Anticoagulation in Transition: Key Concepts to Master

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Objectives

- When managing anticoagulation, successfully manage the following conversions:
  - Transitioning heparin to warfarin therapy
  - Transitioning warfarin to heparin therapies
  - Transitioning from LMWH/fondaparinux to heparin
  - Transitioning from heparin to LMWH/fondaparinux

Case 1

- RW is a 72 year-old male who is admitted to the hospital to have a total knee replacement conducted. Two days after the procedure, he begins having swelling in his right lower extremity which is also warm. Upon ultrasound evaluation, it is found that he has a deep vein thrombosis in his popliteal vein. He weighs 100 kg and is 6' 2" tall. His only chronic medical problem is hypertension for which he took hydrochlorothiazide 25 mg po daily. That patient has an estimated creatinine clearance greater than 50 ml/min.

Case 1

- RW is started on a enoxaparin 100 mg subcutaneously twice daily
- RW is also started on warfarin 5 mg today.
- Which of the following is/are TRUE?
  - A. Enoxaparin should only be used in the hospital when a patient has a DVT
  - B. Enoxaparin can be discontinued when the INR is in range and stable provided 5 days have passed
  - C. The patient could have been started a 7.5 mg dose of warfarin
  - D. This patient should have been "loaded" with 20 mg of warfarin to minimize the duration of enoxaparin therapy

What does CHEST say on transitioning?

- "In patients with acute DVT, we recommend initial treatment with LMWH, UFH, or fondaparinux for at least 5 days and until the INR is > 2.0 for 24 h (Grade 1C)."
- "In patients with acute DVT, we recommend initiation of VKA together with LMWH, UFH, or fondaparinux on the first treatment day rather than delayed initiation of VKA."

Kearon C., et. al. *CHEST* 2008; 133:454S–545S.

What does CHEST say on transitioning?

- "In patients with acute DVT, we recommend initial treatment with LMWH SC once or twice daily, as an outpatient if possible (Grade 1C), or as an inpatient if necessary (Grade 1A), rather than treatment with IV UFH."
- "In patients with acute DVT and severe renal failure, we suggest UFH over LMWH (Grade 2C)."

Kearon C., et. al. *CHEST* 2008; 133:454S–545S.

What does CHEST say on transitioning?

- "In patients beginning vitamin K antagonist (VKA) therapy, we recommend the initiation of oral anticoagulation with doses between 5 mg and 10 mg for the first 1 or 2 days for most individuals, with subsequent dosing based on the international normalized ratio (INR) response (Grade 1B)."
- "In elderly patients or patients who are debilitated, are malnourished, have congestive heart failure (CHF), have liver disease, have had recent major surgery, or are taking medications known to increase sensitivity to warfarin (*eg, amiodarone),* we recommend the use of a starting dose of< 5mg (Grade 1C) with subsequent dosing based on the INR response."

Ansell J, et. al. *CHEST* 2008; 133:160S–198S

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Case 2

- MA is a 82 year-old female who takes warfarin chronically for atrial fibrillation. Her past medical history includes hypertension, TIA, and diabetes mellutus-2. She is taking numerous medications, most notably amiodarone. She is scheduled to undergo an elective left knee arthroplasty. Her current INR, today, is 2.5 and the procedure is scheduled in 1 week. Her current dose of warfarin is 2.5 mg po daily.

When should this patient discontinue her warfarin?

A. 10 days prior to the procedure
B. 7 days prior to the procedure
C. 5 days prior to the procedure
D. 3 days prior to the procedure

Does this patient require a parenteral anticoagulant before surgery?

A. Yes
B. No

Key questions to ask yourself

- Does anticoagulation really need to be interrupted for the procedure?
  - Major surgical procedures, answer is almost always yes
  - Minor procedures like dental extractions, skin procedures, eye procedures require no warfarin hold
- If warfarin will be interrupted, does the patient need parenteral bridge therapy?
  - Largely determined by thromboembolic risk

Douketis JDJ, et. al. *CHEST* 2008; 133:299S–339S

So the need warfarin interrupted and a parenteral heparin will be used……

- Consider standardizing how this situation will be handled by implementing bridging guidelines
  - Covers both the thromboembolism vs. bleeding issues and timing
- My focus will be on the timing as this is a "how to" session

Holy Cross Hospital Outpatient Bridging Procedure

- Greater than 10 days before surgery
  - Determine date of procedure
  - Assess risk of thrombosis vs. bleeding
  - Communicate with MD, Surgeon/Proceduralist and patient to determine appropriate bridging plan
  - Screen for recent heparin exposure and risk of heparin induced thrombocytopenia (HIT)
  - Assess patient's access to LMWH
  - Patient specific bridging education risk vs. benefit
  - Dispense written plan to patient
  - Fax agreed upon plan to all medical parties.

Adapted from Holy Cross Hospital , John Hutchinson.

Holy Cross Hospital Outpatient Bridging Procedure

- 7 days prior to procedure
  - Obtain INR, aPTT, baseline hematology and serum creatinine
  - Assess if antiplatelets can be discontinued
- 5-6 days prior to the procedure
  - Stop warfarin
- 3 days prior to the procedure
  - Start LMWH *(could also admit for heparin if needed, bolus likely not needed)*

Adapted from Holy Cross Hospital , John Hutchinson.

Holy Cross Hospital Outpatient Bridging Procedure

- 1 day prior to procedure
  - Obtain INR. Last dose LMWH (24 hours prior to procedure). Consider PO vitamin K 1-2mg if INR > 1.5 and bleeding risk high.
  - If patienthad been admitted, discontinue heparin 4-6 hours prior to the procedure
- Morning of procedure
  - Recheck INR if it was still elevated

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B. No

Case 3

- KP is an 81 yowm admitted for anemia and weakness. Patient is 6' 2" inches tall and 63 kgs. KP has stage IV chronic lymphocytic leukemia, severe neutropenia due to chemo, chemotherapy-induced anemia, T12 compression fracture, new sternal fracture, history of DVT/PE 4 months ago, and is failing. He is currently using 12,500 units of dalteparin sc daily for treatment of his thrombosis. His current hemoglobin is 9.2 and his platelets are 32,000. The patient has been struggling with nose bleeds, and other minor bleeding issues. Estimated creatinine clearance is 50 ml/min.

