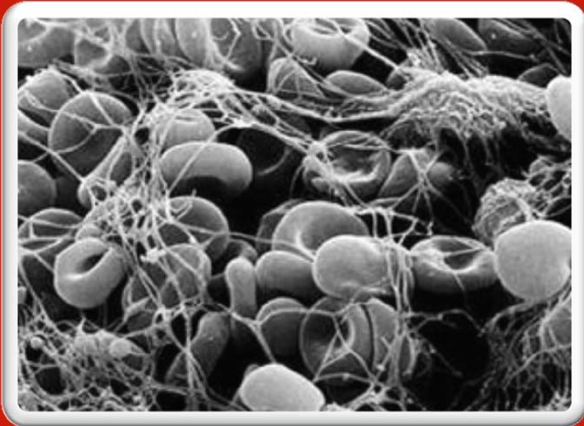


Urgent reversal of hemostasis poisons in a bleeding patient

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Conflict of Interest

- Research funding from CSL Behring Canada Inc.

Outline

- To review risk for major bleeding associated with and strategies for urgent reversal of:
 - Warfarin
 - Direct thrombin inhibitors
 - Factor Xa inhibitors
 - Antiplatelet agents

Every drug is a poison

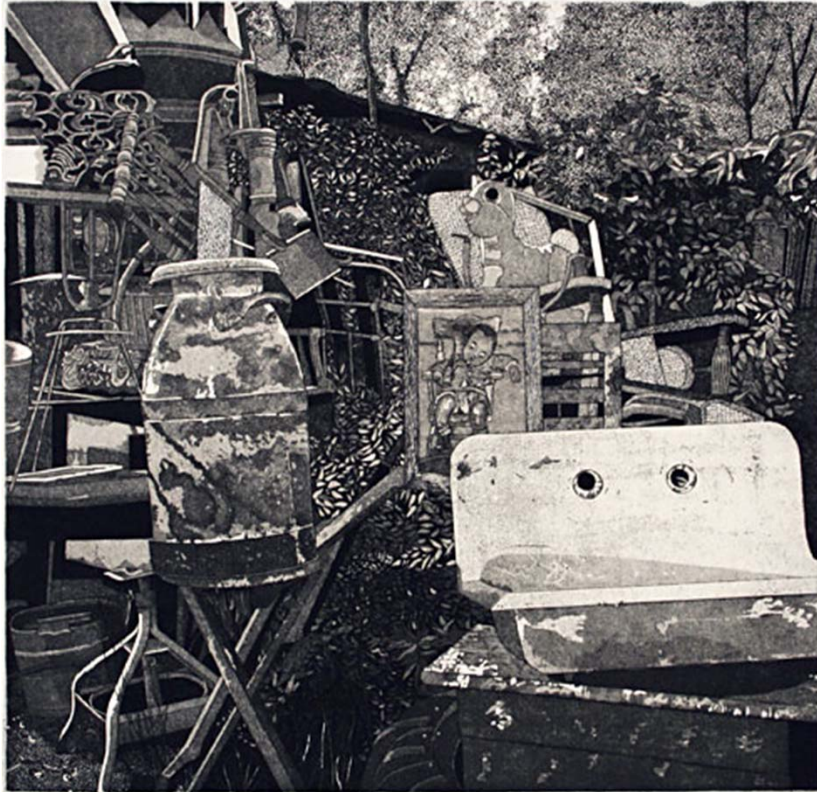


Key Questions



- For invasive procedures, is this a true emergency or can it be safely delayed?
- What is the drug inhibiting/reducing? Are there multiple drugs on board?
- What is the half-life of the drug?
- Are there any relevant comorbidities that will either affect bleeding risk or drug metabolism?
- Is there an effective antidote?
- Are the risks of reversal acceptable?

