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Editorial

Secondary stroke prevention in atrial fibrillation: Still lacking pace?

G.D. Athanassopoulos *, I. Armenis

Onassis Cardiac Surgery Center, Athens, Greece

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The high risk of recurrent stroke due to atrial fibrillation (AF) and the ominous outcome thereafter render secondary prevention with oral anticoagulation (OA) critical [1].

Warfarin has been shown to be superior over antiplatelet agents for stroke prevention in AF. In a relevant metaanalysis [2], OA with warfarin for secondary prevention in 1000 patients with AF prevented 48 strokes per year, at a cost of only 2 extracranial hemorrhages.

Despite available data and supportive guidelines, limited adoption of proper antithrombotic treatment (ATT) in AF overall has been achieved during the last 15 years [3]. With reference to secondary stroke prevention in AF, almost half of the eligible patients are not on OA. Lack of guideline knowledge, clinical factors related to bleeding risk (age, frailty, poor compliance, cognitive/motor problems, previous bleeding) and socio-economic factors (clotting time monitoring availability for warfarin, cost for novel oral anticoagulants-NOACs) may prohibit the use of OA. Greater prevalence of some of the aforementioned parameters in secondary prevention patients might further reduce ATT adoption. Corroborative evidence for the hesitance is the low ATT (<50%) even in less disabled AF patients post-stroke [4].

Management of patients with history of intracranial hemorrhage or with risk markers for intracranial hemorrhage (brain microbleeds, cortical superficial siderosis or leukoaraiosis on magnetic resonance imaging) is particularly challenging with reference to ATT [5].

In the current paper [6], adherence in ATT was assessed both overall and for secondary/primary stroke prevention against the 2010 ESC guidelines for AF management in Europe and North America. In western countries, patients are older, mainly Caucasians with higher prevalence of AF than those from Asia mainly included in the current study.

Secondary prevention group comprised 2.5 fold more patients older than 75 years (28% vs 11%).

The lack of AF-related symptoms characterizing approximately one third of AF patients renders screening for AF necessary, as stroke might be its first clinical manifestation. In the present study, 26% of patients enrolled had no AF symptoms; not surprisingly, this ratio rised to double in secondary prevention cohort (44% vs 22%).

A great proportion of AF cases (43.5%, similar in both secondary and primary stroke prevention cohorts) were newly diagnosed at the enrollment in the study.

A limited number of patients were on antiarrhythmic treatment (12% overall), equally distributed between the cohorts.

Contraindications to OA were more common in secondary prevention cohort (11% vs 8%).

All patients in OA received warfarin, as warfarin was the only OA regiment available at the time of the study. Almost one third (35%) of the study population was on OA, of which 18% were secondary prevention subcohort. Another 20% received OA combined with antiplatelet therapy. Secondary and primary prevention subcohorts shared equal quality of anticoagulation by warfarin control (TTR: 62% vs 57%).

Recurrent strokes have been reported to account for 25–30% of all strokes, being more disabling, fatal and costly compared to first-ever strokes [7]. In the present study, stroke rates in patients with prior stroke were 2.7-fold higher than those without prior stroke (6.3% vs 2.4%). A previous stroke was an independent risk factor for 1-year stroke.

Regardless of primary or secondary stroke prevention, guideline-adherent ATT significantly reduced the risk of stroke compared with non-guideline adherent ATT.

Distribution of non-guideline adherent ATT was similar between primary and secondary stroke prevention cohorts (51% vs 49% respectively). Under- or overtreatment were equally distributed between primary/secondary prevention cohorts (25% vs 27% and 26% vs 22% respectively). Undertreatment was associated with a 2.7-fold greater risk of stroke overall. The relative risk was equally increased in both secondary and primary prevention cohort (3.3 vs 2.7). Overtreatment was associated with a higher probability for 1-year major bleeding rate overall (8.4 fold increase). This is in contrast with previous studies which found no significant association between overtreatment in ATT and a risk of major bleeding [8]. In addition, overtreatment increased the risk of stroke (3.5 fold increase) in primary prevention with low risk $CHAD_2VASc$ cohort. This real-world finding is in concordance with the previous evidence of neutral effect for combination therapy in stroke risk [9].

In the current study a substantial number of patients with OA combined with antiplatelet agents was reported (20%, n = 362). Secondary

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* Corresponding author at: Sygrou Av 356, Athens 17674, Greece.
E-mail address: athan1@otenet.gr (G.D. Athanassopoulos).

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prevention cases were more likely to receive combination therapy than those belonging to primary prevention cohort (25% vs 19%). Overtreated patients receiving combination therapy with no evidence of acute coronary syndrome were subject to similar risk of stroke with those receiving OA monotherapy, independently of prior stroke history. Surprisingly, lack of statistically significant overtreatment effect on major bleeding was found in this subcategory (relative risks: 2.4 and 1.7 for primary and secondary prevention respectively). These results seem to contradict previous evidence that combination therapy has been associated with an increased risk of major bleeding [9].

Stroke risk stratification for current study (conducted from 2009 to 2011) was based on the $CHADS_2$ score, but posthoc modeling was applied for analysis incorporating CHA_2DS_2VASc score. Secondary prevention group had higher CHA_2DS_2VASc score as expected (5.2 ± 1.8 vs 2.3 ± 1.7), partly due to higher incidence of vascular disease (44% vs 32%) compared to primary prevention cohort. More specifically, the Gulf SAFE registry included a significant proportion of vascular disease (34%). However, vascular disease was not related to stroke outcome in either secondary or primary prevention cohort.

In this study, approximately 4% of patients had dementia or cognitive impairment, which was more frequently observed in secondary prevention cohort (12% vs 3%). However the study did not report any specific characteristics about these 66 patients. NOACs in this specific cohort may contribute to better OA efficacy due to an increased need for secondary stroke prevention.

Current study heralds awareness for AF detection, reiterates the importance of ATT adherence to guidelines for secondary stroke prevention in AF, proves its limited application and justifies its necessity in a broader geographic territory.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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