Anticoagulant Reversal

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MCWBD Multidisciplinary Clinic for Women with Bleeding Disorders

Medicine UNIVERSITY OF TORONTO

St. Michael's Inspired Care. Inspiring Science.

Disclaimer

- No relevant financial conflicts of interest

Objectives

- Review why anticoagulant reversal protocols are essential during a MH
- Review different anticoagulant reversal protocols
- Differentiate small versus large hospital anticoagulant reversal challenges

Hemostasis Simplified

Trauma to the endothelium = TRIGGER

-Platelets 1[st] the scen

-VWF glu platelets to endotheli

Coagulation factors assemble to make a clot

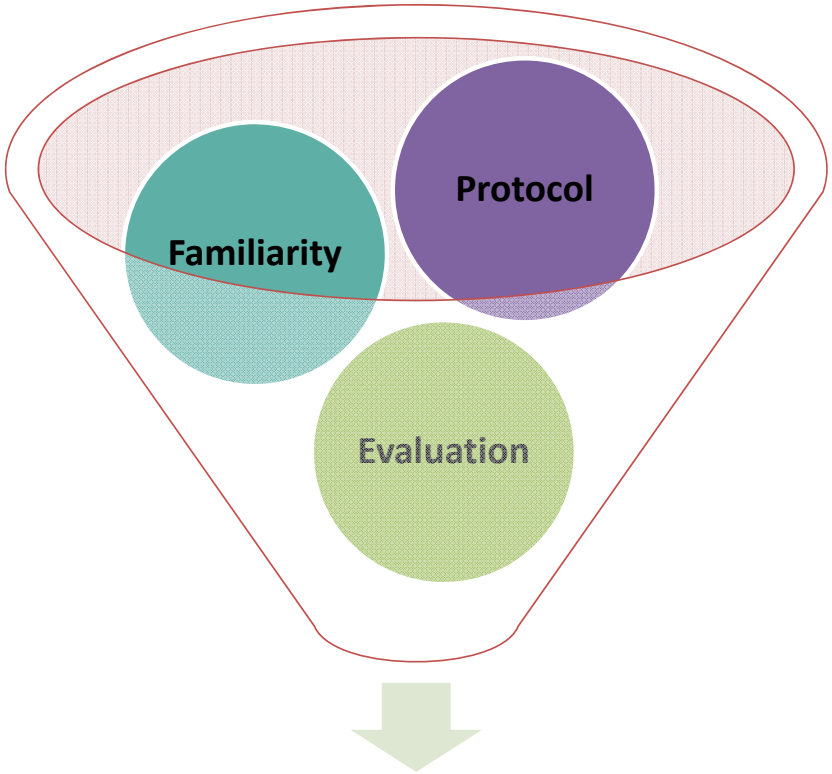
= Thrombin generation → Fibrin clot formation

ditional rs stabilize clot

Fibrinolytic system breaks down clot

MH Involving an Anticoagulant

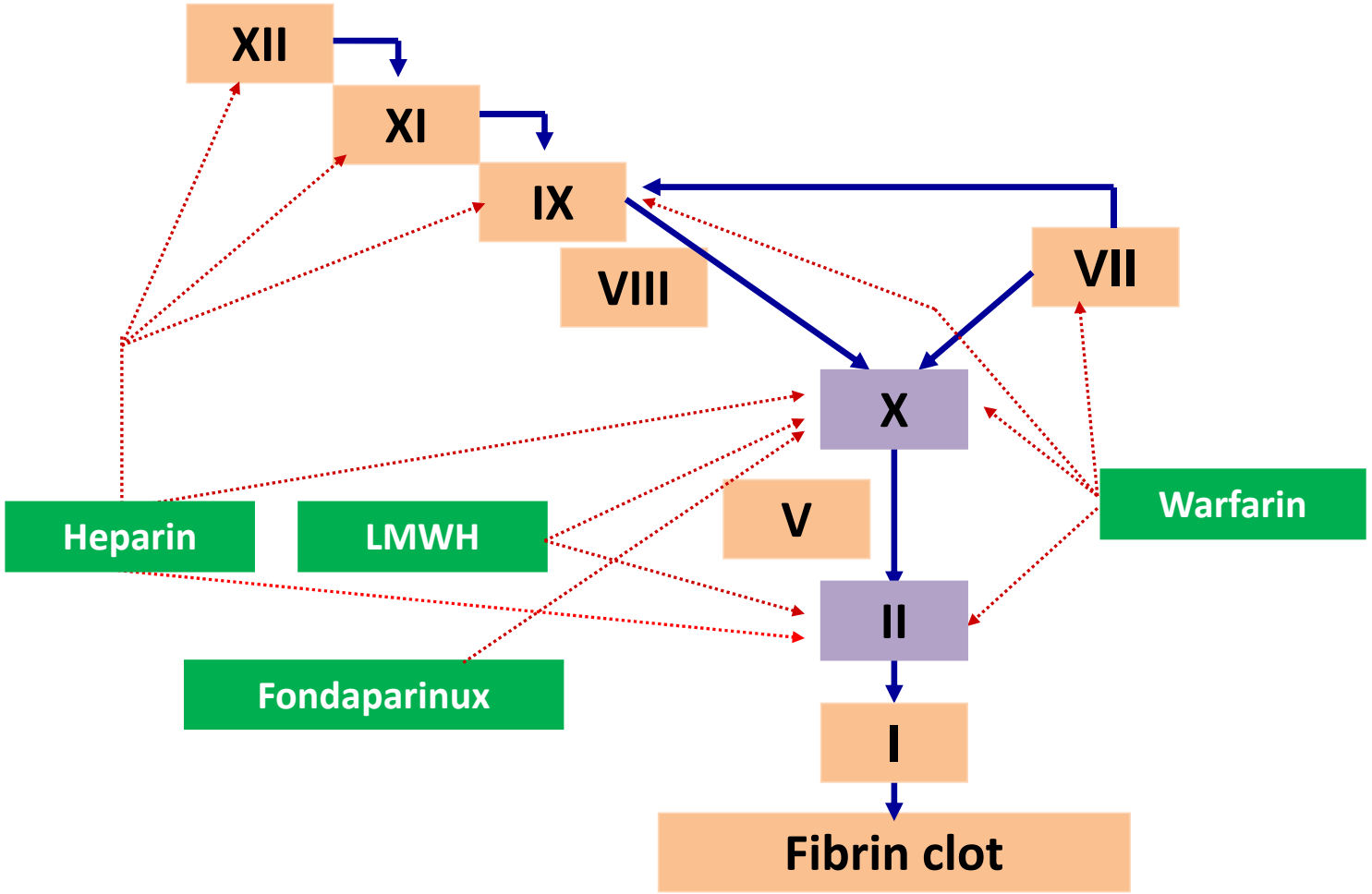
Anticoagulant Reversal Policy



Brave New World

Best practice, Consistency & Speed

Mechanisms of Actions of Traditional Anticoagulant Drugs



- Multi-target
- Majority are inhibitors except **warfarin**
- **Heparin**, **LMWH**, **Fondaparinux** all require binding with Antithrombin to act = "Indirect"

