



13th Congress of the European Hematology Association

Copenhagen, Denmark / June 12-15, 2008

Prevention and Treatment of Venous Thromboembolic Disorders: Future Needs

Copenhagen - Total hip and knee replacement orthopedic surgery patients are in the highest risk category for venous thromboembolic (VTE) sequelae, both deep-vein thrombosis (DVT) and pulmonary embolism, and the risk is known to extend well beyond the hospitalization period. Thromboembolic disorders are a leading cause of morbidity and mortality, accounting for 10% of all hospital deaths. Although current guidelines invariably recommend extended duration anticoagulant prophylaxis, experts at this meeting estimated that almost half of individuals undergoing major orthopedic surgery do not receive appropriate treatment, due in part to the not insignificant limitations of available anticoagulant drugs and fear of bleeding complications. Without prophylaxis, as many as 60% of orthopedic surgery patients will develop DVT. Evidence suggests that a novel direct thrombin inhibitor, which does not require coagulation and platelet count monitoring or dose adjustment, is safe and effective for the prevention of VTE.

According to Dr. David Bergqvist, Head of Vascular Surgery, Uppsala University Hospital, Sweden, "Risk factors for venous thromboembolism (VTE) are numerous, varied and generally cumulative." He cited a recent epidemiologic survey of approximately 68,000 hospital patients which demonstrated that whereas 64% of all surgical patients met the American College of Chest Physicians criteria for being at risk for VTE requiring prophylaxis, only 59% of them received the recommended treatment.

"In addition," he observed, "data from the prospective Global Orthopaedic Registry revealed that of the patients who received recommended thromboprophylaxis procedures, 25% were not still receiving it seven days after surgery. Yet we know that the greatest risk of VTE among total hip arthroplasty patients comes several weeks' post-surgery. We do not know how great the risk is in all patients after discharge from hospital, but one study indicates 25% of patients develop deep vein thrombosis (DVT) in one month after they leave hospital."

Noting the short period of hospitalization now generally associated with orthopedic surgery, Dr. Bergqvist indicated that some orthopedic surgeons do reduce the prophylaxis interval accordingly but, he added, there is no indication that prophylaxis should be shorter than around one week. Moreover, he noted that there is accumulating evidence that in hip replacement surgery, prophylaxis should last at least a month.

Since the lack of appropriate preventive treatment seems largely to result from the limitations of available therapies, Dr. Bergqvist agrees with most opinion leaders who believe that new prophylactic agents are needed for oral long-term use. Low molecular-weight heparins (LMWHs) are safe and effective, but their complex and inconvenient route of administration hampers adherence to clinical guidelines particularly outside the hospital, patients need careful platelet monitoring during LMWH therapy and there exists a potential for heparin-induced thrombocytopenia. Patients who are given

warfarin face potential intra- and interpatient variability, numerous food and drug interactions and the need for frequent coagulation monitoring.

Improved anticoagulant therapies should be administered orally at fixed doses, not require monitoring, block both free and clot-bound thrombin and be cost effective with a favourable safety and tolerability profile.

Answering Unmet Needs

Dr. Ola Dahl, Thrombosis Research Foundation, London, UK, noted that an innovative oral direct thrombin inhibitor (DTI), once-daily dabigatran etexilate, is effective for the primary prevention of VTE following elective hip and knee surgery and has a good safety profile. The convenience of once-daily oral administration at a fixed dose without the need for monitoring should facilitate thromboprophylaxis both in and out of the hospital, he commented.

Dr. Dahl reported results from the European clinical development program which assessed the safety and efficacy of two different doses of dabigatran compared to enoxaparin 40 mg following total hip and knee replacement in two large, randomized, double-blind, non-inferiority phase III trials. The RE-MODEL trial assessed VTE prevention in patients who had undergone total knee replacement (TKR) surgery, while RE-NOVATE examined patients who had undergone total hip replacement surgery (THR).

Dr. Dahl stated that in the RE-MODEL trial, six to 10 days on the new oral DTI (220 mg or 150 mg q.d.) was non-inferior to subcutaneous (s.c.) enoxaparin 40 mg q.d. for preventing VTE after TKR surgery, and had a similar safety profile. In the RE-NOVATE trial, it was as effective and safe as the LMWH in reducing the risk of total VTE and all-cause mortality after THR surgery when given for a median of 33 days. Non-inferiority results were highly statistically significant for both THR and TKR, with no difference between the groups:

in RE-MODEL, $P=0.003$ for the 220-mg dose vs. enoxaparin and $P=0.017$ for the 150-mg dose; in RE-NOVATE, $P<0.0001$ for the 220-mg dose vs. enoxaparin and $P<0.0001$ for the 150-mg dose.