Sink vs. silver bullet



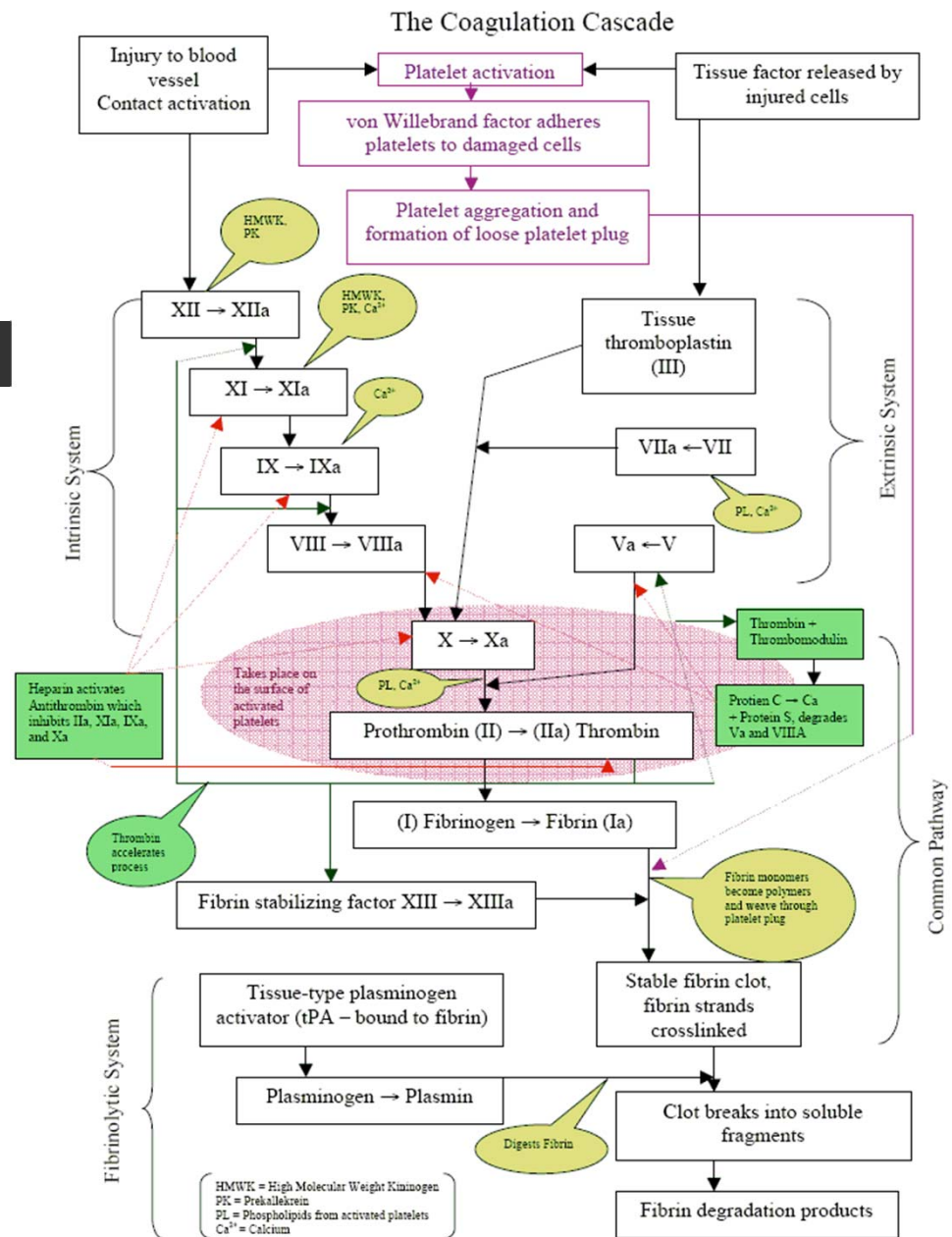
Hemostasis

Players:

- Vascular endothelium
- Platelets (number, function)
- Coagulation factors (production, consumption)
- Fibrinolytic system

Environment:

- Hypocalcemia
- Hypothermia
- Acidosis
- Dilution



Case 1

- 65 yo male brought to ER with decreased level of consciousness following a fall from a ladder
- On warfarin for stroke prevention
- Lab results: INR 2.34, PTT 40
- CT head: acute subdural hematoma
- Plan: to OR ASAP

Case 1

Pick the best answer. To manage his coagulopathy, the patient should receive:

- A. 2 units of frozen plasma
- B. 4 units of frozen plasma
- C. PCC (Octaplex) dosed as per weight and INR and Vitamin K 10 mg IV by slow infusion
- D. rVIIa 5.0 mg IV

Warfarin



- Oral, once daily medication
- Causes Vitamin K deficiency
 - Inhibits vitamin K₁-2,3 epoxide reductase, preventing vitamin K from being reduced to its active form
 - Decreases levels of protein C and S as well as coagulation factors II, VII, IX and X
- Peak concentration within 4 hours; peak anticoagulant activity 24-96 hrs
- Duration of action 2-5 days

