Management of Bleeding in the Anticoagulated Patient

"Short Snappers" CSIM 2015

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Disclosures

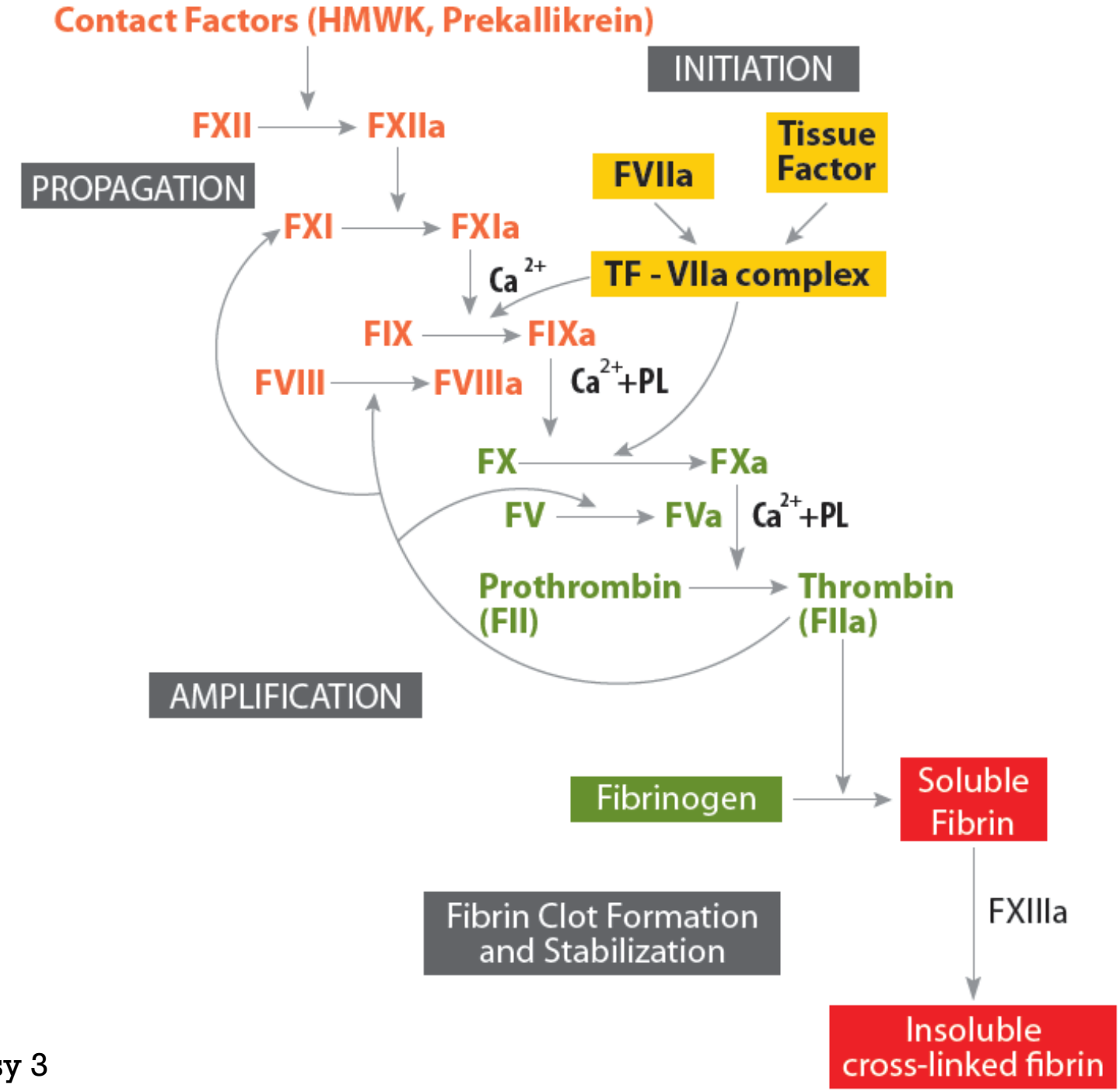
- Off label use of PCC and aPCC will be discussed
- My centre participates in research studies with the following companies
  - Bayer Inc
  - Janssen Research & Development, LLC

