Update on Anticoagulants Monitoring Practice

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Objectives

- Review new direct oral anticoagulants (DOACs), mechanisms of action, and clinical uses
- Understand the effects of DOACs on routine coagulation testing
- Describe approaches to laboratory monitoring of DOACs
- Discuss DOACs potential to interfere with specialized coagulation testing

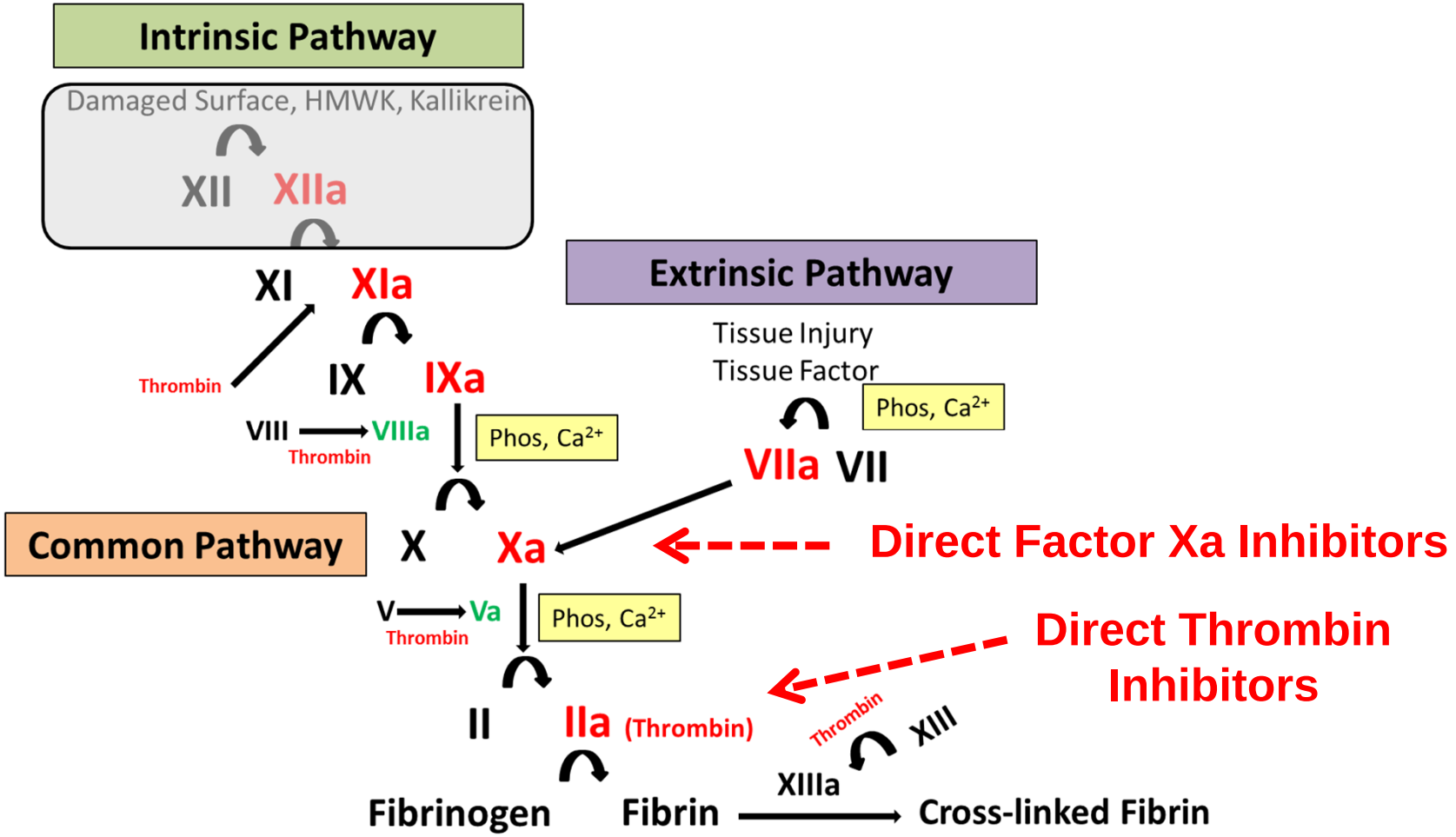
Direct oral anticoagulants (DOACs)

