Comment on "Apixaban *versus* aspirin for stroke prevention in people with subclinical atrial fibrillation and a history of stroke or transient ischemic attack: subgroup analysis of the ARTESiA randomized controlled trial"

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I read with interest the subgroup analysis of the ARTESiA trial recently published in *Lancet Neurology*.[1] The topic deals with subclinical device-detected atrial fibrillation (AF) that in elderly hypertensive patients bearing a pace-maker is present in more than one-third of cases[2] and is associated with a 2.5-fold increased risk of stroke or systemic embolism. The risk (1% per year) is approximately half of the risk increase observed among patients with clinically detected atrial fibrillation.[3] This finding together with the risk of bleeding especially in elderly patients makes the benefit of treatment with oral anticoagulants doubtful.[4] This is the reason why there was the need of a randomized clinical trial to test the efficacy and safety of direct oral anticoagulants (DOACs) in this setting.

In the original ARTESiA study,[5] patients with subclinical device-detected AF lasting a minimum of 6 min to 24 h were randomly assigned in a double blind, double dummy design to receive apixaban 5 mg twice daily (or 2.5 mg twice daily when indicated) or aspirin 81 mg daily. The trial included 4012 patients with a CHADSVASC score of 3 or more followed for a mean of 3.5 years. In the intention-to-treat analysis, the primary efficacy end point (stroke or systemic embolism) was significantly lower in the apixaban group but at the cost of a significant increase of major bleeding at on-treatment analysis. Notably, disabling and fatal stroke were substantially lower in the apixaban group where gastro-intestinal bleeding was prevalent. A meta-analysis of the 2 studies (NOAH-AFNET 6 and ARTESiA)[6] with different direct oral anti Xa anticoagulants reached the same conclusions indicating that the use of anti Xa inhibitors edoxaban and apixaban reduced stroke and systemic embolism but significantly increased major bleeding.

From the large group of patients randomized in the original trial, those with device-detected atrial fibrillation and a history of stroke or transient ischemic attacks (TIA) were analyzed and compared with those without a previous cerebral ischemic accident.[1] The rationale for this sub-study was the known increased risk of stroke recurrence in AF patients with a previous ischemic cerebral event. A history of stroke or TIA was present in 346 (8.6%) participants (172 assigned to apixaban and 174 to aspirin). Treatment with apixaban led to a significant reduction in stroke or systemic embolism in individuals with *vs* those without a history of stroke or TIA (absolute risk difference in incidence of stroke or systemic embolism at 3.5 years of follow-up 7% *vs* 1%). The absolute risk difference in corresponding increase in major bleeding was not significant (3% and 1%, respectively). Therefore, although no firm conclusion could be drawn from the original ARTESiA trial as of benefit of apixaban treatment in patients with device-detected AF, based on subgroup analysis, anticoagulation with apixaban could be indicated in patients with previous stroke or TIA.

What is the practical message here. Oral anticoagulation with apixaban or edoxaban could be prescribed to the subgroup of patients with device-detected subclinical AF and previous stroke or TIA or those with a high CHADVASc score provided a reasonable risk of bleeding (Table 1). Unfortunately, we do not have a robust score to predict major bleeding in the field of AF. Several bleeding scores have been proposed but a cautionary note comes from studies showing low specificity and sensitivity of these scores that have been removed from anticoagulation decision-making in the recent atrial fibrillation guidelines.[8] Rather, individual factors specifically contributing to bleeding risk (such as anemia or previous bleeding) and clinical judgment have been appointed a greater importance.

Reading the NOAHA-AFNET 6 trial, the original ARTESiA work and the subgroup analysis, I found some inconsistencies

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Table 1. Trials on device-detected subclinical fast atrial tachycardia or atrial fibrillation.

	Type of patients	Duration	Drugs	Results
NOAH:AFNET 6[7]	<65y AHREs	>6 min	Edoxaban *vs* placebo	No reduction of composite CV events. Increase composite of MB and death
ARTESiA[5]	Mean age 77 y AF	>6 min to 24 h	Apixaban *vs* aspirin	Lower risk of stroke or SE and higher risk of MB
Meta-analysis NOAH:AFNET 6 and ARTESIA[6]	AHREs + AF	-	Anti Xa oral anticoagulants	Consistent with each other: oral anticoagulation reduces the risk of stroke and increase the risk of major bleeding.
ARTESiA subgroup analysis[1]	>55 y AF CHA_2DS_2-VASc >3	>6 min to 24 h	Apixaban *vs* Aspirin in patients with and without previous stroke or TIA	Apixaban: 7% *vs* 1% absolute RR of stroke or SE in patients with *vs* without previous stroke or TIA. Corresponding MB 3% *vs* 1%

AHREs, atrial high-rate episodes; CV cardiovascular; AF, atrial fibrillation; SE, systemic embolism; MB, major bleeding; TIA, transient ischemic attack; RR, risk reduction.

with the AF terminology. Device-detected atrial high-rate episodes (AHREs) as those described in NOAHA-AFNET 6 trial are atrial arrhythmias detected by implanted cardiac devices that 'resemble' atrial fibrillation. At variance with atrial fibrillation, the atrial contraction in AHREs is maintained in the left atrium appendage avoiding the most important component of thrombus formation (blood stasis). Thus, it is not surprising that few cardioembolic events were found in NOAHA-AFNET 6 and consequent inefficacy of anticoagulant treatment.

Moreover, the general term subclinical atrial fibrillation introduced by Healey in 2012[2] may generate some misunderstanding. It only means that the patient does not report symptoms related to the arrhythmia and is not applicable to device-detected AF only. Indeed, subclinical AF comprise both patients with silent AF (chronic or paroxysmal AF without symptoms) and patients with device-detected AF as those reported in the ARTESiA study. The first category is found in elderly subjects and usually need long-term oral anticoagulation, while device-detected AF might not need such treatment as we have learned from ARTESiA trial.

Finally, an important message coming from the subgroup analysis of the ARTESiA trial is that patients with a first cerebral event (stroke or TIA) should be carefully studied to identify subclinical AF to offer an appropriate treatment for secondary stroke prevention. Data support the recent recommendation to screen these patients and those with embolic strokes of undetermined source through the use of implantable cardiac monitors or other long-term cardiac monitors.[9]

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