Objectives

- Review the mechanism of action of commonly used anticoagulants
- Develop a generalized approach to managing the anticoagulated bleeding patient
- Develop strategies to reverse specific anticoagulants, including antidotes when available

Outline

- Review MOA:
  - Warfarin, UFH, LMWH, Direct oral anticoagulants
- Review a framework to approaching the bleeding patient
  - HASHTI
- Reversal of anticoagulants
  - Antidotes
  - Specific approaches to DOAC associated bleeding
- References
- Questions


Contact Factors (HMWK, Prekallikrein)
INITIATION
FXII
FXIIa
PROPAGATION
FVIIa
Tissue Factor
FXI
FXIa
Ca 2+
TF - VIIa complex
FIX
FIXa
FVIII
FVIIIa
Ca2+ +PL
FX
FXa
FV
FVa
Ca2+ +PL
Prothrombin (FII)
Thrombin (FIIa)
AMPLIFICATION
Fibrinogen
Soluble Fibrin
FXIIIa
Fibrin Clot Formation and Stabilization
Insoluble cross-linked fibrin

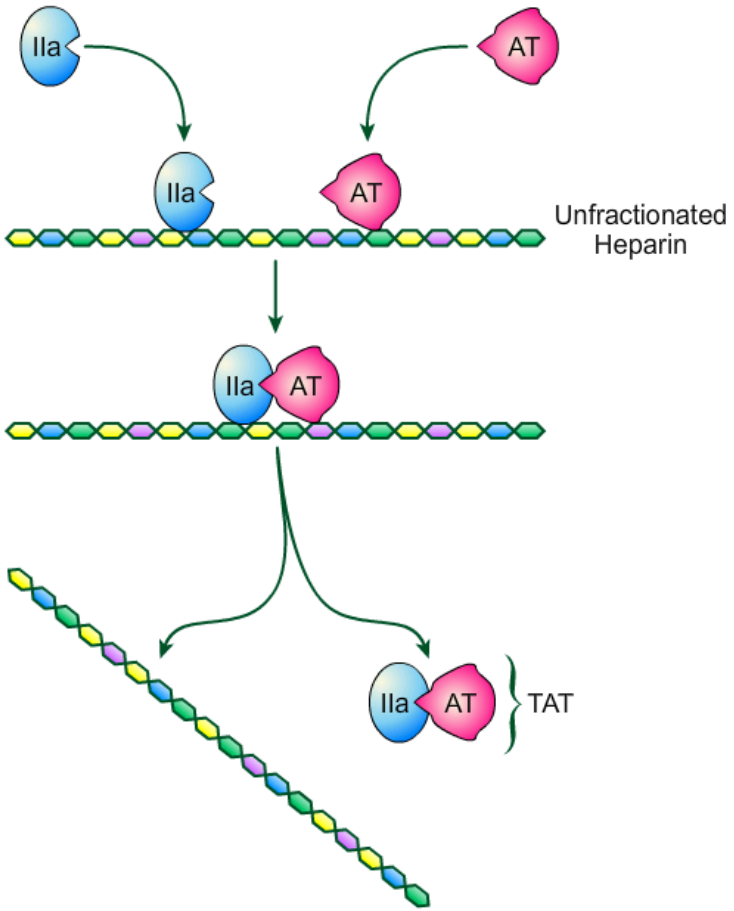
MOA: Warfarin

- Oral vitamin K antagonist
  - Decreases production of vitamin K dependent factors by limiting carboxylation
- Vitamin K dependent factors:
  - FII, FVII, FIX, FX, Protein C and Protein S
- Hepatically cleared
- T½ 36-42 hrs
- Monitored by PT- converted to INR

