Commentary

Stroke prevention in atrial fibrillation – things can only get better

Gregory Y. H. Lip & Timothy Watson

University Department of Medicine, City Hospital, Birmingham, UK

The association between atrial fibrillation (AF) and stroke has long been recognized, where the presence of AF increases the risk of stroke by up to fivefold across all age groups and accounts for approximately 15% of all ischaemic stroke [1, 2]. With age, this figure rises dramatically and approaches 25% in those aged >80 years. However, the absolute risk of stroke in AF does vary widely, from <1% to around 12% per annum, depending upon patient age and the presence of coexisting vascular risk factors such as diabetes mellitus, heart failure and hypertension [1]. Of note, the pathogenesis of thrombus formation (thrombogenesis) in AF is multifactorial and is not solely related to stasis in a poorly contractile left atrium – in fact, there is an increasing body of evidence to support the presence of a prothrombotic or hypercoagulable state, fulfilling Virchow's triad for thrombogenesis [3]. Thrombus in AF is also fibrin rich ('red thrombus') rather than platelet rich ('white thrombus'), in keeping with the benefits of anticoagulation in this condition [4].

Traditionally, a stroke prevention strategy in AF has been effected with either adjusted-dose vitamin K antagonists (e.g. warfarin) or antiplatelet therapy. Although neither strategy is ideal, it is worth considering the relative benefits of each. The evidence in favour of warfarin is robust and supported by ample evidence from clinical trials. Oral anticoagulation significantly reduces the risk of ischaemic stroke or systemic embolism compared with placebo (by two-thirds) or aspirin (by approximately 40%) [5]. This beneficial effect is seen for both primary and secondary stroke prevention, although, predictably, the absolute risk reduction for all stroke was far greater for secondary [number needed to treat (NNT) 12] than for primary prevention (NNT 37) [5].

What about antiplatelet therapy? Aspirin provides a stroke risk reduction of 22% in AF, compared with control, a risk reduction figure which is broadly similar to that seen by antiplatelet therapy in high-risk vascular disease patients [6, 7]. Thus, the 'aspirin effect' for stroke prevention in AF may simply reflect the effect of this drug on vascular disease given the common association of AF with vascular diseases [6]. Indeed, the Antithrombotic Trialists' Collaboration concluded that 'low dose aspirin (75–150 mg) is an effective antiplatelet regimen for long-term use in patients at risk of occlusive vascular events (including AF)' [7].

Given the recurrent debate over aspirin, one argument has been related to the choice of aspirin dose. Again, the view that aspirin at 300–325 mg should be preferred to 75 mg in AF is controversial. The systematic reviews of aspirin against placebo for AF [8, 9] both include trials that used doses between 50 mg and 325 mg per day, and there was no significant heterogeneity between the results of the individual trials. The first Stroke Prevention in AF (SPAF I) trial used aspirin 325 mg and reported the largest stroke reduction, but this was stopped at an interim stage and its result may be exaggerated – given also the internal inconsistency within the trial of the 'anticoagulation eligible' vs. the 'warfarin ineligible' arms [6]. In the most recent systematic review [9], the pooled odds ratio for the aspirin effect was nonsignificant unless the SAFT trial was included, which used aspirin 75 mg and fixed low-dose warfarin. Pharmacologically, near-complete platelet inhibition is achieved with aspirin 75 mg, so it is difficult to conceive what benefit the higher dose might be achieving. This is supported by a recent systematic review of the evidence for aspirin in cardiovascular disease, where 71–81 mg was found to be the most efficacious [10]. Furthermore,

low-dose aspirin (<100 mg) is safer than higher doses (such as 300 mg), given that the rate of bleeding events with higher doses of aspirin is not inconsequential [11].

Which patients benefit most from warfarin thromboprophylaxis? Recurring risk factors across the literature include hypertension, congestive cardiac failure, advancing age and prior stroke or transient ischaemic attack. Such easily identifiable clinical factors have been used to create various 'risk stratification' schemata, which are now available from the various learned bodies [1]. In the UK, the National Institute for Health and Clinical Excellence have recently published an evidence-based national clinical guideline for AF management (<http://www.nice.org.uk/page.aspx?o=cg36>) [12] and the NICE stroke risk stratification scheme has been compared against another common and well-validated stroke risk stratification, the CHADS2 schema – both have been found to be broadly similar for predicting the risk of stroke and vascular events [13].

