

Guest Editorial

Subclinical atrial fibrillation and anticoagulants. Where does the evidence lead us?

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“Subclinical” atrial fibrillation (AF) refers to short, asymptomatic episodes of atrial arrhythmia, typically lasting from a few minutes to several hours.^[1] These episodes are often unnoticed by patients and are most commonly identified through continuous cardiac rhythm monitoring, particularly in individuals with implanted cardiac devices. Studies such as ASSERT II, REVEAL AF, PREDATE AF, and the DANISH LOOP trial have shown that approximately one-third of such patients exhibit subclinical AF.^[2,3]

Data from the ASSERT and TRENDS trials, based on implantable device recordings, have demonstrated that subclinical AF is associated with a 2.5-fold increase in stroke risk compared to patients without AF. This risk, while clinically significant, remains approximately 50–60% lower than that attributed to clinically overt AF, as reported in the Framingham Heart Study, where stroke risk was increased fivefold.^[4]

Two recent randomized controlled trials, ARTESIA and NOAH-AFNET 6, have evaluated the efficacy of anticoagulant therapy in patients with subclinical AF.^[1,5]

The ARTESIA trial enrolled 4,012 patients at elevated risk for stroke (mean age 79 years; 36% women; mean CHA₂DS₂VASc score: 3.9) with device-detected subclinical AF episodes ranging from 6 minutes to 24 hours.^[6] Participants were randomized to receive either aspirin (100 mg once daily) or with apixaban (2.5 mg or 5 mg twice daily, dose-adjusted based on individual criteria). The primary efficacy endpoint was the incidence of stroke or systemic embolism, while major bleeding was the primary safety endpoint. Over a mean follow-up of 3.5 years, apixaban was associated with a 37% relative reduction in the primary outcome (95% CI: 12–55%) compared to aspirin. However, this benefit came at the cost of an 80% relative increase in major bleeding events.

The absolute difference translated into 4.6 fewer strokes or embolic events and 4.1 more major bleeding events per 1,000 patient-years in the apixaban group. Notably, 45% of strokes in the aspirin group resulted in death or significant disability, a figure that was halved among patients treated with apixaban. Conversely, 15% of major bleeds in the apixaban group were life-threatening or required emergency intervention. Based on these findings, apixaban may be considered in selected patients with subclinical AF and elevated thromboembolic risk.

The NOAH-AFNET 6 trial, which included a smaller cohort (2,536 participants), did not demonstrate a statistically significant reduction in stroke incidence with anticoagulation (edoxaban) compared to placebo.^[7] Furthermore, the risk of major bleeding was increased among patients receiving edoxaban.

Key design differences between the two studies may explain the discrepant results:

1. NOAH-AFNET 6 enrolled younger participants (mean age 65 vs 79 years),
2. The minimum CHA₂DS₂VASc score was lower (≥ 2 vs ≥ 3),
3. Subclinical episode duration was unrestricted (vs ≤ 24 hours in ARTESIA),
4. A different anticoagulant was used (edoxaban vs apixaban),
5. Control group received placebo or aspirin for other indications (vs aspirin only),
6. The primary endpoint in NOAH included cardiovascular death (excluded in ARTESIA),
7. The safety endpoint included all-cause mortality (excluded in ARTESIA),
8. The overall sample size was smaller.

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Despite their differences, both studies reported a relatively low absolute annual stroke rate during follow-up, 1.24% in ARTESIA and 1.1% in NOAH-AFNET 6. The absolute risk reduction for stroke in ARTESIA was modest, at just 0.4%.

A recent meta-analysis incorporating data from ARTESIA and NOAH-AFNET 6 demonstrated that anticoagulation in patients with subclinical AF was associated with a 32% relative reduction in stroke or systemic embolism (95% CI: 8–50%) and a 62% increase in major bleeding (95% CI: 5–150%).^[8] The findings are largely influenced by ARTESIA, which had a larger sample size and greater number of events.

CLINICAL IMPLICATIONS AND RECOMMENDATIONS

The management of asymptomatic patients with device-detected AF episodes remains complex. Several clinical considerations are warranted:

1. **Accurate diagnosis:** Clinicians should first ensure that the detected rhythm disturbances represent true atrial fibrillation. Upon confirmation, stroke risk should be stratified using the CHA₂DS₂VASc score.
2. **Symptomatology:** The presence or absence of symptoms should not be the primary determinant for anticoagulation. Patients may be asymptomatic during prolonged AF episodes and symptomatic in sinus rhythm. Moreover, post-ablation monitoring has shown asymptomatic recurrences of AF, underscoring that symptom burden does not reliably correlate with arrhythmic risk.^[9]
3. **Duration of subclinical AF:** There is no universally accepted threshold for AF duration that mandates anticoagulation. However, evidence from heart failure studies suggests that episodes lasting ≥6 minutes may already be clinically relevant.^[10]
4. **Risk-benefit assessment:** In deciding whether to initiate anticoagulation, clinicians must carefully balance the patient's thromboembolic risk against their bleeding risk. For some individuals, particularly those at high risk for stroke and low bleeding risk, anticoagulation may be justified—even in the absence of symptoms.

CONCLUSION

While anticoagulation reduces the relative risk of stroke in patients with subclinical AF episodes under 24 hours, the absolute benefit appears small, especially when weighed against the increased bleeding risk. At present, the routine use

of anticoagulants in such patients is not clearly supported and individualized clinical judgment remains essential. Ongoing research and subgroup analyses may help identify which patients derive the greatest net benefit from anticoagulation in the management of subclinical AF.

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