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Is Cardiac Resynchronization Therapy an Antiarrhythmic Therapy for Atrial Fibrillation? A Systematic Review and Meta-Analysis

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Abstract

The impact of cardiac resynchronization therapy (CRT) on atrial fibrillation (AF) burden is poorly characterized. To assess the influence of CRT on AF, we performed a systematic literature search in MEDLINE using the MeSH headings “cardiac resynchronization therapy” OR “cardiac pacing, artificial” AND “atrial fibrillation.” Selected studies were peer-reviewed and written in English. Most studies enrolled patients meeting traditional CRT criteria. Ten observational studies and two secondary analyses of clinical trials were identified. Although 10 studies suggest that CRT favorably impacts AF, one secondary analysis of a clinical trial showed no effect of CRT on new-onset AF. In a meta-analysis of 3 studies examining the effect of CRT on persistent or permanent AF, the combined rate of conversion from persistent or permanent AF to sinus rhythm was 0.107 (95% confidence interval 0.069–0.163). Prospective studies, particularly among patients not meeting traditional CRT criteria, are needed.

Keywords

Cardiac Resynchronization Therapy; Atrial Fibrillation

Introduction

Atrial fibrillation (AF) and heart failure (HF) are regarded as emerging epidemics of cardiovascular medicine [1]. Among US individuals ≥ 40 years of age, the lifetime risks of newly-diagnosed AF and HF are approximately 1 in 4 and 1 in 5 respectively [2, 3]. Both AF and HF are associated with an increased risk of mortality. While AF is associated with double the risk of mortality over 10 years [4], approximately half of patients diagnosed with HF die within 5 years [5]. AF coexistent with HF is associated with more advanced symptoms [6] and portends a worse prognosis [7].

Clinical trials have shown that cardiac resynchronization therapy (CRT) reduces the symptom burden and risk of death in many HF patients [8–12]. Guidelines from the American College of Cardiology, American Heart Association, and Heart Rhythm Society reflect the weight of this evidence by establishing CRT as a Class I therapy in patients with

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systolic dysfunction, intraventricular conduction delay, heart failure despite optimal medical therapy, and normal sinus rhythm. As patients with AF were excluded from most major clinical trials, CRT was designated as a class IIa indication for AF patients with otherwise similar clinical characteristics [13]. Observational studies suggest that patients with AF benefit from CRT, albeit to a lesser degree [14, 15]. The influence of CRT on AF is less certain. Therefore, in the current analysis we sought to systematically evaluate the available evidence regarding the impact of CRT on (a) the incidence of new-onset AF, (b) the burden of paroxysmal AF, and (c) the conversion of persistent AF (continuously present for at least 1 week or that requires cardioversion) or permanent AF (persistent for more than 1 year) to normal sinus rhythm.

Methods

Study Search

To assess the influence of CRT on AF, we performed a systematic literature search in MEDLINE using the MeSH headings “cardiac resynchronization therapy” OR “cardiac pacing, artificial” AND “atrial fibrillation.” The MEDLINE query was limited to studies written in English. Bibliographies of selected full-length manuscripts were manually searched for additional relevant citations.

Eligibility and Data Abstraction

Peer-reviewed publications on the incidence of new-onset AF, burden of recurrent paroxysmal AF, or the rate of conversion of persistent or permanent AF to normal sinus rhythm after initiation of CRT in adults (aged ≥ 18 years) were included in the analysis. Studies which were not peer-reviewed, lacked novel data on the aforementioned outcomes, or included patients aged <18 years were excluded. A single reviewer assessed citations and consistently applied inclusion and exclusion criteria. Abstracted data consisted of study design (including comparison groups and sample sizes), study baseline characteristics, duration of follow-up, AF-related outcomes, and the methods of AF detection. Figure 1 shows the study selection process according to PRISMA guidelines [16].

Statistical Analysis

The effect of CRT on conversion of persistent or permanent AF to normal sinus rhythm was determined with random-effects modeling using the DerSimonian and Laird method [17]. The measure of treatment effect was reported with an estimated rate. Heterogeneity between studies was assessed using the Cochrane Q statistic. Testing was two-tailed. Significance was declared at $P < 0.05$. Analyses were conducted using the Comprehensive Meta-Analysis program (Biostat, Englewood, NJ).

