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RESEARCH LETTER

# Adaptive Cardiac Resynchronization Therapy Reduces Atrial Fibrillation Incidence in Heart Failure Patients With Prolonged AV Conduction

## The Adaptive CRT Randomized Trial

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Cardiac resynchronization therapy (CRT) is an established treatment for patients with heart failure, prolonged QRS duration, and impaired left ventricular systolic function.[1] In an effort to optimize CRT response, the AdaptivCRT algorithm (adaptive CRT [aCRT]) adjusts atrioventricular (AV) pacing intervals and paces the left ventricle synchronized with intrinsic right ventricular (RV) activation, if AV conduction is normal, or with RV pacing if AV conduction is prolonged. The technical details of the aCRT algorithm and the results of its application in clinical have been described in the publication of the Adaptive CRT trial (URL: http://www.clinicaltrials.gov. Unique identifier: NCT00980057).[2] The study protocol was approved by Institution Review Boards of each participating hospital. All subjects signed written informed consents. In this trial, we randomized 472 patients indicated for a CRT defibrillator in a 2:1 ratio to aCRT (312 patients) versus echocardiography-optimized CRT (conventional CRT [ConvCRT]—160 patients). We showed that aCRT increases responder rates and improves clinical outcomes.[2] More recently, we have also found that aCRT reduces atrial fibrillation (AF) in patients with prolonged AV conduction, a condition occurring in a relevant (262/472 [55.5%]) group of studied patients.[3] Whether AF reduction derives from the minimization of RV pacing or the continuous AV optimization, or both, is still under discussion. We hypothesized that, in patients with long PR, AV optimization plays a major role. Indeed, in the presence of conduction delays in the right atrium, AV node, or right ventricle, the conventional CRT, with fixed AV pacing intervals, may cause left heart AV dyssynchrony. Conversely, aCRT avoids too short and too long AV intervals, ameliorating AV synchrony. We, therefore, designed new analyses to observe whether

1. aCRT reduces AF compared with Conv CRT when Conv CRT is delivered with too short or too long AV intervals
2. Uncoupling the 2 functions of aCRT—AV optimization and RV withholding—the AF reduction is still observed in patients with AV optimization only.

As in the previous Adaptive CRT trial analysis,[3] we chose AF longer than 2 consecutive days as the main end point because such AF duration is considered clinically relevant because of the association with higher risk of embolic events. We evaluated AF incidence by means of the Cox proportional risk regression model and reported the hazard ratio.

Analysis no. 1—The occurrence of AF, in the whole study cohort, is shown in the Figure as a function of sensed AV intervals. For both study arms, the AV pacing intervals were optimized using echocardiographic measurements at baseline; for ConvCRT patients, the AV pacing intervals remained constant during the whole follow-up period, whereas for aCRT patients, they were adapted every minute by the AV optimization algorithm. The 2 dotted curves, representing the polynomial best fits of the data, show that AF incidence was significantly different in the 2

