# Silent atrial fibrillation episodes and cognitive impairment in patients with cardiac implantable devices. Protocol of the SAFE-COG ongoing observational single-center non-experimental case-control clinical study

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## INTRODUCTION

Atrial fibrillation (AF) is highly prevalent among the elderly and is associated with a higher risk of dementia. Silent Atrial Fibrillation Episodes and COGnitive impairment in patients with cardiac implantable devices (SAFE-COG) is an observational clinical trial that aims to assess the relationship between atrial high rate episodes (AHRE), a silent form of short, undiagnosed AF episodes revealed on cardiac implantable device interrogation, and cognitive impairment.

## METHODS

SAFE-COG is an ongoing observational single-center non-experimental case-control clinical study. The study protocol was approved by the bioethics committee of the National Institute of Cardiology in Warsaw (IK-NPIA-0021-78/1800/2019).

We will compare two groups of 50 patients with previously implanted pacemakers or cardioverter-defibrillators that can detect AHRE and record an intracardiac electrocardiogram (EGM). Both groups are matched according to age, sex, educational level, and history of hypertension. Inclusion and exclusion criteria are shown in Table 1. We set the group size at 100 individuals according to the results of previous studies and characteristics of methodology. The use of sensitive diagnostic methods detecting cognitive impairment and implantable device data excluding patients with undetected silent AF from the control group enabled us to set a study group with a lower number of subjects than previous studies [1, 2].

The decision to introduce oral anticoagulation (OAC) will be taken according to the guidelines and the patient's risk profile.

The groups will be evaluated in terms of body weight, height, history of myocardial infarction, hypercholesterolemia, diabetes, and nicotine addiction. Both groups will be

**Table 1.** Inclusion and exclusion criteria

| Inclusion criteria | Exclusion criteria |
|---|---|
| 1. The presence of an implantable device with an atrial electrode, an AHRE detection algorithm, and ECG recording in the atrial canal (at least 3 months after implantation)<br>2. No AF history<br>3. Written informed consent | 1. A history of stroke/transient ischemic attack<br>2. Diagnosed dementia/severe psychiatric disorder<br>3. Current alcohol abuse<br>4. Presence of a prosthetic valve<br>5. Lack of informed consent |

Abbreviations: AF, atrial fibrillation; AHRE, atrial high rate episodes; ECG, electrocardiography

examined for thyroid dysfunction and primary hyperaldosteronism. Transthoracic echocardiography with particular emphasis on left atrium morphology will be performed. We will evaluate cognitive functions at the time of inclusion and after an 18-month observation period to estimate the general level of cognitive functioning and cognitive performance in the following areas: attention and executive functions, verbal memory, language functions, and visual-spatial functions. We will use the following neuropsychological questionnaires: Addenbrooke's Cognitive Examination III (J Hodges), the California Verbal Learning Test (DC Delis), and the Color Trails Test (LF D'Elia).

The risk of obstructive sleep apnea (OSAS) will be assessed using the Berlin Questionnaire.

Division into groups will be based on the presence of AHRE with a frequency of at least 180 bpm and lasting at least 6 minutes, visually confirmed to be AF by EGM.

### Endpoints of the study

1. The assessment-based comparison of the prevalence and severity of cognitive impairment in patients with and without AHRE.
2. The evaluation of the clinical characteristics of patients with AHRE, particularly the factors that may affect the occurrence of AHRE: left atrial and left ventricular remodeling and dysfunction, thyroid disorders, primary hyperaldosteronism, OSAS.

### Statistical analysis

The distribution of variables will be assessed using the Kolmogorov-Smirnov test. To compare intergroup mean and median values, depending on variable type and distribution, we will use the T-test, the Mann-Whitney test, or the Kruskal-Wallis test for independent variables. Intergroup comparison of categorical variables will be conducted using Fisher's exact test. We will compare the variables evaluated at the beginning and during the follow-up depending on the variable type and distribution with the Paired Samples T-test and the Wilcoxon Signed Rank Test for dependent variables, with the Wilcoxon matched-pairs test for continuous and discrete variables, and with McNemar's test for categorical variables. The Pearson or Spearman's rank correlation (depending on variables distribution) will be used to assess the relationships between numerical variables. The value $P$ <0.05 will be considered statistically significant.

