EDITORIALS

Challenges facing anticoagulation among the elderly and frail

The burden of atrial fibrillation (AF) is even greater amongst the elderly, and the lifetime risk for the development of AF are one in four for men and women aged 40 years and older [1]. With a better healthcare system, medical treatment, education and quality of life, the general population is ageing and surviving well into their eighties and beyond. Of note, AF is more common with increasing age, with the prevalence of AF in those aged above 80 approximating 10%. This poses a major public health issue, as AF is associated with a substantial mortality and morbidity, most notably, a 5-fold increase in the risk of stroke and thromboembolism [2]. However, anticoagulation therapy with warfarin is highly efficacious at stroke risk reduction but this therapy is coupled with cumbersome international normalised ratio (INR) monitoring, and warfarin has an erratic pharmacokinetic and pharmacodynamic profile.

Ageing is a complex process which is accompanied by a potential multitude of issues that include numerous health problems, often coupled with reduced mobility and greater frailty, with a tendency to fall. All these conditions are often cited as reasons to preclude the elderly from being anticoagulated [3]. Nonetheless, there is sometimes a great disparity between the chronological and biological age, whereby an apparently elderly subject with AF may have a good quality of life and full activities of daily living, where exclusion from thromboprophylaxis with warfarin may lead to a devastating stroke and severe disability. This is all the more important given that strokes associated with AF tend to be more severe, leading to greater disability, longer hospital stays and less discharges to the patient's own home [4].

Despite the stroke risk being much higher in the elderly, the presence of associated comorbidities and concomitant polypharmacy leads to physicians' being less keen to initiate anticoagulation therapy in the elderly, despite the greater absolute stroke risk reduction by doing so. Increasing age in itself should not be a contraindication to anticoagulation therapy, although it is recognised that increasing age is a risk factor for bleeding, especially in those aged over 85 years [5]. Instead, the elderly patient with AF is often prescribed aspirin, on the presumption that it is safer. In the recent Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) trial, the efficacy of warfarin (INR 2–3) over aspirin 75 mg daily for stroke prevention in an elderly population (aged >75) was clearly shown (1.8% vs. 3.8% per year RR 0.48, 95% CI 0.28–0.80), and most importantly, there was no difference in major bleeding rates between warfarin and aspirin (1.9% vs. 2.0% risks per year) [6]. Thus, elderly patients with AF should be anticoagulated where possible, unless there are sound and compelling reasons against it.

If an increased risk of bleeding is the main concern, would the availability of a bleeding risk predictor tool assist physicians to risk-stratify patients so that bleeding risks could be balanced against stroke risk, and thus, aid decision making in commencing anticoagulation? There are four published bleeding risk models to date, but none have been fully validated in large prospective cohorts of AF patients [7, 8]. Also, a major bleeding event which is intracranial would have a far worse prognosis compared to an extracranial bleeding event, whereby intervention is more likely to help.

Another vital key factor in deciding on anticoagulation therapy is the elderly patients’ propensity to fall. However, the potential harm of falls may be overstated, given an analysis whereby persons taking warfarin must fall about 295 times in a year for warfarin to not be the optimal therapy, given that falls (1 in 10) usually cause major injury (i.e. fractures) and persons who fall are much more likely to suffer other serious morbidity before developing the most serious type of haemorrhage associated with anticoagulation, that is, subdural haematomas [9].

In the current issue of Age and Ageing, Perera et al. [10] report on a prospective observational study of 207 AF patients in an acute-care setting hospital, assessing frail and non-frail patients in association with warfarin usage and the resultant clinical consequences. Their study demonstrated that frail patients were less likely to receive warfarin, both on hospital admission (P = 0.002) and on discharge (P < 0.001). More importantly, such subjects were at greater risk of experiencing embolic strokes [12.3% vs. 3.9% in frail and non-frail patients; relative risk (RR) 3.5, 95% CI 1.0–12.0, P < 0.05]. There was also a nonsignificant trend towards frail patients sustaining a greater risk of major/severe haemorrhage (RR 1.5, 95% CI 0.7–3.0, P = 0.29) as well as a greater mortality (RR 2.8, 95% CI 1.2–6.5, P = 0.01).

Nonetheless, it is uncertain whether the 12.3% of frail patients who sustained cardioembolic strokes can fully be attributed to not being on anticoagulation therapy. There could be other potential contributory factors to stroke in AF, such as poor compliance with warfarin therapy, as well as time spent outside the target INR monitoring. In a recent post hoc analysis by Connolly et al. [11], oral anticoagulation (OAC) therapy was beneficial over antiplatelet therapy only if at least 58–65% of INR were spent in therapeutic ranges.
Indeed, even a 10% increase in time out of therapeutic INR range is associated with an increased risk of mortality and thromboembolic events [12].

Also, low educational background and poor understanding of the importance of a regular blood test and the necessity for warfarin, or so-called warfarin resistance, may contribute. Even though the sample size of this study was modest, the results do illustrate that frailty per se is not just a barrier to the prescription of antithrombotic therapy, but probably to other medical therapies and interventions in medicine.

