New anticoagulants emerge, how can we use them for acute pulmonary embolism?

Jens Eckardt[1], Mads Nybo[2]

[1]Department of Cardiothoracic Surgery, Odense University Hospital, Odense, Denmark; [2]Department of Clinical Biochemistry and Pharmacology, Odense University Hospital, Odense, Denmark

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A patient with acute pulmonary embolism (PE) is a challenge to the clinician because most treatments increase the risk for bleeding complications. Eighty percent of patients with PE have identifiable predisposing factors, while idiopathic or unprovoked PE was about 20% in the International Cooperative Pulmonary Embolism Registry (ICOPER) (1). PE and deep vein thrombosis (DVT) share the same predisposing factors, where the strongest setting-related predisposing factor is major surgery (2) and therefore, PE is a well-known and feared complication following surgery with a mortality up to 50% for massive pulmonary embolism (3).

Patients suspicious for PE are stratified into high risk, intermediate risk and low risk according to the guidelines from the European Society of Cardiology (4). In general, circulatory unstable high-risk patients are considered for either intravenous thrombolysis or embolectomy. Randomized trials have shown that thrombolytic therapy rapidly resolves thromboembolic obstruction and exerts beneficial effects on hemodynamic parameters (4), where pulmonary embolectomy is a valuable therapeutic option in patients with high-risk PE in whom thrombolysis is absolutely contraindicated or has failed (4). Unfractionated heparin has been used for certain patients but is reserved for situations, where thrombolysis is contraindicated because it is less effective than thrombolysis (5). Patients with intermediate risk are treated with anticoagulants, but thrombolysis may be considered in selected patients after thorough consideration of conditions increasing the risk of bleeding (4,6), while low-risk patients are treated with low-molecular weight heparin (LMWH).

Corresponding to: Jens Eckardt, MD. Department of Cardiothoracic Surgery, Odense University Hospital, Sdr. Boulevard 29, Odense, DK-5000 Denmark. Tel: +4524621770; Fax: +4565916935. Email: jens.eckardt@ouh.regionsyddanmark.dk.

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For all stratified groups it is essential that anticoagulant treatment is initiated without delay, i.e. while diagnostic workup is still ongoing. For high-risk PE patients the recommended anticoagulation is unfractionated heparin, while LMWH or fondaparinux is the recommended initial treatment for most patients with non-high-risk PE (4).

At present, a variety of studies are emerging on rapid-acting oral anticoagulants that could replace parenteral agents for anticoagulant treatment, namely Xa and IIa inhibitors. Recently, a randomized trial was published in The New England Journal of Medicine comparing a new factor Xa-inhibitor, Rivaroxaban, with standard treatment in 4,832 patients with acute symptomatic PE (7). The EINSTEIN-PE was a multicenter study, where a broad spectrum of patients with PE with or without DVT recruited from 236 sites in 38 countries were randomized to either Rivaroxaban or standard therapy (LMWH followed by adjusted-dose vitamin K antagonist). In summary, Rivaroxaban was found non-inferior to the current standard therapy in reducing the primary end-point of recurrent symptomatic venous thromboembolism (symptomatic DVT and fatal or non-fatal PE) (2.1% *vs.* 1.8%, respectively; P=0.003 for non-inferiority). Also, Rivaroxaban demonstrated safety results comparable with those obtained with standard therapy in terms of major and non-major clinically relevant bleeding (10.3% *vs.* 11.4%, respectively; P=0.23). Of importance, Rivaroxaban treatment gave a significant reduction in major bleeding events (1.1% *vs.* 2.2%, respectively; P=0.003) compared to the current standard therapy.

It is a well-designed study, but there are several considerations to be dealt with: First issue is if the treated patients are representative for patients with acute PE: Only 36% of the patients in the trial had predisposing factors, where an expected ratio of patients with predisposing factors is 80% (1). Another issue is that the patients were not stratified according to the guidelines from European Society of Cardiology, so it is unsure if the patients were treated according to the guidelines or the indication for anticoagulant therapy was expanded.

As far as safety is concerned Rivaroxaban is comparable to

standard therapy when considering all bleeding events, and superior in regards of major bleeding episodes. However, the absolute numbers were small (26 *vs*. 52 patients), and as for many investigations a larger number of events are needed to elucidate the safety issue more efficiently. Without doubt, intracranial haemorrhage is the most feared complication to anticoagulant treatment, and a reduction would be highly appreciated, especially if the efficacy is still ascertained. In this context the lack of a specific antidote could also be vital, but small studies have indicated that the prothrombin complex concentrate appears to be an effective antidote; this, however, needs to be confirmed in larger trials as well.

Third issue is the cost-beneficial circumstances. Many calculations has been made to describe the cost of these new anticoagulants: For the time being they are considerably more expensive than Warfarin treatment, but in the overall calculation not only efficacy and safety has to be included, but also compliance and laboratory testing: In the EINSTEIN-PE trial patients did not get LMWH injections, which is a positive achievement for the patient as well as for the nursing staff, as it is well-known that adherence to injection protocols from time to time are problematic. Also, costs and time-consumption related to blood sampling and INR measurement is reduced, as monitoring of these new anticoagulants is unnecessary. However, it is a complex calculation, and we will probably not know the exact answer before these drugs are implemented in everyday use.

Finally, monitoring of the treatment may not be necessary in the uncomplicated patient, but bleeding complications *will* occur as well as a need for unplanned surgery, and in those cases monitoring of the anticoagulant regime will be necessary. Unfortunately, the existing coagulation parameters are uncertain for this purpose (aPTT cannot be used, while anti Xa-measurement seems promising), and above all the experience is sparse. An ongoing effort is put into establishing a laboratory profile to help in such cases and hopefully, the need can be met in due time.

Altogether, Rivaroxaban is a new drug with very promising results and the future will show whether the disadvantage with no antidote in case of bleeding is balanced by the obvious advantages of a drug that require no monitoring and is easy to administer.

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