Implantable cardioverter defibrillator treatment : benefits and pitfalls in the currently indicated population

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Chapter 5

Clinical Importance of New-onset Atrial Fibrillation after Cardiac Resynchronization Therapy

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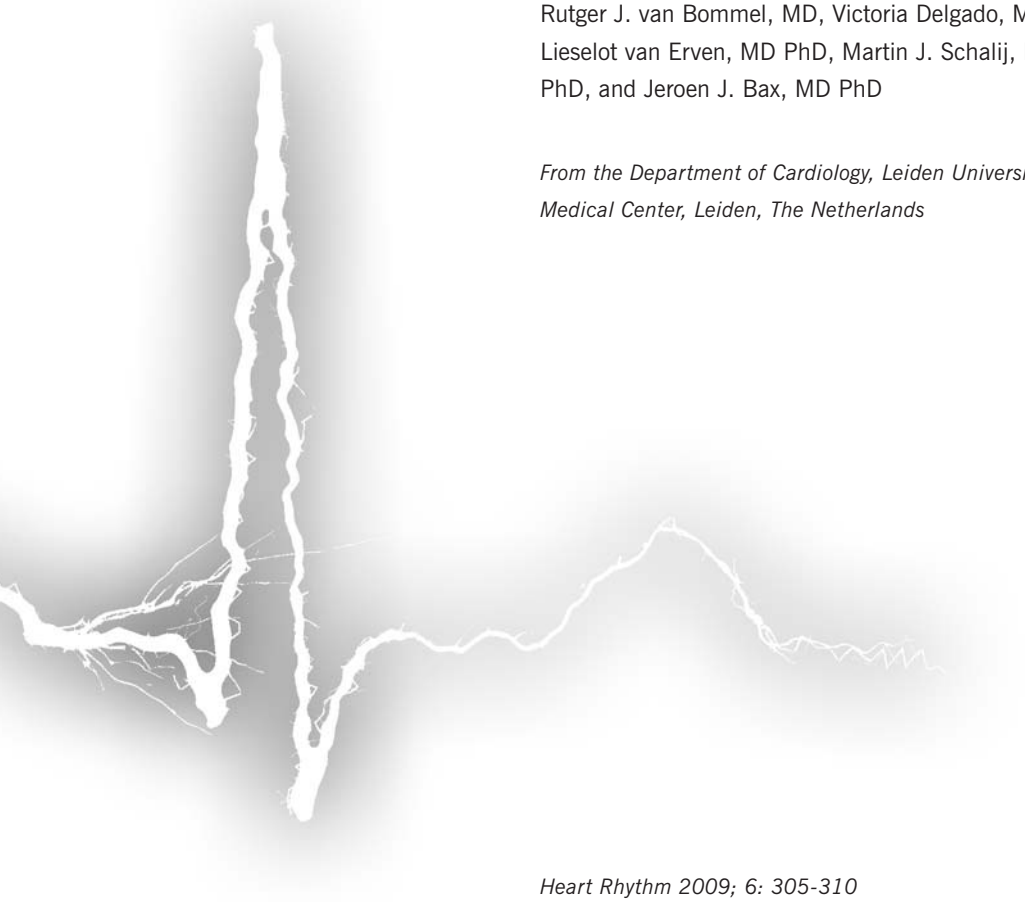

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Abstract

Background: Data on the occurrence and implications of new-onset atrial fibrillation (AF) following cardiac resynchronization therapy (CRT) are scarce. We studied the incidence of new onset AF in CRT-defibrillator (CRT-D) recipients. Furthermore, the influence of new-onset AF on echocardiographic response to CRT and the rate of adverse events were evaluated.

Objective: This study assessed the incidence and implications of new-onset atrial fibrillation following cardiac resynchronization therapy.

Methods: The study population consisted of 223 consecutive patients without a history of AF. New-onset AF was defined as atrial high-rate episodes >180 bpm during >10 minutes/day as detected by the device. Echocardiography was performed at baseline and after 6 months of biventricular pacing. Long-term events included ICD therapy for ventricular arrhythmias, hospitalization for heart failure and all-cause mortality.