Traditional or Older Anticoagulants

Heparin

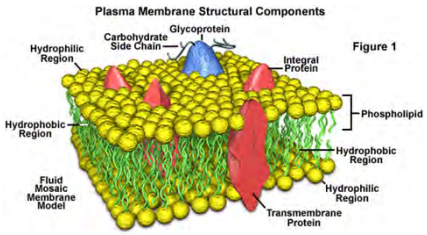
LMWH

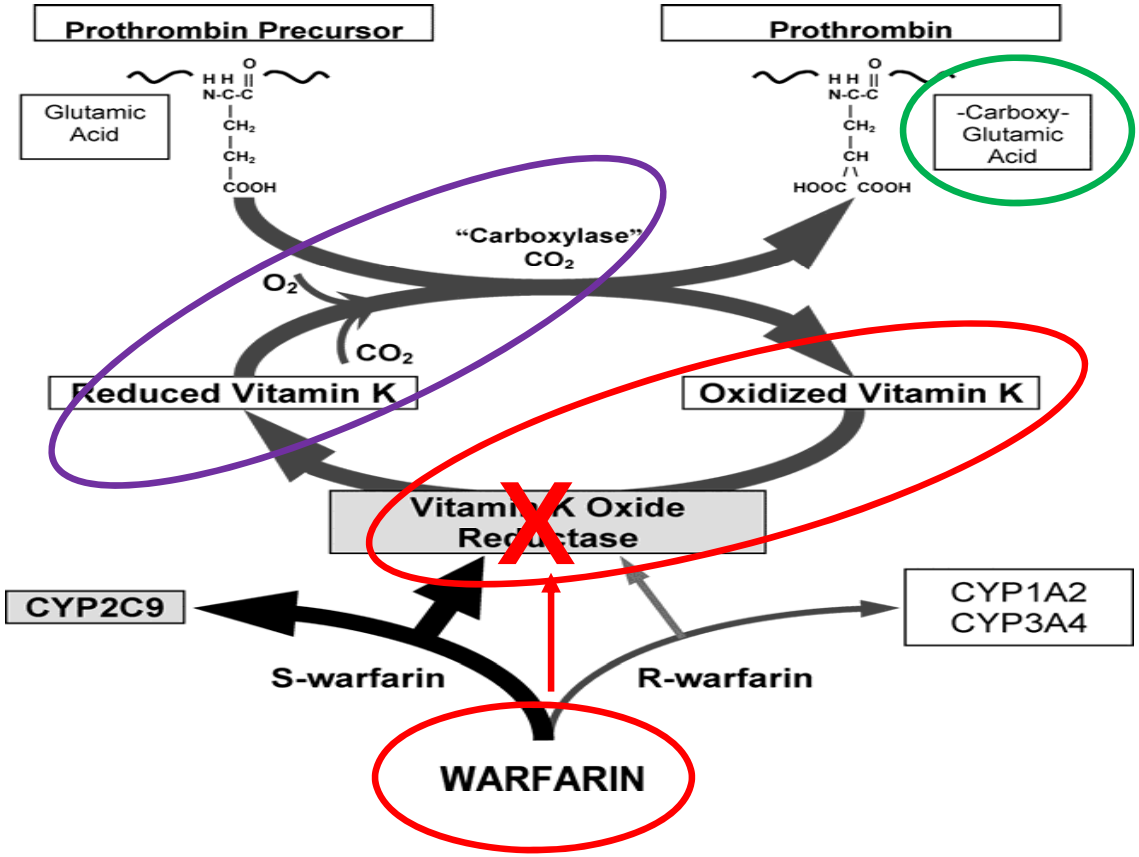
Enoxaparin
Dalteparin
Tinzaparin

Warfarin

Warfarin Reversal

How Warfarin Works





Functional vitamin K dependent factors

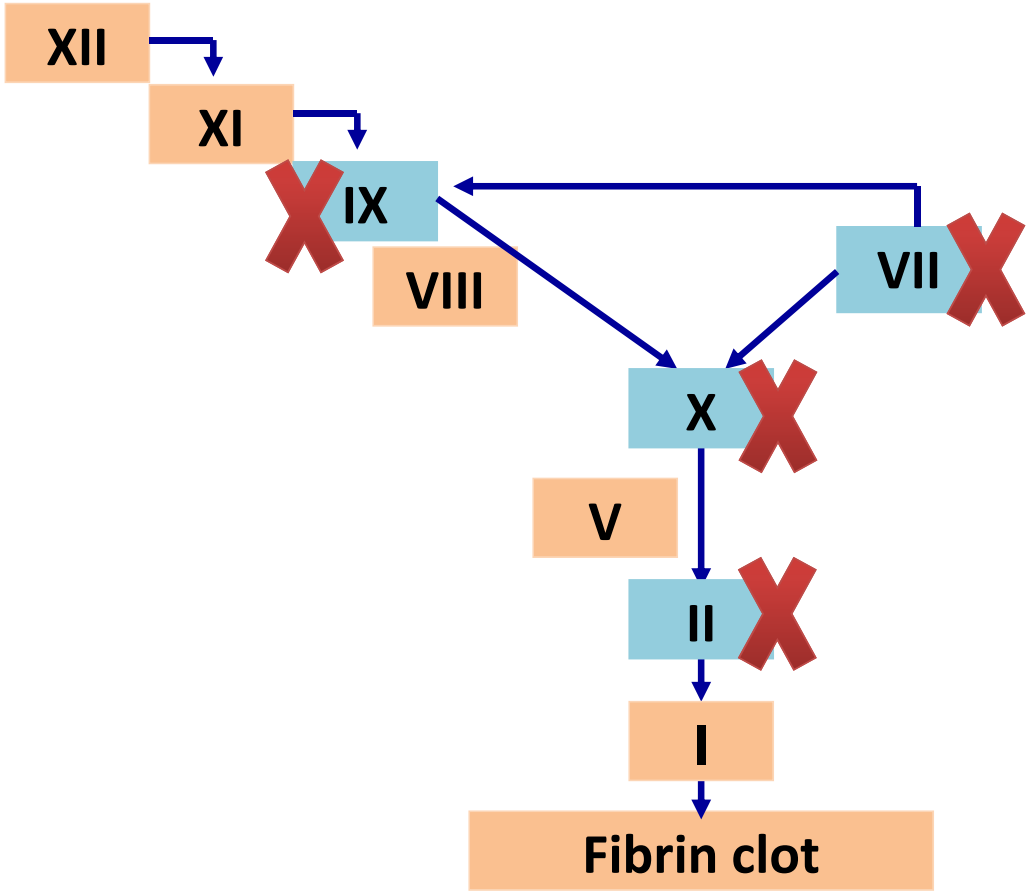
- Require γ-carboxylation
- Addition of carboxyl groups allows them to bind to phospholipids and localize thrombin generation (Ca^{2+} dependent)

- Carboxylase requires reduced vitamin K
- Vitamin K is reduced by vitamin K oxide reductase

- Vitamin K oxide reductase is inhibited by warfarin

Ageno et al. Chest 2012;141:2 suppl:e44S-e88S

Warfarin Cripples Coagulation



International Normalized Ratio (INR)

PT

Effective at determining the amount of warfarin that is present in steady state

$$\left[\frac{\text{PT in seconds of the patient sample}}{\text{Geometric mean of the normal range for PT in seconds}}\right]^{\text{ISI}}$$

- ISI = International Sensitivity Index
- ISI indicates reagent sensitivity to vitamin K dependent factors assessed by the PT
- Standardization → Labs can speak the same language