Case 3

- Due to the possibility of his platelets heading lower and the minor bleeding, the physician and pharmacist managing the case decide it may be safest to convert the patient to an unfractionated heparin infusion until he stabilizes.

What is the best strategy to use?

A. Discontinue the dalteparin, and 10 hours later bolus heparin at 60 units/kg and start an infusion at 15 units/kg/hr
B. Discontinue the dalteparin, and 10 hours later start a heparin infusion at 15 units/kg/hr (no bolus)
C. Discontinue the dalteparin, and 22 hours later bolus heparin at 60 units/kg and start an infusion at 15 units/kg/hr
D. Discontinue the dalteparin, and 22 hours later start a heparin infusion at 15 units/kg/hr (no bolus)

LMWH breakdown

	Enoxaparin	Dalteparin	Tinzaparin	Fondaparinux
Molecular Weight - average (Daltons)	4500	6000	5500-7500	1728
Bio-availability	92%	87%	86.7%	100%
Plasma half-life (hours)	4.5 hrs	2.8 hrs	3.4-3.9 hrs	14-18hrs
Tmax	3-5 hrs	4 hrs	4-5 hrs	2 hrs

Issues to ponder

- When would the next dose of the LMWH be given?
- How do I minimize the risk of over anticoagulation, but also minimize the risk of an large anticoagulation gap?
- Am I more worried about bleeding or thrombosis?
- What idea is most “error” proof

Conversion from SC LMWH/fondaparinux to IV UFH Infusion

- Calculate the appropriate IV UFH dose based on indication for use
- Discontinue SC LMWH or SC fondaparinux and initiate IV UFH 1-2 hours (no bolus) before the next SC LMWH or fondaparinux dose would have been administered:
  - Check patient's renal status and if impaired, the IV UFH dosing initiation intervals suggested above may need to be extended accordingly
- Check aPTT at 6 hours after initiating the IV UFH infusion and adjust appropriately

Adapted from Nutescu, EA, Dager, WE. Heparin, low molecular weight heparin, and fondaparinux. In Gulseth MP ed. Managing Anticoagulation Patients in the Hospital. Bethesda: ASHP; 2007: 177-202.

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Case continued

- 5 days later, the same patient has stabilized, platelet count has rebounded to 75,000, and no more problems are being encountered with bleeding issues. The physician wishes to convert back to dalteparin at the same dose to prepare for discharge.

How should this be handled?

A. Give the dose of dalteparin and discontinue the heparin in 24 hours
B. Give the dose of dalteparin and discontinue the heparin in 12 hours
C. Discontinue the heparin and start the dalteparin in 2 hours
D. Discontinue the heparin and start the dalteparin at the same time

Conversion from IV UFH to SC LMWH/fondaparinux

- Calculate the appropriate LMWH (or fondaparinux) dose based on the specific indication for use and patient weight
- Discontinue IV UFH and initiate the 1st SC LMWH (or fondaparinux) dose within 1 hour

Adapted from Nutescu, EA, Dager, WE. Heparin, low molecular weight heparin, and fondaparinux. In Gulseth MP ed. Managing Anticoagulation Patients in the Hospital. Bethesda: ASHP; 2007: 177-202.

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Conclusion

- Transitions of anticoagulants is an extremely common role for the anticoagulation pharmacist
- Some data does exist that may suggest inappropriate transitions may lead to sub-optimal patient outcomes
- These issues will only get more complex with future anticoagulant development

Vitamin K and Vitamin K Antagonists – Antagonizing the Antagonist

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Warfarin and Vitamin K Use – Case 1

GN: 74 yo white male is on warfarn for atrial fibrillation.

He is using a POC device and reports an INR of 5.8 one week after a stable INR of 3 was reported; and that he was discharged from the hospital 3 days ago on levofloxacin following a 3-day stay for pneumonia

Should he receive vitamin K?

If so, how much and by what route?

Warfarin and Vitamin K Use – Case 2

JG: 73 yo white male, retired law school professor referred from San Antonio (SAT) cardiologist to Houston CT surgeon for dual mechanical heart valve implantation (AVR, MVR both St. Jude)

3 days after returning to San Antonio (8 days after the surgery), and while taking warfarin 5 mg daily, JG presented to the ER at midnight with a subconjunctival bleed – eye totally red, bulging, and leaking fluid. No change in vision, no significant pain, INR = 8

Should he receive vitamin K?

If so, how much and what route?

To Give or Not to Give Vitamin K ?

No	Yes
• Rapid INR Decline	• Only in Some
• Unnecessary	• Serious Bleeding Risk
• Expensive	• P.O. Inexpensive
• Over-Correction	• Not with Low Dose
• Refractory to Warfarin	• Not with Low Dose
• Anaphylaxis	• Not with P.O., ? Slow I.V.

What do we know about Vitamin K reversal of INRs?

- Simply withholding VKA does carry a risk
- Subcut. vitamin K not recommended
- Dose and route of admin depends on:
  - Bleeding or bleeding risk
  - Degree of elevation in the INR
  - Desired time-frame for reversal
  - Risk of over-correcting INR
- Data with 1 mg dose from I.V. form given PO

High INR vs Discontinue Warfarin

- Outcomes (n = 114, INR > 6)
  - Confirmed INR !!!
  - 45 % INR > 4 at 48 Hr.
  - 27 % INR > 4 at 72 Hr.
  - 10 (8.8%) Sig. Bleed – 3 Hospitalized
  - 5 (4.4%) Maj. Bleed – 2 Fatal
  - Risk Persisted at 2 Weeks

Hylek, et al. Arch Intern Med. 2000; 160:1612-1617

Vit K 2 mg I.V. Given PO vs Discontinue Warfarin, INR > 10

	Disc. Warf.	Vit K 2 mg I.V. by PO*
Sig. Bleed	3 of 24	0 of 51
INR > 5 day 3	7 of 15	5 of 45

