Oral Rivaroxaban for the Treatment of Symptomatic Pulmonary Embolism

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General/Introduction:

- **Title/Journal**: The title is appropriate as it defines the therapy being studied and in what disease state. However, the study does not state what standard therapy the experimental therapy is being compared too. The journal is appropriate as the New England Journal of Medicine is a highly reputable and well known journal within the medical community.
- **Potential bias:** Possible bias could have arisen due to the study being sponsored by Bayer Health-care and Janssen Pharmaceuticals. These are the manufacturers of brand name rivaroxaban and therefore they hold stock in reporting positive results in regard to rivaroxaban treatment. However, the trial did try to prevent bias by assigning a central committee to interrupt the results while blinded to study-group assignment. Other bias could have arisen from the open-label design of the trial allowing both researcher and participant to know of treatment assignment.
- **Current Knowledge**: The development of pulmonary embolism is a rather common condition leading to hospitalization and can be fatal. The current standard of care for treatment of pulmonary embolism consists of a heparin product overlapped with a vitamin K antagonist. However, this therapy requires monitoring of drug levels and injections. More recently the use of oral thrombin inhibitors has been considered for anticoagulation therapy for DVTs and PEs. Rivaroxaban has been shown to be an effective alternative for DVT prophylaxis following orthopedic surgery, for stroke prevention in A-fib patients, and for treatment of ACS. This study looked at the use of rivaroxaban in the treatment of symptomatic PE in replacement of heparin and vitamin K antagonist therapy.
- **Objective**: The objective of this study was to determine the safety and efficacy of rivaroxaban compared to standard anticoagulation therapy in the treatment of acute symptomatic PE patients with or without DVT.

Study Design/Methods:

- **Study Design**: randomized, open label, multi-centered, non-inferiority trial
- **Inclusion criteria**: Patients 18 years or older presenting with acute symptomatic pulmonary embolism with objective confirmation, with or without DVT were included in the study.
- **Exclusion criteria**: Patients were excluded from the study if they had received greater than 48 hours of therapeutic unfractionated heparin, fonadaparinux, or low-molecular weight heparin; or if they had received more than one dose of a vitamin K antagonist. Patients having undergone a thrombectomy, vena cava filter placement, or had been given a fibrinolytic agent could not be in the study. Patients were also excluded due to contraindications to vitamin K antagonists or enoxaparin, if they had another indication for vitamin K antagonist therapy, Crcl <30 ml/min, significant liver disease, ALT x3 ULN, bacterial endocarditis, active bleeding or high risk for bleeding, systolic BP > 180 or diastolic > 110, childbearing potential without proper contraception, pregnancy, breast feeding, concomitant use of a strong CYP 3A4 inhibitor or inducer, participation in another experimental study within 30 days, or life expectancy less than 3 months.
- **Real life application**: The patients included in the study were representative of the type of patient that would benefit from therapy. However, the results are limited against the severely ill or the patient with comorbities as the exclusion criteria was extensive and excluded many patients that might present with an acute PE.
- **Intervention**: The intervention of the study was treatment with rivaroxaban 15mg po BID for 3 weeks followed by rivaroxaban 20mg po QD for either 3, 6, or 12 months. This was compared to standard anticoagulation therapy with enoxaparin 1mg/kg sc BID and warfarin or acenocoumarol start within 48 hours and continued for 3, 6, or 12 months with a target INR of 2-3. Enoxaparin was continued until INR was within range for 2 consecutive days and at least 5 days of overlap therapy had occurred.
- **Duration**: The study enrolled patients in 263 sites and 38 different countries presenting from March 2007 to March 2011. Patients were followed for either 3, 6, or 12 months depending on the physician's desired treatment duration for PE.
- **Primary endpoints**: The primary efficacy endpoint of the study was recurrence of symptomatic DVT. The primary safety endpoint was clinically significant bleeding.
- **Secondary endpoints**: Secondary endpoints of the study included major bleeding, death from any cause, vascular events, and net clinical benefit.
- **Clinical measurements**: The primary endpoint of symptomatic VTE was measured through objective findings such as a new intraluminal filling on CT scan or pulmonary angiography, vessel cutoff of > 2.5mm in diameter based on pulmonary angiography, new perfusion defect of 75% with corresponding normal ventilation, a new non-high probability perfusion defect associated with DVT based on ultrasonography or venography, or PE determined on autopsy. The primary safety outcome of clinically relevant bleeding was measured by a hemoglobin decrease of 2g/dL, need for transfusion of 2 or more units of packed RBCs, bleeding that led to death, bleeding that led to hemodynamic compromise, bleeding that led to hospitalization, hematoma larger than $25cm^2$ or $100cm^2$ with traumatic cause, epistaxis lasting greater than 5 minutes, gingival bleeding, hematuria, GI hemorrhage, rectal blood loss, hemoptysis, any other bleeding leading to intervention.