Emergency Reversal of Warfarin

Short-term plan

- **PCC 1000-3000 IU depending on the INR**
- Lasts **6 hours**
- Only contraindication: HIT

Long-term plan

- **Intravenous vitamin K**
- Intravenous is faster than oral
- Intravenous vitamin K is safe
- Starts working in **6 hours** (prevents INR rebound)

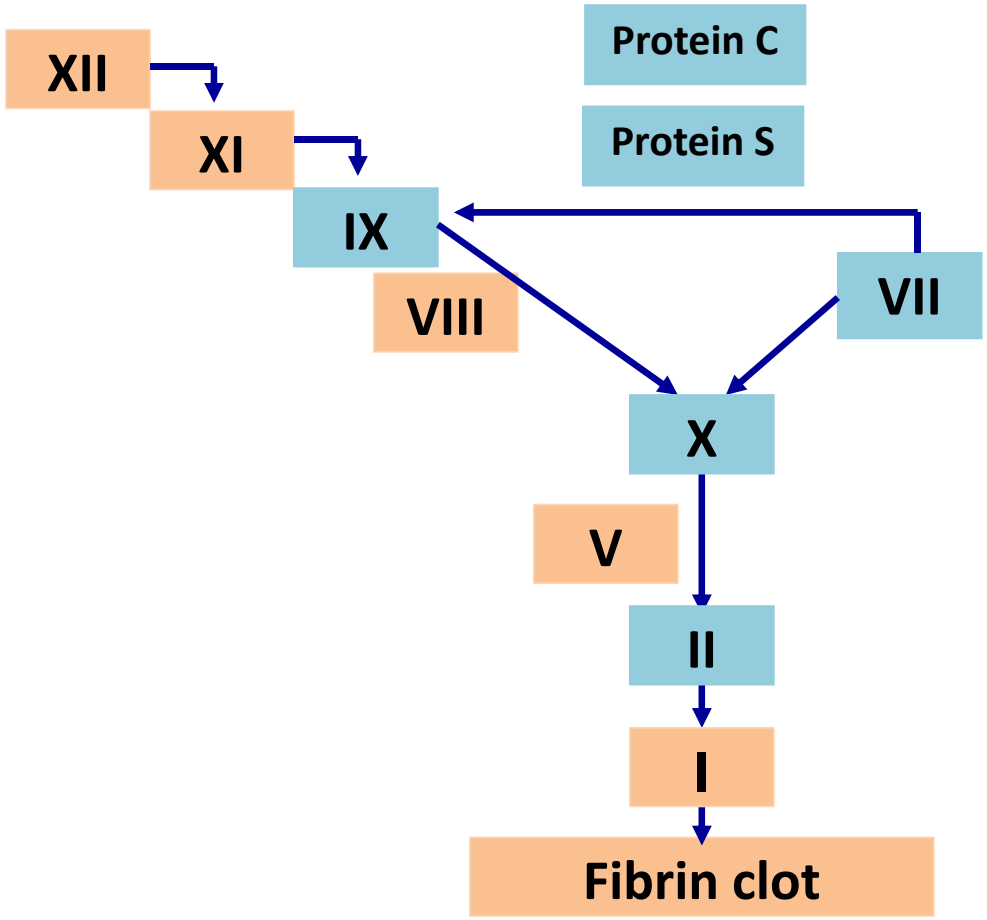
2. INR based dosing: The 2011 NAC recommendation based the dosing of prothrombin complex concentrate on the INR as per the table below but stated that if the INR is unknown and major bleeding is present, 2000 IU (80 mL) should be administered.

	PCC dose if INR > 5	PCC dose if INR 3-5	PCC dose if INR <3
Dose	3000 IU (120 mL)	2000 IU (80 mL)	1000 IU (40 mL)

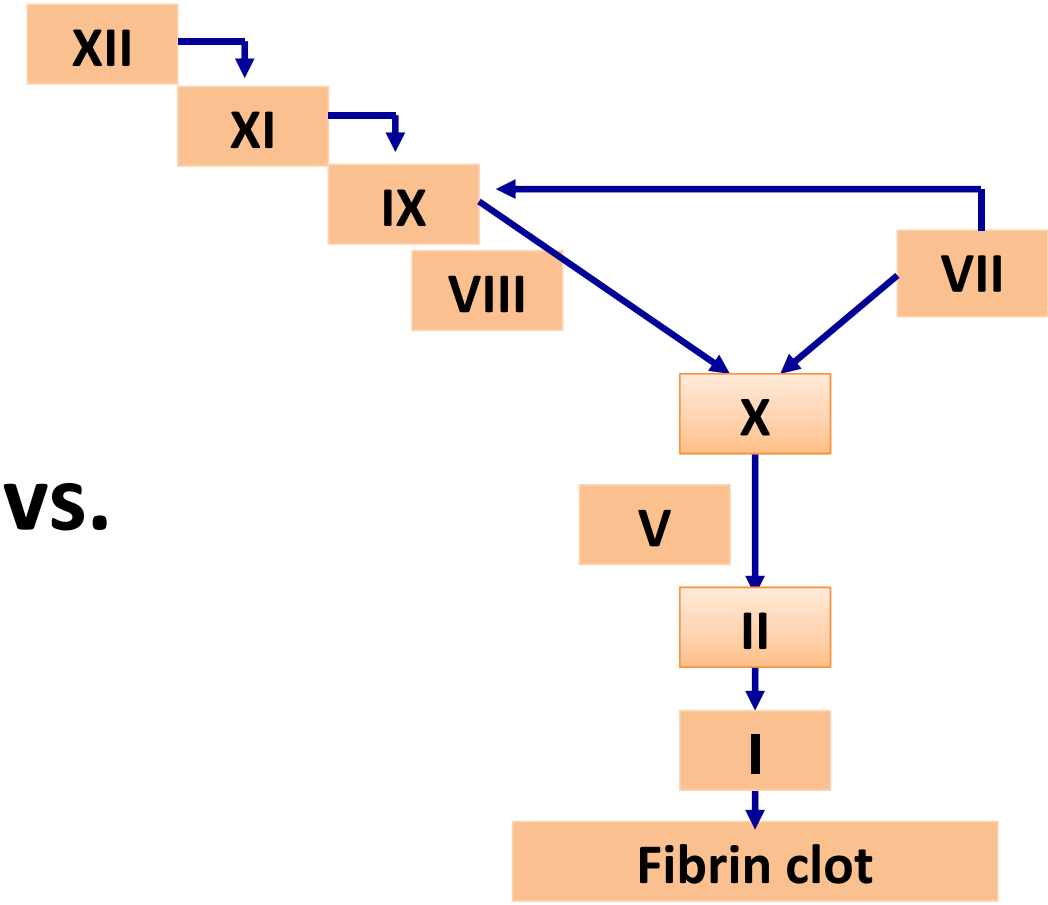
Administration: 1000 IU/5 mins

National Advisory Committee on Blood and Blood Products | Comité consultatif national sur le sang et les produits sanguins