Results: Fifty-five patients (25%) developed new-onset AF during a mean follow up of 32±16 months. When compared to the patients who maintained sinus rhythm (SR) during follow-up, patients developing AF showed less left ventricular (LV) reverse remodeling (ΔLV end systolic volume 37±53 vs. 19±37 ml, $p<0.05$) and less improvement in LV function (ΔLV ejection fraction 6.7±8.9 vs. 3.5±10.3%, $p<0.05$) . Importantly, patients developing AF experienced more appropriate ICD shocks for ventricular arrhythmias, more inappropriate shocks and more hospitalizations for heart failure.

Conclusion: Recipients of CRT-D who develop new-onset AF show less echocardiographic response to CRT and more cardiac adverse events during long-term follow-up.

Introduction

Cardiac resynchronization therapy (CRT) is a well established therapy in selected patients with heart failure and cardiac dyssynchrony. The beneficial effects include improvement in heart failure symptoms and exercise capacity[1-3] and also improvement in echocardiographic parameters such as left ventricular (LV) function, left atrial (LA) function and mitral regurgitation (MR).[4-7]

However, the impact of CRT on new-onset atrial fibrillation (AF) remains controversial.[8-11] Post-hoc analysis of the CARE-HF trial suggested that the CRT had no favorable impact on the incidence of AF when compared to medical therapy alone.[10]

Still, since AF and heart failure often co-exist and are associated with worse clinical outcome,[12] it is important to evaluate the incidence and implications of new-onset AF in CRT-recipients. In addition, asymptomatic AF episodes, which appear to have important prognostic implications as reported in a sub-study of the MOST trial,[13] can be monitored using device-based diagnostics.

Therefore, the aim of the present study was to evaluate the incidence of new-onset AF after CRT using device-based diagnostics. In addition, clinical and echocardiographic parameters, including LA and LV function, were assessed during follow-up and compared between patients developing AF and patients maintaining sinus rhythm (SR). Importantly, long-term clinical outcome is addressed in both groups.

Methods

Patients and study protocol

From January 2000 to July 2005, all patients eligible for cardiac resynchronization with defibrillator therapy (CRT-D) without a history of AF were included in this single-center retrospective study. A history of AF was defined as one or more episodes of AF in the two years preceding implantation, lasting at least 30 seconds as verified by electrocardiogram.[14] Eligibility for CRT-D was based on the standard guidelines and included advanced heart failure (New York Heart Association [NYHA] class III or IV), depressed LV function (LV ejection fraction [LVEF] $<35\%$) and wide QRS complex (>120 ms).[15-17] The study protocol was as follows: before and 6 months after CRT-D implantation, all patients underwent clinical and echocardiographic evaluation. Occurrence of atrial and ventricular arrhythmias after device implantation was assessed, as well as hospitalization and survival during long-term follow-up.

Clinical evaluation

Clinical status was assessed routinely at baseline and 6 months follow-up, including assessment of NYHA functional class, quality of life (QoL, using the Minnesota Living with Heart Failure questionnaire),[18] and evaluation of exercise capacity using the 6-minute walking test (6-MWT).[19]

Echocardiographic evaluation

All patients underwent routine echocardiography in the left lateral decubitus position before and 6 months after CRT-D device implantation. Studies were performed using a commercially available echocardiographic system (VIVID 7, General Electric Vingmed Ultrasound, Milwaukee, USA). Images were obtained using a 3.5 MHz transducer, at a depth of 16 cm in the parasternal (long- and short-axis) and apical (2- and 4-chamber images) views. Standard 2D and color Doppler data, triggered to the QRS complex, were saved in cineloop format. A minimum of 3 consecutive beats were recorded from each view and the images were digitally stored for off-line analysis (EchoPac 6.0.1, General Electric Vingmed Ultrasound, Milwaukee, USA).