## RESULTS AND DISCUSSION

AF increases the risk of dementia (hazard ratio [HR], 2.7) in patients with a history of stroke and patients with no history of stroke (HR, 1.34) [1]. This relationship is stronger in patients below 67 years of age and is related to AF duration. There are three proposed pathophysiological pathways connecting AF and brain damage: stroke and microembolization, microbleeds associated with OAC, and transient central nervous system (CNS) hypoperfusion associated with an inadequate chronotropic response. The risk of dementia depends on the $CHADS_2$ score, regardless of warfarin treatment [2]. In subjects with AF and at least $CHA_2DS_2$-VASc of 2 points, the use of warfarin was associated with only a limited effect on the cognitive decline — a 20% reduction in dementia incidence. The key factor was the percentage of time during which the INR index remained within the therapeutic range. CNS vascular damage is associated with an increased risk of ischemic strokes, brain vessel microembolization, and the occurrence of microbleeds caused by supratherapeutic OAC. Furthermore, periodic hypoperfusion episodes during AF can explain the limited protective effect of OAC against dementia [3]. An average heart rate outside the 50–90 bpm range during AF is clearly associated with decreased cognitive functions. Some studies suggest that the presence of paroxysmal AF also promotes bradycardia and subsequent CNS hypoperfusion in sinus rhythm. There are few reports of lower dementia risk in AF patients who undergo ablation [4]. However, in the EAST-AFNET4 trial, early rhythm control therapy (including 20% early ablation and 80% pharmacological therapy in the interventional arm) did not significantly affect cognitive function [5]. The current technological progress in implantable devices makes it possible to record a high-quality EGM in the atrial channel and distinguish true AHRE artifacts. AHRE episodes are a common finding on cardiac device interrogation [6]. In the ASSERT study, during 2.5 years of follow-up of patients without previous AF history, at least one episode of AHRE lasting more than six minutes was found in about 30% of hypertensive individuals [7]. Interestingly, clinically apparent arrhythmia was eight times less frequent in this group. In the AHRE group, the probability of a stroke or peripheral embolism was twice as high as in patients with a CHADS score of 2 and without arrhythmic episodes in device memory and four times as high in patients with a CHADS score of 3 or higher. The risk of ischemic stroke in AHRE patients is significantly lower than overt AF in studies using EGM monitoring devices. First, in 2016 and subsequently, in 2020, the European Society of Cardiology guidelines on the management of atrial fibrillation recommend the use of OAC in some AHRE patients according to AHRE burden $CHA_2DS_2$VASc score [8]. The recommendation concerns patients with AHRE at a frequency of >180 bpm (beats per minute) and lasting at least 5–6 minutes, with the AF diagnosis confirmed by visually reviewed EGM. Short (<1 hour) and rare AHREs should be instead observed, excluding selected patients with a high/very high risk of stroke. The scale of potential benefit associated with the strategy of early OAC administration is being tested in two major ongoing studies: ARTESiA (Apixaban for the Reduction of Thrombo-embolism in Patients with Device-Detected Sub-Clinical Atrial Fibrillation) and NOAH AFNET 6 (Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial High Rate Episodes) with edoxaban [9, 10]. The results of these studies will have crucial impor-

tance for clinical practice and will provide missing evidence for the advisability of OAC use in AHRE. The data about the effect of AHRE on cognitive decline are limited — there are no studies that assess this issue. Our research aims to verify the suspected influence of AHRE on cognitive functions. We hypothesize that AHRE will be associated with more severe cognitive impairment in the study group. We also expect that at follow-up, the occurrence of AHRE will be associated with a faster decline of cognitive functions.

## *Article information*

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