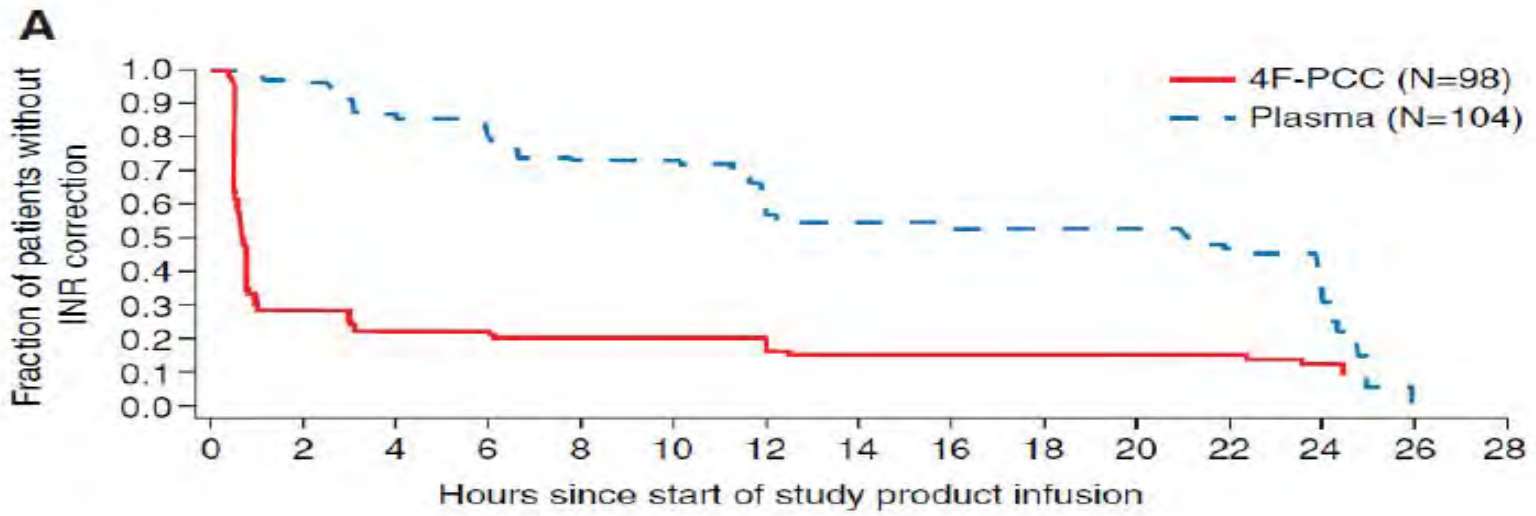
PCC vs. Frozen Plasma



vs.



PCCs vs. FFP RCT for Warfarin Reversal



Circulation. 2013;128:1234-1243

Why use PCCs vs. FFP?

PCC	FFP
Pooled, virally inactivated Prion reduction process	Not virally inactivated
Lyophilized Needs to be reconstituted	Needs ABO group (10min) Needs to be thawed (30min)
Volume 40-80mL Infused over 15-30min	Volume 15mL/kg (~1000mL) Infused over hours
Less risk of transfusion rxns	Risk of transfusion rxns: TRALI, TACO, anaphylaxis
$610 for 1000 units[1]	$396 for 4 units plasma[2]

PCC → Safety, Speed & Superior efficacy for major Surgery

CBS Price List 2015-2016. 2. CBS Blood Component Cost 2013-2014

http://dx.doi.org/10.1160/TH16-04-0266
Thromb Haemost 2016; 116: 879–890

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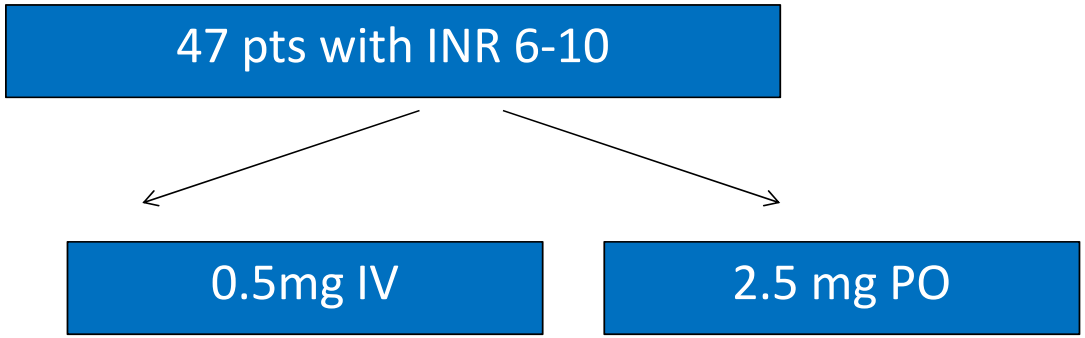
How to give Vitamin K?



Correction at 6 hours	11/24	0/23
Correction at 12 hours	16/24	8/23

Use 10mg of IV Vitamin K for Urgent Reversal

- **IV Vitamin K works fairly quickly – takes ~6 hrs**
- **The factors are already synthesized → just need a final conversion step**

Crowther et al. Arch Intern Med 2003;163:2469-73

Emergency Reversal of Warfarin

Short-term plan

- **PCC 1000-3000 IU depending on the INR**
- Lasts **6 hours**
- Contains factors II, VII, IX, and X (Pr C/S, heparin)
- Only contraindication: HIT

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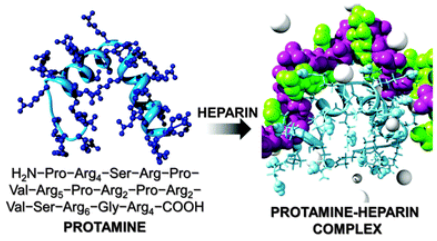
Heparin Reversal



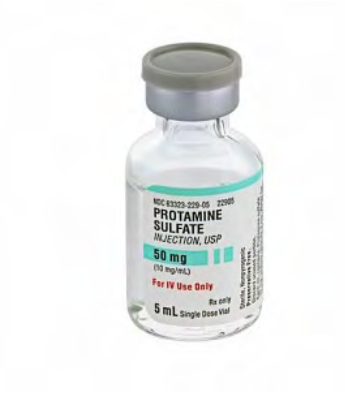
Heparin Reversal

- Protamine sulfate is used for heparin reversal
  - Forms a stable salt complex
  - Can fully reverse the effect of UFH
  - Only partly neutralizes the effect of LMWH or heparinoids
  - Administered IV – not exceeding 50 mg/10 min
    - Potential risk of histamine release → hypotension and bronchoconstriction
    - Protamine has an anticoagulant effect → excessive dosing can lead to increased bleeding

PTT
ACT

Schulman et al, Transfusion Medicine Reviews, Vol 21, No 1 (January), 2007: pp 37 -48

