Pro: 'Warfarin should be the drug of choice for thromboprophylaxis in elderly patients with atrial fibrillation'

Why warfarin should really be the drug of choice for stroke prevention in elderly patients with atrial fibrillation

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As is well recognised, warfarin is the most effective agent that is available in clinical practice for preventing the thromboembolic sequelae of atrial fibrillation (AF), particularly stroke (1, 2). In theory, this makes warfarin a particularly cost-effective agent for treating elderly people with AF: risks of stroke in atrial fibrillation increase with age, so fewer people need to be treated to prevent a stroke (3). However, in everyday clinical practice, the majority of elderly people in AF are not treated with warfarin (4). This partly reflects physician concern over risks of serious haemorrhage in this age group, the difficulty maintaining good international normalised ratio (INR) control, and poor adherence with therapy by patients (4). In this article, I will use the findings of the recently published Birmingham Atrial Fibrillation Treatment of the Aged Study (BAFTA) trial (5) to argue that the risks of warfarin in general are over-estimated in elderly patients, and that warfarin should really be the drug of choice for thromboprophylaxis in elderly patients in AF.

BAFTA was a randomised controlled trial in which 973 people in AF were recruited from primary care and randomised to receive warfarin with a target INR of 2.5 (range 2–3) or aspirin at a dose of 75 mg and followed up for an average of 2.7 years. The context for the trial was that existing evidence on the relative merits of aspirin and warfarin in this age group was limited, since the majority of patients in the trials were under the age of 75 (6). The evidence that was available showed that warfarin was effective at preventing ischaemic stroke in this age group, but that this benefit might be outweighed by the potential harm caused by risk of major bleeding (6). The primary end-point for BAFTA was fatal or disabling stroke (whether ischaemic or haemorrhagic), intra-cranial haemorrhage, or clinically significant arterial embolism.

What did the trial show? The risk of a primary end-point was 50% lower in the warfarin group as compared to the aspirin group – 1.8% per annum versus 3.8% per annum, relative risk 0.48, 95% confidence interval 0.28–0.80. Interestingly, there was no evidence from BAFTA that in this age group, warfarin caused any more major bleeds than aspirin. The annual risk of major extra-cranial haemorrhage was 1.6% per annum on warfarin and 1.8% on aspirin. Therefore, BAFTA confirmed the efficacy of warfarin for stroke prevention and provided evidence that the risks of major bleeding can be low in this age group. BAFTA also demonstrated that good INR control can be achieved in everyday clinical practice in this age group. Patients on warfarin were in the target INR range 67% of the time, and this despite the fact that the individual primary care physicians were left to manage the INR without any set protocol imposed by the trial.

The key question to answer before making warfarin the drug of choice for thromboprophylaxis in AF is whether the results that were achieved in BAFTA, particularly in relation to risk of bleeding, are representative of the general population of elderly people. In an individual patient data meta-analysis of patients aged over 75 enrolled into previous (historical) trials of warfarin versus aspirin, the risk of major haemorrhage was found to be double on warfarin as compared to aspirin – in sharp contrast to the BAFTA findings (6). This is likely to be due to a combination of factors: many of the earlier trials had higher target INR ranges; co-treatments during BAFTA such as better blood pressure control and more use of gastro-protective agents may have reduced the risk of haemorrhage; and 40% of the patients in BAFTA were on warfarin at study entry (hazards of warfarin are higher in people who are new to the treatment) (7). Also, could the low risk of haemorrhage in BAFTA be a consequence of patient selection? Patients with clear contra-indications to warfarin were excluded from the trial – however, these were in the minority. Out of 4,639 patients with AF who were identified for the study, only 112 (2%) were excluded because of an absolute contraindication to warfarin, and a further 417 (9%) because the physician felt that the patient should not be on warfarin (8). The commonest reason that clinicians gave for excluding a patient because they felt they should not be on warfarin was cognitive impairment (93

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patients), followed by other risk factors for haemorrhage (66 patients) risk of falls (53 patients) (8). The commonest reason that patients were excluded from the trial (1,570 patients) was that the clinician felt that they should be on warfarin. This suggests that in a primary care population, the proportion of elderly people in whom warfarin is contra-indicated is low.

At around the same time that the BAFTA results were published, data were published from an inception cohort of patients started on warfarin at the Massachussetts General Hospital (9). In contrast to the BAFTA results, in this study only 58% of the time was spent within target INR range, and the rate of major haemorrhage was 7% per annum (even higher in people aged over the age of 80). The explanation for the discrepancy probably relates to patient selection: the Massachussetts General series was of patients referred to hospital who were often acutely ill (many entered the study as in-patients), whereas the BAFTA study recruited patients who were not acutely ill at the time of study entry. BAFTA did include newly diagnosed atrial fibrillation (about 30% of patients recruited to the study), but in all these cases, the diagnosis was made as a result of opportunistic screening in people who by and large will not have had significant symptoms in relation to their atrial fibrillation. Therefore, it is appropriate to note that the results of BAFTA with regard to bleeding risk are not applicable to acutely ill patients in tertiary care settings. Bleeding risk in hospital out-patient series of patients who are not acutely ill is similar to that observed in BAFTA (10).

In conclusion, warfarin should be the drug of choice for thromboprophylaxis in AF in elderly patients with AF in primary care, and in non-acute secondary care settings. Some of the risk factors for bleeding are recognised, although many are themselves associated with a risk of stroke and thromboembolism (11). Some risk factors for bleeding are preventable – for example, one common risk factor for bleeding is concomitant aspirin use, and the latter should not be used in stable vascular disease patients if they are already anticoagulated for AF (12). As with many decisions in clinical practice, the physician treating the acutely ill patient with AF will need to weigh up the 'pros' and 'cons' of warfarin therapy on a case-by-case basis given the observed high risks of haemorrhage in this population.

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