NEW ANTICOAGULANTS FOR ATRIAL FIBRILLATION

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There is a major problem with under-anticoagulation of patients with atrial fibrillation, particularly the elderly[1]. Warfarin can reduce stroke risk by 60%, versus only a 20% reduction with antiplatelet agents. It is important for physicians to understand that there are two kinds of thrombus: white and red. White thrombus, made up of platelet aggregates, is what antiplatelet agents are for, and that's all they are for. Red thrombus, which is made up of a fibrin polymer mesh with entrapped red cells, requires anticoagulation.

The risk of ischemic stroke from atrial fibrillation increases steeply with age, from 1.5% at age 50–59, to 23.5% at age 80–89. Furthermore the relative benefit of anticoagulation compared with antiplatelet agents increases with age. Unfortunately, it is in the elderly that many physicians are reluctant to prescribe anticoagulants, because of issues such as falls, forgetfulness and other issues.

The benefit/risk ratio with warfarin depends greatly on keeping the INR in the target range, and this is difficult because of many drug interactions, and because there are huge individual differences both in metabolism of warfarin, and in response to a given level of warfarin. Genetic testing for alleles responsible for such variability can help with dosing of warfarin[2].

Fortunately, there are now oral anticoagulants on the horizon that may replace warfarin if they can be priced appropriately. Dabigatran was recently shown to be superior to warfarin for stroke prevention in atrial fibrillation[3], with a slightly higher dropout rate because of dyspepsia. There are some issues with drug interactions with inhibitors of p-glycoprotein such as verapamil, amiodarone and quinidine (grapefruit has not been studied, and may be a problem). Rivaroxaban, another new oral anticoagulant is presently being tested against warfarin in atrial fibrillation.

An important issue that is under-recognized is that high levels of homocysteine, which in the elderly is most commonly due to vitamin B12 deficiency, quadruples the risk of stroke in atrial fibrillation[4]. To safely exclude metabolic B12 deficiency, the serum B12 should be over 400pmol/L, thus a merely "normal" serum B12 is not adequate. Metabolic B12 deficiency is present in 12% of stroke patients below age 50, and 30% over age 70.

Most emboli in atrial fibrillation originate in the atrial appendage; for patients who cannot take or will not take anticoagulants, surgical removal of the atrial appendage is an option. Clinical trials are under way with devices to close the atrial appendage percutaneously.

References:

Spence,J.D. Stroke: Atrial fibrillation, stroke prevention therapy and aging. *Nature Reviews Cardiology* **6**, 448-450 (2009)
Schwarz,U.I. *et al.* Genetic determinants of response to warfarin during initial anticoagulation. *N. Engl. J. Med.* **358**, 999-1008 (2008)
Connolly,S.J. *et al.* Dabigatran versus warfarin in patients with atrial fibrillation. *N. Engl. J Med.* **361**, 1139-1151 (2009)
Spence,J.D. Homocysteine-lowering therapy: a role in stroke prevention? *Lancet Neurol* **6**, 830-838 (2007)