MOA: UFH

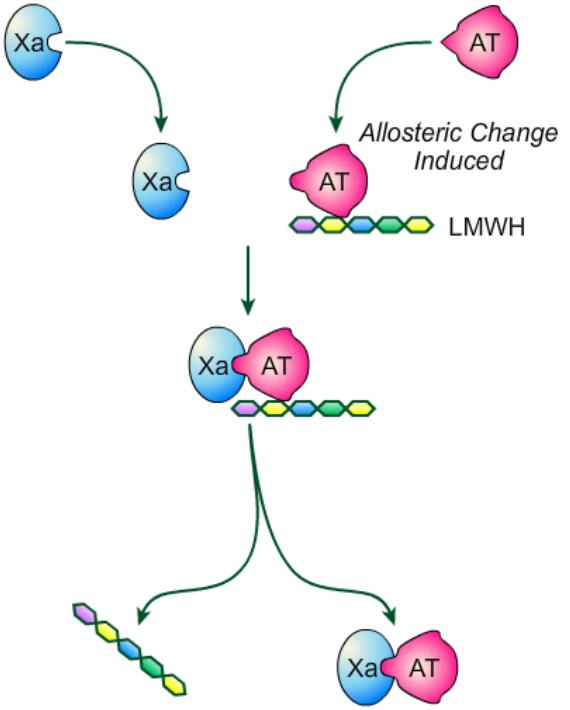
- Long chain glycosaminoglycans that bind thrombin and antithrombin, induce a conformational change
  - Activates Antithrombin
  - "Indirect" anticoag inhibits

    FIIa, Xa, IXa, XIa, XIIa
- Hepatically cleared
- T½ 60-90 mins
- Monitored by PTT



MOA: LMWH

- Shorter chain glycosaminoglycans bind antithrombin and activates antithrombin
  - Less inhibitory effect on thrombin as does not bind
  - Indirect anticoag: inhibits Xa and IIa
- 80% renally cleared
- T½ 3-6 hrs
- Monitored by anti-Xa activity



MOA: Dabigatran

- Oral thrombin inhibitor
- "Direct" anticoag: inhibits IIa
  - Prevents conversion of fibrinogen to fibrin
- Primarily cleared by kidneys
- T½ 12-18 hrs
- Does not requiring monitoring:
  - Will variably affect PT/PTT/TT
  - Generally a normal thrombin time suggests no dabigatran activity

MOA: Rivaroxaban

- Oral inhibitor of Factor Xa
- "Direct" anticoag
- 66% renal excretion
- T½ 11-13 hrs
- Monitoring not required
  - Variably effects PTT and PT

MOA: Apixaban

- Oral inhibitor Factor Xa
- "Direct" anticoag
- 25% renally cleared
- T½ 8-15 hrs
- Monitoring not required:
  - Variably effects PTT, PT

Approach to the Anticoagulated Bleeding Patient

- "HASHTI"
  - Hold further doses
  - Consider Antidote
  - Supportive treatment
    - Fluid rescusitation
    - Hemodynamic support/monitoring
  - Hemostatic measures: local or surgical
    - Anti-fibrinolytics
  - Transfusion
    - RBC: severe or symptomatic anemia
    - Platelets: if low platelets or on long-acting anti-platelet
  - Investigate source of bleeding

Cushman, Lim and Zakai. ASH 2014.

Antidotes : Warfarin

- Vitamin K: 1-10mg IV/PO
  - Takes 6-24 hours to reverse warfarin
- FP: 10-30ml/kg
  - Repletes all coag factors but will not fully correct INR
  - Large volumes
  - Short T ½ life: repeat dosing at 6 hrs
- PCC: 25-50u/kg
  - Rapidly corrects INR in warfarin treated patients
  - Short T½ 6 hrs
  - Give with IV Vitamin K

1. Reversal of Warfarin (Coumadin®, Jantoven®)

Non-Urgent	Urgent (Not bleeding)	Urgent (Bleeding)

• Stop 5 days prior to procedure
• Check INR 1-2 days prior
  ◦ If INR >1.5 administer vitamin K 1-2 mg PO
	• If procedure can be delayed 6-24 hours, vitamin K 5-10 mg PO/IV; otherwise:
	  ◦ FFP or PCC prior to procedure. Repeat in 6-12 hours if INR >1.5 and
	  ◦ Vitamin K 5-10 mg PO/IV if sustained reversal is desired
		• **HASHTI**
		• Vitamin K 5-10 mg IV; repeat in 12 hours as needed
		• PCC or FFP; repeat every 6 hours as needed

Cushman, Lim and Zakai. ASH 2014.

