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CHAPTER

DIRECT ORAL ANTICOAGULANTS

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INTRODUCTION

Since 2010, four direct oral anticoagulants (DOACs) have become commercially available in the United States: dabigatran, a direct thrombin inhibitor (DTI); and rivaroxaban, apixaban, and edoxaban, which are direct factor Xa (FXa) inhibitors (**Table 7-1**). The availability of DOACs has significantly changed the therapeutic

TABLE 7-1: **Commercially Available Direct Oral Anticoagulants**[1-6,*]

	Dabigatran	**Rivaroxaban**	**Apixaban**	**Edoxaban**
Mechanism of action	Direct FIIa (thrombin) inhibitor	Direct FXa inhibitor	Direct FXa inhibitor	Direct FXa inhibitor
Manufacturer	Boehringer-Ingelheim	Bayer with Ortho McNeil	Pfizer with Bristol Myers Squibb	Daiichi Sankyo
Brand name(s)	Pradaxa	Xarelto	Eliquis	Savaysa (U.S.) Lixiana (non-U.S.)
Approved indications	Post-operative VTE prevention in knee or hip arthroplasty** VTE treatment and prevention of recurrence Stroke and systemic embolism prevention in non-valvular atrial fibrillation	Post-operative VTE prevention in knee or hip arthroplasty VTE treatment and prevention of recurrence Stroke and systemic embolism prevention in non-valvular atrial fibrillation Acute coronary syndrome***	Post-operative VTE prevention in knee or hip arthroplasty VTE treatment and prevention of recurrence Stroke and systemic embolism prevention in non-valvular atrial fibrillation	Post-operative VTE prevention in knee or hip arthroplasty**** VTE treatment and prevention of recurrence Stroke and systemic embolism prevention in non-valvular atrial fibrillation

*Betrixaban, another direct factor Xa inhibitor, was recently FDA-approved for extended prophylaxis among medical patients. Due to the recency of approval and the limited uptake in clinical practice to date, this agent will not be discussed in this chapter.

**In the United States, dabigatran is approved only for post-operative VTE prophylaxis in hip arthroplasty.

***European Union only.

****Japan only.

FIIa: thrombin, FXa: Factor Xa, VTE: venous thromboembolism

landscape of anticoagulation. Clinician familiarity with these agents, particularly their markedly different pharmacologies compared to conventional therapies, is needed for optimal patient care (**Table 7-2**). This chapter will provide a concise overview of the pharmacology, safety, and efficacy data as well as some practical management aspects pertaining to DOACs. Refer to other chapters in this book for additional information regarding optimal DOAC management.

Clinical Pearls

- *Based on safety and efficacy data from large, randomized controlled trials* (**Table 7-3**) *of over 100,000 patients,*[7-17] *these agents are now preferred over conventional therapies (e.g., vitamin K antagonists, low-molecular-weight heparins) for common anticoagulation indications (e.g., non-valvular atrial fibrillation, non-cancer-associated venous thromboembolism).*[18-20]

PHARMACOLOGY

The DOACs possess intrinsic anticoagulant activity and do not require binding to cofactors to exert their effect. Thus, they are considered direct anticoagulants. Because of their small molecular size (~500 daltons) and lack of binding to bulky cofactors, DOACs are able to penetrate coagulation complexes on phospholipid surfaces and inhibit both clot-bound and free-floating thrombin. Each DOAC inhibits a single serine protease target (dabigatran inhibits thrombin [FIIa]; rivaroxaban, apixaban, and edoxaban inhibit FXa) within the common pathway of the coagulation cascade (**Figure 7-1**). This specificity provides several practical advantages of DOACs over conventional anticoagulation therapies.[21]

Clinical Pearls

- *Compared to conventional anticoagulants (e.g., heparins, warfarin) that inhibit multiple serine proteases within the coagulation cascade, the DOACs inhibit a single procoagulant target. This increased specificity provides a linear dose response and wide therapeutic index, allows for fixed dosing, and precludes the need for routine monitoring of the anticoagulant effect of DOACs in most patients.*