Results

Of 739 abstracts resulting from our search strategy, most were excluded owing to reasons shown in Figure 1. Forty-four publications were selected for full review, which in turn identified 9 studies which met all inclusion criteria. Review of the bibliographies of these studies yielded 5 additional studies. Two of the 5 papers were excluded due to the absence of novel data, yielding 12 studies that were deemed to be appropriate for inclusion in our study.

Of the 12 identified studies, 10 were observational and 2 were secondary analyses of clinical trials examining the impact of CRT on AF (Table 1) [18–29]. The most common comparison was the burden of AF before and after CRT placement. The majority of studies enrolled patients who met traditional CRT indications, including New York Heart

Association class III–IV symptoms, left ventricular ejection fraction ≤ 35%, and QRS duration ≥ 120 ms on optimal medical therapy. Sample sizes were small (<100 patients) except in the secondary analysis of CARE-HF, which included 813 patients [27], in a secondary analysis of MADIT-CRT, which enrolled 1820 patients [26], and in a study by Gaspirini et al., which enrolled 330 patients [19]. Most studies enrolled patients who were older than 60 years of age, male, and had a nonischemic cardiomyopathy. Median duration of follow-up ranged from 6 to 36 months. To detect AF, studies used electrocardiography, Holter monitoring, and/or device interrogation.

The Effect of CRT on New-Onset AF

Four studies examined the effect of CRT on the development of new-onset AF. In a study by Fung et al., 36 CRT recipients had a lower incidence of new-onset AF than 36 controls matched for age, sex, and ejection fraction (8.3% v. 30.6%, hazard ratio (HR) 0.23, 95% confidence interval (CI) 0.09–0.76) [28]. In the cohort examined by D'Ascia et al., the percentage of patients with new-onset AF was lower among CRT responders compared with non-responders (50.0% v. 15.0%, odds ratio (OR) 5.67, 95% CI 1.36–23.59) [29]. In MADIT-CRT, 731 patients were randomized to receive ICD therapy and 1089 patients were randomized to receive CRT-D (cardiac resynchronization therapy-defibrillator) therapy. Three-year cumulative probabilities of atrial tachyarrhythmia (AT) were similar between CRT-D and ICD-only patients (7% v. 9%, respectively; p=0.63). However, the cumulative probabilities of AT were demonstrated to be related CRT-D response as indicated by reduction in left atrial volume. When using the endpoint of AF rather than AT, the findings were comparable. Whereas the risk of new-onset AF was similar between CRT-D and ICD-only patients, CRT-D responders as indicated by a reduction in left atrial volume experienced a significant reduction in AF risk [26]. In CARE-HF, there was no statistical difference in the incidence of new-onset AF among 409 subjects randomized to CRT therapy compared with 404 individuals randomized to pharmacologic therapy (16.1% v. 14.4%, HR 1.05, 95% CI 0.73–1.50) [27]. In contrast to MADIT-CRT, subgroup analyses comparing CRT responders with non-responders were not performed. In assessing these results, it is important to note that AF detection differed among studies. In the study by Fung et al., AF was detected by electrocardiography and 24-hour Holter monitors [28]. D'Ascia et al. also used device interrogation [29]. MADIT-CRT used device diagnostics alone [26], while CARE-HF used electrocardiography alone [27].

The Effect of CRT on the Burden of Paroxysmal AF

Three studies reported the effect of CRT on paroxysmal AF. In a study of 84 patients by Hugl et al., the percentage of patients with paroxysmal AF decreased from 37% during the first month after implantation to 14% during the third month after implantation with a concomitant reduction in the amount of daily time spent in AF [25]. Similarly, Yannopoulos et al. studied the burden of AT in 28 patients before and after upgrade from a pacemaker or implantable cardioverter-defibrillator to CRT. They found that only 14% of patients were free of AT at 3 months prior to CRT, while 90% of patients were free of AT at 1 year of follow-up. The number of AT episodes and their duration also decreased [23]. By contrast, Adelstein et al. investigated AF burden among 27 patients in whom CRT placement had been unsuccessful compared with 54 controls who underwent successful CRT placement. Half of the control group was classified as CRT responders and half was classified CRT non-responders. They did not detect a significant difference in AF burden between CRT recipients and non-recipients [24]. Each of these studies used device interrogation to detect AF.