*None were refractory to warfarin afterwards

Gunther KE, et al. Thromb Res 2004; 113: 205 - 209

Vit K 1 mg I.V. Given PO vs Discontinue Warfarin, INR 4.5 - 10

	Disc. Warf. N = 46	Vit K 1 mg I.V. by PO*, N = 46
Mean (range) INR day 0	5.9 (4.5 – 9.8)	5.4 (4.5 – 9.8)
INR 1.8 – 3.2 day 1	9 of 44*	25 o 45*
INR increased day 1	4 of 44**	0 of 45**
INR < 1.8 day 1#	0 of 44*	7 of 45*
3 - month bleeds	11 events/8 pats.***	2 events/2 pats.***
1-mo. thromboembolic event	1	2

*p , 0.01, **p = 0.056, ***p = 0.0499
rate of fall proportionate to initial elevation in both groups

Crowther MA, et al. Lancet 2000; 356:1551-1553

Vit K 1 mg I.V. Given PO vs Discontinue Warfarin, INR 6.0 – 12.0

	Disc. Warf. N = 29	Vit K 1 mg I.V. by PO* N = 30
Mean INR day 0	7.72	7.22
Mean INR day 1	5.23	2.99
INR 2.3 – 3.7 day 1	4*	13*
INR < 1.8 day	0	3
INR > 5 at 24 hr	13*	1*
Maj Bld + TE	0	0

$p < 0.001$

Ageno W, et al. JACC 2005; 46(4):732 - 733

Vitamin K vs High INRs

N	Initial INR	Dose (mg)	< 24 hr (n)	24 – 48 hr (n)
Low dose I.V. (0.1 – 0.5 mg) – 1 over corrected at 24 – 48 hr.*				
8*	11.9	0.4	2.3 - 5.1 (6)	1.6, 6.5 (2)
High dose I.V. (1 – 10 mg) – 4 over corrected				
9	13.9	4.2	1.6 – 4.6 (6)	1.2 – 2.1 (5)
Subcutaneous (1 – 10 mg) – None over corrected*				
10*	14.9	2.5	2.8 – 6.7 (8)	2.0 – 6.3 (3)
PO 2.5 mg or 5 mg – None over corrected**				
6	9.4	3.8	2.0, 2.7 (2)	2.5 – 5.3 (4)

*SC gp contained 3 of 4 who did not achieve INR < 6, the other received 0.5 mg I.V. for INR of 16.3

**1 INR > 10 failed to correct with 2.5 mg

Whitling AM, et al. Arch Intern Med 1998; 158:2136-2140.

PO Vitamin K vs High INRs

- 2.5 mg PO, n = 81 (Weibert, et al.)
  - 73 (90%) had INR < 5 at 24 hr to 48 hr.
  - 14 (17%) had INR 1.5 to 2.0 at 24 hr to 48 hr
  - 5 of 8 with INR > 5 at 24 hr to 48 hr had INR > 10
  - Rec.: Larger dose if INR > 10
- Conclusions based on Whitling and Weibert
  - ≤ 0.5 mg I.V. effective and less likely to over correct than lg. dose
  - > 1 mg I.V. effective but over correction common
  - Sub cut. Route inadequate in some (no longer recommended)
  - PO 2.5 mg if INR < 10, 5 mg for INR > 10

Whitling AM, et al. Arch Intern Med 1998; 158:2136-2140.
Weibert RT, et al. Ann Intern Med 1997; 125:959-962.

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Should he receive vitamin K?

- INR < 6 and no evidence of bleeding, could just hold dose
- INR near 6 and likely rising rapidly, higher after held dose?

If so, how much and by what route?

- Held one dose, gave 500 mcg, INR = 2.5 at 24 hrs
- Resume previous warfarin dose

Warfarin and Vitamin K Use – Case 2

JG: 73 yo white male, retired law school professor with dual mechanical heart valves and severe subconjunctival hemorrhage, and INR of 8.

If you decide to give him vitamin K, how would you give it?

A. Orally
B. Subcutaneously
C. Intramuscularly
D. Intravenous

What dose would you use?

A. $\leq$ 0.5 mg
B. 1 mg
C. 2.5 mg.
D. $\geq$ 5 mg.

Warfarin and Vitamin K Use – Case 2

JG: 73 yo white male, retired law school professor with dual mechanical heart valves and severe subconjunctival hemorrhage, and INR of 8. Given 0.5 mg of vitamin K I.V. in ER at midnight seen the next morning at 9 am in clinic with an INR of 3.

Would you choose to:

A. Have him continue his prev. regimen of warfarin 5 mg daily
B. Resume warfarin at 5 mg daily x 2.5 mg M, W, F
C. Resume warfarin at 2.5 mg daily
D. Hold warfarin and recheck INR in 2 days

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[Ultimately required < 2.5 mg daily]

Warfarin and Vitamin K Use – Case 2

JG: 73 yo white male, retired law school professor with dual mechanical heart valves and severe subconjunctival hemorrhage in ER 8 weeks ago. Since then, INRs have fluctuated widely. Patient education, use of weekly "pill" box, and recording date and time of every warfarin dose have failed to stabilize the INR. No changes in diet, meds, supplements, EtOH, smoking, etc. Patient is frustrated.

Warfarin 2 mg daily = INR below target range
Warfarin 2 mg daily with 3 mg on Fri. = INR above target range.

You recommend:

A. Change warfarin to ASA+ clopidogrel
B. Warfarin 2 mg daily with 3 mg every other Friday
C. Add aspirin to warfarin 2 mg daily (accept low INR + asa)
D. Start daily vitamin K

