Optimizing therapy in patients with atrial fibrillation and heart failure
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Abstract

Aims
To study the outcome of patients with atrial fibrillation (AF) treated with cardiac resynchronization therapy (CRT) in a tertiary referral center as data on CRT in these patients are sparse.

Methods
Response was defined as left ventricular end-systolic volume reduction ≥ 15% at 6-months follow-up. Rate control was strictly instituted in order to obtain 100% biventricular pacing (assessed with exercise testing). In case of failure, atrio-ventricular nodal (AVN) ablation was performed.

Results
Of 491 patients, 200 (41%) had a history of AF at baseline, 50 (10%) developed new-onset AF during follow-up. The other 241 (49%) patients never had AF during follow-up. Patients with AF were older and left atrial volume was larger (50 versus 38ml/m²). Twenty-seven patients (12 with AF at baseline) died before response assessment, 15 (56%) due to progression of heart failure. AVN ablation was eventually performed in a total of 28 (11%) AF patients. Echocardiographic CRT response rate was comparable in AF versus sinus rhythm patients (53% versus 56%, p=0.5). After a mean follow-up of 1.9±1.0 years cardiovascular mortality or heart failure hospitalization was comparable between patients with AF and sinus rhythm. Early new-onset AF (< 6 months after CRT implantation) was associated with worse prognosis (p=0.006).

Conclusion
Response and cardiovascular morbidity and mortality were comparable in patients with AF and with continuous sinus rhythm. New-onset AF occurring early after CRT implantation, however, was associated with impaired prognosis.
**Introduction**

Heart failure and atrial fibrillation (AF) are common cardiovascular conditions and frequently occur together.(1) The prevalence of AF in heart failure varies from 10-15% in New York Heart Association (NYHA) II to 50% in NYHA IV.(2) Cardiac resynchronization therapy (CRT) is an established non-pharmacological therapy in patients with symptomatic heart failure and intraventricular conduction delay, despite optimal medication. It improves symptoms and quality of life and reduces hospitalizations for heart failure and risk of death.(3,4)

A prerequisite for optimal benefit of CRT is continuous biventricular pacing. AF may lead to high and irregular ventricular rates, and as a consequence the percentage of biventricular pacing may decrease.(5-10) This has been the main reason for excluding AF in large randomized controlled trials. (3,4) There have been several retrospective cohort studies and substudies of large trials that demonstrate beneficial effects of CRT in patients with either a history of AF or permanent AF, but often atrioventricular node (AVN) ablation was required to ensure continuous biventricular pacing. (3,6,9,11-16) Development of new-onset of AF or recurrences of AF in heart failure patients treated with CRT is also common and is associated with impaired response and cardiovascular outcome.(17-19)

We sought to investigate the clinical and prognostic impact of an history of AF, new-onset AF, and AF burden in heart failure patients treated with a CRT.

**Methods**

Patient population and study protocol

Consecutive patients who received a CRT device in the University Medical Center Groningen from January 2001 to December 2012 were identified in this single-center retrospective observational study (Figure 1). Eligibility criteria for CRT implantation were based on the standard guidelines.(3) The presence of sinus rhythm was not a pre-requisite for CRT implantation. Our standard CRT protocol has been described before.(7,17,20) At baseline and 6-month follow-up patient history, physical examination, treadmill cardiopulmonary exercise testing, 12-lead electrocardiogram, and transthoracic echocardiography were performed. All patients were seen according to standard follow-up protocol at the outpatient clinic for regular follow-up and for CRT interrogation at baseline and 6-monthly thereafter. All patients underwent echocardiographic atrioventricular delay optimization at 2-6 weeks post-implantation (AHM). The percentage biventricular pacing was assessed by monitoring device counters, and all patients performed a treadmill cardiopulmonary exercise tests to ensure biventricular pacing during exercise i.e., during higher heart rates. AF was monitored during follow-up and when encountered our protocol emphasizes aggressive rhythm or rate control strategy. Rhythm control includes institution of amiodarone and multiple electrical cardioversions if required. When rhythm control was no longer an option, AF was accepted and rate control therapy was instituted aiming for pharmacological strict rate control assessed with exercise testing to confirm continuous biventricular pacing. AVN ablation was only performed when pharmacological rate control therapy did not allow continuous biventricular pacing.
Echocardiographic evaluation
Transthoracic echocardiography was performed at baseline and after six months of follow-up. Images were obtained from the parasternal (long- and short-axis) and apical (two- and four chamber) views. Atrial dimensions, ventricular dimensions, septal thickness, and posterior wall thickness were assessed by standard measurements. Left ventricular end-diastolic (LVEDV) and end-systolic volumes (LVESV) were measured with the modified biplane Simpson method using the apical two- and four-chamber views performed by one independent investigator unaware (BAM) of the clinical response of the patient. Left ventricular ejection fraction (LVEF) was calculated from LVEDV and LVESV.

