Oral factor Xa inhibitors for stroke prevention in patients with device-detected atrial fibrillation – Recent evidence from the NOAH-AFNET 6 and ARTESiA trials

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Device-detected atrial fibrillation (AF), also known as atrial high rate episodes, is a frequent finding in patients with a cardiac implantable electronic device such as a pacemaker, or an implantable cardioverter-defibrillator or loop recorder. First described about two decades ago (1), there is now a considerable body of evidence that consistently shows an association of atrial high-rate episodes lasting 5-6 minutes or longer with an increased risk of ischemic stroke or systemic embolism, in the absence of a diagnosis of clinical AF (detected by surface ECG) (1–3). In 2023, two major randomized clinical trials that investigated the efficacy and safety of oral anticoagulation for stroke prevention in this population were completed and published. Here, we provide a brief overview of three key clinical investigations that were conducted over the last 20 years.

Between 2004 and 2009, the Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial (ASSERT) Investigators enrolled 2,580 patients aged 65 years or older, with hypertension and who had recently undergone implantation of a dual-chamber pacemaker or defibrillator (3). The mean age of the study participants was 76 years, 42% were female, and 7% had had a prior stroke. At baseline, a total of 62% of participants were treated with aspirin. At 3 months following enrollment, a total of 261 patients (10.1%) had at least one episode of device-detected AF. During a mean follow-up of 2.5 years, patients with device-detected AF, compared to participants without device-detected AF, had a higher risk of ischemic stroke or systemic embolism (1.7% vs. 0.7% per year, hazard ratio [HR] 2.49, 95% confidence interval [CI] 1.28–4.85). There was a gradual increase in absolute risk according to the presence of additional risk factors; in patients with device-detected AF, the risk of ischemic stroke or systemic embolism varied from 0.6% per year in those with a CHADS2 score of 1, to 3.8% per year in those with a CHADS2 score >2. Device-detected AF was associated with a higher likelihood of developing clinical AF documented on a surface ECG, but was not associated with myocardial infarction or cardiovascular death. A post hoc analysis including 893 ASSERT participants with device-detected AF over the full duration of follow-up showed that device-detected AF was typically short in duration, with the longest episode lasting between 6 minutes and 6 hours in more than half of cases (52%) (4). Moreover, progression of device-detected AF to episodes >24 hours or to clinical AF was associated with an increased risk for hospitalization for heart failure (5). In summary, device-detected AF is typically short-lasting, asymptomatic, and associated with an increased risk of ischemic stroke or systemic embolism. However, both the absolute and relative risks for thrombotic events are markedly lower than those observed in patients with a diagnosis of clinical AF documented on a surface ECG (6, 7). In clinical AF, treatment with a vitamin K antagonist or an oral thrombin or factor Xa inhibitor effectively reduces stroke. Until recently, however, the effects of oral anticoagulation in patients with device-detected AF were uncertain (8).

Between 2016 and 2022, the Non–Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial High Rate Episodes (NOAH)-AFNET 6 Investigators enrolled patients aged 65 years or older, with at least one episode of device-detected AF lasting 6 minutes or longer, and at least one additional stroke risk factor. Study participants were randomized to the oral factor Xa inhibitor edoxaban, or control (9). Patients randomized to control either received an inactive placebo, or, aspirin if
there was a clinical indication for its use (e.g., coronary artery disease). The main analysis included 2,536 patients (mean age 78 years, 37% female, and 10% with a prior stroke or transient ischemic attack). The median duration of device-detected AF episodes prior to enrollment was 2.8 hours. A total of 54% of participants randomized to control had an indication for and were thus treated with aspirin. During a median follow-up of 21 months, edoxaban did not reduce the primary efficacy outcome of a composite of cardiovascular death, stroke or embolic events including systemic embolism, myocardial infarction and pulmonary embolism (3.2% vs. 4.0% per year, HR: 0.81, 95% CI: 0.60–1.08). Edoxaban increased major bleeding (2.1% vs. 1.0% per year, HR: 2.10, 95% CI: 1.30–3.38). The trial was not sufficiently powered to assess the effect of the study intervention on stroke or systemic embolism (1.0% vs. 1.5% per year, HR: 0.65, 95% CI: 0.39–1.07).

Between 2015 and 2021, the Apixaban for the Reduction of Thrombo-Embolism in Patients with Device-Detected Subclinical Atrial Fibrillation (ARTEsIA) Investigators enrolled a similar population of patients with at least one episode of device-detected AF lasting 6 minutes or longer (but no episode lasting longer than 24 hours), and additional risk factors. Study participants were randomized to the oral factor Xa inhibitor, apixaban, or aspirin (10). The main analysis included 4,012 participants (mean age 77 years, 36% female, and 9% with a history of stroke, systemic embolism or transient ischemic attack). The median duration of the longest episode of device-detected AF in the six months prior to enrollment was 1.5 hours. During a mean follow-up of 3.5 years, apixaban, as compared to aspirin, reduced the primary efficacy outcome of stroke of any cause or systemic embolism (0.8% vs. 1.2% per year, HR: 0.63, 95% CI: 0.45–0.88), at the cost of increased major bleeding (1.7% vs. 0.9% per year, HR: 1.80, 95% CI: 1.26–2.57). The reduction in disabling or fatal stroke (i.e., modified Rankin Scale score 3-6) was 49% (0.3% vs. 0.5% per year, HR: 0.51, 0.29–0.88). Fatal bleeding was very rare, and was numerically lower in patients randomized to apixaban (0.1% vs. 0.2% per year, HR: 0.70, 95% CI: 0.31–1.57).

A study-level meta-analysis of the NOAH-AFNET 6 and ARTEsIA trials showed that the results of the two trials are entirely consistent (11). This meta-analysis showed that oral anticoagulation with edoxaban or apixaban, as compared to control/aspirin, reduced stroke or systemic embolism by 35% (relative risk [RR]: 0.65, 95% CI: 0.49–0.86). The reduction in ischemic stroke with oral anticoagulation was 32% (RR: 0.68, 95% CI: 0.50–0.92), and oral anticoagulation also modestly reduced the primary composite efficacy outcome of the NOAH-AFNET 6 trial which included cardiovascular death in addition to stroke and embolic events (RR: 0.85, 95% CI: 0.73–0.99). The meta-analysis further showed that there was a consistent increase in major bleeding with oral anticoagulation (RR: 1.62, 95% CI: 1.05–2.50). Thus, any apparent difference in the interpretation of the two trials is based on the choice of the primary study outcomes and (lack of) statistical power to assess for differences in clinical outcomes that are amenable to antithrombotic therapy (11). In summary, there is a clear association of device-detected AF with an increased risk of ischemic stroke or systemic embolism. Both the absolute and relative risks are lower than that associated with clinical AF documented on a surface ECG. A study-level meta-analysis from the recent NOAH-AFNET 6 and ARTEsIA trials in patients with device-detected AF demonstrated a robust reduction in stroke or systemic embolism with treatment with an oral factor Xa inhibitor (edoxaban or apixaban), as compared to control/aspirin. This reduction came at the cost of more major bleeding. Additional analyses from both trials are underway to determine subgroups that are most likely to derive the largest benefit from either treatment strategy (12–14).

Disclosures

Dr. Benz reports lecture fees from Bristol-Myers Squibb and AstraZeneca, and participation in an educational program supported by Boston Scientific (“Fellowship Herzrhythmus”). Dr. McIntyre reports research support paid to his institution from AOP Pharma and honoraria from Trimed Therapeutics and Servier.

References

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