

Anticoagulation intensity for elderly atrial fibrillation patients: Should we use a conventional INR target (2.0 to 3.0) or a lower range?

Deirdre A. Lane; Gregory Y. H. Lip

University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham, UK

Stroke prevention is of paramount importance in elderly atrial fibrillation (AF) patients, given that both age and AF independently increase the risk of stroke (1). Despite the overwhelming evidence that anticoagulation therapy with warfarin, to maintain the international normalised ratio (INR) between 2.0 and 3.0, reduces the risk of stroke compared to antiplatelet therapy (relative risk [RR] 39%; 95% confidence interval [CI], 0.22 to 0.52) and to placebo (RR 64%; 95% CI, 0.49 to 0.74) (2), such therapy remains under-utilised (3), particularly among elderly patients (4).

Prior to the results of the Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) trial (5), there was no direct evidence of the benefit of warfarin for thromboprophylaxis among those aged ≥ 75 years since few trials enrolled elderly patients. However, the BAFTA study demonstrated that dose-adjusted warfarin, target INR 2.5 (range 2.0 to 3.0), significantly reduced the risk of fatal or non-fatal disabling stroke (ischaemic or haemorrhagic) (odds ratio [OR] 0.48; 95% CI, 0.28 to 0.80) compared to aspirin (75 mg daily) in elderly (all aged ≥ 75 years; mean 81.5 ± 4.2 years) AF patients managed in primary care, with no significant difference in the risk of major bleeding (including intracranial and extracranial haemorrhage) (OR 0.96; 95% CI, 0.53 to 1.75) between the warfarin and as-

pirin-treated patients (5). In addition, the Warfarin versus Aspirin for Stroke Prevention in Octogenarians (WASPO) trial (6), where 75 AF octogenarians were randomised to receive dose-adjusted warfarin (INR 2.0 to 3.0) or aspirin (300 mg), demonstrated significantly more adverse events with aspirin compared to warfarin (33% vs. 6%, $p=0.002$).

Surprisingly, given the greater prevalence of AF and stroke among elderly people, coupled with the evidence of a significant reduction in stroke risk associated with warfarin, together with a similar safety profile to aspirin, why does warfarin therapy remains under-prescribed among elderly AF patients?

Physicians surveys have revealed that reluctance to initiate warfarin treatment among elderly patients is primarily due to a perceived greater risk of bleeding (due to comorbidities, polypharmacy etc) (7), overestimation of the associated risks (particularly falls), and underestimation of the stroke risk (4). Where oral anticoagulant therapy is commenced, warfarin is employed less intensively (lower target INR) (4). The latter reason is the focus of the article by Pengo et al. (8) in the current issue of *Thrombosis and Haemostasis*.

Pengo et al. (8) examined the net clinical benefit of employing oral anticoagulation therapy at a lower intensity, target INR 1.8 (INR range 1.5 to 2.0), compared to the conventional INR target of 2.5 (INR range 2.0 to 3.0), as primary prevention in 267 AF patients aged ≥ 75 years. The primary endpoint, a composite of thromboembolism and major haemorrhage, occurred in 59 patients during a 5.1 year average follow-up (8). The event rate was less in the lower intensity INR group compared to those in the standard INR group (3.5 vs. 5.0 per 100 patient-years, respectively), with a non-significant overall reduction in net clinical benefit (hazard ratio [HR] 0.7; 95% CI, 0.4 to 1.1; $p=0.10$) (8).

However, caution is warranted in the over-interpretation of these results given that the study was not powered for these outcomes analyses. The overall primary event rate (stroke and major bleeding combined) was low for an elderly cohort of AF patients. This may be partially explained by the fact that this was a primary prevention study and the stroke risk score, assessed by CHADS₂, was 2.0 and 2.1 for lower INR and standard INR groups, respectively, indicating that patients only had one stroke risk factor, in addition to age. The lower, non-significant, primary outcome event rate was largely driven by fewer major bleeds among patients in the lower INR intensity group (1.9% vs. 3.0% per 100 patient-years; HR 0.57; 95% CI, 0.28 to 1.17); the thromboembolic event rate was similar in both groups (1.6% vs. 2.0% per 100 patient-years) in low and standard, respectively (HR 0.81; 95% CI, 0.37 to 1.78; $p=0.60$).

