Introduction

Spontaneous intracerebral hemorrhage (ICH) is a major cause of morbidity and mortality worldwide [1]. Of a number of factors that have been linked to ICH (e.g., higher rates in Asians and African Americans, illicit drug use such as cocaine, cigarette smoking, heavy alcohol consumption, antithrombotic medication, cerebral microbleeds, and others) [2], two factors stand out that are frequently conjoint—oral anticoagulant use and hypertension [3]. In this NSA clinical update we discuss contemporary management of bleeding in patients on oral anticoagulant therapy (OAT) and promising new therapies under study. Before we discuss reversal and management of OAT-associated bleeding, we review recent recommendations for management of blood pressure (BP) in acute ICH.

Blood Pressure

American Heart Association/American Stroke Association (AHA/ASA) 2015 evidence-based guidelines recommend the following for ICH patients presenting with systolic BP (SBP) between 150-220 mm Hg and no contraindication to acute BP reduction: acute lowering of SBP to 140 mm Hg is a safe strategy (Class I, level of evidence [LOE] A) and possibly improves functional outcome (Class IIa, LOE B) [1]. For patients with SBP>220 mm Hg, it is reasonable to reduce BP with a continuous intravenous infusion therapy (Class IIb, LOE C) [1].

Warfarin

For patients taking vitamin K antagonists (VKAs) such as warfarin, rapid correct of the international normalized ratio (INR) is recommended [1]. Although administration of intravenous vitamin K (5-10 mg) alone is insufficient for reversal of VKAs early on, it remains part of the acute VKA reversal management plan (Class I, LOE C) [1]. Severe factor deficiency or severe thrombocytopenia should be replaced (Class I, LOE C). The usefulness of platelet transfusion in ICH when there is a history of antiplatelet administration remains uncertain (Class IIb, LOE C) [1].

Over the years, fresh frozen plasma (FFP) has been a mainstay of management for OAT-associated hemorrhage [1]. Prothrombin complex concentrates (PCCs), activated PCC FEIBA (factor VIII inhibitor bypassing activity), and factor VIIa (rFVIIa), however, have emerged as possible preferential reversal therapies [1]. PCCs correct the INR more quickly and are associated with fewer complications, and now are considered more favorably than FFP (Class IIb, LOE B). PCCs include both 3- (factors II, IX and X) and 4-factor (factors II, IX, X and VII such as FEIBA and Kcentra) types. On the other hand, rFVIIa is not recommended for VKA reversal in ICH as clotting may not be effectively restored as all key clotting factors are not replaced with this agent (Class III, LOE C) [1]. Furthermore, although rFVIIa may limit ICH expansion, it is not associated with improved survival or functional outcome and may increase in risk of arterial adverse events.

Non-Vitamin K Antagonist Oral Anticoagulants (NOACs)

A new category of oral anticoagulants is now available—NOACs. This category of drugs includes 4 recently US Federal Drug Administration (FDA)-approved medications for the prevention of stroke and
systemic embolism in non-valvular atrial fibrillation (NVAF). The drugs can be grouped according to mechanism: dabigatran (trade name Pradaxa), a direct thrombin inhibitor; and apixaban (Eliquis), edoxaban (Savaysa), and rivaroxaban (Xarelto), factor Xa inhibitors. Up until recently, the NOACs had no specific US FDA-approved reversal agent. Therefore and according to past evidence-based guidance, when there was acute hemorrhage requiring reversal clinicians were to consider administration of FEIBA, other 3- or 4-factor PCCs, or rFVII. Furthermore, within 2 hours after ingestion of dabigatran, apixaban, edoxaban, and rivaroxaban, activated charcoal may be administered as a reversal strategy, and although there is limited experience, hemodialysis might be of benefit for reversal of dabigatran (Class IIb, LOE C) [1].

The US FDA now has approved a specific reversal agent for dabigatran, idarucizumab, and the other US FDA-approved NOACs have specific reversal agents in development. We now discuss these promising new therapies.

**Dabigatran: Reversal Effects of Idarucizumab on Active Dabigatran (REVERSE AD)**

Idarucizumab is a monoclonal antibody fragment that binds to dabigatran and has an affinity that is 350-fold greater than that observed with thrombin [4]. Idarucizumab works by binding both free and thrombin-bound dabigatran to neutralize dabigatran. In healthy young volunteers with normal renal function, in persons 65-80 years of age, and in persons 45-80 years of age with up to moderate renal dysfunction, idarucizumab was shown to immediately and completely reverse the anticoagulant effects of dabigatran and was not associated with pro-coagulant effects [5, 6].

The above findings led to a major prospective cohort study, REVERSE AD, to assess the safety of 5 grams of intravenous idarucizumab in patients who had serious bleeding or required an urgent procedure and needed reversal of dabigatran [7]. The primary endpoint was the percentage of reversal of the anticoagulant effect of idarucizumab within 4 hours after administration of the agent according to measurement of the following biomarkers: dilute thrombin time (dTT) or ecarin clotting time (ECT). A major secondary endpoint was restoration of hemostasis [7].

