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TITLE: Direct Oral Anticoagulants: Introduction

PRESENTER: Dorothy Adcock

Slide 1:

Hello, my name is Dr Dot Adcock. I am currently the Chief Medical Office and senior vice president of LabCorp. Welcome to this Pearl of Laboratory Medicine on "**Direct Oral Anticoagulants, an introduction**." This program was created with Bob Gosselin from the Thrombosis & Hemostasis Center at the University of California, Davis Health System.

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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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Oral anticoagulation is administered for the treatment of thrombosis (the lay term for thrombus is clot) or used prophylactically for a patient at risk for thrombosis to prevent clot formation. The most common oral anticoagulant administered is warfarin, a vitamin K antagonist. Coumadin® and Jantoven® are brand names. Warfarin functions as an anticoagulant by reducing the amount of functional vitamin K dependent procoagulant factors, specifically factors II, VII, IX, X. It also causes functional levels of anticoagulant proteins, protein C and protein S to decrease. Limitations of warfarin are that full anticoagulant effect requires a number of days of therapy. Patients on warfarin must undergo episodic monitoring. Warfarin interacts with many foods as well as medications which may increase or decrease its anticoagulant effect.

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Given warfarin's limitations there was a goal to develop an oral anticoagulant that is not affected by diet and does not requires routine monitoring. The first such agent developed was ximelagatran, an oral direct anti-IIa (thrombin) inhibitor but this was pulled from the market due to liver toxicity. The next such agent to come to market was dabigatran another oral direct anti-IIa (thrombin) inhibitor. Dabigatran was approved for use in 2010 for stroke prevention in non-valvular atrial fibrillation or NVAF, which is an abnormal heart rhythm due to a heart valve problem. Now there are 4 other FDA approved direct oral anticoagulants (DOACs): rivaroxaban, apixaban, edoxaban and betrixaban, all targeting factor Xa.

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This cartoon of the coagulation cascade demonstrates the various targets for anticoagulant agents and depicts the laboratory testing pathways, drug andassay targets. The currency (dollar bills) in the common pathway is a simple trick to remember those factors in this pathway and their order of reactions, 10, 5, 2 and 1 (also known as fibrinogen). Both direct Xa inhibitors and direct thrombin inhibitors can potentially cause prolongation of the aPTT, PT and Russell's Viper Venom time or DRVVT as they inhibit factors within these pathways. Direct Xa inhibitors however will not affect the thrombin time, dilute thrombin time or ecarin methods. Session 4 will go into more detail about tests outlined here which may be affected by DOAC presence.

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I would like to review the definition of a number of terms that will be used in this and following presentations. Venous thromboembolism or VTE: clots within the veins most commonly known as deep vein thrombosis (or DVT) and pulmonary embolism (or PE)
Pharmacokinetics (PK): drug concentration after administration
Pharmacodynamics (PD): the drug effect after administration
Peak levels: the maximum drug concentration after administration
Trough levels: the drug level just before the next drug dose
Therapeutic range: the recommended target drug effect, usually either a concentration or test effect (e.g. INR and warfarin therapy).

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Let's compare and contrast the characteristics of warfarin and direct oral anticoagulant agents beginning with their mechanism of action. Warfarin is a vitamin K antagonist that requires days to reach therapeutic range while DOACs are direct factor inhibitors that require only several hours to reach desired level or anticoagulation. Warfarin dose is variable and there is significant inter-individual variability while DOACs are administered based on a fixed dose dependent on indication. Warfarin requires frequent and episodic monitoring to assure maintenance in the desired therapeutic range but this is not required with DOACS. Warfarin dosing must be predicated based on daily vitamin K intake (e.g. leafy green vegetable intake) while DOAC dosing is not affected by diet,

although rivaroxaban and betrixaban are taken with food to increase absorption. Finally, and significantly there is less risk for serious hemorrhage with DOACs as compared to warfarin

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Dabigatran which is administered as Dabigatran etexilate, brand name Pradaxa® is an oral direct thrombin inhibitor which is immediate acting with peak concentration 1.5 – 3 hours after administration. It inhibits free and bound thrombin (also known as activated factor II). It is primarily excreted by the kidneys and has a half-life of about 13 hours.

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The current FDA approved indications for dabigatran are stroke prevention in non-valvular atrial fibrillation, treatment of DVT and PE, the secondary prevention of VTE and thromboprophylaxis after knee or hip surgery.

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Rivaroxaban, brand name Xarelto® is an oral direct factor Xa inhibitor, immediate acting with peak concentrations about 2-3 hours after ingestion, increased absorption is noted with food intake. Rivaroxaban inhibits both free and bound activated factor X (FXa) and it is excreted primarily through the kidneys. Drug half-life is approximately 2 – 13 hours and dependent on renal function.

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The current FDA approved indications for rivaroxaban are stroke prevention in non-valvular atrial fibrillation, treatment of DVT and or PE, the secondary prevention of VTE and thromboprophylaxis after knee or hip surgery.

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Apixaban, brand name Eliquis® is an oral direct factor Xa inhibitor, immediate acting with peak concentrations about 3 – 4 hours after ingestion. Apixaban inhibits both free and bound activated factor X (FXa) and it is excreted primarily through the feces. Drug half-life is approximately 12 hours.

Slide 13:

The current FDA approved indications for apixaban are stroke prevention in non-valvular atrial fibrillation, treatment of DVT and or PE, the secondary prevention of VTE and thromboprophylaxis after knee or hip surgery.

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Edoxaban, brand name Savaysa is an oral direct factor Xa inhibitor, immediate acting with peak concentrations about 1 – 2 hours after ingestion. Edoxaban inhibits both free and bound activated factor X (FXa) and about 50% is excreted by the kidneys. Drug half-life is approximately 12 hours.

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The FDA approved indications for edoxaban are stroke prevention in NVAF and treatment of DVT and PE.

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The newest DOAC to be approved is Betrixaban, brand name Bevyxxa is an oral direct factor Xa inhibitor that is only FDA approved for VTE prophylaxis in acutely medically ill hospitalized patients. Its' anticoagulant effect is immediate acting and it should be taken with food. Like other direct Xa inhibitors it Inhibits both free and bound factor Xa with peak concentration about 3 – 4 hours after ingestion. Clearance is primarily through feces and drug half-life is approximately ~20 hours.

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In summary, there are currently 5 FDA approved DOACs for use as an alternative to coumadin for long term anticoagulation. These DOACs are only approved for adult patients, but pediatric clinical trials are underway, as well as adult trials for DOAC use in cancer patients. The performance characteristics of each DOAC and their effect on laboratory testing will be explored in future sessions.

Slide 18: References

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Slide 19: 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

Slide 20: Thank You from www.TraineeCouncil.org

Thank you for joining me on this Pearl of Laboratory Medicine on "**Direct Oral Anticoagulants, an Introduction**".