Anticoagulant Management through the Trauma Experience

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DISCLOSURE

Relevant Financial Relationship(s)
Speaker Bureau – None
Research & Consulting - None

What I am Talking About

1. New Antithrombotic Agents
   - Dabigatran
   - Rivaroxaban
   - Apixaban
2. Antiplatelet
3. Reversal of agents old and new
4. Restarting anticoagulants

New Anticoagulants

- Increasing number of trauma patients on these drugs
- Need to be aware of properties and indications

Dabigatran

- Oral Thrombin Inhibitor
- Bioavailability: 6.5%
- Onset of action: 2-3 hours
- Half-life : 12-14 hours
- Renal excretion: 80%
- Drug interactions: p-glycoprotein

Side Effects

- No difference in liver function tests
  - No liver issues with any new agent
- Increase in dyspepsia
  - May be improved by PPI
  - May be improved by food

Bleeding - FDA 2013

- The Mini-Sentinel assessment suggests that bleeding rates associated with dabigatran are not higher than those with warfarin, a finding that is consistent with the results of RE-LY.
- Although some have noted the lack of an available reversal agent for the anticoagulant effects of dabigatran as an important limitation of its use, data from RE-LY are reassuring with respect to bleeding. We believe that dabigatran provides an important health benefit when used as directed.

Intracranial and Gastrointestinal Bleeding Events in New Users of Dabigatran and Warfarin from the Mini-Sentinel Distributed Database, October 2010 through December 2011.[a]

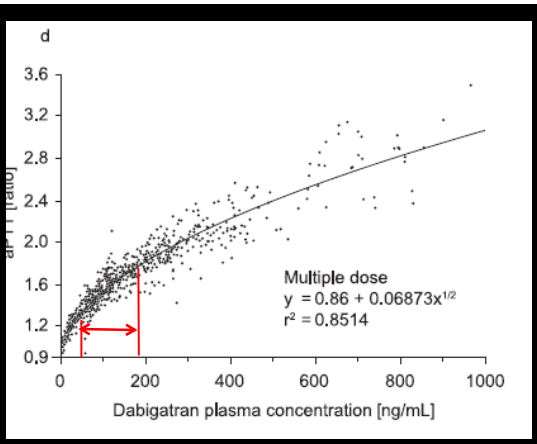
Analysis	Dabigatran			Warfarin		
	No. of Patients	No. of Events	Incidence *no. of events/ 100,000 days at risk*	No. of Patients	No. of Events	Incidence *no. of events/ 100,000 days at risk*
Gastrointestinal hemorrhage						
Analysis with required diagnosis of atrial fibrillation	10,599	16	1.6	43,541	160	3.5
Sensitivity analysis without required diagnosis of atrial fibrillation	12,195	19	1.6	119,940	338	3.1
Intracranial hemorrhage						
Analysis with required diagnosis of atrial fibrillation	10,587	8	0.8	43,594	109	2.4
Sensitivity analysis without required diagnosis of atrial fibrillation	12,182	10	0.9	120,020	204	1.9

Dabigatran

- Effective in DVT prevention
  - 220mg dose in EU/Canada
- Effective in DVT therapy
  - Short and long term
- Effective in stroke prevention in atrial fibrillation

Monitoring

- aPTT
  - 150 mg twice daily the median peak aPTT is approximately 2x control.
  - Twelve hours after the last dose the median aPTT is 1.5x control
- Assess compliance and drug effect
- Reference labs can do specific level
  - Peace Health Labs
- INR insensitive



Van Ryn et al. Thromb Haemost 2010; 103: 1116–1127

Rivaroxaban

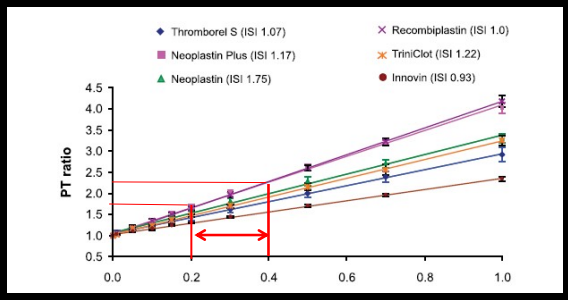
- Oral Xa Inhibitor
- Bioavailability: 80-100%
- Onset of action: 2.5-4 hours
- Half-life : 5-9 hours
- Renal excretion: ~66%
- Drug interactions: CYP 3A4

