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Anticoagulation in Pulmonary Embolism: Update in the Age of Direct Oral Anticoagulants

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The emergence of direct oral anticoagulants (DOACs) represents a major advancement and paradigm shift in the treatment of venous thromboembolism. Currently, dabigatran, rivaroxaban, apixiban, and edoxoban are approved and used routinely for the prevention and treatment of patients with venous thromboembolism. Because each of the DOACs has different doses and dosing regimens, clinicians need to become familiar with their use. This article focuses on the practical considerations of how and when to use the DOACs. It also aims to explore follow-up monitoring, use in special populations, reversal agents, periprocedural management, and how to handle bleeding complications with the DOACs.
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Introduction

Venous thromboembolism (VTE) which includes deep vein thrombosis (DVT) and pulmonary embolism (PE) is a major cause of morbidity and mortality. Although the precise number of people affected by VTE is unknown, it is estimated that 1-2 people per 1000 suffer from a VTE each year in the United States.[1-3] A recent Italian study found that PE was identified in nearly 1 of every 6 patients hospitalized for a first episode of syncope.[4] Moreover, population studies show that the incidence of VTE will continue to rise over time.[3,5]

Up until this decade, the only Food and Drug Administration (FDA) approved oral anticoagulant for the treatment and prevention of VTE was the vitamin K antagonist (VKA), warfarin. However, there are many limitations with warfarin including delayed onset of action, narrow therapeutic window, numerous food and drug interactions, and an unpredictable dose response. Patients require regular monitoring and variable responses to dose adjustments place patients at increased risks of either recurrent VTE or bleeding.

The introduction of the direct oral anticoagulants (DOACS) has offered patients a warfarin alternative. Unlike warfarin, DOACs inhibit only 1 component in the coagulation cascade; dabigatran inhibits factor II (thrombin), and rivaroxaban, apixaban, and edoxaban inhibit factor Xa. The DOACs do not require routine monitoring for safety or efficacy making them more convenient for patients. They also have a rapid onset of action, short half-life, predictable pharmacokinetics and pharmacodynamics, fixed dosing, and few drug and food interactions. Moreover, DOACs have fewer bleeding complications when compared to warfarin in clinical trials.[6-10] These qualities make DOACs attractive anticoagulants and have started to enable providers to consider treating low-risk VTE patients in an outpatient setting.[11] With the development of these DOACs, however, it is imperative that clinicians become familiar with their nuances. The purpose of this article is to provide critical information and guidance on the practical management of DOACs for the treatment for VTE.

Historical Perspective of VTE Treatment

Before we begin the review of the DOACs in the management of DVT/PE, let us reflect on the initial discovery of

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and agents used for the treatment of thromboembolic disease. The first documented description and treatment for a DVT dates back to the middle ages, with a young male named Raoul who developed pain and swelling in his calf, which eventually progressed to leg ulcers.[12,13] The young man was advised to visit the tomb of Saint Louis in the church of Saint Denis and instructed to rub dust onto his ulcers which healed them. Subsequent discoveries and practice of therapies focused on what was believed to be the mechanism behind thrombus formation.[14,15] The idea that DVT was caused by the retention of evil humors was held until the end of the 19th century and led to the technique of bloodletting, often with leeches.[16] The popularity of bloodletting continued when it was believed that inflammation of the vein was the likely cause of DVT.