Furthermore, the physicians’ perception that aspirin is a viable, ‘safe’ alternative to warfarin for stroke prevention amongst frail patients with AF probably does not help. As evidenced by the results of the BAFTA study [6], the risk of major haemorrhage, including intracranial and haemorrhagic strokes, was similar in both the aspirin (2.0% per year) and warfarin (1.9% per year) treated patients. Hence, aspirin is unlikely to be any safer when it comes to elderly AF patients who are in a frail condition. It is also worth emphasising that the data for aspirin efficacy in stroke prevention in AF patients are poor, and even when the data from the aspirin trials are included in a meta-analysis comparing aspirin alone with placebo or no treatment (n = 3,990 participants in seven trials), aspirin was associated with a nonsignificant 19% (95% CI —1 to 35%) reduction in the incidence of stroke [13]. Also, the apparent benefits of aspirin are largely driven by the Stroke Prevention in Atrial Fibrillation trial (SPAF-1) [14] which used aspirin 325 mg and reported the largest reduction in stroke (by 42%); however, since this trial was stopped at an interim stage because of apparent aspirin efficacy, its result may have been exaggerated—and there was important internal inconsistency within the trial results between the ‘anticoagulation eligible’ and the ‘warfarin ineligible’ trial arms. There is no reason to suppose that aspirin in AF is acting any differently from aspirin in general cardiovascular disease prevention, especially given that the effect size in terms of risk reduction is the same [15]. Pathophysiologically, thrombus in AF is fibrin rich (red clot) rather than platelet rich (white clot). In addition, abnormalities of coagulation and haemostasis which are well documented in AF are in keeping with the presence of a prothrombotic state without relation structural heart disease or aetiology of AF itself [16].

Aspirin may have an effect on vascular disease in isolation, but if other vascular risk factors are well managed, the evidence for its benefit is even less impressive. This view is supported by the recent Prevention of Progression of Arterial Disease and Diabetes trial (POPADAD) [17] where aspirin was no better than placebo in the primary prevention of cardiovascular events and mortality amongst a diabetic population with peripheral artery disease. Finally, the practice of adding aspirin or non-steroidal anti-inflammatory drugs to OAC is probably the major culprit contributing to the substantial bleeding risk with OAC usage. In an analysis from the SPORTIF trials, the subgroup taking aspirin and warfarin did not have any benefit in the reduction of stroke or myocardial infarction, but there was a substantial increase in major bleeding (3.9% per year) with combination therapy [18].

In conclusion, the management of frail (and often elderly) patients with AF is a holistic and multidisciplinary one. Where possible, oral anticoagulation would still be the best medicine for stroke prevention, especially after a full evaluation of stroke risk factors [19, 20], but an assessment of bleeding risk [21] would be needed as part of an evaluation of the risk–benefit ratio, as with many scenarios in clinical medicine. Overcoming some of the deficiencies of warfarin, such as the substantial inter- and intra-patient variability, drug/food interactions and the need for anticoagulation intensity monitoring, may perhaps help—and the new oral anticoagulants in development, such as the oral direct thrombin inhibitors and oral factor Xa inhibitors, offer some promise in this regard. Only time will tell.

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References

Commencing antiplatelet therapy in older people after an acute ischaemic stroke

Each year an estimated 150,000 people in the United Kingdom suffer an acute stroke. Of these, approximately one-third are due to recurrent cerebrovascular events. Ischaemic stroke accounts for 85% of first ever strokes, and older persons are at greatest absolute risk of stroke and other occlusive vascular disease. Antiplatelet therapy is key to the secondary prevention of stroke, reducing the risk of serious occlusive vascular events by about one quarter in higher-risk patients [1], but treatment is not without risk. Regular aspirin use causes a wide spectrum of adverse gastrointestinal effects, ranging from an inability to tolerate the drug because of dyspepsia with endoscopically normal mucosa, to symptomatic and asymptomatic lesions such as erosions and ulcers, and is associated with a 2-fold increased risk of upper gastrointestinal bleeding or perforation. The degree of gastrointestinal damage sustained during treatment is related to the dose of aspirin [2], with a comparable bleeding risk to clopidogrel when used in long-term secondary prevention [3].

The body maintains its gastromucosal integrity through a number of inherent mechanisms designed to oppose internal and external aggressive factors. With increasing age, arterial blood supply to the stomach reduces and gastric epithelial cell turnover diminishes. Prostaglandin levels in the gastric mucosa decrease and the production of bicarbonate and mucus by the gastric epithelium also decreases. As a consequence, the integrity of the gastric mucosal surface becomes impaired and progressively susceptible to damage by factors that can overwhelm the stomach’s protective barriers [4].

As a result of these changes, older people are much more susceptible to adverse events. Combined with this susceptibility, advanced age is also a major risk factor for complicated ulcer disease, which itself is associated with a high mortality. These factors are a regular consideration when starting...