Rivaroxaban

- Approved 10mg daily for DVT prophylaxis in TKR and THR
- Approved 20mg daily for afib
  - 15mg if CrCl 15-49mL/m
  - Contraindicated < 15mL/m
- Approved for DVT/PE
  - 15mg BID x 3 weeks
  - 20mg/day

Monitoring: Rivaroxaban

- aPTT not as sensitive
  - Good for dabigatran
- INR is sensitive
  - > 1.5 drug effect
- Prothrombin time
- Anti-Xa calibrated to drug



Apixaban

- Oral Xa Inhibitor
- Bioavailability: 66%
- Onset of action: 1-3 hours
- Half-life : 8-15 hours
- Renal excretion: 25%
- Drug interactions: CYP 3A4
  - Multiple other pathways

Apixaban: Renal Disease

- GRF < 50 mL/min
  - Stroke 0.61 (0.39-0.94)
  - Mortality 0.78 (0.63-0.96)
  - Bleeding 0.48 (0.37-0.64)

  - Eur Heart J. 2012 Nov;33(22):2821-30.

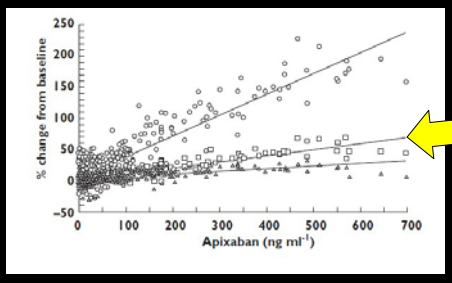
Apixaban

- Effective in
  - Atrial fibrillation
  - Prophylaxis
- Ongoing trials
  - DVT therapy

Monitoring: Apixaban

- aPTT not as sensitive
  - Good for dabigatran
- INR and prothrombin time
  - Not sensitive!
- Anti-Xa calibrated to drug

Monitoring: Apixaban



Br J Clin Pharmacol. 2013 Feb;75(2):476-87.

Comparing Agents

DVT Prevention Orthopedic Surgery

Drug	Thrombosis	Bleeding
Apixaban	Better	Equal
Dabigatran	Equal	Equal
Rivaroxaban	Better	Equal

LMWH: $25-30/ day
Rivaroxaban: $6-8/day

Atrial Fibrillation

Drug	Stroke	Bleeding
Apixaban	Better	Better
Dabigatran	Better	Equal
Rivaroxaban	Equal	Equal

Warfarin: $4/month + monitoring ($20-50/visit)
Rivaroxaban: $247/month
Dabigatran: $235/month

ICH – Atrial Fibrillation

	Stroke		Intracranial Hemorrhage	
	Events/ 100 years	RR	Events/ 100 years	RR
Dabigatran 110	1.53	0.91 (0.74-1.11))	0.23	0.31 (0.20-0.47)
Dabigatran 150	1.11	0.66 (0.53-0.82)	0.30	0.40 (0.27-0.60)
Rivaroxaban	1.76	0.79 (0.66-0.96)	0.49	0.67 (0.47-0.94)
Apixaban	1.19	0.79 (0.65-0.95)	0.33	0.42 (0.30-0.58)

Potential for 10-12,000 less ICH in USA

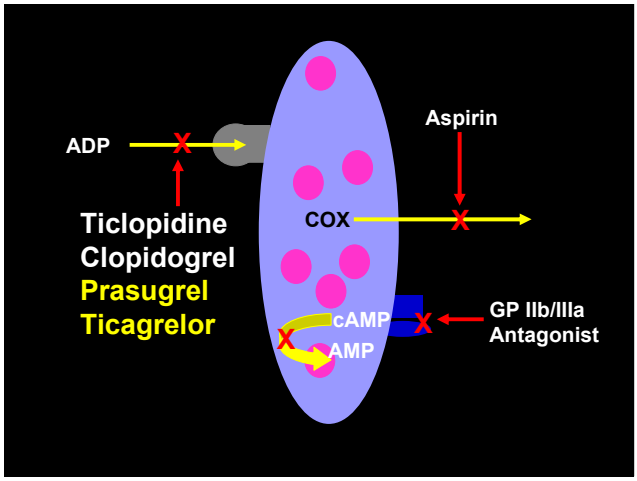
Venous Thrombosis

Drug	Thrombosis	Bleeding
Dabigatran	Equal	Equal
Rivaroxaban	Equal	Equal/Better

Warfarin: $4/month + monitoring ($20-50/visit)
Rivaroxaban: $247/month
Dabigatran: $235/month

