Oral Anticoagulant Therapies: A Balancing Act

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Learning Objectives

At the conclusion of this presentation, participants will be able to

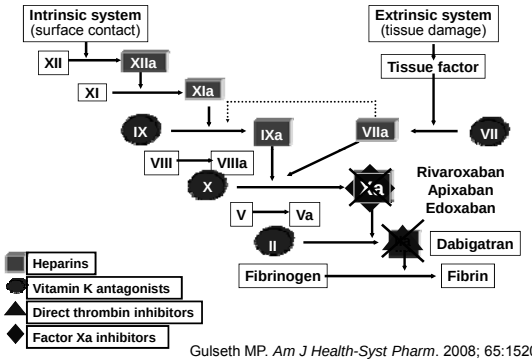
- Identify risk factors for bleeding complications with oral anticoagulant agents
- Discuss strategies for minimizing the risk of bleeding with oral anticoagulant agents

Background

- Due to increase in the U.S. elderly population, prevalence of thrombosis related complications and bleeding associated with anticoagulants is constantly rising
- Various tools exist to assess thrombotic risk but assessment of bleeding risk is often ignored

Roger VL et al. *Circulation*. 2012; 125:e2-e220.

Anticoagulants: Mode of Action



Gulseth MP. *Am J Health-Syst Pharm*. 2008; 65:1520-9.

Warfarin

- Widely used to prevent thromboembolism
- 2009, warfarin Rx for 3 million U.S. patients
- Leading cause of serious drug-related AEs
  - Bleeding 15-20%/yr; life-threatening 1-3%/yr

WARNING: BLEEDING RISK
See full prescribing information for complete boxed warning.

- Warfarin sodium can cause major or fatal bleeding. (5.1)
- Perform regular monitoring of INR in all treated patients. (2.1)
- Drugs, dietary changes, and other factors affect INR levels achieved with warfarin therapy. (7)
- Instruct patients about prevention measures to minimize risk of bleeding and to report signs and symptoms of bleeding. (17)

Budnitz DS et al. *N Engl J Med.* 2011; 365:2002-12.
Holland L et al. *Transfusion.* 2009; 49:1171-7.
Peacock WF et al. *Clin Cardiol*. 2012; [Epub ahead of print].
Coumadin (warfarin sodium) prescribing information. 2011 Oct (URL in ref list).

Warfarin Pharmacokinetics

Elimination half-life of warfarin
- R-warfarin: 45 hours
- S-warfarin: 29 hours

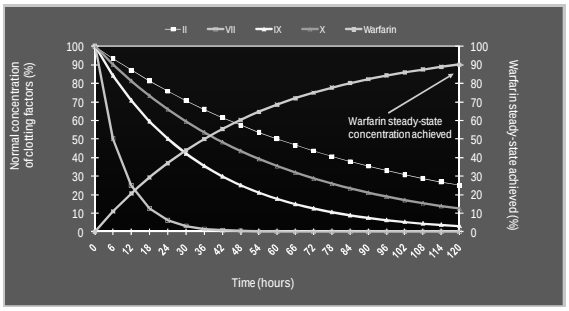
Elimination half-life of vitamin K dependent clotting factors
- II 42-72 hours
- VII 4-6 hours
- IX 21-30 hours
- X 27-48 hours

PT measures depression in factors II, VII, X

$$\text{INR} = \left(\frac{\text{Patient's PT in Seconds}}{\text{Mean Normal PT in Seconds}}\right)^{\text{ISI}}$$

PT = Prothrombin time
INR = International Normalized Ratio
ISI = International Sensitivity Index

Kinetics of Warfarin and Clotting Factors



Eckhoff CD et al. *Ann Pharmacother*. 2004; 38:2115-21.

Clinical Predictors of Prolonged Delay in Return of INR to Therapeutic Range

N	633 patients with INR > 6.0/various indications
Outcome	% patients with INR > 4.0 after holding warfarin x 2 days
Age	69 (25-95) [36% > 75 years]

INR > 4 after holding 2 doses 37% ⟶

	OR	*p* value
Age, per decade of life	1.18	0.04
Index INR, per unit	1.25	<0.001
Clinical CHF	2.79	0.009
Active malignancy	2.48	0.03
Weekly warfarin dose per 10 mg increase	0.87	0.009

Hylek EM et al. *Ann Intern Med.* 2001; 135:393-400.

Properties of Novel Oral Anticoagulants

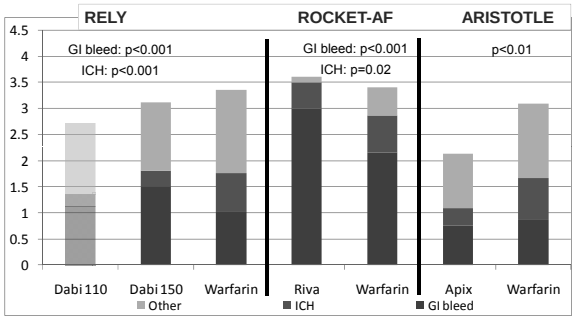
	Apixaban	Dabigatran	Rivaroxaban	Edoxaban
Direct factor inhibition	Xa	IIa	Xa	Xa
Renal clearance	25%	80%	33%	40%
t½ in hours by CrCl (mL/min)				
CrCl > 80	8-15	14-17	5-9h	9-11
CrCl 50 – 79	14.6	16.6	8.7	NA
CrCl 30 – 49	17.6	18.7	9.0	NA
CrCl < 30	17.3	27.5	9.5	NA
Dialyzable	Unlikely	Yes	Unlikely	Unlikely

Decreased renal function is associated with an increase in anticoagulant effect

NA = not available

Adapted from Kaatz S et al. *Am J Hematol*. 2012; 87(suppl 1):S141–5; Wittkowsky AK. *Pharmacotherapy*. 2011; 31:1175–91.

Novel Anticoagulants for SPAF
Safety Endpoint: Major Bleeding



Connolly SJ et al. *N Engl J Med.* 2009; 361:1139-51; Patel MR et al. *N Engl J Med.* 2011; 365:883-91; Granger CB et al. *N Engl J Med.* 2011; 365:981-92.

