CJEM Journal Club

Oral rivaroxaban for the treatment of symptomatic pulmonary embolism: are we ready?

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Clinical question
Can an oral regimen of rivaroxaban be used for the treatment of symptomatic pulmonary embolism?
Article chosen
Büller H, Prins M, Lensing A, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med* 2012;366:1287–97.
Objective
To determine the effectiveness and safety of oral rivaroxaban in the treatment of symptomatic pulmonary embolism when compared to current standard therapy.

Keywords: noninferiority trial, pulmonary embolism, rivaroxaban

BACKGROUND

Pulmonary embolism (PE) is a common diagnosis in the emergency department (ED) and can be associated with significant morbidity and mortality.[1,2] The mainstay of treatment for patients with PE has been the administration of a heparin overlapped with the initiation of a vitamin K antagonist. Use of the latter requires ongoing testing of the patient's international normalized ratio (INR) to avoid supra- or subtherapeutic levels that would increase the risk of bleeding complications or recurrent venous thromboembolism (VTE), respectively. The new generation of oral anticoagulants may change the current treatment approach. Several noninferiority trials concerning the oral factor Xa and direct thrombin inhibitors are currently being used to challenge the vitamin K antagonist era.[3–7] In this noninferiority trial, the EINSTEIN investigators sought to compare the efficacy and safety between the oral factor Xa inhibitor rivaroxaban and standard therapy in the treatment of symptomatic PE.

STUDY DESIGN

This was an industry-funded, randomized, open-label, event-driven, noninferiority trial comparing rivaroxaban to standard therapy (enoxaparin bridged with a vitamin K antagonist).

POPULATION STUDIED

The study was completed at 263 sites in 38 different countries from 2007 to 2011. The population studied was patients of legal age presenting with acute, symptomatic PE, confirmed by imaging, with or without concurrent deep vein thrombosis (DVT). The investigators included patients who were treated with a therapeutic dose of vitamin K antagonist or enoxaparin, heparin, or fondaparinux for less than 48 hours and excluded a broad and justifiable subset of patients, including those with a creatinine clearance less than 30 mL/min and liver disease. In total, 4,833 patients were randomized to two treatment arms after the treating physician determined the intended treatment duration, which varied from 3, 6, or 12 months. No statistically significant differences between the two treatment arms in terms of demographic and clinical characteristics were found. A total of 2,420 patients were randomized to receive rivaroxaban 15 mg twice daily for the first 3 weeks followed by 20 mg once daily

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afterwards, whereas 2,413 patients were assigned to standard therapy with vitamin K antagonists.

OUTCOMES MEASURED

The primary efficacy outcome of the trial was symptomatic recurrent VTE: a composite outcome including fatal or nonfatal PE or DVT. Conversely, the primary safety outcome was clinically relevant bleeding composed of major or clinically relevant nonmajor bleeding. Secondary outcomes, defined a priori, included death from any cause, vascular events, and net clinical benefit.

RESULTS

For rivaroxaban to be considered noninferior, the authors decided that it must not double the risk of recurrent VTE at any point in follow-up and set the noninferiority margin at 2.0. Statistically, this means that the upper bound of the 95% confidence interval (CI) about the adjusted hazard ratios must be less than 2.0. The primary outcome of recurrent VTE occurred in 2.1% of the rivaroxaban group and 1.8% of the standard therapy group (hazard ratio 1.12; 95% CI 0.75–1.68; $p = 0.003$). The primary safety outcome occurred in 10.3% of the rivaroxaban group and in 11.4% of the standard therapy group (hazard ratio 0.90; 95% CI 0.76–1.07; $p = 0.23$), whereas major bleeding was lower in the rivaroxaban group at 1.1% compared to the standard therapy group at 2.2% (hazard ratio 0.49; 95% CI 0.31–0.79, $p = 0.003$). The "net clinical benefit" outcome, defined as a composite of recurrent VTE and major bleeding, occurred in 3.4% of the rivaroxaban group and 4.0% in the standard therapy group (hazard ratio 0.85; 95% CI 0.63–1.14; $p = 0.28$).