Antiplatelet Agents

- Aspirin is the old classic
- Increasing number of patients on new drugs



Thienopyridines

- Ticlopidine, Clopidogrel, Prasugrel
- Bonds to ADP receptors
  - P_2Y_{12} receptor
- Permanently decreases platelet function

Clopidogrel

- Blocks platelet ADP receptor
- Effects last life of the platelet
- Synergistic effect with aspirin

Clopidogrel + ASA

- Useful for:
  - Stents
  - Acute coronary syndromes
  - Before cardiac interventions
- Not useful
  - Harmful when combined with ASA for stroke patients
  - Primary prevention

Prasugrel

- New thienopyridine
  - Still requires activation
  - Inhibits platelets faster and more reliable than clopidogrel
- Better than clopidogrel in patients undergoing procedures but markedly increased risk of bleeding
- One death for every 7 MI prevented

Prasugrel: Bottom Line

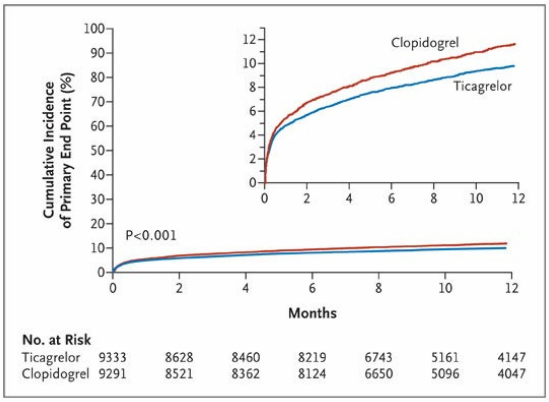
- Consider for younger patients with NO history of stoke who will require PCI
- Not to be used in patient with high chance going to CABG
- Option for clopidogrel failures?
- Only short term use?
- ???

Ticagrelor

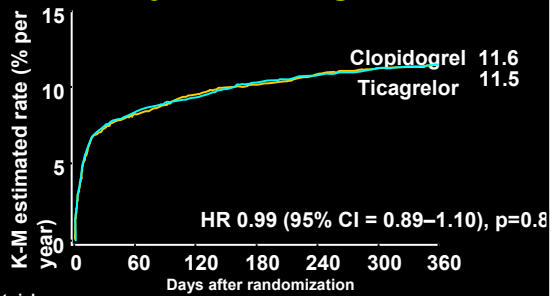
- Reversible P_2Y_{12} receptor inhibitor
  - Does NOT permanently inhibit platelets
- Nonthienopyridine
- Very effective in ACS

– Reduce deaths

– No increase in major bleeding



Primary Safety Event: Major bleeding*



* PLATO definitions

Good

- Ticagrelor very promising
  - Better than clopidogrel
    - No increase in risk of bleeding
  - No concerns about genetics or drug interactions with one curious exception….

However….

- Concerns
  - BID dosing
  - Slight increase in dyspnea
  - Takes days to wear off….
- Results varied by trial site
  - NO benefit in USA patients

Effect of Asprin Dose

Aspirin Dose	US	Non-US
>300	1.62 (0.99-2.64)	1.23 (0.71-2.14)
100-300	-	1.00 (0.71-1.42)
< 100	0.73 (0.4-1.33)	0.78 (0.69-0.87)

- Doses of asprin > 100 seem to impair action of drug
- Majority of US patients received > 100mg aspirin

Ticagrelor: Bottom Line

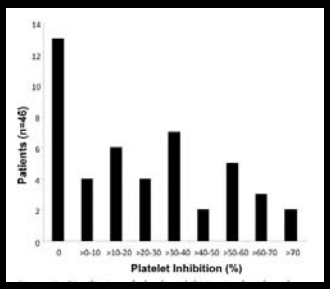
- 180mg load then 90mg bid
- More effective than clopidogrel in acute coronary syndromes
- Cannot use > 100 mg of aspirin

Reversal of Anticoagulants

- Monitoring
- Antiplatelets
- Antithrombotics

Monitoring

- Antiplatelets
  - PFA not sensitive
  - VerifyNow?
    - Trauma study showed ~ 30% of patients with no clopidogrel effect
    - Verfication study in progress



