Pharmacology and Safety of New Oral Anticoagulants

The Challenge of Bleeding Persists

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KEYWORDS

• Bleeding • Safety • Dabigatran • Rivaroxaban • Apixaban
• Prothrombin complex concentrates

KEY POINTS

- Owing to benefits in ease of administration, safety, and efficacy demonstrated in clinical trials, the use of new oral anticoagulants (NOACs) in clinical practice is increasing.
- Compared with standard anticoagulants, these new agents offer a number of advantages, including rapid onset of action, fixed dosing, and no requirement for routine coagulation monitoring.
- There are currently no validated NOAC-specific reversal agents and there is a lack of clinical data assessing the efficacy and safety of existing protocols for bleeding management in NOAC-treated patients. However, an increasing number of studies are being undertaken and new therapeutic approaches developed, as discussed elsewhere in this supplement.
- With all anticoagulation agents, the management of life-threatening bleeding presents a significant challenge, and will continue to evolve as new therapeutic approaches and data emerge.

INTRODUCTION AND BACKGROUND

The prevalence of cardiovascular diseases, such as atrial fibrillation (AF) and venous thromboembolism (VTE), sustains a demand for safe and effective anticoagulation therapies. In the United States alone, AF is estimated to affect approximately 2.3 million people,[1] whereas projections suggest that the number of adults with VTE

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in the United States may exceed 1.5 million by 2050.[2] Warfarin has long been a standard of antithrombotic therapy; however, there is a growing trend toward replacing it and the older parenteral agents, such as unfractionated and low molecular weight heparin (UFH and LMWH, respectively), with new oral anticoagulants (NOACs) that are perceived to offer better efficacy, safety, and ease of administration with oral use.[3]

Four NOACs are currently approved worldwide. The thrombin (factor IIa [FIIa]) inhibitor dabigatran (Pradaxa) is used primarily for stroke prevention in patients with nonvalvular AF and is approved for this indication in the United States and Canada,[4,5] European Union (EU),[6] Australia,[7] and Japan.[8] In Europe, Canada, and Australia, dabigatran also is approved for the prevention of VTE in patients undergoing hip or knee surgery.[5–7] Three different factor Xa (FXa) inhibitors also are approved. Apixaban (Eliquis) is approved in the EU, United States, and Canada for the prevention of stroke and systemic embolism in patients with nonvalvular AF[9–11] and in the EU and Canada for the prevention of VTE after hip or knee replacement surgery.[9,11] Rivaroxaban (Xarelto) is approved in the United States and Canada for stroke prevention in patients with nonvalvular AF and for the treatment and prevention of VTE,[12,13] but has EU approval only for coadministration (with acetylsalicylic acid and/or other agents) for the prevention of atherothrombotic events in acute coronary syndrome.[14] Edoxaban (Lixiana) is currently approved only in Japan, where it is indicated for the prevention of VTE after hip or knee replacement.[15] Other oral anticoagulants are in development, including the FXa inhibitor betrixaban, which is currently under investigation in a phase III clinical trial (NCT01583218).[16]

Compared with standard anticoagulants, such as UFH, LMWH, and vitamin K antagonists (VKAs), NOACs offer several advantages. These include rapid onset of action, predictable pharmacokinetics, a predictable anticoagulant effect (which obviates the need for routine laboratory monitoring), and few food or drug interactions.[3] Furthermore, the risk of bleeding is generally lower compared with VKAs.[17,18] However, bleeding associated with all anticoagulants remains a significant challenge. For the NOACs, major bleeding rates of 2.1% to 3.6% per year have been reported in clinical trials.[19–22] In another trial, in which short-term treatment with apixaban was evaluated for thromboprophylaxis after hip replacement, 0.8% of patients in the apixaban arm experienced major bleeding during a treatment and evaluation period of approximately 5 weeks.[23] In these trials, the definition of major bleeding was based on that proposed by the International Society on Thrombosis and Haemostasis (ISTH) (fatal outcome, involvement of a critical anatomic site, fall in hemoglobin concentration of $\geq$2 g/L, or transfusion of $\geq$2 units of blood or red cells),[24] with minor variations from the ISTH definition in some of the studies.[19,22,23] Clearly, when bleeding occurs or patients require surgery, therapeutic approaches are important to consider.[3] A lack of NOAC-specific reversal agents compounds the challenge, whereas some standard anticoagulants (eg, UFH and warfarin) have accepted, validated, acute reversal agents (protamine sulfate and 4-component prothrombin complex concentrates [PCCs], respectively). However, it was not until late 2013 that a 4-component PCC became available in the United States.[25]

This article reviews the available safety data, including bleeding profile, and major strategies for NOAC-induced bleeding management associated with the 3 NOACs approved in North America: dabigatran, rivaroxaban, and apixaban.

SUMMARY OF PHARMACOLOGY

Dabigatran is a reversible direct thrombin (FIIa) inhibitor that binds clot-bound and free thrombin without the need for antithrombin.[3,4] It is administered as the prodrug,