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Clinical Reviews

MANAGING BLEEDING IN ANTICOAGULATED PATIENTS IN THE EMERGENCY CARE SETTING

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☐ **Abstract—Background: Orally administered anticoagulants that offer alternatives to warfarin have been developed in recent years and are currently available for reduction of stroke risk in patients with non-valvular atrial fibrillation, the prophylaxis of venous thromboembolism after hip or knee replacement surgery, and the treatment and secondary risk reduction of deep vein thrombosis and pulmonary embolism. Objectives: This article will provide a brief introduction to these new oral anticoagulants and then review the approaches that can be taken for the emergency management of hemostasis in patients bleeding or at risk for bleeding while receiving warfarin or one of two newer agents, the direct thrombin inhibitor dabigatran or the factor Xa inhibitor rivaroxaban. Discussion: Oral anticoagulant use is widespread and likely to continue to increase. Warfarin has been the standard of care in oral anticoagulation for many years; its bleeding risks are well known and associated emergency protocols are well established. As newer oral anticoagulants become more widely used, similar procedures will need to be developed. Although there are as yet no specific reversal agents for these newer drugs, recommendations for overdose, emergency hemostasis, and preoperative management are available. Further, while the newer agents do not require routine coagulation monitoring, assays for use in non-routine situations are being explored. Conclusions: The introduction of alternative oral anticoagulants will require emergency procedures that differ in some respects from those currently in place for warfarin and it will be necessary for Emergency Medicine professionals to become familiar with these procedures. Clinical stabilization of the bleeding or at-risk patient remains the emergency physician's priority.** © **2013 Elsevier Inc.**

☐ **Keywords—anticoagulant; dabigatran; rivaroxaban; bleeding; antidote**

INTRODUCTION

To achieve and preserve physiologic hemostasis, it is critical to establish a balance between clotting and bleeding; to this end, a precisely regulated cascade of reactions is responsible for maintaining hemostasis in healthy individuals (1,2). Certain disease states, however, such as non-valvular atrial fibrillation (NVAF), some physiologic insults such as injury and surgery, and a number of inherited and acquired risk factors may be associated with an increased propensity for thrombotic events. In many cases these have severe consequences, and anticoagulation therapy—unless otherwise contraindicated—is warranted to prevent them (3,4). Such regimens must strike a careful balance between preventing thrombotic events and increasing the risk of bleeding. For warfarin—the most widely used oral anticoagulant (OAC) for decades—balance is sought by attempting to maintain the patient within a narrow therapeutic window of international normalized ratio (INR) values, usually ranging from 2.0 to 3.0 (5,6).

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Warfarin is a coumarin-derived OAC that interferes with the coagulation cascade by inhibiting the vitamin K epoxide reductase subunit C1, thereby preventing the reduction of oxidized vitamin K that is required for the γ-carboxylation of factors II, VII, IX, and X, which is necessary for efficient coagulation (7,8). Warfarin is indicated for the prophylaxis and treatment of venous thrombosis such as deep vein thrombosis and pulmonary embolism; reduction of the risk of thromboembolic complications associated with NVAF and cardiac valve replacement; and also to reduce the risk of death, recurrent myocardial infarction, and thromboembolic events such as stroke or systemic embolization after myocardial infarction.

Despite its perennial ranking among the top five drugs with serious adverse events reported to the United States (US) Food and Drug Administration (FDA), warfarin use remains extensive. It is the most widely prescribed OAC in North America, with more than 30 million prescriptions annually (9,10). There are sound data that support this level of use, in both prevention and treatment of venous thromboembolism and in stroke prevention in patients with atrial fibrillation (11–13). Consequently, in a recent study it was found that the number of outpatient prescriptions for warfarin increased by 45%, from an estimated 21 million prescriptions dispensed in the US in 1998 to nearly 31 million in 2004 (10).

As warfarin use is so widespread, it is reasonable to expect that a significant fraction of patients seeking care in an Emergency Department (ED) will have been taking this agent. In fact, a retrospective cohort analysis of over 1.2 million patients admitted to 402 trauma centers reported that warfarin use increased significantly from 2002 to 2006 among all patients (2.3% vs. 4.0%) and among patients over 65 years (7.3% vs. 12.8%) ($p < 0.001$ for both) (14). Further, an analysis of national adverse event data has shown that warfarin, either alone or in combination, was implicated in one-third of emergency hospitalizations for drug-related adverse events in older adults between 2007 and 2009 (15).

In October 2010, the FDA approved the oral, direct thrombin inhibitor, dabigatran etexilate (Pradaxa®; referred to here as dabigatran; Boehringer-Ingelheim, Ridgefield, CT), for reduction of the risk of stroke and systemic embolism in patients with NVAF, and it has now been included in major clinical guidelines for the treatment of NVAF (6,16–18). A recent analysis of a national prescription database has shown that by late 2011, dabigatran accounted for almost 17% of OAC prescriptions in patients with AF in the US (19). Dabigatran does not require routine coagulation monitoring. Although in certain circumstances, activated partial thromboplastin time (aPTT), thrombin clotting time (TT), or ecarin clotting time (ECT) could be used to assess degree of anticoagulation, none of these assays are recommended for routine monitoring of dabigatran use. Dabigatran has a predictable pharmacokinetic profile and pharmacodynamics; it is not metabolized by cytochrome P450 isoenzymes, has a low potential for drug–drug interactions, and no clinically meaningful interactions with food (20).

The orally active direct factor Xa (FXa) inhibitor rivaroxaban was approved by the FDA in November 2011 for reduction of the risk of stroke and systemic embolism in patients with NVAF, and it is also approved for the prevention of venous thromboembolism in adult patients undergoing elective hip or knee replacement surgery, and for the treatment and secondary risk reduction of deep vein thrombosis and pulmonary embolism (21,22). The orally active direct FXa inhibitor apixaban has now also been approved by the FDA for reduction of the risk of stroke and systemic embolism in patients with NVAF (23,24). These oral FXa inhibitors also do not require routine dose monitoring and have relatively predictable pharmacologic properties. As the uptake of dabigatran, rivaroxaban, and apixaban is likely to grow, patients who seek emergency care are increasingly likely to have been prescribed one of these newer oral anticoagulants.

The objective in treating patients with OACs is to reduce the risk of thromboembolic events, such as ischemic stroke. However, anticoagulation places the patient at increased risk of bleeding. In the ED, treatment of bleeding events in patients taking OACs requires action to control bleeding; if possible, reversal of the anticoagulant effect of the drug while bleeding is controlled, and physiologic and other support during these processes. If a patient on an OAC requires an urgent invasive or surgical procedure, the bleeding risks related to their OAC therapy will need to be considered and appropriate steps taken to reduce this risk. Compared with warfarin, experience and data for management of the newer agents in emergency situations are as yet relatively limited, a situation that will likely change and emergency protocols evolve more fully with time. This article will review methods for managing bleeding in the emergency care setting for warfarin and the two currently available newer oral agents, dabigatran and rivaroxaban.

DISCUSSION

What Options are Available for Managing Bleeding in Patients Anticoagulated with Warfarin in the Emergency Department?

Patients treated with warfarin may present to the ED as a direct result of their treatment, requiring emergency