Challenging pulmonary embolism - A new generation of oral anticoagulants

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Acute pulmonary embolism (PE) is a relatively common cardiovascular emergency, with an estimated annual incidence of 70 cases per 100,000 individuals (1). Occlusion of the pulmonary arterial bed may lead to acute life-threatening but potentially reversible right ventricular failure, highlighting the need for an early and accurate diagnosis. Initial therapy aims primarily at restoration of flow through occluded pulmonary arteries and the prevention of early recurrences.

Anticoagulant treatment plays a pivotal role in the management of patients with PE. The need for immediate anticoagulation in patients with PE is based on a landmark study that was performed in the 1960s and demonstrated the benefits of unfractionated heparin in comparison with no treatment (2). Traditionally, clinicians have treated patients with acute deep vein thrombosis (DVT) or PE in the hospital setting with IV unfractionated heparin, followed by conversion over to oral vitamin K antagonist therapy. Over the last 15 years, subcutaneously administrated low-molecular-weight heparins have replaced much of IV unfractionated heparin therapy, facilitating outpatient treatment because of fast antithrombotic effect, fixed weight-based dose and no need for daily anticoagulant monitoring (3).

Oral anticoagulants with no need for laboratory monitoring and dose adjustment have been under investigation in the last few years. At least two types of oral agents, the selective thrombin inhibitor dabigatran and the factor Xa inhibitors rivaroxaban and apixaban, have shown promising results in the prevention of venous thromboembolism (VTE) following orthopedic surgeries (4-6). Although apixaban is currently still being tested in a randomized double-blind study for the prevention of venous thromboembolic recurrence or death in patients with DVT or PE (*Efficacy and Safety Study of Apixaban for the Treatment of Deep Vein Thrombosis or Pulmonary Embolism*), dabigatran and rivaroxaban have already demonstrated its potential value in the treatment of VTE.

In *RE-COVER*, a randomized, double-blind, noninferiority trial involving patients with acute VTE, a fixed dose of dabigatran was as effective as warfarin for the prevention of 6-month recurrent symptomatic VTE and related deaths, and had a safety profile similar, if not better, than that of warfarin (7).

Rivaroxaban, an orally active direct factor Xa inhibitor, does not require laboratory monitoring, has no food interactions and only few drug interactions (8). Along with its ability to prevent VTE following orthopedic surgery, randomized controlled trials have demonstrated its efficacy/safety for the prevention of stroke in patients with atrial fibrillation (9) and in the treatment of acute coronary syndromes (10). After establishing the feasibility of single-agent therapy with rivaroxaban in patients with DVT (11), the EINSTEIN program was initiated, comprising three randomized trials of rivaroxaban: one for the treatment of acute DVT (*Acute DVT Study*), one for the treatment of acute PE (*Acute PE Study*) and one for continued treatment in patients who had received treatment for acute DVT or PE (*Continued Treatment Study*).

The *Acute DVT Study* was a randomized open label study that compared the efficacy and safety of rivaroxaban with standard therapy with enoxaparin and vitamin K antagonist in patients with acute, symptomatic DVT. It showed that rivaroxaban alone was not inferior to standard therapy, with similar safety, for the treatment of acute DVT. The *Continued Treatment Study* assessed treatment beyond 6-12 months with rivaroxaban compared to placebo, suggesting benefit in the prevention of recurrences, at expense of an acceptable risk of bleeding (0.7% incidence of major hemorrhage, none fatal) (12).

The *Acute PE Study* was a randomized, open-label, event-driven, noninferiority trial involving 4,831 patients with acute symptomatic PE, with or without DVT, which compared rivaroxaban (15 mg twice daily for 3 weeks, followed by 20 mg once daily, given to 2,420 patients) with standard therapy with

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enoxaparin followed by vitamin K antagonist (given to 2,413 individuals) for 3, 6 or 12 months (13). Patients were ineligible if they had received a therapeutic dose of low-molecular-weight heparin, fondaparinux or unfractionated heparin for more than 48 hours, if they had received more than a single dose of vitamin K antagonist before randomization or if a fibrinolytic agent had been administered. The primary efficacy outcome was symptomatic recurrent VTE, defined as a composite of fatal or nonfatal PE or DVT, while the primary safety outcome was clinically relevant bleeding, defined as a composite of major or clinically relevant nonmajor bleeding. Oral rivaroxaban alone was not inferior to standard therapy as far as efficacy was concerned, regardless of age, sex, presence or absence of obesity, level of renal function and extent of PE. The compound primary safety outcome occurred at similar rates in both groups, even during the first three weeks of intensified rivaroxaban treatment. Nevertheless, major bleeding was significantly less frequent in the rivaroxaban arm, mainly due to the lower number of episodes of intracranial bleeding or bleeding in critical areas.

The EINSTEIN project and the *RE-COVER* study are of pivotal importance and will have great impact in clinical practice, supporting the use of new single oral agents for patients with VTE. Nevertheless, several aspects of the *Acute PE Study* deserve a comment:

(I)As the authors explain, their population is representative of the spectrum of patients who present with symptomatic PE, with the exception of those for whom fibrinolytic therapy was planned. The current American College of Chest Physicians guidelines recommend fibrinolytic therapy in patients with hemodynamic instability or with high risk indicators despite hemodynamic stability (ill appearing, significantly dispneic, low oxygen saturations, elevated troponin, significant right ventricular dysfunction), if at low risk of bleeding (14). Five per cent of patients will present with shock and be categorized as experiencing a massive PE or demonstrating a high-risk presentation (15), being eligible for fibrinolysis. Unfortunately, the *Acute PE Study* does not tell us whether rivaroxaban can be used in this sub-group and this issue should be further addressed in the future.

(II)Patients with a creatinine clearance below 30 mL per minute were also excluded. Anticoagulation should not be denied to patients with renal failure and admitted for PE (in the absence of an absolute contraindication) and it would be interesting to analyze whether rivaroxaban is safer than warfarin in this particular sub-group of patients. According to the manufacturer, rivaroxaban is not contraindicated in patients with severe renal impairment (creatinine clearance 15-29 mL/min), although careful monitoring for signs of bleeding is warranted.

(III)Patients with alanine aminotransferase levels increased three times over the upper limit of normal were not included, although the manufacturer does not state such contraindication.

(IV)In the standard therapy group, the INR was in the therapeutic range 62.7% of the time, exceeding 3.0 in 15.5%. These results compare favorably with the findings of other contemporary studies of VTE (7,16) and atrial fibrillation (17), but probably are not representative of real-life clinical practice, as an excellent INR control is very often hard to attain. Efficacy and safety of vitamin K antagonists in real-life patients may be somewhat less satisfactory.

(V)The authors mentioned "less than 2% of patients received more than 2 days of treatment" with low-molecular-weight heparin before enrollment, although ineligibility criteria should have excluded all patients who had received a therapeutic dose of low-molecular-weight heparin for more than 48 hours.

(VI)It would have been useful to provide group risk stratification of enrolled patients according to currently available risk scores (18-20). This would allow the evaluation of the consistency or potential heterogeneity of results according to estimated risk at presentation, like recently evaluated in the RE-LY sub-analysis for CHADS2 score in non-valvular atrial fibrillation (21).

In conclusion, oral rivaroxaban may provide an effective, safe, single-drug approach to the initial and continued treatment of venous thrombosis, without the need for laboratory monitoring, enriching, along with dabigatran and hopefully some newer agents, the growing therapeutic arsenal available for the treatment of venous thromboembolism.

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