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EINSTEIN–PE Investigators. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med 2012; 366:1287-97.

Oral vitamin K antagonists such as warfarin have been the mainstay of treatment in venous thromboembolism and pulmonary embolism since its approval in 1954. Clinicians can not only attest to its effectiveness but also the burden that patients face in maintaining a therapeutic level. In 2010 the EINSTEIN-PE investigators published its review on rivaroxaban in the treatment of venous thromboembolism (1). The results of this large 3449 pt trial were favorable showing non inferiority to vitamin K antagonists. This study now looks at rivaroxaban as a therapeutic alternative to vitamin K antagonists in the treatment of pulmonary embolism. The main advantage of rivaroxaban is a standard once daily dosing regimen without the need for blood monitoring.

The study was a large randomized open label trial performed at 263 sites over 38 countries between 2007–2011. Inclusion criteria were imaging confirmed symptomatic pulmonary embolism with or without deep vein thrombosis. Exclusion criteria were extensive, however they did allow for 1 single dose of a vitamin K antagonist, or enoxaparin, heparin, fondaparinux to be given for less than for 48 hours. This is certainly reasonable as it would be unethical to leave diagnosed pulmonary embolism untreated for 48 hours. 4833 patients were included in the study. 2413 patients were randomized to standard therapy with vitamin K antagonists while 2420 were assigned to receive rivaroxaban 15mg twice daily for 3 weeks then 20mg daily thereafter. The average treatment length was 9 months and there were statistically significant differences in patient demographics. The primary outcomes were rates of recurrent venous thromboembolism as well and major and minor bleeding.

This study set out to prove that rivaroxaban was not inferior to vitamin K .antagonists. It accomplished this goal. The results showed that there were no statistically significant differences in rates of recurrent venous thromboembolism, however, there were increased incidences of major bleeding episodes within the standard (vitamin K antagonist) group at 52 events vs. 26 events in the rivaroxaban group (p=0.003).

Is rivaroxaban ready for prime time and will it replace warfarin as the new standard of care in the treatment of venous thromboembolic disease?

The initial data certainly looks promising, although we need to proceed with caution given that this is a non reversible, non-dialyzable agent. Cost will be a major limiting factor as 1 month supply of rivaroxaban is estimated at $900 vs. $20 for warfarin. A cost-effectiveness analysis looking at laboratory fees and rates of readmission for bleeding events will most likely be needed. Further longitudinal studies extending beyond 1 year may also be needed to establish safety and efficacy. For now this medication offers promise that the treatment of venous thromboembolic disease is about to change.

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Reference

1. The EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med 2010; 363:2499-2510.