Patients with short atrial arrhythmias do not benefit from anticoagulation, finds clinical trial

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Atrial high-rate episodes (AHRE) are short and rare atrial arrhythmias that resemble atrial fibrillation detected by implanted pacemakers, defibrillators, and loop recorders that enable long-term monitoring of heart rhythm. AHRE are found in 10–30% of patients with implanted devices. AHRE episodes resemble atrial fibrillation. Therefore, patients with AHRE are often offered treatment with blood thinners (oral anticoagulation) without ECG-documented atrial fibrillation. So far, the

efficacy and safety of oral anticoagulation has never been tested in patients with AHRE.

The Non vitamin K antagonist Oral anticoagulants in patients with Atrial High rate episodes trial (NOAH-AFNET 6) compared the anticoagulant edoxaban to placebo in an international investigator-initiated, randomized, double-blind, double-dummy outcomes trial. The paper is published in the *New England Journal of Medicine*.

NOAH-AFNET 6 randomized patients with AHRE episodes lasting six minutes or longer detected by implantable devices, and aged 65 years or more with at least one additional stroke risk factor of heart failure, hypertension, diabetes, prior stroke or transient ischemic attack, vascular disease, or age from 75 years. This patient population was outside of the approved indication of edoxaban.

Prof. Paulus Kirchhof, University Medical Center Hamburg-Eppendorf (UKE), Hamburg, Germany, principal investigator of NOAH—AFNET 6 explained, "Whether anticoagulants can prevent strokes in patients with device-detected AHRE, was not known. Although AHRE resemble atrial fibrillation, NOAH—AFNET 6 demonstrates that patients with AHRE are better managed without anticoagulation."

Between 2016 and 2022, NOAH—AFNET 6 enrolled 2,536 patients in 206 sites across 18 European countries. Patients were randomly allocated in a 1:1 fashion to anticoagulation or no anticoagulation.

Anticoagulation consisted of edoxaban in the dose approved for stroke prevention in atrial fibrillation (60 mg once daily, reduced to 30 mg once daily according to approved dose reduction criteria for stroke prevention in atrial fibrillation). No anticoagulation consisted of placebo containing no active compound or aspirin 100 mg once daily in patients with an indication for antiplatelet therapy.

The analysis included the data of 2,536 patients aged 78 on average; 37% were women. The patients had additional stroke risk factors (median CHA2DS2-VASc score 4.0±1.3) and a median AHRE duration of 2.8 hours. All patients were followed until the end of the trial.

In September 2022 it was decided to terminate the trial after enrollment of all patients due to the observed trend towards futility for efficacy combined with expected safety concerns. The analysis of the full data confirms this:

Stroke, systemic embolism, or cardiovascular death occurred in 83 patients in the anticoagulation group and 101 patients in the no anticoagulation group (stroke: 0.9% versus 1.1% per year, systemic embolism: 0.5% versus 1.1% per year, cardiovascular death: 2.0% versus 2.2% per year). This means no significant difference between treatment groups (HR 0.81 [0.6;1.08], p=0.15).

A major bleeding event or death occurred in 149 patients in the anticoagulation group (5.9% per year) and in 114 patients in the no anticoagulation group (4.5% per year), thus more often in patients randomized to anticoagulation (HR 1.3 [1.02;1.67], p=0.03). This was mainly driven by a doubled rate of major bleeding (2.1% versus 1.0% per year), a known side effect of all anticoagulants.

Prof. Kirchhof commented, "As expected, anticoagulation increased bleeding. The low stroke rate with and without anticoagulation was unexpected. The results of NOAH—AFNET 6 clearly suggest to demand ECG documentation of atrial fibrillation prior to initiation of oral anticoagulation. The results also call for randomized trials evaluating anticoagulation in people in whom smartwatches detect arrhythmias that resemble atrial fibrillation."

Prof. Andreas Goette, St. Vincenz Hospital, Paderborn, Germany,

NOAH—AFNET 6 sponsor representative, concluded, "Our results underpin evidence from other trials which indicated that in patients with AHRE anticoagulants may not be as effective in preventing strokes as previously thought. Further research is needed to identify patients with AHRE at high stroke risk and to find the optimal treatment for these persons."

More information: Paulus Kirchhof et al, Anticoagulation with Edoxaban in Patients with Atrial High-Rate Episodes, *New England Journal of Medicine* (2023). DOI: 10.1056/NEJMoa2303062

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