference in mortality between groups ($P = .469$) Lower mortality for patients in SR at follow-up vs those in AF ($P = .048$) Improvement in LVEF seen in both groups, but LVESV reduction only seen in group A ($P = .018$ vs baseline)
Schwartzman et al (2015)	Single-center RCT	Persistent AF NYHA class III Mean HR $>$ 85 LVEF \leq 35% LVEDD $>$ 55 mm LBBB QRSd $>$ 130 ms	Rhythm control* Standard care [§] *DCCV \pm AAD [§] DCCV + reinduction of AF	26 26	12	Age Sex (% M) LVEF (%) QRSd (ms) NYHA class	70.0 (8.0) 71.2 28 (7.6) 143.5 (12.6) 3.3 (0.5) No significant difference between groups for incidence of CRT response or change in: NYHA class, MLWHF score, 6MWT, LVEF, LVEDD Higher hospital encounters in rhythm control group (11.7% vs 3.2%; $P = .002$) NB 4 patients with failed rhythm control excluded from analysis
PilotCRAFT (2021)*	Single-center RCT	CRT Perm AF or pers AF lasting $>$ 6 months BiVp% $<$ 95%	Rhythm control* Rate control [§] *DCCV [§] Drugs \pm AVNA NB both groups received amiodarone	22 21	12	Age Sex (% M) LVEF (%) QRSd (ms) NYHA class	68.4 (8.3) 97.7 30 (8) NA NA No difference between groups in improvement in BiVp%, VO2max, QOL / clinical endpoints In per-protocol analysis, higher LVEF in rhythm control group at follow-up (36.8% vs 29.9%; $P = .039$)
AF Ablation							
Fink et al (2019)	Single-center retrospective observational	AF and CRT nonresponse* who underwent AF ablation *at least 1 of: - BiVp% $<$ 95% - Δ NYHA $<$ 1 - Δ LVEF $<$ 5%	No control group	38	12	Age Sex (% M) LVEF (%) QRSd (ms) NYHA class	67.8 (9.8) 78.9 30.4 (7.2) NA 3.0 68% in sinus rhythm at follow-up Significant improvements from baseline in:* BiVp% (Δ 7.5%; $P < .001$) LVEF (Δ 2.2; $P = .0225$) NYHA class ($P < .0001$) *6 patients underwent AVNA during follow-up and were excluded in analysis
CASTLE-AF (2018)	Multicenter RCT (subgroup analysis)	Symptomatic pers AF or pAF LVEF \leq 35% Failed AAD Biotronik ICD / CRT-D	AF ablation Medical therapy Subgroup of total cohort who had CRT-D	48 52	37.6	Not reported for subgroup of patients with CRT-D	No significant difference in primary endpoint of death or HFH (HR 0.65; 95% CI 0.43-0.98) NB No significant interaction between presence of CRT-D vs ICD on primary endpoint on Cox logistic regression analysis ($P = .6$)

Continuous baseline characteristics expressed as mean (standard deviation).

6MWT = 6-minute walk test; AAD = antiarrhythmic drug; AF = atrial fibrillation; AVNA = atrioventricular node ablation; BiVp% = biventricular pacing percentage; CI = confidence interval; CRT = cardiac resynchronization therapy; DCCV = DC cardioversion; F/U = mean follow-up; HFH = heart failure hospitalization; HR = hazard ratio; ICD = implantable cardioverter-defibrillator; LBBB = left bundle branch block; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; MLWHF = Minnesota Living with Heart Failure Questionnaire; NA = not available; NYHA = New York Heart Association; pAF = paroxysmal AF; pers AF = persistent atrial fibrillation; QOL = quality of life; QRSd = QRS duration; RCT = randomized controlled trial SR = sinus rhythm.