Institute for Safe Medication Practices: Serious Bleeding with Dabigatran

- ISMP QuarterWatch Report 2011
- Dabigatran linked to
  - 3781 serious adverse events
  - 2367 cases of hemorrhage
  - 542 patient deaths

Table 4. Suspect drugs ranked by number of direct reports to FDA 2011

Rank	Drug Name	Brand Name	Year Approved	Report Type Direct	Mfr
1	DABIGATRAN	PRADAXA	2010	817	2,964
2	WARFARIN	COUMADIN	1954	490	616
3	LEVOFLOXACIN	LEVAQUIN	1996	393	583
4	CARBOPLATIN	N/A	1989	376	140

http://www.ismp.org/QuarterWatch/pdfs/2011Q4.pdf

Ying – Yang Principle: Thrombosis vs. Bleeding

- With every approach to reduce thrombosis, there is an accompanying risk of increasing bleeding complications
- Conversely, reducing bleeding complications may increase thrombotic events
  - Both increase morbidity and mortality
- Balancing both ends of the spectrum is essential, and an individualized approach to therapy is advocated

Patient Case

- 69-year-old African American woman
- HTN (uncontrolled 165/95), DM, CRI (CrCl 35 mL/min) and HLD
- Presents to ER with dizziness and palpitations
- EKG: Atrial fibrillation, rate of 110 bpm
- Exam: normal, Labs: WNL, Cr 1.5
- Meds: lisinopril, simvastatin, glipizide
- SH: ETOH (+), 2-3 drinks/day
- Patient started on oral diltiazem XR 120 mg daily

Q1: This patient's risk of a cardioembolic stroke is

a. Low
b. Moderate
c. High
d. Super high…ticking time bomb

Stroke Prevention in Atrial Fibrillation: Assessing Stroke Risk

$CHADS_2$ Score

Risk Factor	Score
Congestive heart failure	1
Hypertension	1
Age ≥ 75 years	1
Diabetes	1
Stroke or TIA history	**2**
MAXIMUM	**6**

CHA_2DS_2-Vasc Score

Risk Factor	Score
Congestive heart failure / ***LV dysfunction***	1
Hypertension	1
Age ≥ 75 years	**2**
Diabetes	1
Stroke/TIA/***TE history***	**2**
***V**ascular disease*	1
***A**ge 65 – 74 years*	1
***S**ex **c**ategory, female*	1
MAXIMUM	**9**

Gage BF et al. *JAMA.* 2001; 285:2864-70.
Lip GY et al. *Chest.* 2010; 137:263-72.

Stroke Prevention in Atrial Fibrillation: Guideline Recommendations

$CHADS_2$ score	Chest (Grade of rec)	ACCF/AHA/HRS (Class of rec)
0 (low)	No therapy (2B)	Aspirin (I)
1(moderate)	OAC (1B) **Dabi > warfarin***	OAC or aspirin (IIa) **Dabi alt to warfarin†**
≥ 2 (high)	OAC (1A) **Dabi > warfarin***	OAC (I) **Dabi alt to warfarin†**

*Except in patients with CrCl < 30 mL/min, mitral stenosis, stable CAD, recent ACS, or s/p intracoronary stent
†Except in patients with prosthetic heart valves, hemodynamically significant valvular heart disease, CrCl < 15 mL/min, or advanced liver disease
Rivaroxaban and apixaban not approved at time of guideline publication; not included

You JJ et al. *Chest*. 2012;141(suppl 2):e531S-75S.
Fuster V et al. *Circulation.* 2011; 123:e269-367. Wann SL et al. *Circulation.* 2011; 123:1144-50.

Q2: This patient's risk of bleeding is

a. Low
b. Moderate
c. High
d. Super high…ticking time bomb

Q3: What is this patient's HAS-BLED score?

a. 1
b. 2
c. 3
d. 4

Stroke Prevention in Atrial Fibrillation
Balancing Stroke and Bleeding Risk

$HEMORR_2HAGES$ Score

Risk Factor	Score
Hepatic or renal disease	1 ea
Ethanol use	1
Malignancy	1
Older age: > 75 years	1
Reduced platelet count or Fxn	1 ea
Re-bleeding	**2**
Hypertension, uncontrolled	1
Anemia	1
Genetic factors	1
Elevated fall risk ± neuropsychiatric disease	1
Stroke	1
MAXIMUM	14

HAS-BLED Score

Risk Factor	Score
Hypertension, SBP > 160 mmHg	1
Abnormal renal or liver function	1 ea
Stroke	**2**
Bleeding history or predisposition	1
Labile INRs	**2**
Elderly: age > 65 years	1
Drugs or alcohol Antiplatelet or NSAID	1
Alcohol use: > 8 servings/week	1
MAXIMUM	11

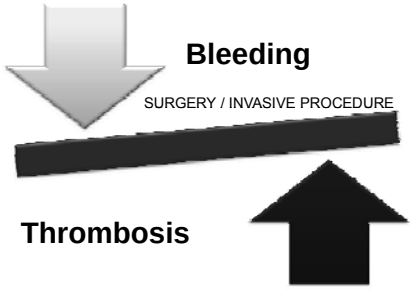
Gage BF et al. *Am Heart J.* 2006; 151:713-9.
Pisters R et al. *Chest.* 2010; 138:1093-100.
Lip GY et al. *J Am Coll Cardiol*. 2011; 57:173-80.

Stroke Prevention in Atrial Fibrillation: ESC 2012 Guidelines

Recommendations for prevention of thromboembolism in non-valvular AF—bleeding		
Assessment of the risk of bleeding is recommended when prescribing antithrombotic therapy (whether with VKA, NOAC, aspirin/clopidogrel, or aspirin).	I	A
The HAS-BLED score should be considered as a calculation to assess bleeding risk, whereby a score ≥3 indicates 'high risk' and some caution and regular review is needed, following the initiation of antithrombotic therapy, whether with OAC or antiplatelet therapy (LoE = A).	IIa	A
Correctable risk factors for bleeding [e.g. uncontrolled blood pressure, labile INRs if the patient was on a VKA, concomitant drugs (aspirin, NSAIDs, etc.), alcohol, etc.] should be addressed (LoE = B).	IIa	B
Use of the HAS-BLED score should be used to identify modifiable bleeding risks that need to be addressed, but should not be used on its own to exclude patients from OAC therapy (LoE = B).	IIa	B
The risk of major bleeding with antiplatelet therapy (with aspirin–clopidogrel combination therapy and – especially in the elderly – also with aspirin monotherapy) should be considered as being similar to OAC.	IIa	B

Camm AJ et al. *Eur Heart J.* 2012 Aug 24 [Epub ahead of print].

Perioperative Management Considerations



Perioperative Management Considerations

- PRE-operative
  - Timing of when AC is stopped is anchored on agent PK characteristics and half-life
  - Aim to stop AC agent before surgery so there is **minimal or NO residual AC effect** at the time of surgery
- POST-operative
  - Consider the effect of surgery, risk of bleeding, and bowel motility
  - Resume once adequate hemostasis has been achieved

PRE-operative Management Considerations

- Minor surgery
  - Low bleeding risk
  - Can have some residual AC effect at time of surgery
- Major surgery
  - High bleeding risk
  - Spinal anesthesia
  - Aim to have minimum or NO residual AC effect at time of surgery

PRE-Operative Management Considerations

Number of half-lives elapsed	% of Drug Effect Remaining
1	50
2	25
3	12.5
4	6.25
5	3.125

Allow longer period of time before surgery
- Elderly
- Known impaired renal function
- Known clinical factors to cause delay in INR drop or drug elimination for novel oral anticoagulants

Recommendations for Timing of Warfarin around Invasive Procedures

Discontinuation	5 days before scheduled procedure
Resumption	"12-24 hours after surgery and when there is adequate hemostasis" (To minimize bleeding risk, use patient's pre-operative dose rather than reloading)

Douketis JD et al. *Chest.* 2012; 141(suppl 2):e326S-50S.