The Effect of CRT on Persistent or Permanent AF

Four studies explored the influence of CRT on persistent or permanent AF before and after CRT placement [18–22]. One study was judged to be of poor quality since it did not report baseline patient characteristics and was excluded from the meta-analysis [18]. Among the remaining studies, the rate of conversion from AF to sinus rhythm ranged from 7% after 6 months of CRT [22] to 17% after 22 months of CRT [20]. The combined rate of conversion from persistent or permanent AF to normal sinus rhythm was 0.107 (95% confidence interval 0.069–0.163) (Figure 2). There was no evidence of heterogeneity (Q value = 4.43, p=0.180). In the largest study by Gaspirini et al., a multivariable analysis identified end-diastolic diameter ≤ 65 mm, left atrial size ≤ 50 mm, and atrioventricular junction ablation as factors associated with resumption of normal sinus rhythm [19]. Lellouche et al. found that the prevalence of persistent of AF was lower after 6 months of CRT in comparison to before CRT placement among 54 responders (17% v. 2%, p=0.02) but not among 42 non-responders (10% v. 19%, p=ns) [21].

Discussion

Our study has three major findings. First, scant data on the impact of CRT on AF exist and are largely observational. Second, although 10 of 12 studies suggest that CRT favorably impacts AF, a secondary analysis of a large randomized clinical trial showed no effect of CRT on new-onset AF. Third, most studies have been limited to those in whom CRT is currently indicated.

Atrial reverse remodeling serves as the biologic basis for an atrial anti-arrhythmic effect of CRT. Reduced left atrial size and better atrial hemodynamics may result from improved left ventricular hemodynamics and reduced mitral regurgitation [19]. Less atrial stretch [30] and more balanced neurohormonal activation may also contribute to a favorable response. These biologic underpinnings are indirectly supported by the findings of the current study.

Ten of 12 studies indicate CRT may be associated with a reduction in AF. While Fung et al. suggest the risk of new-onset AF is lower among CRT recipients [28], D'Ascia et al. and Brenyo et al. show this reduction is likely limited to CRT responders [26, 29]. Hugl et al. and Yannopoulos et al. similarly demonstrate that CRT is associated with a lower burden of paroxysmal AF [23, 25]. Four studies examining the influence of CRT on persistent or permanent AF reach similar conclusions [18–20, 22]. Like D'Ascia et al. and Brenyo et al., Lellouche et al. found that CRT responders experienced a lower incidence of persistent AF in comparison to CRT non-responders [21].

The strength of the aforementioned evidence must be weighed against and reconciled with that of the post hoc analysis of CARE-HF, a multicenter, randomized clinical trial that failed to show an atrial antiarrhythmic effect of CRT. This discrepancy may be explained in part by the method of AF surveillance. While most studies used device interrogation to determine AF burden, the analysis of CARE-HF used electrocardiography. Investigators likely opted for the latter approach so as not to bias the study against CRT, as costs of rigorous monitoring in CRT non-recipients can be prohibitive. This study design likely led to lower estimates of patients' true AF burden by under detecting asymptomatic AF episodes [31]. The lower number of AF episodes may have reduced the power of the study to detect a statistically meaningful difference between groups. Further, ascertainment bias could not be entirely eliminated, as device diagnostics may have led to enhanced electrocardiographic monitoring among CRT recipients. Finally, the absence of a subgroup analysis comparing CRT responders with either CRT non-responders or CRT non-recipients may also explain the absence of a significant signal in this study.

Most included studies enrolled patients in whom CRT is currently indicated. Standard CRT criteria include New York Heart Association III or IV symptoms, a reduced left ventricular ejection fraction (≤ 35%), and QRS duration ≥ 120 ms [13]. However, subgroups not meeting the aforementioned CRT placement criteria may also experience an antiarrhythmic benefit from CRT. A growing body of evidence suggests CRT also positively impact patients with mild heart failure symptoms. Improvements in left ventricular ejection fraction and concomitant left ventricular reverse remodeling [32] have been observed, as have reductions in symptoms [33], heart failure events [34], and death [35]. As atrial remodeling is likely closely tied to CRT response, the atrial antiarrhythmic effect observed in the secondary analysis of MADIT-CRT, which enrolled patients with NYHA class I–II symptoms, is not unexpected. These findings from MADIT-CRT should be verified in future studies enrolling patients with less advanced HF symptoms.

