PROPHYLAXIS AND TREATMENT OF THROMBOEMBOLISM III

NEW ORAL ANTICOAGULANTS. RESULTS OF PIVOTAL TRIALS IN ORTHOPEDIC SURGERY

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The development of new anticoagulant agents is supported by our present understanding of the coagulation cascade, with drug development focused on the identification of orally active, synthetic compounds that act on distinct serine protease enzymes that drive clot propagation and fibrin deposition. The principal targets are factor IIa (FIIa) and factor Xa (FXa). Two oral, synthetic compounds are in late-stage development: one FIIa inhibitor (dabigatran etexilate) and a direct FXa inhibitor (rivaroxaban) seems to have the best chance of emerging as new oral anticoagulants. Orthopaedic surgery, arthroplasty of hip and knee, is the preferred testing ground for anticoagulant drug development, since the risk of venous thromboembolic complications is high and major bleeding complications are well characterized. Because of this, relatively small, dose-finding and registration-track studies proving anticoagulant efficacy and safety can be conducted. Determining the optimal efficacy/safety balance for each new anticoagulant agent is the central issue in the development process, with any reduction in the risk of VTE balanced against the risk of bleeding. Optimising the design of clinical trials remains a challenging proposition. A number of subtle issues, including choice of study endpoints, method of endpoint assessment, sample size, timing of first peri-operative dose, and definition/assessment of study endpoints all influence study outcome and therefore require careful consideration when evaluating study results with new agents and in the comparison with established agents. In the development of new anticoagulants the choice of relevant endpoints is crucial. High resolution venography detecting also small distal thrombi has been decisive in development programs, although the clinical relevance of such asymptomatic thrombi has been questioned. However, data on more clinically oriented endpoints such as proximal DVT, symptomatic DVT or PE has demonstrated that the level of risk reduction correlates with the risk reduction of the primary endpoint which includes distal DVT. A key issue is also to find the optimal balance between efficacy and safety. The design of recent clinical trials evaluating new anticoagulant compounds reflects the view that, although there remains an unmet need for improved efficacy, physicians tend to focus on the bleeding profile of new compounds. Maybe a strategy of equivalent efficacy, increased convenience and less bleeding is the best option for a new anticoagulant. Two new oral anticoagulants, dabigatran etexilate and rivaroxaban, have entered a late stage of clinical development and results from phase 3 trials in orthopaedic surgery will be presented at the meeting. These results will be decisive in determining if these agents can provide an efficacious and safe oral anticoagulant without monitoring. If this is accomplished the door opens to a much wider range of therapeutic indications.

THE RIVAROXABAN PROGRAM

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Rivaroxaban is a novel, oral, direct Factor Xa inhibitor in advanced clinical development for the prevention and treatment of thromboembolic disorders. In phase III trials it was effective in reducing thromboembolic complications (deep vein thrombosis and pulmonary embolism) after orthopedic surgery and it is under investigation for the treatment of DVT and PE and for anticoagulation in atrial fibrillation. In RECORD3, a phase III trial, the efficacy and safety of once-daily (od) rivaroxaban was compared with od enoxaparin for the prevention of venous thromboembolism (VTE) in patients undergoing total knee arthroplasty (TKA). In this multicenter, double-blind, double-dummy trial, patients undergoing TKA were randomized to receive either oral rivaroxaban 10 mg od or subcutaneous enoxaparin 40 mg od. Enoxaparin was initiated 12 hours before surgery, and rivaroxaban 6-8 hours after surgery; both were continued for 10-14 days. The primary outcome was the composite of deep vein thrombosis (DVT), pulmonary embolism (PE), and all-cause mortality. Secondary efficacy outcomes included major VTE (the composite of proximal DVT, PE and VTE-related death) and symptomatic VTE. The main safety outcome was major bleeding, and secondary outcomes included non-major bleeding and adverse events. A total of 2531 patients were randomized; 2459 were eligible for inclusion in the safety population and 1702 for the modified intention-to-treat population. The primary efficacy outcome occurred in 9.6% of patients receiving rivaroxaban compared with 18.9% of those receiving enoxaparin (relative risk reduction 49%; $p<0.001$). Rivaroxaban was also significantly more effective than enoxaparin at reducing major VTE, with a relative risk reduction of 62%. Symptomatic VTE was also lower with rivaroxaban than with enoxaparin. The incidences of major and non-major bleeding were similar in both the rivaroxaban and enoxaparin groups, as was the incidence of other adverse events. During the treatment period, there were no deaths or PEs in the rivaroxaban group, and two deaths and four PEs occurred in the enoxaparin group. In conclusion, Rivaroxaban was superior to enoxaparin for the prevention of VTE after TKA in this study, with a similar, low rate of bleeding. This is the first study to demonstrate the safety and efficacy of a fixed, unmonitored regimen of an oral, direct Factor Xa inhibitor – rivaroxaban – for the prevention of VTE after major orthopaedic surgery. The extended thromboprophylaxis with rivaroxaban was compared with short-term thromboprophylaxis with enoxaparin after total hip arthroplasty in the RECORD2 trial. Pharmacologic thromboprophylaxis is recommended for patients undergoing total hip arthroplasty (THA) for a minimum of 10 days, and up to 35 days. However, extended thromboprophylaxis is not universally used.