There were no significant differences between the groups with regard to symptomatic pulmonary embolism or overall mortality, he added. In particular, Dr. Dahl noted that DTI prophylaxis demonstrated a low incidence of major bleeding events in patients following major orthopedic surgery and a favourable hepatic and cardiac safety profile.

“When choosing an appropriate thromboprophylactic treatment it is important to optimize the balance between antithrombotic efficacy and the risk of bleeding complications following orthopedic surgery,” he said. “Although it is important to use an agent that effectively prevents VTE events, this should not come at the expense of an excessive rate of bleeding complications. In addition to the bleeding profile, further parameters, such as hepatic and cardiac safety need to be considered as well as tolerability. Thus, a holistic approach is needed when considering choice of VTE prophylaxis following major orthopedic surgery.”

“These results demonstrate that once-daily dabigatran is effective for the primary prevention of VTE following elective THR and TKR surgery and has a good safety profile,” Dr. Dahl concluded. “Importantly, the convenience of once-daily oral administration at a fixed dose without the need for monitoring should facilitate prophylaxis both in and out of the hospital.

Direct Thrombin Inhibition

According to Dr. Jeffrey Weitz, Professor of Medicine, Division of Hematology and Thromboembolism, McMaster University, Hamilton, Ontario, thrombin plays a central role in coagulation and is an attractive target for new anticoagulant therapy. It converts fibrinogen to fibrin, which is the essential step in clot formation and major protein component of a thrombus. It is not only responsible for fibrin formation but also for stabilization of this fibrin through factor 13a-mediated cross-linking.

“We also must not forget that thrombin is the most potent platelet agonist, so it also activates platelets, which then aggregate and—together with their thrombin-generated fibrin—form the insoluble clot. There is no question that thrombin is a good target,” he told delegates. But in terms of indirect thrombin inhibitors, the heparins do not inhibit clot-bound thrombin, so they are not fully able to suppress the clotting process and they also pose the problem of heparin-induced thrombocytopenia. Vitamin K antagonists have a slow onset and offset of action, interact with numerous other medications and have a narrow therapeutic window.

As Dr. Weitz explained, DTIs specifically block both free and clot-bound thrombin, as well as thrombin bound to other surfaces. The resulting down-regulated thrombin-mediated feedback mechanism attenuates thrombogenesis and thereby leads to reduced coagulation and platelet aggregation. “We have seen an evolution in DTIs from parenteral agents to oral agents and now dabigatran which have longer half-lives that permit once- or twice-daily dosing,” he remarked.

He explained that dabigatran is a new reversible oral DTI which interacts with the active site of either clot-bound or free thrombin and binds that site with high affinity and specificity. It has a bioavailability of about 6.5%, and 80% of the drug is excreted unchanged via the kidneys. It has a half-life of 12 to 17 hours after oral administration and shows no interaction with food. The cytochrome P450 system is not involved in its metabolism, so there is a very low risk drug-drug interactions. It produces a very predictable anticoagulant response with fixed-dose therapy, avoiding the need for coagulation or platelet monitoring. In patients who have been treated with this drug for over a year, there has been no evidence of liver toxicity.

Dr. Weitz mentioned that the DTI is presently undergoing extensive evaluation in a large phase III program involving more than 38,000 patients for primary VTE prevention in orthopedic patients and for acute venous thromboembolic disease and secondary prevention with extended treatment.

Researcher Dr. Joanne van Ryn, Biberach, Germany, tested the hypothesis that DTIs, factor Xa inhibitors and enoxaparin could inhibit platelet aggregation if the stimulus to initiate aggregation was higher up in the cascade than factor Xa, such as tissue factor. To that end, she tested dabigatran, the direct Xa factor inhibitor rivaroxaban and the LMWH enoxaparin in human whole blood. She reported that the DTI was the most potent inhibitor of platelet aggregation (IC_{50} 35 nM) followed by rivaroxaban (312 nM) and enoxaparin (13 μ M). She concluded that DTIs and factor Xa inhibitors might not only be effective in venous/stasis thrombotic episodes in which fibrin formation plays a role, but might also be beneficial in more platelet-dominant arterial thrombosis settings.

Summary

Almost half of patients undergoing high-risk orthopedic surgery do not receive recommended anticoagulant prophylaxis. Trials demonstrate the need for oral fixed-dose DTIs that do not require complex monitoring, are free from heparin-induced thrombocytopenia and inhibit both free and clot-bound thrombin. □

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