There are limited data on factors discriminating between CRT responders and non-responders. There is a corresponding dearth of data on factors distinguishing patients who derive an atrial antiarrhythmic effect compared with those who do not. The only model currently available suggests the conversion of permanent AF to sinus rhythm is associated with an end-diastolic diameter ≤ 65 mm, left atrial size ≤ 50 mm, and AV junction ablation [19]. Factors associated with CRT response in MADIT-CRT such as female sex, nonischemic cardiomyopathy, and QRS duration [36] were not independently associated with an atrial antiarrhythmic effect. The presence of left bundle-branch block, an additional factor which has previously been associated with CRT response, [37] was not examined. The considerable difference in sample size between MADIT-CRT and the study by Gaspirini et al. (1761 v. 330 HF patients) may, in part, explain why important covariates associated with CRT response in MADIT-CRT did not maintain significance in the model examining factors associated with an atrial antiarrhythmic effect constructed by Gaspirini et al.

The current analysis has several important implications. First, although atrioventricular node ablation has been associated with improvement in symptoms and a reduction in mortality in patients with AF receiving CRT [38, 39], a small fraction of patients with persistent or permanent AF may in fact convert to sinus rhythm after several months of CRT. Therefore, it may be prudent to wait for a period of time after CRT placement before performing atrioventricular node ablation, particularly in light of the potential for making patients pacemaker-dependent with the latter procedure. To be implemented clinically, more data on identifying patients who are most likely to derive an atrial antiarrhythmic effect from CRT are needed. Second, because a number of patients with persistent or permanent AF may ultimately convert to sinus rhythm after CRT placement, placement of an atrial lead during the index procedure may be warranted. Third, since CRT appears to impact AF in CRT recipients who meet current indications, subgroups of patients who fall outside of traditional CRT inclusion criteria may also benefit from an atrial antiarrhythmic effect. In fact, rather than a curiosity or desirable byproduct, reduction in AF burden by CRT, particularly among patients refractory to pharmacologic therapy, may become a therapeutic goal. Further prospective studies are necessary.

The current study has several limitations. First, most of the included studies were observational and thus were unable to establish a causal relationship between CRT placement and a reduction in AF. Most of the included studies also had small sample sizes. Based on these studies, the current analysis is similarly limited. Additionally, as with any literature search, the current analysis likely has a publication bias. Finally, the exclusion of non-peer-reviewed publications may contribute to a selection bias.

Conclusions

Data on the potential influence of CRT on AF burden are largely observational. While existing data suggest that CRT is associated with a lower risk of new-onset AF, a secondary analysis of a large randomized clinical trial did not find an association between CRT and incidence of new-onset AF. Although this may be due to differences in monitoring for AF, this controversy deserves further study. Studies suggesting a beneficial effect of CRT on the burden of paroxysmal AF are limited not only their observational designs but also by their small sample sizes. CRT is associated with conversion of persistent or permanent AF to sinus rhythm. Most studies enrolled patients who meet traditional CRT criteria, including advanced HF symptoms, reduced EF, and electrocardiographic intraventricular dyssynchrony. Well-designed, prospective studies among such patients as well as among patients not meeting traditional CRT criteria are needed.