LV end-diastolic volumes (LVEDV), LV end-systolic volumes (LVESV) and LVEF were measured from the apical 2- and 4-chamber images, using the modified biplane Simpson's rule.[20] The LA volume was calculated using the ellipsoid model with the measured LA diameters in parasternal long axis (LA PLAX) and the LA long-axis (LA LAX) and short-axis (LA SAX) in the apical 4-chamber view.[21] All LA volumes were indexed by body surface area.[22] LV diastolic function was estimated using the ratio of early transmitral flow velocity (E) over early diastolic septal mitral annulus velocity (E') and categorization into normal filling pattern, abnormal relaxation filling pattern = I, pseudonormal filling pattern = II, and restrictive filling pattern = III.[23, 24] For quantification of MR, the apical 4-chamber images were used. MR was characterized as: none, mild = 1+ (jet area/LA area <10%), moderate = 2+ (jet area/LA area 10% to 20%), moderate-severe = 3+ (jet area/LA area 20% to 45%), and severe = 4+ (jet area/LA area >45%).[25] Baseline LV dyssynchrony was assessed using tissue Doppler imaging. The sample volume was placed in the LV basal portions of the anterior, inferior, septal, and lateral walls (using the apical 2- and 4-chamber views) and, per region, the time interval between the onset of the QRS complex and the peak systolic velocity was derived. LV dyssynchrony was defined as the maximum delay between peak systolic velocities among the four walls within the LV (most frequently observed between the interventricular septum and the lateral wall).[26] Based on previous observations, a delay of ≥65 ms reflects substantial LV dyssynchrony.[27]

CRT-D interrogation/long-term follow-up

During follow-up device interrogation was scheduled every 3-6 months. All printouts were checked for new-onset AF, appropriate and inappropriate shocks. New-onset AF after

implantation was defined as atrial high-rate episodes (≥180 bpm) lasting at least 10 minutes, determined with device based diagnostics.[10] Shocks were classified as appropriate when they occurred in response to ventricular tachycardia or ventricular fibrillation and as inappropriate when triggered by sinus or supraventricular tachycardia, T-wave oversensing, or electrode dysfunction.

In addition, long-term follow-up included all hospitalizations for cardiac cause (unstable angina, decompensated heart failure or symptomatic ventricular arrhythmias), and all-cause mortality.

CRT-D implantation

A coronary sinus venogram was obtained using a balloon catheter, followed by the insertion of the LV pacing lead into 1 of the posterolateral veins through an 8-F guiding catheter (Easytrak 4512-80, Guidant Corp., St. Paul, Minnesota; or Attain-SD 4189, Medtronic Inc., Minneapolis, Minnesota). The right atrial and ventricular (pacing and shock) leads were positioned conventionally. All leads were connected to a dual-chamber CRT-D device (Contak CD or Renewal, Guidant Corporation; Insync Sentry, Insync-III or Marquis, Medtronic Inc; Epic, St Jude Medical). Procedural success was accomplished when pulse generator and the 3 leads were positioned without complications.

Defibrillators were programmed as follows: ventricular arrhythmia faster than 150 bpm was monitored by the device without consequent defibrillator therapy. Ventricular arrhythmias faster than 188 bpm were initially attempted to be terminated with two bursts of anti tachycardia pacing and, after continuation of the arrhythmia, with defibrillator shocks. In the case of a ventricular arrhythmia faster than 210 bpm, device shocks were the initial therapy. Furthermore, atrial arrhythmia detection was set to >170 bpm with SVT discriminators enabled. Settings were adapted, only when clinically indicated (i.e. hemodynamic well tolerated ventricular tachycardia at high rate; ventricular tachycardia in the monitor zone).

Statistical analysis

Continuous data are expressed as mean ± SD; dichotomous data are presented as numbers and percentages. Comparison of data was performed with the Student's *t* test for paired and unpaired data and Chi-square tests with Yates correction when appropriate. Non-normally distributed data within patient groups (NYHA, MR and grade of LV diastolic function) were compared by the use of the Wilcoxon signed-rank test. Differences in event rates (hospitalizations, appropriate and inappropriate shocks and death) over time were analyzed by method of Kaplan-Meier and log-rank test. For all tests, a p-value <0.05 was considered significant.

Results

Baseline characteristics

A total of 320 consecutive heart failure patients who received a CRT-D device were screened with 97 patients having a history of AF. The remaining 223 patients (171 men, mean age 65±11 years) without a history of AF were included in the current study. The baseline characteristics are summarized in Table 1. Before implantation, mean NYHA functional class was 3.0±0.5 and QRS duration was 161±31 ms. Patients had severe LV systolic dysfunction (LVEF 23±7%) with LV dilatation (LVEDV 246±89 ml and LVESV 190±77 ml). Medication included diuretics in 90%, ACE-inhibitors in 85% and β-blockers in 65%.

