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Online publish-ahead-of-print 21 September 2009


Atrial fibrillation is an increasingly common arrhythmia, now said to stand at epidemic proportion in Western societies: >2.3 million people in the USA and >4.5 million people in Western Europe. It is an expression of underlying heart disease and a threat to life and living. In particular it is associated with 4.5-fold risk of stroke,\(^1\) predominantly ischaemic in nature, largely due to embolization of a left atrial clot. Over the last several decades a formidable evidence base has been developed for the use of anticoagulant therapy,\(^2\) mostly warfarin/coumadin, and antiplatelet therapy, predominantly aspirin and more recently clopidogrel plus aspirin.\(^3\)

Although warfarin is undoubtedly an effective anticoagulant therapy, its application is associated with a highly significant risk of bleeding such that it has been necessary to provide regular and sometimes intense monitoring of coagulation parameters, and stringent control of diet, alcohol, and co-medications. Recently it has been suggested that it might be necessary to apply modern pharmacogenomic principles of personalized medicine to warfarin recipients to optimize the safety of anticoagulant control.\(^4\) Despite all this, warfarin therapy remains problematic, especially in the elderly because of non-adherence to medication, falls, and polypharmacy. The alternative approach is aspirin, the efficacy of which is doubted unless combined with clopidogrel, although the bleeding risk when used alone is not negligible, and is considerable in combination with clopidogrel. As a result, neither physicians nor patients have been confident about anticoagulant/antithrombotic therapy, and its utilization for atrial fibrillation has been inconsistent and often inappropriate.\(^5\)

There has been a very determined effort on the part of basic scientists, clinical researchers, and the Pharma industry to find a better anticoagulant. Two main avenues of research emerged: direct thrombin inhibitors (e.g. ximelagatran and dabigatran) and factor Xa inhibitors (e.g. rivaroxaban, apixaban, edoxaban, etc.). Ximelagatran was compared against warfarin in patients with atrial fibrillation and, although probably as effective as warfarin, it appeared to be unsafe, predominantly because of liver toxicity.\(^6\) Large-scale clinical trials of the factor Xa inhibitors against warfarin, and in one case (apixaban) against aspirin, are underway. The trial of dabigatran vs. warfarin has been reported at the 2009 ESC Annual Congress in Barcelona and has been published in the New England Journal of Medicine.\(^7\)

The RE-LY study\(^8\) is a trial of >18 000 patients with atrial fibrillation who were randomized between warfarin or one of two doses of dabigatran etexilate (110 mg b.i.d. or 150 mg b.i.d.), a direct thrombin inhibitor which has already been proven valuable for the prophylactic treatment of venous thromboembolism.\(^7\) A previous pilot study in patients with atrial fibrillation had been used to define the appropriate dosing schedule.\(^10\) The trial population consisted of typical patients with atrial fibrillation and cardiovascular/thromboembolic risk: average age 72 years, mean CHADS score 2.1, and history of myocardial infarction (17%), stroke (20%), and heart failure (32%). Half the patients had no previous exposure to warfarin treatment.

The trial design was prospective, randomized, and open, with blinded adjudication of events (PROBE).\(^11\) Patients were treated for an average of 2 years with practically complete follow-up. Those on warfarin were in the therapeutic range for 64% of visits. At the 2-year time point ~15% of warfarin patients and 20% of those taking dabigatran had discontinued therapy, usually for adverse gastrointestinal events in all three limbs of the trial. The primary endpoint was stroke or systemic embolism, and the results were remarkable: warfarin, 198 patients (1.7% per annum); dabigatran 110 mg b.i.d., 182 patients (1.55% per annum, \(P = 0.37\) for superiority and \(P < 0.001\) for non-inferiority); and dabigatran 150 mg b.i.d., 133 patients (1.11% per annum, \(P < 0.001\) for superiority). Compared with warfarin (3.46), major bleeds were less for dabigatran 110 mg b.i.d. (2.74, \(P = 0.002\)) but similar for 150 mg b.i.d. (3.22, \(P = 0.32\)). Importantly, intracranial bleeds were significantly less with both doses of dabigatran than with warfarin. The
death rate was reduced with dabigatran 150 mg b.i.d., and hospitalization was reduced with dabigatran 110 mg b.i.d. There was a trend for less myocardial infarction with warfarin. Liver function abnormalities were not seen in association with dabigatran.