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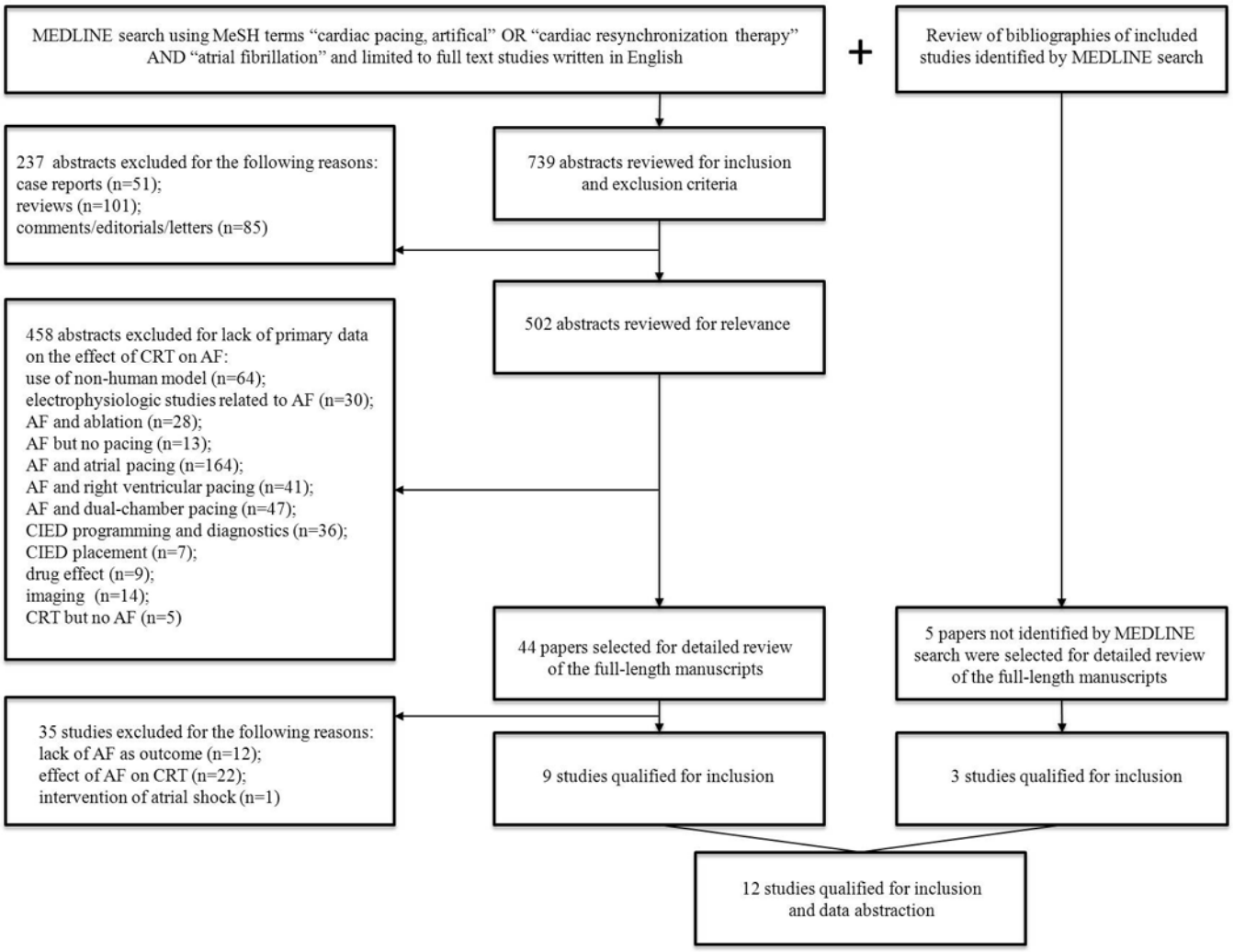

Figure 1.

Systematic Literature Review Search Flow Diagram. AF = atrial fibrillation; CIED = cardiovascular implantable electronic device; CRT = cardiac resynchronization therapy.

