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**Stop the Bloodshed: What a Pharmacist Needs to Know About Emergent Reversal of Anticoagulation**

Session Overview

This case-based interactive session will allow participants to gain critical understanding of how to use novel reversal agents in the setting of a life-threatening bleed. Further, the participants will be able to discuss the evidence behind reversal agents and contrast risks and benefits of reversing a diverse patient population. The following topics will be covered: prothrombin complex concentrates, vitamin K, idarucizumab, and andexanet alfa. The risks, benefits, population evidence to date, and study bias will be discussed for each agent. We will also present data to highlight how commonly available labs can be used to interpret the degree of anticoagulation, and which novel anticoagulant is responsible. Dr. Hayes' session will focus on dabigatran.

Objective

1. Discuss the literature related to the pharmacologic reversal of direct thrombin inhibitors during life-threatening bleeding.

Introduction

Dabigatran was the first non-warfarin oral anticoagulant to be introduced to the U.S. market, approved by the FDA in 2010. The drug is classified as a direct thrombin inhibitor that inhibits both free and fibrin-bound thrombin. Current indications include prevention and treatment of deep vein thrombosis and pulmonary embolism, nonvalvular atrial fibrillation, and postoperative thromboprophylaxis. A major advantage, as touted by its manufacturer Boehringer Ingelheim, was that use of the medication did not require routine monitoring like warfarin.

It did not take long for patients to begin presenting to Emergency Departments with bleeding events, including serious gastrointestinal bleeding and intracranial hemorrhage. At the time dabigatran hit the market, there was no reversal agent, or antidote, available. However, in 2015, idarucizumab was approved by the FDA. Idarucizumab is also marketed by Boehringer Ingelheim, the same pharmaceutical company that makes dabigatran. Idarucizumab is a monoclonal antibody fragment the binds specifically to dabigatran and rapidly neutralizes the anticoagulant effect (Schiele 2013). Other treatments have also been used in an attempt to reverse dabigatran-related bleeding, such as prothrombin complex concentrate.

Laboratory Monitoring

In my opinion, the best article on laboratory testing for oral anticoagulants was published in *Seminars in Thrombosis and Hemostasis* (Favaloro 2015).

- Significant prolongations of PT, aPTT, and Thrombin Time (TT) are observed in most instances of measurable dabigatran concentration
    - Most sensitive is TT, followed by aPTT and PT (least)

