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TITLE: Direct Oral Anticoagulants: Reversal strategies for DOACs: Laboratory role?

PRESENTER: Bob Gosselin

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Hello, my name is Bob Gosselin. I currently serve as a volunteer with UC Davis Thrombosis & Hemostasis Center after my retirement in 2017 from the university health system as the senior Clinical Laboratory Scientist in special coagulation. Welcome to this Pearl of Laboratory Medicine on "**Reversal strategies for DOACs: Laboratory role?**." This program was created with Dr Dot Adcock, the Chief Medical Officer and SVP of LabCorp.

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This session is a joint effort between the American Association for Clinical Chemistry (AACC) and the North American Specialized Coagulation Laboratory Association (NASCOLA)

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The first DOAC, dabigatran or Pradaxa, was approved for use in the US in 2010. The next several years, factor Xa DOAC, including rivaroxaban and apixaban were approved for use. In the early years, there were no specific reversal agents or antidotes for these drugs. To neutralize dabigatran, activated charcoal could be used if recently ingested, or dialysis to physically remove drug. Other traditional means of reversing anticoagulants, such as fresh frozen plasma or activated factor VIIa had limited efficacy. For factor Xa DOACs, the reversal strategies included activated factor VIIa, prothrombin complex concentrates or PCCs, in both activated and inactivated forms.

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In 2015, Praxbind was FDA approved as a specific reversal agent for dabigatran. In 2018, Andexxa was FDA approved as a specific reversal agent for rivaroxaban and

apixaban. However, the use of activated and nonactivated PCCs are still being used for DOAC reversal, although primarily limited to factor Xa DOACs.

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The clinical indications for DOAC reversal include hemorrhage or major bleeding, especially into critical organs or spaces, the need for emergent invasive procedures, or reducing drug exposure prior to thrombolysis in acute thrombotic stroke. Additionally, it has been proposed that demonstrable DOAC levels should be present prior to using reversal agents. Of particular note, that safe or acceptable DOAC thresholds or levels for emergent invasive procedures or thrombolysis is based on limited data.

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As a reminder, the DOAC targets are represented in this cartoon of the simplified coagulation cascade. Dabigatran, currently the only direct thrombin DOAC, inhibits thrombin or factor IIa. The factor Xa DOAC, includes rivaroxaban, apixaban, edoxaban and betrixaban and inhibit factor Xa in the common pathway.

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Using the same coagulation cartoon, the specific reversal strategies or factor supplements such as PCCs will be detailed.

Praxbind targets Dabigatran and thrombin

Andexxa targets Factor Xa DOACs and factor Xa

FEIBA will add mostly factor VIIa but also factor IX, Factor X, and factor II prothrombin

Profilnine is a 3 factor PCC and will add Factor IX, Factor X, and prothrombin

Kcentra is a four factor PCC and will add Factor VII, Factor IX, Factor X, and prothrombin

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Praxbind or idarucizumab from Boehringer Ingelheim, is a humanized monoclonal antibody fragment derived from IgG1 molecule. The current dose consists of two separate 2.5g doses that will bind to both dabigatran and it's acylglucuronide metabolites. A single 5.0g dose of Praxbind will neutralize up to 1000ng of dabigatran, but drug rebound or reappearance has been noted in some patients 12 – 24 hours after treatment.

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Of particular note for the laboratory, Praxbind does not have any thrombogenicity or ability to generate clots, but will correct prolongation of the PT, APTT, thrombin time, dilute thrombin and ecarin clotting times due to dabigatran. These tests may also detect the reappearance of the drug, although the more sensitive methods, such as drug calibrated ecarin-based or anti-FIIa assays, to assess post-Praxbind treatment efficacy may be warranted, especially if the patients pretreatment levels exceed 1000ng/mL. Partial or incomplete correction of screening assays such as the PT or APTT after Praxbind treatment would suggest either concomitant coagulopathy such as a factor deficiency or inhibitor, or pre-treatment dabigatran concentration of >1000ng/mL.

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Andexxa or andexanet alfa from Portola pharmaceuticals is a recombinant inactivated factor Xa. This drug is currently only FDA approved for rivaroxaban and apixaban reversal. There are two doses for Andexxa, the low dose consisting of 400mg of the drug, and the higher 800mg dose. It has been demonstrated that Andexxa poses some thrombogenicity by reducing tissue factor pathway inhibitor or TFPI and increasing thrombin generation.