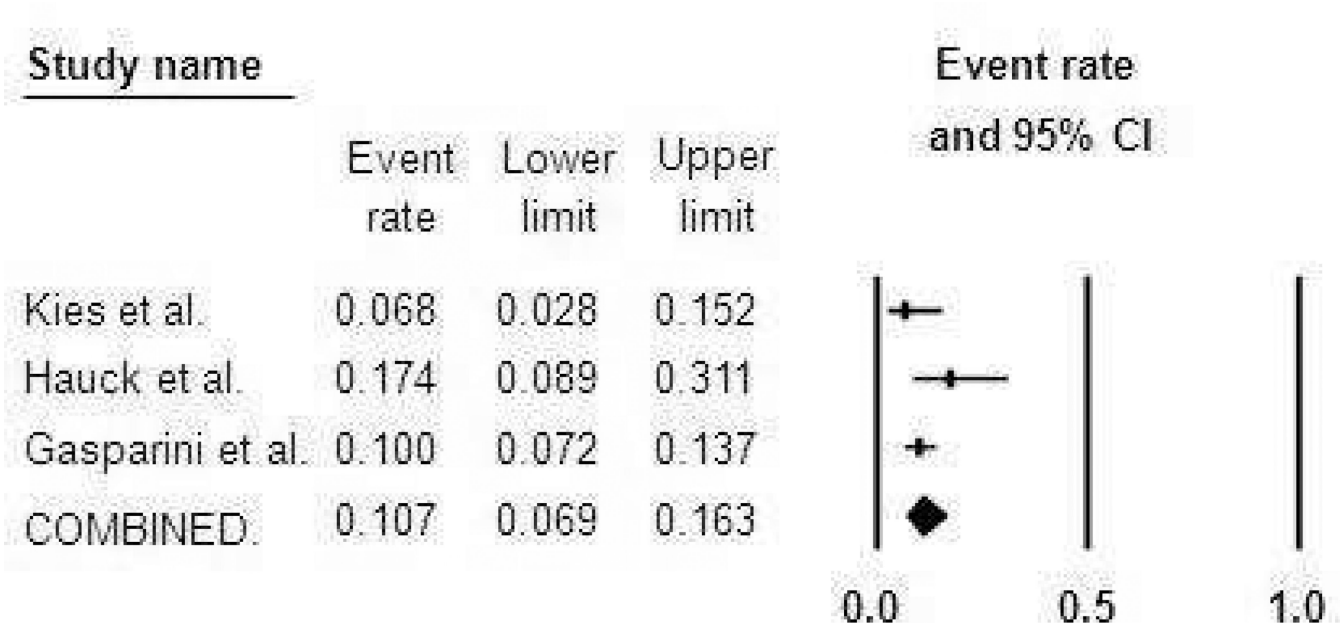

Figure 2.
Rates of Conversion from Persistent or Permanent AF to Normal Sinus Rhythm.

Table 1

Studies of CRT Effect Stratified by Type of AF

Type of AF	Source	Publication Year	Study Design	Comparison(s)	Exceptions to Traditional CRT Indications*	Sample size (n)	Median Age (y)	Male (%)	Ischemic Cardiomyopathy (%)	Median Follow-up (months)	AF Endpoints	Method of AF detection
New-Onset												
	Fung et al.	2005	Observational	CRT recipients v. matched non-recipients	LVEF < 40%	72	66	72	35	36	Incidence of new-onset AF	ECG, event recorders, 24-hour Holter monitors
	Hoppe et al.	2006	2° analysis of clinical trial	CRT v. pharmacologic therapy	-	813	66	73	38	29	Incidence of new-onset AF	ECG
	D'Ascia et al.	2011	Observational	CRT responders v. non-responders	-	58	63	64	-	36	Incidence of new-onset AF	ECG, 24-hour Holter monitors, device interrogation
	Brenyo et al.	2011	2° analysis of clinical trial	CRT-D recipients v. ICD recipients	NYHA Class I-II	1820	65	75	52	30	Incidence of AT, incidence of AF	Device interrogation
				LAV responders v. ICD recipients	LVEF ≤ 30%							
					QRS ≥ 130 ms							
Paroxysmal												
	Hügl et al.	2006	Observational	1 month v. 3 months after CRT placement	-	84	67	42	63	3	Number of patients with episodes, AF burden (hours/day)	Device interrogation
	Adelstein et al.	2007	Observational	CRT recipients v. matched non-recipients	-	81	67	48	48	17	Time to first episode, AF burden (hours/day, number of episodes)	Device interrogation
	Yannopoulos et al.	2007	Observational	Before and after CRT placement	-	28	69	90	76	24	Number of patients with episodes of AT, AT burden (episodes/month or episodes/year, duration of episodes, rate of episodes)	Device interrogation
Persistent or Permanent												
	Kies et al.	2006	Observational	Before and after CRT placement	LVEF < 35%	74	68	91	43	6	Incidence of reversion to normal sinus rhythm	ECG, 48-Holter monitors, and device interrogation
					Left bundle branch block							
	Lellouche et al.	2007	Observational	CRT responders v. non-responders	-	96	59	78	-	6	Incidence of persistent AF	Device interrogation
	Hauck et al.	2008	Observational	Before and after CRT placement	LVEF < 35%	46	66	87	54	22	Incidence of reversion to normal sinus rhythm, time from device implantation to reversion	ECG, device interrogation
					Left bundle branch block							
					QRS > 130 ms							
	Gasparini et al.	2010	Observational	Before and after CRT placement	-	330	70	83	44	42	Incidence of reversion to normal sinus rhythm, time from device implantation to reversion, predictors of reversion	Not specified
	Luedorff et al.	2011	Observational	Before and after CRT placement	-	27	-	-	-	6	Incidence of reversion to normal sinus rhythm	ECG

Abbreviations: AF, atrial fibrillation; AT, atrial tachyarrhythmia; CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy-defibrillator; ECG, electrocardiography; LAV, left atrial volume; NYHA, New York Heart Association

*Traditional CRT indications are NYHA class III-IV symptoms, LVEF ≤ 35%, and QRS duration ≥ 120 ms