EINSTEIN-PE study results, with South African expert comment

Rivaroxaban revolutionises treatment of pulmonary embolism

Rivaroxaban has been shown to be as effective as initial and long-term treatment with enoxaparin and warfarin for pulmonary embolism (PE), with a potentially improved risk profile benefit. The results of the Einstein-PE study were announced at the recent American College of Cardiology meeting in Chicago and simultaneously published in the March issue of New England Journal of Medicine 2012.

Commenting on the study results, Dr Harry Buller, Academic Medical Centre, Amsterdam pointed out that in the overall EINSTEIN-DVT and EINSTEIN-PE programme of 10 000 patients, there was a very convincing 50% lower rate of major bleeding, particularly intra-cranial haemorrhage and retroperitoneal bleeds with rivaroxaban compared with the difficult-to-manage warfarin standard therapy. ‘One of the patient groups who particularly benefited with regard to major bleeding with rivaroxaban was those over 75 years of age’, Dr Buller noted.

The EINSTEIN-PE study was been heralded as a landmark study in the field of pulmonary embolism and marks a turning point in its management. It is the largest-ever study of PE, recruiting 4 833 patients from 36 countries, including South Africa.

Designed as a non-inferiority study, oral rivaroxaban was given as 15 mg bid for three weeks, followed by 20 mg daily. This was compared to the standard treatment of subcutaneous injections for five to 10 days with a low-molecular weight heparin (LMWH) and an oral vitamin K antagonist (warfarin) for the prevention of recurrent thromboembolism.

‘Rivaroxaban was given as monotherapy, which was a very brave step and it is the first study to really bite the bullet with regard to its challenge of conventional LMWH therapy’, Dr Buller said. Rivaroxaban, an oral factor Xa inhibitor, has already been shown in phase III trials to be as effective as standard anticoagulant therapy for the treatment of deep-vein thrombosis and stroke prevention in atrial fibrillation and is currently registered in South Africa for the prevention of venous thromboembolism in patients undergoing major orthopaedic surgery of the lower limbs.

The EINSTEIN-PE study recruited a broad spectrum of patients with PE with and without deep-vein thrombosis. Exclusions included patients treated with LMWH, fondaparinux or unfractionated heparin for more than 48 hours or if they had already received more than a single dose of a vitamin K antagonist before randomisation. Also patients who had undergone thrombectomy or other surgical procedures were excluded. Patients with contra-indications to vitamin K were also excluded, as were patients with active bleeding or at high risk of bleeding, contra-indicating anti-coagulant therapy. Randomisation was stratified according to country and the attending physician’s intention-to-treat duration of three, six or 12 months. Importantly, standard therapy was well controlled and time in therapeutic range (TTR) of the target INR (2–3) was 62.7%. The TTR percentage did vary from 57.8% during the first month, to 72.7% during month 11. In the rivaroxaban group, adherence to therapy was above 80%.

In the study, rivaroxaban demonstrated efficacy comparable to that of the current standard therapy in reducing the primary endpoint of recurrent symptomatic VTE, a composite of symptomatic deep-vein thrombosis and non-fatal or fatal pulmonary embolism (2.1 vs 1.8%, respectively; p = 0.003 for non-inferiority). Rivaroxaban also demonstrated similar safety results compared to current standard of care for the principal safety outcome measuring a composite of major and non-major clinically relevant bleeding events (10.3 vs 11.4%, respectively; p = 0.23). Importantly, rivaroxaban treatment resulted in a significant reduction in major bleeding events (1.1 vs 2.2%, respectively; p = 0.003) compared to the current standard therapy.

Acute coronary events were low (0.6%) and were equally distributed between the two groups.


Prof Guy Richards comments on the importance of the EINSTEIN-PE study for South African clinicians

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This is an interesting study, the first assessing utilisation of one of the new orally available anticoagulants to treat pulmonary embolism. The outcomes were similar with regard to prevention of recurrence but there were differences with regard to safety.

Whereas overall major or clinically relevant non-major bleeding was the same, overall major bleeding episodes did differ, with 26 (1.1%) occurring in the rivaroxaban group and 52 (2.2%) in the standard-therapy group. This difference had a standard deviation of 0.49 (95% confidence interval of 0.31–0.79) and was significant (p = 0.003). Within this latter group was included other non-fatal episodes in critical sites, and a large proportion of the differences within the group of major bleeds was made up of intra-cerebral bleeds, which occurred in one patient (< 0.1%) with rivaroxaban, and 10 (0.4%) with standard therapy.

Will this study change therapy? The important considerations are firstly efficacy, and in this regard rivaroxaban is non-inferior to standard therapy. Second is safety, and certainly with regard to major bleeding episodes, it is superior, although the numbers are small. Third is the issue of cost. If it is priced too high, the cost efficacy may make this therapy non-justifiable and this may prove to be an obstacle. Fourthly, some patients do not like injecting themselves and may prefer to take a tablet that has been proven
to be equally efficacious.

Bayer is to be congratulated, however, on successfully completing an arduous study without any pre-knowledge as to what the outcome would be. This study adds significantly to our knowledge of these new drugs and offers different options for the treatment of pulmonary embolus in the future.