Statistics

- **Sample size:** A total of 4832 patients were enrolled in the study. 2419 patients were randomized to receive rivaroxaban and 2413 received standard therapy with enoxaparin and a vitamin K antagonist.

Statistical tests: Statistical tests were performed to determine non-inferiority of rivaroxaban compared to standard therapy. It was determined that 88 events would provide a power of 90% to show non-inferiority with a margin of 2.0 for the upper limit of the 95% CI with a two-sided P value of 0.05. The primary outcome was analyzed using intention to treat with the Cox proportional hazards model. Kaplan-Meier curves were used to display the development of events over time.

Results

- **Baseline Characteristics:** Baseline characteristics were similar between both groups. The average patient was 58 years old with it equally split between men and women. No statisitcal differences were reported between the groups.
- **Study Groups:**
  - **Primary Endpoints:** In the rivaroxaban group 2.1% of patients suffered a recurrent VTE while 1.8% of patients in the standard therapy developed a recurrent VTE. This difference was not found to be statistically significant as the confidence interval included 1 (CI = 0.75 to 1.68). This showed non-inferiority of rivaroxaban compared to standard therapy. In the safety primary endpoint 10.3% of patients in the rivaroxaban group and 11.4% in the standard therapy group experienced a first major or clinically significant non-major bleeding episode. This difference was not found to be statistically significant with a P value of 0.23.
  - **Secondary Endpoints:**. Major bleeding occurred in 1.1% of rivaroxaban patients compared to 2.2% of standard therapy patients. This difference was found to be statistically significant with a P value of 0.003. Death from any cause occurred in 2.4% of rivaroxaban patients and 2.1% of standard therapy patients. This was found to not be statistically significant with a P value of 0.53. A net clinical benefit was determined in 3.4% of rivaroxaban patients and in 4.0% of standard therapy patients. This difference was not found to be statistically significant with a P value of 0.28. An acute coronary event occurred in 0.6% of rivaroxaban and in 0.9% of standard therapy patients. These results can not be accurately evaluated as a P value or confidence interval was not reported.
  - **Subgroup analysis:** In the subgroup analysis the primary efficacy and safety endpoints were consistently found to be the same as in the overall analysis.
- **Study Dropouts:** 10.7% of rivarxoxaban patients and 12.3% of standard therapy patients dropped out of the study. The difference between the two groups was not found to be statistically significant with a P value of 0.07. Reasons for premature withdrawal from the study included development of an adverse event, consent withdrawn, and loss to follow-up.
- **Adverse Outcomes**: There were no statistically significant differences in the reporting of adverse events between the two groups.
- **Strengths**:
  - It was a randomized, multi-center trial.
  - The sample size was large with 4832 patients.
  - Followed patients throughout total treatment duration.
- **Limitations**:
  - Patients were only followed for the period of treatment. Longer term studies are needed looking at recurrence after therapy has ended.
  - While not found to be statistically significant, absolute number of cases were higher for DVT recurrence in the rivaroxaban group and net clinical benefit was lower.
  - Non-inferiority trial therefore can not show that rivaroxaban use is better than standard therapy.
  - Patients received LMWH prior to diagnosis confirmation and entry into the study.
  - Open label design may have created diagnostic-suspicion bias since both researchers and participants were aware of randomization to which treatment group.
  - Patients with CrCl < 30ml/min were excluded and therefore proper renal adjustment dosing in these patients is not known.

Application to Pharmacy Practice

The results of this study found rivaroxaban to be an appropriate alternative to traditional DVT and PE treatment. Rivaroxaban is currently being used for prophylaxis treatment in some patients at risks for developing a VTE. This study extends the use of rivaroxaban to include treatment of VTEs. Its use in the hospital can simplify dosing and monitoring of these patients as rivaroxaban is given in a fixed dosed without any monitoring needed. However, drawbacks to the new medication include unfamiliarity, no reversal agent, no monitoring to know when patient is therapeutic, and no long term studies of possible adverse events or complications to therapy. The results of this study show promise for the use of rivaroxaban in simplifying VTE treatment. This intense initial dosing also shows improved outcomes with steady state levels being achieved sooner without the increase of bleeding. However, it is still only considered an alternative and the risks vs benefits need to be calculated when considering its use over traditional standard of care therapies.