Therefore, this trial was conducted to evaluate the potential benefits of extended thromboprophylaxis after THA. RECORD2 is the largest, prospective, randomized clinical trial conducted to date, in this indication. This global, phase III, double-blind trial, was designed to compare short-term thromboprophylaxis with a low molecular weight heparin – enoxaparin – with extended thromboprophylaxis for up to 5 weeks with a novel, oral, direct Factor Xa inhibitor – rivaroxaban – after THA. Patients received subcutaneous enoxaparin 40 mg once daily (od), beginning the evening before surgery, continuing for 10-14 days (short-term prophylaxis), and followed by placebo until day 35±4, or oral rivaroxaban 10 mg od beginning 6-8 hours after surgery and continuing for 35±4 days (extended prophylaxis). Mandatory, bilateral venography was conducted at the end of the extended treatment period. The primary efficacy endpoint was the composite of any deep vein thrombosis (DVT), non-fatal pulmonary embolism (PE), and all-cause mortality. The main secondary efficacy endpoint was major VTE; the composite of proximal DVT, non-fatal PE, and VTE-related death. Major and non-major bleeding during double-blind treatment were the primary and secondary safety endpoints, respectively. A total of 2509 patients were randomized; 2457 were included in the safety population and 1733 in the mITT population. Extended thromboprophylaxis with rivaroxaban was associated with a significant reduction in the incidence of the primary efficacy endpoint and major VTE, compared with short-term thromboprophylaxis with enoxaparin. The incidences of major and non-major bleeding were similar in both groups. In conclusion, extended duration rivaroxaban was significantly more effective than short term enoxaparin for the prevention of VTE, including major VTE, in patients undergoing THA. Furthermore, this large trial demonstrated that extended thromboprophylaxis provides substantial benefits for patients undergoing THA, and that the oral, direct Factor Xa inhibitor rivaroxaban provides a safe and effective option for such a strategy. Rivaroxaban was also compared with subcutaneous enoxaparin both given as extended thromboprophylaxis after total hip arthroplasty in the RECORD1 Trial. This was a phase III, multinational, randomized, double-blind, double-dummy trial, conducted to determine the efficacy and safety of oral rivaroxaban, compared with subcutaneous enoxaparin, for 5 weeks of thromboprophylaxis in patients undergoing THA. Patients received rivaroxaban 10 mg beginning 6-8 hours after surgery and once daily (od) thereafter, or enoxaparin 40 mg od, beginning the evening before surgery (restarting 6-8 hours after surgery). Therapy continued for 35±4 days and mandatory, bilateral venography was conducted the next day. The primary efficacy endpoint was the composite of any deep vein thrombosis (DVT), non-fatal pulmonary embolism (PE), and all-cause mortality. The primary efficacy analysis was a test for non-inferiority in the per-protocol (PP) population, followed by a test for superiority in the modified intention-to-treat (mITT) population. The main secondary efficacy endpoint was major venous thromboembolism (VTE): the composite of proximal DVT, non-fatal PE and VTE-related death. Major and non-major bleeding during the active treatment period were the primary and secondary safety endpoints, respectively. A total of 4541 patients were randomized; 4433 were eligible for the safety population, 3153 for the mITT population, and 3029 for the PP population. The criteria for non-inferiority were met and testing for superiority was performed. Rivaroxaban significantly reduced the incidence of the primary efficacy endpoint ($p<0.001$) and major VTE ($p<0.001$), compared with enoxaparin, in the mITT population. The incidence of major and non-major bleeding events was similar in both groups. Rivaroxaban was here also significantly more effective than enoxaparin for extended prophylaxis after THA, with a similar safety profile.