Antidotes: Heparin

- Protamine sulfate: 12.5-50mg IV

3. Protamine Dose for Reversal of Heparin and LMWH

Agent*	Half-Life	Protamine Sulfate Dosing for Reversal
All		**Maximum dose is 50 mg**
Heparin	1-2 hours	• 1 mg per 90-100 units heparin given in previous 2-3 hours ◦ e.g., 25-35 mg if 1000-1250 units/hour heparin infusion
Enoxaparin	4.5 hours	• 1 mg per 1 mg Enoxaparin in previous 8 hours
Dalteparin	2.2 hours	• 1 mg per 100 units Dalteparin in previous 8 hours
Tinzaparin	3.9 hours	• 1 mg per 100 units Tinzaparin in previous 8 hours

Cushman, Lim and Zakai. ASH 2014.

Antidotes: DOACs

- Idarucizumab
- Andexanet Alfa
- PER977

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Idarucizumab for Dabigatran Reversal

Charles V. Pollack, Jr., M.D., Paul A. Reilly, Ph.D., John Eikelboom, M.B., B.S., Stephan Glund, Ph.D., Peter Verhamme, M.D., Richard A. Bernstein, M.D., Ph.D., Robert Dubiel, Pharm.D., Menno V. Huisman, M.D., Ph.D., Elaine M. Hylek, M.D., Pieter W. Kamphuisen, M.D., Ph.D., Jörg Kreuzer, M.D., Jerrold H. Levy, M.D., Frank W. Sellke, M.D., Joachim Stangier, Ph.D., Thorsten Steiner, M.D., M.M.E., Bushi Wang, Ph.D., Chak-Wah Kam, M.D., and Jeffrey I. Weitz, M.D.

Antidote: DOACs

- Idarucizumab: monoclonal antibody fragment
  - Binds dabigatran with affinity 350 times that of thrombin
  - Neutralizes dabigatran activity
  - T½ 45 mins
  - Complete reversal of dabigatran activity

Antidotes: DOACs

- REVERSE-AD:
  - Interim results of 90 patients on dabigatran and requiring emergency surgery or uncontrolled bleeding
    - Primary endpoint % reversal based on diluted Thrombin Time or Ecarin clotting time
  - 5 g idarucizumab given
    - dTT normalized in 98% and 93% of patients
    - ECT normalized in 89% and 88% of patients
    - Sustained reversal over 12hrs in >90%
  - Thrombotic events: 1 early DVT
    - 4 events 7-26 days after

Pollack et al. Pollack et al. NEJM 2015; 372(6):511-520.

Antidotes: DOACs

- Andexanet Alfa
  - Recombinant human FXa variant
  - Target: FXa inhibitors
  - Currently in clinical development
  - IV bolus and infusion with short ½ life
- PER977
  - Small synthetic molecule
  - Targets: UFH, LMWH, FXa inhibitors, anti-thrombin
  - Currently in clinical development

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Cushman, Lim and Zakai. ASH 2014.

Specific approaches for DOACs

- Coagulation Factor Replacement
  - PCC: no high quality evidence establishing efficacy and safety of PCC for reversal
  - Appears to normalize PT and endogenous thrombin potential in people on rivaroxaban
    - Similar results were not seen with dabigatran
    - Animal models inconclusive
  - Preferred agent for rivaroxaban and apixaban

Siegal et al. Blood. 2014.

Specific Approaches for DOACs

- Activated PCC (FEIBA)
  - Contains FII, VI, IX, X in activated form
  - Low risk of thrombosis
  - Clinical evidence lacking
  - In vitro data suggests that aPCC corrects lab abnormalities caused by DOACs
  - Case report of aPCC use in dabigatran-treated patient
  - Preferred agent for dabigatran

Siegal et al. Blood. 2014.

Specific approaches for DOACs

- Recombinant FVIIa
  - Rapidly corrects elevated INR due to warfarin
    - Does not restore hemostasis as only replaces FVIIa
  - Short T ½ : dosing q2 hrs
  - No clinical studies
  - Animal models: failed to ameliorate bleeding in animals treated with dabigatran or rivaroxaban
  - Variable effects on lab coagulation abnormalities
  - Higher risk of thrombosis (5-10%)

Cushman, Lim and Zakai. ASH 2014.