A number of other points are also worth highlighting. First, all the patients enrolled in the Pengo et al. study (8) were warfarin-experienced, having been on a stable dose of warfarin for at least three months and thus the results may not be applicable to warfarin-naïve AF patients, as previous studies have shown that the majority of warfarin-associated complications occur within the first 90 days of initiating warfarin (9–10).

Bleeding is an extremely important consideration when deciding whether or not to initiate warfarin therapy (7), and often physicians may choose to adopt a lower INR intensity, such as in the study by Pengo et al. (8), to reduce the risk of major bleeding whilst still attempting to afford some protection against stroke. This was the approach suggested by Hart and Halperin (11), and also mentioned in the 2006 ACC/AHA/ESC guidelines (12) that aiming for an INR of 1.8 to 2.5 would confer $>90\%$ of protection of thromboprophylaxis whilst

Correspondence to:

Dr. Deirdre Lane
University of Birmingham
Centre for Cardiovascular Sciences
City Hospital
Dudley Road
Birmingham B18 7QH, UK
Tel.: +44 121 507 5080, Fax: +44 121 507 5907
E-mail: deirdre.lane@swbh.nhs.uk

Received: December 16, 2009

Accepted: December 16, 2009

Prepublished online: January 13, 2010

doi:10.1160/TH09-12-0843

Thromb Haemost 2010; 103: 254–256

Thrombosis and Haemostasis 103.2/2010

minimising bleeding risk. However, bleeding rates are low and fairly constant at $\text{INR} < 2.0$ and comparable to rates seen with $\text{INR} 2.0$ to 3.0 (13–14). In other words, simply aiming for an INR target of < 2.0 does not in itself lower the risk of bleeding but – in other cohort studies – significantly increases the risk of thromboembolism.

Intracranial haemorrhage (ICH) is the most feared complication of warfarin; however, the absolute risk of warfarin-associated ICH in AF patients is relatively low at 0.2% (2). Although age has been shown to increase the risk of serious bleeding on oral anticoagulant therapy (HR 1.61; 95% CI, 1.47 to 1.77) (15), the BAFTA study demonstrated a similar risk of major bleeding on warfarin and aspirin (1.4% vs. 1.6%) (5). The risk of ICH is greater among the very elderly (≥ 85 years), conferring a 2.5-fold increased risk compared to those aged 70–74 years (13). Among warfarin-naïve patients the risk of major bleeding is almost three-fold higher among patients aged ≥ 80 years (RR 2.75, 95% CI, 1.27 to 5.95) (9). However, age *per se* should not be a contraindication to oral anticoagulant therapy.

The most important thing to prevent bleeding and reduce strokes in patients on oral anticoagulant therapy is good INR control. The risk of major bleeding increases dramatically when the INR is ≥ 3.5 (9, 13). Compared to an INR of 2.0 to 3.0 , the relative odds of ICH was 4.6 (2.3–9.4) when INR was 3.5 – 3.9 and increased dramatically to 8.8 (95% CI, 4.6 to 19.0) at $\text{INR} \geq 4.0$ (13). Among elderly patients initiating on warfarin the risk of major haemorrhage was almost 20-times greater (RR 19.34, 95% CI, 8.3 to 45.3) when INR was ≥ 4.0 (9).

More relevant to the current study (8), the risk of ICH at INR intensities < 2.0 was not significantly different to the risk at the standard therapeutic INR intensity of 2.0 to 3.0 (13). Therefore, employing a lower than standard INR intensity does not confer a lower risk of ICH. Further, a more recent study demonstrated that when a lower INR target was employed, patients spent 42.7% of the time with an $\text{INR} < 2.0$ compared to 18.8% for patients with a standard INR target range (16).

