REVIEW ARTICLE

Novel oral anticoagulants in gastroenterology practice CME

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Atrial fibrillation (AF), the most common sustained cardiac arrhythmia, is associated with a 5-fold increase in the risk of ischemic stroke, and AF-related strokes have worse outcomes than those not associated with AF.[1,2] Warfarin reduces the risk of stroke in patients with AF by approximately two-thirds and is more effective than aspirin or dual antiplatelet therapy with aspirin and clopidogrel.[3] Although effective, warfarin has limitations that complicate its use. These include unpredictable pharmacokinetics and pharmacodynamics related to genetic polymorphisms and to variations in dietary vitamin K intake and numerous drug-drug interactions. Therefore, frequent monitoring is needed to attempt to keep the international normalized ratio (INR) within the therapeutic range. Such monitoring is inconvenient for patients and physicians and costly for the healthcare system. The limitations of warfarin contribute to its underuse in eligible patients with AF, and even when warfarin is given, the INR is frequently outside the therapeutic range.

For the first time in over 50 years, novel oral anticoagulants (NOACs) are available. Instead of reducing the effective levels of multiple coagulation factors, the NOACs specifically target either factor Xa or factor IIa (thrombin), thereby attenuating thrombosis. Currently, 3 NOACs are approved for stroke prevention in AF: rivaroxaban and apixaban, which target factor Xa, and dabigatran etexilate, which targets thrombin. The NOACs are at least as effective as warfarin for stroke prevention in AF, result in about half the rate of intracranial hemorrhage, and are more convenient to administer because they can be given in fixed doses without routine coagulation monitoring. Higher drug cost is one concern with NOAC treatment. A second is that the frequent measurement of effect and the associated healthcare provider interaction required with warfarin therapy likely improves medication adherence, and strategies to assure adherence to NOAC therapy are currently needed.

Of particular relevance to gastroenterologists, rivaroxaban and dabigatran are associated with an increased risk of major GI bleeding compared with warfarin, and dabigatran is associated with an increased risk of non-bleeding upper GI symptoms such as dyspepsia and heartburn. Consequently, although practicing gastroenterologists may never prescribe a NOAC, they are likely to encounter NOAC-related GI adverse events, and they will need to manage NOACs around the time of endoscopy. In this review, we describe the pharmacology and GI safety profile of the NOACs and provide clinical management suggestions.

PHARMACOLOGY

Whereas warfarin antagonizes vitamin K-dependent posttranslational modifications of factors II, VII, IX, and X in the liver, the NOACs directly inhibit the biologic activity of factor Xa or thrombin, which are critical proteases in the clotting cascade (Fig. 1). In contrast to warfarin, the NOACs have a rapid onset and offset of action (Fig. 2). Dietary vitamin K does not influence the anticoagulant effect of the NOACs, and there are few drug-drug interactions.

Abbreviations: AF, atrial fibrillation; aPTT, activated partial thromboplastin time; ARISTOTLE, apixaban for reduction in stroke and thromboembolic events in atrial fibrillation; ASGE, American Society for Gastrointestinal Endoscopy; INR, international normalized ratio; NOAC, novel oral anticoagulant; NSAID, nonsteroidal anti-inflammatory drug; PCC, prothrombin complex concentrate; PPI, proton pump inhibitor; PT, prothrombin time; RE-LY, randomized evaluation of long term anticoagulant therapy; ROCKET-AF, rivaroxaban once daily oral direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation; RR, relative risk.