Patients with versus without new-onset AF

During follow-up (33±16 months), new-onset AF was documented in 55 of 223 patients (25%). The first episode of AF occurred 13±11 months (range 0 to 41 months) after CRT-D implantation. In patients developing AF during follow-up, the average burden of AF since CRT-D implantation was 6.7%. The percentage of biventricular pacing during follow-up did not differ significantly between both groups (biventricular pacing in AF group 97±6% vs. no AF group 96±4%, p=0.7).Baseline characteristics between the patients developing AF (AF group) and the patients remaining in sinus rhythm (SR group) were comparable, except for a larger LA volume index in the AF group (25±10 vs. 30±14 ml/m^2, p=0.011), caused mainly by longitudinal LA enlargement (LA LAX 49±7 vs. 52±9 mm, p=0.038) (see Table 2).

Six-month follow-up clinical evaluation: Patients with versus without new-onset AF

After 6 months of follow-up, patients in the SR group showed significant improvement in clinical parameters; mean NYHA class improved from 3.0±0.4 to 2.0±0.6, QoL score reduced from 39±16 to 22±16 and exercise tolerance improved as demonstrated by an increase in 6-MWT from 303±120 to 404±138 meters (p<0.001 for all). Similar clinical improvements were noticed in the patients developing new-onset AF; mean NYHA class improved from 2.9±0.5 to 2.1±0.8, QoL score reduced from 34±17 to 22±20 and exercise tolerance improved as demonstrated by an increase in 6-MWT from 308±133 to 391±142 meters (p<0.001 for all). As demonstrated in Table 3 the magnitude of improvement in clinical parameters was not significantly different in both groups. However, a trend towards a larger improvement in QoL could be seen in the SR group (Δ QoL SR 17±17 vs. AF 11±16, p=0.065).

Table 1. Baseline characteristic

	All patients (n=223)
Clinical parameters	
Male gender	171 (77%)
Age (yrs)	65±11
Ischemic etiology	138 (62%)
Renal clearance (ml/min)*	68±31
NYHA class (II / III / IV)	26 / 177 / 20
QoL score	38±17
6-MWT (m)	305±123
QRS-duration (ms)	161±31
Echocardiographic parameters	
LVEF (%)	23±7
LVEDV (ml)	246±89
LVESV (ml)	190±77
MR (none / 1 / 2 / 3 / 4)	42 / 65 / 68 / 34 / 14
LV dyssynchrony (ms)	84±54
Medication	
Diuretics	201 (90%)
ACE inhibitors	189 (85%)
Beta-blockers	145 (65%)
Cardiovascular history	
Previous infarction	107 (48%)
Previous PCI	46 (21%)
Previous CABG	47 (21%)
Previous valve surgery	20 (9%)
Previous device	
Pacemaker	17 (8%)
ICD	33 (15%)
Co-morbidity	
Diabetes	45 (20%)
Stroke/TIA	23 (10%)
Peripheral vascular disease	22 (10%)
COPD	28 (13%)

* Renal clearance was determined with the formula of Cockroft-Gault.
6-MWT = six-minute walking test; ACE = angiotensin-converting enzyme; CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; ICD = implantable cardioverter defibrillator; LV = left ventricular; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; MR = mitral regurgitation; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; QoL = quality of life; TIA = transient ischemic attack.

Six-month follow-up echocardiographic evaluation: Patients with versus without new-onset AF

Regarding echocardiographic changes after 6 months of follow-up, the SR group showed significant improvements in LV volumes and function (LVEDV at baseline 246±86 vs. at 6

Table 2. Differences in baseline characteristics between patients remaining in sinus rhythm after device implant (SR) and patients developing atrial fibrillation during follow-up (AF).

	SR	AF	p-value
Variables	(n = 168)	(n = 55)	
Men	131 (78%)	40 (73%)	0.4
Age (yrs)	65±11	65±10	0.9
Ischemic etiology	101 (60%)	37 (67%)	0.3
NYHA class (II / III / IV)	18 / 135 / 15	9 / 42 / 4	0.4
QRS-duration (ms)	161±30	161±32	1.0
LVEF (%)	23±7	24±7	0.5
LVEDV (ml)	246±86	246±99	1.0
LVESV (ml)	190±74	191±86	1.0
LA PLAX (mm)	47±7	49±9	0.1
LA LAX (mm)	49±7	52±9	0.038
LA SAX (mm)	39±7	41±8	0.3
LA Volume Index (ml/m^2)	25±10	30±14	0.011
LV diastolic function (normal / I / II / III)	23 / 69 / 47 / 29	11 / 22 / 9 / 13	0.7
E/E'	17±10	20±15	0.2
MR (none / 1 / 2 / 3 / 4)	29 / 45 / 56 / 27 / 11	13 / 20 / 12 / 7 / 3	0.1
LV dyssynchrony (ms)	88±53	72±54	0.1

