A Comprehensive Overview of Direct Oral Anticoagulants for the Management of Venous Thromboembolism

Anthony J. Comerota, MD and Eduardo Ramacciotti, MD, PhD

ABSTRACT

Venous thromboembolism (VTE) is a prevalent, potentially fatal health problem. Although standard anticoagulant therapy is effective when compared with the newer direct oral anticoagulants (DOACs), it has disadvantages. Heparin and its derivatives must be administered parenterally, whereas use of oral vitamin K antagonists is complicated by unpredictable pharmacokinetics and pharmacodynamics, drug-food and drug-drug interactions and the requirement for frequent laboratory monitoring. Randomized phase 3 trials have demonstrated that patients receive similarly effective anticoagulation with the DOACs dabigatran, edoxaban, rivaroxaban and apixaban when compared with warfarin, with similar or reduced risk of bleeding. Extended therapy trials have consistently demonstrated superior effectiveness for DOAC treatment when compared with placebo in preventing VTE recurrence. This article presents a comprehensive review of the pharmacokinetics, pharmacodynamics and accumulated clinical trial evidence for each DOAC for short-term, long-term and extended VTE therapy, and it considers the potential implications these agents have for the clinical management of VTE.

Key Indexing Terms: Venous thromboembolism; Anticoagulants; Hemorrhage. **[Am J Med Sci 2016;352(1):92–106.]**

INTRODUCTION

Venous thromboembolism (VTE) is a prevalent and potentially fatal health problem affecting over 900,000 people in the United States and more than 1 million people in Europe annually.[1,2] Recent studies have shown that VTE-related deaths exceed those caused by acute myocardial infarction (MI) and stroke.[1-3] An estimated 28% of patients will not survive past 1 month, with pulmonary embolism (PE) associated with higher fatality rates than deep vein thrombosis (DVT); this exceeds the case fatality rate reported for MI.[3] Although age is a risk factor, VTE is a common problem affecting all segments of the population. Those surviving VTE potentially face significant morbidities, including postthrombotic syndrome and chronic thromboembolic pulmonary hypertension. Recurrent events increase long-term morbidity.

Since the classic study by Barritt and Jordan,[4] anticoagulation has been the mainstay of therapy, initially with unfractionated heparin (UFH) being converted to vitamin K antagonists (VKAs). This was the standard of care until low–molecular-weight heparin (LMWH) compounds were developed, offering incremental benefits over standard UFH, and in some instances VKAs.[5-8] LMWHs offer rapid absorption from subcutaneous tissue, the possibility of initiating treatment in the outpatient setting and an apparent improvement in thrombus resolution. Moreover, compared with UFH, there is a reduced risk of heparin-induced thrombocytopenia and osteopenia when used over the long term.[5,9,10]

Fondaparinux, a pentasaccharide, shares many of the advantages of LMWH, but with its long half-life requires only once-daily injection.[11,12] The LMWHs and fondaparinux require parenteral administration, although monitoring is not generally required.

Until recently, VKAs have been the only oral anticoagulants available for the management of VTE. Unfortunately, VKAs have a number of disadvantages that complicate patient care such as unpredictable pharmacokinetics (PK) and pharmacodynamics (PD); food and drug interactions and functioning within a narrow therapeutic window, which requires frequent laboratory monitoring.[13,14] As a result, the management of patients receiving VKAs is often cumbersome, and even with expert management, many patients are frequently outside the therapeutic range.[15] This is a major concern because time spent within the therapeutic range is inversely correlated with the incidence of thromboembolic or hemorrhagic events.[16]

The most recent advance in the management of patients with VTE is the development of the direct oral anticoagulants (DOACs) that directly inhibit factor Xa or factor IIa, factors strategically positioned in the coagulation cascade (Figure 1). Factor Xa is located at the intersection of the intrinsic and extrinsic coagulation pathways before its interaction with factor II (prothrombin). Factor IIa (thrombin) forms the basic structure of thrombus, and it activates fibrinogen, which is the final step in the coagulation cascade. The DOACs directly bind to activated factors X and II. These new fixed-dose oral agents, unlike VKAs, do not require laboratory monitoring or dose adjustment, and have a low potential for food and drug interactions. Additionally, these agents reach peak concentration within 1-4 hours after

ingestion,[17-22] which is in sharp contrast to the extended time required for warfarin to achieve a therapeutic international normalized ratio (INR). This extended timing necessitates parenteral anticoagulation with either UFH or LMWH for a minimum overlap of therapy for 5 days. Despite these conveniences, and the similar or lower bleeding risk observed in clinical trials of DOACs versus standard therapy, clinicians are concerned because the DOACs are not monitored and their anticoagulant effect cannot be reversed by methods customary with warfarin use.