CONCLUSION

The authors concluded that their data support the use of rivaroxaban as a single oral agent for patients with symptomatic PE.

COMMENTARY

The treatment of PE appears to represent an appropriate clinical situation to use a noninferiority trial. Current treatment requiring INR monitoring incurs a specific cost that could be avoidable if testing were not used. This cost saving could be offset, however, if the new agent itself were to be more costly or if its adverse event rate generated additional costs not seen with current therapy. In addition, demonstration of comparable safety is important.

Unlike superiority trials, biases that direct results toward the null hypothesis in noninferiority trials act to strengthen the equivalence of the two treatment options and can aid in proving "noninferiority." To avoid this, a noninferiority trial must be rigorous in its methods, especially with respect to blinding, specifying the noninferiority margin, sample size calculations, and analysis.

Blinding in a noninferiority trial is not as effective in protection against bias as in superiority trials because the aim is to prove a relatively similar outcome between the two treatment arms. Regardless, appropriate blinding can still protect against several misclassification biases that may have affected the results of this study.

Given the morbidity and mortality risk of recurrent VTE, the trial's noninferiority margin of 2.0 does seem somewhat high, and although the results were well within that risk margin, the noninferiority margin impacts the determination of sample size. Accordingly, noninferiority trials tend to have larger sample sizes than placebo-controlled trials. This is because the noninferiority margin is often much smaller than the expected treatment difference in superiority trials. Having a sample size that is too small would inadequately power the study and may raise questions about study conclusions.

In applying these principles, it is apparent that there are several issues that question the validity of this trial. First, the lack of blinding in this trial automatically raises questions of possible observer expectation bias, attention bias, and obsequiousness bias that threaten the internal validity of the study. Although identical checklists were used, one may also raise the question of possible differences between the quality of follow-up and surveillance that the rivaroxaban arm may have received and subsequent compliance bias by the study participants. Although the authors state a diagnostic suspicion bias toward the rivaroxaban group in terms of suspected VTE, an opposing argument could be made for the vitamin K antagonist group with respect to not pursuing VTE in individuals with known therapeutic INRs. It is surprising that an industry-sponsored study chose against including such a fundamental research principle in their methodology.

A blinding protocol including sham INRs seems reasonable considering the potential impact of the study drug.

The EINSTEIN investigators decided to drive their study by prespecified events. This is in contrast to traditional hypothesis testing, which requires a set sample size to assess the number of events that occur. Using the noninferiority margin of 2.0, it was determined that 88 total events would provide a power of 90%. Although the possibility exists of equivalence bias inherent in the implementation of an event-driven trial, the authors did exceed their expected patient enrolment of 3,000 patients.

In terms of analysis, the authors used an intention-to-treat analysis that revealed similar results to the on-treatment and per protocol analyses, adding to the validity of the data. The primary efficacy outcome showed that the rivaroxaban group experienced recurrent VTE 1.12 times more frequently in 1 year than the standard therapy group. With the noninferiority margin of 2.0 and a 95% CI of 0.75 to 1.68 ($p = 0.003$), this result was deemed noninferior to that of standard therapy.

CONCLUSION

The EINSTEIN investigators have been the major force behind rivaroxaban and its use in the treatment of symptomatic VTE and PE. The use of a reversible single oral agent that does not require monitoring could drastically simplify the treatment of PE from the perspective of both the physician and the patient.[8] However, the lack of blinding raises some questions concerning the validity of the trial despite its promising results. With other trials supporting the cost-effectiveness of rivaroxaban compared to warfarin in other clinical scenarios requiring anticoagulation,[9] we may see rivaroxaban being supported as a first-line treatment for symptomatic PE in the ED. Until further

supporting evidence is published and greater clinical experience is gathered, it may be wise to use rivaroxaban with caution and only in those patients who understand the risks but wish to avoid the need for monitoring.

Competing interests: None declared.

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