**Clinical Focus**

**Paroxysmal atrial fibrillation, stroke risk and thromboprophylaxis**

Gregory Y. H. Lip

Haemostasis Thrombosis and Vascular Biology Unit, University Department of Medicine, City Hospital, Birmingham, UK

Atrial fibrillation (AF) is the commonest sustained cardiac rhythm disorder, which has particularly attracted much clinical and research interest from the mortality and morbidity associated with stroke and thromboembolism. The more chronic presentations of AF have clinical subtypes based on the temporal pattern of the arrhythmia – AF is considered recurrent when a patient experiences two or more episodes, which may be paroxysmal if they terminate spontaneously, defined by consensus as seven days, or persistent if the arrhythmia requires cardioversion for termination of the arrhythmia (1).

Although paroxysmal AF is common, the associated stroke risk is less defined, given the limited information on its clinical epidemiology and the under-representation of these patients in clinical trials. As Gladstone et al. (2) highlight, it really depends on how hard we look for paroxysmal AF in patients who present with an acute stroke or thromboembolism. It has long been recognized that paroxysmal AF is frequently asymptomatic, and it has been estimated that only 1 in 12 paroxysms of AF are symptomatic (3). In their data from the prospective Registry of the Canadian Stroke Network, Gladstone et al. (2) found that 17% of 12,849 consecutive hospitalised ischemic stroke patients had a history of AF, and an additional 6% had new AF detected whilst in hospital (4% on admission electrocardiogram [ECG] and 2% detected later in hospital). In a study by Jabaudon et al. (4), a standard 12-lead ECG identified AF in 2.7% of 149 acute stroke and transient ischemic attack (TIA) patients at admission and in 4.1% of remaining patients within five days; however, a 24-hour ECG recording (Holter) detected AF in 5% of patients who had a normal standard ECG, whereas seven-day ambulatory ECG monitoring using an event-loop recording (ELR) device detected AF in 5.7% of patients with a normal standard ECG and normal Holter.

Unsurprisingly, a recent systematic review of a series of cohort studies reemphasises the importance of screening for occult AF after ischemic stroke and TIA given that an extended duration of ECG monitoring (e.g. event loop recorder [ELR], etc) after stroke/TIA identifies many more patients with (usually paroxysmal) AF than standard ECG and Holter monitoring alone (5). Another recent report found that in patients with acute ischemic stroke, even frequent atrial premature beats (APBs) recorded in 24-hour ECG (≥70 per 24 hours) were a marker for subsequent paroxysmal AF (6). Clearly, more rhythm monitoring investigations would be needed for subjects with acute stroke and/or thromboembolism, to define the relationship between paroxysmal atrial arrhythmias and stroke.

What is the evidence of stroke risk in paroxysmal AF?

As a whole, the paroxysmal AF population tends to be younger, with less comorbidities (and stroke risk factors) or structural heart disease compared to permanent AF subjects. For example, Hart et al. (7) reported that patients with intermittent (paroxysmal) AF in the “Stroke Prevention in Atrial Fibrillation” studies were younger (66 vs. 70 years), more often women and had less heart failure than those with sustained (permanent) AF. In the ACTIVE-W dataset, patients with paroxysmal AF were also younger, had a shorter AF history, more hypertension, and less valvular disease, heart failure, and diabetes mellitus than patients with sustained AF (8).

What is less clear is the required ‘burden’ of AF necessary for precipitating stroke and thromboembolism, given that the number of AF episodes per day – as well as AF burden – can vary greatly (9). The only published data on AF burden related to thromboembolism comes from the Italian AT500 Registry Investigators, where the adjusted risk of thromboembolism in a cohort of elderly patients suffering from bradycardia and wearing a pacemaker with antiarrhythmic pacing therapies, was 3.1-fold increased (95% confidence interval [CI] 1.1–10.5, p = 0.044), but only in patients with device-detected AF episodes of ≥24 hours during follow-up (10). Given the nature of this study cohort (elderly, pacemaker, multiple comorbidities, etc), further studies in ‘general’ populations of paroxysmal AF are still needed, to provide insights into the epidemiology and pathophysiology of AF burden and thromboembolism.

What do we really know about stroke and thromboembolic risk in paroxysmal AF, compared to permanent AF? The data on stroke and thromboembolism in paroxysmal AF patients per se...
largely comes from the non-warfarin arms of trial cohorts, and there are three publications of this nature (7, 10, 11).

In 2000, Hart et al. (7) reported a longitudinal cohort study comparing 460 participants with intermittent AF, who were compared with 1,552 with sustained AF treated with aspirin in the Stroke Prevention in Atrial Fibrillation studies. After an average of two years’ follow-up, the annualized rate of ischemic stroke was similar for those with paroxysmal (3.2%) and sustained (permanent) AF (3.3%). Of those predicted to be high risk, the observed stroke rate was 7.8% per year.

In 2007, Holmloser et al. (10) reported a post-hoc subgroup analysis of the patients with paroxysmal AF (n = 1,202) from the ACTIVE W (Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events). The latter was a trial comparing warfarin to combined antiplatelet therapy with aspirin and clopidogrel for the prevention of vascular events in 6,706 AF patients. The annualized risk of stroke or systemic embolism was 2.0% in paroxysmal AF compared with 2.2% in persistent or permanent AF (adjusted relative risk 0.94 (95% CI 0.63–1.40, p = 0.755).