The DOACs approved for use include the following:

(1) the direct thrombin inhibitor, dabigatran and
(2) the factor Xa inhibitors—rivaroxaban, apixaban and edoxaban. Other agents in this class are in the preliminary stages of development.

Recently, evidence supporting the DOAC options for VTE treatment has emerged. This review summarizes the PK and PD of these agents and the accumulated clinical trial evidence for each DOAC for the management of VTE, and it considers the potential implications these agents have for the clinical management of VTE.

PD AND PK

Pharmacokinetic Characteristics of DOACs

Pharmacologic profiles of the DOACs are summarized in Table 1. These nonpeptidic, orally available agents directly inhibit 1 of the 2 key serine proteases in the coagulation cascade, thrombin (factor IIa) or activated factor X. Although several of the agents may have a similar mechanism of action, it is possible that differences in the PD and PK properties will influence how and when specific drugs are used for patient care.

Dabigatran

Dabigatran etexilate is the prodrug of dabigatran, which is a nonpeptidic small molecule that reversibly inhibits free and clot-bound thrombin.[23-25] Dabigatran also inhibits tissue factor–induced thrombin generation in human platelet-poor plasma.[24] In addition, dabigatran inhibits thrombin-activated platelet aggregation and tissue factor–induced platelet aggregation.[26]

Dabigatran has low oral bioavailability. Dabigatran etexilate was developed to improve gastrointestinal absorption. Absorption of dabigatran etexilate in the stomach and small intestine depends on an acidic environment. To establish such an environment, dabigatran etexilate contains a tartaric acid core.[27] With this acidic environment, drug absorption occurs independently of physiological variations in gastric pH. Coadministration with food has no effect on its bioavailability.[28]

Dabigatran etexilate is rapidly absorbed, with a time to maximum plasma concentration (t_{max}) of 1-3 hours.[29] It has a mean plasma half-life of 12-17 hours, which is independent of the dose.[21,29,30] Thirty-five percent of dabigatran is bound to plasma proteins, and 80% is excreted unchanged by the kidneys.[21,29] Patients with compromised renal function (creatinine clearance $<$ 50 mL per minute) have lower excretion rates, elevated plasma concentrations and require dose reduction.[31] Dabigatran is dialyzable.

Neither dabigatran etexilate nor dabigatran itself inhibits cytochrome P450 (CYP) isoenzyme systems. These hepatic enzyme systems interact importantly with antifungal agents, statins and proton-pump inhibitors.

Edoxaban

Edoxaban is an orally active small molecule, which reversibly inhibits factor Xa that is bound within the

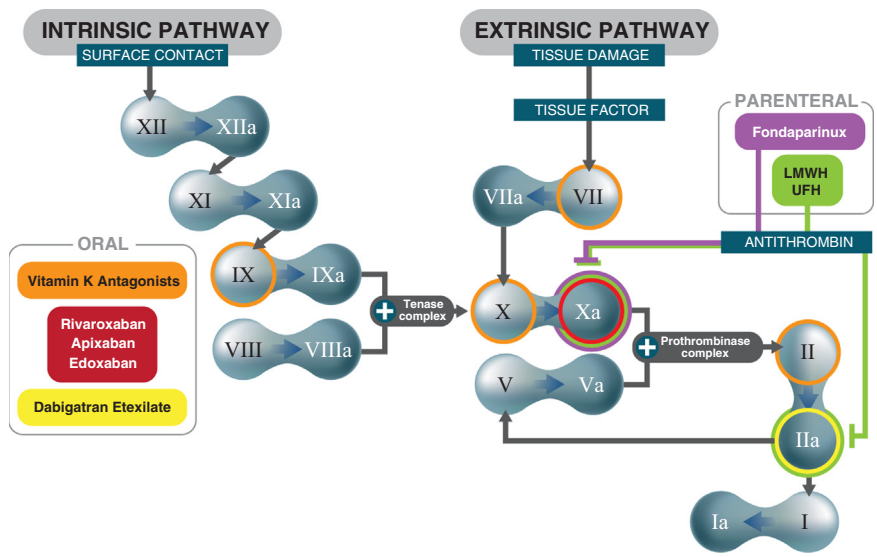

FIGURE 1. Schematic diagram of coagulation cascade and mechanism of action of anticoagulants. LMWH, low–molecular-weight heparin; UFH, unfractionated heparin.