



Therapeutics Today

February 2009
Number 2

For personal use only. Not to be reproduced without permission of the editor



Management of Stroke Prevention in Atrial Fibrillation. It is recognised that stroke is a major hazard for patients with atrial fibrillation (AF). A number of recent articles have evaluated the practical issues associated with the management of stroke prevention in AF.

The first study evaluated the use of oral anticoagulation (OAC) with warfarin in acute stroke patients admitted to 12 designated Canadian stroke centres from 2003-7 (*Stroke* 2009; 40: 235-40). AF patients were included in the study if they presented with an acute ischaemic stroke, were judged to be at high risk of developing a stroke and had no identifiable contraindications to OAC use. [Contraindications included history/evidence of previous intracranial haemorrhage, peptic ulcer disease, previous GI bleed, cirrhosis, metastatic cancer, renal failure requiring dialysis, dementia of any type, lack of independent living for 3 months prior to the stroke.] A total of 597 patients with a first stroke and 323 with a prior stroke/TIA were identified. **Only 40% of "high-risk" patients with a first stroke were taking OAC prior to admission, of whom 75% had an INR < 2 at admission; 29% had no antithrombotic prophylaxis.** A total of 57% of those with a prior stroke/TIA were taking OAC prior to admission but the INR was sub-therapeutic in 68%; 25% were receiving neither aspirin nor OAC. The investigators noted that the strokes were disabling in 60% and fatal in 20% of those with a first stroke. They concluded that more widespread implementation of OAC clinics / other interventions to optimise stroke prevention therapy in AF patients would reduce mortality and morbidity and their associated direct and indirect costs.

The second study (*Eur Heart J doi:10.1093/eurheartj/ehn599*) investigated whether there are differences in the risk of stroke between paroxysmal (Px) and permanent (Perm) AF. All patients treated for either PxAF (n=855) or PermAF (n=1126) in one Scandinavian hospital during 2002 were followed up for a median of 3.6 years regarding incidence of stroke. **Results showed no difference in the incidence of a first ischaemic stroke between the groups** (rate of 21 vs. 25 events/1000 patient-years in PxAF vs. PermAF groups, corresponding to 6 and 17 strokes). Those PxAF patients who were on OAC had approximately half as many ischaemic strokes as those not on OAC. The authors concluded that it is important to consider OAC in patients with PxAF if they have additional risk factors (see below).

A review editorial discussed the "better use" of OAC in AF (*Heart* 2009; 95: 95-7). Several stroke risk factors in AF have been identified and are included in the so-called CHADS₂ score: **C**ardiac failure (=1) **H**ypertension (=1), **A**ge >75 years (=1), **D**iabetes (=1) and **p**rior **S**troke/TIA (=2). Aspirin reduces the risk of stroke by 22% compared with placebo while OAC reduces the risk by 67%. However, the risk of bleeding also needs to be included in the assessment of a patient with AF. **International guidelines recommend that patients with AF who have a CHADS₂ score of ≥2, should be treated with OAC (unless there is a contraindication to its use)** because the risk of bleeding is outweighed by the benefit in stroke prevention. AF patients with a CHADS₂ score of 0 may be treated with either no therapy or aspirin while the prescriber is free to choose between aspirin and OAC for the remaining (CHADS₂ score =1) AF patients. Once OAC has been instituted, **the challenge is to achieve and subsequently maintain adequate control of the INR in the therapeutic range (2-3)**; studies have shown that the risk of stroke in AF patients who achieve the therapeutic range <60% of the time was almost double that of AF patients who are in the therapeutic range >70% of the time. Factors influencing maintenance of the therapeutic range include patient compliance, use of OTC medicines and alcohol as well as methods used to adjust OAC dose. Dedicated OAC clinics are effective as they adjust dose according to a treatment algorithm, while initial studies of patient self-monitoring have produced very good safety and efficacy results in appropriate patients. Although there are new OAC agents currently under development it is likely that warfarin will continue to be the standard therapy for high-risk AF patients for the foreseeable future, therefore improvements should be sought to enable improved patient selection and better control of INR [Editor's note: the NMIC bulletin on the Management of Atrial Fibrillation (2006; Vol 12; number 3) is available at www.nmic.ie]



Update on tibolone and breast cancer risk. Tibolone is a synthetic steroid used for the treatment of menopausal symptoms and prevention of osteoporosis. Tibolone is also used by some patients with breast cancer to reduce vasomotor symptoms, even though it is contraindicated for this indication. There has been limited data on its use in patients with breast cancer; observational studies have shown conflicting evidence on the risk of breast cancer with tibolone, while

experimental studies showed no significant effect on tumour-cell proliferation. A recent randomised controlled trial evaluated if tibolone was "non-inferior" to (i.e. no worse than) placebo in patients with surgically treated breast cancer in terms of risk of breast-cancer recurrence (*Lancet Oncol* 2009;10:135-46). Secondary endpoints included mortality, vasomotor symptoms, bone-mineral density (BMD) and health-related quality of life. There were 3098 women included in the intention to treat analysis (1556 in the tibolone group and 1542 in the placebo group). The trial was stopped early due to an increased risk of breast cancer recurrences observed in patients on tibolone: **after a median follow-up of 3.1 years 15.5% of women on tibolone had breast cancer recurrence, compared with 10.7% of women on placebo** (Hazard Ratio 1.40 [95%CI 1.14-1.70] p=0.001). No differences were noted between the groups in terms of other safety outcomes (mortality, cardiovascular events or gynaecological cancers) but the vasomotor symptoms and BMD improved significantly with tibolone compared with placebo. The authors concluded that the use of tibolone for women with a known, past or suspected breast cancer should remain contraindicated. An accompanying editorial concluded that the study provides strong evidence against the use of tibolone in patients with a history of breast cancer.



Should minocycline be used in the management of acne?

The use of minocycline for the treatment of acne was recently reviewed (*DTB* 2009 47(1):7-8). While minocycline is an effective treatment for some patients with acne, there is a lack of evidence that it is any better than other options. The authors cite a recent systematic review, which concluded that there was insufficient evidence to support the use of one oral tetracycline over another.

Similar to other tetracyclines, minocycline has adverse effects including: gastrointestinal upset, candidiasis, hypersensitivity reactions and benign intracranial hypertension. However the use of minocycline is also associated with **hyperpigmentation, lupus-like syndrome, arthropathies, autoimmune hepatitis and vasculitis associated with production of a range of autoantibodies**. Patients who are on minocycline for > 6 months, need to be monitored at 3 monthly intervals for signs and symptoms of hepatitis, SLE or unusual pigmentation. In a case control study the likelihood of lupus-like syndrome with minocycline was 8.5 (95% CI 2.1 to 35) times that in non-users and past users of tetracyclines. A more recent observational study (n=97,694) found that minocycline was associated with increased likelihood of drug-induced lupus erythematosus (hazard ratio corrected for age and gender 3.11, 95% CI 1.77 to 5.48). The review notes that use of minocycline has fallen gradually in the UK following publication of the reports of systemic lupus erythematosus or autoimmune hepatitis associated with its use in 1996. Oxytetracycline and tetracycline are often used as first line oral tetracycline for acne but need to be taken twice daily on an empty stomach. If once daily treatment is preferred, doxycycline (may cause photosensitivity) or lymecycline can be used. Neither of these medicines needs to be taken on an empty stomach. These tetracyclines are as effective as minocycline but appear to be safer and less expensive. The authors conclude that they do not see a role for minocycline in the management of acne. [Editor's note: The NMIC recently published a bulletin on the Management of Acne Vulgaris (2008; Vol 14: Number 1) which is available at www.nmic.ie]