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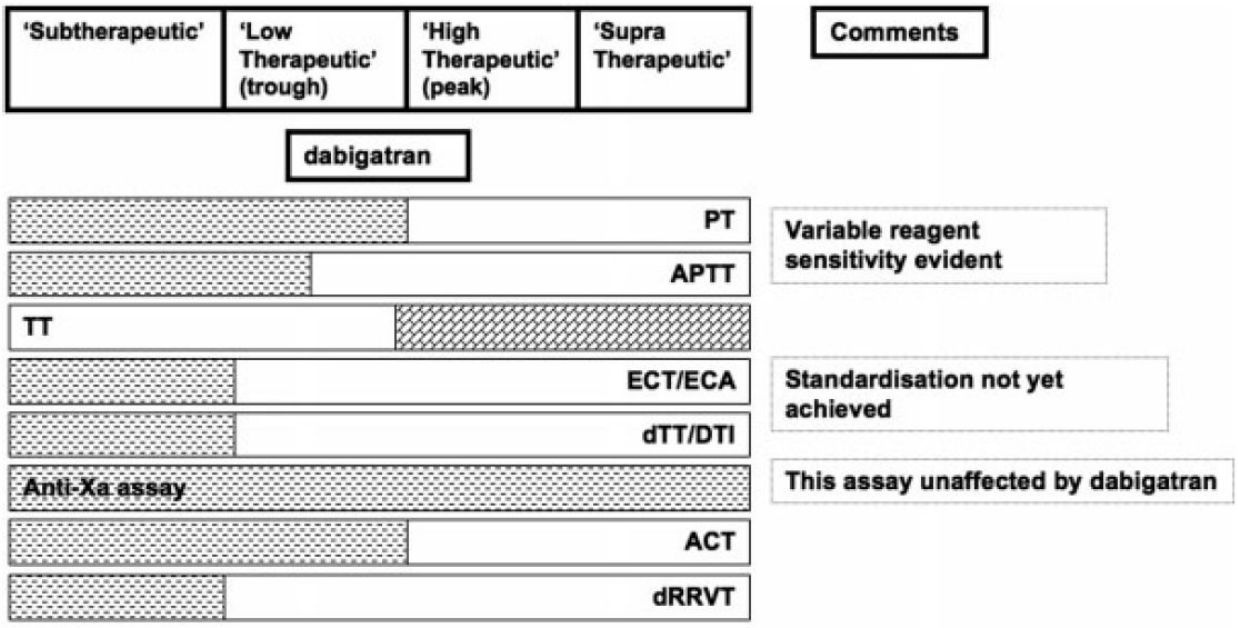
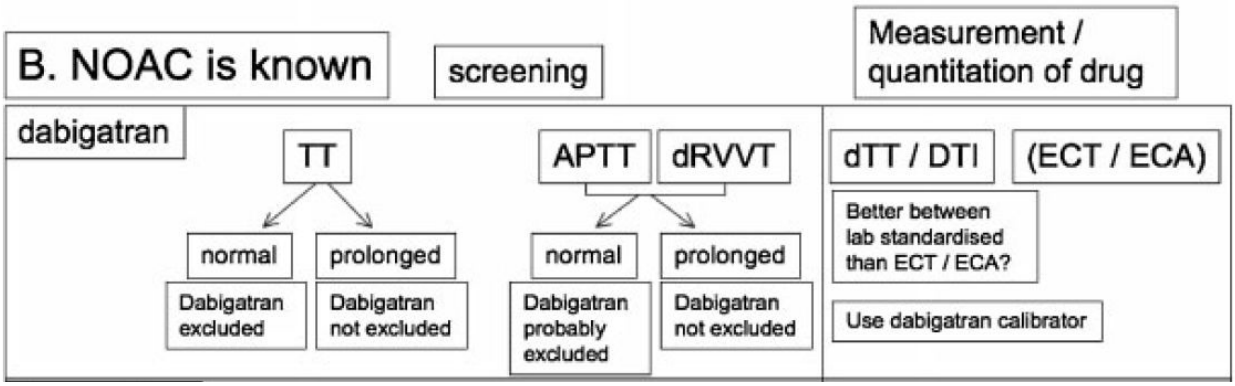
- aPTT can be used for urgent assessment of the presence of dabigatran, although a normal aPTT will not always exclude the presence of the drug
- Standard Thrombin Time (TT) is most useful to screen for absence of dabigatran (normal TT) or potential presence of dabigatran (elevated TT), but is not useful for assessment of dabigatran level
- The dRVVT, using a "confirm" LA reagent, shows good sensitivity to dabigatran and has been proposed a useful screen by some
- Hemoclot thrombin inhibitor/dilute thrombin time (HTI/dTT) and ecarin clotting time/ecarin chromogenic assays (ECT/ECA) assays can be used for a more accurate estimation of the anticoagulant effect of the drug and to "quantify" drug level




- If the patient is known to be on dabigatran, this algorithm may help determine presence or absence of the drug (Favaloro 2015):



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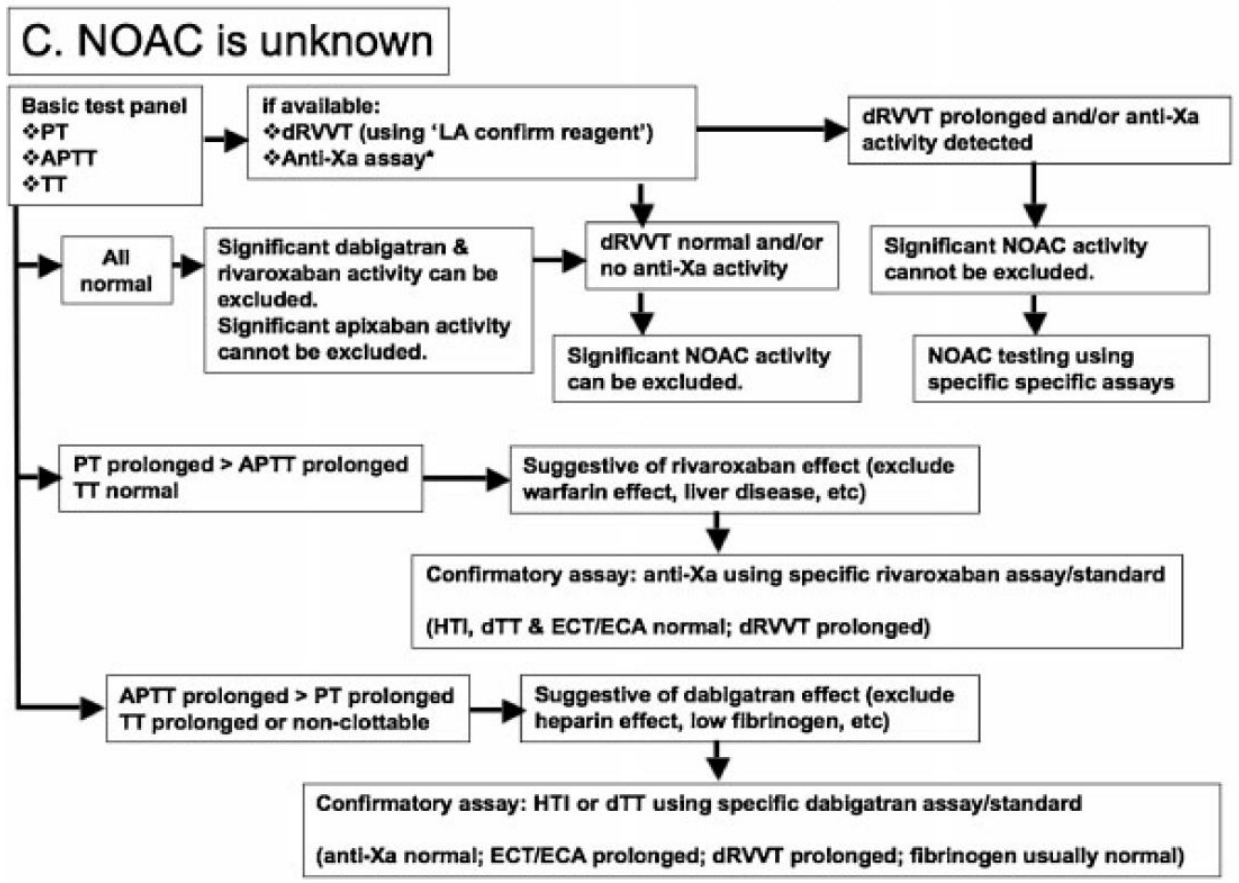
- If dabigatran use is unknown, this algorithm may help determine presence or absence of the drug (Favaloro 2015):