Definitions
AF or atrial tachyarrhythmias were defined as any episode lasting at least 30 seconds with an atrial rate > 180 beats per minute as verified by electrocardiogram, Holter recording, or device interrogation. Documented AF before implantation was considered as history of AF. New-onset AF or atrial tachyarrhythmias were defined as atrial tachyarrhythmias occurring during follow-up in patients without a history of AF. AF burden was defined as the time being in AF during follow-up as assessed by device counters. CRT response was defined as a reduction in left ventricular end-systolic volume of 15% or more at six months of follow up. Early new-onset AF was defined as AF occurring within first six months after CRT implantation, late new-onset AF occurred after the first six months. Biventricular pacing was based on device counters. Cardiovascular mortality or heart failure hospitalization during long-term follow-up (beyond six months) was a secondary outcome of the study. Appropriate and inappropriate ICD shocks were also a secondary endpoint. Appropriate shocks were defined as shocks delivered by the ICD to terminate ventricular tachycardia or ventricular fibrillation documented by stored ICD electrograms. Inappropriate ICD shocks were defined as shocks that were not delivered for ventricular arrhythmias (eg, during AF with a high ventricular response) or because of oversensing as a result of lead problems (eg, lead fractures and lead dislocation or T wave oversensing). All shocks were evaluated by experienced electrophysiologists (ICVG and AHM) for appropriateness.

Statistical analysis
Baseline descriptive statistics are presented as mean±standard deviation or median (range) for continuous variables and counts with percentages for categorical variables. Differences between patient characteristics were evaluated by the Student-t-test, Mann-Whitney-U test, Chi-square test, and Fisher’s exact test depending on normality and type of the data. To compare data within patient groups, paired Student’s t test was used for normally distributed data and Wilcoxon signed rank test for not normally distributed data. Differences among groups with respect to several outcome measures were evaluated with a chi-squared test for linear trend. The first occurrence of the outcome was assessed by Kaplan-Meier curves. Logistic regression was used to assess the association between co-variates and response. A stepwise approach based on z-score was used to include variates into the final model. All tests of significance were two-tailed, with p-values of <0.05 assumed to indicate significance.

Results
Baseline characteristics
A total of 491 patients were included in this analysis, 200 (41%) had a history of AF at baseline, 50 (10%) developed new-onset AF during follow-up, and 241 (49%) never had AF (Figure 1, Table 1). Those with ever AF were older. Ischemic heart disease was equally common. Peak VO\textsubscript{2} was lower in those with ever AF compared to patients with continuous sinus rhythm. NT-proBNP levels were higher in patients with ever AF (2019 versus 1154 pg/ml, p<0.001). There were no differences between patients with early or late new-onset AF (data not shown). In the first six months AF burden was for most patients either low (<10% AF burden, 42% of AF patients) or high (> 90% AF burden, 41% of AF patients, Figure 2).