Warfarin and Vitamin K Use - Case

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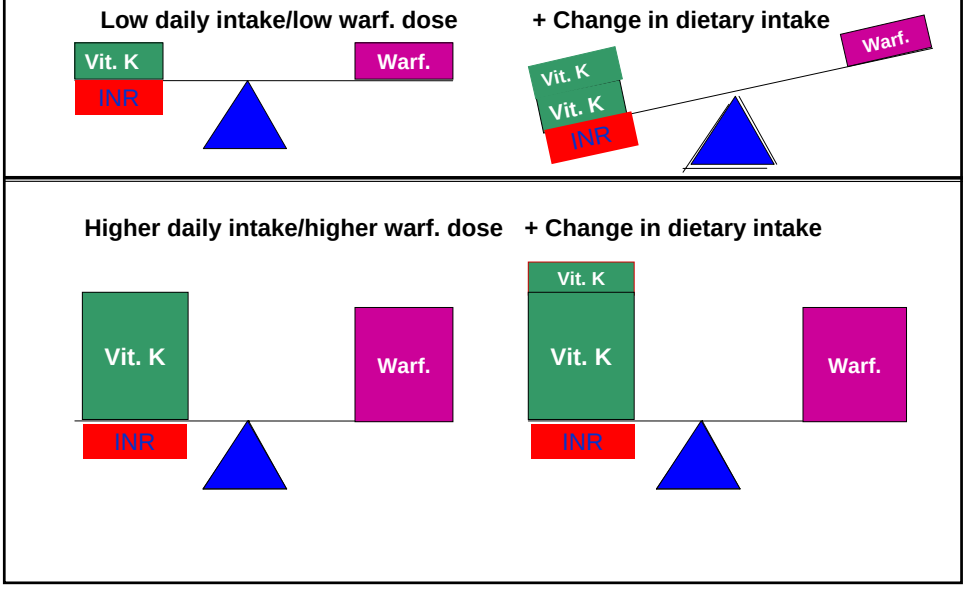
Warfarin 2 mg daily = INR below target range
Warfarin 2 mg daily with 3 mg on Fri. = INR above target range.

You recommend:

A. Change warfarin to ASA+ clopidogrel = less protection, more bleeding
B. Warfarin 2 mg daily with 3 mg every other Friday = comples regimen
C. Add aspirin to warfarin 2 mg daily (accept low INR + asa) = more bleeding
D. Start daily vitamin K – Chosen option

Daily Vitamin K vs. INR Stability



Warfarin and Daily Vitamin K

	% INRs in range		% INRs in range ± 0.2	
Patient	Before	After	Before	After
1	54	60	69	77
2	0	41	33	55
3	7	53	36	76
4	9	18	17	47
5	8	38	33	46
6*	37	36	37	36
7	0	100	0	100
8	27	30	45	38
Group	**18**	**42**	**32**	**57**
	Absolute inc. 23%		**Absolute inc. 25%**	
	Rel. inc. 128%		**Rel inc. 76%**	

*Lupus anticoag. and hyperfunctioning thyroid nodule

Reese AM, et al. Pharmacotherapy 2005; 25:1746-1751
http://www.clotcare.com/clotcare/vitaminkstabilizesinr.aspx

Warfarin and Daily Vitamin K

	Standard Deviations in INRs+	
Patient	Before	After
1	1.78	1.03
2	1.26	0.79
3	0.94	0.40
4	2.17	1.31
5*	0.78	0.84
6**	1.45	1.09
7	1.45	0.26
8	0.87	1.05

+ p = 0.039 for all patients, 0.031 patient 2, 0.047 patient 4.
*"After" includes low INRs with warfarin interruption for procedures twice
**Lupus anticoag. and hyperfunctioning thyroid nodule

Reese, et al. Pharmacotherapy 2005 in press

Vit. K vs. Placebo in Unstable** Patients

	Before	Vit. K 150 mcg. n = 35	Before	Placebo n = 33
SD of INR	0.72	0.47*	0.7	0.59*
% Time in range	59	87*	63	78*
Improved/Stable		33/19		24/7
Inc. in dose		16%		1.5 %
Vit. K conc pg/ml		1502*		619*
# dose chg./6 mo.	5	2*	5	3*

****Unstable: INR SD > 0.5 and ≥ 3 dosage changes in prev. 6 months**

Ref: Sconce E et al. Blood 2007; 109:2419 -2423

Phenprocoumon + Vit. K or Placebo (x 6 mo)

		Vit. K 100 mcg. n = 94		Placebo n = 95
	Before		Before	
% Time in range	79	89.5	80	85
% Time below range		2.1		3.1
% Time above range		8.5		11.4
% in range 100%		43		24
% dosage change		7		0.8

Rombouts EK et al. J Thromb Haemostasis online July, 2007
DOI:10.1111/j.1538-7836.2007.02715.x

Vitamin K and Warfarin – Key Considerations

- Reversing INR
  - –Subcutaneous: slow, ineffective in some, not recommended
  - – I.V. 0.1 to 0.5 mg rapidly effective, unlikely to over-correct
  - – I.V. 1 to 10 mg rapidly effective, over-correction common
  - – PO 2.5 mg if INR < 10 consider 5 mg for INR > 10
  - – Chest Rec. 1 mg PO but studies used I.V. formulation
- Stabilizing INR with daily low dose
  - – 100 mcg to 200 mcg daily improves INR stability and TTR

Managing Complications of Anticoagulation Therapy

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What is the goal for reversal

- Reversing bleeding
  - Symptomatic
  - Asymptomatic, but high risk/concern
- Reversing critical value
  - Verify value true (Hemidilution ?)
- Plan for a procedure
  - Target value (Full or partial reversal)

2

Bleeding on Anticoagulants: Risks

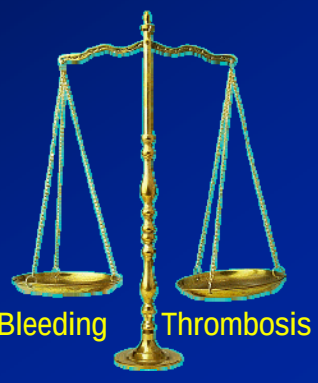
- Major vs Minor
- Pt Clinical Presentation
  - Trauma/Clinical disorder
  - Location:CNS, Pericardium
    - Open/Closed Cavity
  - Drains at site
  - Risk factor present
- Quality: Anticoagulation Management
- Intensity of Anticoagulation
  - Combination Therapy
  - Dose response
  - Drug/Disease Interactions

Bleeding risk

Invasive Procedure
Rebleeding
Anemia
Thrombocytopenia
Chronic renal insufficiency
Other antithrombotic therapy
Uncontrolled hypertension
Malignancy
Alcohol abuse
Increased age
Neuropsychiatric
Stroke

Anticoagulant Reversal Strategy

- Hold Anticoagulation ??
- Site: Mechanical Intervention
- Transfuse
- Pharmacological Reversal
  - Ideal Reversal Agent:
    - Short Acting Agent
    - Dose Relationship
    - Pharmacodynamic Measure of Reversal
  - May require combination reversal therapy
- Goal/Need for re-initiating therapy
  - Risk of thrombotic event
- Monitor for Thrombosis



4

UFH Bleeding

Bleeding Rate: IV infusion	
Major	Fatal
0-7%	0-2%

- Hold Heparin
  - Rapid Elimination
- Protamine
  - Dose: over 3 min
    - 1mg/100u heparin
  - Hypotension, Bradycardia
  - Anaphylaxis Risk Group:
    - Vasectomy; Fish Sensitivity; Hx protamine insulin
- Transfuse

5

Reversing Heparin post Cardiothoracic Surgery

- Protamine
- ACT (High Heparin Dose card)
  - Is back to baseline fully reversed?
- Is rFVIIa the answer?