In the interim analysis, there were 51 patients enrolled with serious bleeding and 30 with an urgent procedure [7]. At baseline, 68 had an elevated dTT and 81 had an elevated ECT, with the median maximum percentage reversal being 100%. The biomarkers of interest normalized within minutes in 88% to 98% of the patients and provided a sustained correction of the hemostatic abnormality. Other key findings included: 1. Concentrations of unbound dabigatran remained below 20 ng/ml at 24 hours in 79%; 2. Hemostasis was restored at a median of 11.4 hours in 35 patients (69%) with serious bleeding; 3. 33 of 36 patients (92%) requiring a procedure had normal intraoperative hemostasis; and 4. Within 72 hours of reversal agent administration, there was only 1 thrombotic event in a patient who did not have reinstitution of anticoagulant medication [7].

Beyond the biomarker information, REVERSE AD captured select clinical outcome data, but as a single-arm study it was not designed to be a comparative study. There were 21 serious adverse events. In addition to 18 deaths, there were thrombotic events in 5 patients, gastrointestinal hemorrhage in 2, and wound infection, delirium, right heart failure, and pulmonary edema in one patient each [7].
Idarucizumab (trade name Praxbind) was approved by the US FDA for reversal of the anticoagulant effects of dabigatran in patients requiring emergency surgery/urgent procedures and in life-threatening or uncontrolled bleeding [8]. The initial US FDA approval of idarucizumab was based on reduction of unbound dabigatran and normalization of coagulation parameters in healthy persons.

**Reversal of Xa inhibitors**

Andexanet alfa is a factor Xa inhibitor antidote [9], not yet available for routine clinical use. It is a recombinant modified factor Xa molecule that acts as a factor Xa decoy and targets and sequesters with high specificity both direct and indirect factor Xa inhibitors in the blood. Andexanet alfa agents are being developed for reversal of the commercially available factor Xa inhibitors, apixaban, rivaroxaban and edoxaban [9-11]. In addition, there is another reversal agent, PER977 (aripazine or ciraparantag), which binds to the oral factor Xa inhibitors and has been tested as a reversal agent for edoxaban [12,13].

**Summary of Clinical Trial or Other Testing of Other Reversal Agents for Factor Xa Inhibitors**

**Apixaban.** Andexanet alfa has been tested for reversal of apixaban-induced anticoagulation in older healthy persons 50-75 years of age [11]. In the Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of FXA Inhibitors-Apixaban (ANNEXA-A) study, subjects received apixaban 5 mg twice daily for 3.5 days to achieve steady-state plasma levels. In the first part of the study, three hours after the last dose of apixaban on day 4, these participants received andexanet alpha 400 mg intravenous bolus (30 mg per minute). In the second part of this study, participants received andexanet alfa 400 mg intravenous bolus followed by a continuous infusion of 4 mg/min for 120 minutes. The percentage change in anti-factor Xa activity was the primary endpoint. The andexanet alfa bolus significantly and rapidly achieved anticoagulant activity reversal 94±2% [mean (± SD)]; p<0.001) which was sustained after completion of a 2-hour continuous infusion (97±2%; p<0.001) compared to placebo[11].

**Rivaroxaban.** In the ANNEXA-Rivaroxaban (ANNEXA-R) study, subjects were treated with rivaroxaban 20 mg once daily for 4 days. On day 4, at 4 hours after the last dose of rivaroxaban, an 800 mg intravenous bolus of andexanet alfa was administered or an 800 mg intravenous bolus followed by a continuous infusion of 8 mg/min for 120 minutes was utilized. The primary end point was the same as in ANNEXA-A. The andexanet alfa bolus significantly and rapidly achieved anticoagulant activity reversal (92±11 %; p<0.001) which was also sustained after completion of a 2-hour continuous infusion (97±2%; p<0.001) compared to placebo [11].

**Edoxaban.** PER977 (ciraparantag or aripazine) is a synthetic molecule that binds with factor Xa inhibitors [12]. After 60 mg of edoxaban in 80 healthy persons, a single intravenous dose of PER977 (5 to 300 mg) was studied in a double-blind, placebo-controlled trial [13]. Whole blood clotting time was a primary outcome. After a single intravenous dose of PER977 (100 to 300 mg) 3 hours after administration of edoxaban, whole blood clotting time decreased to within 10% above the baseline value in <= 10 minutes, whereas this was achieved in a much longer time frame in those receiving placebo (~12 to 15 hours) [13]. Potential adverse events included transient mild perioral and facial flushing and dysguesia; and moderate headache, and moderate muscle cramping with creatinine phosphokinase elevation, in one person each.
Conclusion

NOACs have become popular treatment options for prevention of stroke and systemic embolism in persons at risk who have NVAF. Some clinicians have hesitated to administer direct thrombin inhibitors and factor Xa inhibitors in NVAF in the absence of a specific reversal agent. Currently, one such agent, idarucizumab, is commercially available for reversal of dabigatran, and others as discussed in our update are being studied and currently are or will be evaluated by the US FDA for approval and use in practice. For additional information about reversal of antithrombotics in intracranial hemorrhage, the reader is referred to a recently published guideline from the Neurocritical Care Society and Society of Critical Care Medicine [14].

References