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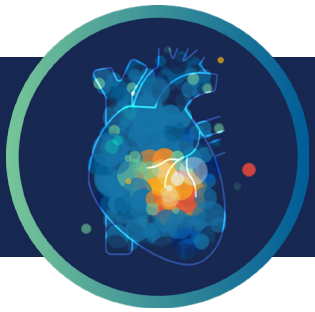
EXPERT INSIGHTS: Q&A WITH PROF. PAULUS KIRCHHOF



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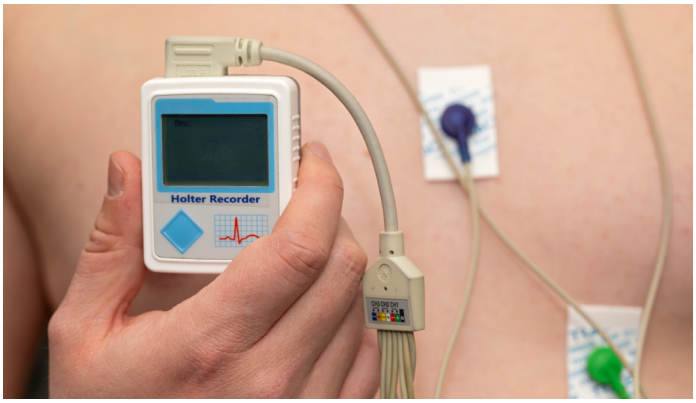
In plain language, how would you describe what sub-clinical atrial fibrillation (AF) is to a patient, and why is it increasingly important to recognize it?

Atrial high-rate episodes, also called "sub-clinical AF", refer to very rare and typically short episodes of AF. These can only be detected when the heart rhythm is monitored long-term and are currently reserved for patients without ECG-documented AF. The best term to describe them is therefore device-detected AF. We do not know enough to state this with certainty, but one main difference between device-detected AF and ECG-documented AF is that patients with ECG-documented AF spend a considerable amount of time in AF while patients with device-detected AF spend on average only very little time in AF.



Given the combined results of the ARTESIA and NOAH-AFNET 6 trials, a substudy of the latter and subsequent meta-analysis, is the role of oral anticoagulants to prevent stroke in subclinical AF now more certain?

Until August 2023 there was no evidence on the efficacy and safety of oral anticoagulation in patients with device-detected AF, and therapeutic decisions had to rely on opinion and extrapolation of other data. Now we have two randomized trials evaluating anticoagulation compared to no anticoagulation (or to aspirin) in patients with device-detected AF. The results contain two pieces of good news for patients with device-detected AF.

1. The rate of ischemic stroke is much lower than we thought, around 1%/year, although both studies enrolled elderly patients with multiple comorbidities (age 77 years, median CHA_2DS_2-VASc score 4).
2. Anticoagulation further decreases the slow rate of stroke by one-third, but also almost doubles rates of major bleeding. In NOAH-AFNET 6, a composite of major bleeding and death was doubled. ARTESiA only counted major bleeding in its main safety outcome.
3. All patients in both trials had an ECG every six months, and 6-9% of the patients had ECG-documented AF per year with an indication for anticoagulation.

These results suggest that patients with device-detected AF should have 6-monthly ECGs to diagnose ECG-documented AF. In the absence of ECG-documented AF, the stroke risk is low. Anticoagulation has ambiguous effects. The risks and benefits of anticoagulation therapy now can be discussed with patients based on good evidence to inform individual decisions. As a clinician, I would really like to have better methods to identify patients with device-detected AF at high risk of stroke.

Both apixaban in ARTESIA and edoxaban in NOAH-AFNET 6 were associated with a significantly increased risk of bleeding compared to aspirin or placebo respectively. Is there a duration of atrial high-rate episodes threshold beyond which the stroke prevention benefits of these direct-acting oral anticoagulants outweigh their bleeding risk?

When ARTESiA was planned, there was a feeling that very long episodes of AF (>24 hours longest duration) may need anticoagulation without a need for testing in a controlled trial. So these patients were not enrolled in ARTESiA. The design of NOAH-AFNET 6 included patients with long episodes. A subanalysis of these patients (Becher et al EurHJ 2023) suggests that the stroke risk is not different in patients with long episodes. The best determinant of a duration of device-detected AF episodes that requires anticoagulation is currently ECG-documentation of AF using simple ECGs, e.g. every six months.

Rather than use the duration of device-detected subclinical AF as the sole arbiter of deciding whether to commence long-term oral anticoagulation, is there an argument for using a high CHA_2DS_2-VASc score instead, or should we be combining the two?

Current guidelines, written before these two trials were published, suggest to combine age, cardiovascular comorbidities, and episode duration when anticoagulation is considered in patients with device-detected AF. We can expect to see further analyses of the trial data sets. I would not be surprised if even a combination of episode duration and cardiovascular comorbidities only creates a small increase in absolute risk. We may need new approaches to identify patients with device-detected AF at high risk of stroke. Cardiovascular biomolecules and imaging may provide additional information to identify patients with device-detected AF at high risk of stroke.

Both ARTESIA and NOAH-AFNET 6 recruited a relatively high proportion of female participants, which is to be lauded, but the study cohorts in both trials were predominantly white Caucasian. How do we improve the ethnic diversity of large cardiovascular outcomes trials?

Many efforts are ongoing to facilitate participation of under-represented groups in clinical trials. Ethnic diversity is very important for this, but also enrolment of patients from all walks of life with different educational and social status. This is difficult to achieve as some parts of the population are less prone to contact the health system. Conducting trials in countries with different ethnicities and providing simple information about clinical trials in multiple languages is helpful. Simplifying trial procedures is another key area that enables broad participation. Data-driven methods to identify and invite patients may in the future help to improve diversity in trials.

Do you think the combined results of ARTESIA and NOAH-AFNET 6 are strong enough to change the guideline recommendations for the management of stroke prevention for subclinical AF?

The results will certainly be used by guideline writers to update recommendations. The low rate of stroke is unexpected and robust. The low stroke rate may partially be due to the initiation of anticoagulation based on 6-monthly ECGs, but we need further analyses to confirm this. The weak stroke-preventing effect of anticoagulation and the increase in bleeding will be considered. It does not seem easy to me to draft a new recommendation that reflects the new evidence. One research gap appears obvious to me: We need better methods to identify patients with device-detected AF at high risk of stroke.