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Cardiac Resynchronization Therapy in Patients With Atrial Fibrillation

The CERTIFY Study (Cardiac Resynchronization Therapy in Atrial Fibrillation Patients Multinational Registry)

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Objectives The purpose of this study is to determine whether, in patients with atrial fibrillation (AF) undergoing cardiac resynchronization therapy (CRT), atrioventricular junction ablation (AVJA) is associated with a better outcome than treatment with rate-slowing drugs.

Background Different trials have demonstrated that CRT is effective in treating heart failure (HF) patients who are in sinus rhythm (SR). No trials have addressed whether CRT confers similar benefits on AF patients, with or without AVJA.

Methods The clinical outcomes of CRT for patients with permanent AF undergoing CRT combined with either AVJA (n = 443) or rate-slowing drugs (n = 895) were compared with those of SR patients (n = 6,046).

Results Median follow-up was 37 months. Total mortality (6.8 vs. 6.1 per 100 person-years) and cardiac mortality (4.2 vs. 4.0) were similar for patients with AF+AVJA and patients in SR (both p = NS). In contrast, the AF+drugs group had a higher total and cardiac mortality than the SR group and the AF+AVJA group (11.3 and 8.1, respectively; p < 0.001). On multivariable analysis, AF+AVJA had total mortality (hazard ratio [HR]: 0.93, 95% confidence interval [CI]: 0.74 to 1.67) and cardiac mortality (HR: 0.88, 95% CI: 0.66 to 1.17) similar to that of the SR group, independent of known confounders. The AF+drugs group, however, had a higher total mortality (HR: 1.52, 95% CI: 1.26 to 1.82) and cardiac mortality (HR: 1.57, 95% CI: 1.27 to 1.94) than both the SR group and the AF+AVJA group (both p < 0.001).

Conclusions Long-term survival after CRT among patients with AF+AVJA is similar to that observed among patients in SR. Mortality is higher for AF patients treated with rate-slowing drugs. (J Am Coll Cardiol HF 2013;1:500–7)

Cardiac resynchronization therapy (CRT) is an established treatment for patients with mild to severe heart failure (HF), sinus rhythm (SR), a prolonged QRS duration, and impaired left ventricular (LV) systolic function (1–4). In the CARE-HF (Cardiac Resynchronization in Heart Failure) study (4), CRT was associated with 40% relative reduction

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in all-cause mortality. This and other studies have shown that CRT also improves symptoms, exercise capacity, and quality of life, and induces LV reverse remodeling (5,6).

It is well recognized that the development of atrial fibrillation (AF) in HF heralds a poor prognosis (7–9). There is also evidence to suggest that CRT may not be as effective for patients with AF undergoing CRT (10,11–15). That may be due to several factors. Firstly, AF precludes atrioventricular optimization of CRT. Secondly, a high intrinsic ventricular response leads to electrical fusion and reduces biventricular pacing capture and, consequently, cardiac output. Importantly, randomized, controlled clinical outcome trials of CRT have almost always excluded patients with AF. Yet, among the general HF population, AF is common, occurring in 10% to 25% of patients in New York Heart Association (NYHA) class II to III and in as many as 50% of patients in NYHA class IV (16).

Rate-slowing drugs have been the mainstay of treatment for the control of the ventricular response in patients with AF. Atrioventricular junction ablation (AVJA) has also been used as an alternative to drug therapy for controlling the ventricular response in patients with permanent AF. Observational studies have suggested that, in patients with HF and permanent AF undergoing CRT, AVJA is associated with a longer survival compared to treatment with rate-slowing drugs (14,15,17). In this large multinational, multicenter, "real-world," prospective observational study, we have explored the effects on clinical outcome of AVJA and rate-slowing drugs in patients with HF and AF undergoing CRT. The clinical outcome was compared with that of patients in SR treated with CRT.

Methods

Design. The CERTIFY (Cardiac Resynchronization Therapy in Atrial Fibrillation Patients Multinational Registry) study was a prospective, multicenter, international, longitudinal, observational study of 7,384 consecutive patients undergoing CRT in the period from October 1999 to September 2011 in 95 European centers (see the Online Appendix). Data collection and analysis was approved by the individual sites' institutional review board or clinical ethics committee. The study conformed to the Declaration of Helsinki. All patients gave written, informed consent for data collection and analysis.

