Rivaroxaban, a new oral factor Xa inhibitor, provides new data on anticoagulation

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Venous and arterial thromboembolic disorders have a significant impact on human morbidity and mortality, and as such, novel therapies for providing thromboprophylaxis remain of immense interest [1]. Numerous anticoagulants are currently available to prevent and treat venous and arterial thromboembolic disorders. For many years, the vitamin K antagonists (VKAs), such as warfarin, were the only type of oral anticoagulation. However, there is marked variation in the therapeutic effects of VKAs, with significant inter- and intra-patient variability in anticoagulation response, thus requiring regular monitoring. Injectable anticoagulants such as heparin are inactivated if taken orally and need to be given paraenterally – thus, they are of limited utility for prolonged therapy. The oral antiplatelets aspirin and clopidogrel have been shown to be much less effective than VKAs for the treatment of venous thrombosis and the prevention of thromboembolic events [2].

Given the limitations with the VKAs, there has been an ever-increasing need for the development of new anticoagulant therapies. New oral anticoagulants fall into two broad classes – the oral direct thrombin inhibitors (such as dabigatran) and the oral factor Xa inhibitors (e.g., rivaroaxban and apixaban). As recently highlighted in this journal [3], dabigatran was recently given a license for the prophylaxis of venous thromboembolism following orthopedic surgery. More recently, rivaroxaban has been given similar approval, and in addition, new data from a Phase II trial in acute coronary syndrome (ACS) have been presented at the American Heart Association meeting in November 2008, LA, USA. These data follow similar Phase II trial data for apixaban in ACS, presented at the European Society of Cardiology meeting in September 2008.

Rivaroxaban (BAY-59–7939) is an inhibitor of activated factor Xa, which has been developed by Bayer AG (Leverkusen, Germany) and Ortho-McNeil Pharmaceutical Inc. (NJ, USA) for the treatment and prevention of arterial and venous thrombosis. Unlike some older anticoagulants with antifactor Xa activity (e.g., heparins), rivaroxaban has a direct mechanism of action, thus bypassing the need for antithrombin. Another advantage of rivaroxaban over most existing standard therapies is its oral administration, and potential for once-daily dosing. This drug is currently indicated for the prevention of venous thromboembolism (VTE) in adult patients undergoing elective knee- or hip-replacement surgery. In September 2008, the drug was launched for the prevention of VTE in Canada, and in October 2008, rivaroxaban also became available in the EU for the prevention of venous thrombosis in adults undergoing elective hip- or knee-replacement surgery.

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What are the data supporting the use of rivaroxaban for the prevention of venous thromboembolism following orthopedic surgery? In December 2005, Bayer started a large Phase III program named REgulation of Coagulation in major Orthopedic surgery reducing the Risk of Deep vein thrombosis and pulmonary embolism (RECORD) for assessment of rivaroxaban (10 mg once daily) in comparison with enoxaparin. These trials were to assess rivaroxaban in the treatment (RECORD 1) and prevention (RECORD 2) of thromboembolism in patients undergoing total hip-replacement surgery. The RECORD 1 data demonstrated a significant reduction in deep venous thrombosis (DVT), pulmonary embolism, major VTE and all-cause mortality in the rivaroxaban group. Bleeding

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events were recorded at similar rates for rivaroxaban and enoxaparin [4]. RECORD 2 also showed a significant improvement in the prevention of DVT, pulmonary embolism, major VTE and all-cause mortality in the rivaroxaban group, with a comparable number of bleeding events observed for rivaroxaban and enoxaparin [5]. The RECORD 3 trial began in August 2006 and again showed rivaroxaban to be superior to enoxaparin for thromboprophylaxis after total knee arthroplasty, with similar rates of bleeding [101]. In January 2007, a randomized, double-blind, Phase III trial, RECORD 4, was initiated to assess the efficacy of 10 mg daily rivaroxaban administered following elective total knee replacement. The results of this trial also showed rivaroxaban to be superior to enoxaparin with similar adverse event profiles. Although the rate of major bleeding was 0.7% in rivaroxaban-treated patients, compared with 0.3% in the enoxaparin group, this difference was not significant [101].

