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Dabigatran is as effective as Warfarin in the treatment of acute venous thromboembolism – the RE-COVER study

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The current standard treatment for acute venous thromboembolism is rapidly acting parenteral anticoagulation for 5 to 7 days followed by at least 3 months of treatment with a vitamin K antagonist. Treatment with a vitamin K antagonist requires frequent monitoring of the international normalized ratio (INR), and multiple interactions of vitamin K antagonists with foods and other drugs have been reported.

Dabigatran is an orally available, potent, direct inhibitor of thrombin. It is rapidly converted by ubiquitous esterases to the active drug, is administered in fixed doses without the need for coagulation monitoring, is excreted by the kidney, and has a half life of 12 to 17 hours. Dabigatran has similar efficacy and safety to enoxaparin for the prevention of venous thromboembolism in patients who have had elective hip or knee arthroplasty. Recently, dabigatran, as compared with warfarin, was shown to have superior safety with equivalent efficacy (when it was administered at a dose of 110 mg twice daily), or superior efficacy with similar safety (when it was administered at a dose of 150 mg twice daily), for the prevention of stroke in patients with atrial fibrillation (the RE-LY study).

The RE-COVER study, was a double-blind, doubledummy, randomized trial, in which were compared 6 months of treatment with dabigatran, at a fixed dose of 150 mg twice daily, with dose-adjusted warfarin therapy, after initial parenteral anticoagulation.

From April 2006 through November 2008, a total of 2564 patients were randomly assigned to a study group. Patients were recruited from 228 clinical centers in 29 countries. Patients 18 years of age or older who had acute, symptomatic, objectively verified proximal deep-vein thrombosis of the legs or pulmonary embolism and for whom 6 months of anticoagulant therapy was considered to be an appropriate treatment were potentially eligible.

Exclusion criteria were duration of symptoms longer than 14 days, pulmonary embolism with hemodynamic instability or requiring thrombolytic therapy, another indication for warfarin therapy, recent unstable cardiovascular disease, a high risk of bleeding, liver disease with an aminotransferase level that was two times the local upper limit of the normal range, an estimated creatinine clearance of less than 30 ml per minute, a life expectancy of less than 6 months, a contraindication to heparin or to radiographic contrast material, pregnancy or risk of becoming pregnant, or a requirement for long-term antiplatelet therapy.

The diagnosis of venous thromboembolism was established with the use of compression ultrasonography or venography of leg veins and ventilation–perfusion lung scanning, angiography, or spiral computed tomography of pulmonary arteries.

Patients were assigned in a 1:1 ratio to receive a fixed dose of dabigatran (150 mg twice daily taken orally – no 1274) or warfarin (no 1265). Initial treatment with an approved parenteral anticoagulant (generally unfractionated heparin administered intravenously or low-molecular-weight heparin administered subcutaneously) was usually started before random assignment. Warfarin or a placebo that looked identical to warfarin was generally started on the day of random assignment and was adjusted to achieve an INR of 2.0 to 3.0 on a point-of-care coagulometer that was programmed, in conjunction with the randomization schedule, to yield either a true INR or a sham INR ("singledummy phase"). Administration of dabigatran or a placebo that looked identical to dabigatran was initiated, and the parenteral anticoagulant was stopped, once the parenteral anticoagulant had been given for at least 5 days and the true or sham INR was recorded as 2.0 or higher on 2 consecutive days. The first dose of dabigatran was given within 2 hours before the time that the next dose of initial parenteral therapy would have been due or at the time of discontinuation of intravenous unfractionated heparin. Active dabigatran and warfarin- like placebo or active warfarin and dabigatran- like placebo were then given for 6 months ("doubledummy phase").

Patients were assessed at 7 days and then monthly until 6 months and were told to contact their study site immediately if symptoms developed that were suggestive of venous thromboembolism or bleeding.

Symptoms suggestive of recurrent venous thromboembolism were evaluated with the use of the same diagnostic methods that had been used for the initial diagnosis. Bleeding was defined as major if it was clinically overt and if it was associated with a fall in the hemoglobin level of at least 20 g per liter, resulted in the need for transfusion of 2 or more units of red cells, involved a critical site or was fatal.

Regarding efficacy – as compared with warfarin, dabigatran was noninferior with regard to the prevention of recurrent or fatal venous thromboembolism ($p<0,001$ for the criteria of both hazard ratio and the difference in risk).

Regarding safety – the relative risk of bleeding with dabigatran as compared with warfarin eas similar among the subgroups. The only type of bleeding that showed a trend to higher incidence in the dabigatran group was gastrointestinal hemorrhage. There were no significang differences between the two treatment groups in the frequency of any adverse events, except for dyspepsia which had a higher incidence in the dabigatran group.

In the RE-COVER study, treatment with dabigatran was as effective as warfarin therapy, which achieved INR values within the therapeutic INR range 60% of the time – a rate that is consistent with good quality of warfarin dosing.

The trial provides data to support dabigatran as a fixed-dose oral treatment for acute deep-vein thrombosis and pulmonary embolism. For patients and health care providers, dabigatran is a far more convenient drug than warfarin because it has no known interactions with foods and minimal interactions with other drugs and therefore does not require routine blood-coagulation testing. ❑

Comment on a paper:
Schulman S, Kearon C, Kakkar AK et al – Dabigatran versus Warfarin in the Treatment of Acute Venous Thromboembolism. *N Engl J Med* 2009; 361:2342-2352