Both doses of dabigatran were therefore better than warfarin. Dabigatran 110 mg b.i.d. had similar efficacy with fewer major bleeds and fewer hospitalizations, and dabigatran 150 mg b.i.d. had better efficacy with less mortality and similar major bleeding rates. All of this was achieved with no need for monitoring, and no excess of other unwanted serious side effects.

So far I have been able to examine only the top line results of this trial. Much more information will be needed before regulators can decide on the approbability of the drug for the management of patients with atrial fibrillation with thromboembolic risk (CHADS scores \(^2\)). However, at first sight, the implications of this trial seem to be enormous—not only offering another therapy to reduce the risk of stroke in atrial fibrillation, but also signalling the opportunity for a paradigm shift with regard to physician/patient acceptability of anticoagulant therapy for atrial fibrillation. Dabigatran will surely replace warfarin as the treatment of choice (a better therapy), and the standard of care (the accepted therapy). Of course a daily dose of dabigatran will be more expensive than warfarin, but there will be obvious cost reductions from the reduced number of strokes. This lower stroke rate could be far greater in everyday clinical practice than in the clinical trial because treatment with dabigatran will be easier to handle, and is more likely to be prescribed and adhered to than treatment with warfarin. Large savings should also accrue since there will be no need to monitor the anticoagulant effect. Expensive genotyping to avoid warfarin metabolic jeopardy will not be necessary with dabigatran.

The trial will be criticized: the potentially unsafe nature of the PROBE trial design will be raised—ximelagatran results were encouraging in an open design trial, but a similar but fully double blind trial did not confirm the result. \(^1,2\) However, in almost every other way this trial seems exemplary with regard to its design and conduct.

We are not yet ready to prescribe dabigatran to all our patients with atrial fibrillation. Which dose should we choose—does the trial database help us to decide? There will be a clamour to change warfarin-treated patients to therapy with dabigatran—how did such patients in the trial fare in comparison with warfarin-naive patients? Does the very elderly patient do as well with dabigatran as the trial group as a whole? Does it matter that we have no antidote to dabigatran? However, vitamin K was never an immediate solution to stem serious bleeding from overanticoagulation from warfarin. What should we do if we need to cardiovert the patient—is treatment with warfarin then necessary? Will the patient and the physician feel uneasy when the anticoagulant effect is not monitored? Many of these initial concerns may be answered, at least in part, when further results are made available at the ESC in Barcelona and later in the medical press.

The RE-LY trial is a landmark study with regard to the management of patients with atrial fibrillation and thromboembolic risk. However, it does not answer all our questions and it raises many more. The study should not impede other ongoing trials with direct thrombin inhibitors or factor Xa inhibitors. Eventually trials comparing different molecules or different mechanisms may be needed. The clinical effectiveness of dabigatran, which acts at the end of the coagulation cascade, \(^15\) seems to be quite different from the blunderbuss effect of warfarin acting at almost every level of the coagulation pathway, and may be quite different, both qualitatively and quantitatively, from that of the factor Xa inhibitors. For example, the effects on stroke prevention may not extend to a reduction of myocardial infarction.

We must look forward with eager anticipation to further results from the RE-LY trial and from the half dozen other trials comparing new anticoagulants with warfarin or aspirin. ‘One swallow does not make a summer’ and we need more results to corroborate and extend what appears to be a major breakthrough. However, we should not wait for all of this before we are obliged to make fundamental changes to our clinical practice.

Conflict of interest: A.J.C. is an adviser to Boehringer Ingleheim.

References