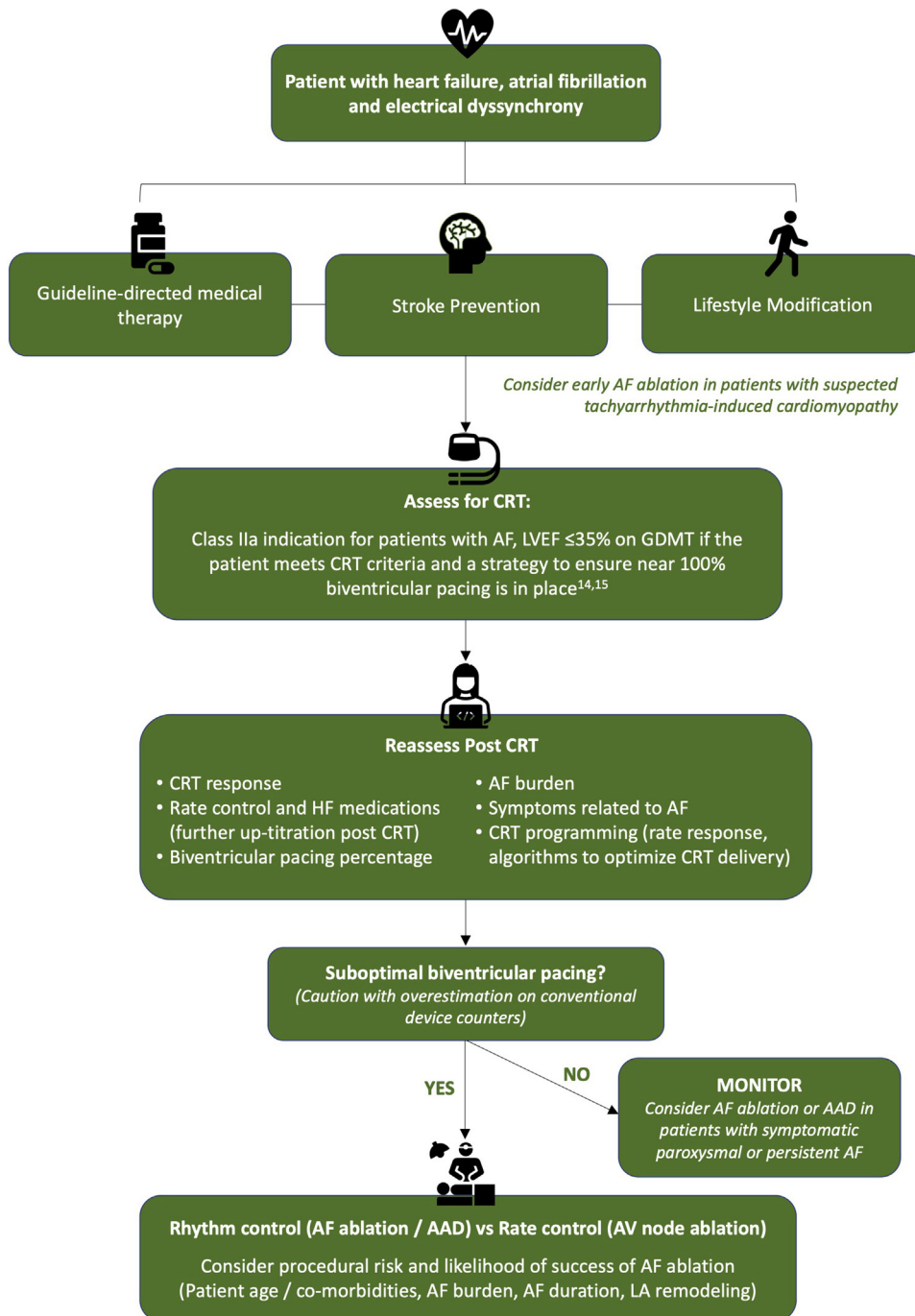


Figure 5 Clinical flowchart of the management of patients with atrial fibrillation (AF) and cardiac resynchronization therapy (CRT). AAD = antiarrhythmic drugs; AV = atrioventricular; GDMT = guideline-directed medical therapy; HF = heart failure; LA = left atrial; LVEF = left ventricular ejection fraction.

permanent AF.⁷¹ However, this therapy was assessed in combination with an algorithm to reduce right ventricular pacing in patients with bradycardia, and has not been assessed in CRT.

Conclusion

The presence of AF attenuates the response to CRT in patients with heart failure, likely owing to a combination of suboptimal biventricular pacing and a loss of AV synchrony. AV

node ablation improves biventricular pacing percentage and has been demonstrated to improve mortality after CRT implantation in large observational studies. AF ablation is feasible in patients with CRT, and may provide a benefit over AV node ablation by allowing AV resynchronization; however, randomized trials are required to demonstrate if this theoretical benefit improves clinical outcomes. The requirement for repeat AF ablation procedures, with associated cost and risk to the patient, must also be considered. A randomized study of AV node ablation vs AF ablation in

patients with heart failure, CRT, and suboptimal biventricular pacing secondary to AF is currently enrolling (NCT04664686) and will hopefully help address this important question. Device programming in patients with AF is challenging, and various algorithms are available to help optimize CRT delivery and potentially reduce AF burden.

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Authorship

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

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