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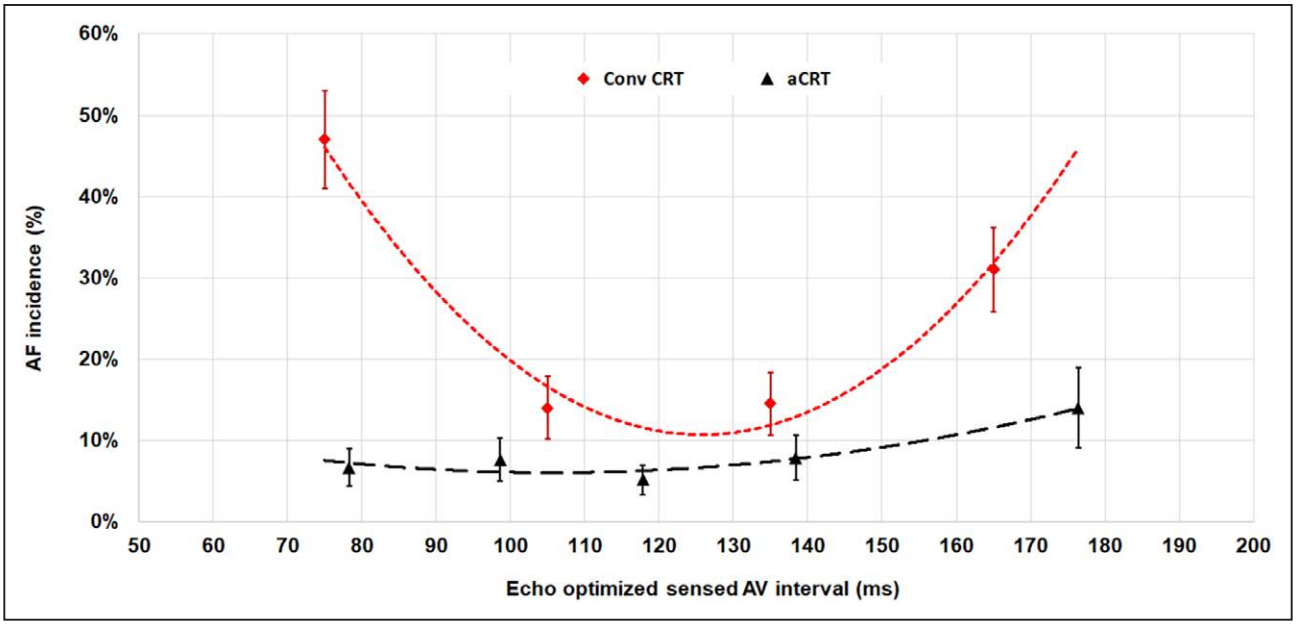


**Figure. Incidence of atrial fibrillation (AF) as a function of the echocardiography (echo)-optimized sensed atrioventricular (AV) interval for the 2 randomization arms (adaptive CRT [aCRT] vs conventional CRT [ConvCRT]).**
CRT indicates cardiac resynchronization therapy.

study arms (likelihood ratio test p=0.031). In particular, convCRT patients, when paced with too short AV (<100 ms) or too long AV (>150 ms) intervals, were associated with higher AF risk, despite these intervals were found as the optimal ones, during baseline echo measurements. These results suggest that aCRT avoids too short and too long AV intervals, whereas conventional CRT, in specific settings, may cause too early or too delayed ventricular stimulation, reduced time for atrial contribution to ventricular filling, and hemodynamic issues due to asynchronous mitral valve closure.[4]

Analysis no. 2—We selected the subgroup of patients who were paced in biventricular mode most of time (>99.9% of time) and, therefore, benefit from the continuous AV optimization algorithm, but not from RV pacing withholding algorithm. In this cohort, comprising 75 aCRT patients and 69 ConvCRT patients, AF incidence at 2 years was 29.0% (95% CI, 19.3%–42.2%) in ConvCRT and 12.3% (95% CI, 6.6%–22.3%) in aCRT (hazard ratio, 0.41; 95% CI, 0.18–0.90; *P*=0.026). The superiority of aCRT in this subgroup of patients confirms that automated continuous adjustment of AV intervals is the mechanism determining AF reduction in patients with long PR intervals.

In conclusion, our analyses show that conventional CRT with nonphysiological pacing AV intervals is associated with higher risk of long duration AF compared with aCRT, suggesting that the continuous optimization of AV pacing intervals results in AV synchrony. Our results also confirm that the aCRT feature, that continuously adapts AV pacing intervals, determines AF reduction in patients with long PR. Altogether, these findings, in line with those described by Olshansky et al,[5] suggest that AV synchrony is important in CRT patients. Although our study has limitations, mainly because it is a post hoc analysis, with a modest sample size, we think that it provides clinically relevant information since AV prolongation is present in half of CRT patients and because AF in CRT patients may herald a poor prognosis because of reduced atrial contribution to cardiac stroke volume and to reduced biventricular pacing.

We declare that the data, methods used in the analysis, and materials used to conduct the research are available, in persistent repositories, to researchers for purposes of reproducing the results or replicating the procedure.

## ARTICLE INFORMATION

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