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Looking through the PRISM: New Insights for Young Patients with Atrial Fibrillation and Stroke

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The scale of the global burden of stroke is unquestionable and future increases are predicted with changing demography and ageing populations [1, 2]. As a major risk factor for stroke [3] and as a cause of morbidity and mortality in its own right, atrial fibrillation (AF) represents an opportunity for both primary and secondary prevention against stroke [4], where patients with one or more stroke risk factors should be considered for thromboprophylaxis [5]. Indeed, tremendous advances have taken place and continue to occur in how we approach thromboprophylaxis in AF by balancing stroke and bleeding risk [6–9].

In order to implement this knowledge, reliable data about the risk factors and outcomes of AF must be gathered at several levels from clinical trials and single-centre studies to analyses at the health system level in ‘real-world’ populations. As demographic factors and treatment guidelines and practices change, there is also a growing need for surveillance data [1].

In this issue, Gatellari et al. [10] report a study of adult in-hospital stroke admissions in New South Wales and the outcomes related to concomitant AF between 2000 and 2006 from A Program of Research Informing Stroke Management (PRISM). They found that 25.4% of 26,960 patients with ischaemic stroke had AF recorded during admission, which is comparable to previous studies. The authors are to be commended on this timely large-scale study which illustrates the potential utility of analyses at health system level.

The PRISM study confirms several well-characterised features of AF in the setting of stroke. First, AF prevalence and rates of all complications increased with age. Second, AF patients were more likely to suffer complications of every type and mortality than stroke patients without AF. Third, AF patients are more likely to have comorbidities, such as hypertension and heart failure, and these comorbidities increase with age.

Risk stratification scores have been validated for AF and risk of stroke and are increasingly used by clinicians in order to assess and individualise patient risk [11]. Gatellari et al. [10] assessed the pre-admission risk of stroke (using CHADS₂ [12] and CHA₂DS₂-VASC [13] scores) and bleeding (using the HAS-BLED score [14]). As shown in other real-world populations [11], the CHA₂DS₂-VASC score stratified more patients at high stroke risk than the

CHADS₂ score. A substantial proportion of patients at ‘high risk’ in both risk scoring schemes were not on anticoagulation, despite very few patients having HAS-BLED scores of ≥ 3 , which would signify high bleeding risk.

Gatellari et al. [10] considered the potentially modifying effect of age, sex and comorbidity on the association between AF and outcomes. Interestingly, although increased age was associated with increasing mortality, this interaction effect illustrated that the differences in mortality between AF and non-AF stroke decreased with increasing age. In other words, the effect of AF versus non-AF in stroke patients was greatest in young patients. At 30 days, the relative risk of mortality due to AF was 3.16 (95% CI 1.92–5.25) amongst those younger than 50, decreasing to 1.23 (95% CI 1.13–1.33) in patients aged >85 years. Moreover, the differences in proportion of patients needing rehabilitation and length of hospital stay between AF and non-AF patients were greatest in younger patients (p value interaction <0.0006 and <0.0001 respectively).

Young patients with stroke and AF clearly represent an under-recognised ‘at-risk’ population [15]. In the PRISM study, half of AF-related stroke patients aged <65 years had a CHA₂DS₂-VASC score of ≥ 2 (51.3%) and 39.8% had a CHADS₂ score of ≥ 2 , signifying a high risk of stroke [10]. We do know that AF patients in ‘real-world’ clinical practice receiving antiplatelet/no therapy have much higher rates of ischaemic stroke than patients receiving anticoagulation [16]. Antiplatelet therapy and no therapy are associated with similar bleeding rates to oral anticoagulation, especially in the elderly [4]. Therefore, there is a strong argument in terms of stroke prevention for increasing the utilisation of anticoagulants in clinical practice, given current under-treatment rates [16]. One recent analysis examining the net clinical benefit balancing the risk of ischaemic stroke and intracranial haemorrhage found a neutral or positive net clinical benefit (ischaemic stroke vs. intracranial haemorrhage) with oral anticoagulation in patients with a CHADS₂ score of ≥ 0 , and CHA₂DS₂-VASC score of ≥ 1 , whilst there was a negative net clinical benefit at a CHA₂DS₂-VASC score = 0 (reflecting the ‘truly low risk’ status of these patients) [17]. Indeed, the net clinical benefit was even greater at HAS-BLED scores of ≥ 3 .

Further studies of young stroke patients with AF are warranted in order to establish potential differences in aetiology and pathophysiology of stroke compared with older stroke patients with AF, as illustrated by the study by Gatellari et al. [10]. Such patients may require different diagnostic and treatment strategies. For example, in a recent hospital-based cohort study of French patients with AF, the risk of stroke and thromboembolism was independently increased by the presence of heart failure, previous stroke, or vascular disease in patients <65 years of age [18], suggesting that these factors are particularly important in younger AF patients.

With the advent of novel anticoagulants [19, 20], there are new therapeutic options without the potential harms of warfarin, particularly for younger patients with indications for lifelong anticoagulation. Future clinical trials and prospective cohort analyses of new treatments should be statistically powered to consider the comparative effectiveness of treatment in younger patients. Although the major increase in burden of stroke and AF will be a result of ageing populations, the importance of stroke prevention in young AF patients must not be neglected. Things can only improve.

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