Interruption of Novel Oral Anticoagulant Therapy for Invasive Procedures and Surgery[a]

Drug (Renal Function)	No. of Doses to Skip before Minor Procedure[b]	No. of Doses to Skip before Major Surgery[b]
Dabigatran (CrCl > 50 mL/min)	1 or 2	4
Dabigatran (CrCl ≤ 50 mL/min)	3 or 4	6-8
Rivaroxaban (CrCl > 50 mL/min)	1 or 2	3 or 4
Apixaban	1 or 2	3 or 4

[a]Resume therapy 24-48 hr after minor procedure, 48-72 hr after major surgery. If UFH or LMWH is used as bridging therapy in patients with atrial fibrillation, mechanical heart valve, or venous thromboembolism who are at high risk for thromboembolism, oral anticoagulant therapy should be resumed at least 1 hr after UFH infusion is discontinued and at least 10 hr after last dose of LMWH.

[b]Assuming dabigatran is taken twice daily, rivaroxaban is taken once daily, and apixaban is taken twice daily.

Viles-Gonzalez JF et al. *J Cardiovasc Electrophysiol.* 2011; 22:948-55.

Measurement of Anticoagulation Effect

- Under- or overdosing
- Drug interactions
- Progressive renal insufficiency
- Adherence assessment
- Invasive procedures, surgery
- Thrombolytic therapy
- Triple antithrombotic therapy
- Extremes of age, weight

Hematology Testing: Novel Oral Anticoagulants

	Usefulness of Lab Test	Dabigatran	Rivaroxaban	Apixaban
Lab tests	Strong	• ECT	• Chromogenic anti-Xa	• Chromogenic anti-Xa
		• TT • aPTT	• aPTT, PT	
	Weak	• PT/INR		

Palladino M et al. *Am J Hematol.* 2012; 87(suppl 1):s127-32.

Summary

- Assessment of bleeding risk must be objective with the use of bleeding risk scores
- Health care providers must maintain a fine balance between thrombosis and bleeding in choosing and managing oral anticoagulant therapy
- Novel agents with multiple doses and indications
  - Special attention to half-life and renal function
  - Various agents will require different algorithms for managing invasive procedures and reversal approaches

Options for Reversing the Effects of Oral Anticoagulants

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Learning Objectives

At the conclusion of this presentation, participants will be able to

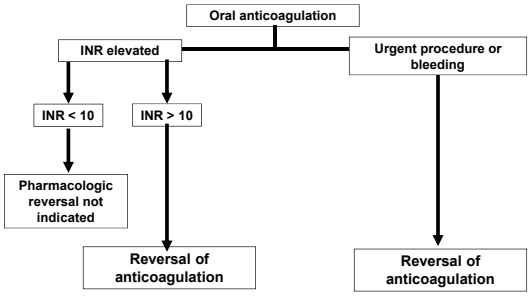
- Describe the relative benefits and limitations of emergent anticoagulant reversal strategies
- Discuss the clinical evidence supporting the use of emergent anticoagulant reversal strategies

WARFARIN

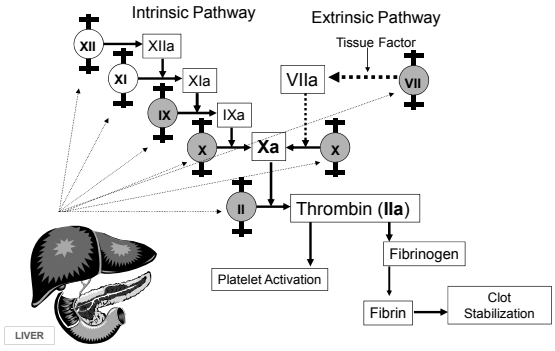
Q4: Which of the following patients taking warfarin would require pharmacologic reversal of anticoagulation? Select all that apply.

a. INR of 4, presenting to ED with complaints of hematemesis
b. INR of 12 and no signs or symptoms of bleeding
c. INR of 2.2, requiring emergent coronary artery bypass graft surgery
d. INR of 7 and no signs or symptoms of bleeding

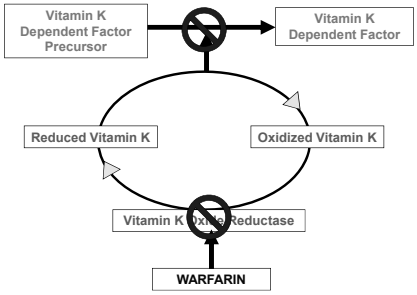
Clinical Scenarios for Reversal



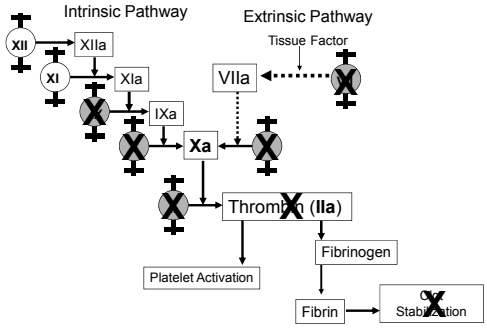
Basis for Understanding Reversal



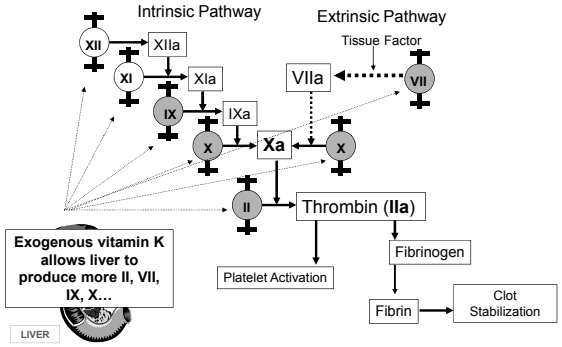
Vitamin K Dependent Factor Formation



Basis for Understanding Reversal



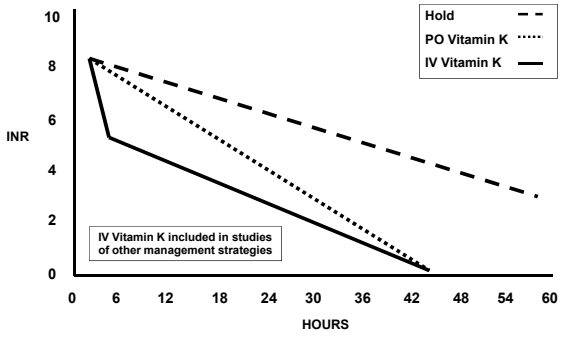
Reversal with Vitamin K



Vitamin K

- Dosing issues
  - Supratherapeutic INR
    - Oral is preferred
  - Urgent situations
    - IV is preferred
    - NO subcutaneous or IM
- Adverse events
  - Anaphylactic reaction to IV
  - May be refractory to warfarin when restarted
    - Use lowest dose possible to avoid

IV Vitamin K for Reversal of Warfarin



Warfarin Reversal: Vitamin K

INR	Hold	PO Vitamin K	IV Vitamin K
4.5 – 10	Yes	**No advantage to vitamin K use in these patients**	
>10	Yes	2 – 2.5 mg	No
Any + bleeding	Yes	No	5 – 10 mg slow

Holbrook A et al. *Chest*. 2012; 141(2 suppl):e152s-84s.