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APIXABAN - A NEW DIRECT FACTOR Xa INHIBITOR

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Thrombosis is a significant contributor to worldwide morbidity and mortality. Anticoagulation remains the cornerstone of therapy for prevention and treatment of venous thromboembolic events (VTE) and for stroke prevention in AF; however, currently available anticoagulants have significant limitations. An ideal novel anticoagulant should not only be easier to administer than current therapies, but also demonstrate an improved benefit/risk profile. Apixaban is a highly selective, oral, direct factor Xa inhibitor currently in development for the prevention of deep vein thrombosis and for the prevention of stroke in patients with atrial fibrillation. In preclinical models and in healthy human subjects, apixaban achieved a specific antithrombotic effect with a wide therapeutic window. APROPOS, a Phase II study of apixaban determined the dose-response relationship among three daily (QD) and three twice daily (BID) dose regimens. This randomized, double-blind, 8-arm study with ~150 subjects/arm consisted of the following groups: 3 twice-daily apixaban doses (2.5, 5, 10 mg BID), 3 once-daily apixaban doses (5, 10, 20 mg QD), enoxaparin (30 mg BID), and open-label warfarin (target INR 1.8-3.0). The primary endpoint was 'all venous thromboembolism (VTE) + all-cause death' in subjects treated for 10-14 days following elective knee replacement surgery. The incidence rate of primary composite events was 8.6% for all apixaban treatment regimens combined, 15.6% for enoxaparin ($p<0.02$), and 26.6% for warfarin ($p<0.001$).

The overall adverse event profile in the apixaban arms, including reported serious and non-serious adverse events, was comparable to conventional therapy. Major bleeding occurred in 1.3-3% of patients treated with apixaban Twice-daily dosing of apixaban is anticipated to provide greater clinical benefit than once-daily dosing based on the phase II study results. In the phase II study, among the range of once and twice daily doses tested, the regimen of 2.5 mg administered twice daily (5 mg total daily dose) provided a better benefit/risk profile than other apixaban dosing regimens in the study when both VTE/death events and bleeding were considered. An ambitious Phase III apixaban development program, ADVANCE, has been initiated for the prevention and treatment of venous and aterial thromboembolic disease, which will initially involve more than 30,000 patients.

MECHANISMS IN HEMOSTASIS AND THROMBOSIS II

BLOOD CLOTTING ON MEMBRANE NANODOMAINS

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Blood clotting involves a series of enzyme activation reactions, each of which requires the coordinated assembly of a serine protease, its cognate regulatory protein (protein cofactor), and protein substrates on a membrane surface. In particular, the outer leaflet of the membrane must contain exposed anionic phospholipids such as phosphatidylserine (PS) in order to support the assembly and function of blood clotting reactions. In spite of the critical nature of membrane binding in blood clotting, our understanding of how the membrane contributes to catalysis, or even how blood clotting proteins interact with phospholipids, is incomplete. In addition, membranes containing mixtures of PS and neutral phospholipids have been shown to spontaneously coalesce into PS-rich membrane microdomains in the presence of plasma concentrations of calcium ions. We therefore hypothesize that blood clotting proteases partition into these PS-rich microdomains. Unfortunately, however, little is known about how membrane microdomain composition influences the activity of blood clotting proteases. Our laboratories are developing and applying new technologies for studying membrane proteins, in order to gain insights into how blood clotting protease-cofactor pairs assemble and function on membrane surfaces. Our studies include the use of a novel, nanometer-scale lipid bilayer system (Nanodiscs), which permits us to assemble blood clotting protease-cofactor pairs on stable bilayers containing from 65 to 250 phospholipid molecules per leaflet (in which the phospholipid composition is under strict experimental control). This system allows insights into how local (nanometer-scale) changes in phospholipid bilayer composition modulate TF:VIIa activity, and how different phospholipid types can synergize to support blood clotting reactions. We have also applied detailed molecular dynamics simulations of nanoscale bilayers to provide atomic-scale models of how membrane-binding domains in blood clotting interact with PS in bilayers. This work was supported by grants from the National Institutes of Health and the Roy J. Carver Charitable Trust.