

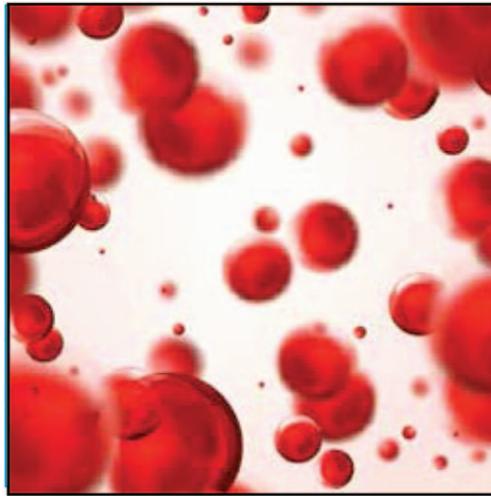
Bleeding and the New Anticoagulants

Strategies and Concerns

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THE non-vitamin K antagonist K oral anticoagulants (NOACs) represent a major step forward as compared with low-molecular-weight heparins and vitamin K antagonists.¹ Four active molecules are now available on the market. Only one direct thrombin inhibitor (anti-IIa agent) has been developed: dabigatran (Pradaxa[®]) from Boehringer-Ingelheim (Biberach, Germany). Three anti-Xa agents are now marketed: rivaroxaban (Xarelto[®]) from Bayer (Leverkusen, Germany) and Johnson & Johnson (New Brunswick, NJ), apixaban (Eliquis[®]) from the alliance BMS (Princeton, NJ) and Pfizer (New York, NY), and edoxaban (Lixiana[®]) from Dai-ichi-Sankyo (Parsippany, NJ).

Although efficacy of NOACs administration was reported in different clinical trials, several issues deserve our attention. Both pharmacokinetics and pharmacodynamics for these agents are associated with significant intra- and interindividual variabilities and a huge number of drug interactions, and elimination is significantly affected by renal function, which could be associated with significant variations in plasmatic concentrations and an increased bleeding risk.² Although new tests become more readily available for monitoring, which include the diluted thrombin time for dabigatran (Hemoclot[®]; Hyphen BioMed, Neuville sur-Oise, France), and specific anti-Xa assays for other direct Xa inhibitors, ranges that allow an optimal balance between effective anticoagulation and lower bleeding risk still need to be better defined for these agents.³ Finally, although clinical trials are underway, no specific antidotes are yet available and leave prothrombin complex concentrates (PCCs) as the principal therapeutic option. These hemostatic agents have been tested with conflicting results in different animal models^{4,5} and healthy volunteers,⁶ but efficacy has only been reported in a few bleeding cases.⁷



“When life-threatening bleeding occurs with any anticoagulant, a multimodal approach should be considered with hemodynamic and hemostatic resuscitation.”

reversal agent becomes available for dabigatran with an already approved, widely available nonspecific procoagulation agent. However, even if the results herein are supportive regarding the efficacy of four-factor PCC, it has to be emphasized that the major part of these experiments has been performed *in vitro* and that their “modest dose” of dabigatran mimics a 472 ng/ml concentration in humans, which already represents a very high plasma concentration that is several-fold greater than a therapeutic level.^{9,10} Furthermore, the *in vivo* data uses a mouse saphenous bleeding model that is difficult to extrapolate to humans, and the safety of this potential prothrombotic coagulation factor approach cannot be addressed based on their animal model.

Several important issues regarding dabigatran should be considered. Dabigatran has a very low bioavailability (~6%), has a long terminal half-life (13 to 17h in healthy volunteers), and is eliminated *via* the kidney (80%). The published pivotal trials in venous thromboembolism prophylaxis¹¹ and

In this issue of *ANESTHESIOLOGY*, the article by Hoffmann *et al.*⁸ adds new potential data. Using their cell-based model of thrombin generation, the authors have compared the efficacy of recombinant factor VIIa and a four-factor PCC in the presence of dabigatran. While enhancing the rate of thrombin generation and peak thrombin level mainly with PCC, the authors have observed a good correlation with hemostasis *in vivo* in a mouse saphenous vein bleeding model. Effects of PCC have been seen *in vitro* at both therapeutic and markedly supra-therapeutic dabigatran levels, while beneficial effects of recombinant factor VIIa decreased as the dabigatran level increased.

This interesting scientific study performed by a well-known group in the field of the fundamental mechanisms of hemostasis represents a potential approach until a specific

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Accepted for publication October 13, 2014. From the Department of Anaesthesia and Intensive Care Medicine, Cochin University Hospital, Paris, France (C.M.S.); and Cardiothoracic Intensive Care Unit, Duke University Hospital, Durham, North Carolina (J.H.L.).

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treatment, or the Randomized Evaluation of Long-Term Anticoagulation Therapy trial in atrial fibrillation patients,¹² have demonstrated a high level of efficacy and safety. Nevertheless, real-life settings sometimes differ, and following major bleeding events in patients treated with this agent, numerous regulatory agencies have issued alerts or caution for the need for monitoring renal function.¹³ Dosing is also different in Europe and in the United States, with different dosing strategies. In addition, a recent controversy dealing with the potential benefits of a biological monitoring to optimize the safety and efficacy of dabigatran has reemerged.¹⁴ However, it is important to realize that all anticoagulants can cause bleeding, and their relative risk *versus* benefits should be considered. When life-threatening bleeding occurs with any anticoagulant, a multimodal approach should be considered with hemodynamic and hemostatic resuscitation.³

In summary, all of the NOACs do represent important therapeutic approaches for our patients. Indeed, we need well-performed experimental studies as Hoffman *et al.*'s,⁸ to try to find a scientific rationale for a nonspecific reversal in patients treated with NOACs and scheduled for an emergent procedure or for bleeding patients. However, specific monitoring tests are increasingly becoming clinically available to help better manage patients with all the different NOACs. Although a specific antidote is not yet available for all of the agents (both anti-IIa and anti-Xa), studies are underway with idarucizumab, a monoclonal antibody fragment for dabigatran,* and with andexanet, a Xa reversal agent.†

Acknowledgments

Support received from NovoNordisk (Bagsvaerd, Denmark), CSL Behring (King of Prussia, Pennsylvania), and LFB (Les Ullis, France) (to Dr. Samama).

Competing Interests

Dr. Samama received speaker fees from the Bayer (Leverkusen, Germany), Bristol-Myers Squibb (BMS, Princeton, New Jersey), Boehringer-Ingelheim (Biberach, Germany), CSL Behring (King of Prussia, Pennsylvania), Daiichi-Sankyo (Parsippany, New Jersey), LFB (Les Ullis, France), Octapharma (Lachen, Switzerland), and Pfizer (New York, New York). He is the member of the advisory committees for Bayer, BMS, Boehringer-Ingelheim, Daiichi-Sankyo, Pfizer, Portola (San Francisco, California), and Roche (Basel, Switzerland). He is the primary investigator for Bayer, BMS, Boehringer-Ingelheim, and LFB. Dr. Levy is the member of the research steering committees for CSL Behring, Boehringer-Ingelheim, Johnson & Johnson (New Brunswick, New Jersey), Marathon (Northbrook, Illinois), and Portola.

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* Available at: <http://clinicaltrials.gov/ct2/show/NCT02104947?term=dabigatran+bleeding&rank=3>. Accessed October 5, 2014.

† Available at: <http://clinicaltrials.gov/ct2/show/NCT02220725?term=portola&rank=1>. Accessed October 5, 2014.

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