Stroke prevention in non-valvular atrial fibrillation: Can warfarin do better?

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Patients with non-valvular atrial fibrillation (NVAF) have a substantial risk of stroke and thromboembolism compared with age-matched people in sinus rhythm. This risk ranges from less than 1% to more than 20% per year depending on associated comorbidities and demographic characteristics (1). Thus, the prime challenge facing physicians caring for patients with NVAF is to identify patients at substantial risk for stroke and thromboembolism, and provide appropriate antithrombotic treatment whether as primary or secondary prevention. This has led to the development of stroke risk stratification schema, such as the CHADS2 score, whereby 'high risk' patients can be targeted for oral anticoagulation therapy; this is despite limitations of simple risk scores (2, 3).

Until recently the vitamin K antagonists (VKAs) were the only orally administered agents able proven to lower the risk of stroke and mortality in patients with NVAF, although these benefits were balanced against small changes in the annual rate of major haemorrhage, including intracranial bleeding (4, 5). One recent 'real world' nationwide cohort analysis found that the net clinical benefit (balancing stroke against intracranial haemorrhage) was only negative for warfarin compared to no treatment in 'truly low risk' patients, defined using the ESC guidelines (1). Given the improvement in efficacy and safety with the new oral anticoagulants, the net clinical benefit is likely to be even greater. The absolute reduction in stroke risk attributable to oral anticoagulation highlights the effectiveness of anticoagulation, which is even greater amongst elderly subjects.

Nonetheless, treatment with VKAs has important caveats. Indeed, the optimal anticoagulation intensity for patients with NVAF has been a subject of debate, although anticoagulation intensities with international normalised ratios (INRs) between 2.0 and 3.0 appear to provide the best protection from stroke and death, when balanced against the risk of bleeding (6, 7).

Even with the optimal anticoagulation intensity established, keeping patients in the VKAs therapeutic range has not been an easy task. In general, implementation of evidence in practice has been proved slow and incomplete in the field of stroke prevention in AF. As a result, a large proportion of patients at high risk are either not treated or suboptimally treated with VKAs. Thus, it become crucial to evaluate the quality of anticoagulation and the time in therapeutic range (TTR) emerged as the most promising index.

The TTR is the ratio of estimated duration of anticoagulation intensity within a pre-determined range to total duration, and Rosendaal et al. designed a method to calculate TTR based on the assumption that anticoagulation intensity shifts linearly between any two consecutive measurements (8). TTR is recognised as a marker of the quality of anticoagulation control in patients taking VKAs, and used to demonstrate the effectiveness of patient education and self-monitoring (9, 10). Moreover TTR has been used to appraise the quality of anticoagulation in the VKA arms of randomised clinical trials that evaluated the efficacy of novel antithrombotic drugs. In the latter setting it become apparent that even in the ideal environment of clinical trials the mean time spent in the therapeutic range rarely exceeds 65% (11).

In the current issue of Thrombosis and Haemostasis, Gallagher et al. (12) evaluated the association between TTR and the risk of stroke and mortality, in a study cohort that included 37,907 AF patients from the UK General Practice Research Database. The large sample size allowed the authors to compare outcomes of VKA users with different percentages of time spent within therapeutic range. The authors concluded that good anticoagulation control was associated with a reduction in the risk of stroke versus no therapy, whilst TTR was a strong predictor of the risk of stroke. Indeed, poorer anticoagulation control was generally associated with a much larger risk of stroke (12).

Previous studies have reported similar results regarding the importance of TTR on the outcome of VKA-treated patients with NVAF. For example, in an ancillary analysis of the ACTIVE W trial the benefit of anticoagulation compared with antiplatelet therapy was demonstrated only at medical centres where the average TTR was above 65% (the mean TTR for all patients in the study was 63.4%) (13). Similarly, a meta-analysis that included data from 21 studies and a total of 6,248 patients concluded that in patients with NVAF, the risk of ischaemic stroke with insufficient VKA anticoagulation (defined as INR < 2), and the risk of bleeding events with over anticoagulation (defined as INR > 3) are significantly higher relative to patients with AF maintained within the recommended INR (14).

Beyond the anticipated concluding remarks, the study by Gallagher et al. (12) has important unique points, including the use of data from the ‘real world’ practice. Until now, most data on the impact of TTR on the outcome of VKA-treated patients have come from the VKA arms of randomised clinical trials (15). Secondly, in this ‘real
In the ‘real world’ setting, the TTR was 63.1% which is rather impressive, suggesting high quality anticoagulation control in the UK General Practice setting. This is in contrast to other studies reporting TTR rates ranging from 49% to 55% (16). Thirdly, the study by Gallagher et al. is also the first study that assessed the impact of TTR in patients risk stratified with the CHA2DS2-VASc score, which is used in the ESC guidelines (1, 17).

When their study population was stratified by the CHA2DS2-VASc score, several observations in current clinical practice became apparent. As expected, there was a higher risk of stroke the less time the patient spends within the therapeutic range. Also, the high risk patients were more likely to be undertreated (more time below the therapeutic range, INR <2.0) than over-treated (more time above the therapeutic range, INR >3.0). In the Kaplan-Meier curves presenting time to stroke in AF patients stratified by percentage of TTR, the benefit from anticoagulation therapy (as assessed by stroke free survival) is diminished, if TTR falls <50%.

In the era of new oral anticoagulant drugs (10), the paper by Gallagher et al. reminds us that when optimally controlled VKA can sufficiently protect AF patients. One recently published paper suggests that there is clearly a place for improvement in anticoagulation control since TTRs >75% are achievable in properly organised centres (18). Clearly, monitoring the quality of anticoagulation control is a high priority in the management of AF where VKAs are used, with implications for stroke prevention and minimising bleeding risks (19).

Conflict of interest
S. Apostolakis has received research funding and honoraria from various pharmaceutical companies in relation to atrial fibrillation for meetings and educational symposia. He is financially supported by the 2010-2011 ESC Atherothrombosis Research Grant. G. Lip has served as a consultant for Bayer, Astellas, Merck, AstraZeneca, Sanofi, BMS/Pfizer, Biotronik, Portola and Boehringer Ingelheim and has been on the speakers bureau for Bayer, BMS/Pfizer, Boehringer Ingelheim and Sanofi Aventis.

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