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<p>New oral anticoagulants (NOACs) are increasingly replacing vitamin K antagonists and older parenteral agents in clinical practice. NOACs offer several advantages compared with standard agents, including rapid onset of action, fixed dosing, and no requirement for routine coagulation monitoring. However, like all anticoagulants, NOACs carry a risk of bleeding. Here, we discuss the pharmacology and safety of NOACs, with particular emphasis on the risks of bleeding associated with NOACs versus standard anticoagulants, and we provide an overview of current bleeding management strategies.</p>	
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<p>New oral factor Xa inhibitors are intended to progressively substitute the oral vitamin K antagonists and parenteral indirect inhibitors of factor Xa</p>	

in the prevention and treatment of venous and arterial thromboembolic episodes. This article focuses on the main clinical studies and on biological measurements of new oral factor Xa inhibitors, and addresses several safety issues. These newer agents do not require any routine laboratory monitoring of blood coagulation; however, biological tests have been developed in order to assess the plasma concentration of these drugs in several clinical settings. This article reviews these 4 oral direct factor Xa inhibitors.

Treatment and Long-Term Management of Venous Thromboembolism

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Ahmed Al-Badri and Alex C. Spyropoulos

Venous thromboembolism covers a range of conditions from deep vein thrombosis to pulmonary embolism. Treatment aims to alleviate symptoms, minimize acute morbidity and mortality by preventing the extension or potentially fatal embolization of the initial thrombus, and avoid post-thrombotic syndrome. Anticoagulant therapy is the mainstay of treatment, but treatment decisions and the choice of an appropriate anticoagulation agent are modified according to the predisposition for venous thromboembolism, the site and extent of thrombus, the presence or absence of symptomatic embolism, and patient's bleeding risk. Newer oral anticoagulants have been developed to overcome the drawbacks of other agents, improve patient care, and simplify and improve management.

Anticoagulation Strategies for the Management of Postoperative Atrial Fibrillation

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Eric Anderson, Cornelius Dyke, and Jerrold H. Levy

Patients undergoing thoracic and cardiac procedures are at the highest risk for postoperative atrial fibrillation (POAF). POAF is associated with poor short-term and long-term outcomes, including high rates of early and late stroke, and late mortality. Patients with POAF that persists for longer than 48 hours should be anticoagulated on warfarin. Three new oral anticoagulants are available for the treatment of nonvalvular atrial fibrillation and have been found to be as efficacious or superior to warfarin in the prevention of stroke in high-risk patients, with similar to lower rates of major bleeding, and lower rates of intracranial hemorrhage.

Management of Anticoagulation Agents in Trauma Patients

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C. Cameron McCoy, Jeffrey H. Lawson, and Mark L. Shapiro

A lack of consensus on anticoagulant reversal during acute trauma is compounded by an aging population and the expanding spectrum of new anticoagulation agents. Developments in laboratory assays and transfusion medicine, including thromboelastography, recombinant factors, and factor concentrates, have revolutionized care for anticoagulated trauma patients. Accordingly, clinicians must be fully aware of drug mechanisms, assays to determine drug activity, and appropriate reversal strategies for patients on anticoagulants. Drugs include vitamin K antagonists, direct thrombin inhibitors, direct factor Xa inhibitors, low molecular weight heparin, and antiplatelet agents. This article discusses the appropriate assessment and management of trauma patients receiving these agents.

New Oral Anticoagulant–Induced Bleeding: Clinical Presentation and Management 575

Jerrold H. Levy and Marcel Levi

Bleeding is a significant complication of anticoagulant therapy. With the emergence of new oral anticoagulants (NOACs; ie, direct factor IIa or Xa inhibitors), this risk is further compounded by the lack of validated reversal strategies for these agents. Emerging postmarketing evidence suggests that the bleeding risks are in line with results observed in head-to-head clinical trials of NOACs versus traditional anticoagulants. Several guidelines have recommended the use of hemostatic agents for NOAC reversal in patients with life-threatening bleeding. Ultimately, adequately powered studies will be crucial for full assessment of the effectiveness and safety of any proposed reversal strategies.

