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Subject Review

Emergent Bleeding in Patients Receiving Direct Oral Anticoagulants

Richard L. Summers, MD *, Sarah A. Sterling, MD

Department of Emergency Medicine, University of Mississippi Medical Center, Jackson, MS, USA

A B S T R A C T

Direct oral anticoagulants (DOACs) offer clinical advantages over warfarin, such as minimal medication and food interactions and fixed dosing without the need for routine monitoring of coagulation status. As with all anticoagulants, bleeding, either spontaneous or provoked, is the most common complication. The long-term use of these drugs is increasing, and there is a crucial need for emergency medicine service professionals to understand the optimal management of associated bleeding. This review aims to describe the indications and pharmacokinetics of available DOACs; to discuss the risk of bleeding; to provide a treatment algorithm to manage DOAC-associated emergency bleeding; and to discuss future directions in bleeding management, including the role of specific reversal agents, such as the recently approved idarucizumab for reversal of the direct thrombin inhibitor dabigatran. Because air medical personnel are increasingly likely to encounter patients receiving DOACs, it is important that they have an understanding of how to manage patients with emergent bleeding.

Oral anticoagulants are available for the prophylaxis and treatment of thromboembolic disease, including the acute treatment and secondary prophylaxis for venous thromboembolisms (VTEs) and the risk reduction of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (NVAF). They include the well-established vitamin K antagonist (VKA), warfarin, and newer agents such as direct thrombin inhibitor, dabigatran etexilate, and the direct factor Xa inhibitors rivaroxaban, apixaban, and edoxaban.[1-4] These newer classes of drugs are known as direct oral anticoagulants (DOACs) because their mechanisms of action involve direct inhibition of specific serine proteases in the coagulation cascade, whereas VKAs indirectly inhibit several steps in the cascade. DOACs offer clinical advantages over warfarin.[5,6] These include predictable pharmacokinetic and pharmacodynamic effects, minimal medication and food interactions, and fixed dosing without the need for routine laboratory monitoring of coagulation status. DOACs provide antithrombotic efficacy comparable with dose-adjusted warfarin for most indications tested; in phase III randomized clinical trials in patients with NVAF, treatment with DOACs was as effective as or better than warfarin in reducing the risk for stroke.[7-10] Similarly, phase III trials with DOACs in patients with VTE showed noninferiority to warfarin for the recurrence of VTE or related death.[11-14] DOACs have also been associated with a lower risk for devastating intracranial hemorrhage (ICH) than adjusted-dose warfarin in patients with NVAF.[5] However, as with all anticoagulants, bleeding, either spontaneous or provoked, is the most common complication.[15]

The long-term use of oral anticoagulants (warfarin and DOACs) is widespread and increasing. The most recently published data suggest that there are > 30 million prescriptions for warfarin annually in the United States.[16] Since their introduction, DOACs have been steadily taken up by physicians and patients—either newly diagnosed or long-time warfarin users.[17] Dabigatran etexilate was the first DOAC approved in the United States in October 2010, and by late 2011, it accounted for nearly 17% of oral anticoagulant prescriptions in patients with atrial fibrillation in a national database.[17] These data suggest that air medical personnel are increasingly likely to encounter a significant fraction of patients taking oral anticoagulants, including DOACs.[18] This is likely to apply to both trauma and nontrauma patients. For example, significant increases in the portion of patients on chronic warfarin were observed in a retrospective cohort analysis of > 1.2 million patients admitted to 402 trauma centers, with the proportion increasing from 2.3% in 2002 to 4.0% in 2006 ($P < .001$). This increase was especially apparent in patients > 65 years of age (7.3%-12.8%, $P < .001$).[19] National adverse event (AE) data between 2007 and 2009 also found that warfarin (alone or in combination) was implicated in one third of emergency hospitalizations for drug-related AEs in older adults.[20]

* Address for correspondence: *Richard L. Summers, MD, Department of Emergency Medicine, University of Mississippi Medical Center, 2500 North State Street, Jackson, MS 39216.*

E-mail address: rsummers@umc.edu (R.L. Summers).

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Table 1
Indications for Available DOACs[1-4]

	Dabigatran Etexilate	Edoxaban	Rivaroxaban	Apixaban
Approved indication				
Reduce the risk of stroke and systemic embolism in patients with NVAF	✓	✓	✓	✓
Treatment of DVT and PE	✓	✓	✓	✓
Reduce the risk of recurrence of DVT and PE	✓		✓	✓
Prophylaxis of DVT, which may lead to PE in patients undergoing knee or hip replacement surgery	✓ (hip only)		✓	✓

AF = atrial fibrillation; DOAC = direct oral anticoagulant; DVT = deep vein thrombosis; NVAF = nonvalvular atrial fibrillation; PE = pulmonary embolism.