Patient population. Inclusion criteria were as follows: systolic HF in NYHA class III or ambulatory IV (or II in the case of a recent HF hospitalization); LVEF $\leq$35% and QRS $\geq$120 ms, despite maximum tolerated pharmacologic therapy with angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, beta-adrenergic blockers, diuretics, and spironolactone for at least 2 months. The clinical diagnosis of HF was made on the basis of documented evidence of systolic dysfunction on echocardiography. The diagnosis of ischemic cardiomyopathy was made if systolic dysfunction was associated with a history of myocardial infarction and/or if there was angiographically significant coronary heart disease. Exclusion criteria were contraindications to cardiac pacing; myocardial infarction or acute coronary syndrome within the previous 3 months; severe structural valvular heart disease; and presence of comorbidities likely to curtail survival to 12 months or less.

Abbreviations and Acronyms

AF = atrial fibrillation
AVJA = atrioventricular junction ablation
CRT = cardiac resynchronization therapy
CRT-D = cardiac resynchronization defibrillation
CRT-P = cardiac resynchronization pacing
HF = heart failure
HR = hazard ratio
LV = left ventricular
LVESV = left ventricular end-systolic volume
NYHA = New York Heart Association
SR = sinus rhythm

Endpoints. The primary endpoint was total mortality. The secondary endpoint was cardiovascular mortality. Deaths were classified as cardiac, noncardiac, or unknown (18). Patients undergoing LV assist device implantation or urgent heart transplantation were classified as cardiac deaths. When the cause of death could not be determined by means of all available sources, it was classified as unknown. Each center adjudicated the cause of death.

Clinical assessment and follow-up. Baseline clinical assessments were undertaken before CRT device implantation, and the follow-up visits were scheduled according to each center's routine practice. The assessment included evaluation of NYHA class, an electrocardiogram, and a transthoracic echocardiogram. The latter was undertaken before CRT device implantation and at 6 and 12 months after implantation, and yearly thereafter. The following parameters were assessed according to the Simpson's biplane method: LV end-diastolic volume, left ventricular end-systolic volume (LVESV), and LVEF (19). Rate-slowing drugs were given to all AF patients before device implantation, and were up-titrated after implantation to reach adequate rate control (20), and to maximize the biventricular pacing capture. The AVJA was performed within 3 months if clinical improvement and/or adequate biventricular pacing percentage did not occur with rate-slowing drugs (11).

Device therapy. Transvenous CRT-pacing (CRT-P) or CRT-defibrillation (CRT-D) device implantation was undertaken using standard transvenous techniques under local anesthesia. A lateral or posterolateral LV site was considered optimal for LV lead by most implanters. In patients with SR, the CRT device was programmed in atrial-synchronous sequential pacing. Atrioventricular optimization was undertaken within 24 h of device implantation and at 6 months, using Doppler echocardiography and the iterative method (21). For patients with AF, the minimum heart rate was set at $\geq$70 beats/min and the maximum rate was set at 70% of the theoretical maximum heart rate. A rate-adaptive response was activated in patients with AVJA and without AVJA. For 1,401 patients with save-to-disk or home monitoring data

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available, the biventricular pacing percentage was evaluated at 12 months.

Statistical analysis. Continuous and categorical variables were expressed as means and standard deviations, and counts as percentages. Groups were compared using the Kruskal-Wallis test or the likelihood chi-square test. Median follow-up (interquartile range) was computed according to the inverse Kaplan-Meier method. The impact of performing AVJA (at implant or during follow-up) on survival was assessed by means of a time-dependent Cox model for this discrete time-varying covariate, on both univariable and multivariable analyses with adjustment for potential confounders (age, sex, coronary artery disease, NYHA functional class, implantable cardioverter-defibrillator as the inserted device, LVEF, QRS duration). Only covariates with a proportion of missing values <25% were considered. Hazard ratios (HRs) and 95% confidence intervals (CIs) were reported. All models were stratified per center to allow for between-center heterogeneity in baseline risk. The Harrell's c statistic for discrimination and the Royston explained variation (based on a testing/validating sample strategy) were computed to assess model performance. Mortality rates per 100 person-years and 95% CI were computed. Longitudinal changes in LVEF and LVESV among the 3 groups were compared using generalized linear regression models for repeated measures (with Huber-White robust standard errors, accounting for intracenter correlation). Models included a main group effect, a main effect for time and their interaction. Stata 12 (StataCorp, College Station, Texas) was used for statistical analysis. A 2-sided p value <0.05 was considered statistically significant. The Bonferroni correction was applied for post-hoc comparisons.