- Traditional anticoagulants warfarin, heparin, and low-molecular-weight heparin have been used for decades
  - Medical and laboratory personnel are familiar with when and how these should be monitored
  - Prior to 2010, warfarin was the only option for oral anticoagulation
- Now there are several new oral anticoagulants with a direct mechanism of action (DOACs)

Direct oral anticoagulants (DOACs)

DOAC	Mechanism of action	Date of first FDA approval	Indications
Dabigatran (Pradaxa)	Direct thrombin inhibitor (DTI)	October, 2010	DOACs are variably approved to: • Prevent stroke and systemic embolism in non-valvular atrial fibrillation • Treat and prevent VTE • Prevent VTE after major orthopedic surgery
Rivaroxaban (Xarelto)	Direct factor Xa inhibitor	July, 2011	
Apixaban (Eliquis)	Direct factor Xa inhibitor	December, 2012	
Edoxaban (Savaysa)	Direct factor Xa inhibitor	January, 2015	

Direct oral anticoagulants (DOACs)



DOACs - advantages

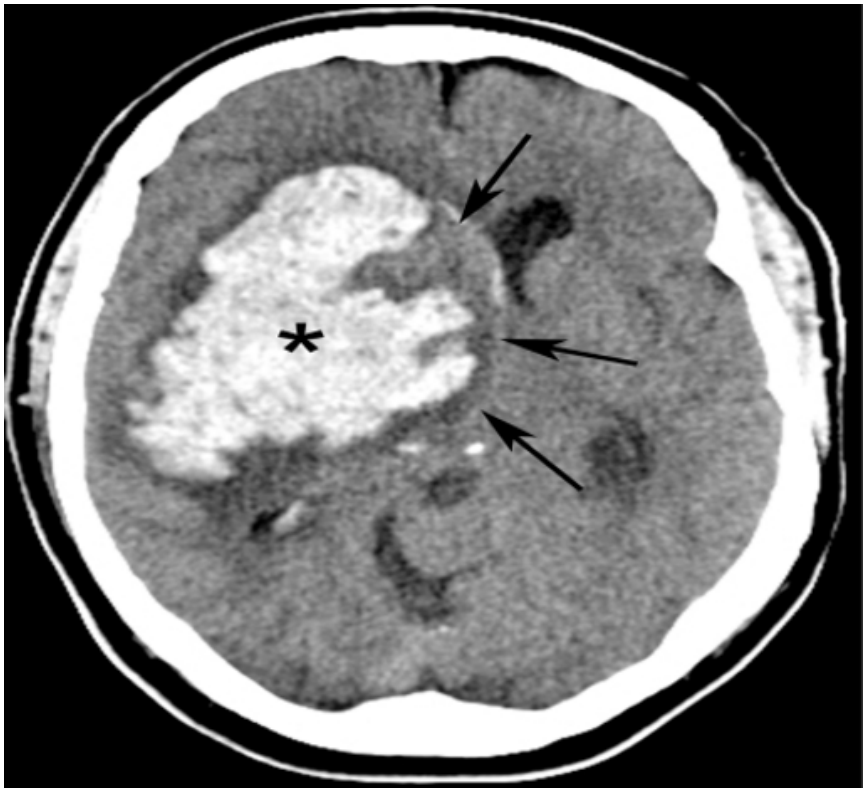
Characteristic	Warfarin	DOACs
Mechanism	Indirect	Direct
Onset of Action	Slow	Rapid
Dosing	Variable	Fixed
Food Interactions	Many	Few
Drug Interactions	Many	Few
Monitoring	Yes	No
Offset	Long	Short

DOACs - disadvantages

Characteristic	Warfarin	DOACs
Dosing Frequency	Once daily	• Once or twice daily, depending on drug and indication
Renal Clearance	None	Variable: • Dabigatran ~80% • Xa Inhibitors ~30% or more depending on drug
Specific antidote	Yes	Variable: • Dabigatran - Idarucizumab (Praxbind) • Xa Inhibitors – none currently
Cost	Very low	Higher