Evidence: INR > 10 and No Bleeding

	n	Oral Vitamin K Dose	Any Bleeding (n)	Major Bleeding (n)
Gunther 2004	89	2 mg	Vitamin K = 0[a] No vitamin K = 3[a]	n/a
Crowther 2010	107	2.5 mg	16[b]	1[b]

[a]Day 3
[b]Day 7

Low rate of bleeding with oral vitamin K
No patients refractory to warfarin with oral vitamin K

Gunther KE et al. *Thromb Res*. 2004; 113:205-9.
Crowther MA et al. *Thromb Haemost*. 2010; 104:118-21.

Reversal of Warfarin: Bleeding or Need for Emergent Surgery

Options

- IV vitamin K
  PLUS
- Fresh frozen plasma (FFP)
  OR
- Prothrombin complex concentrate (PCC)
  OR
- Recombinant factor VIIa (rFVIIa)
  OR
- Activated PCC (aPCC)

Fresh Frozen Plasma

- How does it work?
  - Contains all blood factors found in plasma
- Dosing
  - 1 unit ~ 200 – 250 mL
    - Weight based
      - 10 – 20 mL/kg → 20 – 30% increase in any factor level
    - "2 units FFP"
- Disadvantages
  - Volume of fluid administration – 400 mL or more!
  - Thawing may delay therapy
  - Infectious disease concerns
  - Hemolytic transfusion reactions and hypersensitivity

DomBourian M et al. *J Infusion Nursing*. 2012; 35:28-32.

Concentrated Blood Factor Products

	rFVIIa	3-factor PCC	4-factor PCC	aPCC
Brand Names	Novo-Seven®	Bebulin VH® Profilnine SD®	Octaplex® Beriplex P/N® Cofact® Kanokad®	FEIBA®
U.S. Availability	Yes	Yes	No	Yes
Factors Provided	VII	II, IX, X	II, VII, IX, X	II, VII, IX, X
Activated?	Yes	No	No	Yes

Samama CM. *Eur J Anaesthesiol.* 2008; 25:784-9.

Prothrombin Complex Concentrates (PCCs)

Approximate Factor Concentrations in Available PCCs[a,b]

Factor	Profilnine SD®	Beriplex P/N®	Octaplex®	Cofact®
II	≤ 35-40	31	38	14-35
VII	≤ 10	16	24	7-20
IX	25	29	25	25
X	≤ 25	41	30	14-35

[a]Concentration expressed as units/mL. [b]Actual concentrations vary from lot to lot.

Profilnine SD (factor IX complex) prescribing information. 2010 Aug (URL in ref list).
Samama CM. *Eur J Anaesthesiol.* 2008; 25:784-9.

Concentrated Blood Factors

- Dosing issues
  - Fixed dosing vs. weight based
  - Extrapolating results reported in literature
    - Variability in factor concentrations by PCC product
- Adverse events
  - Prothrombotic potential
    - Especially with "activated" products
      - rFVIIa, aPCC
    - Anticipated benefit must outweigh prothrombotic risk
      - WHO should be reversed will be discussed in the next presentation

Warfarin Reversal with a 3-Factor PCC

Study	Holland and Colleagues
n	40 PCC/42 Controls
Patients	INR > 5 with bleeding or at risk for bleeding ICH excluded Control group: historical controls
Dosing	PCC low: profilnine 25 units/kg; High: profilnine 50 units/kg FFP ~ 2 units per prescriber; Vitamin K 1 - 10 mg
Findings	Target INR < 3 within 24 hours Baseline INR: 8.6 – 9.4 Low and high dose had similar effect on INR PCC alone: 43 – 55% achieved INR target FFP alone: 62% achieved INR target PCC + FFP: 89 – 93% achieved INR target p < 0.01 p ≤ 0.01

ICH = intracranial hemorrhage

Holland L et al. *Transfusion.* 2009; 49:1171-7.

Warfarin Reversal with 3-Factor PCC

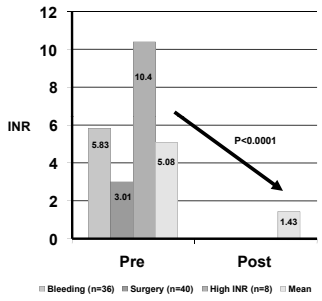
Summary of Evidence

- Shortened time to reduction in INR
  - Faster than FFP alone
  - Data limited by nonstandard monitoring after PCC
- 3-factor PCCs mostly studied in addition to FFP
  - Reduced FFP requirements
- Dose is typically 25 – 50 units/kg (IX)
- Lack of clinical outcome data

Boulis NM et al. *Neurosurgery.* 1999; 45:1113-8.
Chapman SA et al. *Ann Pharmacother*. 2011; 45:869-75.
Holland L et al. *Transfusion*. 2009; 49:1171-7.
Joseph B et al. *J Trauma Acute Care Surg*. 2012; 72:828-34.

Warfarin Reversal with a 4-Factor PCC

- Case series
  - 85 doses/82 patients
- Reversal strategy
  - Octaplex
    - 1792 ± 601 units
  - Vitamin K (69/85 doses)
    - 4.9 ± 5.5 mg
  - FFP – not used
- Results
  - Mean INR ↓
    - 3.98 ± 5.86
  - Thrombosis: 3
  - Death: 7
    - 4 surgical
    - 3 bleeding



Song MM et al. *Thromb Res.* 2012; 129:526-9.

Warfarin Reversal with a 4-Factor PCC: Impact on Outcomes

- Reversal due to bleeding
  - n = 212
- Randomized, open-label
  - 4-factor PCC (25 – 50 units/kg, based on INR)
  - FFP (10 – 15 mL/kg, based on INR)

KEY FINDINGS

- Bleeding: similar at 24 hours
- INR correction: faster with 4-factor PCC
- Fluid overload: less with 4-factor PCC

Sarode R et al. Thrombosis and Hemostasis Summit of North America, Chicago, IL: May 3-5, 2012.

Warfarin Reversal with a 4-Factor PCC

Summary of Evidence

- INR "normalized" in minutes to hours
  - May normalize in as little as 15 – 20 minutes
- 4-Factor PCCs effective for reducing INR *without* FFP
  - Effect on bleeding similar to FFP
- Dosing is often 25 – 50 units/kg (IX)
  - Maybe fixed doses or INR-specific doses
- Thromboembolic complications
  - Infrequent, but have occurred
- Surrogate endpoints

Khorsand N et al. *Transfus Med*. 2011; 21:116-23.
Lubetsky A et al. *Thromb Res*. 2004;113:371-8.
Pabinger I et al. *J Thromb Haemost* . 2008; 6:622-31.
Preston FE et al. *Br J Haematol*. 2002; 116:619-24.
Song MM et al. *Thromb Res*. 2012; 129:526-9.

