Apixaban for Treatment of embolic stroke of Undetermined Source - ATTICUS randomized trial - explorative analysis of AF burden in the ATTICUS cohort

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Background: Secondary prevention after embolic stroke of undetermined source (ESUS) has not yet been established. It is likely that a relevant number of ESUS patients have significant episodes of atrial fibrillation (AF) that is not detected by conventional Holter ECGs. Despite high prevalence of occult atrial fibrillation, secondary prevention with acetylsalicylic acid (ASA) is the current standard therapy in ESUS patients. The ATTICUS cohort has been selected for prevalence of at least one suggestive risk factor for cardiac embolism (RF) creating an enriched ESUS population.

Purpose: This work aims to evaluate overall AF burden in the ATTICUS cohort; to determine the correlation between AF detection and new ischemic lesions; and to explore predictors for atrial fibrillation within the enriched ESUS population.

Methods: The study enrolled ESUS patients with a risk profile for cardiac thromboembolism. Patients were randomized 1:1 into the ASA or apixaban arm, respectively. Study drug was initiated within 3–28 days after minor/moderate stroke and 14–28 days after major stroke. Cardiac monitoring by either implantable or mobile ECG devices was required during the follow up period. MRI (Flair/DWI) was conducted within 7 days of AF detection and 12 months after randomization.

Results: Enrollment was stopped after interim analysis including 200 patients, due to futility. Overall, 373 patients were screened with 352 being enrolled in the ITT population (178 and 174 in apixaban and ASA arms, respectively). Mean age of the ATTICUS population was 68.4 years with 51.4% males. 86.1% of the subjects suffered from hypertension. 63.4% of the population showed only one RF, all others showed two or more RFs, whereof most common were CHA2DS2-VASc ≥ 4 (93.8%), PFO (20.5%) and atrial high-rate episodes (AHRE, 13.1%). Analysis of the correlation of AF with each suggestive RF revealed an increased AF detection rate with increased amount of RF (Figure 1) and the most predictive RF to be atrial high-rate episodes. Prevalence of AF increased the risk for new embolic ischemic lesions (OR 2.05 (95% 1.01–4.15)). Newly detected AF was reported in 89 patients (25.3%), 49 occurring in the ASA arm, leading to an immediate switch (from ASA to) apixaban, as required by protocol.

Conclusions: In contrast to the recently published NAVIGATE and RESPECT ESUS trials, patients enrolled in ATTICUS had to exhibit additional predicting factors for (but no previously diagnosed) AF. These were significantly associated with the incidence of clinical AF with AHRE as the strongest predictor. Continuous cardiac remote monitoring will help to elucidate the AF burden and risk for stroke recurrence in this cohort and the effects of early oral anticoagulation with apixaban compared to antiplatelet therapy with ASA on the incidence of stroke recurrence.
Atrial fibrillation

Probability of event (%)

Time since randomization (weeks)

Number at risk

Risk factors
one  223  200  192  184  179  177  175  168  167  157  12
  two  108  94   91  83  80  77  76  73  73  70  4
  three or more  21   16  15  13  12  11  11   10  10  10  0

Risk factors  one  two three or more