Subclinical Atrial Fibrillation and the Risk of Recurrent Ischemic Stroke

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In 2014, Hart et al introduced the clinical construct of "embolic stroke of unknown source" (ESUS).[1] In brief, it describes a subgroup of stroke patients in whom, based on brain imaging, cardioembolism is highly suggestive to be the putative stroke mechanism. Anticoagulation should be a better choice for these patients than antiplatelet therapy and this concept was subsequently investigated in three randomized trials.

The NAVIGATE-ESUS trial randomized 7,213 patients with a recent ESUS to either rivaroxaban 15 mg or aspirin 100 mg.[2] The trial was stopped prematurely for futility and harm: the primary endpoint of stroke and systemic embolism was not different in both groups (5.1%/year [rivaroxaban] vs. 4.8%/year [aspirin]), while major bleedings were nearly tripled with rivaroxaban (1.8 vs. 0.7%/year).

The RESPECT-ESUS trial assigned 5,390 patients with ESUS to either dabigatran (150 or 110 mg twice daily based on age and kidney function) or aspirin.[3] The primary endpoint of recurrent stroke was not different between the groups (4.1%/year with dabigatran vs. 4.8%/year with aspirin). Nonmajor bleedings were also not different between the groups, but clinically relevant nonmajor bleeding occurred more often with dabigatran (1.6%/year) than with aspirin (0.9%/year).

A third trial called ATTICUS is smaller with a planned inclusion of only 500 patients and a brain imaging endpoint,[4] but was stopped recently for futility (Sven Poli, personal communication).

So, does the concept of ESUS belong to the "dustbin of history" (R. Hart, quote)? Yes, in terms of generally using anticoagulation in all with ESUS. No, in terms of pointing to a need to further identify a subgroup of ESUS with cardioembolism that may benefit from anticoagulation.[5]

One group that without any doubt benefits from anticoagulation for stroke prevention is patients with atrial fibrillation (AF). But AF might escape routine diagnostics in stroke patients as it is often paroxysmal.[5] The most sensitive method for AF detection is continuous monitoring by an implantable cardiac monitor. This type of device-detected AF is also called subclinical AF (SCAF) or atrial high rate episodes if found in implanted cardiac devices like pacemakers with an atrial lead.[5] Recent evidence suggests that SCAF is a frequent phenomenon in patients with implanted cardiac devices,[6] but also in patients with cardiovascular risk factors having continuous electrocardiogram monitoring by a subcutaneous implanted cardiac monitor.[7–9] It is important to note that the risk of stroke is substantially lower than in patients with clinical AF, though structural changes of the left atrium have to be taken into account—a higher stroke risk in those with left atrial dilatation.[10] The efficacy of oral anticoagulants in patients with SCAF is currently being investigated in two randomized trials: ARTESIA (NCT01938248) and NOAH-AFNET6 (NCT02618577). However, the percentage of patients with a history of stroke is rather low (e.g., 4.5% in ARTESIA [Jeff Healey, personal communication]).

The role of SCAF in stroke patients is uncertain.[11,12] In this issue of *Thrombosis and Haemostasis*, Kitsiou et al report the 3-year follow-up data of a prospective observational study in 123 patients with ESUS,[13] which extends the initial findings published in 2017.[14] They report a cumulative SCAF prevalence of 41% and a stroke recurrence rate of 23%. The proportion of patients with SCAF is rather similar to studies in patients with cardiovascular risk factors or implanted devices, but the stroke recurrence rate is six to 10 times higher (►**Fig 1**). Therefore, the analysis of patients who