Heparin Reversal

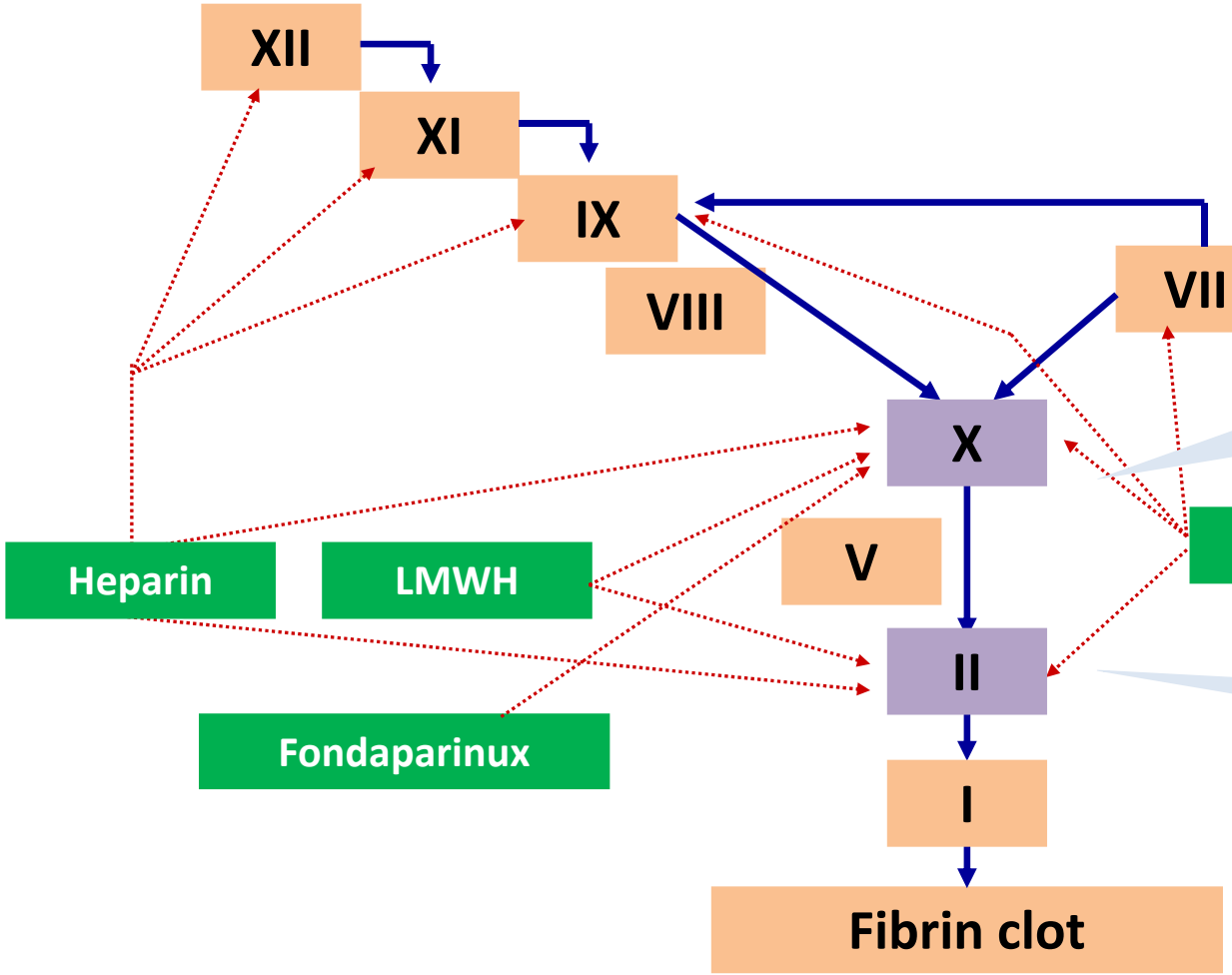


- Dose of protamine sulfate
  - Better to err on the low side and repeat doses after a pause
  - 1 mg of protamine sulfate neutralizes ~100 units of UFH
  - Take into account the short half-life of UFH (~ 60-90 min)
    - <u><30 min:</u> 1-1.5 mg/100 units of heparin
    - <u>30-120 min:</u> 0.5-0.75 mg/100 units of heparin
    - <u>>120 min:</u> 0.25-0.375 mg/100 units of heparin

Schulman et al, Transfusion Medicine Reviews, Vol 21, No 1 (January), 2007: pp 37 -48

DOAC Reversal

Mechanisms of Actions of DOACs



- Single-target
- All oral inhibitors
- "Direct" – not mediated via Antithrombin

Oral Xa Inhibitors
- Rivaroxaban
- Apixaban
- Edoxaban

Oral IIa Inhibitors
- Dabigatran

Approved DOACs

- “Direct” oral anticoagulants
  - Dabigatran - Pradaxa®
  - Rivaroxaban - Xarelto®
  - Apixaban - Eliquis®
  - Edoxaban - Lixiana®

Coagulation testing is not required to adjust DOAC dosing

But that does not mean that coagulation assays are not affected

LABORATORY TEST—DRUG MATCHING CHART

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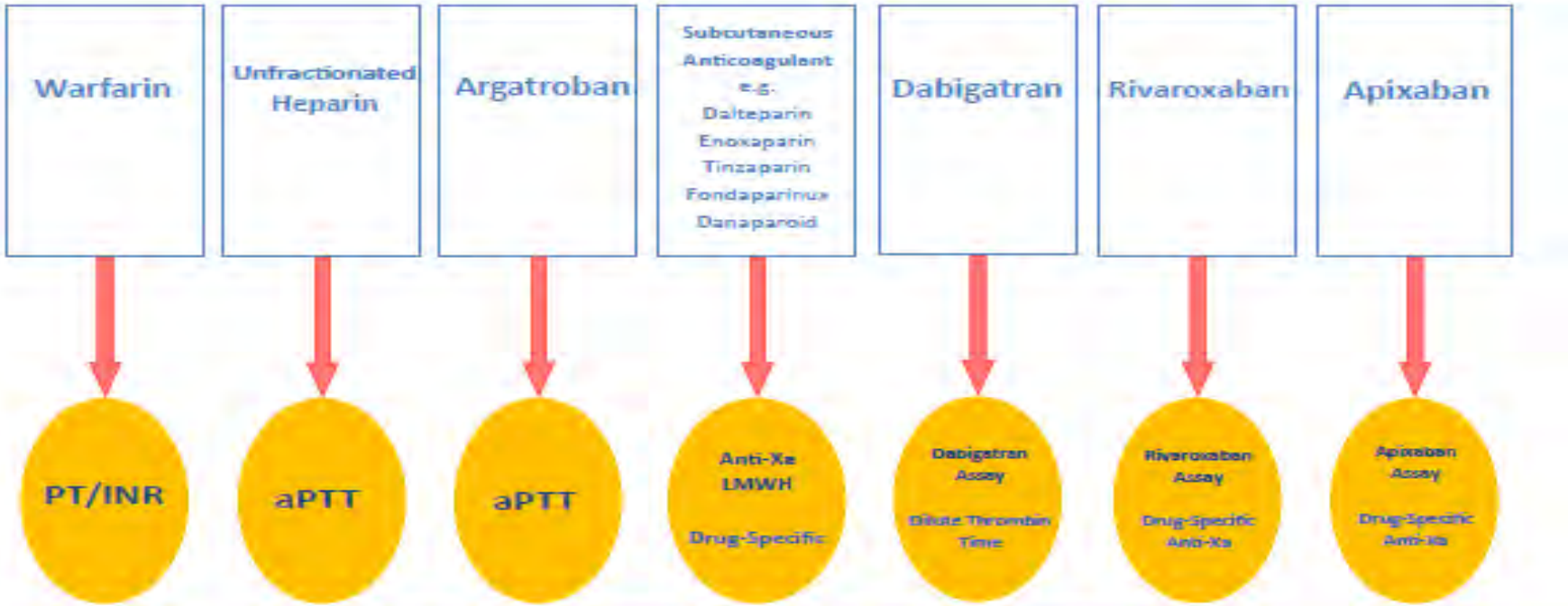
Inspiring Science



How to Reduce Medical Error

Always indicate what anticoagulant your patient is on in your test order.