Warfarin Reversal with Factor VIIa

Retrospective, Observational Study

≥ 18 y/o + traumatic ICH + warfarin use w/ INR > 1.3

Standard Management (n = 20)	Factor VIIa Management (n = 20)
FFP ± vitamin K Other supportive measures or surgical interventions	Factor VIIa (mean = 17.7 ± 6.2 mcg/kg) FFP ± vitamin K Other supportive measures or surgical interventions

Nishijima DK et al. *Acad Emerg Med*. 2010; 17:244-51.

Warfarin Reversal with Factor VIIa

	Standard (n=20)	FVIIa (n=20)	p-value
Initial INR	2.51	2.87	>0.05
FFP (units)	4.6	2.3	0.001
Vitamin K	800%	95.0%	>0.05
Time to surgery	74.6	5.6	0.30
In-hospital mortality	35.0%	35.0%	1.0
Thromboembolism	5.0%	20.0%	0.15
INR < 1.3	68.4%	100%	0.02
Time to INR < 1.3 (hr)	17.5	4.8	<0.001

Nishijima DK et al. *Acad Emerg Med*. 2010; 17:244-51.

Warfarin Reversal: 3-Factor PCC vs. Factor VIIa

Design: Retrospective cohort

Patients: Adult patients presenting with ICH, taking warfarin

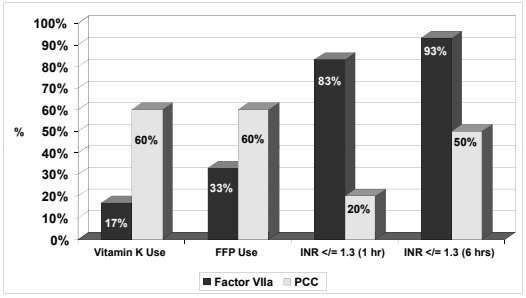
	Factor VIIa (n = 15)	**PCC* (n = 9)**
Baseline INR	6.1#	2.3^
1-hour INR	1.1#	1.48^
Treatment dose	53.4 mcg/kg	27.8 units/kg
Vitamin K dose	17.8 ± 14.6 mg	17.1 ± 12.9 mg
FFP	1025 ± 828 mL	778 ± 484 mL

*Bebulin VH, 3-factor PCC

#n = 6; ^n = 5

Pinner NA et al. *World Neurosurg*. 2010; 74:631-5.

Warfarin Reversal: 3-Factor PCC vs. Factor VIIa



Unexpected response to PCC due to low use of FFP ± vitamin K?

Pinner NA et al. *World Neurosurg*. 2010; 74:631-5.

"Building" a 4-Factor PCC

Patients
- Warfarin related ICH, INR ≥ 1.6 (46)
- Historical controls (12)

Reversal strategy
- IV Vitamin K 5 mg slow IV
- PCC 4000 units
- Factor VIIa 1 mg

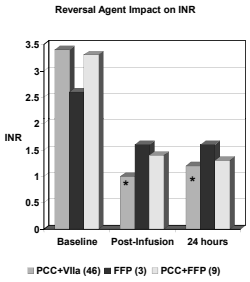
Complications

2 NSTEMI
- 1 occurred 8 hours post PCC+FVIIa
- 1 occurred 3 days later

Mortality

24 hours – 5/46

72 hours – 8/46



*PCC+VIIa less than FFP and PCC+FFP (p<0.05)

Sarode R et al. *J Neurosurg*. 2012; 116:491-7.

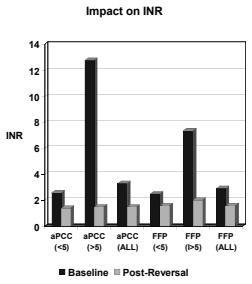
Warfarin Reversal: aPCC

Patients
- Patients requiring reversal (n = 72)
- Historical controls receiving FFP (n = 69)

Reversal strategy
- IV Vitamin K 10 mg slow IV
- aPCC 500 units if INR < 5
- aPCC 1000 units if INR ≥ 5
- FFP dosing in control patients
  - Discretion of prescriber (~2 units)

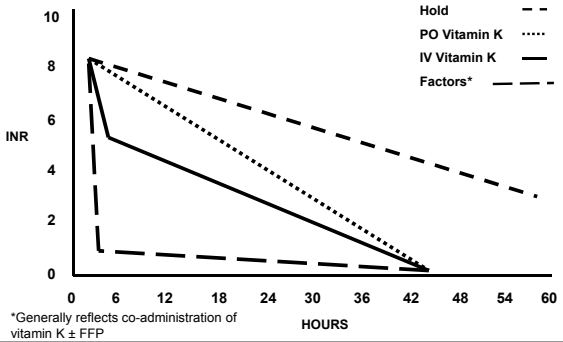
Other results
- Time to INR < 1.4
  - 2 hr vs. 25 hr (p = 0.006)

Thromboembolic complications
- 1 venous thromboembolism
- 3 possible episodes of cardiac ischemia



Wojcik et al. *Int J Emerg Med*. 2009; 2:217-25.

Options for Reversal of Warfarin



*Generally reflects co-administration of vitamin K ± FFP

Urgent Warfarin Reversal: Bleeding or Surgery

Clinical Scenario	Reversal Approach
Bleeding	Vitamin K 5 – 10 mg slow IV + 4-factor PCC†
Surgery in < 24 hours	IV vitamin K 5 – 10 mg slow IV + Either 4-factor PCC#, factor VIIa or aPCC‡
Surgery in > 24 hours	May have time to use IV vitamin K alone‡

†Recommendation based on CHEST Guidelines (2C).
‡Recommendation based on published literature and pharmacodynamics of vitamin K.
#Note: 4 factor PCC not yet available in the United States, FFP or factor VIIa may be needed in addition to a 3-factor PCC to achieve desired effect on INR.

Cartmill M et al. *Br J Neurosurg*. 2000; 14:458-61; Fredriksson K et al. *Stroke*. 1992; 23:972-7; Holbrook A et al. *Chest*. 2012; 141(Suppl):e152s-184s; Huttner HB et al. *Stroke*. 2006; 37:1465-70; Makris M et al. *Thromb Haemost*. 1997; 77:477-80; Nishijima DK et al. *Acad Emerg Med*. 2010; 17:244-51; Wojcik C et al. *Int J Emerg Med*. 2009; 2:217-25.

What can we do in the United States?

- Add FFP to either 3-factor PCC or factor VIIa
  - FFP may not be tolerated by all
- 3-factor PCC + Factor VIIa
- aPCC alone

4-factor PCC approval soon?