Echocardiographic response
Twenty-seven patients (12 patients with AF at baseline) died before response assessment, 17 (63.4%) due to progression of HF, and 10 due to non-cardiovascular causes. Of the remaining 464 patients response was assessed (Table 2). In patients with AF and continuous sinus rhythm, left ventricular end systolic volume and left ventricular end diastolic volume reduced at six
months, and left ventricular ejection fraction improved. Response with >15% decrease in LVESV at six months was comparable for patients with AF versus patients with continuous sinus rhythm, p=0.5. In patients with new-onset AF comparable percentages of response were attained. Figure 3 shows the percentages of response amongst several categories of AF and percentage of AVN ablation in each group. Mean biventricular pacing in the first six months between the history of AF, new-onset AF and continuous sinus rhythm were 90±16, 93±15 and 96±11, respectively (P<0.001)

**Determinants of echocardiographic response**

A larger left ventricular end systolic volume at baseline was associated with a higher response rate whereas a larger left atrial size at baseline and ischamic cardiomyopathy were associated with a lower response rate (Table 4). Neither ever AF, new-onset AF nor AF burden were associated with response.

**Outcome**

After mean follow-up of 1.9±1.0 years, cardiovascular mortality (35 [14.0%] versus 25 [10.4%]) and heart failure hospitalizations (18 [7.2%] versus 24 [9.6%]) were comparable between patients with AF and those with continuous sinus rhythm (P=0.13). Non-Left bundle branch block – no. (%) 41 (16.4) 23 (9.5) P-value 0.001 Ventricular paced – no. (%) 60 (24.0) 18 (7.5) P-value <0.001 Beta-blocker (including sotalol) 209 (83.6) 214 (88.8) P-value 0.096 ACEI 189 (75.6) 181 (75.1) P-value 0.891 ARB 49 (19.6) 48 (19.9) P-value 0.930 Diuretic 218 (87.2) 200 (83.0) P-value <0.001 Digoxin 56 (22.4) 21 (8.7) P-value <0.001 Amiodaron 54 (21.6) 21 (8.7) P-value <0.001 Statin 138 (55.2) 132 (52.3) P-value 0.517 Nitrate 34 (13.6) 38 (15.6) P-value 0.497 Oral anticoagulation 214 (85.6) 147 (61.0) P-value <0.001 Aspirin 54 (21.6) 79 (32.8) P-value 0.005 Echocardiographic parameters Left atrial size, parasternal – Mean±SD – mm 50±9 45±7 P-value <0.001 Left atrial size, length – Mean±SD – mm 52±8 69±10 P-value <0.001 Left atrial size, width – Mean±SD – mm 47±8 69±10 P-value <0.001 Left atrial volume index – Mean±SD – mL/m2 50±23 (207) 38±13 (212) P-value <0.001 Right atrial size, length – Mean±SD – mm 62±10 54±8 P-value <0.001 Right atrial size, width – Mean±SD – mm 49±8 43±7 P-value <0.001 Septal thickness – Mean±SD – mm 9±2 9±2 P-value 0.843 Posterior wall thickness – Mean±SD – mm 9±2 9±1 P-value 0.555 LV end-diastolic volume – Mean±SD – mL 224±93 235±100 P-value 0.202 LV end-systolic volume – Mean±SD – mL 171±77 179±84 P-value 0.236 Left ventricular ejection fraction – Mean±SD – % 25±9 24±9 P-value 0.157 Mitral valve regurgitation, no. (%) 81 (32.4) 54 (22.4) P-value 0.013 Tricuspid valve regurgitation, no. (%) 36 (14.4) 15 (6.2) P-value 0.003 TAPSE – mm 16±4.6 20±4.6 P-value <0.001

**Laboratory values**

Creatinine – µmol/l – Median (IQR) 119 (88-137) 108 (81-122) P-value 0.001 NT-proBNP – pg/ml – Median (IQR) 5891 (900-3607) 5613 (461-2640) P-value <0.001

* Plus–minus values are means±SD. SD = Standard deviation; ACEI = angiotensin converting enzyme inhibitor; ARB = Angiotensin receptor blockers; IQR = interquartile range; LV=left ventricular; NYHA= New York Heart Association; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; TAPSE = Tricuspid annular plane systolic excursion.

‡The body-mass index is the weight in kilograms divided by the square of the height in meters.

Figure 2. AF burden during the first six months in 215 patients with AF during follow up.
cardiovascular mortality or heart failure hospitalization, hazard ratio 1.28 (95% confidence interval 0.60-2.73, Figure 4-A). Figure 4-B shows that patients who develop early new-onset AF within 6 months after CRT implantation have a worse prognosis as compared to patients with sinus rhythm and late-onset of AF (> 6 months after implantation, log rank 0.006). AF burden did not influence cardiovascular mortality or heart failure hospitalization (data not shown).