6

LMWH

Enoxaparin
Dalteparin
Tinzaparin

- Prolonged Duration of effect
  - (T ½ 5x > UFH) q12 or q 24hr
- Protamine
  - Dose:
    - 1mg/100 LMWH anti-Xa units
    - Repeat 0.5mg/kg if bleeding persists
    - Lower if > 8 hr post dose
- rFVIIa:Limited case reports

Bleeding Rate: LMWH	
Major	Fatal
0-3%	0-1%

7

Crowther MA et al. BJH 2002;116:178-86; NG et al. Ann Hematol 2003

Protamine Neutralization of LMWH

- Factor II reversed
- Partial (~60%) anti-Xa reversal
  - ↓ Sulfate Charge = ↓ Reversal
- May not correct bleeding

Agent	% Anti-Xa activity Neutralized	Total Sulfate (% SO_4^{-2})
Tinzaparin	86 %	39%
Dalteparin	74 %	37%
Enoxaparin	54 %	32%

8

Crowther MA Br J Haematology 2002;116:178-86

Fondaparinux

Major Bleeding
DVT/PE ~1.2%
-Fatal, Critical Site, ICH: 0.1%
-Clinically overt: 1%
Medically Ill: 0.2%
Ortho: 2.7% "Post OP time dependent"

T ½ 15-20 hr: QD Dosing

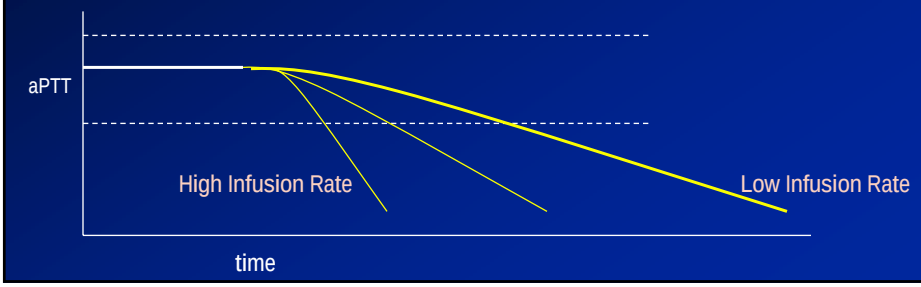
- No Monitoring
- Reversal: rVIIa ?
  - May reverse effects for 2-6 hours (90mcg/kg studied)

Bijsterveld NR, Circulation 2002;106:2550-2554;Lisman T et al J Thromb Haemost 2003;1:2368-73

DTI: Argatroban, Lepirudin, Bivalirudin

- Dose adjusted for Renal, Hepatic, Cardiac function
  - Steady-state longer than healthy subjects studied
  - aPTT: DTI range (1.5-2.5/3x control) ≠ UFH range
- False + INR elevation
- Reversal Agent: None (Bivalirudin hemofiltrated)

Major Bleeding
ACS Dose vs HIT Dosing
2-11%



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WARFARIN

INR Assay

- 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?)

Reversal

- Speed: (ICH vs Elective Procedure)
- Hold Dosing
  - Higher maintenance dose → Faster ↓
- Vitamin K, FFP/PCC or rFVIIa

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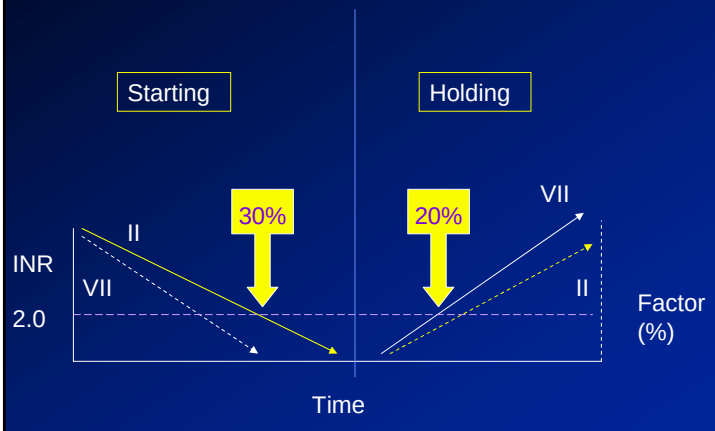
Warfarin: INR and Factor II



Clotting Factor

II	42-72 hr
VII	4-6 hr
IX	21-30 hr
X	27-48
Protein C	9 hr
Protein S	60 hr

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Warfarin Decline: Hyleck et al

INR > 6 → Risk Factors for INR ≥ 4 after holding 2 days

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

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

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VIT K: IV vs PO

- IV: Effect in 4-12 hr
  - Dose: 0.25-10mg (0.25-1mg will decrease INR > 6 to <3.0)
  - Related to:
    - Initial INR
    - Daily Warfarin Dose
    - Target INR to reverse to
  - 10-40mg IV: 11days to 3.5 week effect
  - Anaphylaxis: Incidence: ~1:3500
    - Infuse over > 15 minutes
- PO = IV at 24-48 hr
  - (INR and Clotting Factors levels)
    - PO (5mg unscored tablets) or IV given PO
    - Dose 1-5mg

Whitling AM Arch Intern Med 1998; Shetty HGM Thromb Heamost 1992; Watson BJH 2001; Fugate S Pharmacother 2004; Riegert-Johnson DL Ann Allergy 2002

VIT K: PO vs SC

Mean INR	1mg PO* n=26	1mg SC n=25
Initial INR (4.5-10)	5.6	6.2
Day 1	2.9	4.2
Day 2	2.2	3.1
Day 3	2.7	2.8

