

## Editorial Focus

# Atrial fibrillation and stroke risk prevention in real-life clinical practice

Kok Hoon Tay; Gregory Y. H. Lip; Deirdre A. Lane

University Department of Medicine, City Hospital, Birmingham, United Kingdom

Patients with atrial fibrillation (AF) have a substantial risk of stroke and thromboembolism compared with age-matched people in sinus rhythm, which varies with associated comorbidities and risk factors (1, 2). When a stroke occurs in patients with AF, the severity of the stroke is much greater, as is mortality and disability compared to those in sinus rhythm (3). Unsurprisingly, the biggest challenge facing physicians caring for patients with AF is the prevention of stroke and thromboembolism, whether as primary or secondary prevention.

Examination of stroke rates from the non-warfarin arms of trial cohorts and one epidemiological study have informed the development of stroke risk stratification schema for AF (4). More than a dozen stroke risk stratification schemes for AF patients have been proposed, but all have modest predictive value for stroke (1, 5). These risk stratification schemes are used in many guidelines, which generally recommend anti-thrombotic therapy with warfarin for AF patients at 'high-risk' of stroke and aspirin for those at 'low-risk'. For those patients who fall into the 'moderate-risk' category (usually those with one single stroke risk factor), either aspirin or warfarin is recommended, due to the lack of evidence in favour of either drug, as well as the close margin between stroke reduction and bleeding risk of anticoagulation with warfarin. Thus, many guidelines recommend that anti-thrombotic therapy is decided on an individual basis. However, such an approach is confounded by new trial evidence from the Birmingham Atrial Fibrillation Treatment of the Aged Study (BAFTA) showing the substantial benefits – even in subjects aged >75 – of warfarin over aspirin for stroke prevention (1.8% vs. 3.8% events per year, respectively: relative risk [RR] 0.48, 95% confidence interval [CI] 0.28–0.80), with no difference in rates of major haemorrhage between warfarin or aspirin (6). The merits or otherwise of why warfarin should really be the drug of choice for stroke prevention in elderly patients with AF have recently been debated in this journal (7, 8).

It is said that guidelines beget guidelines, and in real-life clinical practice, such guidelines on anti-thrombotic therapy for AF are often not adhered to (9). In the Euro Heart Survey, prescription of antithrombotic therapy was based on the type of AF and availability of warfarin monitoring clinic, rather than the

stroke risk profile per se (9). The type of AF should not be a consideration, given that paroxysmal AF has a similar stroke risk to persistent or permanent AF, in the presence of risk factors, and such patients would derive much benefit from anticoagulation (10).

In the current issue of *Thrombosis and Haemostasis*, Rietbrock et al. (11) evaluate the incidence of stroke in routine clinical practice among >51,000 chronic AF patients aged ≥40 years taking either aspirin or warfarin, by examining the United Kingdom General Practice Research Database from 1987 onwards. Virtually all the patients had been treated with warfarin or aspirin, with almost 10,000 patients who had received both (either concomitantly or separately). They compared non-use (never) with both 'current use' (defined as the time from the prescription date until three months after the expected duration of use) and 'past use' (defined as the period of time starting three months after the expected end of a prescription) and found that current use of warfarin was associated with a 38% (RR 0.62, 95% CI 0.54–0.71) reduction in stroke compared to past use after adjustment for age, sex, and stroke risk profile. Compared to no warfarin use, current and past use were both associated with a significant reduction in stroke rate, by 67% (RR 0.33, 95% CI 0.30–0.35) and 44% (RR 0.56, 95% CI 0.50–0.63), respectively. The benefits were more evident amongst the elderly, whereby the risk of stroke was reduced by 45% in elderly warfarin users (aged 75 years or older) and by 14% in younger users. As emphasised by the BAFTA trial (6), elderly patients with AF should not be denied warfarin thromboprophylaxis, given the impressive benefits of stroke prevention with anticoagulation in elderly AF patients.

