Shobana Rajan, M.D.  Staff Anesthesiologist, Cleveland Clinic, Cleveland, Ohio

Quiz team: Shaheen Shaikh, M.D; Suneeta Gollapudy, M.D; Verghese Cherian, M.D

This quiz is being published on behalf of the Education Committee of the SNACC.
1. A 67 year old man was on rivaroxaban for atrial fibrillation. One morning he sustained a fall in the bathroom and subsequently developed a headache. A CT scan was done which showed intra-cerebral bleed. What is the mechanism of action of rivaroxaban?

A. It is an inhibitor of factors II, VII, IX and X.
B. It is an inhibitor for factor Xa.
C. It inhibits conversion of plasminogen to plasmin.
D. It inhibits thrombin.
A. It is an inhibitor of factors II, VII, IX, and X

This is not correct.
Warfarin inhibits vitamin K-dependent γ-carboxylation of coagulation factors II, VII, IX, and X, reducing activity of clotting factors. The vitamin K antagonists are warfarin, acenocoumarol, phenprocoumon, dicoumarol, tecarfarin, and fluindione.
B. It is an inhibitor for Xa

This is correct. Rivaroxoban prevents factor Xa-mediated conversion of prothrombin to thrombin. Other drugs which are direct inhibitors of factor Xa are apixaban and edoxaban. The half lives are 5h, 12h and 10-14 h for rivaroxaban, apixaban and edoxaban respectively.
C. It inhibits conversion of plasminogen to plasmin.

This is not the mechanism of action of rivaroxoblan. The thrombolytics like alteplase, reteplase and tenecteplase act through this mechanism.
D. It inhibits thrombin.

Heparin and its low molecular counterparts bind to the enzyme inhibitor antithrombin III (AT), causing a conformational change which subsequently inhibits thrombin. Some of the newer agents like dabigatran, argatroban and bivaluridin cause direct thrombin inhibition.
2. The patient is in the intensive care unit and neurosurgery is being consulted. The following are the principles guiding reversal of rivaroxoban except:

A. Factor Xa inhibitors should be discontinued.
B. Administration of activated charcoal.
C. 4-Factor PCC(prothrombin complex concentrate)
D. Hemodialysis.

Go to Q 3
A. Factor Xa inhibitors should be discontinued.

Factor Xa inhibitors should be discontinued when intracranial hemorrhage is present or suspected. As with all anticoagulants, oral factor Xa inhibitors are associated with a risk of intracranial hemorrhage. Guidelines recommend discontinuing factor Xa inhibitors when intracranial hemorrhage is present or suspected (Good Practice statement).

B. Administration of activated charcoal.

The guidelines suggest administration of activated charcoal (50 g) to intubated intracranial hemorrhage patients with enteral access and/or those at low risk of aspiration who present within 2 h of ingestion of an oral direct factor Xa inhibitor.

The guidelines suggest administering a 4-factor PCC (50 U/kg) if intracranial hemorrhage occurred within 3–5 terminal half-lives of drug exposure or in the context of liver failure. Studies on healthy volunteers have shown partial or complete reversal of rivaroxaban-induced coagulation abnormalities with 4-factor PCC (50 U/kg) activated PCC and rFVIIa. The extent of reversal appears to depend on the coagulation parameter assessed.

Hemodialysis does not reverse the effect of oral direct factor Xa inhibitors (rivaroxaban, apixaban, edoxaban) because these drugs are highly protein bound.
3. A 59 year old male patient with a subarachnoid hemorrhage needs an urgent craniotomy. He has been on warfarin from a previous deep vein thrombosis. The following options would be useful except:

A. Four factor prothrombin complex concentrate.
B. Fresh frozen plasma.
C. Recombinant Factor VIIa.
D. Oral vitamin K1

Go to Q 4
A. Four factor prothrombin complex concentrate.

PCCs are virally inactivated, vitamin K-dependent coagulation factors prepared from pooled plasma agents that are lyophilized and designed to be dissolved in saline as needed. They contain factors II, VII, IX and X. They are very useful in this situation. PCCs have 2 important advantages over FFP: 1) they can be administered more quickly (thawing and blood typing are not required), with repletion achieved within 15 minutes; and 2) there is no risk of volume overload. However, PCCs are more expensive and carry a low but finite risk of correction thrombosis.

B. Fresh frozen plasma.

Fresh frozen plasma can rapidly restore coagulation factors in this setting. However, it has several disadvantages; it requires thawing for approximately 30 minutes between 30°C and 37°C, as well as patient blood typing. In addition, large volumes of FFP are required which subjects patients to risk of volume overload and can cause pulmonary microvascular damage, potentially leading to TRALI (transfusion associated acute lung injury).

C. Recombinant Factor VIIa.

The clinical experience with rFVIIa in OAC-ICH (oral anticoagulant) is limited to very small case series. Nevertheless, rFVIIa is mentioned as a therapeutic option both in American and European management guidelines based on its hemostatic efficacy to decrease the INR value. rFVIIa is readily available and can be rapidly infused. However, it is considerably more expensive and carries a higher risk of thromboembolic complications than prothrombin complex concentrate.