SQ: unpredictable, and lower reversal vs PO

Crowther MA Ann Intern Med 2002;137:251-254

Fresh Frozen Plasma (FFP)

- 15 ml/kg
- Batch Variable Clotting Factors
- CHF: Volume overload potential
- Delay to thaw
- Slow Administration
- Partial Reversal of INR in hours
- Rebound
- INR = 1.0

Nitu IC Clin Lab Haematol 1998; Markis M Thromb Haemost 1997; Cartmil M Br J Neurosurg 2000; Hanley JP J Clin Path 2004

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Prothrombin Complex Concentrates (PCC)

- 30-50 units/kg
- Reversal in Minutes (> FFP)
- Rapid Administration
- Rebound
- Expensive
- Variable products
  - 3-4 Factors:II,IX,X (+/- VII)
  - Factor IX not part of INR
- Factor IX complex
  - **AlphaNine SD, Bebulin VH, BeneFix, Konyne 80, Mononine, Profilnine SD, Proplex T)**

Nitu IC Clin Lab Haematol 1998; Markis M Thromb Haemost 1997; Cartmil M Br J Neurosurg 2000; Hanley JP J Clin Path 2004

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rFVIIa anticoagulation reversal

- Warfarin: Small Dose 10-40 or 1.2mg has been reported

UCDMC: (n=24) Warf/Bleeding - rFVIIa 1.2mg (16 mcg/kg) INR 3.05 → 1.1

  - INR reversal in 15 minutes
  - ↑ VII > X >> II
  - Bleeding decreased
  - INR can rebound
- Biopsy: Heart Failure/Fluid Restriction
- Platelet Count

Dager W et al Pharmacotherapy 2006:26:1091-8; Deveras RA:et al: Ann Intern Med 2002;137:884-888; Dutton RP et al. J Trauma 2004;57:709-19; Sorensen B et al. Blood Coagul fibrinolysis 2003;14:469-77; Lin J et al. J Neurosurg 2003;98:737-40; Roitberg B et al Neurosurgery 2005;57:832-6;

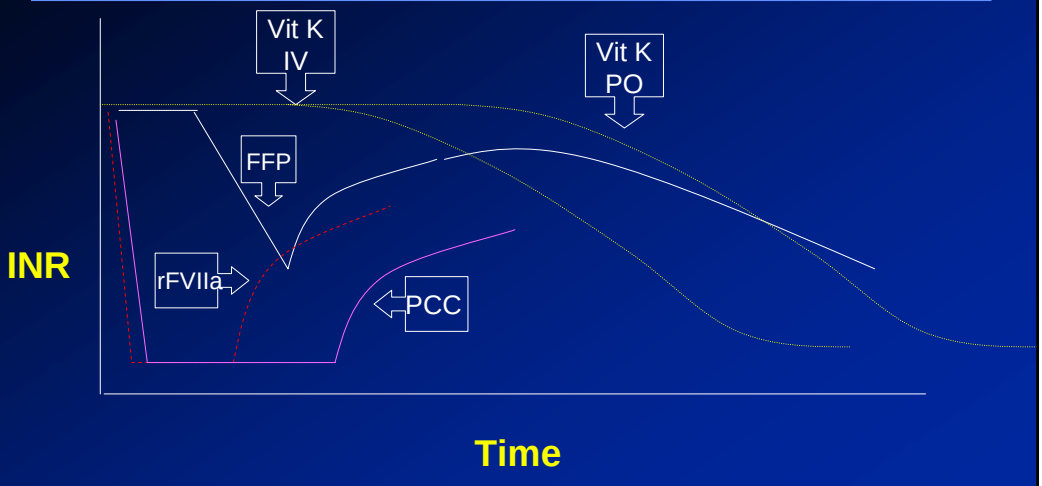
18

rFVIIa-Recombinant Activated Factor Seven

- N= 18 rFVIIa - 20-106 µg/kg
  - 1 dose in 17 pts
  - LMWH = 6
  - UFH = 8
  - VKA = 4
- Traditional attempts to control bleeding failed
- Bleeding Outcomes:
  - Cessation in 10
  - Decrease in 5
  - Slowed in 3
  - 12/16 stopped within 2 hr
- Requirement for blood products and fluids was markedly reduced

Ingerslev J. *J Postgrad Med* 2007; 53: 17-22.

Rebound



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Case: 1

- 62 y/o on warfarin for idiopathic PE and post phlebitic swelling
- INR = 6.5
- No bleeding or bruising
- INR had previously been reasonably stable.
- What is the most cost effective approach

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Case 2

- 68 yo female with mechanical AVR and MVR
- Has arrhythmias and INR of 4.5.
- Pacemaker being considered

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Case 3

- 86 yo male with CKD 4, HTN and history of ETOH abuse
- On warfarin for AF
- Has fallen several times recently, and now is admitted with Large GI bleed, INR 4.2
  - rFVIIa only requested

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Defining immune-mediated "HIT"

- **Acute HIT: new onset**
  - **Initial phase with low platelets**
  - **Post platelet recovery period**
- **Isolated HIT (HIT without thrombosis)**
- **HITTS (+ HIT-related thrombosis)**
- **History of HIT**

Timing:
Rapid – Immediate (hours)
Typical – 5-10 days
Delayed – up to 40 days after stopping

24

What should I know about HIT?

- Onset - Immune mediated: Acute, Typical, Delayed
- Have a plan to recognize
- Have a plan to manage
  - Avoid just stopping the Heparin/LMWH
  - DTI: Available and how to use
  - Don't stop if INR increases

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HIT Probability Testing

Warkentin 4 T's (Pretest)

0-2 point each

- Thrombocytopenia
- Timing of ↓ Plt count
- Thrombosis
- Other Causes

High: 6-8

Intermediate: 4-5

Low: 0-3

Chong (Post-test)

- Onset of Thrombocytopenia
  - 4-14 days: 3 pt
  - < 4; > 14: 1 pt
- Exclude other causes: 2pt
- Resolves w/ D/C Heparin: 2 pt
- Recurs with heparin: 1 pt
- Associated Thrombosis: 1 pt
- Assay: + Immuno or functional assay: 2 pt (2 step Functional) 3 pt

