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PEARLS OF LABORATORY MEDICINE

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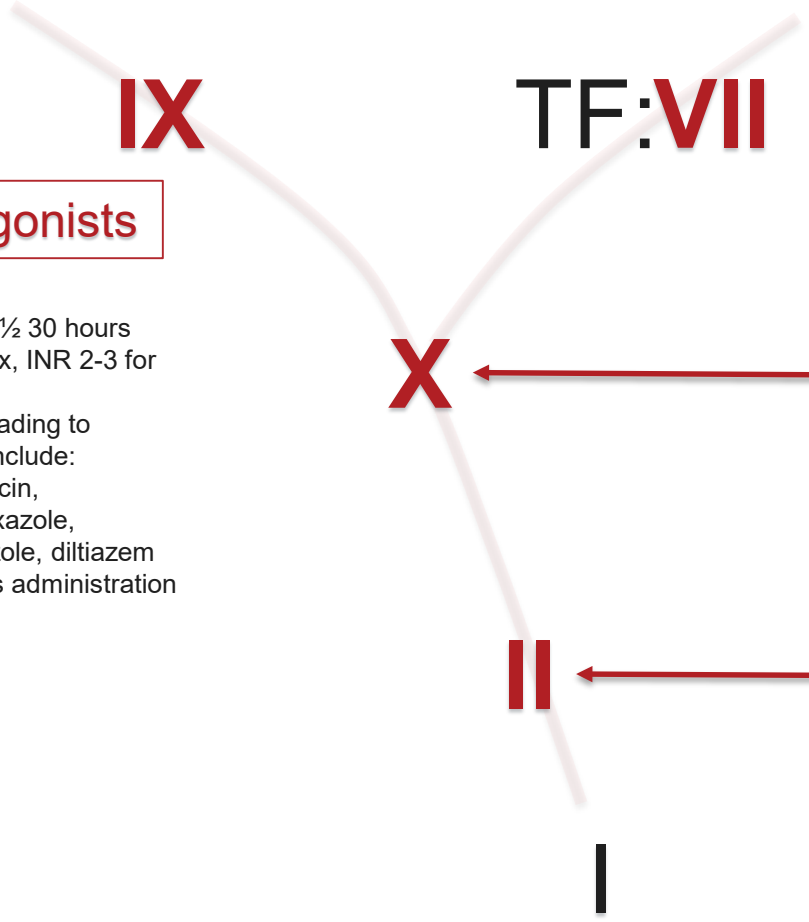
Principles of Oral Anticoagulant Reversal

Learning Objectives

After Participating in this Activity, Learners Will be Able to:

- Describe general pharmacologic properties of modern anticoagulants
- Understand aspects of principal reversal strategies
- Develop a therapeutic approach toward anticoagulant related bleeding

Learning Objective 1:
Describe general pharmacologic properties of modern anticoagulants



Vitamin K Antagonists

- Warfarin
- Long duration of effect, t ½ 30 hours
- Narrow Therapeutic Index, INR 2-3 for most applications
- Drug-drug interactions leading to increased bleeding risk include: ciprofloxacin, clarithromycin, trimethoprim sulfamethoxazole, metronidazole, voriconazole, diltiazem
- Durable reversal requires administration of vitamin K

NOACs
Non-vitamin K Oral Anti-Coagulants

- Short duration of effect, t ½ <15 hrs
- No standard laboratory monitoring
- Prolongation of PT, PTT, mixing studies

Factor Xa Inhibitors

- Rivaro-Xa-ban, Api-Xa-ban, Edo-Xa-ban
- 30% renally cleared; 50% Edoxaban
- Anti-Factor Xa activity level.
- Drug-drug interactions leading to increased/prolonged effect include: azole antifungals, amiodarone, dronedarone, quinidine, verapamil

Direct Thrombin Inhibitors

- Dabigatran
- 80% renally cleared
- Thrombin Time – qualitative test
- Drug-drug interactions leading to increased/prolonged effect include: azole antifungals, HIV protease inhibitors

Learning Objective 2:
Understand characteristics of principal reversal strategies

- Restoration of Endogenous Hemostatic Potential
  - Stop the anticoagulant
  - If warfarin, administer vitamin K
- Administration of Exogenous Clotting Factors
  - Plasma or Prothrombin Complex Concentrate
  - PCC Contains vitamin K dependent factors
- Administration of a Targeted Antidote
  - Andexanet alfa (reverses FXa Inhibitor effect)
  - Idaracizumab (reverses Dabigatran effect)

Learning Objective 3:
Develop a therapeutic approach toward the bleeding patient

- **Assess for and address presence of concomitant coagulopathy**
  - Examples may include: disseminated intravascular coagulation, hypofibrinogenemia, uremia, ongoing antiplatelet therapy.