Case study

- Patient with non-valvular atrial fibrillation treated with dabigatran sustains a ground-level fall with head trauma and is transported to the ED with headache and confusion
  - Intraparenchymal hemorrhage identified on CT scan
- Lab values
  - PT: 13 seconds (12.0-15.5), INR 1.0
  - aPTT: 37 seconds (28-35), mildly prolonged
- **Question**
  - **Is there a significant amount of dabigatran present and should the anticoagulant effect be reversed?**



DOACs - laboratory testing

- Liquid chromatography/tandem mass spectrometry (LC-MS/MS) is the gold standard for measuring DOAC concentrations
  - Wide variability in drug concentrations between trough and peak
  - Wide variability in drug concentrations between different patients
- Therapeutic ranges have not been developed for DOACs
  - There is information about steady-state on-therapy ranges
  - Limited information on the relationship between drug levels and clinical outcomes

DOACs - laboratory testing

- FDA: Does not require or recommend routine laboratory monitoring due to predictable pharmacodynamics and pharmacokinetics and wide therapeutic windows
  - There are currently no FDA approved assays for monitoring DOACs
- Physicians: Want option to monitor DOACs in certain clinical scenarios
    - Evaluation of compliance, treatment failure (thrombosis), or patient group where decreased drug exposure is expected (obesity)
    - Life-threatening bleeding or need for emergent/urgent surgery or thrombolysis
    - Overdose or bioaccumulation due to renal failure or other causes
    - Non-urgent periprocedural management

DOACs – laboratory testing

Cuker et al. Hematology Am Soc Hematol Educ Program (2015)
Shih AW and Crowther MA. Hematology Am Soc Hematol Educ Program (2016)
Adcock DM and Gosselin R. Thromb Res 2015;136:7-12

- DOACs target factors in the common pathway of coagulation and so may theoretically prolong most routine clot-based coagulation tests such as PT/INR, aPTT, thrombin time (TT, dabigatran only)
- However……. routine assays demonstrate different sensitivities to different DOACs and across a range of drug concentrations (trough versus peak)
  - Variable sensitivity of different reagents for the same assay type
  - Routine assays are the only tests likely to be available 24 hrs./day but do not reliably determine drug concentration
    - Should laboratories perform dose-response studies using drug standards to determine sensitivities of their reagents? Studies show this may over-estimate reagent sensitivity.

Dabigatran and routine coagulation assays

- **PT/INR** is insensitive to dabigatran and may be normal at typical on-therapy or even above on-therapy drug levels
- **aPTT** is more sensitive to dabigatran than PT/INR but has a curvilinear response curve
  - Normal aPTT suggests little anticoagulant effect
  - aPTT may not be prolonged at on-therapy trough levels in some patients
  - Differences in sensitivity between aPTT reagents

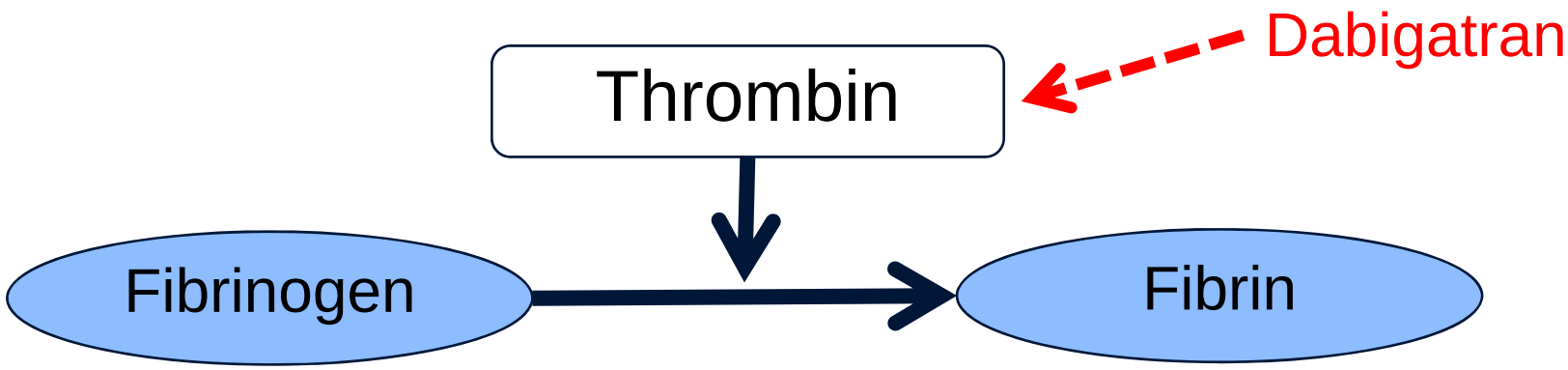
Cuker et al. Hematology Am Soc Hematol Educ Program (2015)