LA = left atrial; LAX = long axis; LV = left ventricular; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; MR = mitral regurgitation; NYHA = New York Heart Association; SAX = short axis.

months follow-up 212±77 ml, LVESV 190±74 vs. 151±68 ml, LVEF 23±7 vs. 30±9%, p<0.001 for all). In addition, a modest decrease in LA PLAX was noted from 47±7 to 45±8 mm (p<0.05). The other LA parameters remained unchanged. Furthermore, diastolic function improved (mean grade 1.5±0.9 vs. 1.2±0.8, p=0.007, Figure 1) and mitral regurgitation decreased (mean grade 1.7±1.1 vs. 1.4±1.1, p<0.005).

In the AF group, significant LV reverse remodeling was noted as well; LVEDV decreased from 246±99 to 221±91 ml, LVESV from 191±86 to 168±85 ml and LVEF increased from 24±7 to 27±10% (p<0.05 for all). No changes were observed in LA dimensions. Furthermore, MR did not change significantly (mean grade 1.4±1.2 vs. 1.2±1.1, p=0.2) and diastolic function showed a trend towards worsening in function (mean grade 1.4±1.1 vs. 1.7±0.9, p=0.1, Figure 1).

Thus, at 6 months follow-up both groups showed significant improvements in echocardiographic parameters regarding LV function. However, the magnitude of LV reverse remodeling and improvement in LV function was significantly less in the AF-group (Table 3). Decrease in LVESV was 37±53 ml for the SR group and 19±37 ml for the AF group (p=0.024). Systolic function showed less improvement in the AF group (ΔLVEF SR 6.7±8.9 vs. AF 3.5±10.3 %, p=0.034).

Table 3. Clinical and echocardiographic changes in LV systolic function after 6 months of CRT-D in patients remaining in sinus rhythm (SR) as compared to patients with new-onset atrial fibrillation (AF) after implantation.

	SR	AF	p-value
Variables	(n = 168)	(n = 55)	
Δ NYHA class	-1.0±0.6	-0.8±0.8	0.3
Δ QoL score	-17±17	-11±16	0.065
Δ 6-MWT (m)	+105±106	+90±118	0.4
Δ LVEF (%)	+6.7±8.9	+3.5±10.3	0.034
Δ LVEDV (ml)	-31±58	-21±43	0.2
Δ LVESV (ml)	-37±53	-19±37	0.024

Abbreviations as in Table 2.

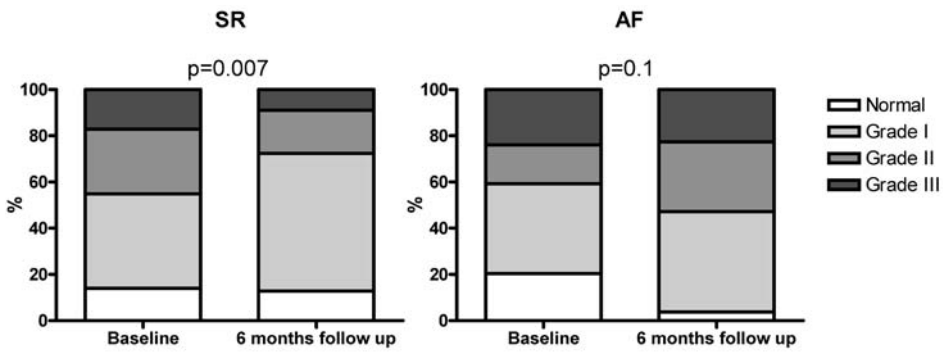

Figure 1. Changes in LV diastolic function at baseline and after 6 months of follow-up in patients with sinus rhythm (SR) and patients with new-onset atrial fibrillation (AF) after CRT-D implantation.

Long-term outcome

During follow-up, 41 patients (18%) received appropriate shocks and 27 patients (12%) received inappropriate shocks. Patients developing AF experienced significantly more appropriate shocks (27% vs. 16%, $p<0.050$), as well as significantly more inappropriate shocks (31% vs. 6%, $p<0.001$, Figure 2).

