REVIEW

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Re-Initiation of Dabigatran and Direct Factor Xa Antagonists After a Major Bleed

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ABSTRACT

Direct oral anticoagulants (DOACs) are a relatively recent addition to the oral anticoagulant armamentarium, and provide an alternative to the use of vitamin K antagonists such as warfarin. Regardless of the type of agent used, bleeding is the major complication of anticoagulant therapy. The decision to restart oral anticoagulation following a major hemorrhage in a previously anticoagulated patient is supported largely by retrospective studies rather than randomized clinical trials (mostly with vitamin K antagonists), and remains an issue of individualized clinical assessment: the patient's risk of thromboembolism must be balanced with the risk of recurrent major bleeding. This review provides guidance for clinicians regarding if and when a patient should be re-initiated on DOAC therapy following a major hemorrhage, based on the existing evidence.

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The incidence rates of atrial fibrillation (AF) in North America were estimated at 264 per 100,000 person-years for men and 196 per 100,000 person-years for women in 2010,[1] and approximately 76 million prescriptions for oral anticoagulant (OAC) therapy for all indications were dispensed in the United States during 2013.[2] Yet OACs are underused in many patients with AF, and an elevated risk of stroke,[3] contrary to the recommendations of multiple current guidelines,[4-6] with rates of OAC prescribing in appropriately risk-stratified patients ranging from 40% to 60%.[7,8] The most common complication of OAC therapy is gastrointestinal (GI) bleeding, but the main cause of bleeding-related morbidity and mortality is intracranial hemorrhage (ICH).[9-11] Physicians consistently underestimate the risk of stroke in patients with AF and overestimate the risk of hemorrhage with OAC therapy, leading to undertreatment, despite evidence of the benefits of OACs.[8,12] This bias is exacerbated once a patient suffers a major hemorrhage while receiving OAC therapy, particularly for clinicians involved in the acute care of these episodes, as the bleeding is apparent and dramatic, while the stroke that may be prevented by OAC therapy is not. Although often counterintuitive, restarting OACs after OAC-associated major hemorrhage is usually appropriate; however, the main issue concerns the timing of the restart. Evidence-based data from prospective, randomized, controlled clinical trials to address this question are needed, particularly in direct oral anticoagulant (DOAC)-treated patients but are unavailable at present.

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There are multiple definitions for assessing the severity of bleeding episodes. Major hemorrhage is defined by the International Society on Thrombosis and Haemostasis as fatal bleeding, or symptomatic bleeding in a critical area or organ, or bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L or 2 g/dL) or more, or leading to transfusion of ≥2 units of whole blood or red cells.[13] Consequently, patients enrolled into studies of OAC-associated International Society on Thrombosis and Haemostasis-defined major bleeding consist of a heterogeneous population arising from different clinical specialties, which compounds the difficulties of studying these scenarios. Estimates of the risk of major hemorrhage related to OAC range from 2% to 3% in clinical trials to approximately 1% to 7% in population cohort studies.[10,11,14] The exact incidence of major hemorrhage is unknown because of uncertainty regarding the intensity of OAC therapy, and patient-related factors such as history of bleeding, concomitant disease, alcohol use, age, and risk of falls.[10] Regarding types of major hemorrhage related to OAC, the largest amount of published data is for ICH and GI bleeding, and this review will focus on these 2 clinical entities. Recommendations for restarting OAC therapy in other major bleeding situations, which are relatively rare, will remain as risk−benefit decisions for the individual clinician and patient.