Results

Patients were classified into 3 groups: AF+AVJA (n = 443); AF+drugs (n = 895), and SR (n = 6,046). As shown in Table 1, patients with AF were older, more likely to be male, had a higher NYHA class, were less likely to have an ischemic HF etiology or left bundle branch block, and had a lower incidence of CRT-D rather than CRT-P (all $p < 0.001$) than patients in SR. Patients with AF+AVJA had smaller LVESV and higher LVEF (all $p < 0.001$) than patients in the SR group or the AF+drugs group. As expected, AF+AVJA patients were less frequently treated with amiodarone or digoxin ($p < 0.001$). The mean biventricular pacing percentage in the AF+AVJA group and the SR group was significantly higher than in the AF+drugs group ($p < 0.001$).

Clinical outcomes. Over a maximum follow-up of 10 years (median 37 months [interquartile range: 14 to 58 months], equating to 230,000 patient-years), 1,301 patients died. In 144 cases, the cause of death was unknown, and another 297 cases were classified as noncardiac. The remaining 860 deaths were classified as cardiac deaths; 33 patients who underwent urgent cardiac transplantation or LV assist device implantation were considered cardiac deaths (Fig. 1). As shown in Table 2, and in Kaplan-Meier survival analyses (Fig. 2), total mortality (6.8 vs. 6.1) and cardiac mortality (4.2 vs. 4.0 per 100 person-years; both p = not significant) were similar in patients with AF+AVJA and patients in SR. In contrast, the AF+drugs group had a higher total and cardiac mortality than the SR and the AF+AVJA groups (11.3 and 8.1, respectively; $p < 0.001$). Importantly, the survival curves for these 3 groups started to diverge at

Table 1 Baseline Characteristics

Variables	SR (n = 6,046)	AF+Drugs (n = 895)	AF+AVJA (n = 443)	p Value	Post-Hoc Comparison*
Age, yrs	66.4 ± 10.3	69.7 ± 9.3	68.4 ± 9.1	<0.001	1, 2, 3
Male	4,714 (78%)	764 (85.4%)	374 (84.2%)	<0.001	1, 3
Ischemic cardiomyopathy	2,803 (47.0%)	318 (36.4%)	179 (41.0%)	<0.001	1
NYHA functional class III–IV	4,235 (73.8%)	703 (83.1%)	357 (85.0%)	<0.001	1, 3
CRT-D	4,890 (80.9%)	635 (70.9%)	302 (68.2%)	<0.001	1, 3
Diabetes mellitus	1,488 (25.7%)	161 (21.8%)	109 (24.4%)	0.13	—
LBBB	5,579 (91.5%)	558 (86.7%)	242 (60.2%)	<0.001	1, 2, 3
QRS, ms	157.6 (31.9)	155.4 (33.5)	159.2 (37.9)	0.16	—
Biventricular pacing percentage, %	92 ± 13	87 ± 14	96 ± 6	<0.001	1, 2, 3
LVEF, %	25.9 ± 6.5	25.9 ± 6.9	27.0 ± 6.6	<0.001	2, 3
LVESV, ml	164.2 ± 72.1	163.4 ± 73.4	146.6 ± 52.2	<0.001	2, 3
ACEI/ARB	4,783 (85.0%)	688 (84.0%)	391 (87.3%)	0.38	—
Beta-blocker	4,432 (79.8%)	603 (74.8%)	338 (76.3%)	<0.001	1
Spironolactone	2,977 (53.8%)	556 (47.8%)	210 (47.6%)	<0.001	1, 3
Loop diuretic	5,448 (92.0%)	805 (93.2%)	424 (89.6%)	0.17	—
Amiodarone	2,163 (37.1%)	270 (31.7%)	121 (26.0%)	<0.001	1, 3
Digoxin	1,249 (24.0%)	549 (25.8%)	192 (17.8%)	<0.001	2, 3

Values are mean ± SD or n (%). *Post-hoc comparisons are as follows: 1) sinus rhythm (SR) versus atrial fibrillation (AF) plus drugs; 2) AF plus atrioventricular junction ablation (AVJA) versus AF plus drugs; 3) SR versus AF plus AVJA.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; CRT-D = cardiac resynchronization therapy defibrillation; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; NYHA = New York Heart Association.