In the current study almost half of the thromboembolic events (6/11 in the lower

and 6/14 in the standard INR intensity groups) occurred at $\text{INR} < 1.5$. Target INR was achieved in the lower INR group (mean 1.86) but not in standard INR group (mean 2.24) despite significantly more frequent INR testing (8). Therefore, the findings of the Pengo et al. study highlight the importance of maintaining a therapeutic INR .

As stated previously, the most important component of warfarin treatment is achieving good INR control, given that even a 10% time out of range is associated with an increased risk of death, ischaemic stroke, thromboembolic events, and hospitalisation (17). A recent secondary analysis of the ACTIVE-W cohort demonstrated that the minimum threshold for time in therapeutic range (TTR) is $\geq 58\%$ to confer a reduction in stroke risk with warfarin (18), whilst another analysis from an observational record linkage cohort of AF patients demonstrated that TTR needs to be $\geq 71\%$ for a reduction in the time to first stroke (19). Furthermore, antithrombotic medication at the time of stroke has been shown to be an independent predictor of 30-day mortality and stroke severity (20). Those not on warfarin and those on warfarin with an $\text{INR} < 2.0$ at the time of stroke, suffered a more severe stroke (assessed by the Rankin scale) than those on warfarin with an $\text{INR} \geq 2.0$ (20). In addition, an $\text{INR} < 2.0$ confers a 3.4-fold (95% CI, 1.1 to 10.1; $p=0.03$) increased risk of death within 30-days compared to an INR in target range (20).

Pengo and colleagues (8) ran a specialist INR service with a dedicated team and this level of service may not be achievable in real-life clinical practice, although they do not report the percentage of time in therapeutic range by INR intensity. However, good INR control has been demonstrated in other elderly AF populations, BAFTA (67% TTR managed in primary care) (5) and among warfarin-naïve elderly patients (58% managed at one hospital) (9).

Finally, when prescribing oral anticoagulant therapy for AF patients we must consider the net clinical benefit of such treatment. A recent analysis of the ATRIA cohort (21) demonstrated that the benefit of oral anticoagulants, with good INR control (TTR 65%), was greater for those aged ≥ 85 years (2.34% per year; 95% CI, 1.29 to

3.30). Further, a secondary analysis by van Walraven et al. (15) demonstrated that as age increased the efficacy of antiplatelet therapy decreases but the benefit remains unchanged for oral anticoagulant therapy. Therefore, given the increased risk of stroke with age, the net clinical benefit of oral anticoagulants rises as patients' age (15).

The discussion regarding INR targets for AF patients may soon be academic given the much anticipated arrival of new oral anticoagulants, the direct-thrombin inhibitors and oral factor Xa inhibitors, with their stable pharmacokinetic profiles which will eliminate the need for INR monitoring and concerns about the patients ability to control their INR . However, in the meantime, we should advocate tight INR control at conventional levels (target $\text{INR} 2.5$, range 2.0 to 3.0) where there exists a wealth of evidence for benefit, rather than 'mudding the waters' with a lower INR target. Lower INR targets are not associated with significant reductions in major haemorrhage compared to conventional INR targets and stroke outcomes (greater 30-day mortality and stroke severity) are worse when INR is < 2.0 .

