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 arterial thromboembolic disease, which will initially involve more than 30,000 patients.

**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.
In our previous studies, we...
vention and treatment of venous thromboembolism (VTE) and in some countries for the treatment of acute coronary syndromes. Idraparinux, a subcutaneous, long-acting, indirect Factor Xa inhibitor, is in development. Direct inhibition of thrombin or Factor Xa with synthetic, small molecules is an attractive strategy for the development of novel anticoagulants. After the withdrawal of ximelagatran, dabigatran is now the furthest advanced oral, direct thrombin inhibitor, and an extensive phase III clinical trial programme (the REVOLUTION trials) has recently determined its efficacy and safety in the prevention of VTE in major orthopaedic surgery. Direct Factor Xa inhibitors in development that show clinical promise in various indications include rivaroxaban, apixaban, betrixaban, LY-517717, YM150, and DX-9065a and its derivative Du-176b. Of these rivaroxaban and apixaban are the furthest advanced. Rivaroxaban has a favourable efficacy and safety profile, relative to enoxaparin, for the prevention of VTE after major orthopaedic surgery as shown in the RECORD trials. The results of trials of rivaroxaban for the treatment of proximal deep vein thrombosis are expected soon. It is likely that these new anticoagulants will revolutionize oral anticoagulant therapy.

BLEEDING DISORDERS

SURGERY AT HIGH RISK OF BLEEDING
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"Some loss of blood is always inevitable". In spite of sharp and innovative advances in surgical techniques, massive blood loss is still one of the major perioperative complications, able to impact on both morbidity and mortality.

Major thoraco-abdominal vascular surgery, major liver surgery including transplantation, neurosurgery, spine surgery, obstetrics complicated by postpartum hemorrhage are among the surgical procedures at risk of critical bleeding (defined as severe, unexpected, and uncontrollable bleeding), a condition able to raise mortality rate from <1% to above 20%. Management of critical perioperative bleeding includes prompt evaluation, early and (hopefully) correct diagnosis, timely, appropriate and, not infrequently, multimodal approach for the treatment. Complex haemostatic derangements and the related bleeding complications have to be managed understanding the specific physiological change(s), thus giving a solid rationale to the treatment, which could not be "simply" or only symptomatic ("give blood and FFP") but causative ("find the defect and treat it"). Generally speaking, perioperative bleeding could be subdivided in "surgical" and "non-surgical or haemostatic bleeding". The so called "surgical" blood loss, responsible for up to 70% of the cases is mainly attributable to surgical technical problems and is characterized by uncontrolled bleeding at the operative site, where the problem is usually confined.

Proper patient selection and anticipation of technical problems may substantially contribute in reducing surgical bleeding in high-risk patients (eg. patients with portal hypertension or frequent bacterial peritonitis in major liver surgery; reoperations in case of previous extensive cardiac, thoracic, or abdominal surgery). The "non-surgical or haemostatic bleeding", on the contrary, is usually due to a dysfunction/failure in one (or more) of the phases of the haemostatic system: it appears as a generalised oozing with spontaneous, multiple sites bleeding (traumatized tissues, puncture sites, surgical wounds etc) without any apparent single bleeding point.

Main causes of the "non surgical bleeding" are:

a) pre-existing, previously undetected bleeding disorder;
b) changes induced by drugs (eg.: aspirin, clopidogrel, NSAIDs, warfarin, LMWH, UFH);
c) coexisting pathologies (eg: liver failure, chronic renal failure);
d) haemostatic derangements induced by:
   - the surgical procedure itself (cardiopulmonary bypass, orthotopic liver transplantation, prostate surgery, fusion spinal surgery, neurosurgery, complicated obstetrics)
   - massive blood loss and massive transfusion in complicated surgery.

Since mechanical treatment of this kind of hemorrhage by clipping or vessel ligation is frustrating and useless at