Vitamin K dependent factors



1 factor X

9 factor IX

7 factor VII

2 factor II

Canada protein C

Soviet Union protein S

Warfarin: Risk of Bleeding

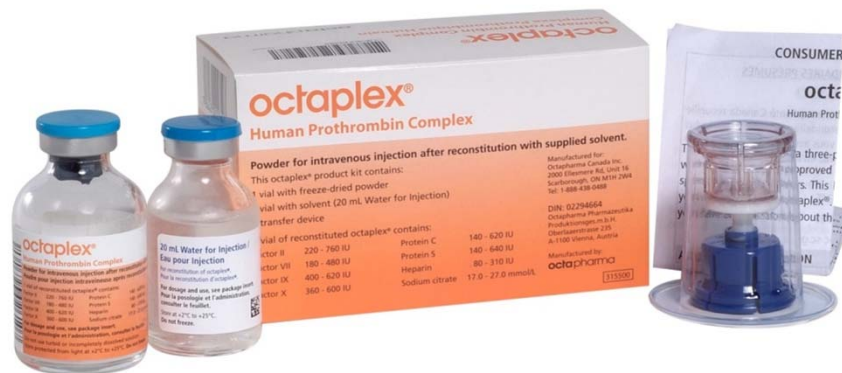
- 2 series of about 9,000 patients – major bleeding in 1.1% and 1.5% (Lancet 1996; 384: 423-8 & JAMA 2003; 290: 2685-92)
- 3.36% per year (RE-LY), 1.9% in RE-COVER

Warfarin: Treatment of Acute Bleeding

- Labs: isolated **elevated INR**
- Treatment:
 - Antidote available!
 - Vitamin K – 5-10 mg, IV vs. po AND
 - Prothrombin complex concentrate (PCC)
OR
 - Frozen plasma – 15cc/kg (3-4 units)

Prothrombin Complex Concentrate (PCC)

- Derived from pooled human plasma and pathogen inactivated
- **Contains FII, VII, IX, and X and proteins C and S (and heparin)**
- Effect on INR is immediate and lasts about 6 hours



PCC: Contraindications

- DIC
- HIT (contains heparin)
- Coagulopathy of liver disease
- Patients with **recent MI, high risk of thrombosis or angina** (except in life-threatening bleeds due to overdose of oral anticoagulants, or when an emergency surgical procedure is indicated in patients on vitamin K antagonists and INR > 3)

PCC: Efficacy

- No RCTs comparing the efficacy of FP to PCC in the management of warfarin reversal and bleeding
- A handful of retrospective studies have shown that PCC provided more rapid and complete correction of INR as compared to FP (Ageno 2009)
 - However, it is unclear how this correlates with clinical outcomes

PCC: Safety

- Current PCC does not contain activated factors
- The reported rate of thrombotic events post PCC varies: 1.5% (Leissinger 2008), 3.6% (Song 2010), 6.8% (Varga 2010)
- Other considerations:
 - Patients at high risk of thrombosis
 - Their anticoagulation is rapidly reversed
 - What is the rate of thrombotic events in patients receiving FP for warfarin reversal?

FP vs. PCC

- FP

- Human
- No viral inactivation
- Large volume (15 mL/kg; 770-1500 mL)
- Risk of TRALI, TACO and anaphylaxis
- Needs to be thawed
- Requires ABO group

- PCC

- Human
- Virally inactivated, prion reduction process
- Small volume 40-80 mL
- Risk of thrombosis, allergic reaction
- Lyophilized, needs to be reconstituted
- Does not require ABO group

rVIIa in warfarin-associated ICH

- 8 studies address warfarin related CNS bleeding
 - All show that rVIIa rapidly corrects INR
 - Clinical impact is not clear
 - Retrospective, case reports or case series, number of patients per study 1-16, no adequate controls
 - Co-administration of other hemostatic therapy (FP, etc.)
 - Recommendation: against routine use of rVIIa in acute warfarin reversal

Case 1, version 2

- 65 yo male brought to ER with decreased level of consciousness following a fall from a ladder
- On **dabigatran** for stroke prevention
- Lab results: INR 2.34, PTT 40
- CT head: acute subdural hematoma
- Plan: to OR ASAP

Case 1, version 2

Pick the best answer. To manage his coagulopathy, the patient should receive:

- A. 2 units of frozen plasma
- B. 4 units of frozen plasma
- C. PCC (Octaplex) dosed as per weight and INR and Vitamin K 10 mg IV by slow infusion
- D. rVIIa 5.0 mg IV

Dabigatran



- Oral, twice daily reversible competitive direct thrombin (IIa) inhibitor
- Time to maximum plasma concentration 1-2 hrs
- Half-life 12-17 hours
 - Half-life extended in renal and hepatic failure
 - The drug is >80% renally excreted

Dabigatran: Risk of Bleeding

- Depends on dose (110 vs. 150 vs 220 mg)
- 2.7-3.1%/year major bleeding (RE-LY)
 - Less major bleeding (incl. ICH vs. warfarin)
- 0.6-2.0% major bleeding (RE-NOVATE, RE-MODEL, RE-MOBILIZE)
- 1.6% major bleeding (RE-COVER)

Dabigatran: Labs

- Standard coagulation tests may be completely normal despite therapeutic anticoagulation
 - Generally no or little effect on PT/INR
 - PTT prolonged (different reagents and not dose dependent)
 - “qualitative”
 - TT will be prolonged – too sensitive
 - Other tests: Haemoclot thrombin inhibitor assay, ecarin clotting time
 - Other facts: fibrinogen and clotting factors II-XII plasma levels will appear falsely low in a patient with dabigatran potentially leading to unnecessary interventions