References

1. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham study. *Stroke* 1991; 22: 983–988.
2. Hart RG, Pearce LA, Aguilar MI. Adjusted-dose warfarin versus aspirin for preventing stroke in patients with atrial fibrillation. *Ann Intern Med* 2007; 16: 590–592.
3. Nieuwlaet R, Capucci A, Lip GY, et al. Antithrombotic treatment in real-life atrial fibrillation patients: a report from the Euro Heart Survey on Atrial Fibrillation. *Eur Heart J* 2006; 27: 3018–3026.
4. Lane DA, Lip GYH. Barriers to anticoagulation in patients with atrial fibrillation: changing physician-related factors. *Stroke* 2008; 39: 7–9.
5. Mant J, Hobbs FD, Fletcher K, et al. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged study, BAFTA): a randomized controlled trial. *Lancet* 2007; 370: 493–503.
6. Rash A, Downes T, Portner R, et al. A randomised controlled trial of warfarin versus aspirin for stroke prevention in octogenarians with atrial fibrillation (WASPO). *Age Ageing* 2007; 36: 151–6.
7. Tay KH, Lip GY, Lane DA. Bleeding rates in elderly patients on vitamin K antagonist therapy for non-valvular atrial fibrillation. *Blood Coagul Fibrinolysis* 2009; 20: 392–393.

8. Pengo V, Cucchini U, Denas G, et al. Lower versus standard intensity oral anticoagulant therapy (OAT) in elderly warfarin-experienced patients with non-valvular atrial fibrillation: a randomised primary prevention trial. *Thromb Haemost* 2009; 103: 442-449.
9. Hylek EM, Evans-Molina C, Shea C, et al. Major hemorrhage and tolerability of warfarin in the first year of therapy among elderly patients with atrial fibrillation. *Circulation* 2007; 115: 2689-2696.
10. Palareti G, Leali N, Coccheri S, et al. Bleeding complications of oral anticoagulant treatment: an inception-cohort, prospective collaborative study (ISCOAT). *Italian Study on Complications of Oral Anticoagulant Therapy. Lancet* 1996; 348: 423-428.
11. Hart RG, Halperin JL. Do current guidelines result in overuse of warfarin anticoagulation in patients with atrial fibrillation? *Ann Intern Med* 2009; 151: 355-356.
12. Fuster V, Rydén LE, Cannom DS, et al. ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation* 2006; 114: e257-354.
13. Fang MC, Chang Y, Hylek EM, et al. Advanced age, anticoagulation intensity, and risk for intracranial hemorrhage among patients taking warfarin for atrial fibrillation. *Ann Intern Med* 2004; 141: 745-752.
14. Singer DE, Fang MC, Go AS. The international normalized ratio range of 2.0 to 3.0 remains appropriate for atrial fibrillation. *Arch Intern Med* 2009; 169: 2032.
15. van Walraven C, Hart RG, Connolly S, et al. Effect of age on stroke prevention therapy in patients with atrial fibrillation: the Atrial Fibrillation Investigators. *Stroke* 2009; 40: 1410-1416.
16. Rose AJ, Ozonoff A, Henault LE, et al. Warfarin for atrial fibrillation in community-based practise. *J Thromb Haemost* 2008; 6: 1647-1654.
17. Jones M, McEwan P, Morgan CL, et al. Evaluation of the pattern of treatment, level of anticoagulation control, and outcome of treatment with warfarin in patients with non-valvar atrial fibrillation: a record linkage study in a large British population. *Heart* 2005; 91: 472-477.
18. Connolly SJ, Pogue J, Eikelboom J, et al. Benefit of oral anticoagulant over antiplatelet therapy in atrial fibrillation depends on the quality of international normalized ratio control achieved by centers and countries as measured by time in therapeutic range. *Circulation* 2008; 118: 2029-2037.
19. Morgan CL, McEwan P, Tukiendorf A, et al. Warfarin treatment in patients with atrial fibrillation: observing outcomes associated with varying levels of INR control. *Thromb Res* 2009; 124: 37-41.
20. Hylek EM, Go AS, Chang Y, et al. Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. *N Engl J Med* 2003; 349: 1019-1026.
21. Singer DE, Chang Y, Fang MC, et al. The net clinical benefit of warfarin anticoagulation in atrial fibrillation. *Ann Intern Med* 2009; 151: 297-305.