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Direct Oral Anticoagulants: A Patient-centered Review

Jenna M. Solomon, PharmD, and Anne L. Hume, PharmD, FCCP, BCPS

ABSTRACT

Since 2010, 4 new oral anticoagulants have been approved by the Food and Drug Administration with additional drugs in development. Major studies of atrial fibrillation and venous thromboembolism have shown the noninferiority, and the potential superiority, of these anticoagulants compared with warfarin. However, important limitations exist in these studies including suboptimal warfarin management and the inclusion of few participants with significant chronic kidney disease and concomitant drug therapy. The new oral anticoagulants offer both advantages and disadvantages over standard warfarin therapy.

Keywords: atrial fibrillation, chronic kidney disease, oral anticoagulants, venous thromboembolism

Warfarin has been the most commonly used oral anticoagulant in the United States for many years. Although effective in treating deep venous thrombosis (DVT) and pulmonary embolism (PE), as well as reducing the risk of stroke in atrial fibrillation (AF), the safe use of warfarin is challenging, especially in older adults.

In the past 5 years, dabigatran, rivaroxaban, apixaban, and edoxaban have been approved by the Food and Drug Administration. Labeled indications have included the treatment of DVT and PE, prevention of recurrent DVT and PE, the prevention of stroke in patients with nonvalvular atrial fibrillation (AF), and prophylaxis after joint replacement surgery. The purpose of this review is to present a concise summary of the new oral anticoagulants.

OVERVIEW

Multiple terms have been used to classify these drugs including novel/new/non-vitamin K antagonists (VKA) oral anticoagulants, target-specific oral anticoagulants, and direct oral anticoagulants (DOACs). The Subcommittee on Control of Anticoagulation of the International Society of Thrombosis and Haemostasis has recommended that DOAC be the preferred term in that individual drugs inhibit only 1 site.[1]

Pharmacologic Considerations

Key considerations with the DOACs are summarized in Table 1.[2-6] Unlike warfarin, the new drugs have predictable pharmacokinetic properties so that their anticoagulant effect is more consistent. DOACs have shorter half-lives than warfarin, which has both advantages and disadvantages. For example, if the patient has adherence problems and misses doses, a more rapid loss of efficacy and potentially a greater risk of thrombosis may result.

Drug-drug Interactions

The drug interactions with warfarin are well-known and potentially life-threatening.[8] One advantage of the new anticoagulants is the decreased number of drug interactions based on their pharmacokinetic properties. The importance of their specific drug interactions may depend on the presence or absence of concomitant chronic kidney disease (CKD).

In terms of pharmacokinetic drug interactions, concomitant use of rivaroxaban and apixaban with combined potent inhibitors of CYP3A4 and P-glycoprotein (P-gp), such as ketoconazole and ritonavir, would be expected to increase the risk of bleeding. Similarly, rivaroxaban and apixaban should not be administered concomitantly with combined

Table 1. Pharmacokinetic and Pharmacodynamic Parameters of Oral Anticoagulants

Property	Warfarin (Coumadin)[3]	Dabigatran (Pradaxa)[4] FDA 10/19/10	Rivaroxaban (Xarelto)[5] FDA 11/4/11	Apixaban (Eliquis)[6] FDA 12/28/12	Edoxaban (Savaysa)[7] FDA 1/8/2015
Mechanism of action	Vitamin K antagonist	Reversible direct thrombin inhibitor	Reversible direct factor Xa inhibitor	Reversible direct factor Xa inhibitor	Reversible direct factor Xa inhibitor
Prodrug	No	Yes	No	No	No
Bioavailability	>90%	3%-7%	80%	50%	62%
Protein Binding	>99%	>35%	>90%	87%	55%
Half-life	S-isomer 2-4 times more potent than R; S-isomer 36 hours; R-isomer 46 hours	12-17 hours	5-9 hours	9-11 hours	10-14 hours in elderly; 5-9 hours in general population
Metabolism	S-isomer CYP2C9; R-isomer CYP3A4; 1A2; 2C19	Serum esterases; non-CYP metabolism	CYP3A4/5; CYP2J2; hydrolysis	CYP3A4 (major)	CYP3A4 (minimal) and CES1 oxidation
P-glycoprotein substrate	No	Yes; slight ↑ in level	Yes	Yes	Yes
Elimination	Urine: 90%; predominantly as inactive metabolites	Urine: 80% of unchanged drug	Urine: 33%; as active unchanged drug	Urine: 27%; as inactive unchanged drug	Urine: 50%; as inactive unchanged drug

CYP = cytochrome P450; CES = Carboxylesterase.

potent inducers of CYP3A4 and P-gp, such as rifampin and carbamazepine.[4,5] If the benefit outweighs the risk, the apixaban dosage should be halved. Dabigatran should not be coadministered with strong P-gp inhibitors, such as cyclosporine.[3] For patients with CKD who are taking a P-gp inhibitor, dabigatran should be avoided or prescribed at a reduced dosage. Edoxaban is not to be coadministered with P-gp inducers, most notably rifampin, whereas strong caution is advised with respect to concomitant P-gp inhibitors.[6]

Pharmacodynamic interactions with DOACs may occur when used in combination with drugs with antiplatelet effects. Concomitant use with aspirin, clopidogrel, prasugrel, and nonsteroidal anti-inflammatory drugs (NSAIDs) may increase the risk of bleeding, but data are limited. Dual therapy with up to 100 mg aspirin daily was an independent risk factor for major bleeding in patients taking rivaroxaban and edoxaban.[4,6] However, the interaction between rivaroxaban and NSAIDs is unclear. In addition, selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors might also be expected to increase the risk of bleeding with DOACs because of their effects to decrease platelet aggregability and activity.[3-6]

Monitoring

The requirement for monitoring of the international normalized ratio (INR) has been a barrier to the use of warfarin. The new anticoagulants generally do not need to be monitored. Patient characteristics such as age over 80, presence of CKD, and concomitant drug therapy have been used to guide dosing. In instances in which an individual with AF experiences a stroke or bleeding while taking a new anticoagulant, the lack of a laboratory assay to identify the cause can be a limitation.

EFFICACY

The studies of new anticoagulants for nonvalvular AF and venous thromboembolism (VTE) have been randomized, double-blind, double-dummy non-inferiority trials and are summarized in Tables 2[8-11] and 3,[12-15] respectively.