In total, 41 patients with a history AF (20.5%) experienced ICD shocks after a median follow-up of 0.7 years (interquartile range 0.2 – 2.1 years). Twenty-three patients received appropriate ICD shocks, 17 received inappropriate ICD shocks, and 4 experienced both appropriate and inappropriate shocks. Appropriate shocks were more common in patients with (ever or new-onset) AF as compared to sinus rhythm (p=0.013). New-onset AF patients experienced more inappropriate shocks than patients with continuously sinus rhythm (p<0.001 for trend).

Discussion
Our results suggest that response to CRT and cardiovascular morbidity and mortality was comparable in AF and continuous sinus rhythm patients when AF was carefully treated with attention for continuous biventricular pacing. Only patients who developed AF shortly after CRT implantation appeared
to have a worse prognosis. Interestingly, inappropriate shocks seldom occur in patients with continuous sinus rhythm.

**Atrial fibrillation in cardiac resynchronization therapy trials**

AF is the most common arrhythmia in patients with heart failure and increases with severity of heart failure.(1,2) Despite its high prevalence, AF has always been considered an exclusion criterion in large CRT trials. (3,4) The reason for that has always been that AF limits biventricular pacing by loss of atrioventricular synchrony, which may lead to fusion or pseudo-fusion beats and suboptimal biventricular pacing. Whereas landmark trials showed benefit in outcome in terms of cardiovascular morbidity and mortality for patients with sinus rhythm(3,4), only one post-hoc analysis from a randomized trial showed results for patients with permanent AF.(16) The Cardiac Resynchronization in Heart Failure (CARE-HF) showed that CRT improved outcome regardless of whether new-onset AF developed.(16,21) There have been several retrospective cohort studies that demonstrate beneficial effects of CRT in patients with permanent AF, but often AVN ablation was required to ensure continuous biventricular pacing.(3,6,11-15) Whether the latter is applicable to all patients is uncertain as patients with dilated cardiomyopathy appear to benefit the most. (22) The Resynchronization for Ambulatory Heart Failure Trial (RAFT) concluded that in patients with permanent AF who are otherwise CRT candidates appear to gain minimal benefit from the addition of CRT compared to a standard implantable cardioverter defibrillator therapy.(16) Although no effect on mortality was observed, there was a trend toward less heart failure hospitalizations in the group randomized to CRT.(16) An earlier study in patients with permanent AF compared CRT with right ventricular pacing only.(23) In 37 patients CRT improved exercise tolerance compared to right ventricular pacing.(23) Patients in whom AVN node ablation was performed who were then randomized to either CRT or right ventricular pacing only, showed that CRT was superior in reducing morbidity.(24) The Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization therapy (MADIT-CRT) substudy, recently showed, however, that the clinical benefit was not attenuated by a history of atrial tachyarrhythmias.(9) The present study supports the use of CRT in patients with AF, with similar response rates compared to current literature when careful attention is paid to continuous biventricular pacing including biventricular pacing assessment with an exercise test.(11,25,26) This was observed, there was a trend toward less heart failure hospitalizations in the group randomized to CRT.(16) An earlier study in patients with permanent AF compared CRT with right ventricular pacing only.(23) In 37 patients CRT improved exercise tolerance compared to right ventricular pacing.(23) Patients in whom AVN node ablation was performed who were then randomized to either CRT or right ventricular pacing only, showed that CRT was superior in reducing morbidity.(24) The Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization therapy (MADIT-CRT) substudy, recently showed, however, that the clinical benefit was not attenuated by a history of atrial tachyarrhythmias.(9) The present study supports the use of CRT in patients with AF, with similar response rates compared to current literature when careful attention is paid to continuous biventricular pacing including biventricular pacing assessment with an exercise test.(11,25,26) This was achieved with AVN ablation being only performed when pharmacological rate control therapy did not allow continuous biventricular pacing. Not only response for patients with AF, also long-term all-cause mortality or heart failure hospitalization was comparable.