Dabigatran: Treatment of Acute Bleeding

- No antidote
- General hemostatic measures
 - Surgical hemostasis, RBC
 - Plasma, cryoprecipitate to replace losses of factors due to bleeding
- Oral charcoal (if ingested <2hrs earlier)
- Hemodialysis/hemofiltration (low protein binding)
- rVIIa, FEIBA corrects prolonged bleeding time in rats (van Ryn 2008)
- PCC (what dose?) – recommended by expert opinion, no literature – unpublished rabbit study with Beriplex

Factor Xa inhibitors

	Rivaroxaban	Apixaban
Mechanism of action	Reversible direct inhibitor of Xa	Reversible direct inhibitor of Xa
Route of administration	po	po
T _{max}	30 min to 3 hrs	30 min to 2 hr
Half-life	9-13 hrs	8-15 hrs
Frequency of administration	od	bid
Renal excretion	66%	30% (70% hepatic/GI)

Galanis et al 2011, Samama 2011

Factor Xa inhibitors: Bleeding Risk

- Trials
 - Rivaroxaban – 0.3-0.7% major bleeding excluding surgical site bleeding (RECORD studies)
 - Apixaban – 2.9% to 3.5% major and clinically relevant non-major bleeding, 0.6-0.7% major bleeding (ADVANCE studies)

Factor Xa inhibitors: Labs

- Prolong PT and PTT depending on reagent used
 - Prolongation minimal at therapeutic concentrations
 - Most conventional and commercially available PT tests do not reliably reflect intensity of anticoagulation
- The most accurate is measurement of anti-Xa inhibition
 - Must standardized for each drug
 - Not available in all labs

Anti-Xa inhibitors: Management of Acute Bleeding

- No antidote
- General measures
- FEIBA or rVIIa may be tried

Antiplatelet agents

	ASA	Clopidogrel	Prasugrel	Ticagrelor
Mechanism of action	Inhibits synthesis of TXA2	Antagonist of platelet receptor P2Y12 (irreversible)	Antagonist of platelet receptor P2Y12 (irreversible)	Antagonist of platelet receptor P2Y12 (reversible)
Route of administration	po	po	po	po
Time to peak effect	20 min (650 mg)	6 h (300 mg)	1 h	2-4 hrs
Drug elimination half-life	ASA <20 min Salicylate 3-5 hrs	7.2-7.6 hrs	3.7 hrs	12 h
Duration of action	1-3 days	5-10 days	5-10 days	24 hrs

Antiplatelet Agents: Bleeding

- New(er) antiplatelet drugs (trials)
 - Prasugrel – 2.4% of patients experienced at least one major bleeding event (TRITON-TIMI)
 - Clopidogrel – 1.8% of patients experienced at least one major bleeding event (TRITON-TIMI)

Case 2

- 75 yo male in ER with hematemesis
- Patient is on multiple medications, including Clopidogrel (Plavix)
 - Despite feeling unwell, took all his meds this am
- Labs: Hgb 67 g/L, platelets 158×10^9 , coagulation tests are essentially normal

Case 2

To control bleeding, the following blood products may be indicated (pick the best answer):

- A. None required
- B. rVIIa
- C. 1 adult dose of platelets
- D. 4 units of frozen plasma

Clopidogrel: Bleeding



- Bleeding is a known side effect
 - GI tract is the commonest site; ICH is uncommon but is associated with a high MR
 - Risk factors include concomitant use of other antithrombotic therapy, female, elderly, renal failure
- Labs: no reliable, readily available test to diagnose Clopidogrel-associated platelet dysfunction

Clonidogrel: Treatment of Acute Bleeding

- Biological half-life 5-6 days, no antidote
- General hemostatic measures
- Platelet transfusions
 - Need 2 pools to improve platelet function (in vitro data) (J of Thromb and Haemostasis 2007; 5: 82-90)
 - Evidence of effect is poor/non-existent
 - Transfused platelets may be inactivated by the circulating drug (elimination half-life approx. 8 hrs)

Clopidogrel: Treatment of Acute Bleeding

- Other strategies that have been described in literature
 - DDAVP (epistaxis), antifibrinolytics (post-CABG bleeding), rVIIa (post-CABG bleeding, ICH)
 - Note: these do not directly reverse platelet-inhibitory effect of Clopidogrel but may “bypass” it

Conclusions

- Concerns re: new anticoagulant drugs
 - do not have a readily available lab test to measure the degree to which the patient is anticoagulated or platelet inhibited
 - do not have specific antidotes
 - there is limited/non-existent scientific data on the management of bleeding in patients on these drugs