Additional References:
WHEN TO ORDER COAGULATION TESTS (PT/INR & aPTT)
FACTS ABOUT DOAC TESTING

FACTS ABOUT DOAC TESTING

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Inspiring Science.

PT/aPTT testing is not indicated for routine monitoring

PT = Prothrombin Time

aPTT = Activated Partial Thromboplastin Time

TT = Thrombin Time

Testing may be indicated in the following situations:

- Need for urgent procedures/surgery
- Bleeding
- Breakthrough thromboembolism
- Drug interactions
- Renal (dabigatran)/ liver dysfunction (rivaroxaban/apixaban) where drug accumulation becomes a concern

Suggest Hematology Consultation

We have specialized DOAC testing available at SMH

- Clinical threshold for the efficacy and safety of DOAC related to drug concentrations are not well established.
- Discussion with medical director for interpretative assistance is suggested.

DOAC TESTING OPTIONS

DABIGATRAN

↑ **aPTT -** Suggests dabigatran presence

N **aPTT -** Does not rule out dabigatran presence

↑ **TT -** Dabigatran is present

N **TT -** Dabigatran is absent

Dabigatran Assay

Dilute Thrombin Time

APIXABAN / RIVAROXABAN

↑ **PT** - Suggests apixaban or rivaroxaban presence

N **PT** - Does not rule out apixaban/rivaroxaban presence

Apixaban and Rivaroxaban Assay

Drug Specific Anti-Xa

For all DOAC-specific assays a result of **< 30 ng/mL** suggests no significant anticoagulant effect. (Thrombosis Canada 2015)

Thrombosis Canada, 2015. http://thrombosiscanada.ca/?page_id=18&search=Search

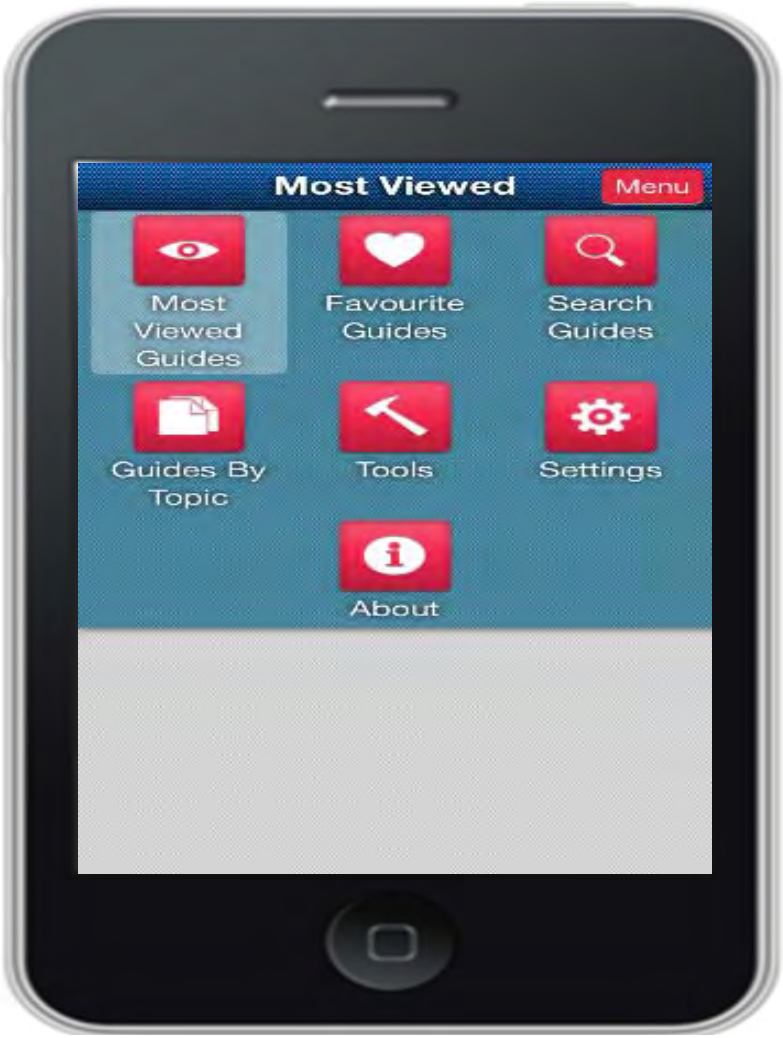
"There is no data to establish a hemostatic threshold below which drug levels are unlikely to affect hemostasis. These estimates are extrapolated from observations in clinical trials and are in agreement with other guidelines."

DOACs: Effect on Coagulation Assays

Laboratory Test	Dabigatran	Rivaroxaban, Apixaban or Edoxaban
PT and INR	Variable effect (usually INR<2.0 at peak blood levels)	Rivaroxaban and Edoxaban can increase PT/INR; Apixaban has a minimal effect
PTT	Non-linear increase	Rivaroxaban and Edoxaban can increase aPTT; Apixaban has a minimal effect
Thrombin time (Not widely available)	Increases Thrombin time; if normal, no detectable anticoagulant effect	No effect
Anti-Xa level (Not widely available)	No effect	Specific Apixaban, Edoxaban or Rivaroxaban calibrators are required to quantify the specific oral Xa-inhibtor levels.

Adapted from Thrombosis Canada clinical guide

There’s an App for that !



When might you need to obtain a DOAC level?

- **Urgent management / reversal needed**
  - **Bleed**
  - **Urgent surgery / procedure**
  - **Intentional overdose**
  - **Stroke on a DOAC and need to give tPA**

- Extremes of weight, age
- Renal dysfunction
- Drug interactions

Local Availability of Quantitative DOAC Assays

- **Anti-Xa assay for apixaban and rivaroxaban – Sunnybrook, St. Mike's**
- **Hemoclot assay for dabigatran – St. Mike's, McMaster**

- 16/170 labs in Ontario can do Anti-Xa assays for heparin and LMWH

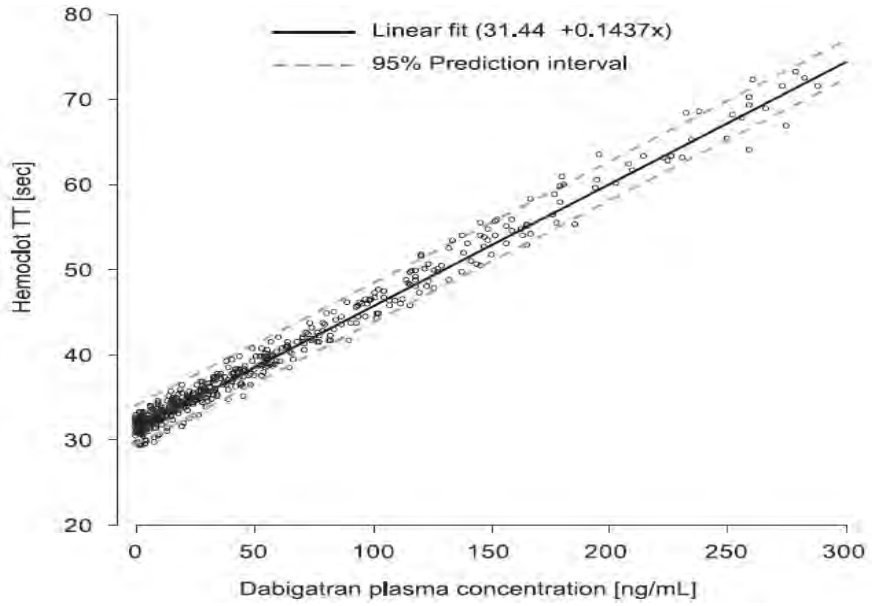
Expected steady-state Peak & Trough Concentrations of DOACs