Therefore, it is crucial that emergency medicine service (EMS) professionals have a clear understanding of DOACs and the optimal management of associated bleeding. Warfarin has been the standard of care in oral anticoagulation for many years, and its bleeding risks are well-known. Supportive measures for a hemorrhaging patient include intravenous (IV) fluids to maintain volume, packed red blood cells, and fresh frozen plasma. Although no reversal agent for warfarin is available, vitamin K and prothrombin complex concentrates (PCCs, including 4-factor PCC[21]) may be administered to restore coagulation. However, PCCs may increase the risk for prothrombotic events.[21] For patients receiving DOAC therapy, there have been concerns among physicians with regard to the management of serious bleeds, as highlighted by published case reports in the literature.[22-26]

This review is for air medical personnel and aims to describe available DOACs, including their indications and pharmacokinetics; to discuss the risk of bleeding associated with different DOACs; to provide a treatment algorithm to manage DOAC-associated emergency bleeding; and to discuss future directions in the emergency management of DOAC-associated bleeding, including the potential role of DOAC-specific reversal agents.

General Overview of Oral Anticoagulants

Indications for Oral Anticoagulants

The direct thrombin inhibitor dabigatran and the factor Xa inhibitors apixaban, edoxaban, and rivaroxaban are indicated for the following: risk reduction of stroke and systemic embolism in patients with NVAF (dabigatran, apixaban, edoxaban, and rivaroxaban); treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) (rivaroxaban and apixaban); treatment of DVT and PE after parenteral anticoagulant therapy for 5 to 10 days (dabigatran and edoxaban); risk reduction of recurrence of DVT and PE (apixaban, dabigatran, and rivaroxaban); and prophylaxis of DVT, which may lead to PE in patients undergoing hip replacement surgery (dabigatran) or knee or hip surgery (apixaban and rivaroxaban) (Table 1).[1-4] Warfarin is indicated for the prophylaxis and treatment of DVT and PE; risk reduction of thromboembolic complications associated with NVAF and/or cardiac valve replacement; and to reduce the risk of death, recurrent myocardial infarction, and thromboembolic events after myocardial infarction.[27]

Characteristics of DOACs

DOACs all have predictable, dose-dependent pharmacokinetics/pharmacodynamics, and so, unlike warfarin, they do not require routine monitoring of their anticoagulant activity.[28] DOACs also have a shorter half-life, resulting in a quicker “offset time” and quicker time to maximum effect than warfarin (Table 2).

After oral administration, dabigatran etexilate is rapidly metabolized to dabigatran, which reversibly inhibits both free and clot-bound thrombin through interaction with its active site.[1,29] Both peak plasma dabigatran levels and its peak effect on coagulation parameters are achieved within 2 hours, and it has a half-life of 12 to 17 hours.[29] Dabigatran is excreted predominantly by the kidneys, with more than 80% of systemically available dabigatran eliminated via urine.[30] As a result, exposure to dabigatran increases, and half-life is prolonged with worsening renal function, with an approximately 3-fold increase in dabigatran exposure and a 1.5-fold increase in half-life with moderate impairment.[1,31]

Rivaroxaban selectively and competitively inhibits free and prothrombinase/clot-associated factor Xa through reversible interactions with its active site. It achieves peak plasma levels 3 to 4 hours after oral administration, with maximum prolongation of coagulation tests reached 1 to 4 hours after administration.[2,32] It has a half-life of 6 to 9 hours and is partially excreted by the kidneys (66%).[2,32,33]

Apixaban is an oral, reversible, direct active site inhibitor of free and clot-bound factor Xa.[3,34] It achieves peak plasma levels within 3 to 4 hours after oral administration and maximum increases in clotting times at 3 hours.[35] Apixaban has a half-life of 8 to 15 hours and is partially excreted by the kidneys (25%-29%).[34,35] For edoxaban, plasma levels peak in 1 to 2 hours, with maximum activated partial thromboplastin time (aPTT) occurring 1 to 3 hours after administration.[4,36] The drug is partially excreted by the kidneys (35%) and has a half-life of 6 to 11 hours.[4,36,37]

Bleeding Risks

The following factors have been identified as increasing the risk of bleeding in patients receiving oral anticoagulants: intensity of anticoagulation, increasing age, genetic factors affecting VKA metabolism and antithrombotic effect, prior stroke, history of bleeding, anemia, comorbidity (hypertension, renal insufficiency, and liver disease), and use of concomitant medication (eg, antiplatelet drugs or nonsteroidal anti-inflammatory agents) or alcohol.[38]

Bleeding Risks Associated With DOACs

As with all anticoagulant agents, treatment with DOACs is associated with a risk of bleeding, either spontaneously or as a result of trauma. Potential for uncontrolled bleeding may also force delays in urgent surgery or invasive procedures until a patient is satisfactorily coagulated.

In clinical trials, the incidence of major bleeding or nonmajor, clinically relevant bleeding with DOACs was generally comparable with or lower than warfarin (depending on dose), and the incidence of ICH was lower than with warfarin.[7-10] The variability observed across clinical trials is likely caused by differences in patient characteristics and indication as well as drug dosage and the duration of treatment. Nonetheless, DOACs are associated with ~50% less intracranial bleeding than VKAs.[39]

Studies using aggregated data have shown a decreased or similar risk of major bleeding with DOACs versus VKAs depending on the indication and drug dosage. However, it should be noted that there are limitations with meta-analyses because of the heterogeneity of study populations, protocols, intervention, and follow-up between trials, with some of these differences (especially bleeding definitions) being difficult to control for.

In a meta-analysis of 19 trials (all VTE or AF trials except 1 knee surgery trial, N = 40,364), DOAC use was associated with