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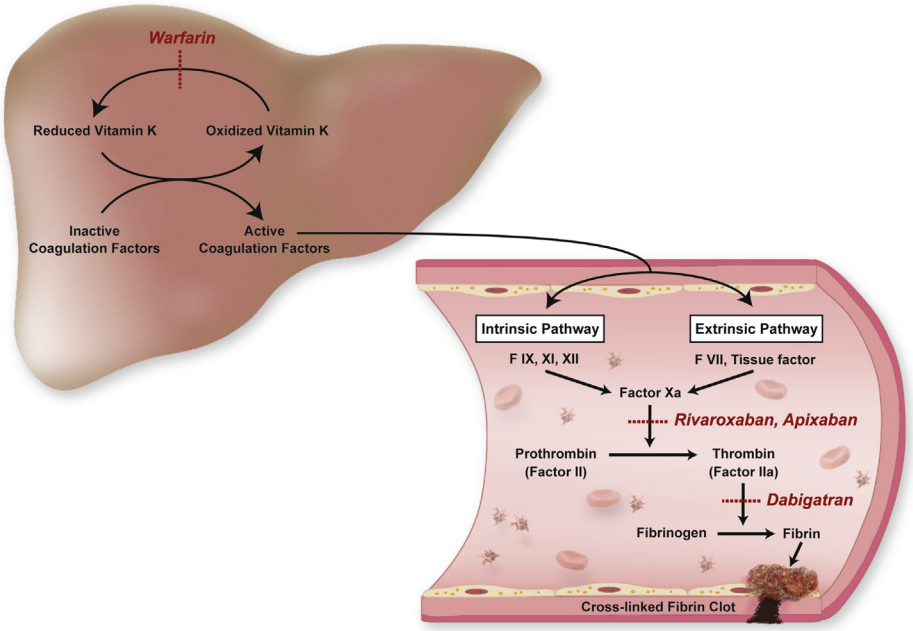

Figure 1. Sites of action of warfarin, apixaban, dabigatran, and rivaroxaban. Warfarin inhibits the synthesis of the vitamin K-dependent clotting factors (II, VII, IX, and X) in the liver, whereas the novel oral anticoagulants competitively inhibit the binding of factor Xa (apixaban and rivaroxaban) or thrombin (dabigatran) to their substrates in the blood. *F,* factor.

Consequently, the NOACs produce a more predictable anticoagulant response than warfarin, which obviates the need for routine coagulation monitoring (Table 1). The individual NOACs have different pharmacologic properties, and an understanding of these differences is important in clinical practice (Table 2).

Dabigatran

In order to achieve oral absorption, dabigatran is administered as a prodrug (dabigatran etexilate), which after absorption is cleaved by serum and hepatic esterases to active dabigatran.[4] Absorption is increased in an acidic milieu, and therefore the drug is compounded with tartaric acid. Despite this requirement, coadministration of a proton pump inhibitor (PPI) decreases absorption but does not appear to decrease efficacy. The bioavailability of dabigatran etexilate is approximately 7%. The capsule is designed for release in the stomach, and the molecule is absorbed in the proximal small intestine. The nonabsorbed drug passes though the luminal GI tract, where the majority is converted to dabigatran and is excreted in the stool. Dabigatran reversibly binds to thrombin, inhibiting its activity (Fig. 1). Dabigatran has a half-life of 9 to 17 hours, depending on age and renal function. The drug is primarily eliminated by the kidney as unchanged drug; consequently, in patients with renal impairment, not only is there a risk of accumulation, but the half-life of the drug also is prolonged. In the United States, 2 doses of dabigatran are approved for stroke prevention in AF: 150 mg twice daily and 75 mg twice daily. Dose reduction is recommended in individuals with severe renal dysfunction,[5,6] and the drug is contraindicated in individuals with a creatinine clearance <15 mL/minute. Dabigatran levels are increased by potent p-glycoprotein intestinal efflux transport inhibitors, such as fluconazole and are decreased by p-glycoprotein enhancers, such as rifampin. Modest inhibitors, like amiodarone or verapamil, increase plasma concentration modestly.

Rivaroxaban

Rivaroxaban directly and reversibly binds to the active site of factor Xa, thereby attenuating thrombin generation (Fig. 1). In the United States, rivaroxaban is approved at 20 mg daily, to be taken with the evening meal; the dose is reduced to 15 mg daily in patients with a creatinine clearance of <50 mL/minute. Rivaroxaban is absorbed primarily in the proximal small intestine and at the 20-mg dose has a bioavailability of approximately 66% (Table 2).[7-9] The half-life is approximately 6 to 13 hours;[8] one-third is excreted unchanged by the kidneys, and the remainder is metabolized by the liver in a CYP3A4-dependent fashion. Inactive metabolites are excreted equally in feces and urine. The drug is contraindicated in patients with creatinine clearance <15 mL/minute, with advanced liver disease, and with coagulopathy. At doses above 10 mg, absorption is increased by food intake and unaffected by PPIs.[10] Rivaroxaban levels are increased by concomitant administration of drugs that are potent inhibitors of both p-glycoprotein and CYP3A4, such as the azole antifungal agents or protease inhibitors, and are decreased by drugs that are strong inducers of p-glycoprotein or CYP3A4.