Eventually, in 1856, Rudolph Virchow described the consequences of a pulmonary embolus that migrated from the venous circulation, and this later formed what it known as Virchow's triad.[17] The triad of venous stasis, endothelial injury, and hypercoagulability was then widely accepted as a model for understanding the pathophysiology of thrombosis. With this acceptance, a number of new therapies were discovered, mostly by accident. Heparin was the first parenteral anticoagulant discovered by a second year medical student, Jay McClean, at Johns Hopkins University when he isolated a fat-soluble phosphatide anticoagulant in canine liver tissue.[18] Shortly after in 1954, warfarin, originally synthesized from spoiled sweet clover plants that caused spontaneous fatal bleeding in cattle and initially used as a rodenticide, was adopted to allow for extended treatment for DVT.[19] Notably, when President Eisenhower suffered a myocardial infarction, he was treated with warfarin. Low-molecular-weight heparin (LMWH) was the third agent discovered in 1976 and was unique in the management of VTE since it was given subcutaneously, rapidly achieved anticoagulation effect, did not require monitoring and could be used short term to bridge to warfarin or used as monotherapy.[20] LMWH not only changed the management of DVT/PE by reducing the need for hospitalization but also has been effective in the prevention of thromboembolic events in surgeries, medically ill hospitalized patients, and the cancer population. The synthetic pentasaccharide, Fondaparinux sodium was then approved in 2001 to treat DVT and PE. It was not until a decade later that the DOACs followed.

Overview of DOACs

The 4 DOACs that have emerged in the management of VTE over the past decade gained approval from the FDA after demonstrating noninferiority to warfarin in regards to the prevention and treatment of VTE.[6-10] Rivaroxaban, apixaban, and edoxaban are factor Xa inhibitor whereas dabigatran is a factor II or thrombin inhibitor. Because these new agents have a number of advantages over the older anticoagulants and the fact that they do not require routine monitoring for safety or efficacy make them more convenient for patients. According to the most recent CHEST guidelines, in patients with DVT of the leg or PE and no evidence of cancer, anticoagulation therapy with dabigatran, rivaroxaban, apixaban, or edoxaban is suggested over VKA therapy as long-term (grade 2B).[21]

It is often difficult to decide which anticoagulant to use when treating a patient with DVT or PE. This decision ultimately depends on a variety of factors including patient-related factors (comorbidities, bleeding risks, adherence behaviors, preferences, medications, and weight) as well as medication-related factors (properties of the drugs and potential drug-drug interactions) and procedures available and deemed necessary. An additional deciding factor and one that is often the most influential is what medication is covered by the patient's insurance. The treatment strategy for VTE is frequently divided into 3 phases as follows: acute (the first 5-10 days), short-term (3-6 months), and long-term (>6 months). During the acute setting, anticoagulation options include unfractionated heparin (UFH), LMWH, fondaparinux, rivaroxaban, or apixaban. Dabigatran and edoxaban are effective treatments as well, but both require 5-10 days of an initial parenteral anticoagulant and are currently not approved for stand-alone therapy intially.[27,28] The length of anticoagulation then depends on the presence or resolution of thrombotic risk factors.[21] For patients in whom a transient risk has resolved, short-term (eg, 3 months) therapy may be reasonable. Alternatively, for patients with an unprovoked VTE, long-term or even lifelong anticoagulation may be warranted.[21,22]

A Detailed Look at the DOACs

The DOACs, dabigatran (a direct thrombin inhibitor) and apixaban, rivaroxaban, and edoxaban (direct factor Xa inhibitors), are FDA approved in the United States and elsewhere for prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation, treatment and secondary prevention of VTE, and prevention of VTE after major orthopedic surgery. In this section the pharmacology of DOACs, drug interactions, dosing schedules, laboratory monitoring, and indication in VTE are reviewed.

Pharmacology DOACs

The pharmacologic profile of the DOACS is summarized in Table 1.[23-27] These medications share similar properties, such as rapid onset of action, hepatic metabolism through interactions with the CYP-450 system and/or P-glycoprotein pathway, and renal excretion.

Dabigatran Etexilate (Direct Thrombin Inhibitor)

Dabigatran etexilate is a direct thrombin inhibitor that is converted to the active form dabigatran by esterase catalyzed hydrolysis in plasma and is independent of the cytochrome CYP-450 but is metabolized by P-glycoprotein system.[28] It is administered orally as a fixed dose twice daily. It is not protein bound and therefore can be