For many decades, OAC therapy consisted of vitamin K antagonists (VKAs), typically warfarin in the United States, although other VKAs (eg, phenprocoumon and acenocoumarol) are used in other geographical areas. VKAs act by blocking vitamin K epoxide reductase to inhibit the activation of clotting factors (F) II, VII, IX, and X, and natural anticoagulant proteins C and S. However, in recent years, small-molecule DOACs have become available, the first of which was the direct thrombin inhibitor, dabigatran, which gained U.S. Food and Drug Administration approval in 2010 for the risk reduction of stroke and systemic embolism in patients with nonvalvular AF (NVAF). This was quickly followed by the arrival of drugs that directly inhibit FXa (apixaban, rivaroxaban, and edoxaban), which is 1 step proximal to the action of direct FIIa inhibitors such as dabigatran in the clotting cascade. Data from phase 3 clinical trials in patients with NVAF demonstrated that these 4 DOACs were either noninferior or superior to warfarin in terms of efficacy (ie, reducing the rates of stroke and systemic embolism),[15-18] and showed equivalence or improved safety (ie, major hemorrhage and clinically relevant nonmajor hemorrhage) vs warfarin.[15-18] DOACs were associated with an approximately 30%-70% reduction in the rates of ICH vs warfarin,[15-18] although they were associated with generally higher rates of GI bleeding (not further defined; annualized rate ranged from approximately 0.8% to 3.2% for DOACs [depending on the agent and dose] vs approximately 1.0% to 2.2% for warfarin).[15,16,18] DOACs are also approved for the treatment and prevention of venous thromboembolism (VTE), for which they were noninferior to conventional therapy in terms of efficacy outcomes, and showed equivalence or improvement in the overall safety profile.[19-22]

To date, comparatively few data have been published on restarting OAC therapy after a major hemorrhage and the data that do exist are almost exclusively from patients receiving VKAs, with very few data concerning DOACs. Furthermore, some expert opinion recommends approaching the re-initiation of DOACs similarly to restart scenarios with warfarin.[23] This is reflected in the discussion below. This review aims to summarize the key evidence and provide guidance for clinicians regarding if and when a patient should be restarted on DOAC therapy following a major hemorrhage.

INTRACRANIAL HEMORRHAGE AND RE-INITIATION OF OACS

Intracranial hemorrhage has a heterogeneous etiology, including spontaneous ICH (eg, lobar and deep hemispheric hemorrhages, aneurismal subarachnoid hemorrhages, and bleeding arteriovenous malformations) and traumatic ICH (eg, extra-axial subdural, epidural hematomas, traumatic subarachnoid hemorrhages, and intra-axial hemorrhagic contusions). The risk of ICH recurrence can be related to etiologic factors. For example, superficial (lobar) hemorrhages are often caused by cerebral amyloid angiopathy, a condition that affects cerebral arteries and arterioles and increases the risk of hemorrhage, and is associated with recurrence rates of up to 22%.[24] The incidence of nontraumatic ICH is approximately 25 per 100,000 person-years.[25] It has been estimated that there are approximately 67,000 cases of spontaneous ICH per year in the United States,[26] and anticoagulant-associated ICH accounts for nearly 20% of those.[26] The 30-day case fatality rate is as high as 50%, and most survivors are left with some degree of disability, which is often severe.[26]

In cases of OAC-related ICH, the therapeutic dilemma is that stopping anticoagulation increases the risk of cerebral ischemia, while continuing or restarting treatment after stopping it increases the risk of recurrent bleeding.[24] This has been referred to as "steering between Scylla and Charybdis," meaning to have to choose between 2 evils.[24] The published reports described below are all retrospective analyses of OAC-related ICH, with varying patient populations (eg, some studies focus on patients with NVAF or patients with mechanical heart valves, while other studies include patients treated for VTE). It should be noted that DOACs are not approved for use in patients with mechanical heart valves.

A recent report from a German multicenter, retrospective study (2006-2012) assessed the effects of OAC resumption in patients with anticoagulation-related (VKAs) spontaneous ICH.[27] Of the 1176 patients with data available, 719 patients were part of the OAC resumption analysis (the remainder were analyzed for hematoma enlargement [n = 853] or long-term outcomes [n = 1083]). OAC was restarted in 172 of 719 (23.9%) patients (including 34/50 [68.0%] with mechanical heart valves, and 110/566 [19.4%] with AF).[27] Median time to OAC resumption was 31 days