

Traffic Alert: Rivaroxaban Blocks Clots at the Xa Intersection

By Margaret Ragni, MD, MPH

At the Plenary Session yesterday, the results of an exciting phase III study evaluating the thromboprophylaxis with a new oral inhibitor of factor Xa, rivaroxaban, were presented by Bengt I. Eriksson, MD, PhD, of the Sahlgrenska University Hospital, Östra, Gothenburg, Sweden. This study, also known as RECORD 1, is a randomized, double-blind study that evaluated the efficacy and safety of rivaroxaban, formerly BAY59-7939, in the prevention of venous thromboembolism (VTE) following hip arthroplasty. The study enrolled nearly 4,500 subjects, with randomization to either 10 mg rivaroxaban orally daily or 40 mg enoxaparin subcutaneously following total hip arthroplasty. There was an 88 percent reduction in major VTE, $p < 0.001$, among rivaroxaban-treated subjects, as compared with enoxaparin-treated subjects, with no difference in bleeding complications, 0.3 percent vs. 0.1 percent. There was also a 70 percent reduction in the composite endpoint of DVT, non-fatal PE, and/or all-cause mortality, $p < 0.001$.

Factor Xa is an ideal target for anticoagulation. It is at the focal intersection of the intrinsic and extrinsic pathways and is the rate-limiting step in thrombin generation. Unlike warfarin, rivaroxaban is not limited by frequent monitoring or food and drug interactions. Unlike heparin, low-molecular-weight heparin, indirect Xa inhibitor fondaparinux, or direct thrombin inhibitors lepirudin and argatroban, rivaroxaban does not require parenteral administration.

In preclinical studies, it has been established that rivaroxaban, a chloro-substituted carboxamide, is a potent inhibitor of factor Xa and has predictable dose-dependent effects, including once-daily dosing with no requirement for monitoring. In addition, the lack of potentiation of aspirin effect suggests rivaroxaban may be a potential agent for both venous and arterial thrombosis prevention.

Previous *in vitro* studies have shown there are no heparin-associated thrombocytopenia (HIT) antibodies. Pharmacokinetics studies have also demonstrated that rivaroxaban levels were not influenced by gender or weight, up to ≥ 120 kg. As the drug is excreted through the kidneys, it is anticipated that a lower dose may be required in those with kidney disease. Other ongoing phase II and III studies are evaluating rivaroxaban in acute coronary syndromes, in atrial fibrillation, and after knee replacement.

Two other oral abstracts to be presented today provide further results on phase III studies of rivaroxaban thromboprophylaxis following hip and knee arthroplasty. The first abstract, #2379, presented by Ajay K. Kakkar, MD, PhD, will focus on the results of the RECORD 2 study, which required venography confirmation of all VTE. Thromboprophylaxis with rivaroxaban led to a 79 percent reduction ($p < 0.001$) in VTE, PE, and/or all-cause mortality following hip arthroplasty, as compared with enoxaparin. In a second abstract, #2447, Michael R. Lassen, MD, will report on the RECORD 3 trial, which evaluated rivaroxaban thromboprophylaxis following knee arthroplasty. This randomized controlled study demonstrated a 62 percent reduction with rivaroxaban in major postoperative VTE and a 49 percent reduction in composite endpoint VTE, PE, and/or mortality as compared with enoxaparin. There was no difference in the frequency of bleeding complications, 0.1 percent with each drug.

Three related abstracts include #4003 by Barbara Haertlein, BS, which demonstrates that rivaroxaban is effective in the prevention of arterial thrombotic occlusion in the rat carotid artery injury model; abstract #1880 by Wolfgang Mueck, PhD, et al. which reports that the pharmacokinetic and pharmacodynamic data on 870 patients across several studies are consistent with a one-compartment model with overlap of 90 percent confidence intervals for daily or twice-daily dosing; and abstract #935 by Elisabeth Perzborn, which shows rivaroxaban to be effective in preventing disseminated intravascular coagulation (DIC) in a rat endotoxin model.