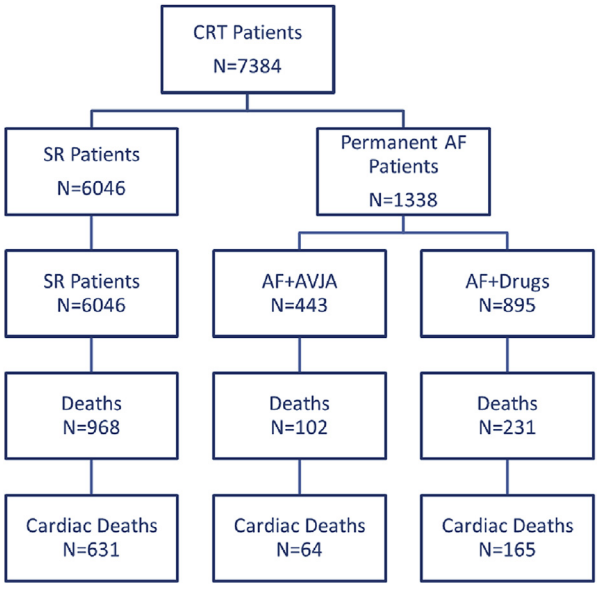

Figure 1 The CONSORT Flowchart

AF = atrial fibrillation; AVJA = atrioventricular junction ablation; CONSORT = Consolidated Standards of Reporting Trials; CRT = cardiac resynchronization therapy; SR = sinus rhythm.

6 months and continued to do so up to the end of the follow-up period. On multivariable analysis (Table 3), after stratification by center and adjustment for potential confounders (age, sex, HF etiology, NYHA class, implantable cardioverter-defibrillation as inserted device, LVEF, QRS duration), AF+AVJA patients had a total mortality (HR: 0.93, 95% CI: 0.74 to 1.67) and cardiac mortality (HR: 0.88, 95% CI: 0.66 to 1.17) similar to the SR group. The AF+drugs group, however, had a higher total mortality (HR: 1.52, 95% CI: 1.26 to 1.82) and cardiac mortality (HR: 1.57, 95% CI: 1.27 to 1.94) than both the SR group and the AF+AVJA group (all $p < 0.001$) (Fig. 3).

Echocardiographic results. All 3 patient groups—namely, the AF+AVJA, AF+drugs, and SR groups—showed improvements in LVEF (AF+AVJA 27 ± 7%; AF+drugs 26 ± 7%; SR 26 ± 6%) at 6 months (AF+AVJA 35 ± 11%; AF+drugs 30 ± 12%; SR 32 ± 11%; all $p < 0.001$). The increase in LVEF observed in the AF+AVJA and SR groups was higher than that observed in the AF+drugs group ($p < 0.001$ and $p = 0.003$, respectively). Similarly, the 3 groups showed a reduction in LVESV at 6 months (all $p < 0.001$) (Fig. 4). Although there was no further reduction in LVESV after 6 months in the AF+drugs group, the reduction in LVESV for the SR group and AF+AVJA group was sustained over the 3-year follow-up. The difference in LVESV between the AF+AVJA group and AF+drugs group increased from 25 ml at 6 months to 50 ml at 3 years ($p < 0.001$).

Table 2 Mortality to Rhythm and Atrioventricular Junction Ablation (Time-Dependent Cox Models Stratified by Center): Univariable Model

