Updates on thrombosis treatment

American Society of Hematology Annual Meeting, December 8–11, 2007, Atlanta, GA, USA

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Each year, approximately 2 million Americans are afflicted with deep-vein thrombosis (DVT). Up to 600,000 of these patients subsequently develop pulmonary embolism (PE), and in as many as 200,000 people this event will be fatal. In fact, PE is the third most common cause of hospital-related death in the USA. Thus, venous thromboembolisms (VTEs) kill more people than AIDS, breast cancer and highway crashes combined. Despite its large impact on public health, there is not enough awareness of this problem among patients and health providers. The American Society of Hematology Meeting held in December 2007 had placed special interest on VTE prevention, treatment and basic science that relates to VTE. Regarding thrombosis treatment, several interesting and novel trials were introduced.

Several major presentations relating to direct antifactor Xa inhibitors were delivered at this meeting.

At the plenary session, the results of a Phase III study, the REgulation of Coagulation in ORthopedic surgery to prevent DVT and PE (RECORD) 1 trial, were presented by BI Eriksson (Sahlgrenska University Hospital Ostra, Gothenburg, Sweden) *et al.*. This international randomized, double-blind trial was set to determine the efficacy and safety of rivaroxaban, a new oral direct factor Xa inhibitor, compared with subcutaneous enoxaparin in the prevention of VTE following hip arthroplasty.

The study enrolled 4500 patients randomized to oral rivaroxaban 10 mg once-daily or enoxaparin 40 mg daily for 5 weeks. The evaluation of VTE was made by bilateral venography. Rivaraxban significantly reduced the incidence of major VTE (RR: 88%; $p < 0.001$) compared with the enoxaparin group, with no difference in bleeding complications (0.3 vs 0.1%). There was also a 70% reduction in the composite end point of DVT, nonfatal PE and all-cause mortality ($p < 0.001$). This was the first pivotal trial to demonstrate the efficacy and safety of a new oral anticoagulation compound for extended thromboprophylaxis after hip arthropathy.

The advantage of this oral anticoagulant drug is that, unlike warfarin, there is no need for monitoring or food and drug interaction and, unlike heparin or low-molecular-weight heparin, indirect anti-Xa inhibitor (fondaparinux) or direct thrombin inhibitors (lepirudin and argatroban), rivaroxaban is administered by an oral route.

AK Kakkar (Barts and the London School of Medicine, London, UK) *et al.* presented the RECORD 2 study in which extended thromboprophylaxis with rivaroxaban was compared with short-term enoxaparin after hip arthroplasty. A total of 2400 patients were included in the safety population and 1700 in the intention-to-treat group.

Thromboprophylaxis with rivaroxaban led to a 79% reduction for the extended period ($p < 0.001$) in VTE, PE and for all causes of mortality following hip arthroplasty as compared with the short-period enoxaparin-treated group (10–14 days). In addition, an 88% reduction in major VTE ($p < 0.001$) was observed among rivaroxaban-treated patients as compared with enoxaparin-treated patients, with no difference in bleeding incidence between the two groups. Thus, extended-duration rivaroxaban was significantly more effective than short-term enoxaparin for VTE prevention after hip arthroplasty.

The RECORD 3 study was conducted by MR Lassen (Nordsjaellands Hospital, Copenhagen, Denmark) *et al.*, and was presented in an oral session. This study examined rivaroxaban as thromboprophylaxis in patients undergoing knee arthroplasty as compared with enoxaparin for 10–14 days after this operation. A total of 2500 patients were randomized. Relative risk reduction of 49% ($p < 0.001$) was observed in the study drug group regarding composite end point VTE, PE and/or mortality as compared with enoxaparin and 62% risk reduction with rivaroxaban in major postoperative VTE. Again, there was no difference in the frequency of bleeding complications (0.1% for each group).

Thus, rivaroxaban was superior to enoxaparin for the prevention of VTE after knee arthroplasty.

Another interesting oral presentation discussed the tailoring of optimal duration of oral anticoagulants (OAC) for DVT by the presence or absence of residual vein thrombosis (RVT). SM Siragusa (Universitario di Palermo, Palermo, Italy) *et al.* evaluated the safety of withholding OAC in patients with idiopathic DVT, without RVT 3 months after DVT onset. This was a prospective, controlled study: patients without RVT stopped OAC after 3 months, while those with RVT continued for an additional 3 months. All patients were followed for a mean of 3 years.

A total of 520 patients were included in the study. RVT was absent in 40% of patients, and in these

10.2217/14750708.5.2.149 © 2008 Future Medicine Ltd ISSN 1475-0708

patients the recurrence rate of VTE was 0.9% as compared with 20% in the RVT-positive patients ($p < 0.005$).

This finding holds for approximately a third of the entire DVT population. Thus, it is possible to select a group of patients with a very low risk for recurrence over 3 years.

A very practical and important issue is the management of patients who need thromboprophylaxis but have renal failure. The Dalteparin's Influence on Renally Compromised: anti Ten A (DIRECT) study presented by J Douketis (McMaster University, Ontario, Canada) *et al.* aimed to determine if dalteparin prophylaxis leads to bioaccumulation of the drug and bleeding. This was a multicenter, prospective cohort study in patients with a creatinine clearance time of less than 30 ml/min who received dalteparin 5000 units/day for up to 30 days. In total, 138 patients were enrolled, and the medium duration of dalteparin treatment was 7 days. In 120 patients who had one or more troughs of anti-Xa measured, none had dalteparin bioaccumulation. The authors concluded that in critically ill patients with severe renal failure, thromboprophylaxis with dalteparin is safe.

A special session had addressed the problem of VTE from a number of different perspectives. This special session, the first of its kind at the American Society of Hematology, assembled a group of leaders to provide brief topical overviews of VTE as a major public health problem.

Another special symposium had focused on VTE among the elderly. The incidence of VTE increases at an exponential rate beginning at approximately age 50 years, and among octogenarians the annual incidence approaches one in 100. VTE is likely the most common cause of preventable death in hospitalized patients. This symposium was chaired by Dr RI Silverstein (Cleveland Clinic Lerner College of Medicine, OH, USA) and the speakers were Dr C Esmon (Howard Hughes, Medical Institute Oklahoma, OK, USA), Dr W Ershler (National Institute on Aging, NIH, MD, USA) and Dr KA Bauer (VA Boston Health Care System and Beth Israel Medical Center, Boston, MA, USA).

Financial & competing interests disclosure

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No writing assistance was utilized in the production of this manuscript.