Data from the recently concluded Phase II Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Aspirin With or Without Thienopyridine Therapy in Subjects with Acute Coronary Syndrome – Thrombolysis in Myocardial Infarction 46 (ATLAS ACS TIMI 46) trial was presented at the late-breaking clinical trials session at the American Heart Association 2008 Scientific Sessions, which took place in New Orleans, LA, USA, on November 8–12, 2008. In this Phase II randomized, double-blind, placebo-controlled, multicenter study, the safety of different doses of rivaroxaban administered in addition to aspirin or a combination of aspirin and clopidogrel in 3491 patients with stabilized ACS was investigated. Patients were randomized to placebo or rivaroxaban in a number of dosing regimens for 6-month treatment: 5, 10 or 20 mg of rivaroxaban once daily or 2.5, 5 or 10 mg twice daily. The results of the trial indicated that while there was an increase in bleeding with dosing, there was no TIMI major bleeding. Although the study was not powered to look at efficacy, it was reported that the rate of death, myocardial infarction, stroke or severe ischemia requiring revascularization was 7.0% in the placebo group by the end of 6-month treatment, compared with 5.6% in the rivaroxaban groups combined ($p = 0.10$), indicating the trend to clinical efficacy [102]. The ATLAS ACS-TIMI 46 trial identified two doses of rivaroxaban – 2.5 and 5 mg twice daily – that will be taken forward into a Phase III trial that is expected to start in 2009, and enroll up to 16,000 patients.

However, despite the promising results of the ATLAS ACS TIMI 46 trial, a triple combination of antithrombotic agents affecting the coagulation system could be required for ACS management. Based on this, it has been argued whether the newer thienopyridine prasugrel might negate the benefit of rivaroxaban. Once again, there are no head-to-head comparisons available between prasugrel and rivaroxaban, and results of future Phase III studies will judge which therapy should be recommended.

Why would the new oral anticoagulant have advantages over the VKAs? Rivaroxaban is an orally active compound and produces a predictable anticoagulant response, thus negating the need for continuous monitoring. The RECORD trials have established that it is as efficacious as enoxaparin with comparable safety. It has also been noted that rivaroxaban has so far not been associated with any increased incidence of liver toxicity, which had led to the withdrawal of the earlier direct thrombin inhibitor ximelagatran. However, further data on a larger number of patients over an increased duration will be required before its safety can be proven in this regard.

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Another new oral anticoagulant, dabigatran etexilate, which is a direct thrombin inhibitor (DTI), has recently been approved by NICE as a possible treatment option for the primary prevention of venous thromboembolic events in adults undergoing elective total hip- or knee-replacement surgery. Dabigatran has been shown to be noninferior to an equal duration of subcutaneous enoxaparin for prevention of VTE after total-hip arthroplasty [3]. While there are no head-to-head studies available at present comparing dabigatran and rivaroxaban, it has been suggested that increased bleeding may be inevitable with DTIs when higher concentrations are being administered [3]. This may be partly explained by their mechanism of action, since they have been shown to also inhibit platelet aggregation [6], while factor Xa inhbitors like rivaroxaban do not affect the activity of residual thrombin in blood circulation, thus maintaining the ability to initiate platelet activation for hemostasis. An additional advantage of rivaroxaban is that it might be potentially used once daily for long-term

applications, such as prevention of thromboembolic events in atrial fibrillation, while dabigatran etexilate has to be taken twice daily, which is one consideration when addressing patient compliance issues.

Rivaroxaban brings with it the promise of a newer, safer and more convenient anticoagulant therapy. However, its utility in stroke prevention in patients with atrial fibrillation, as well as its effectiveness in patients with ACS, remains to be established. It can only be hoped that ongoing Phase III trials will shed further light on these aspects. After more than 50 years of using VKAs, perhaps the time has come for effective and safe new oral anticoagulants to help improve measures at thromboprophylaxis.

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