	Overall Mortality				Cardiac Mortality			
	n (%)	Rate/100 Person-Yrs (95% CI)	HR (95% CI)	p Value	n (%)	Rate/100 Person-Yrs (95% CI)	HR (95% CI)	p Value
Univariable model				<0.001				<0.001
Rhythm								
SR	968 (16.0%)	6.1 (5.8–6.5)	1.00		631 (10.4%)	4.0 (3.7–4.3)	1.00	
AF+Drugs	231 (25.8%)	11.3 (9.9–12.9)	1.55 (1.33–1.80)	<0.001	165 (18.4%)	8.1 (6.9–9.4)	1.57 (1.31–1.88)	<0.001
AF+AVJA	102 (23.02%)	6.8 (5.6–8.2)	1.03 (0.83–1.27)	0.79	64 (14.4%)	4.2 (3.3–5.4)	0.99 (0.76–1.29)	0.95
			AF+AVJA vs. AF+Drugs				AF+AVJA vs. AF+Drugs	
			0.67 (0.52–0.85), p = 0.001				0.63 (0.46–0.86), p = 0.003	

CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

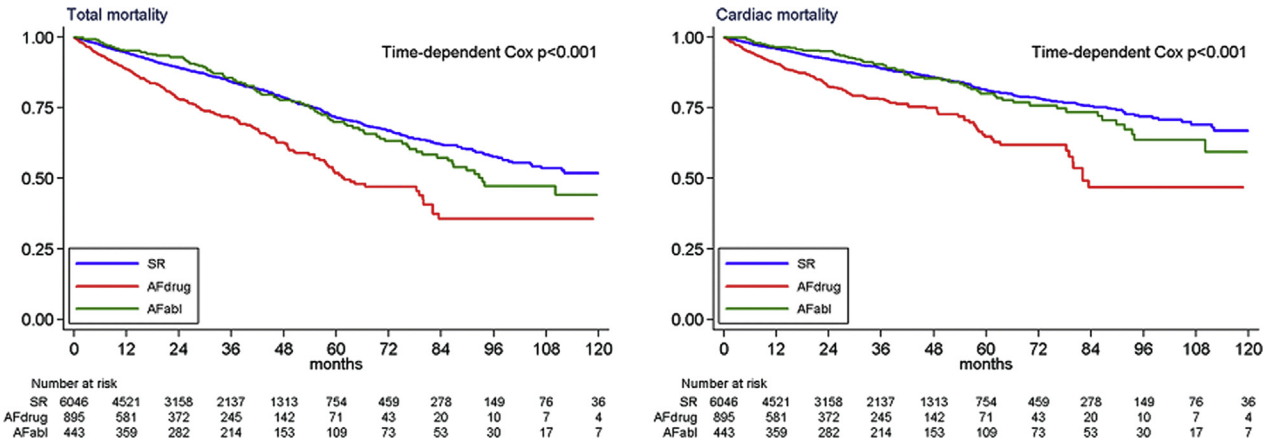

Figure 2 **Survival After CRT**

Kaplan-Meier survival after cardiac resynchronization therapy (CRT) from total mortality **(left panel)** and cardiac mortality **(right panel)** for the 3 patient groups: sinus rhythm (SR) **(blue lines)**; atrial fibrillation (AF) plus drugs **(red lines)**; and AF plus ablation **(green lines)**.

Discussion

This is the largest study of patients with permanent AF undergoing CRT, comprising a total of 1,338 AF patients and a total of 230,000 patient-years. This is approximately 10-fold higher than all randomized trials of CRT put together. We have compared the clinical and echocardiographic outcome of CRT in patients with AF+AVJA, AF+drugs, and patients in SR. We have found that for AF patients, AVJA was associated with 52% lower mortality than rate-slowing drug therapy, independent of age, sex, etiology of HF, NYHA class, device type, LVEF, and QRS duration. No difference in mortality was observed between the AF+AVJA group and the SR group. Interestingly, the Kaplan-Meier curves of the AF+AVJA group and the SR group diverged from the AF+drugs group at 6 months, and continued to do so throughout the follow-up period. These findings suggest that the benefit of CRT for both the SR group and the AF+AVJA group starts at 6 months and continues to increase over the long term.

Clinical outcomes. The clinical outcome of patients with AF+AVJA, in terms of total and cardiac mortality, was comparable to that of SR patients. In contrast, patients in the AF+drugs group had higher total and cardiac mortality. Moreover, the LV reverse remodeling response in patients with AF+AVJA was comparable to that observed in the SR group, and better than that observed in the AF+drugs group. These findings are of particular relevance, given that no randomized controlled trial of CRT has addressed this patient population, although the prevalence of AF in such CRT studies approaches 25% (22,23).