Lip et al. (11) reported patients enrolled in the prospective SPORTIF III and V clinical trials (n = 7,329) where 836 subjects (11.4%) had paroxysmal AF. The annual event rates for stroke/systemic embolism were 1.73% for persistent AF and 0.93% for paroxysmal AF. In a multivariate analysis, after adjusting for stroke risk factors, gender and aspirin usage, the differences remained statistically significant, with a higher hazard ratio (HR) for stroke/systemic embolism in persistent AF (vs. paroxysmal AF, HR 1.87, 95%CI 1.04–3.36; p = 0.037). In ‘high risk’ patients (with ≥2 stroke risk factors) annual event rates for stroke/systemic embolism were 2.08% for persistent AF and 1.27% for paroxysmal AF (adjusted HR = 1.68, 95%CI 0.91–3.1, p = 0.098). Thus, this ancillary analysis of anticoagulated subjects in the SPORTIF trial found those with paroxysmal AF had stroke rates which were lower than patients with persistent AF, although both groups had broadly similar stroke risk factors. Nonetheless, subjects with paroxysmal AF at ‘high risk’ had stroke/systemic embolism rates that were not significantly different to persistent AF subjects.

In short, the stroke and thromboembolism risks in paroxysmal AF should be considered to be comparable to that seen in permanent AF, especially when risk factors are present. In the Euro Heart Survey registry data, paroxysmal AF patients had a comparable risk for thromboembolic events as persistent and permanent AF (12).

These clinical observations of comparable stroke and thromboembolic risk between paroxysmal and permanent AF is compatible with pathophysiological data, showing that paroxysmal AF patients have abnormalities of haemostasis, platelets and endothelial damage/dysfunction, comparable to permanent AF (13, 14). It is probably worth highlighting that whilst there is a degree of excess of platelet activation in AF compared with healthy controls, there was no significant difference between AF patients and ‘disease control’ subjects in sinus rhythm (15). Thus, platelet activation in AF may be due to underlying cardiovascular diseases, rather than due to AF per se.

What are the predictors of stroke in paroxysmal AF?

A recent systematic review, conducted as part of the evidence-based National Institute for Health and Clinical Excellence (NICE) national clinical guidelines for AF management, a history of stroke or TIA, increasing age, hypertension and structural heart disease (left-ventricular dysfunction or hypertrophy) were good predictors of stroke risk in AF patients (16). The evidence for stroke risk regarding diabetes mellitus, gender and other characteristics were found to be less consistent risk factors in the overall AF population per se, although it was accepted that diabetes was an important risk for stroke generally, and thus, incorporated into most stroke risk stratification schemes for AF.

As recently highlighted in this journal, several clinical and echocardiographic measures may also distinguish the clinical presentation of thromboembolism in non-valvular AF (17). In an analysis of 72 subjects with incident peripheral embolism in the setting of non-valvular AF, small emboli are more likely to lodge in the cerebral circulation as a result of hydrodynamic, anatomic, and physical factors AF (17). Interestingly, these investigators suggest that advanced age, atrial enlargement and other co-morbidities may increase the propensity for the formation of ‘larger thrombi’ which may bypass the carotid orifice merely as a function of size.

Hart et al. (7) reported that the independent predictors of ischemic stroke in patients with paroxysmal AF who were participating in the Stroke Prevention in AF trials, were advancing age (relative risk [RR] = 2.1 per decade, p < 0.001), hypertension (RR = 3.4, p = 0.003) and prior stroke (RR = 4.1, p = 0.01). This list of risk factors is in keeping with a recent systematic review from the Stroke Risk in Atrial Fibrillation Working Group (18) which found that prior stroke/TIA (RR 2.5, 95%CI 1.8 to 3.5), increasing age (RR 1.5 per decade, 95%CI 1.3 to 1.7), a history of hypertension (RR 2.0, 95%CI 1.6 to 2.5), and diabetes mellitus (RR 1.7, 95%CI 1.4 to 2.0) were the strongest, most consistent independent risk factors. Female sex was inconsistently associated with stroke risk, whereas the evidence was inconclusive that either heart failure or coronary artery disease was independently predictive of stroke.

Nonetheless, the risk factors identified represent those risk factors which were documented for the respective clinical trial purposes, and many factors for thromboembolism – for example, atherosclerotic vascular disease – were not systematically looked for.

Unanswered questions

The limited data from general populations with paroxysmal AF necessitates prospective longitudinal studies linking AF burden to stroke and thromboembolism. However, given the high proportion of paroxysmal AF patients who have ‘lone’ or idiopathic AF, the event rates may be low, and large numbers of patients would need to be followed up for a long period. Also, if patients have high-risk features, clinical practice would be to start anticoagulation, which would confound any ‘natural history’ analysis of thromboembolism rates in such patients.
Furthermore, if there is a real link between AF burden and thromboembolism, would a strategy of aggressive rhythm control reduce thromboembolic risk? Indeed, some patients with paroxysmal AF achieve ‘cure’ following new ablation techniques, and the question which remains unanswered is whether ablation of paroxysmal AF completely abolishes thromboembolism. Recent consensus guidelines from the European Heart Rhythm Association on antithrombotic therapy in the setting of electrophysiological procedures still advocate some caution, due to the limited evidence, recognizing that late thromboembolism can still occur following AF ablation, especially in the presence of risk factors (19).

Conclusion
In the presence of similar stroke risk factors, the data suggests that paroxysmal AF patients have broadly similar stroke rates to patients with permanent AF and thus, should be given appropriate thromboprophylaxis. Stroke risk stratification schemes should therefore apply equally to paroxysmal AF and those identified as being at ‘high-risk’ based on clinical or echocardiographic risk factors should be given oral anticoagulation. This approach for now – until more evidence is available – would improve efforts at stroke prevention amongst all AF subjects.

References