When there is a need for urgent anticoagulation reversal, warfarin should be discontinued and reversal of anticoagulation should occur immediately. Patients should first receive 2.5 mg to 10 mg of intravenous (IV) vitamin K1 over a 30-minute period. This allows the liver, which may be depleted of vitamin K1 and its associated coagulation factors, to synthesize vitamin K-dependent coagulation factors. However, this synthesis can take up to 24 hours. Oral vitamin K would take too long to work in this situation.
4. 72 year old male comes for a subdural hematoma evacuation. He has been on antiplatelet therapy (aspirin and clopidogrel) for coronary stent placement. Which of the following is false with regards to antiplatelet medications?

A. Aspirin inhibits COX-1
B. Both clopidogrel and ticagrelol are P2Y12 antagonists.
C. Prasugrel is a glycoprotein 2b3a inhibitor.
D. Aggregometry is useful to identify the extent of inhibition of platelets
Aspirin is an irreversible cyclooxygenase inhibitor (COX-1). Because platelets are anucleate, **denovo** synthesis of COX-1 by platelets is absent. As a result the effect of aspirin lasts for the lifetime of the platelets (8-10 days).
B. Both clopidogrel and ticagrelol are P2Y12 antagonists

This is true, however clopidogrel acts indirectly on the P2Y12 while Ticagrelor acts directly on the P2Y12 receptor.

Thienopyridines, such as clopidogrel and Prasugrel, inhibit platelet activation by blocking the ADP-binding site of the P2Y12 receptor. Ticagrelor is a nucleoside analogue that, unlike thienopyridines, does not bind to the ADP-binding site but to a separate site of the P2Y12 receptor.
C. Prasugrel is a glycoprotein-2b3a inhibitor.

Prasugrel is a P2Y12 blocker and acts through the adenosine diphosphate mechanism. The glycoprotein IIb/IIIa also known as integrin αIIbβ3 is an integrin complex found on platelets. It is a receptor for fibrinogen found exclusively on the surface of platelets and aids platelet activation. The αIIbβ3 receptor can be blocked with several αIIbβ3 inhibitors, such as abciximab, eptifibatide and tirofiban.

D. Aggregometry is useful to identify the extent of inhibition of platelets.

The capacity of the platelets to aggregate when exposed to a stimulus is aggregometry and is a measure of platelet reactivity. It can be used to measure the extent of platelet inhibition in patients receiving antiplatelet therapy. MEA (multiple electrode aggregometry) can be used for monitoring of both aspirin and P2Y12 inhibitors;

A. Platelet transfusion is recommended if neurosurgical intervention is planned
B. Platelet transfusion is not recommended if neurosurgical intervention is not planned
C. Platelet transfusion is recommended for patients on GPIIb/IIIa inhibitors.
D. DDAVP is recommended in intracranial hemorrhage associated with Clopidogrel
A. Platelet transfusion is recommended if neurosurgical intervention is planned.

Guidelines suggest platelet transfusion for patients with aspirin- or ADP inhibitor-associated intracranial hemorrhage who will undergo a neurosurgical procedure. (Conditional recommendation, moderate quality of evidence). In candidates for platelet transfusion, guidelines suggest an initial dose of one single-donor apheresis unit of platelets. Platelet testing is suggested prior to repeat platelet transfusion.

Guidelines recommend against platelet transfusion for patients with antiplatelet-associated intracranial hemorrhage who will not undergo a neurosurgical procedure, regardless of the type of platelet inhibitor, platelet function testing, hemorrhage volume, or neurological exam. (Conditional recommendation, low-quality evidence).
C. Platelet transfusion is recommended for patients on GPIIb/IIIa inhibitors

Guidelines suggest against platelet transfusion in NSAID or GP IIb/IIIa inhibitor-related intracranial hemorrhage, even in the context of neurosurgical intervention (Conditional recommendation, very low-quality evidence). GP IIb/IIIa inhibitors prevent platelet aggregation via fibrinogen-platelet crosslinking. In an in vitro study of platelets exposed to either tirofiban or eptifibatide, fibrinogen supplementation using either cryoprecipitate or fresh frozen plasma resulted in improved platelet aggregation in a dose-dependent manner. The use of cryoprecipitate in GP IIb/IIIa-related intracranial hemorrhage may be considered, though there is little literature to support its use.

D. DDAVP is recommended in intracranial hemorrhage associated with Clopidogrel

The guidelines suggest consideration of a single dose of desmopressin (DDAVP) in intracranial hemorrhage associated with aspirin/COX-1 inhibitors or ADP receptor inhibitors. In patients deemed appropriate (e.g., those undergoing a neurosurgical procedure), DDAVP can be used in addition to platelet transfusion. (Conditional recommendation, low-quality evidence)