Dabigatran – other tests

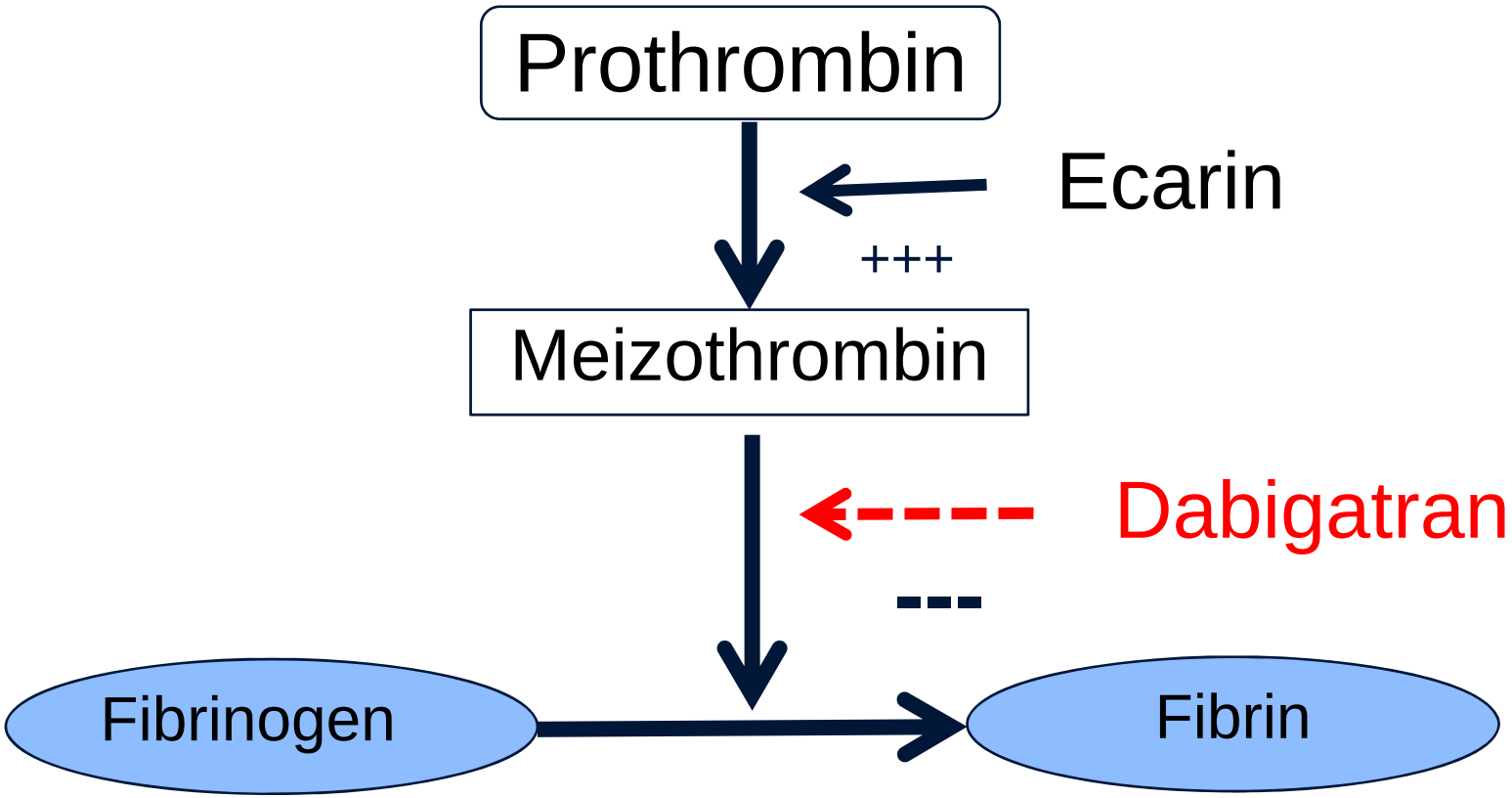
- Thrombin Clotting Time (TT)
  - Thrombin reagent converts fibrinogen to fibrin
  - Ultrasensitive to inhibitory effects of heparin or DTIs (dabigatran) on thrombin
  - Widely available and often used qualitatively
  - Not quantitative unless modified/diluted (dTT)
    - dTT quantitative across range of drug concentrations
    - **dTT not widely available**
- Ecarin Clotting Time (ECT) or chromogenic assay (ECA)
  - Ecarin- a snake venom that converts prothrombin to meizothrombin
    - Meizothrombin inhibited by DTIs (dabigatran) but not by heparin
  - Quantitative across range of drug concentrations
  - **Not widely available**