Despite the ready availability of such clinical guidelines, the under-prescription of warfarin in AF remains commonplace, particularly amongst the elderly and those at highest risk of stroke. Generally, the main concern is of significant haemorrhage or that elderly patients will not be able to manage the complexities of anticoagulation, be it for fear that poor mobility may restrict attendance for therapeutic monitoring, or that dosage changes may be confusing. These must certainly be considered, but patient preference and the necessity for lifestyle restrictions (e.g. alcohol) are also important factors and are frequently used to justify the choice of aspirin in place of warfarin.

Of additional concern is that physicians tend to be poor at assessing both risk of stroke risk and of bleeding complications. Frequently, there appears to be an assumption that the risk of haemorrhage with anticoagulants is likely to exceed the risk of thromboembolism with alternative strategies. Such judgements are often fuelled by the psychological impact of major bleeding upon future prescribing, particularly within the next 90 days, although long-term prescribing habits appear to be unaltered [14].

Is practice improving? In this issue of *British Journal of Clinical Pharmacology*, Mahmud *et al.* [15] report on the underuse of antithrombotic therapy in Irish patients with AF. Using digoxin as a surrogate marker for the presence of AF, they assessed the relative proportion of these patients receiving either aspirin or warfarin using the National General Medical Service Prescription Database for Ireland. Although digoxin prescription has already been demonstrated as an acceptable surrogate marker for the presence of AF [16], it is worth noting that

such a strategy has some limitations. First, this drug is no longer considered as first line for most patients with AF (particularly in those with paroxysmal AF). Thus, it becomes immediately apparent that many patients with AF may be excluded from the analysis. Second, aside from age, it is impossible to identify other high-risk comorbidities, such as hypertension, congestive cardiac failure and diabetes mellitus and prior stroke, thereby preventing accurate assessment of stroke risk based on these criteria in the younger age group. This has consequently led to the assumption that all these patients are at low(er) risk. Nevertheless, some important findings are apparent. Most notable is that prescription of warfarin in elderly patients (age >75 years) is particularly poor compared with their younger counterparts. Indeed, Mahmud *et al.* [15] demonstrate that older patients are three times less likely to be prescribed warfarin [odds ratio 0.32, 95% confidence interval (CI) 0.30, 0.36, $P < 0.01$]. Given that these older patients are, as a consequence of their age, automatically considered high risk for stroke, these data are of concern and must be used to drive the application of stroke risk stratification schema to aid appropriate targeting of anticoagulation. Of further concern is a marked gender preference, with fewer women than men receiving anticoagulation (33% vs. 40%; $P < 0.01$). Although males have a preponderance towards developing AF, the reverse appears to be true in relation to stroke risk. For example, the AnTicoagulation and Risk factors In Atrial fibrillation (ATRIA) study has found that AF was more common in men than in women (1.1% vs. 0.8%, $P < 0.001$), but non-anticoagulated women had a significantly increased annual rate of thromboembolic events over men (3.5% vs. 1.8%; adjusted rate ratio 1.6; 95% CI 1.3, 1.9), even after correction for other stroke risk factors [17].

Although the underuse of anticoagulation has been frequently demonstrated, it is troubling that little improvement has been seen in recent studies, such as that by Mahmud *et al.* [15]. Certainly, the greater application of risk stratification schema should aid identification of high-risk patients. Yet the reluctance to prescribe anticoagulation persists despite continued efforts in the form of the various practice guidelines now available. In the large AF clinic at our centre, it is all too frequent an occurrence to see newly referred AF patients for whom no stroke risk stratification has been made and who are consequently anticoagulation naive. Things can only get better.

Competing interests

G.Y.H.L. has received funding for research, educational symposia, consultancy and lecturing from different

manufacturers of drugs used for the treatment of atrial fibrillation and thrombosis. He is Clinical Adviser to the Guideline Development Group writing the United Kingdom National Institute for Health and Clinical Excellence (NICE) Guidelines on atrial fibrillation management (<http://www.nice.org.uk>).