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For laboratory considerations, the efficacy of Andexxa can be measured using anti-Xa assays, as Andexxa will reduce anti-Xa levels, whether those tests are DOAC or heparin calibrated. The initial Portola studies suggested a rebound in anti-Xa after the cessation of Andexxa infusion, but it was later determined that the laboratory method they used had a high sample pre-dilution (~1:30) which created an in-vitro dissociation of the drug:substrate. When lower sample predilutions (e.g. ~1:4), no anti-Xa rebound was observed. There are no FDA recommendations for measuring anti-Xa before or after Andexxa treatment with doses predicated on last known exposure or dose, and if that is unknown, to use the higher dose of 800mg

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FEIBA, or factor VIII bypassing agent from Baxlta was initially approved in 1986 for use treatment of hemophilia A patients with inhibitors. This product is also described as an activated prothrombin complex concentrate, and contains mostly activated factor VII, with non-activated factors IX, X and prothrombin. There are case reports of FEIBA use in DOAC reversal.

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As FEIBA was used in Hemophilia A patients with inhibitors, the APTT was a common measurement to detect drug efficacy, with a reduction in the APTT if the treatment was working. As this product contains factors II and X, it is presumed that the PT will correct

if these factors are deficient or DOAC to either thrombin or factor Xa are present. However, there is unclear utility of the laboratory in assessing FEBIA efficacy in FXa DOAC reversal.

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Profilnine is a 3 factor PCC from Grifols Biologics. This is a lyophilized product containing inactivated factors II, IX and X. Profilnine is FDA for use in the treatment of Hemophilia B patients, with case reports for use in both DOAC and warfarin reversal.

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As Profilnine contains factors II, IX and X, this product would presumably correct the PT and APTT due to deficiencies or inhibitors to these factors. At this time, there is unclear utility of the use of these tests for assessing profilnine reversal of FXa DOACs.

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Kcentra is a 4 factor PCC from CSL Behring, containing non-activated factors II, VII, IX and X. The current FDA indications for Kcentra is for reversal of vitamin K dependent procoagulant factors II, VII, IX and X induced by oral vitamin K antagonists such as warfarin or coumadin. There are case reports of Kcentra use in FXa DOAC reversal.

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For laboratory considerations and Kcentra use, as this product contains factors II, VII, IX, and X, this drug would presumably correct the PT and/or APTT due to deficiencies or inhibitors to these factors. At this time, there is unclear utility of the laboratory or laboratory tests in assessing Kcentra use for FXa DOAC reversal

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At this point, we would like to caution using LMWH values for estimating FXa DOAC concentration, as these tests have been reported for use in determining acceptability and avoidance for thrombolysis. The first premise is that a LMWH of 0.1IU/mL can reliably determine relatively low concentrations of FXa DOACs, with a general acceptability that lower limit of quantitation can assure <30-50 ng/mL of FXa DOACs, which is a true statement.

The second premise is that alteplase should be avoided due to high DOAC concentrations if >50ng/mL, which is also generally a true statement.

However, conversely, the <0.50IU/mL threshold would not be an appropriate threshold if the acceptable “safe” FXa DOAC concentration is <50ng/mL.

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To summarize, for dabigatran Praxbind is generally accepted as the ideal choice for reversal. For factor Xa DOACs, this is less uncertain, as the cost of Andexxa has led to less universal acceptance of the use of this reversal agent. The low dose cost is estimated to be ~$25,000, whereas the high dose estimated to be ~$40,000. There are published reports and institutional experience about the efficacy of PCCs in FXa DOAC reversal. There are currently no laboratory recommendations for DOAC reversal, but our institutional experience suggests that providing a pretreatment DOAC level assisting the clinical staff in PCC dosing.

Importantly, the laboratory should verify the local use of heparin calibration anti-Xa testing is such tests are used for FX DOAC estimation, and verify locally any clinician threshold used to determine safe intervention or reversal strategies in DOAC anticoagulated patients.

Slide 20: References

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Slide 21: Disclosures

Dorothy Adcock has received honoraria from Siemens Healthcare Diagnostics and is a consultant to Instrumentation Laboratory.

Robert Gosselin has provided expert testimony for dabigatran and rivaroxaban testing, has received honoraria from Siemens Healthcare Diagnostics, Machaon Laboratories, Diagnostica Stago and serves as a consultant for Diagnostic Grifols and UniQure, and advisory board member for BioMarin

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Thank you for joining me on this Pearl of Laboratory Medicine on "**Reversal strategies for DOACs: Laboratory role?**".