Our findings lend support to early CRT observational studies, in which AVJA was associated with a better clinical outcome than rate-slowing drug therapy for AF patients (11,12,24). Two meta-analyses (25,26) have also suggested that for CRT patients with AF, AVJA is associated with a >50% reduction in all cause-mortality, compared with

Table 3 **Mortality to Rhythm and Atrioventricular Junction Ablation (Time-Dependent Cox Models Stratified by Center): Multivariable Model**

	Overall Mortality		Cardiac Mortality	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Multivariable model		<0.001		<0.001
Rhythm				
Sinus rhythm	1.00		1.00	
AF+Drugs	1.52 (1.26–1.82)	<0.001	1.57 (1.27–1.94)	<0.001
AF+AVJA	0.93 (0.74–1.67)	0.52	0.88 (0.66–1.17)	0.39
	AF+AVJA vs. AF+Drugs 0.61 (0.46–0.81), p = 0.001		AF+AVJA vs. AF+Drugs 0.56 (0.40–0.79), p = 0.001	
Harrell's C	0.71 (0.68–0.74)		0.74 (0.71–0.78)	
Royston explained variation	0.19 (0.12–0.28)		0.22 (0.13–0.33)	

Abbreviations as in Tables 1 and 2.

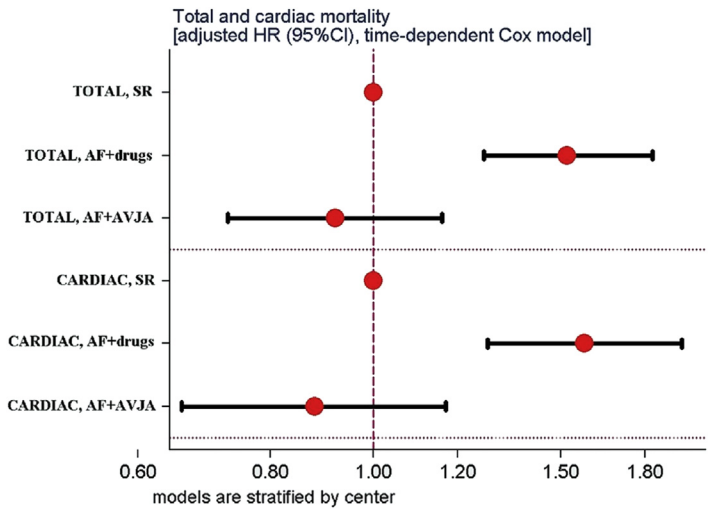

Figure 3 **Mortality After CRT**

Hazard ratio (HR) for total mortality and cardiac mortality after cardiac resynchronization therapy (CRT) comparing sinus rhythm (SR) and permanent atrial fibrillation (AF) patients, respectively, with or without atrioventricular junction ablation (AVJA). The SR group was the reference.

rate-slowing drugs. It is on this basis that both the European Society of Cardiology (ESC) and the American Heart Association guidelines (27,28) now consider patients with HF and permanent AF as candidates for CRT (Class IIa, Level of Evidence: B), provided AVJA is undertaken. According to the ESC, a lower level of evidence (Class IIb, Level of Evidence: C) pertains to CRT for patients with AF treated with rate-slowing drugs.

We have previously shown that above an arbitrary 85% cut-off of biventricular pacing capture in the context of AF, CRT is associated with a more favorable clinical outcome and LV reverse remodeling response (11,12). Koplan et al (29) subsequently found that the greatest reductions in HF hospitalization and all-cause mortality were observed above a biventricular capture cut-off of 92%. Recently, Hayes et al. (30) found an inverse relationship between mortality and percentage of biventricular pacing. The longest survival was observed above a biventricular pacing percentage of 98.5. In a recent subanalysis of the RAFT (Resynchronization-Defibrillation for

