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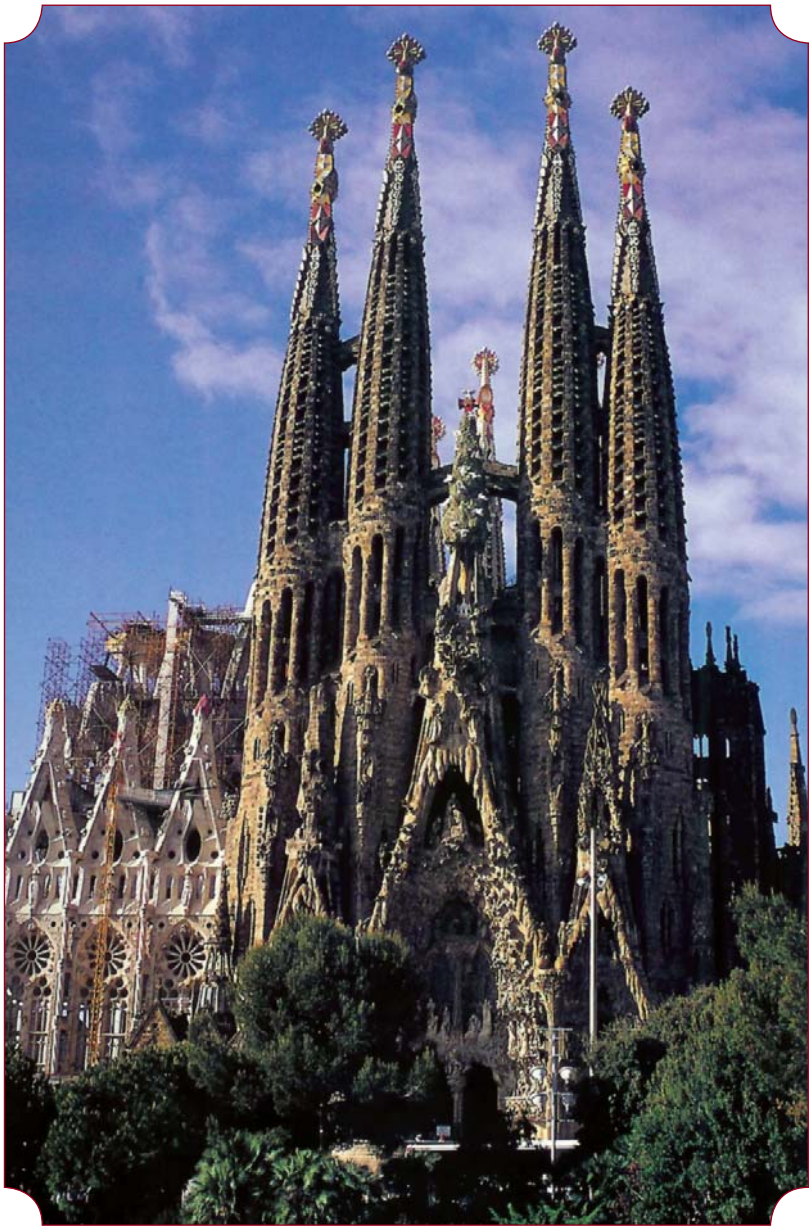

A new oral anticoagulant treatment proves noninferior to warfarin in patients with atrial fibrillation – the RE-LY study

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This year, the ESC Congress in Barcelona was the stage where results from important clinical trials were published. One such trial was the RE-LY trial – non-inferiority trial that evaluated the use of a new oral anticoagulant – a direct thrombin inhibitor, dabigatran – versus warfarin, in the prevention of stroke and systemic embolism in patients with atrial fibrillation.

Vitamin K antagonists (e.g. warfarin) are currently the only drugs approved for oral anticoagulation in atrial fibrillation. However, their use is extremely difficult because of their narrow safety margin, the need for frequent laboratory monitoring, multiple interactions with food and drugs, and inadequate anticoagulation in a significant number of patients. Oral thrombin inhibitors, such as dabigatran – which is currently approved for the prevention of venous thrombembolism in orthopaedic patients – do not require laboratory monitoring.

The RE-LY study included more than 18,000 patients who were followed for a median duration of 2 years. The patients were randomized in a 1:1:1 fashion to receive dabigatran 150mg, dabigatran 100mg (blinded doses) or unblinded adjusted-dose warfarin.

The higher dabigatran dose was superior compared with warfarin for the prevention of stroke and systemic embolism (relative risk reduction 34%/year, $p<0.001$), had equal incidence of major bleeding (3.1%/year vs. 3.4%/year, $p = 0.31$), but had a lower incidence of haemorrhagic stroke (0.1%/year vs. 0.4%/year, $p < 0.001$). There was a trend towards decreased mortality with the higher dose of dabigatran compared with warfarin (3.6%/year vs. 4.1%/year, $p = 0.051$).

The lower dabigatran dose was non-inferior compared with warfarin for the prevention of stroke and systemic embolism (1.53% vs. 1.69%, $p < 0.001$ for non-inferiority). However, the rate of severe bleeding was significantly lower with the 110mg dabigatran dose compared with warfarin (2.7% vs 3.4%, $p = 0.003$), and the rate of haemorrhagic stroke was also lower (0.1%/year vs 0.4%/year, $p < 0.001$). Mortality was similar between the lower dabigatran dose and warfarin.

The study was sponsored by the same company that released Ximelagatran a few years ago for the same indication. Ximelagatran was an oral thrombin inhibitor that was banned from use due to severe hepatotoxicity. The RE-LY study was carefully planned to detect any

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hepatotoxicity with dabigatran, but this safety profile was similar compared with warfarin (2% incidence of transaminase levels > 3 times the upper limit of normal). The only side effect that was more frequent in the dabigatran groups was dyspepsia (12% vs 6%, $p < 0.001$) which is probably due to the tartaric acid from the capsules containing dabigatran (dabigatran requires a low pH for absorption).

In conclusion, dabigatran promises to become the new treatment of choice for stroke and systemic embolism prevention in patients with atrial fibrillation. The dose of 110mg is non-inferior compared with warfarin for the prevention of stroke and systemic embolism and is associated with a lower rate of major bleeding. The dose of 150mg was superior compared with warfarin for the prevention of stroke and systemic embolism and had similar rate of major bleeding. The major advantage should be the lack of continuous monitoring of the therapy, like it is in the case of warfarin. ❑

Reference
Connolly SJ, Ezekowitz MD, Yusuf S et al – Steering Committee and Investigators. Dabigatran versus Warfarin in Patients with Atrial Fibrillation. *N Engl J Med* 2009; 361, DOI 10.1056/NEJMoa0905561