In addition, 52 patients (23%) died and 50 patients (22%) were hospitalized for cardiac causes. Patients in the AF group accounted for more hospitalizations as compared to the SR group (36% vs. 18%, $p<0.005$). However, survival was not significantly different between the 2 groups (18% vs. 25%, $p=0.3$).

Importantly, patients developing new-onset AF showed worse event-free (hospitalizations, appropriate and inappropriate shocks) survival as compared to the SR group; 1-year event-free survival was 65% and 76% in respectively AF and SR patients (log-rank $p=0.021$) (Figure 3).

Further stratification by AF burden did not result in a better estimation of the risk for adverse events during follow-up.

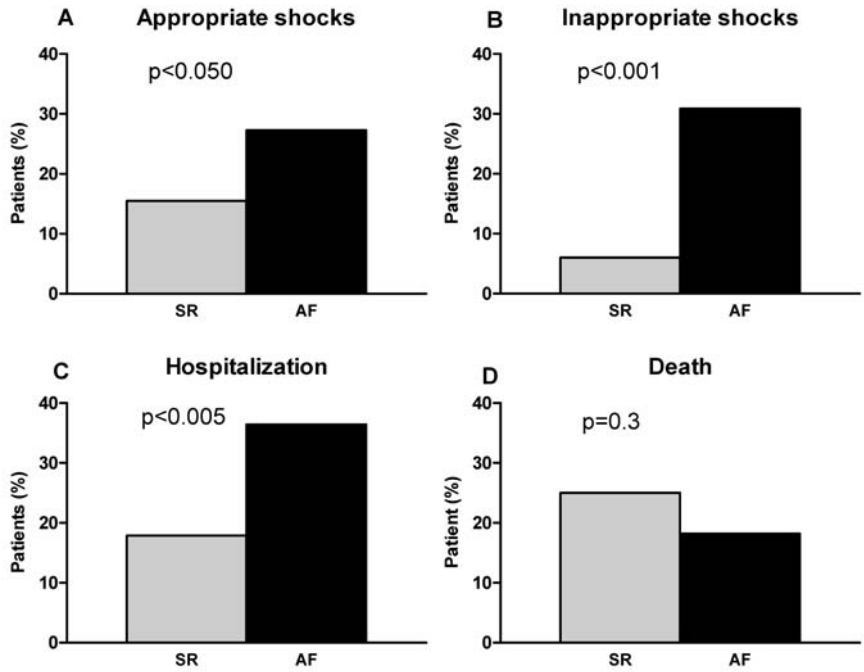

Figure 2. Occurrence of events (panel A appropriate shocks, panel B inappropriate shocks, panel C hospitalization for cardiac causes and panel D death) during long-term follow-up in patients with sinus rhythm (SR) as compared to patients with new-onset atrial fibrillation (AF) after device implantation.

Discussion

The findings in the current study can be summarized as follows: 1) During long-term follow-up, 25% of CRT-D implanted patients without a history of AF, developed new-onset AF; 2) Patients developing AF showed similar clinical improvements after 6 months of biventricular pacing as patients remaining in SR; 3) However, regarding echocardiographic parameters, the AF patients revealed less LV reverse remodeling and less improvement in LV function without improvement in MR, LA volumes and diastolic function as compared to SR patients; 4) Patients with new-onset AF showed worse event-free survival after long-term CRT-D.

Incidence of new-onset AF after CRT-D

Data on the incidence of new-onset AF after CRT-D device implantation are scarce. Post-hoc analysis of the CARE-HF trial reported an incidence of new-onset AF after CRT (mean follow-up of 29 months) of 16% using frequent ECG recordings. Using device based diagnostics, the number of patients with new-onset AF was even higher (23%). However, of all implanted patients, 19% had a history of AF, which was strongly associated with

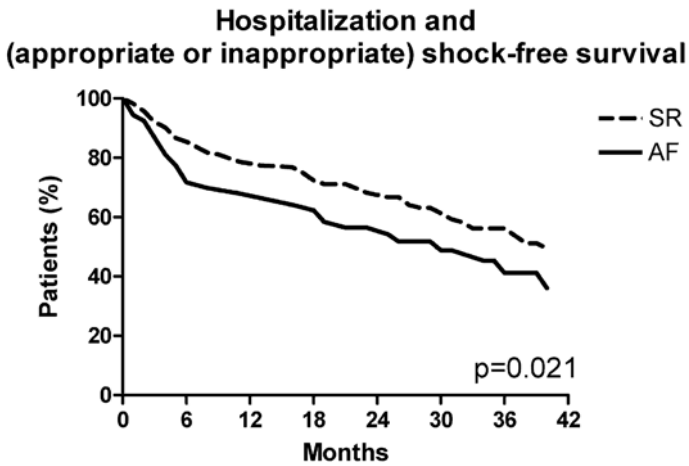

Figure 3. Event-free survival curves for patients with sinus rhythm (SR) and new-onset atrial fibrillation (AF) after device implantation.