The Journal of Trauma: Injury, Infection, and Critical Care
Issue: Volume 70(1), January 2011, pp 65-70

Monitoring

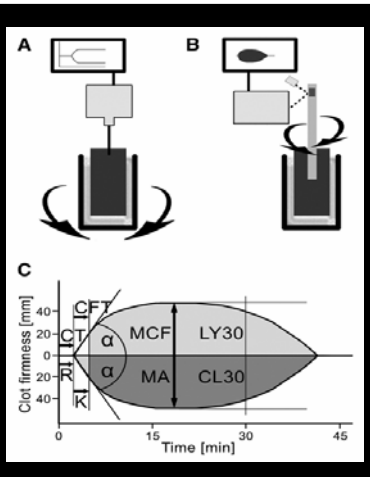
- "Heparins"
  - UFH – aPTT
  - LMWH – anti-Xa
  - Fondaparinux – anti-Xa

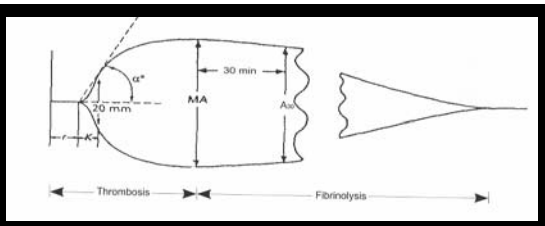
Monitoring

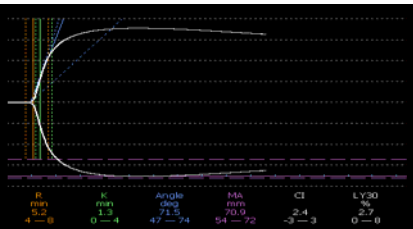
- Warfarin – INR
- Dabigatran – aPTT
- Rivaroxaban – INR, anti-Xa
- Apixaban – anti-Xa

Thromboelastrography

- Point of care test using fresh whole blood
- Measures tensile strength of forming thrombosis

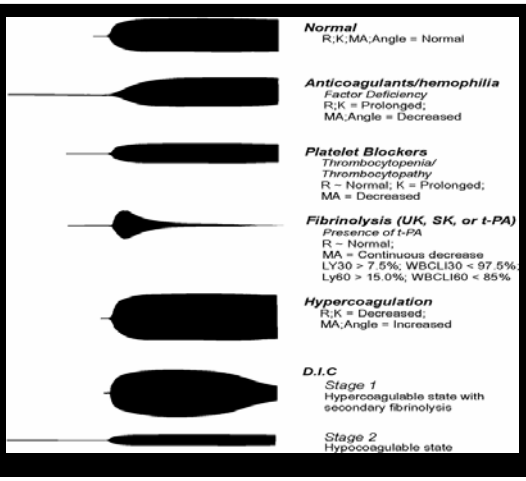






TEG Results

- r time: time from start until clot formation.
- K time: time 2 mm to 20 mm.
- Alpha angle: slope between r time and K time.
- Maximal amplitude: greatest amplitude of TEG tracing.
- Whole blood lysis index: amplitude of tracing 60 minutes after MA.



TEG Parameter	Level	Action
r time	Increased	FFP
K time	Increased	Cryoprecipitate
Alpha Angle	Decreased	Cryoprecipitate
MA	Decreased	Platelets
Lysis index	Increased	Antifibrinolytics

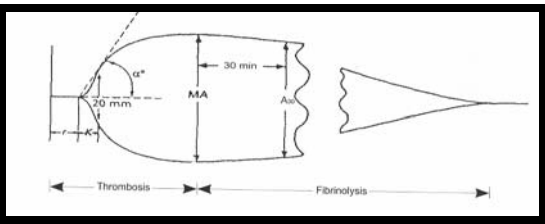
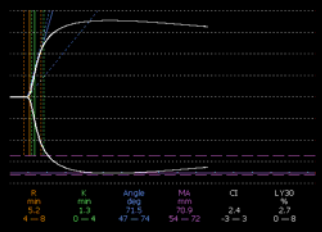


TABLE 7. Current Memorial Hermann Hospital Transfusion Recommendations Based on Abnormal r-TEG Values in Bleeding Patients