- **In warfarin treated patients, a negligible impact of plasma/PCC upon the INR is expected when:**
  - Pretransfusion INR is minimally elevated (ie, < 2.0)
  - ***Replacement therapies generally have their greatest impact upon the INR when the INR > 2.0***

- **Regardless of anticoagulant, aggressive hemostatic use should likely be avoided when thrombotic risk high and consequences of bleeding low**
  - Such treatment *may induce* thrombotic complication

Learning Objective 3:
Develop a therapeutic approach toward the bleeding patient

Incorporate Thrombotic Risk Assessment into Decision Making

High Thrombotic-Risk Conditions*

$CHADS_2$ Score of 5-6*

Mechanical Heart Valve
Especially: Mitral Valve Position or Caged Ball/Tilting Disc Aortic Valve

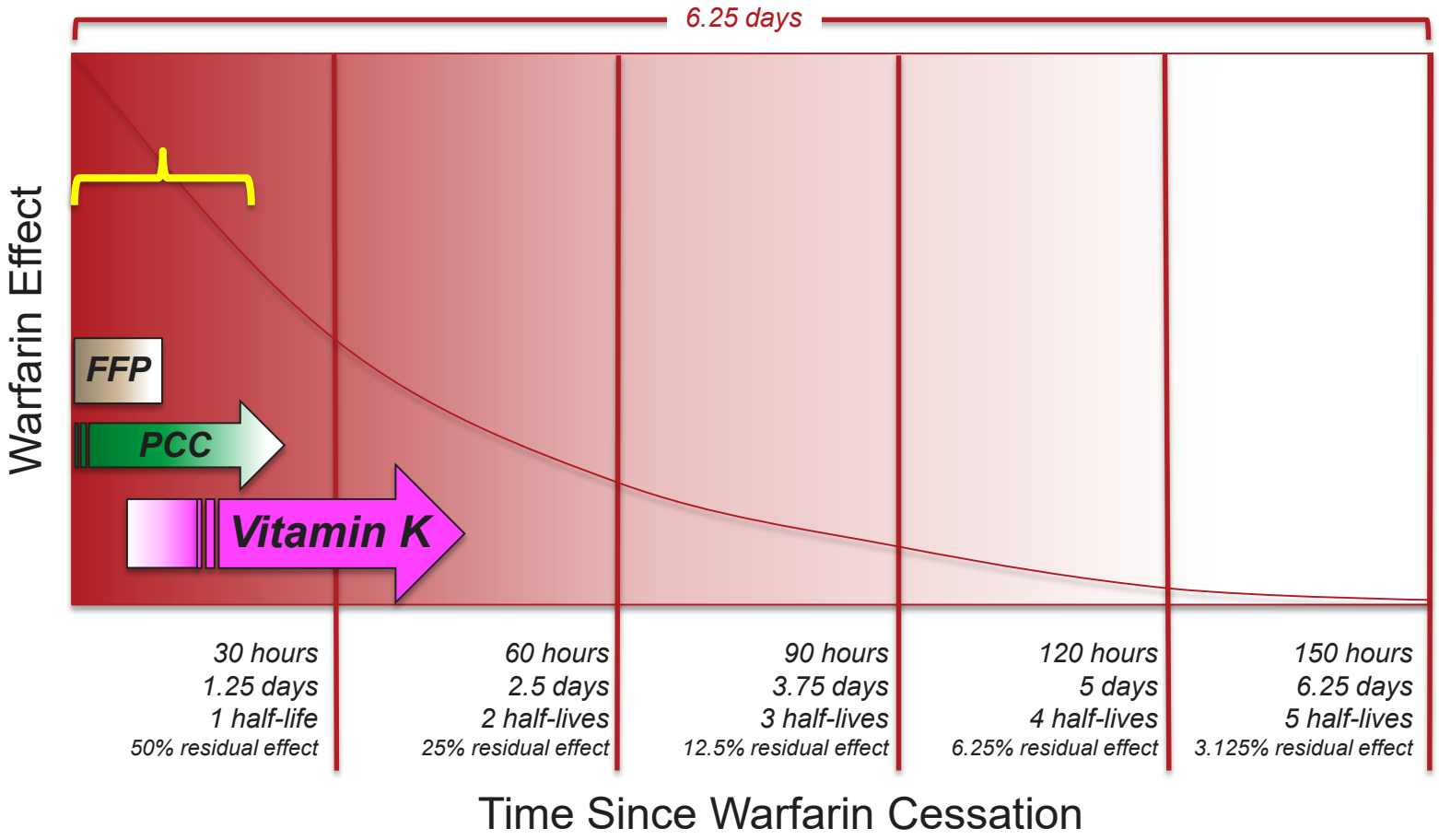
History of thrombotic event, MI, DIC, CVA, TIA, unstable angina pectoris, severe PVD within 3 months