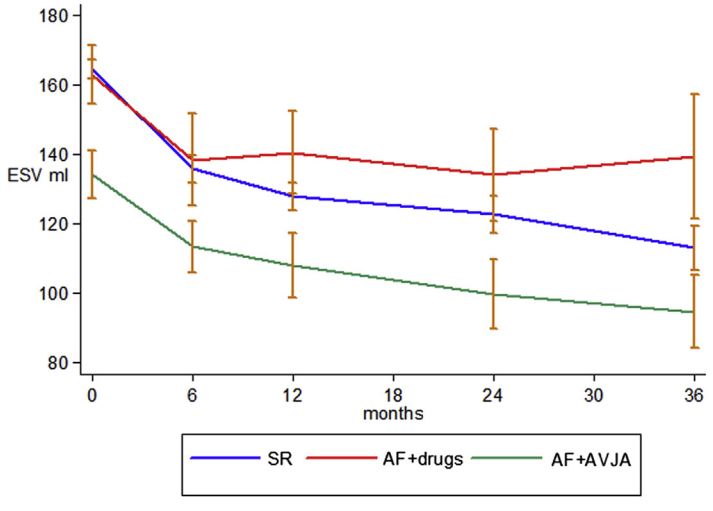

Figure 4 **Left Ventricular Reverse Remodeling After CRT**

Progression in left ventricular end-systolic volume (ESV) after cardiac resynchronization therapy (CRT) throughout the 3-year follow-up for the 3 groups: sinus rhythm (SR) **(blue line)**; atrial fibrillation (AF) plus drugs **(red line)**; and AF plus atrioventricular junction ablation (AVJA) **(green lines)**.

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Ambulatory Heart Failure) study, CRT for patients with AF was associated with a minimal benefit, compared with the implantable cardioverter-defibrillator therapy group. Importantly, however, AVJA had been performed in only 1 AF patient, and a biventricular pacing capture >95% was observed in <35% cases (31).

Our data confirm and reinforce the importance of achieving a biventricular pacing capture >95%, particularly in AF patients; in fact, the mean biventricular pacing percentage was significantly higher in the AF+AVJA group (96 ± 6%) than in the AF+drugs group (87 ± 14%; $p < 0.001$); this difference may have played an important role in the different mortality observed in these 2 groups. Together, these findings suggest that reaching 100% of effective biventricular capture is extremely important in optimizing CRT, particularly for AF patients (32).

LV reverse remodeling. The LV reverse remodeling effect of CRT in patients in SR has been shown by numerous studies (3,4) Among patients with AF, Kies et al. (33) showed that CRT led to a reduction in LV diameters. We have previously shown a better LV reverse remodeling response for AF+AVJA than for AF+drugs (11), and this is confirmed by the present study. The progression of LVESV in the 3 groups is consistent with the long-term outcome of CRT in the 3 groups. It is noteworthy that in the AF+drugs group, no further reductions in LVESV were observed after 6 months, in contrast to the continued long-term reduction observed in the AF+AVJA and SR group.

Clinical implications. Although the evidence base from randomized studies of CRT relates to patients in SR, clinicians are understandably reluctant to deny patients with AF such a life-saving treatment. That is reflected in registries (22,23) and the inclusion of AF in clinical guidelines for CRT. The present study supports this approach. Admittedly, we have not assessed fusion and pseudofusion beats in relation to outcome. In this respect, it has been shown that even at a biventricular pacing capture of 90%, assessed by means of device counters, fusion and pseudofusion beats can approach 40% (34). Even small gains in the biventricular pacing percentage might be clinically important (11,12). Although we have not addressed this in the present study, assessment of fusion and pseudofusion beats should be a fundamental part of the clinical assessment of patients with AF treated with rate-slowing drugs and CRT.

Study limitations. The observational nature of this study is its main limitation. The absence of a control group did not allow us to determine the proportional benefit of CRT in the study groups. In particular, we could not ascertain whether the patients with the worst outcome, namely, the AF+drugs group, still derived a benefit from CRT. In addition, the adjudication of the cause of death performed locally could have been responsible for a few of the observed differences in cause-specific mortality. Our inability to ascertain the cause of death for a proportion of patients is another limitation. That, however, does not affect our principal findings with respect to total mortality.

Conclusions

This large, prospective multicenter study of "real-world" practice shows that the clinical outcome after CRT for patients with AF treated with AVJA is similar to that observed for patients in SR. In contrast, patients in AF treated with rate-slowing drugs have a worse outcome. Further randomized studies on the role of AVJA in patients with AF undergoing CRT are warranted.

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Key Words: ablation of atrioventricular junction ■ atrial fibrillation ■ cardiac resynchronization therapy ■ heart failure.

APPENDIX

For a complete list of the European centers participating in the study, please see the online version of this article.