Laboratory Values	Blood Product Transfusion
ACT > 128	Plasma and RBCs
r-value > 1.1	Plasma and RBCs
k-time > 2.5	Cryoprecipitate / fibrinogen / plasma
α-angle < 56	Cryoprecipitate / fibrinogen / platelets
MA < 55	Platelets / cryoprecipitate / fibrinogen
LY30 > 3%	Tranexamic acid
PT > 18.0	Plasma
aPTT > 35	Plasma
INR > 1.5	Plasma
Platelet count < 150 × 10^9/L	Platelets
Fibrinogen < 180 g/L	Cryoprecipitate / fibrinogen

(*Ann Surg* 2012;256: 476–486)

Patient 1



- Normal R
- High normal α angle
- High normal MA
- Normal LY30
- Overall – Normal

- INR 2.21
- Platelets – 128,000

Thromboelastography

- Pro
  - Assess all hemostasis
  - Quick turn-around of basic labs
- Con
  - Lack of familiarity
    - TEG based protocols
  - Need to run sample in 4 minutes
  - QI/QA

TEG – Where We Use IT

- Surgery
  - Cardiac
  - Liver
- Trauma
  - Most protocol driven (1:1)
  - Unusual bleeding
- Liver disease
- Unusual bleeding

Antiplatelet Agents

Aspirin

- Blocks thromboxane A_2 production
- Duration of effect: 5 – 7 days
- Tx: Desmopressin, platelet transfusions

Clopidogrel, prasugrel, ticagrelor

- Blocks ADP receptor
- Duration of effect: 5-7 days
- Tx: Desmopressin(?), platelet transfusions (2 units), rVIIa (?)

Platelets Transfusion

- All data is *in-vitro*
- For major bleeding:
- Aspirin: one pheresis unit
- Clopidogrel: two units

Antiplatelet Agents

Glycoprotein IIb/IIIa inhibitors

- Abciximab (Reopro)
  - Duration: hours
  - Tx: Desmopressin, platelet transfusions
- Tirofiban (Aggrastat), Eptifibatide (Integrilin)
  - Duration: hours
  - Tx: Desmopressin, platelets, cryoprecipitate

"Heparins"

www-heparin.rpi.edu/pentsacc-antithrombin.jpg

Standard heparin

- Half-life: 1 hour
- Protamine

LMW Heparin

- Half-life: 4 hours
- Protamine

Fondaparinux (Arixtra)

- Half-life: 16-20 hours
- Protamine ineffective!
- rVIIa

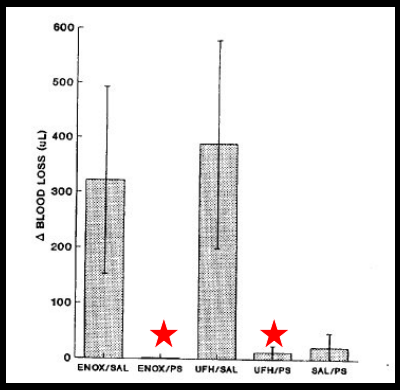
Standard Heparin

- Rapid $T_{1/2}$ makes reversal unnecessary in most patients
- Protamine
  - Side effects
  - ~ 1% pulmonary hypertension
- Dose
  - < 30 mins: 1mg/100 units heparin
  - 30-60 mins: 0.5mg/100 units
  - 60-120 mins: 0.25 mg/100 units

LMW Heparin

- Protamine effective!
- 0-4 hours: protamine 1mg: 1mg enoxaparin then 4 hours later ½ dose protamine
- 4-8 hours protamine 0.5 mg:1mg enoxaparin
- Other LMWH protamine 1mg:100 units

Protamine and LMWH



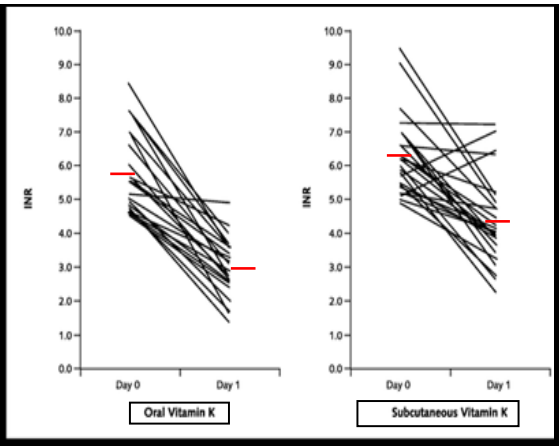
Thromb Haemost. 1990 Apr 12;63(2):271-4

Warfarin Reversal

- General approach
- Patient risk factors
  - Bleeding
  - Thrombotic risk
- Level of INR
  - Risk of bleeding with INR > 6 varies from 0.6-4%
- Higher risk in older patients anticoagulated for arterial reasons