Drug	Dose	Peak (ng/mL)	Trough (ng/mL)
Dabigatran	150 mg bid	64-443	31-225
Rivaroxaban	20 mg daily	189-419	6-87
Apixaban	5 mg bid	91-321	41-230
Edoxaban	60 mg daily	120-250	10-40

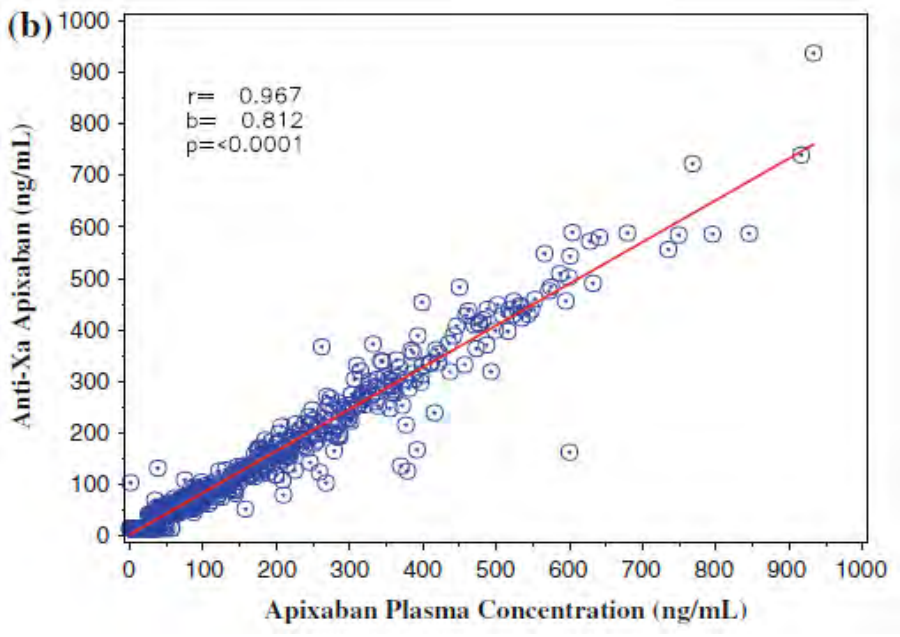
Samuelson et al. Chest 2017;151(1):127-138

Quantitative assessment of DOACs

Hemoclot ® (dilute thrombin time) assay for dabigatran



Anti-Xa assays for oral Xa-inhibitors



Lack of clinically validated reference range is biggest challenge !

“Evidence” for “Safe” DOAC Levels

- < 30ng/mL for high risk surgery
- **> 50 ng/mL + serious bleeding = consider reversal / antidote**
- > 200 ng/mL – concentration associated with a consistent peri-procedural bleeding risk

BASED ON PK/PD DATA, PUBLISHED SUB-ANALYSES OF THE PHASE 3/4 RANDOMIZED CLINICAL TRIALS AND “EXPERT OPINION”

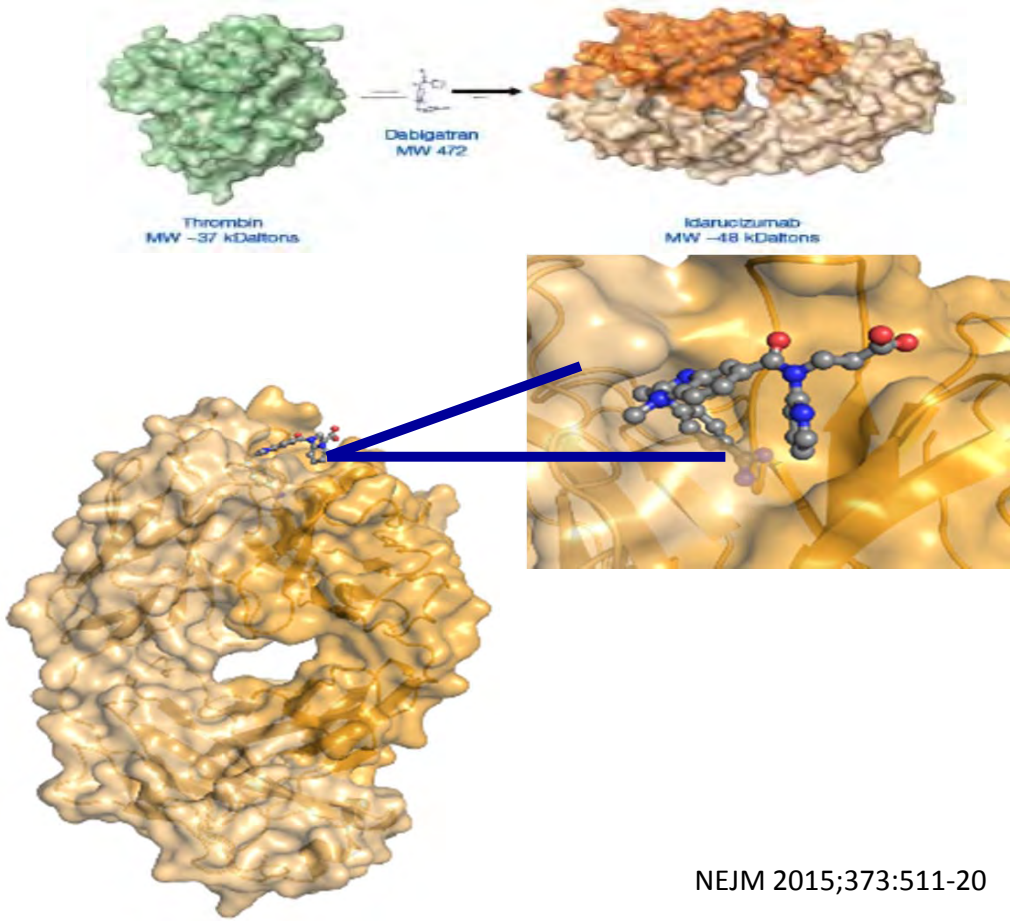
Levy et al, J Thromb Haemost 2016;14:623-7
Pernod et al, Arch Cardio Dis 2013;106:382-393
Steiner et al, Clin Res Cardiol 2013;102:399-412

DOACs – Major, life-threatening Bleeding Management

- Hold DOAC, Resuscitate, **Consult expert**
- Apply local hemostatic measures if applicable
- Obtain STAT CBC, PT/INR, PTT, CrCl
- **Determine "likely" drug presence and expected elimination rate – time of last dose, half-life and CrCl**
- **? Drug level if available**
- MTP, tranexamic acid, endoscopy, surgery etc as indicated
- ANTIDOTE if available, PCC if not
- Review concomitant meds (ASA, NSAIDS)