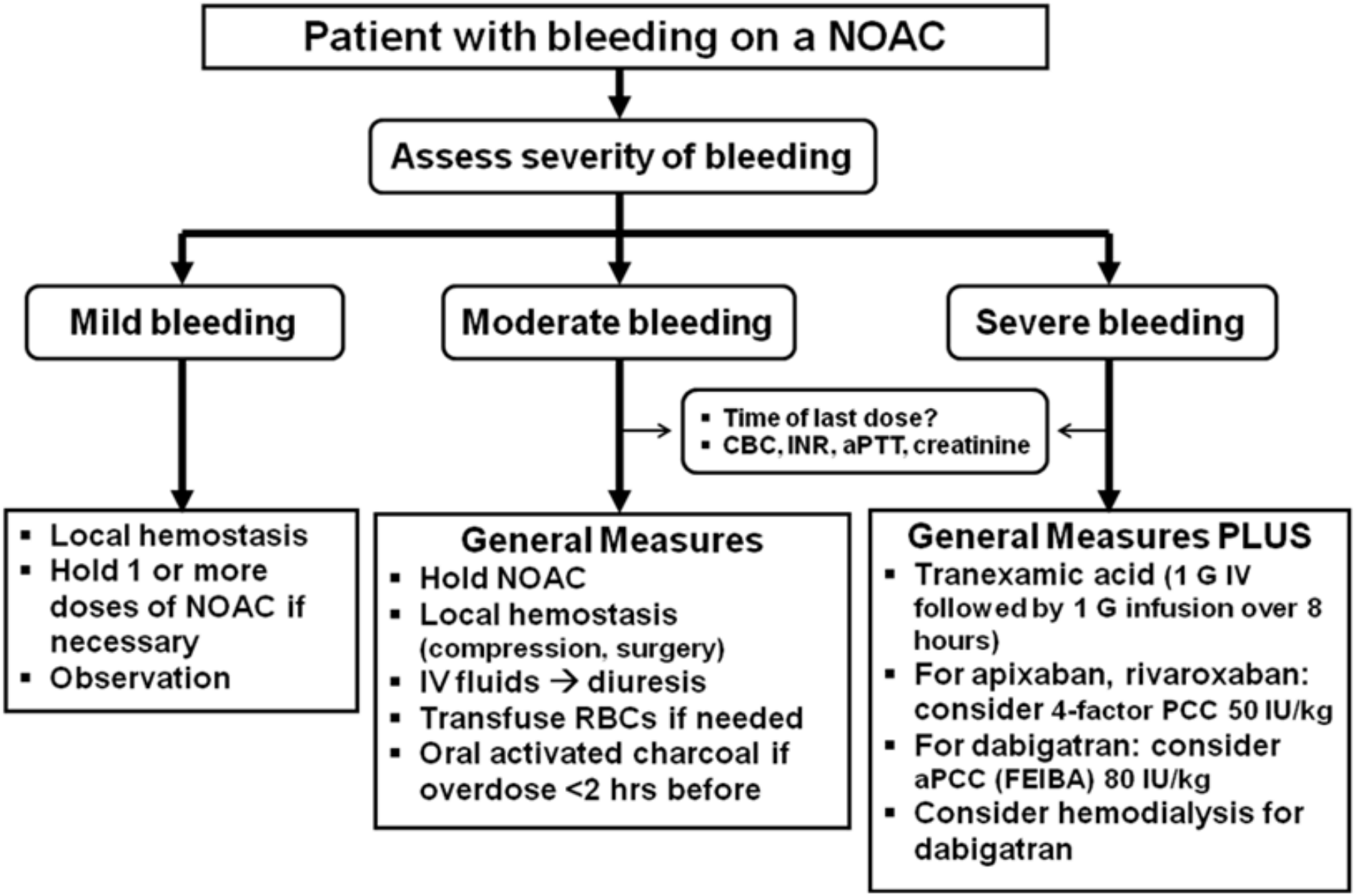
Specific Approaches to DOACs

- Hemodialysis
  - Rivaroxaban and apixaban: protein bound, HD not effective
  - Dabigatran:
    - 49-68% of active drug removed by HD
    - Better removal with longer duration of dialysis