Cost Implications of Reversal

Agent	FFP + PCC	PCC + VIIa	aPCC
FFP (15 mL/kg)	$300		
3-factor PCC (25 units/kg)	$1932	$1932	
Factor VIIa (20 mcg/kg)		$2820	
aPCC (1000 units)			$1800
Cost/reversal regimen	$2232	$4752	$1800

- Assumes 80-kg patient and rounding to nearest vial size.
- Acquisition cost (average wholesale price) for FFP = $60 per unit, PCC = $0.97/unit, factor VIIa = $1410/1-mg vial, aPCC = $1800/1056 units.

Q5: 75-year-old patient presents with new onset loss of consciousness and is found to have ICH. She takes warfarin 2.5 mg daily, and her INR is 3.2 today.
Which of the following could be used alone to lower her INR?

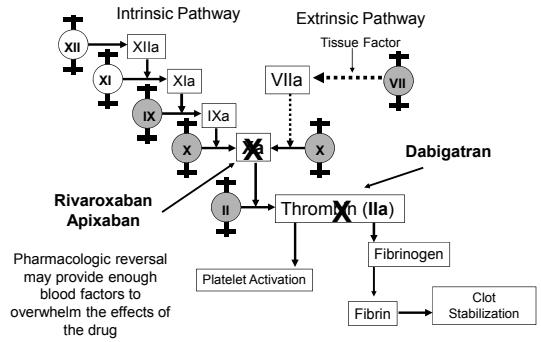
a. Oral vitamin K
b. An activated PCC
c. A 3-factor PCC
d. IV vitamin K

DABIGATRAN and RIVAROXABAN

How do we reverse them?

- Not really sure
- Largely theoretical
- Based on very limited data
  - Animal models
  - Healthy volunteer studies
  - Case reports

Theoretical Support for Reversal



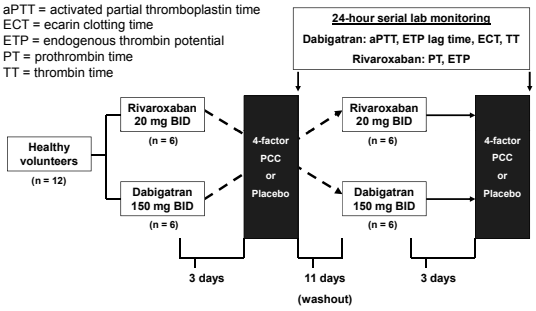
Animal Data

Effect on Bleeding Time or Models of Bleeding in Animals

Reversal Agent	Dabigatran	Rivaroxaban
3-factor PCC	???	???
4-factor PCC	Yes	No
Factor VIIa	Yes/No	Yes/No
aPCC	Yes	Yes
FFP	No	???

Godier A et al. *Anesthesiology.* 2012; 116:19-102.
Gruber A et al. *Haematologica.* 2009; 92(suppl 2):181.
Gruber A et al. *Blood.* 2008;112: abstract 3825.
van Ryn J et al. *Haematologica.* 2008; 93(s1):148. Abstract 0370.
Zhou W et al. *Stroke*. 2011; 42:3594-9.

Human Data: Dabigatran and Rivaroxaban



Eerenberg ES. *Circulation.* 2011; 124:1573-9.

Human Data: Dabigatran and Rivaroxaban

Dabigatran

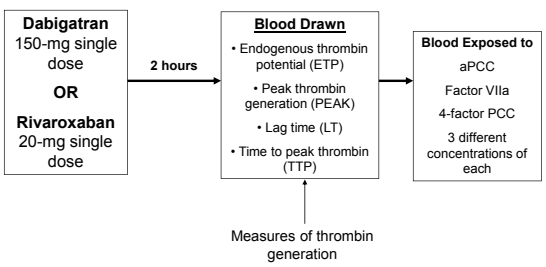
- No effect of PCC on ANY measure of coagulation

Rivaroxaban

- PT
  - Normalized within 15 minutes ($p<0.001$)
- ETP
  - Normalized within 15 minutes ($p<0.001$)

Eerenberg ES. *Circulation.* 2011; 124:1573-9.

Ex Vivo Study: Dabigatran and Rivaroxaban



Marlu R et al. *Thromb Haemost*. 2012; 108:217-24.

Ex Vivo Study: Dabigatran and Rivaroxaban

Summary of Findings

- 4-factor PCC and factor VIIa
  - Inconsistent impact on thrombin generation
    - Dabigatran patient blood
    - Rivaroxaban patient blood
- aPCC
  - Consistent impact on thrombin generation
    - Rivaroxaban patient blood
  - Less consistent impact on thrombin generation
    - Dabigatran
      - Still better than PCC and factor VIIa

Marlu R et al. *Thromb Haemost*. 2012; 108:217-24.

Dabigatran: Factor VIIa and Hemodialysis

- 79-year-old man, CrCl = 36 mL/min
- Dabigatran 150 mg twice daily
- Required aortic valve replacement/CABG
  - Dabigatran held x 2 days prior to surgery
- Massive bleeding postoperatively
  - Managed with 5 doses of factor VIIa
    - 2.4 mg/dose x 3 dose + 7.2 mg/dose x 2 doses
  - Hemodialysis x 6 hours
- Supports previous pharmacokinetics study data suggesting 60 – 70% removal of dabigatran dose

Warkentin TE et al. *Blood.* 2012; 119:2172-4.
Stangier J et al. *Clin Pharmacokinet*. 2010; 49:259-68.

Dabigatran: Perioperative Management

DABIGATRAN

Renal function (CrCl, mL/min)	Half-life (hours)	Time of last dabigatran dose before surgery	
		Standard bleeding risk	High bleeding risk
> 80	13	24 hours	2 – 4 days
> 50 to 80	15	24 hours	2 – 4 days
> 30 to 50	18	At least 48 hours	4 days
≤ 30	27	2 – 5 days	> 5 days

A high bleeding risk is associated with cardiac surgery, neurosurgery, abdominal surgery, and surgeries involving a major organ, advanced age, spinal anesthesia and other procedures in which complete hemostatic function is required, comorbid conditions (e.g., major cardiac, respiratory, or liver disease) and concomitant use of antiplatelet therapy.

van Ryn J et al. *Thromb Haemost.* 2010; 103:1116–27.

Rivaroxaban: Perioperative Management

RIVAROXABAN

CrCl (mL/min)	**>80** (n = 8)	**50 – 79** (n = 8)	**30 – 49** (n = 8)	**<30** (n = 8)
Half-life (hr)	8.3	8.7	9.0	9.5

- AUC ↑ as CrCl ↓
- Most rivaroxaban clearance
  - Non-renal (hepatic)
  - Renal secretion
- High protein binding
- Limited clearance by glomerular filtration

Kubitza D et al. *Br J Clin Pharmacol.* 2010; 70:703-12.

Urgent Reversal of Novel Anticoagulants: Bleeding or Surgery

Possible strategies

- aPCC
  - Supported by animal and limited human data
- 3-factor PCC plus factor VIIa
  - Mimic effects of aPCC
- Maybe a 4-factor PCC
  - Conflicting animal data, limited human data

Urgent Reversal of Novel Anticoagulants: Practical Considerations

Dabigatran

- Charcoal after recent ingestion
- Renal impairment complicates reversal
  - Role for hemodialysis

Rivaroxaban

- Less reliance on renal clearance

Dosing

- Very little guidance
  - Higher doses than usual?