Idarucizumab (Praxbind®): Dabigatran Antidote

- Humanized mouse monoclonal antibody fragment (Fab)
  - specifically and potently binds dabigatran
  - ~350x higher affinity than for thrombin
- **No prothrombotic** or anti-thrombotic effects since Fab only targets dabigatran
- REVERSE-AD Phase 3, single arm cohort study in bleeding and urgent surgery patients
  - **92% major bleeds ceased within 3-4 hours**
  - 97% urgent surgery patients proceeded to surgery in 1.6 hours



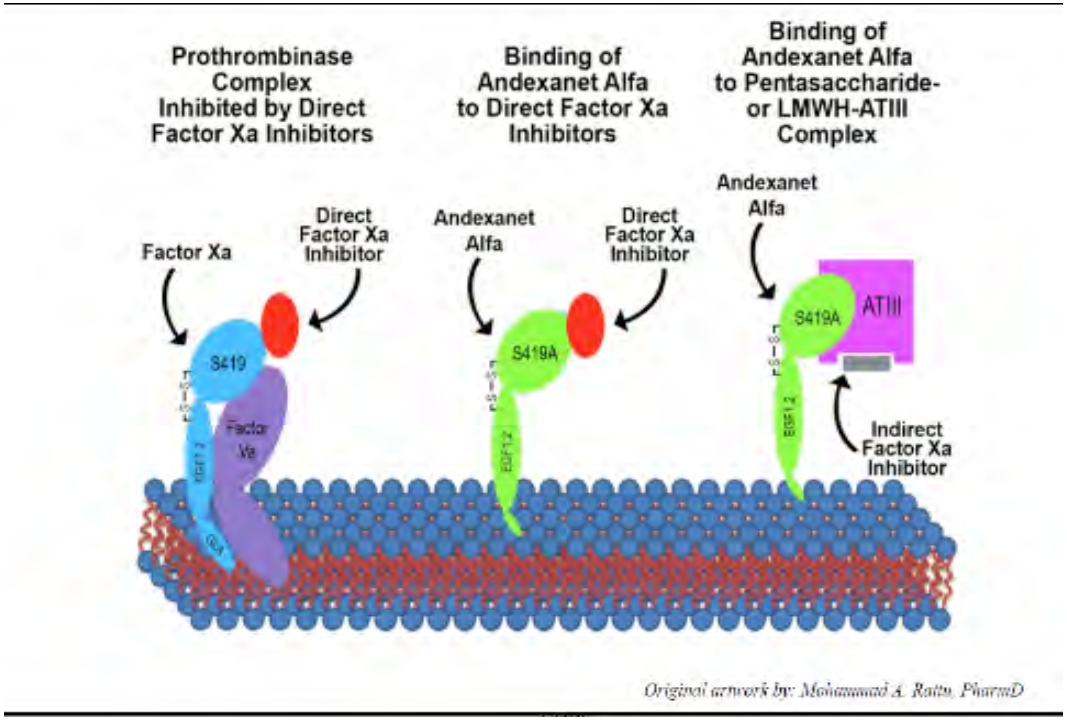
NEJM 2015;373:511-20

Idarucizumab (Praxbind®): Current Status

- Approved and licensed in Canada since 2016
- Dose – 5 gms provided in 2 separate vials with 2.5 gms/50 ml given as intermittent infusions X 2
- Issued by blood bank or pharmacy
- ~15 cases - June 2016 to present

Andexanet Alfa (AnnexXA): Universal Factor Xa Inhibitor Antidote

- Recombinant, human Factor Xa "decoy"
- Binds and neutralizes Factor Xa inhibitors and LMWH / pentasaccharide-FXa complexes



Andexanet Alfa: Current Status

- **ANNEXA-A & ANNEXA-R**
  - Randomized, double blind, placebo controlled, Phase 3/4 study in 145 healthy volunteers aged 50-75
  - Andexanet rapidly reversed apixaban-induced and rivaroxaban-induced changes in anti–factor Xa activity and thrombin generation without serious adverse events or clinical thrombosis
- **ANNEXA-4**
  - **Phase 4 clinical outcomes RCT in bleeding patients with major cardiovascular burden**
  - **Interim results Mar 12/2018 at ACC**
  - **132/238 adjudicated for efficacy – 83% bleeding stopped for over 12 hour period**

Siegal et al. N Engl J Med 2015; 373:2413-424. Dec 17, 2015
Connolly et al. N Engl J Med 2016; 375:1131-1141.Sept 22, 2016

PCC and Xa inhibitors

- One healthy volunteer study (lab abnormality reversal) and one small case series, n=18 (clinical outcome)

- **2 Prospective Observational Studies (Rivaroxaban and Apixaban related bleeding) - UPRATE**
  - **25 Swedish hospitals**
  - **84 patients with major bleeding**
  - **1500-2000 U PCC (25 IU/kg)**
  - 70% ICH, 15.5% GI
  - "Hemostatic effectiveness"
    - 69% effective
    - 30% ineffective
    - 2 ischemic strokes; 27 deaths
  - **9 Canadian hospitals**
  - **66 patients with major bleeding**
  - **2000 U PCC (25 IU/kg)**
  - 55% ICH, 16% GI
  - "Hemostatic effectiveness" (good 65%; mod 20%; poor 15%)
    - 68% effective
    - 32% ineffective
  - (Post-hoc analysis (ISTH criteria))
  - 5 major TE events; 9 deaths

- Door-to-PCC 5.4h (similar to reports for warfarin, 4.5h)
- Only 17% of patients had drug-specific anti-Xa levels done
- 21% poor in ANNEXA-4; 27.6% poor PCC for warfarin

Majeed et al., Blood August 2017, Schulman et al., Thromb Haemost March 2018; Sarode et al., Circulation 2013; Connolly et al. N Engl J Med 2016

Small vs. Large Hospital Anticoagulant Reversal Challenges

- Important differences in knowledge gaps and resource availability
- **Small**
  - Limited laboratory capacity – personnel, space, instrumentation, $
  - Limited TAT
  - Many lack TT and fibrinogen testing
  - Policies, pathways, guidelines may not have multiD input (may not exist)

25/170 (15%) labs can do thrombin time
75/170 (44%) labs can do fibrinogen

- **Large**
  - Rapid response team → get the sample to the lab
  - Special coagulation lab, Specialized Blood Bank
  - Rapid TAT should be available
  - Ability to detect DOACs at some (not all) large hospitals
  - Policies, pathways, guidelines reviewed by committees with multiD input

<u>Approach Applicable to Both:</u>

CHANGE THE PROCESS (DO NOT RELY ON EDUCATION ALONE) →SIMPLE ORDER ORDER SETS (ELECTRONIC WITH PAPER COPY REDUNDANCY)

Summary

- Anticoagulant reversal policies allow for delivery of consistent, rapid and best in care practice

- Challenge: multiple classes of anticoagulant drugs which necessitate various reversal strategies
  - Simple, electronic order sets
  - Consultation with experts

- Small versus large hospital anticoagulant reversal challenges are different due to different gaps in knowledge and resource availability
  - Requires a different approach

Objectives Revisited

- Review why anticoagulant reversal protocols are essential during a MHP
- Review different anticoagulant protocols
- Differentiate small versus large hospital anticoagulant reversal challenges

Thank you

Questions?

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