Cuker et al. Hematology Am Soc Hematol Educ Program (2015)

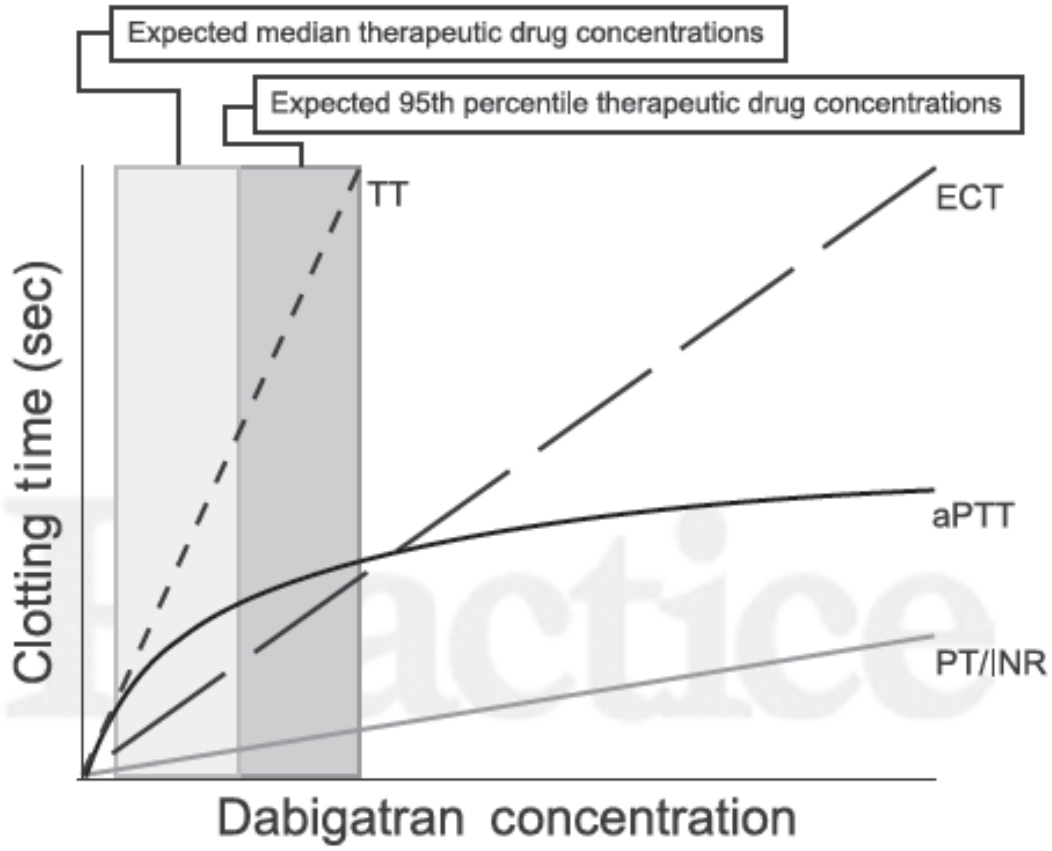
Thrombin clotting time (TT or dTT)



Ecarin clotting time (ECT)



Dabigatran test summary



Abbreviations: aPTT, activated partial thromboplastin time; ECT, ecarin clotting time; INR, international normalized ratio; PT, prothrombin time; TT, thrombin time.