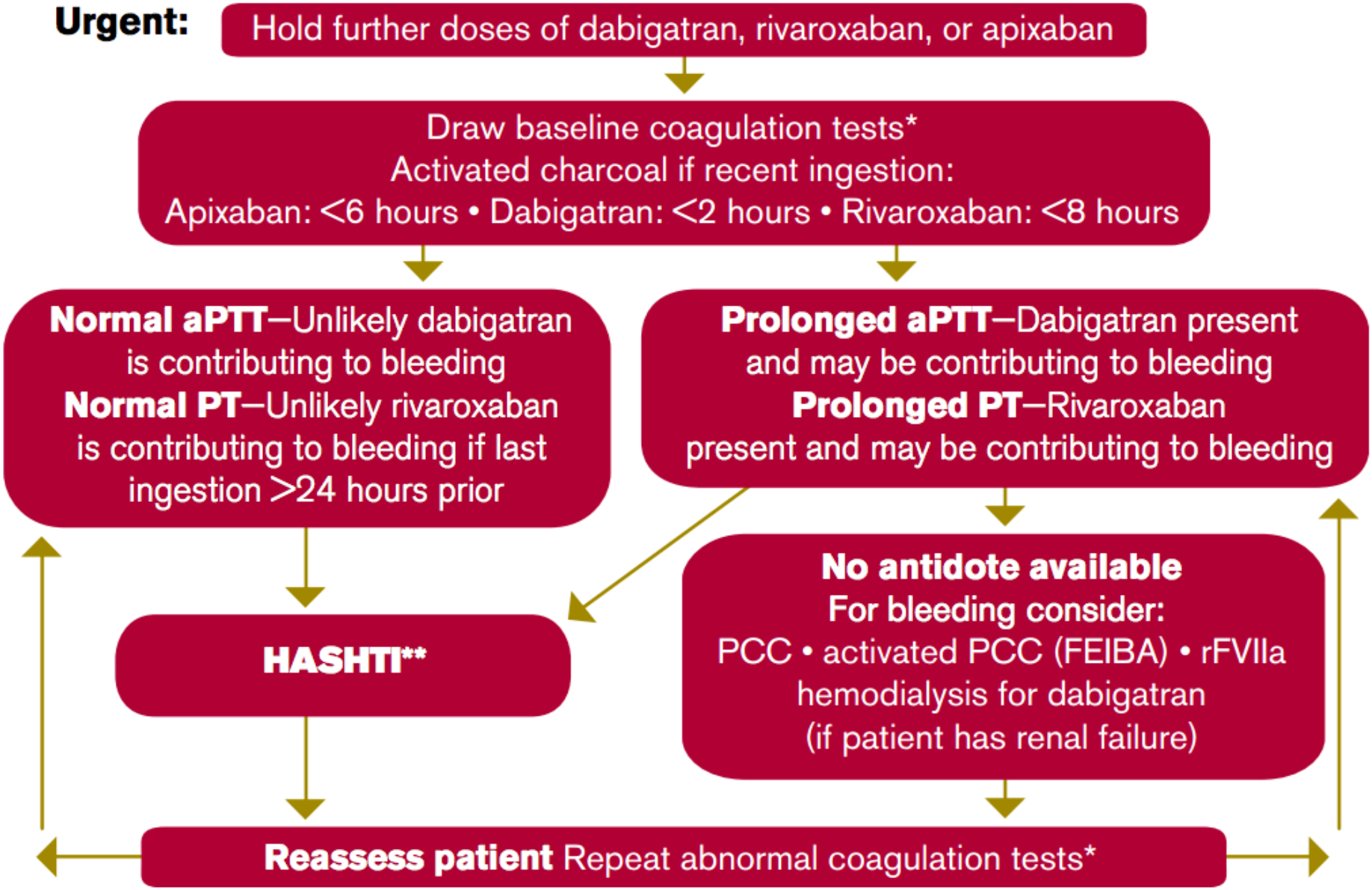
Table 1: Pro-Hemostatic Agents and Their Potential Role in NOAC-Associated Bleeding[a]

Agent	Dabigatran	Rivaroxaban or Apixaban[b]
4-Factor Prothrombin Complex Concentrate (PCC; Beriplex, Octaplex)	Possibly beneficial	Probably beneficial
3-Factor Prothrombin Complex Concentrate	No available evidence	No available evidence
Activated 4-Factor Prothrombin Complex Concentrate (FEIBA)	Probably beneficial	Probably beneficial
Recombinant activated Factor VII (Novoseven, Niastase)	Possibly beneficial	Possibly beneficial
Fresh frozen plasma	Probably ineffective	Probably ineffective
Cryoprecipitate	Probably ineffective	Probably ineffective
Antifibrinolytic agents (aminocaproic acid - Amicar; tranexamic acid - Cyclokapron)	No available evidence but may be helpful	No available evidence but may be helpful

Figure 1: Suggested Strategy for Management of NOAC-Associated Bleeding



Adapted from Segal DM, et al (2014).