>7 Definite; 5-6 Probable; 3-4 Possible; <3 Unlikely

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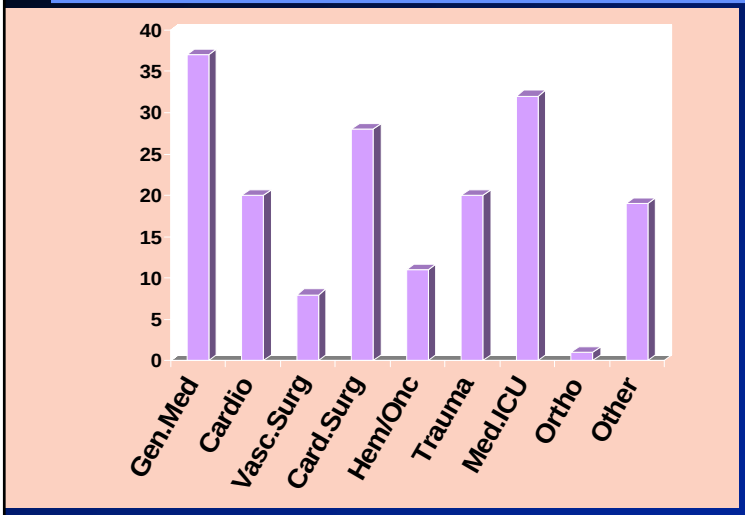
Warkentin TE Br J Haematol 2003;121:535-55; Chong BH Expert Rev Cardiovasc Ther 2004;2:547-59

Platelet Monitoring: ACCP 2008 Guidelines

Heparin	Risk	Platelet Count Monitoring	Level
Yes	> 1%	Recommended	1C
Yes	0.1%-1%	Recommended	2C
UFH or LMWH	UFH past 100 days	Baseline and within 24 hours	1C
Within 30 minutes of UFH bolus	Anaphylactoid reaction	Immediate and compare to prior count	1C
Therapeutic UFH		Every 2-3 days (Day 4-14 or until D/C UFH)	2C
Prophylactic UFH	Post-Operative (HIT risk > 1%)	Every other day (Day 4-14 or D/C Heparin)	2C
Prophylaxis	Medical/OB (UFH) or LMWH post-operative (HIT Risk 0.1-1%)	Every 2-3 days (Day 4-14 or D/C Heparin)	2C
	Medical/OB LMWH (UFH catheter Flush (HIT Risk 0.1-1%)	Not recommended	2C
Fondaparinux		Not recommended	1C

Warkentin TE et al. *Chest.* 2008;133:340S-80S.

Where is HIT found?



A consecutive series of 180 patients with a suspicion of HIT high enough to initiate a DTI

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Dager WE et al. ISTH 2007

Are you prepared to manage HIT?

- Acute: HITTS or Isolated vs History
- ✓ Remove all heparin
  - Stopping heparin alone does not stop HIT
- ✓ DTI initially (Available ?)
- ✓ Guidelines for use
  - Clinical Setting
- ✓ Monitor:
  - aPTT, Thrombosis, Platelet count
- ✓ Long term Anticoagulation
  - Isolated HIT
  - HITTS

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Initiating a DTI: Is the package labeling the dose to use?

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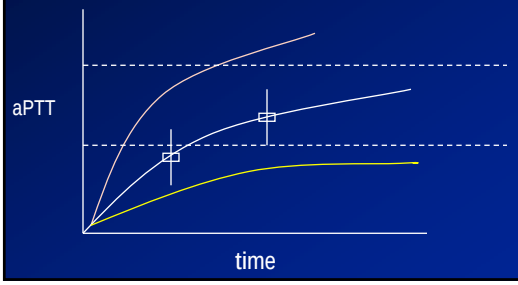
DTI's: Argatroban, Lepirudin, Bivalirudin

- Dose adjusted for Renal, Hepatic, Cardiac function
  - Low dose at Steady State "may" suggest reduced clearance
- Monitoring: aPTT 1.5-2.5/3x control (depending on thrombosis vs bleeding risk)
  - Steady-state longer than healthy subjects studied
  - aPTT: DTI range ≠ UFH range
- False + INR elevation
- Reversal Agent: None (Bivalirudin hemofiltrated)



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ACCP 2008 Recommendations

1. **For patients with strongly suspected or confirmed HIT:**
   - Start non-heparin anticoagulant (1B-2C depending on agent)
   - Avoid LWMH 1B
   - Reverse warfarin if present (Vitamin K 10 mg PO or 5-10 mg IV) 1C
   - Lepirudin: 0.1 mg/kg/hr (reduce if renal function impaired) 1C
     No bolus unless life- or limb-threatening (0.2 mg/kg) 1C
     aPTT every 4 hours 1C
   - Argatroban: heart failure, MSOF, anasarca, post CT surgery 0.5-1.2 μg/kg/min
   - VKA (5 mg or less) once platelet count recovered (usually >150,000/μL) 1B
     - Overlap 5 days and INR at target 1B
2. **Routine lower extremity ultrasonography is recommended. 1C**
3. **Avoid platelet transfusion 2C**

Warkentin TE et al. *Chest.* 2008; 133:340S-80S.

Evaluating Response to Therapy

- Platelet Count Response
  - Mixed Thrombocytopenia
  - True HIT: Increase in 2 days
- Mixed Thrombocytopenia
- Reassessing diagnosis

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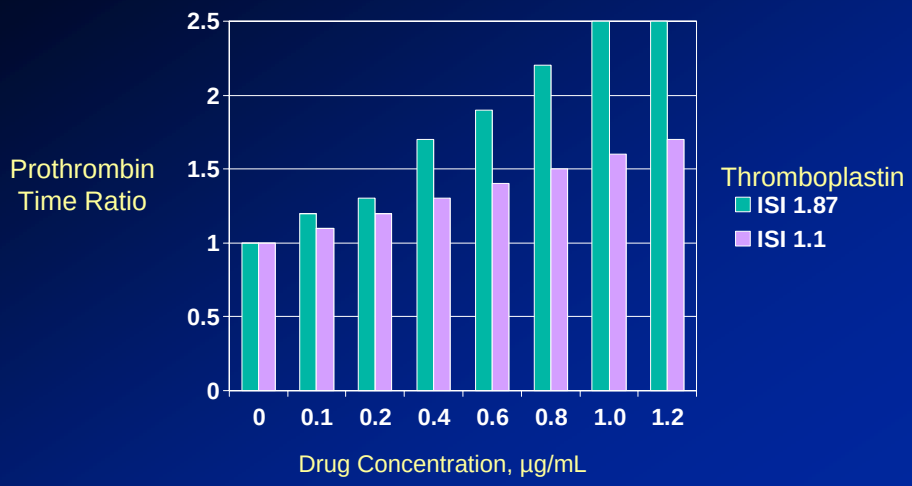
Effect of Argatroban on INR



Gosselin RC et al. *Am J Clin Pathol.* 2004; 121:593-9.