the development of AF during follow-up. Unfortunately, no data were presented on the incidence of new-onset AF in the group without episodes of AF prior to CRT implantation.[4, 10] Another study, by Hügl et al reported that one-third of the patients developed AF (defined as episode >30 sec using devise based diagnostics) within the first few months after implantation. Similarly, 40% of the patients had a history of AF.[11]

The novelty of the current study is the reporting on the incidence of new-onset AF after CRT-D in patients without a history of AF. Episodes of AF lasting more than 10 minutes were documented by device-based diagnostics in 55 of 223 (25%) of CRT-D recipients.

New-onset AF and response after CRT-D

Previous large trials have shown a beneficial effect of CRT on clinical and echocardiographic parameters in SR patients with severe heart failure, depressed LVEF and wide QRS complex.[1-3] In addition, a positive response has been reported in patients with paroxysmal or persistent AF.[10, 28-30] In contrast, limited data are available on the echocardiographic response of patients without a history of AF who develop AF after CRT-D implantation. The findings in the current study demonstrated significantly lesser reverse LV remodeling with a lesser increase in LVEF after CRT-D in patients who developed AF as compared to the patients who remained in SR. Furthermore, the AF-group showed no improvement in MR and a trend towards worsening of LV diastolic function.

During long-term follow-up, patients in the AF-group had significantly more adverse cardiac events, including cardiac hospitalizations, appropriate shocks for ventricular arrhythmias and inappropriate shocks. These findings are in line with previous studies

showing an increase in hospitalizations,[12] an increase in ventricular arrhythmias causing defibrillator therapy,[31, 32] and more inappropriate shocks in patients with AF.[33]

Clinical implications

LA size is a powerful predictor of adverse clinical events including mortality in patients with cardiovascular disease.[34, 35] Indeed, patients developing AF showed significantly larger LA volumes and larger LA LAX at baseline. In addition, reduction in LA diameter was only noted in patients with SR. Consequently, one may assume that in patients with severe heart failure, small LA at baseline or an improvement in LA diameter may be important for maintaining SR after device implantation. It remains hard however, to differentiate between cause and effect; less response to biventricular pacing and the concomitant less favorable echocardiographic changes, may predispose for future development of AF. On the other hand, the development of AF during follow-up may be a marker of an initially worse cardiac status, less capable to show significant response to biventricular pacing.

The present findings extend the results of a sub-study of the MOST trial, showing that (asymptomatic) atrial tachyarrhythmias as detected by the device are an independently predictive of death, stroke or symptomatic AF.[13] An incidence of new-onset AF of 25% was demonstrated using device-based diagnostics in patients without a history of AF. Importantly, these patients exhibited less echocardiographic benefit from biventricular pacing with more adverse events during follow-up. These results emphasize the clinical relevance of (asymptomatic) atrial tachyarrhythmias, as detected by the device. Furthermore, the findings may warrant a more aggressive strategy to maintain SR.

Study limitations

The definition of AF was arbitrarily defined as episodes of atrial high rate (>180 bpm) lasting longer than 10 minutes, similar to a large sub-study of the CARE-HF trial reported by Hoppe and coworkers.[10] Other studies have used a variety of different definitions for AF, which makes comparison with the current study difficult. Furthermore, some of the patients might have had unrecognized AF prior to implantation causing them to be assumed without a history of AF and consequently to be erroneously included in the study. Finally, asymptomatic or symptomatic episodes of AF were not differentiated; it may be of potential interest to evaluate in future studies whether asymptomatic and symptomatic AF episodes have a different prognostic value.

Conclusion

A substantial proportion of patients undergoing CRT-D developed new-onset AF. These patients showed less echocardiographic improvement at mid-term follow-up which was associated with less favorable outcome during long-term follow-up.

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