Cushman, Lim and Zakai. ASH 2014

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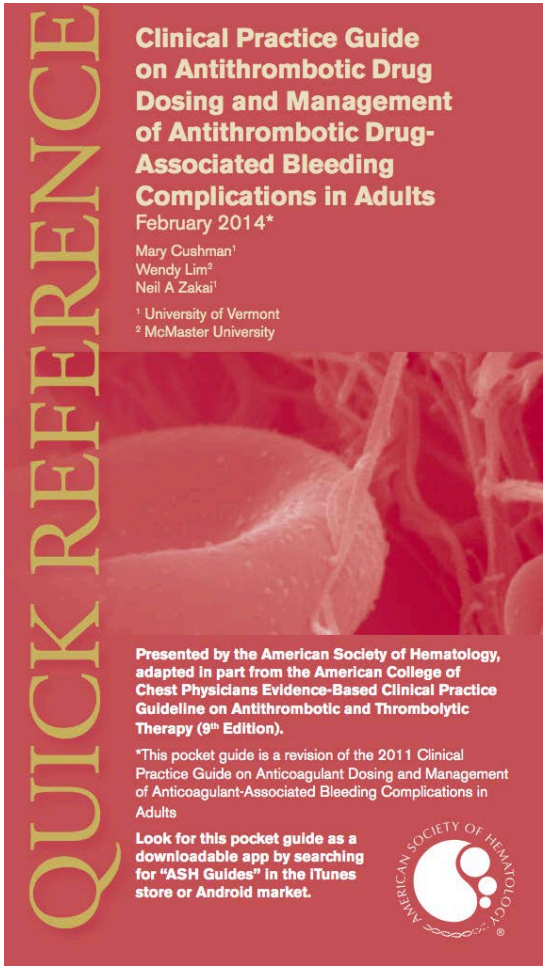
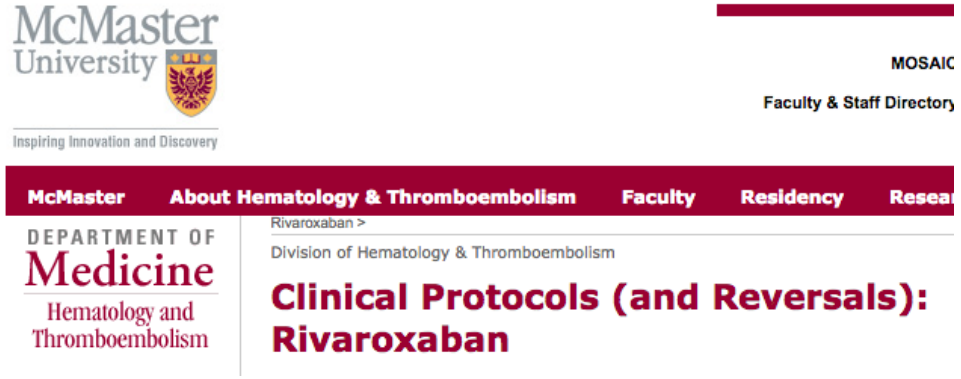
Resources





Thrombosis Canada
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DEDICATED TO FURTHERING EDUCATION & RESEARCH IN THROMBOTIC DISEASE

References

- Cushman, Lim and Zakai. Clinical practice guide on antithrombotic drug dosing and management of antithrombotic drug-associated bleeding complications in adults. ASH 2014.
- Siegal et al. How I treat target-specific oral anticoagulant-associated bleeding. Blood. 2014;123(8):1152-1158.
- New/Novel Oral Anticoagulants (NOACs): Management of bleeding. www.thrombosiscanada.ca accessed October 2015.
- Mechanisms in Hematology. www.mechanismsinhematology.com
- Pollack et al. Idarucizumab for dabigatran reversal. NEJM 2015; 372(6):511-520.

Questions?