Vitamin K

- Both oral and IV very effective
  - PO "targeted" to liver
- Sub-q and IM <u>not</u> effective in RCT and should not be used!
- Lower doses (1-2.5 mg) effective and does not lead to warfarin resistance
- SLOW (~1 hour) infusions of vitamin K has very low incidence of anaphylaxis
- No "rebound" with reversal



Ann Intern Med, Aug 2002; 137: 251 - 254.

rVIIa

- Makes INR normal
- But does not reverse bleeding defect
- Not effective for warfarin reversal

Prothrombin Complex Concentrates

- In theory, ideal for warfarin reversal
- However, all PCC in US are only "3-factor" concentrates
- 4-factor PCC available in July in US
  - INR 2-4: 25 units/kg
  - INR 4-6: 35 units/kg
  - INR > 6: 50 units/kg

Guidelines

- INR 4.5-10 and not bleeding:
  - Vit K 1 mg po *or*
  - Hold warfarin (may take up to 36 hours to see effect)
- INR > 10 and not bleeding:
  - Vit K 2.5 mg po

Guidelines

- INR 4.5-10 and bleeding
  - Vit K 2.5-5 mg po or IV
  - Plasma (15 ml/kg)*
- INR > 10 and bleeding
  - Vit 5-10 mg IV
  - Plasma (15 ml/kg)*

*PCC in life/limb threatening bleeding

Warfarin - ICH

- Intracranial hemorrhage:
- 4000 units 3F PCC + 1mg of rVIIa
  - PCC – II, IX, X
  - rVIIa – VII
- 4-Factor PCC
  - INR 2-4: 25 units/kg
  - INR 4-6: 35 units/kg
  - INR > 6: 50 units/kg

New Agents

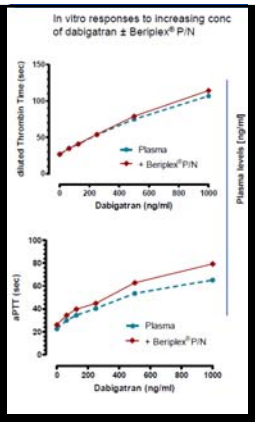
- Warfarin: "The Gold Standard"
  - Prothrombin Complex Concentrates (PCC) standard
    - FFP not effective for rapid reversal
  - 75% patients dead or disabled after intracranial hemorrhage

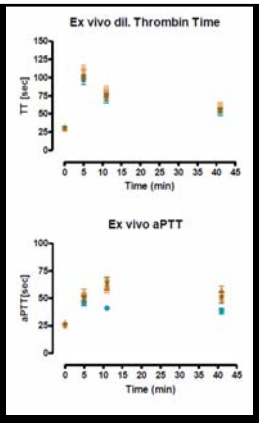
New Agents: Reversal

- Ximelagatran trials
  - No clear difference in outcomes reversible vs irreversible agents
- RE-LY study
  - ICH fatal 36%(W) vs 35% (D)
  - Traumatic ICH fatal 31% vs 30%

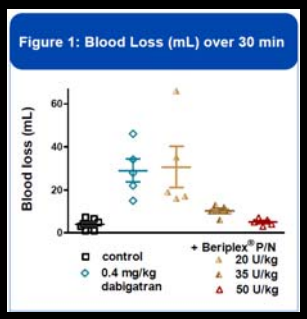
Dabigatran

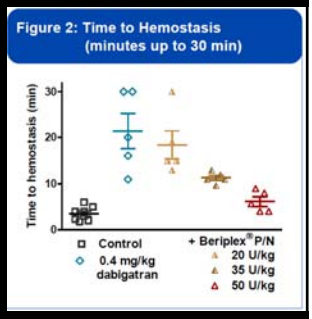
- Reversal
  - Animal modes
    - Activated prothrombin complex concentrates
    - Prothrombin complex concentrates
  - Human
    - PCC did not effect *in-vitro* tests
- Dialyzable
- Specific antibody in development





