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Ischemic Stroke and Atrial Fibrillation – A Deadly Serious Combination

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Stroke is among the leading causes of death and disability worldwide [1]. Over 80% of strokes are ischemic in origin, with a cerebral arterial occlusion caused by either thrombosis in situ (atherothrombosis) or blood clot dislodgement from the site of formation (thromboembolism) [2]. The overall 30-day mortality rates for ischemic stroke range between 10 and 17% [3].

Atrial fibrillation (AF) is the commonest sustained cardiac arrhythmia and an independent risk factor for death, with a relative risk of 1.5 for males and 1.9 for females in all age groups [4]. AF is also an independent risk factor for ischemic stroke, whereby $\geq 15\%$ of all strokes occur in the setting of AF, and the proportion substantially increases with age; indeed, one third of patients with stroke who are >65 years old also have AF [5]. Most AF-related strokes are due to the embolism of (usually large) thrombus formed in the left atrial appendage, which causes the embolic occlusion of a main cerebral artery or its branches with a large area of cerebral infarction [6]. Hence, AF-related cardioembolic strokes are often more severe, with substantial neurologic disability or increased mortality (almost doubled) compared with stroke from other etiologies [5, 6].

A number of common risk factors (including age, hypertension, heart failure, structural heart diseases, diabetes mellitus, etc.) are significantly associated with both the occurrence of AF or ischemic stroke and the development of AF- or stroke-related complications [7, 8]. These common stroke risk factors have been used to formulate stroke risk stratification schemata [8]. These schemata artificially categorise patients into low-, moderate- and high-risk strata, so that the 'high-risk' patients can be targeted for anticoagulation with warfarin, given the many limitations and concerns with bleeding of the latter drug [9, 10]. On the other hand, the likelihood of a poor outcome of stroke depends not only on the infarct size and location, but also on age and coexistent comorbidities (such as ischemic heart disease and diabetes mellitus) [3].

In this issue of *Cerebrovascular Diseases*, Tu et al. [11] reported a retrospective analysis of the placebo arm of 6 randomized controlled trials from the Virtual International Stroke Trials Archive (VISTA) on 2,865 patients with acute ischemic stroke, of whom 819 (29%) also had AF. At baseline, AF patients were older, more

likely to be female (consistent with female gender being an independent risk factor for stroke in AF patients [9]) and more likely to have cardiac comorbidity (namely, a history of hypertension and/or prior MI) compared with patients without AF (all $p < 0.05$). Unfortunately, a history of heart failure was not routinely recorded in VISTA, and many studies have documented a higher incidence of thromboembolism (including stroke) in patients with heart failure (particularly with 'systolic' heart failure) even in the absence of AF [12]. Not surprisingly, Tu et al. [11] also found that AF patients had a greater neurologic impairment at baseline, as measured by the National Institutes of Health Stroke Scale (NIHSS) (15 vs. 12 points, $p < 0.001$).

During the 3-month follow-up, AF patients were more likely to have any serious cardiac adverse event (SCAE), heart failure, ventricular tachycardia or fibrillation, or cardiac death, as compared to those without AF. In the multivariate model, AF was an independent risk factor for SCAE (odds ratio 2.1; 95% CI: 1.6–2.9; $p < 0.001$), along with age, prior MI and baseline NIHSS (all $p < 0.005$). Importantly, most of SCAE occurred within 3 days from stroke onset, which emphasizes the need for cardiac monitoring longer than the first 24 h, as recommended by the guidelines [13, 14]. Of note, a 7-day outpatient cardiac monitoring after ischemic stroke would detect 44 new AF cases that would benefit from oral anticoagulation per 1,000 patients monitored, which would gain 34 quality-adjusted life years, as recently shown [15]. Unfortunately, data on the AF burden and occurrence of AF during follow-up were not available in the study by Tu et al. [11].

Compared with patients without AF, 90-day all-cause mortality and functional deficit measured by the modified Rankin scale were higher in AF patients in their study; indeed, AF was a multivariate predictor of all-cause mortality (odds ratio 1.4; 95% CI: 1.1–1.8; $p = 0.002$) along with age, diabetes mellitus and the extent of baseline neurologic impairment (all $p < 0.005$), but (surprisingly?) AF did not predict a greater functional deficit ($p = 0.2$) in their survivors of ischemic stroke. However, it would have been of great interest to look at the *quality* of thromboprophylaxis *prior* to stroke if the full data had been available, the use of (well-controlled, i.e. high time in therapeutic range) warfarin with the resultant International Normalized Ratio of 2.0–3.0 reduces not only the risk of stroke but also the stroke severity and the risk of death from stroke [16]. In addition, data on the use of antihypertensive and lipid-lowering drugs prior to stroke, which could also potentially modify the stroke outcomes, were not available [14]. Data on the CHADS₂ (Congestive heart failure, Hypertension, Age >75 years, Diabetes mellitus, previous Stroke/TIA) and CHA₂DS₂VASc scores (Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, previous Stroke/TIA, Vascular disease, Age 65–74 years and Sex category [female gender]) would also be of interest, given the association of these scores with the risk of ischemic cardiovascular mortality (fatal MI or stroke), as was recently reported [17].

In summary, Tu et al. [11] have confirmed a substantial mortality and morbidity associated with the combination of AF and ischemic stroke. To prevent this 'deadly serious' combination, appropriate prevention of stroke using oral anticoagulation is needed in most AF patients [18, 19]. A considerable list of disadvantages of vitamin K antagonists precluded their optimal use, but new oral anticoagulants with a substantially more favorable profile (that is, direct thrombin inhibitors [e.g. dabigatran] and direct factor Xa inhibitors [e.g. rivaroxaban, apixaban]) are expected to change the scope of anticoagulation dramatically [20], facilitating the clinical uptake of the concept that only patients without any stroke risk factor would not need any thromboprophylaxis, whilst all other AF patients with ≥ 1 stroke risk factors should be considered for oral anticoagulation [10]. Things can only get better.

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