First published in Hospital Practice 2011;39:23-34 © Hospital Practice, a division of JTE Multimedia, LLC

Dabigatran test summary

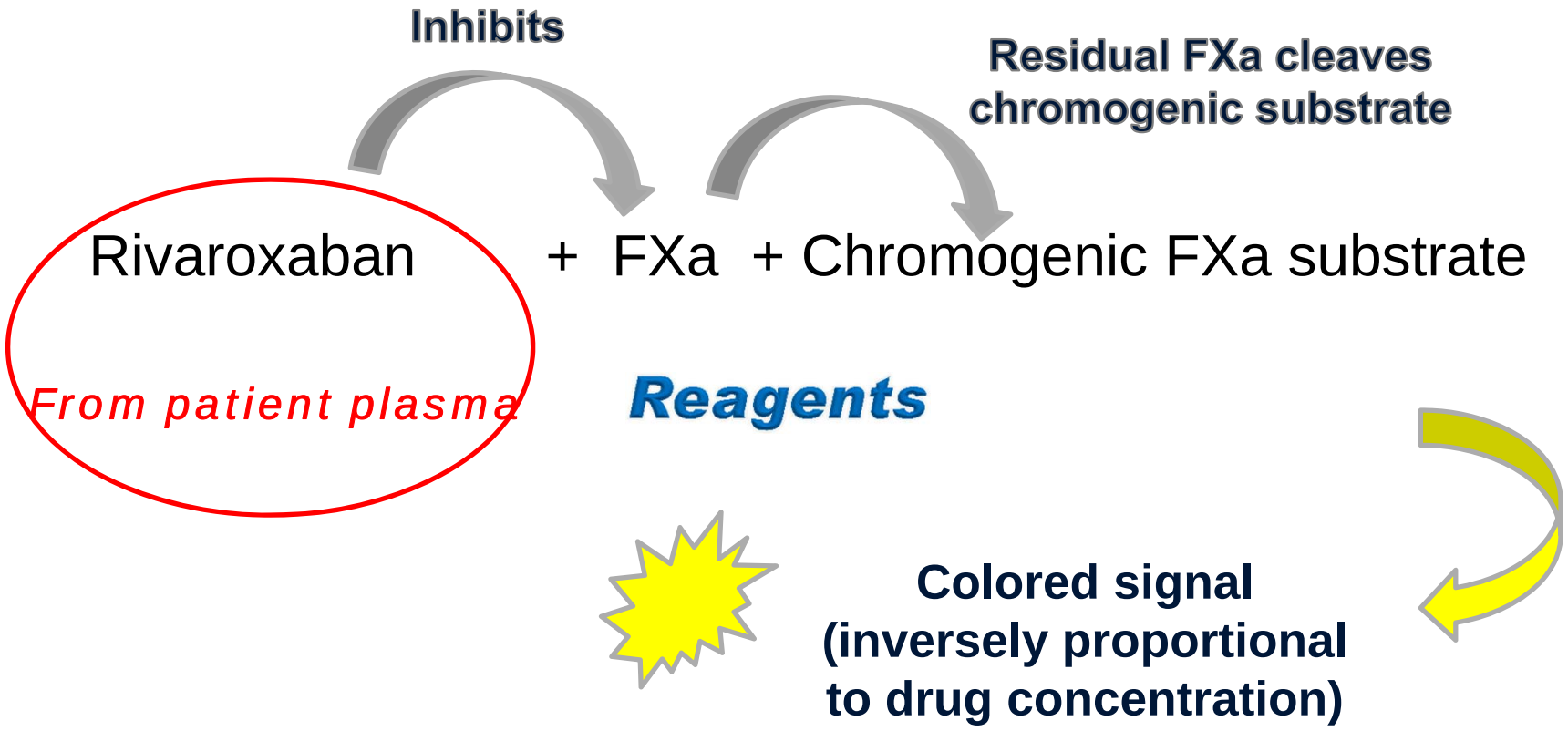
Test	Sensitivity	Availability	Recommendation
PT/INR	Insensitive	Wide	Do not use
aPTT	Relatively sensitive	Wide	Qualitative use; normal aPTT excludes above on-therapy levels; trough levels can have normal aPTT; mild prolongation can represent significant amount of drug; TT may help clarify
TT	Very sensitive/ too sensitive	Wide	Qualitative use; normal TT excludes significant amount of drug
dTT, ECT, or ECA	Quantitative across range of drug concentrations	Limited, not FDA approved*	Most useful for all clinical situations but likely not available
*No FDA-approved dabigatran calibrators or controls are available			