Reversal

1. Step 1 - D/C the drug
2. Step 2 - Antidote
    a. Idarucizumab first studied in 110 healthy male volunteers aged 18-45 yrs to investigate pharmacokinetics, safety, and tolerability (Glund 2015)
        i. Increasing doses administered as 5-minute or 1-hour infusions and compared to placebo
        ii. Half-life determined to be 45 minutes with rapid peaks and rapid clearance
        iii. No effect on coagulation parameters or endogenous thrombin potential was found in the absence of dabigatran
        iv. Adverse events rare in both idarucizumab and placebo groups
        v. Funded by Boehringer Ingelheim
    b. The same authors published the results of a randomized, placebo-controlled, double-blind phase I study to assess the safety, tolerability, and efficacy of idarucizumab on the reversal of dabigatran-induced anticoagulation (Glund 2015).
        i. Single center study consisted of two parts

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1. Part I was a rising-dose assessment of idarucizumab in healthy male volunteers
2. Part II was a dose-finding, proof-of-concept of idarucizumab in volunteers pretreated with dabigatran

ii. Volunteers aged 18 to 45 years were randomized sequentially into 4 idarucizumab dose groups (1 g, 2 g, 4 g, and 5 g). Patients in the 5 g dose group received an additional 2.5 g approximately 1 hour after the initial dose. Patients within each group were randomized in a 3:1 ratio to idarucizumab or placebo.

iii. The diluted thrombin time, ECT, TT, aPTT, and endogenous thrombin potential were used to assess the anticoagulant effect of dabigatran.

iv. 47 male volunteers completed the study. Immediate and sustained reversal of dabigatran-associated increases in ECT, aPTT, and TT were noted with doses of idarucizumab of 2 g or more. Volunteers who received 1 g of idarucizumab did not have sustained reversal at 72 hours.

v. Similar to prior studies, the current trial did not measure the effect of idarucizumab on bleeding patients. In addition, Boehringer Ingelheim was involved in the study design, data collection, data analysis, data interpretation, and manuscript preparation for this trial.

c. REVERSal Effects of Idarucizumab in Patients on Active Dabigatran (RE-VERSE AD™)

i. Prospective, phase 3 trial currently underway in patients on dabigatran with life-threatening bleeding or requiring urgent surgery (Pollack CV Jr 2015)

ii. An interim analysis was published in 2015, including 90 patients of the planned enrollment goal of 300 (Pollack CV Jr 2015)

1. 51 patients had serious bleeding and 39 required an urgent procedure
2. There was no control group
3. Idarucizumab seems to reverse laboratory markers of anticoagulation from dabigatran rapidly and completely, including dTT and ECT
    a. Not all institutions have these assays available
4. Dose that seems to work best is 5 gm given IV (two-2.5 gm infusions given no more than 15 min apart)
5. Median investigator-reported time to cessation of bleeding was 11.4 hrs
6. 21 of the 90 patients had 'serious adverse effects' including 5 thrombotic events (direct association with idarucizumab is unclear)
7. Key limitation is that only 75% of patients had elevated thrombin times prior to idarucizumab, meaning this cohort may not have needed the drug for reversal in the absence of dabigatran activity
8. Study supported by Boehringer Ingelheim

d. There are already failures being reported with corrected labs but continued bleeding (Alhashem 2016)