In contrast, there was no difference in the rate of stroke between current and past use of aspirin (RR 1.04, 95% CI 0.94 – 1.15). Thus, the stroke risk reduction with warfarin in routine clinical practice is similar to that achieved in clinical trials, in a UK general practice cohort involving >30,000 elderly AF patients, demonstrating that the evidence from clinical trials can translate into real-life clinical practice. Indeed, current or past use of aspirin did not seem to matter, and in fact, there were no significant changes in the rates of stroke were observed with dis-

Correspondence to:  
Dr. Deirdre Lane  
University Department of Medicine  
City Hospital, Birmingham  
B18 7QH, United Kingdom  
Tel.: +44 121 507 5080, Fax: +44 121 507 5907  
E-mail: Deirdre.Lane@swbh.nhs.uk

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continuation of aspirin! This is an important message since many current guidelines recommend 'use warfarin or aspirin' for AF patients at 'moderate risk' for stroke. Given that aspirin is not necessarily safer in terms of bleeding risk (6), perhaps we should move towards a risk factor-based approach to stroke prevention, rather than an artificial categorization into low, moderate and high risk categories (4). Thus, all AF patients with one or more risk factors (that is, the 'moderate risk' and 'high risk' categories) should all be seriously considered for warfarin, whilst those with no risk factors at all (essentially, the 'low risk' category) could be considered for aspirin or no antithrombotic therapy.

These results from Rietbrock et al. (11) are very encouraging in terms of the stroke-risk reduction associated with warfarin use (past or current) compared to no therapy and are broadly similar to the risk reduction reported from a meta-analysis of clinical trials of dose-adjusted warfarin (12). This recently up-dated meta-analysis of 29 randomised trials in over 28,000 AF patients demonstrated that dose-adjusted warfarin resulted in a 64% (95% CI 49%-74%) reduction in stroke compared to placebo or control, whilst antiplatelet treatment (eight trials) with aspirin compared to placebo or no treatment was associated with a 22% (95% CI 6%-35%) reduction in the risk of stroke. Twelve randomized trials compared dose-adjusted warfarin with antiplatelet therapy alone, and warfarin was associated with a 39% (95% CI 22%-52%) reduction in stroke risk (12). Of note, the effect of aspirin on stroke risk reduction in the study by Rietbrock et al. (11) may have been underestimated since aspirin is available over the counter in the UK and is a cheaper off-prescription for people aged <65 years, who have to pay for prescriptions.

The data presented by Rietbrock et al. (11) are also supported by two other studies that have examined the stroke risk reduction in AF patients in 'usual care' clinical practice (13, 14). The study by Go et al. (13) of almost 12,000 AF patients in North California found that warfarin was associated with a 51% (95% CI

39%-60%) reduction in thromboembolism compared to no therapy, whilst the Danish study (14) demonstrated a 40% reduction in stroke associated with current warfarin use but the risk reduction was only significant among men.

Despite the overwhelming evidence of the benefit of thromboprophylaxis, such therapy still remains under-utilised. The reasons for this are numerous but include overestimation of the bleeding risk, underestimation of the stroke risk, the necessity of regular International Normalised Ratio (INR) monitoring, and interactions of warfarin with drugs, food, and alcohol. Further, the patients included in clinical trials are not seen as 'representative' of the types of AF patients usually encountered in clinical practice. Indeed, clinical trials unusually under-represent the elderly, have less risk of falls, and have better INR-control. However, the observation by Rietbrock et al. (11) of a 45% stroke risk reduction in patients aged  $\geq 75$  years currently taking warfarin (compared to past use) is consistent with the benefit of warfarin in the elderly AF patient, as recently shown in the BAFTA study (6).

Another interesting observation from the study by Rietbrock et al. (11) is that the stroke-risk reduction was only apparent after 6–12 months of treatment, possibly reflecting poor INR control in the first six months, although the authors do not report the percentage of time the INR was in the therapeutic range. Maintenance of a therapeutic INR is essential to prevent ischaemic stroke (INR < 2.0) or haemorrhagic stroke (INR > 3.0) (15). Clearly, the limitations of warfarin, by the substantial inter- and intra-patient variability in anticoagulation intensity mean that new oral anticoagulant alternatives to warfarin are eagerly awaited. A number of novel anticoagulants for the prevention of stroke in AF patients being developed and tested in phase III trials will hopefully have a more stable pharmacokinetic/pharmacodynamic profile than warfarin, thus removing the need for regular INR checks and enabling more patients to benefit from anticoagulant therapy, thereby further reducing the stroke risk.

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