21st International Congress on Thrombosis 2010 , 6 - 9 Jul 2010,

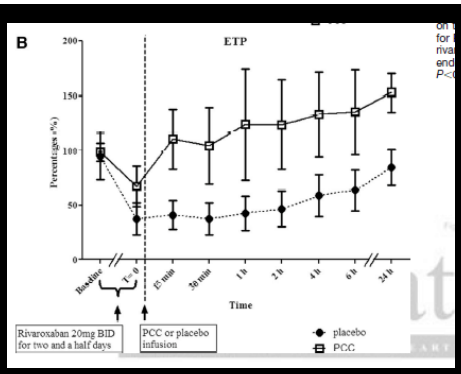




21st International Congress on Thrombosis 2010 , 6 - 9 Jul 2010,

Xa Blockers

- rVIIa
  - Human studies
- Prothrombin Complex concentrates
  - Animal and human studies



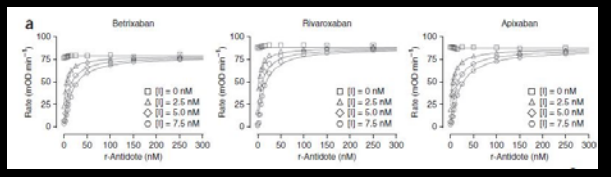
Reversal of Rivaroxaban and Dabigatran by Prothrombin Complex Concentrate : A Randomized, Placebo-Controlled, Crossover Study in Healthy Subjects
Elise S. Eerenberg, Pieter W. Kamphuisen, Meertien K. Sijpkens, Joost C. Meijers, Harry R. Buller and Marcel Levi

Circulation published online September 6, 2011

PRT064445

- "R-antidote"
- Recombinant fXa derivative
  - Catalytically inactive
  - Lacks the Gla-domain
- Reverses both direct and indirect Xa inhibitors
- In clinical trials

PRT064445



ADVANCE ONLINE PUBLICATION NATURE MEDICINE

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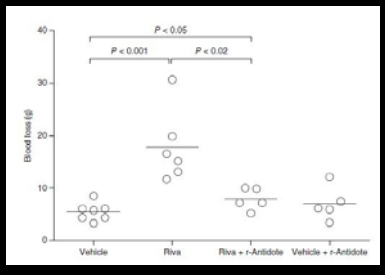

ADVANCE ONLINE PUBLICATION NATURE MEDICINE

What We Do

- Warfarin and all new agents
- 4000 units 3 factor PCC + 1mg of rVIIa
  - PCC – II, IX, X
  - rVIIa – VII
- The future:
  - 50 units/kg of 4 factor PCC

Warfarin: When to Restart after a Bleed

- Very common problem
- Increasing data on subject
- Risk of rebleed varies with site of bleed and presence of anatomic lesions

Risk of Rebleeding

- ICH/SDH: long term risk of recurrence ~2%
  - Higher if cerebral amyloid angiopathy present
- Gastrointestinal
  - Higher (10-20%?) especially if lesion present

Risk of Rebleeding

Risk of Rebleeding	Odd Ratio	CI
GI	4.9	(2.6-9.3)
ICH	-	-
Other	3.3	(1.4-7.5)
Timing		
< 14 days	4.1	(1.9-8.4)
> 14 days	1.9	(0.8-4.6)

J Thromb Haemost. 2006 Nov;4(11):2367-72

GI Bleeding: 2012

- N = 442 patients with GI bleed
- Warfarin restarted in 90 days or not
- 50% on aspirin at time of bleeding
- Arch Intern Med. 2012 Sep 17:1-8.

Results

- Warfarin resumption
  - Less thrombosis: 0.4% vs 5.5%
  - Same bleeding: 10% vs 5.5%
    - Less bleeding if > 7 days
      - 6.23% vs 12.4%
  - Less death RR = 0.3

Restarting

- Review indication for anticoagulation
- Review need for antiplatelet agents

Should Warfarin ever be Added to Aspirin?

- Increases risk of bleeding significantly
- Good Idea
  - Mechanical Valve
  - Stents
  - (ACS)
- Bad idea
  - Primary prevention
  - Long term secondary prevention
  - Peripheral vascular disease
- Always think before combing ASA and warfarin

When to Restart

- Data for valve patients and ICH suggest anticoagulation can be safely restarted in 1-7 days
- For GI/GU lesions may be longer (7 days?) but need to be aggressive at finding and fixing lesions
- Muscle/Retroperitoneal – 2 weeks?

What I Talked About

1. New Antithrombotic Agents
   - Dabigatran
   - Rivaroxaban
   - Apixaban
2. Antiplatelets
3. Reversal
4. Restarting