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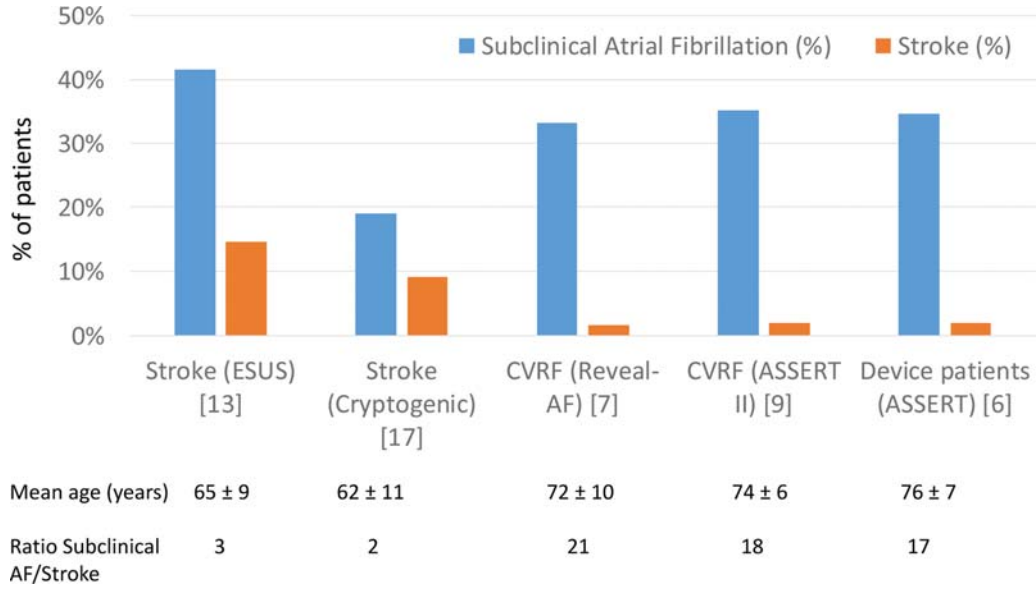

Fig. 1 Ratio of rate of subclinical AF and rate of stroke in implanted monitors and cardiac devices. Percentage of patients with subclinical atrial fibrillation detected by continuous monitoring and stroke rate in the two stroke studies (ESUS patients in the current study,[13] cryptogenic stroke patients in the CRYSTAL-AF study[17]), in two studies of patients with cardiovascular risk factors (CVRF) (Reveal-AF,[7] ASSERT-2[9]) and in one study in patients with implanted devices (ASSERT[6]). The mean age was higher in the nonstroke studies, but the stroke risk substantially lower.

experience SCAF and a recurrent stroke is of crucial importance. In five patients, SCAF preceded the stroke while in the other four, recurrent stroke occurred before the SCAF. Two patients with SCAF were insufficiently anticoagulated when the stroke occurred.

Most evidence regarding the risk for stroke comes from the ASSERT trial.[6] While the overall risk of stroke was 2.5 higher in patients with SCAF, there was no clear temporal relationship between SCAF and the stroke event, i. e., only 8% of patients had SCAF within 30 days before stroke.[15] This seems similar to patients after ESUS as found in the current study[13]: none of the patients had SCAF in the 30 days before the stroke. Another subanalysis from the ASSERT trial informed that SCAF increases the risk only if one episode exceeds 24 hours.[16] A total of 78% of the recurrent stroke events were again ESUS.

Some limitations have to be acknowledged. The duration of the longest SCAF episode during follow-up was not collected in the study because the implantable cardiac monitor was explanted after the first detection of SCAF. The study is single-center study and all patients with SCAF received anticoagulation, which limits conclusions to be made on the natural history of SCAF post-ESUS.

So, what do we learn from the current study? SCAF is a frequent finding after ESUS and the stroke recurrence risk in these patients is very high (23% in 3 years). There is no temporal relationship between SCAF and stroke though the impact of longer duration of SCAF on stroke risk was not assessed. This evidence suggests that an atrial myopathy may cause both the stroke and the SCAF.[12] Future studies with implantable loop recorders should continue monitoring after the first documentation of SCAF and ideally randomize these patients to anticoagulation versus antiplatelet therapy. And other studies such as the ongoing ARCADIA study (NCT03192215), which is randomizing patients with prior ESUS and evidence of atrial cardiomyopathy to apixaban or aspirin, should help determine whether evidence of atrial myopathy might be used as a guide to the need for anticoagulation rather than intensively looking for SCAF.

Conflict of Interest
None declared.

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