Optimal Reversal of Novel Anticoagulants in Trauma

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KEYWORDS

• Novel anticoagulants • NOACs • Coagulopathy of trauma • Reversal agents
• Anticoagulants in trauma

KEY POINTS

- Patients are increasingly using novel oral anticoagulants such as dabigatran, rivaroxaban, apixaban, and edoxaban for both the prophylaxis and treatment of a wide spectrum of diseases, including atrial fibrillation, stroke, myocardial infarction, valvular disease, deep venous thrombosis, and pulmonary embolism.
- Urgent or immediate reversal of anticoagulants in patients with trauma with major or critical bleeding can predispose to catastrophic thrombotic complications such as stroke, myocardial infarction, and pulmonary embolism. The risk versus benefit balance of reversal should therefore be individualized and based on the severity of the hemorrhage or need to perform an emergent procedure and the patient's underlying thromboembolic risk.
- Target-specific antidotes are currently being evaluated, and some just recently approved, for the reversal of these novel oral anticoagulants. Meanwhile, evidence supporting advanced therapies such as antifibrinolytics, prothrombin complex concentrates, and these new target-specific antidotes is largely limited to healthy human volunteers, animal models, and in vitro studies.
- It is important to address resumption of anticoagulation before patient discharge so as not to expose the patient to an extended period of thromboembolic risk after traumatic bleeding has been stopped.

INTRODUCTION

Trauma is the third leading cause of death in the United States and accounts for 30% of all life-years lost.[1] Recent trends suggest that trauma centers are seeing an increasing number of severely injured elderly patients. Falls, head injuries, and

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hemorrhagic complications account for a substantial proportion of these fatalities.[2] Coagulopathy and associated bleeding have always beset patients with trauma, but in the elderly trauma population the incidence of pharmacologically induced coagulopathy poses a new and substantial risk for worsening hemorrhage.

Anticoagulants have long been the mainstay of therapy for the acute and long-term prevention or treatment of numerous thromboembolic disorders. For years, warfarin (vitamin K antagonist [VKA]) was the only available oral anticoagulant. Its usage was often plagued by unpredictable pharmacokinetics, narrow therapeutic windows, multiple food and medication interactions, need for frequent monitoring, and a high complication rate. In North Americans taking warfarin for atrial fibrillation who present to an emergency department, only about 59% are in the therapeutic range.[3]

Over the last decade, the pharmaceutical industry has focused on developing novel oral anticoagulants (NOACs) by means of direct thrombin or factor Xa inhibitors for patients requiring treatment or prevention of thromboembolic disorders. These novel direct and indirect inhibitors of coagulation are being increasingly used for both the prophylaxis and treatment of a wide spectrum of diseases: atrial fibrillation, stroke, myocardial infarction, valvular disease, deep venous thrombosis, and pulmonary embolism (**Table 1**).

Compared with warfarin, these NOACs have far more reliable pharmacokinetics, an ability to quickly achieve therapeutic levels in the blood stream, reliable drug elimination rates, and are largely unaffected by food or other medications. NOAC efficacy has been best studied in the setting of atrial fibrillation. A large systematic review and meta-analysis of 44,563 patients across 3 randomized controlled trials (RCTs) that compared NOACs (dabigatran, rivaroxaban, or apixaban) with warfarin in patients with atrial fibrillation reported a decreased risk of all-cause stroke and systemic embolism, ischemic stroke, hemorrhagic stroke, all-cause mortality, and vascular mortality with NOAC use.[4]

Patients and clinicians alike must be cognizant of the NOACs' adverse effects as well. Individual results from these 3 large RCTs (RE-LY,[5] ROCKET-AF,[6] ARISTOTLE[7]) documented that the rates of major bleeding in patients receiving NOACs were 2.13% to 3.6% per year versus 3.09% to 3.4% in those taking warfarin. Similarly, rates of hemorrhagic stroke were lower for NOACs (NOACs 0.1%–0.5% vs warfarin 0.38%–0.70%). Both the incidence and outcomes of NOAC-associated bleeding seem favorable compared with warfarin.

A recent meta-analysis of 13 RCTs, which included 102,707 patients being treated with a NOAC or warfarin for atrial fibrillation or venous thromboembolism,[8] confirmed a reduced mortality for major bleeding in patients on NOACs (7.6% NOAC vs 11% warfarin). Additional analysis favored NOACs, compared with warfarin, with reductions in the relative risk (RR) of fatal bleeding (RR, 0.53; 95% confidence interval [CI], 0.43–0.64), cardiovascular mortality (RR, 0.88; 95% CI, 0.82–0.94), and all-cause mortality (RR, 0.91; 95% CI, 0.87–0.96).

Albeit justified, the initial high enthusiasm for these NOACs must be tempered by 3 notable concerns: there is often no readily available means for assessing the degree of pharmacologic coagulopathy in patients on these agents, the optimal reversal strategy for many of these NOACs is still in development, and there is a threat of life-threatening bleeding complications after any injury in patients taking these new agents. Therefore, it is important to have clarity for optimal reversal strategies and proper management when treating critically ill patients with trauma on NOACs.

PATIENT EVALUATION OVERVIEW

The initial evaluation and management of critically ill patients with trauma must always include the establishment of an effective airway, rapid and continuous hemodynamic