3. Step 3 - Factor Replacement

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a. Single-center, randomized, placebo-controlled, crossover study evaluated PCC (Cofact, Sanquin Blood Supply, Amsterdam, the Netherlands) to reverse the anticoagulant effect of dabigatran (Eerenberg 2011).
    i. 12 healthy male volunteer received 150 mg of dabigatran twice a day for 2.5 days.
    ii. On the third day, patients received an additional dose and then were admitted to the hospital for an infusion of PCC or placebo.
    iii. Based on prior research, investigators chose a PCC dose of 50 U/kg.
    iv. aPTT, TT, and ECT were used to assess dabigatran anticoagulation.
    v. PCC did not reverse the prolongation of aPTT, ECT, and TT due to dabigatran. No major or clinically relevant bleeding complications occurred during treatment.
    vi. Importantly, this trial was limited by its small size.
b. Randomized, crossover study evaluated effect of non-specific reversal agents on the anticoagulant activity of dabigatran in healthy volunteers (Marlu 2012)
    i. 10 healthy, white, male patients, ages 18-45 yrs were administered dabigatran 150 mg orally X 1
    ii. Blood samples were drawn at 2 hrs post-administration to represent peak anticoagulant activity
    iii. Three reversal agents tested were recombinant factor VIIa (rFVIIa, Novoseven®, NovoNordisk, Copenhagen, Denmark), activated prothrombin complex concentrate (FEIBA®, Baxter AG, Vienna, Austria, aPCC), and the four factor prothrombin complex concentrate (PCC) Kanokad® (LFB, Courtaboeuf, France), all at various concentrations
    iv. Although PCC increased endogenous thrombin potential, only rFVIIa and FEIBA corrected the altered lag-time
c. Arellano-Rodrigo et al enrolled healthy volunteers to receive dabigatran 150 mg orally every 12 hours for 5 days (Arellano-Rodrigo 2015)
    i. Concentrations of rFVIIa equivalent to 270 µg/kg, aPCC at 75 U/kg, and the 4-factor PCC (Beriplex; CSL Behring GmbH, Marburg, Germany) at 50 IU/kg were spiked into blood samples
    ii. Dabigatran treatment significantly prolonged both PT and aPTT in blood samples drawn 2 to 3 hours after the last intake
    iii. While rFVIIa or aPCC partially improved all the parameters, PCC did not modify the prolonged aPTT observed after dabigatran treatment
d. Based on these ex vivo studies, only aPCC, and possibly rFVIIa, may be effective in reversing anticoagulation parameter alterations secondary to dabigatran. All three studies enrolled healthy volunteers and tested against therapeutic levels of dabigatran. The studies attempted to use doses of factor similar to what would be used in actual patients, but may not be generalizable as ex vivo extrapolation. Patients with multiple medical conditions and those with dabigatran overdose were not studied. Further, correction of anticoagulation parameters may not translate into cessation of clinical bleeding.

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4. Step 4 - Adjunctive therapy
    a. Charcoal
        i. Theoretically binds dabigatran
        ii. Probably not helpful in GI bleeding, patient already has life-threatening bleeding
        iii. May be helpful if patient overdoses intentionally and presents to hospital within the following 12 hours
    b. HD/CVVH
        i. Intermittent HD removes dabigatran effectively but is not always available and requires a hemodynamically stable patient (Liesenfeld 2016).
        ii. CVVHD does not reach comparable elimination rates and is not fast enough to prepare for urgent interventions in patients with high bleeding risks.
5. Guidelines
    a. Guideline for Reversal of Antithrombotics in Intracranial Hemorrhage: A Statement for Healthcare Professionals from the Neurocritical Care Society and Society of Critical Care Medicine (Frontera 2016)

**Conclusion**

Only prothrombin complex concentrates, recombinant factor VIIa, and idarucizumab have been studied in trials meeting the Clinical Practice Committees predefined methodology standards according to the GRADE criteria. All of the studies investigating prothrombin complex concentrates and recombinant factor VIIa were conducted in healthy volunteers and measured laboratory reversal of anticoagulation parameters. Idarucizumab rapidly reverses laboratory coagulation markers from dabigatran. An interim analysis of the REVERSE-AD trial reported 11.4 hours until clinical cessation of bleeding in patients with life-threatening hemorrhage or requiring reversal for urgent procedures. Each of the idarucizumab studies were supported by the antidote's manufacturer. While there may be a role for idarucizumab, its clinical efficacy in patients with serious bleeding from dabigatran is still unclear.