**New-onset atrial fibrillation**

New-onset AF is associated with poor outcome.(17-19,27) Development of new-onset or recurrences of AF is common and is associated with impaired response, cardiovascular outcome and appropriate shocks.(7,17,18,28) The present study showed that new-onset AF itself was not associated with
less response or long-term heart failure hospitalization or cardiovascular mortality, in contrast to earlier reports.(17,18,29,30) We showed, however, that the development of new-onset AF occurring shortly after CRT implantation is associated with unfavorable outcome. New-onset AF or recurrent episodes of AF have been shown to negatively impact prognosis not only in terms of heart failure hospitalization or cardiovascular mortality but also in functional status.(8,17,18,28,30,31) Whether or not our new onset AF patients did have AF before implantation remains unknown. However, it seems reasonable to monitor AF carefully during the first few months after implantation to ensure adequate therapy for AF (32,33) and biventricular pacing.(20) Perhaps home monitoring could be a way to ensure early detection and appropriate treatment of AF, also in severe heart failure. Currently, this is investigated in the Clinical effect of heart failure management via home monitoring with a focus on AF (EffecT, NCT00811382). (34) In addition, risk assessment of patients at risk for AF may contribute to improved outcome of CRT therapy.(35)

### Conclusions

Response and outcome was comparable in patients treated with CRT with either AF or continuous sinus rhythm. Patients with early new-onset AF after implantation appeared to have a worse prognosis. Careful ECG monitoring to adequately treat AF may be beneficial for these patients.

### Strengths and Limitations

Strength of the present analysis is our CRT protocol allowing collecting of patient data treated according to our routine clinical protocol. Follow-up was substantial and a large percentage of patients with a history of AF were included. Furthermore data on AF were carefully collected and documented throughout the study and patients who had new-onset AF were not analyzed as sinus rhythm allowing observing a true sinus rhythm population. Whether or not patients who had early new-onset AF suffered from AF episodes before implantation is unknown. The present study was a retrospective analysis and was therefore not powered to assess outcome (in terms of response or cardiovascular mortality or heart failure hospitalization) in patients with AF comparing to those with sinus rhythm.

### Table 4. Determinants of echocardiographic response (defined as >15% reduction in left ventricular end systolic volume).

<table>
<thead>
<tr>
<th>OR (95% CI)</th>
<th>Univariate Analyses</th>
<th>Multivariate Analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR (95% CI)</td>
<td>P value</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Ischemic cardiomyopathy</td>
<td>0.68 (0.47-0.99)</td>
<td>0.043</td>
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<tr>
<td>QRS duration (per 10msec increase)</td>
<td>1.09 (1.00-1.18)</td>
<td>0.047</td>
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<tr>
<td>Beta-blocker</td>
<td>1.81 (1.08-3.03)</td>
<td>0.025</td>
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<tr>
<td>Left atrial size, length (per 5mm increase)</td>
<td>0.88 (0.80-0.97)</td>
<td>0.010</td>
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<tr>
<td>Right atrial size, length (per 5mm increase)</td>
<td>0.90 (0.82-0.99)</td>
<td>0.039</td>
</tr>
<tr>
<td>Left ventricular end diastolic volume (per 25ml increase)</td>
<td>1.07 (1.02-1.12)</td>
<td>0.009</td>
</tr>
<tr>
<td>Left ventricular end systolic volume (per 25ml) increase</td>
<td>1.00 (1.00-1.01)</td>
<td>&lt;0.001</td>
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<tr>
<td>History of AF</td>
<td>0.91 (0.63-1.33)</td>
<td>0.634</td>
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<tr>
<td>New-onset AF</td>
<td>0.90 (0.49-1.66)</td>
<td>0.736</td>
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<tr>
<td>AF burden in first six months</td>
<td>0.99 (0.99-1.00)</td>
<td>0.600</td>
</tr>
<tr>
<td>Biventricular pacing in first six months</td>
<td>1.01 (0.99-1.03)</td>
<td>0.129</td>
</tr>
</tbody>
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OR = odds ratio; CI = confidence interval. Multivariate analysis is adjusted for sex and age.
References