Known history of antiphospholipid antibody syndrome

Active Cancer (within 6 months or palliative; particularly if thrombotic event in association with active cancer)

- ***Each patient should be considered on a case-by-case basis, other factors may also contribute to thrombotic risk***
- ***This list compiled from references 3, 7.***

Learning Objective 3:
Develop a therapeutic approach toward the bleeding patient



Learning Objective 3:
Develop a therapeutic approach toward the bleeding patient

- NOAC related bleeding
  - Short duration of effect (<15 hours)
    - *Tincture of time*
  - Assess for scenarios that prolong duration of effect
    - *Renal Dysfunction (especially with dabigatran)*
    - *Drug-Drug interactions*
  - Idaracizumab, Andexanet alfa, PCC

Conclusions

- Information Gathering:
  - Specific anticoagulant, time of last dose, presence of drug-drug interactions or acute kidney injury (especially for dabigatran)

- Clinical Assessment:
  - Severity of coagulation laboratory derangement, site and severity of bleeding, hemostatic measures already taken
  - Response thus far to ongoing support and resuscitation – is the patient hemodynamically and neurologically stable?

- Thrombotic Risk:
  - Presence of high-risk features that raise:
    - risk of iatrogenic thrombosis during aggressive reversal, or
    - concern for prolonged absence of anticoagulation

Conclusions

- If Warfarin:
  - Discontinue warfarin, vitamin K hastens recovery of hemostatic capacity
  - Onset of vitamin K effect is delayed; 15 hours or more with IV therapy
  - Clinical severity and need for emergent surgery may therefore necessitate replacement therapy (PCC vs Plasma)

- If New Oral Anticoagulant:
  - Discontinue agent; short duration of action → tincture of time
  - Supportive measures, assess for factors that may prolong drug effect
  - Praxbind is a specific antidote for dabigatran
  - Andexanet alfa, the specific antidote for Factor Xa inhibitors, not yet available; PCC may be considered but clinical data is limited

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Reference Slide: Additional Pharmacologic Information

Agent	Mechanism	Typical Dosing	Half-Life (hrs)
Warfarin	Inhibition of VKORC1	2-10 mg/day	S-Enantiomer (CYP2C9) T ½: 24-33 hrs R-Enantiomer (CYP3A4, others) T ½: 35-48 hrs
Rivaroxaban	FXa Inhibitor	A Fib: 20 mg/day VTE Px/Tx: 10/20 mg/day	33% Renal Clearance T ½: 8-9 (healthy 29-45 y/o) T ½: 11-13 (elderly)
Apixaban	FXa inhibitor	Afib: 5 mg BID VTE Px/Tx: 5 mg BID	27% Renal Clearance T ½: 7-8 hrs (Cr Clr >50) T ½: 17-18 hrs (Cr Clr 30-50)
Edoxaban	FXa inhibitor	Afib: 30-60 mg QD VTE Tx: 30-60 mg QD	50% Renal Clearance T ½: 10-14 hrs
Dabigatran	FIIa inhibitor	Afib: 75-150 mg BID VTE Tx: 150 mg BID	80% Renal Clearance T ½: 14-17 hrs (Cr Clr >50) T ½: 16-18 hrs (Cr Clr 30-50)

Disclosures/Potential Conflicts of Interest

Upon Pearl submission, the presenter completed the Clinical Chemistry disclosure form. Disclosures and/or potential conflicts of interest:

- **Employment or Leadership**: No disclosures
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- **Honoraria:** No disclosures
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