Direct factor Xa inhibitors and routine coagulation assays

- **PT/INR** is sensitive to rivaroxaban and edoxaban
  - Normal PT suggests little anticoagulant effect
  - PT may not be prolonged at on-therapy trough levels in some patients
  - Marked differences in sensitivity between PT reagents
- **PT/INR** is inadequately sensitive to apixaban and may be normal at typical on-therapy or even above on-therapy drug levels
- **aPTT** is less sensitive than PT/INR to direct factor Xa inhibitors and may be normal at typical on-therapy levels
- Calibrated chromogenic anti-Xa test is quantitative across a range of drug concentrations

Cuker et al. Hematology Am Soc Hematol Educ Program (2015)

Method for chromogenic anti-Xa test



Patient result is read from a calibration curve

Direct factor Xa inhibitors – test summary

Test	Sensitivity	Availability	Recommendation
PT/INR	Variable: • Relatively sensitive for rivaroxaban and edoxaban • Insensitive for apixaban	Wide	• Qualitative use for **rivaroxaban and edoxaban only**; normal PT excludes above on-therapy levels of rivaroxaban and edoxaban; trough levels can have normal PT/INR • Do not use for apixaban
aPTT	Insensitive	Wide	Do not use
anti-Xa	Quantitative across range of drug concentrations when calibrated with drug-specific standards	• Wide for heparin • Limited, not FDA approved for DOACs*	Most useful for all clinical situations, but likely not available

*No FDA-approved calibrators or controls are available for the direct factor Xa inhibitor drugs; if not calibrated for specific drug, qualitative use of LMWH-calibrated anti-Xa in emergency situations- if no activity detected suggests little anticoagulant activity; quantitative results are inaccurate

DOACs testing approach

- No routine monitoring
- Appropriate routine and widely available coagulation tests may be used qualitatively in emergent clinical situations to rule out significant anticoagulant effect when effects on local tests are known
  - May guide decision to use idarucizumab to reverse dabigatran
- Due to the lack of FDA approved reagents, and infrequent need for testing, quantitative tests are not widely available
  - Could consider sending to a reference lab in rare less urgent clinical scenarios when turnaround time is not critical

DOACs – interfere with many specialized coagulation tests

- DOACs directly inhibit factors in the common pathway of the coagulation cascade
- Many coagulation tests are functional measurements of coagulation reactions/factors (clot-based, chromogenic substrate) and can be affected by DOACs
  - Antigen measurements are not affected but are usually not the recommended first-line tests
- Best to avoid specialized coagulation testing in patients on DOACs
  - Many assays are optimized to diminish the effects of traditional anticoagulants (warfarin, heparin) but this is not currently possible for DOACs (no neutralizing agents for lab use)
  - Have a low threshold for suspecting test interference if results are unexpected in a patient on a DOAC

DOACs - interfere with many specialized coagulation tests

https://arupconsult.com/content/hypercoagulable-states
Adcock DM and Gosselin R. Thromb Res 2015;136:7-12

- Fibrinogen assays
  - Potential under-estimation of activity
- Factor assays
  - Potential under-estimation of activity
- Lupus anticoagulant testing
  - Potential false-positive or false-negative results
- Thrombophilia testing
  - Potential false-negative for APC resistance
  - Potential over-estimation of activity for proteins C, S, antithrombin

Note: Effects are method dependent

Summary

- The direct oral anticoagulants (DOACs) currently include one direct thrombin inhibitor (dabigatran) and three direct factor Xa inhibitors (rivaroxaban, apixaban, edoxaban) which have various approvals for treatment and prevention of thromboembolic events
- DOACs do not require routine laboratory monitoring due to predictable pharmacodynamics, pharmacokinetics, and wide therapeutic windows
- DOACs have variable effects on routine coagulation tests, such as PT/INR and aPTT, depending on the specific drug/concentration, patient/indication, and assay/reagent
- Understanding DOAC effects on local routine coagulation tests may allow qualitative use of routine tests in emergent clinical situations but these tests do not reliably determine drug concentrations
- Quantitative tests for the new drugs exist but are not widely available and none are FDA approved
- DOACs can interfere with specialized coagulation testing and this testing should generally be avoided when DOACs are present

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