Patient selection

- Risk vs. benefit

Conclusions

Warfarin reversal

- Concentrated blood factors > FFP alone
  - All studies have some methodologic limitations

Reversal of dabigatran and rivaroxaban

- Concentrated blood factors may have a role
  - aPCC or 4-factor PCCs may be best approach
  - Extremely limited data
  - Human data lacking

Lack of clear benefit + risk of blood factor products

- Proper patient selection is critical

Practical Issues in Developing an Oral Anticoagulant Reversal Strategy

William E. Dager, Pharm.D., BCPS (AQ-Cardiology)
Pharmacist Specialist
UC Davis Medical Center
Sacramento, California

Learning Objectives

At the conclusion of this presentation, participants will be able to

- Explain patient-specific treatment options for reversing the effects of oral anticoagulants using laboratory observations
- Develop an approach to managing major bleeding in a patient on oral anticoagulation therapy

Warfarin Situations

- 75 yo with AF, CKD V, heart failure, and CVA on warfarin 1 mg/day and has a GI bleed. INR = 12
- 56 yo with mechanical MVR brought into ED after crashing his motorcycle. Had notable abdominal injuries with hemorrhage apparent. INR = 3.0
- 27 yo with PE 1 year ago being assessed for colonoscopy. Warfarin 15 mg/day. INR = 2.5

Skill: Assess the Situation

- Bleeding?
  - Site: risk of a complication
- Level of anticoagulation
  - Laboratory assay
  - Antiplatelet agents?
- Hold anticoagulant

Skill: Explore Options

- Mechanical intervention
- Pharmacologic intervention
  - Intensity of anticoagulation (prior and post)
  - Goal or need for re-initiating therapy
  - Neutralize the drug
  - Reverse the effects of the drug independently

Skill: Consider the Entire Needs of the Patient

- Replace losses
- Optimize management of co-morbid situations
- Create a plan and request necessary follow up
- Evaluate thrombosis risks

Reversing Warfarin

Vitamin K (IV or PO) – 0.25 – 10 mg

Fresh frozen plasma (FFP)

Prothrombin complex concentrate (PCC)

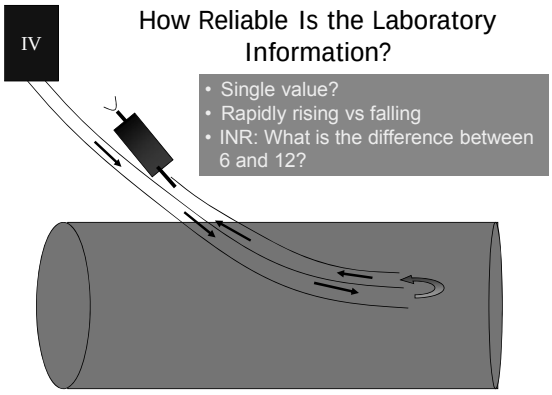
- PCC3 vs. PCC4 vs. activated PCC
- 25-50 units/kg depending on patient's weight, INR, and bleeding

Recombinant activated factor VII (rFVIIa)

- Low (1-2 mg) vs. high dose

Dougherty J. In Dager WE et al. Anticoagulation therapy. 2011:123-54.
Dager WE. *Ann Pharmacotherapy.* 2011; 45:1016-20.

How Reliable Is the Laboratory Information?



Warfarin

INR assay (How High)

- Rising vs. falling INR (? 1.8 > 2.2)
  - Not reliable in first days (factor VII driven)
- False DTI, UFH elevation
  - UFH (neutralization step in Lab?)

Hylek et al: INR > 6 → Risk Factors - INR ≥ 4 post 2-day hold

- Age per decade of life
- Initial INR (per 1.0 unit)
- Heart failure
- Weekly warfarin dose (per 10-mg increase)
- Active cancer

Hylek EM et al. *Ann Intern Med.* 2001; 135:393-400.

Using Vitamin K

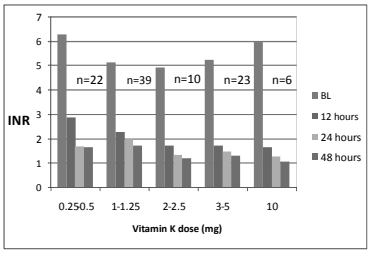
- What dose?
  - How fast do we need a response
- What route?
  - PO or IV (avoid SC or IM)
- Are other more rapid therapies planned (PCC, rFVIIa, FFP)
- Administration
  - Infusion rate – Max 1 mg/min (over ~15 – 20 min)
  - Light sensitive (~50 mL, avoid delay using large volumes)
  - Anaphylaxis concerns (3:10,000 risk)

Riegert-Johnson DL et al. *Ann Allergy Asthma Immunol*. 2002; 89:400-6.

Vitamin K for Reversing Warfarin

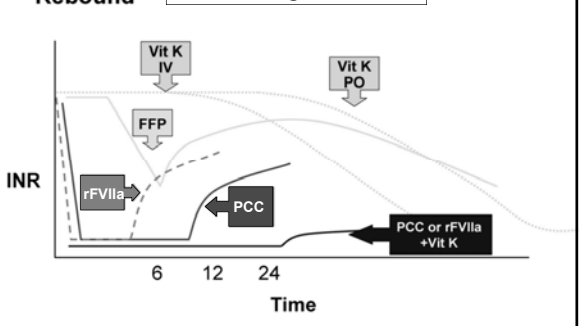
Vit K IV: doses > 2 mg IV

- Did not increase rate of reversal
- ↑ dose → prolonged periods of bridging therapy



Tsu LV et al. *Annals Pharmacother*. In press.

Reversing Warfarin



What Improves Outcomes in Warfarin-related ICH?

- A good stitch
  - **STICH Trial: ? Any impact of neurosurgery on improved outcomes**
- Dowlatshahi et al. *Stroke.* 2012
  - **PCC rapidly reversed the INR, but did not change mortality and morbidity**
- PCC shorten time to surgical procedures
  - **Surgery may improve ICU-related outcomes**
- Caution rebound
- Effects rapid
  - **Retrospective studies may not have control on INR times**

Mendelow AD et al. *Lancet*. 2005; 365:387-97; Dowlatshahi D et al. *Stroke*. 2012; 43:1812-7; Demeyere R et al. *Vox Sang.* 2010; 99:251-60; Chong CT et al. *Anaesth Intensive Care*. 2010; 38:474-80; Dager WE. *Ann Pharmacother*. 2011; 45:1016-20.

Hemostatic Agents and Thrombosis: After all... the patient was being anticoagulated!

