Early detection of atrial high rate episodes predicts atrial fibrillation and thromboembolic events in patients with cardiac resynchronization therapy

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BACKGROUND In patients without any history of atrial fibrillation (AF), detection of subclinical atrial high rate episodes (AHRE) by implanted devices has been associated with an increased thromboembolic risk. The predictive value of AHREs in patients with cardiac resynchronization therapy (CRT) is uncertain.

OBJECTIVE We aimed to investigate the prognostic value of early detected AHRE in patients with CRT.

METHODS This observational study included patients who received CRT and no history of AF. Patients had standard indication for CRT treatment. They were screened for early detected AHREs longer than 6 minutes occurring before 6-month follow-up, and the longest duration of AHREs was recorded. Information on clinical AF and thromboembolic events was obtained from the Danish National Patient Registry. The Cox regression model was used to compute hazard ratios (HRs) with 95% confidence intervals (CIs).

RESULTS Of 394 eligible patients, 79 patients (20%) had early AHRE detected. During a median follow-up of 4.6 years, patients with early detected AHREs had an increased risk of clinical AF (HR 2.35; 95% CI 1.47–3.74; $P < .001$) and thromboembolic events (HR 2.30; 95% CI 1.09–4.83; $P = .028$). For patients with AHREs longer than 24 hours, these associations were stronger. The risk of mortality was not higher with early detected AHREs (HR 0.97; 95% CI 0.64–1.45; $P = .87$). Of the 27 patients with thromboembolic events, only 10 patients (37%) had AHREs detected within a 2-month period before the thromboembolic event.

CONCLUSION In patients without any history of AF, detection of early AHREs after CRT implantation is associated with a significantly increased risk of clinical AF and thromboembolic events, particularly AHRE longer than 24 hours.

KEYWORDS Cardiac resynchronization therapy; Atrial high rate episodes; Atrial fibrillation; Thromboembolic event; Mortality

ABBREVIATIONS **AF** = atrial fibrillation; **AHRE** = atrial high rate episode; **CHA_2DS_2-VASc** = congestive heart failure, hypertension, age ≥75 years, diabetes, stroke, vascular disease, age 65–74 years, sex category; **CI** = confidence interval; **CRT** = cardiac resynchronization therapy; **HAS-BLED** = hypertension, abnormal renal/liver function, stroke/thromboembolic event, bleeding history or predisposition, labile international normalized ratio, elderly (age >65 years), drugs/alcohol concomitantly; **HF** = heart failure; **HR** = hazard ratio; ***ICD-10*** = *International Classification of Diseases, Tenth Revision*; **IQR** = interquartile range; **NYHA** = New York Heart Association

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Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia and is associated with an increased risk of thromboembolic events and mortality.[1,2] Episodes of AF are often asymptomatic[3] and of such short duration that they would be detected only by continuous monitoring.[4] The increased use of cardiac implantable electronic devices with an atrial lead, and thereby the opportunity to continuously detected atrial high rate episodes (AHRE), has added substantial understanding about the incidence of AF in patients with pacemakers.[5,6] Studies[6–10] have shown that AHREs are associated with an increased risk of clinical AF, stroke, and death in patients with cardiac pacemaker or implantable cardioverter-defibrillator.

Patients with heart failure (HF) frequently develop AF, and new-onset AF often leads to worsening of HF symptoms and may result in a poorer long-term outcome.[10,11] Furthermore, most patients with HF will have a thromboembolic risk score, indicating treatment with oral anticoagulation in the presence of AF.[12] Thus, the clinical relevance of detected

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AHREs is important to evaluate in patients with a cardiac resynchronization therapy (CRT) device. In patients with CRT and no history of AF, AHREs appear in about one-third after implantation,[13,14] but the relationship between AHREs and clinical AF, thromboembolic events, and death remain largely unknown.

The aim of the present study was to evaluate the prognostic effect of early detected AHREs on the development of clinical AF, thromboembolic events, and death during long-term follow-up in patients treated with CRT without any history of AF. A secondary aim was to study the temporal relationship between AHREs and thromboembolic events in this group.