References

- 1 Lip GY, Boos CJ. Antithrombotic treatment in atrial fibrillation. *Heart* 2006; 92: 155–61.
- 2 Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham heart study. *Circulation* 1998; 98: 946–52.
- 3 Choudhury A, Lip GY. Atrial fibrillation and the hypercoagulable state: from basic science to clinical practice. *Pathophysiol Haemost Thromb* 2003; 33 (5–6): 282–9.
- 4 Wysokinski WE, Owen WG, Fass DN, Patrzalek DD, Murphy L, McBane RD 2nd. Atrial fibrillation and thrombosis: immunohistochemical differences between *in situ* and embolized thrombi. *J Thromb Haemost* 2004; 2: 1637–44.
- 5 Lip GY, Edwards SJ. Stroke prevention with aspirin, warfarin and ximelagatran in patients with non-valvular atrial fibrillation: a systematic review and meta-analysis. *Thromb Res* 2006; 118: 321–33.
- 6 Lip GY, Watson T. Stroke prevention in atrial fibrillation: antiplatelet therapy revisited. *Eur Heart J* 2007; 28: 926–8.
- 7 Antithrombotic Trialists Collaboration. Collaborative meta-analysis of randomised trials of anti platelet therapy for prevention of death, myocardial infarction, and stroke in high-risk patients. *BMJ* 2002; 324: 71–86.
- 8 Hart RG, Benavente O, McBride R, Pearce LA. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. *Ann Intern Med* 1999; 131: 492–501.
- 9 Aguilar M, Hart R. Antiplatelet therapy for preventing stroke in patients with non-valvular atrial fibrillation and no previous history of stroke or transient ischemic attacks. *Cochrane Database Syst Rev* 2005; 4: CD001925.
- 10 Campbell CL, Smyth S, Montalescot G, Steinhubl SR. Aspirin dose for prevention of cardiovascular disease: a systematic review. *JAMA* 2007; 297: 2018–24.
- 11 Serebruany VL, Steinhubl SR, Berger PB, Malinin AI, Baggish JS, Bhatt DL, Topol EJ. Analysis of risk of bleeding complications after different doses of aspirin in 192,036 patients enrolled in 31 randomized controlled trials. *Am J Cardiol* 2005; 95: 1218–22.
- 12 National Collaborating Centre for Chronic Conditions. National Guidelines for the Management of Atrial Fibrillation. London: Royal College of Physicians 2006.
- 13 Lip GY, Lane D, Van Walraven C, Hart RG. Additive role of plasma von Willebrand factor levels to clinical factors for risk stratification of patients with atrial fibrillation. *Stroke* 2006; 37: 2294–300. Erratum in *Stroke* 2006; 37: 2444.
- 14 Choudhry NK, Anderson GM, Laupacis A, Ross-Degnan D, Normand SL, Soumerai SB. Impact of adverse events on prescribing warfarin in patients with atrial fibrillation: matched pair analysis. *BMJ* 2006; 332: 141–5.
- 15 Mahmud A, Bennett K, Okechukwu I, Feely J. National under use of antithrombotic therapy in chronic atrial fibrillation identified from digoxin prescribing. *Br J Clin Pharmacol* 2007;
- 16 Fang MC, Singer DE, Chang Y, Hylek EM, Henault LE, Jensvold NG, Go AS. Gender differences in the risk of ischemic stroke and peripheral embolism in atrial fibrillation: the AnTicoagulation and Risk factors In Atrial fibrillation (ATRIA) study. *Circulation* 2005; 112: 1687–91.
- 17 Sudlow M, Rodgers H, Kenny RA, Thomson R. Identification of patients with atrial fibrillation in general practice: a study of screening methods. *BMJ* 1998; 317: 327–8.

Received

13 April 2007

Accepted

13 April 2007

Published OnlineEarly

19 June 2007

Correspondence

Professor G. Y. H. Lip, University Department of Medicine, City Hospital, Birmingham B18 7QH, UK. Tel: +44 12 1554 3801; Fax: +44 12 1554 4083; E-mail: g.y.h.lip@bham.ac.uk