New Oral Anticoagulants

Their Role in Stroke Prevention in High-Risk Patients with Atrial Fibrillation

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KEYWORDS

• Anticoagulation • Novel oral anticoagulants • Atrial fibrillation • Factor IIa inhibitors • Factor Xa inhibitors • Stroke

KEY POINTS

- Novel oral anticoagulants (NOACs) make up approximately 20% of new anticoagulant prescriptions.
- NOACs have advantages of fixed-dose oral dosing, rapid onset and offset, and fewer interactions with food and drugs compared with vitamin K antagonists (VKAs).
- NOACs are at least as effective as VKAs in patients with atrial fibrillation (AF) and venous thromboembolism.
- NOACs have similar, if not lower, rates of serious hemorrhagic complications.
- Common errors in NOAC use include inappropriate patient selection, inappropriate dose selection, and inappropriate monitoring.

INTRODUCTION

AF is the most common sustained arrhythmia and the leading cause of stroke in adults worldwide.[1,2] Traditionally, warfarin and other VKAs have been the mainstay treatment option for patients with increased risk of stroke. Their use is, however, limited by a narrow therapeutic index and interactions with multiple foods and other medications, requiring frequent monitoring and dose adjustments.[3] In the last 5 years, NOACs that inhibit thrombin or activated factor X (fXa) have been approved as an alternative to warfarin for stroke risk reduction in AF. Dabigatran etexilate, an oral reversible direct thrombin inhibitor, was the first of these agents. It was followed by rivaroxaban, apixaban, edoxaban, and, recently, betrixaban (phase 3 trials).[4–7] The NOACs offer several advantages over VKAs, such as rapid onset and offset of action, fewer drug interactions, and an absence of an effect of dietary vitamin K intake on drug activity (**Fig. 1**).[8–12] This article reviews the pharmacologic and evidence-based data as well

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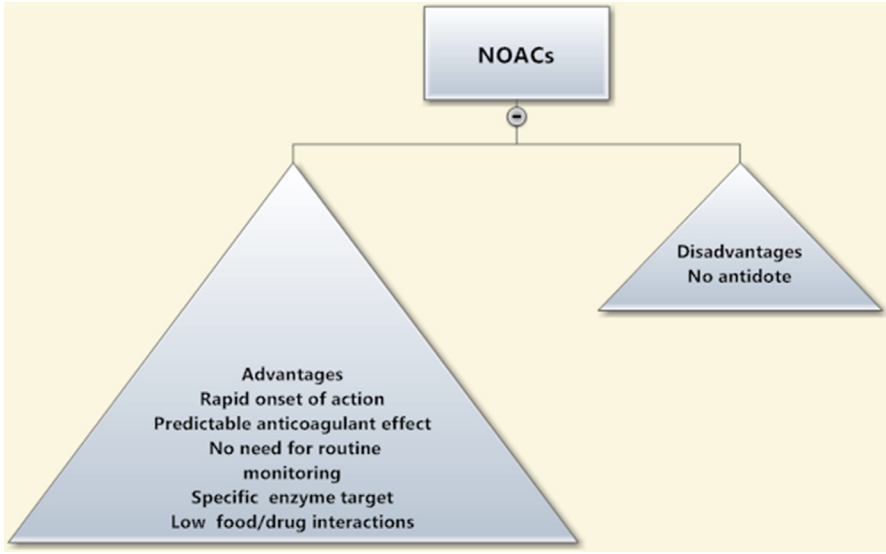

Fig. 1. Advantages and disadvantages of newer anticoagulants.

as the clinical characteristics of NOACs and their role in preventing stroke and thromboembolic events in high-risk patients with nonvalvular AF (NVAF). Rivaroxaban and apixaban are also approved for the primary prevention of embolic events in patients who undergo hip and knee replacement surgery. Dabigatran, rivaroxaban, and apixaban are approved for deep vein thrombosis and pulmonary embolism (DVT/PE) treatment and prevention. Edoxaban is awaiting US Food and Drug Administration (FDA) approval.

PHARMACOLOGY

NOACs are small molecules that specifically target individual clotting factors. As thrombin is the final effector in blood coagulation, it is a logical target for newer agents. Thrombin converts fibrinogen to fibrin and also amplifies its own generation by feedback activation of factors V, VIII, and XI. Thrombin is also a potent platelet agonist. Therefore, thrombin inhibition not only attenuates fibrin formation but also reduces thrombin generation and platelet activation. The NOACs target either thrombin or fXa (**Fig. 2**). Dabigatran etexilate is a direct thrombin inhibitor, whereas rivaroxaban, apixaban, edoxaban, and betrixaban work by direct fXa inhibition.[2,13–19] **Tables 1** and **2** detail the characteristics and drug interactions of the NOACs.[20–36]

Dabigatran Etexilate

Dabigatran etexilate, a substrate of the P-glycoprotein (P-gp) transporter, is a potent, competitive, reversible inhibitor of thrombin that acts by binding clot-bound and free thrombin with a high affinity and specificity. The prodrug, or etexilate form, is rapidly converted to dabigatran by esterases and has an oral bioavailability of 6.5%. Drug capsules are filled with tartaric acid, as drug absorption is enhanced with a low pH. Levels usually peak 2 hours after oral administration. The half-life of dabigatran is 8 hours after single dose and 14 to 17 hours after multiple doses, enabling once or twice daily administration. Dabigatran is primarily excreted by the kidneys, and therefore caution must be exercised in patients with renal dysfunction (creatinine clearance

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