Method

Study Population

An observational study was conducted in consecutive patients who received a CRT device at Aarhus University Hospital, Denmark, between 2000 and 2010. Patients with standard indication for CRT treatment who had no history of AF or atrial flutter were eligible for the study. Patients underwent device interrogation 1 and 6 months after implantation, respectively, and subsequently every 6–12 months afterward. Data obtained from device interrogation recordings from the time of implantation until the 6-month follow-up visit were included for detecting early AHREs. We excluded patients without device interrogation beyond 1 month due to follow-up at the referral hospital, patients who died or underwent system downgrade to a cardiac pacemaker or an implantable cardioverter-defibrillator without CRT within the 6 month follow-up visit, and patients with prosthetic valves (Figure 1). Patients were followed from the time of CRT implantation until death or September 2013. The study was approved by the Danish Health and Medicines Authority and the Danish Data Protection Agency.

Data Sources

In Denmark, information on all prescriptions dispensed from Danish pharmacies since 1995 has been recorded in the Danish National Prescription Registry[15] according to the international anatomical therapeutic chemical classification system. In the Danish National Patient Registry, all admissions from Danish hospitals have been registered since 1978, with a primary discharge diagnosis and, if relevant, 1 or more secondary diagnoses according to the *International Classification of Diseases, 8th Revision* or *International Classification of Diseases, Tenth Revision* (*ICD-10*).[16] The Civil Registration System contains information on vital status of all Danish citizens and has recorded the date of birth and the exact date of death or emigration. In Denmark every resident is, at the time of birth or immigration, provided with a unique and permanent civil registration number, which enables linkage between nationwide administrative registers on the individual level.

Study Outcome

The predefined outcomes included all-cause mortality, the incidence of clinical AF, and thromboembolic events. Vital data were obtained from the Civil Registration System. *Thromboembolic events* were defined as a discharge diagnosis of ischemic stroke or unspecified stroke, transient ischemic attack, or peripheral artery embolism (*ICD-10* codes I63, I64, I74, and G45), and *clinical AF* was defined as a discharge diagnosis of AF or atrial flutter (*ICD-10* code I48); information was obtained from the Danish National Patient Registry.

Patient Characteristics

Clinical data and information on the history of AF at the time of implantation were retrieved from patient charts. Information on the percentage of atrial and biventricular pacing as well as the number of AHREs and their longest duration was collected through review of device interrogation recordings. Manufacturer-specific nominal settings for AF detection were used as default. We included AHREs lasting longer than 6 minutes, while patients with AHREs shorter than 6 minutes were defined as having no AHREs.

Thromboembolic risk was assessed using the CHA_2DS_2-VASc (congestive heart failure, hypertension, age $\geq$75 years [2 points], diabetes, stroke [2 points], vascular disease, age 65–74 years, and sex category [female]) score at the time of implantation.[17] Information on sex, age, HF, vascular disease, and diabetes was obtained from patient charts, while information on previous thromboembolism and hypertension was identified from discharge diagnoses. Patients were categorized according to CHA_2DS_2-VASc scores into 2 groups: 2–3 and $\geq$4.

The risk of bleeding was assessed using HAS-BLED (hypertension, abnormal renal/liver function, stroke/thromboembolic event, bleeding history or predisposition, labile

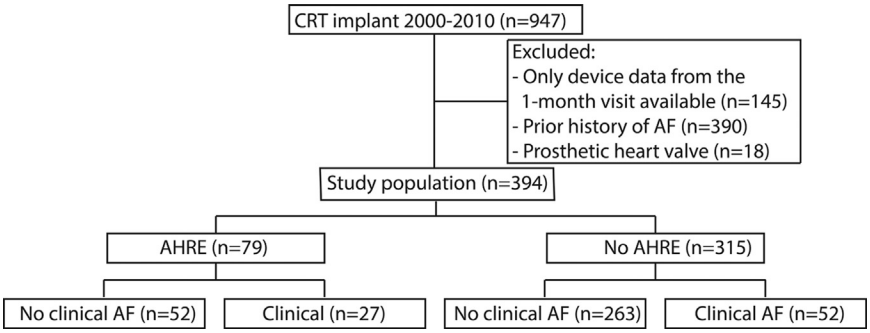

Figure 1 Study flowchart. AF = atrial fibrillation; AHRE = atrial high rate episode; CRT = cardiac resynchronization therapy.