Treatment of Intracerebral Hemorrhage Associated with New Oral Anticoagulant Use: The Neurologist’s View 587

Roland Veltkamp and Solveig Horstmann

Intracerebral hemorrhage (ICH) associated with the use of oral anticoagulants (OAC-ICH) results in particularly severe strokes. A key target for the treatment of OAC-ICH is rapid restoration of effective coagulation. In patients receiving vitamin K antagonists, hemostatic factors such as prothrombin complex concentrate (PCC), fresh frozen plasma, and recombinant activated factor VII, in addition to vitamin K, can be used for anticoagulation reversal. However, emergency management of ICH during treatment with the new direct OACs (NOACs) is a major challenge. In the absence of specific antidotes, PCCs are recommended for NOAC reversal, mainly based on preclinical data.

Periprocedural Management of Patients on Anticoagulants 595

Lance A. Williams III, James M. Hunter Jr, Marisa B. Marques, and Thomas R. Vetter

Every year, new studies are undertaken to address the complex issue of periprocedural management of patients on anticoagulants and antiplatelet medications. In addition, newer drugs add to the confusion among clinicians about how to best manage patients taking these agents. Using the most recent data, guidelines, and personal experience, this article discusses recommendations and presents simplified algorithms to assist clinicians in the periprocedural management of patients on anticoagulants.

Four-Factor Prothrombin Complex Concentrate Versus Plasma for Urgent Vitamin K Antagonist Reversal: New Evidence 613

Ravi Sarode

Vitamin K antagonist (VKA) therapy is a mainstay of treatment for patients at risk of thromboembolic events. Despite widespread use, a major limitation of VKA therapy is the substantial risk of serious bleeding complications, which often require rapid reversal of anticoagulation. A recent randomized multicenter comparison between a 4-factor prothrombin complex concentrate (4F-PCC) and plasma in patients with acute major bleeding has provided important new evidence of the benefit of 4F-PCC over plasma for urgent VKA reversal.

Prothrombin Complex Concentrates as Reversal Agents for New Oral Anticoagulants: Lessons from Preclinical Studies with Beriplex 623

Gerhard Dickneite

Although new oral anticoagulants (NOACs) represent an advance in anti-coagulant therapy over vitamin K antagonists (VKAs), they nevertheless have a low, but significant risk for bleeding complications. Reversal agents for VKAs, such as prothrombin complex concentrates (PCCs), are currently being evaluated in preclinical studies for NOAC reversal. This article reviews the preclinical data for the most extensively studied PCC for NOAC reversal, Beriplex, a 4-factor PCC. The results from the Beriplex studies are also compared with those obtained with other reversal agents, including different nonactivated PCCs, activated PCCs, and recombinant activated factor VII.

Perioperative Management of Patients Receiving New Oral Anticoagulants: An International Survey 637

David Faraoni, Charles Marc Samama, Marco Ranucci, Wulf Dietrich, and Jerrold H. Levy

New oral anticoagulants (NOACs) are increasingly replacing standard anticoagulants. These new drugs have been recently introduced in clinical practice, and specific knowledge regarding preoperative interruption, anti-coagulation assessment, and reversal therapies is needed. In this article, 3 main areas related to perioperative NOACs management are discussed: (1) physicians' knowledge, (2) current practices, and (3) perspectives to improve management of patients treated with NOACs.

Management of Anticoagulation and Hemostasis for Pediatric Extracorporeal Membrane Oxygenation 655

Arun Saini and Philip C. Spinella

Compared to in situ vascular physiology where pro and anti-hemostatic processes are in balance to maintain hemostasis, the use of ECMO in a critically ill child increases the risk of hemorrhagic or thromboembolic events due to a perturbation in the balance inherent of this complex system. The ECMO circuit has pro-hemostatic effects due to contact activation of hemostasis and inflammatory pathways. In addition, the critical illness of the child can cause dysregulation of hemostasis that may shift between hyper and hypocoagulable states over time.

The Influence of Various Patient Characteristics on D-dimer Concentration in Critically Ill Patients and Its Role as a Prognostic Indicator in the Intensive Care Unit Setting 675

Jenna L. Spring, Anne Winkler, and Jerrold H. Levy

This study examines the relationship between D-dimer concentration and patient age, gender, race, and renal function, and the role of D-dimer concentration as a predictor of in-hospital mortality, in a critically ill patient population. The results demonstrate there is a correlation between increased D-dimer concentration and renal impairment in critically ill patients, with patients in renal failure having the highest D-dimer concentrations. Peak D-dimer levels were higher among female patients than in

male patients, but there was no association between peak D-dimer levels and other patient characteristics. D-dimer concentration was also not predictive of in-hospital mortality.

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