Hsia et al: Retrospective, single center analysis of off-label use (n=69)
- Mean dose = 8.2 mg rFVIIa
  - 36 thrombotic events, mean 8.8 days post rFVIIa
  - MD questioner: Not aware of any thrombotic events in these patients

Thromboembolism: PCC4 (~1.8%) vs. PCC3 (0.7%)

rFVIIa or PCC → Tissue Factor Expression → Thrombosis

TF also expressed on monocytes

Hsia CC et al. *Transfus Med*. 2009;19:43-9.
Dentali F et al. *Thromb Haemost*. 2011; 106:429-38.

PCC Considerations

- INR > 4.5 may not have sufficient rFVIIa (needs confirmation)
- UFH in PCC may increase risk for HIT
- Not recommended if AT deficiency
- Balanced PCC may be advantage in VKA reversal to decrease complications (needs confirmation)
  - **↓ Regulatory anticoagulant proteins C and S → ↑ thrombogenicity**
- PCCs reduce the INR within 10 minutes
- PCC 4 in the USA soon?

Rodgers GM. *Am J Hematol.* 2012; 87:898-902.

Warfarin Situations

- 75 yo with AF, CKD V, heart failure, and CVA on warfarin 1 mg/day and has a GI bleed. INR = 12
- 56 yo with mechanical MVR brought into ED after crashing his motorcycle. Had notable abdominal injuries with hemorrhage apparent. INR = 3.0
- 27 yo with PE 1 year ago being assessed for colonoscopy. Warfarin 15 mg/day. INR = 2.5

Dabigatran Reversal Case

AC Jr. is a 85 yo man with acute decompensated heart failure and receiving dabigatran 150 mg PO BID for AF. He has fallen and hit his head and is being admitted to the ED.

Q6: Which of the following tests would you NOT request?

a. PT/INR
b. Antifactor Xa activity
c. Thrombin time
d. Serum creatinine

Dabigatran Reversal Case

AC Jr. is a 85 yo man with acute decompensated heart failure and receiving dabigatran 150 mg PO BID for AF. He has fallen and hit his head and is being admitted to the ED.

- Baseline INR in ED = 2.0
- Thrombin time = > 200 seconds
- Scr = 2.0 mg/dL

MD orders Vit K 10 mg IV and FFP

Q7: Will you process this order?

a. Yes
b. No
c. I'm not sure

Is There a Way to Reverse these Agents?

ETP = endogenous thrombin potential	Dabigatran T ½ 14-17 hr	Rivaroxaban T ½ 5-9hr; Elderly 11-13 hr
Hemodialysis	Yes ~2/3 in 2 hr	Not expected (> 90% bound) (Apixaban: 87% bound)
Antidote	In development	
Hemostatic Agents		
PCC4 (50 units/kg)	- Did not restore aPTT, ECT, TT - rFVIIa alt. ETP lag time - PCC corrected ETP responsive > rFVIIa	PT reversed, normalized ETP (114% Normal) PCC corrected ETP
Activated PCC (aPCC) (25-50 units/kg)	Altered ETP lag time Effective – single case	Corrected all parameters
rFVIIa (high dose)	CABG: Limited effect high dose single case	Corrected lag time

van Ryn J et al. *Thromb Haemost*. 2010; 103:1116-27; Eerenberg ES et al. *Circulation*. 2011; 124:1573-9; Dager WE et al. *Crit Care Med*. 2011; 39:243 (Abstract 867); Warkentin TE et al. *Blood*. 2012; 119:2172-4; Marlu R et al. *Thromb Haemost*. 2012; 108:217-24.

Assessing Intensity of Anticoagulation Effects

	Dabigatran	Rivaroxaban/Apixaban
Drug present	**Thrombin time**	**? Chromogenic anti-factor Xa High sensitive INR**
Quantitative test	**? Dilute thrombin time or Chromogenic ECT**	**Chromogenic anti-factor Xa**
Sensitivity: PT vs. aPTT	**aPTT > PT (Point-of-care INR > central lab)**	**PT > aPTT**
No or limited effect		**ECT, TT**

- INR/aPTT - Potential for normal values at trough/active levels

What does a value mean?

- Is there a safe level to operate?
- Is it too high where the dose should be lowered?

Lindhoff-Last E et al. *Ther Drug Monit*. 2010; 32:673-9.
Lindahl TL et al. *Thromb Haemost*. 2011; 105:371-8.
van Ryn J et al. *Am J Med*. 2012; 125:417-20.
van Ryn J et al. *Thromb Haemost.* 2010; 103:1116-27.

Dialysis of Dabigatran

Stangier et al: *Clin Pharmacokinet* 2010; 49:259-68

- Design: Dabigatran 50 mg x 1 + 2 HD sessions; CKD V
  - Not 150 mg multiple doses or AKI
- Result: Hemodialysis ~2/3rds removed
  - 2 hr Cp Arterial 12.5 ng/mL > Cp Venous 4.4 ng/mL

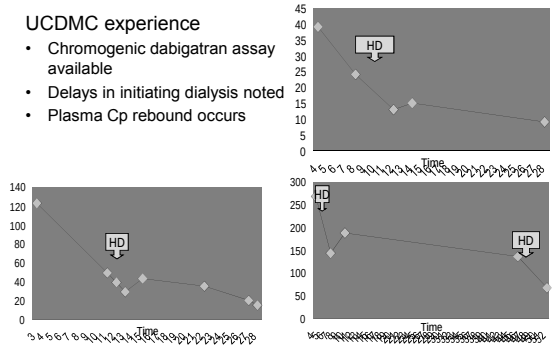
Wanek et al: Case report. 2.5 hr HD (BFR 500 mL/hr): ↓ TT 90 – 60 sec

Stangier J et al. *Clin Pharmacokinet.* 2010; 49:259-68.
Wanek MR et al. *Ann Pharmacother*. 2012 ;46:e21.

Hemodialysis of Patients on Dabigatran

UCDMC experience

- Chromogenic dabigatran assay available
- Delays in initiating dialysis noted
- Plasma Cp rebound occurs



Reversing Dabigatran: A Case Experience

Setting: AF and undergoing ablation, on dabigatran

Situation: Transeptal perforation, pericardial window, and > 3L blood loss

Action: FFP, protamine, PRBCs with limited to no effect on bleeding

- aPCC: 25 units/kg over 15 minutes
- Bleeding slows in first few minutes and has stopped before infusion completed

- Limited impact on TT, ECT, INR, or aPTT
- Low dose effective
- Single case report – Use caution

Dager WE et al. *Crit Care Med*. 2011; 39:243 (Abstract 867).

Dabigatran Reversal Case

AC Jr. is a 85 yo man with acute decompensated heart failure and receiving dabigatran 150mg PO BID for AF. He has fallen and hit his head and is being admitted to the ED.

- Baseline INR in ED = 2.0
- Thrombin time = > 200 seconds
- Scr = 2.0 mg/dL

- CT scan to assess damage
- Arrange management options (dialysis, hemostatic agent, calcium if blood given)
- Check time of last dose
- Assess bleeding
- Consider anticoagulation options
- Patient and physician education

Systems Support

- 24-hour process
- Correct labs available
- Guidelines on how to use the available agents
  - Easy for clinicians to locate
- Rapid ability to implement management options