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Predicting Warfarin effect during concurrent DTI therapy

- Change in INR and aPTT
  - ↑ aPTT → ↑ INR
    - Warfarin can ↑ aPTT independently
  - Variables in INR and aPTT reagents creates numerous variables
- INR ↑ with limited aPTT change → Probable warfarin response
  - Time from initial warfarin dosing
  - INR increase of ~ 1.5 – 2.0 may suggest target achieved
    - Hold DTI if platelet count recovery occurring
    - Check aPTT with INR for residual DTI effect

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Dager WE et al. Pharmacotherapy 2007; 4:564-587

Day 5: Argatroban Infusion Transition to Warfarin

Day	Warfarin	INR (early am)	aPTT	HCT	Plt
6	None yet	4.6	120	22	100
7	4 mg/1700	2.0	58	28	97
8	2 mg/1700	2.9	82	27	148
9	2 mg/1700	2.5	70	25	189
10	Withhold	3.0	61	27	295
10	(Stop Argatroban at 2400)				
11	2 mg/1700	3.5	55	28	410
12		2.4	34		

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Managing a Complicated Patient Throughout the Continuum of Care

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Sanford-USD Medical Center
Sioux Falls, SD

Objectives

- By participating in a discussion regarding a complicated anticoagulation case, the learner should:
  - Identify the signs and symptoms of heparin induced thrombocytopenia (HIT)
  - Appropriately justify the dosing and management of the anticoagulants chosen
  - Organize a strategy to transition a complicated HIT patient to the outpatient setting

Case Presentation

- AB is a 51 yowf. She presents to Duluth Clinic on 3/21 for routine follow up for type 2 diabetes mellitus
- During her visit, she relates:
  - She has had increasing chest discomfort with activity requiring more NTG use
  - Two nights ago, she awoke with bilateral arm symptoms, chest discomfort in her neck; lasting 2 hours
  - Today, she had chest discomfort and arm aching while walking into this appointment
  - She is promptly sent to the St. Mary's Medical Center ED

History of Present Illness

- AB has been having difficulty with her angina for the past year
  - 8/07 had a Cardiolite stress test that showed ischemia in the inferoapical area, managed medically

Past Medical History

- Severe allergies to clopidogrel and ticlopidine which both produce a severe rash; failed clopidogrel desensitization
- DM-type 2
- Hypertension
- CAD with stent placement in the left anterior descending (LAD) and 1st diagonal in 2001
  - Jan. 2002, had cutting balloon angioplasty of due to instent stenosis in LAD stent and vascular brachytherapy
  - Procedure was repeated again in July 2005
- Hyperlipidemia-intolerant of multiple statins
- Social history
  - No tobacco and very little alcohol
  - Ran a fine dining restaurant where they used lots of butter

Home Medications

- Exenatide 5 mcg sc within 60 minutes of a meal twice daily
- Isosorbide mononitrate 60 mg po in AM and 30 mg at night
- Glyburide 10 mg po twice daily with meals
- Metformin 1 gram po twice daily
- Aspirin 81 mg po daily
- NTG 0.4 mg SL prn chest pain
- Fish oil 1000 mg po twice daily
- Metoprolol succinate 150 mg po daily

Review of Symptoms

- She had some problems with headaches and occasional blurred vision with high blood sugars
- Shortness of breath with ambulation
- Occasional "fluttering" heart rate

Vitals/Physical Exam

- BP-125/65, HR-73, RR-18
- EKG-no acute changes seen
- No other remarkable findings

Admit Labs

- WBC-5.7
- HGB-14
- Platelet-177
- INR-0.9
- APTT-24
- Na-140
- K-3.7
- Cl-105
- HCO_3-24
- HGB A1C-7.9
- BUN-11
- SrCr-0.6
- Glucose-184
- Phos-3.3
- Albumin-4
- Bili, AST, ALT-nrml
- Lipids (1/17/08)
  - TC-196
  - TG-324
  - HDL-34
  - LDL-97
- CK-71
- CK-MB-2.5
- Troponin-0.57

Impression

- Unstable angina/NSTEMI
  - Chest pain was relieved in ED with 0.4 mg SL NTG X 3, patient then started on NTG gtts
  - Unfractionated heparin started per ACS protocol
  - Another 162 mg po aspirin given
- DM with poor control
  - Insulin added
- Cardiology consulted

Question for the Audience/Panel

- If you hospital directly monitors Xa's for heparin infusions or if you correlate aptt to Xa levels to set a aptt therapeutic range, what Xa range do you use for a target?
  a) 0.1-0.5
  b) 0.2-0.6
  c) 0.3-0.7
  d) 0.4-0.9
  e) Don't know

3/22/08 Cardiology Consultation

- Starts eptifibatide and decides to evaluate in the cardiac catheterization lab
  - Clopidogrel intolerance limits stent options
- Cardiac cath, on 3/24, reveals:
  - 100% occlusion beyond the stent in the LAD
  - 90% occlusion in left circumflex
  - Apical anterior wall motion abnormality
  - Eptifibatide stopped 12 hour after procedure
- CV surgery consulted due to limited invasive cardiology options

3/24 CV Surgery Consult

- (Heparin had been discontinued on 3/24)
- Decision is made to proceed with bypass surgery on 3/27
  - Successful bypass of LAD and first obtuse marginal 1
  - Patient was given heparin during the procedure (reminder, typically very high doses)

Platelet Counts

- 3/21 177 (heparin started, eptifibatide started on 3/22)
- 3/23 169
- 3/24 187 (eptifibatide stopped)
- 3/25 192 (heparin stopped)
- 3/27 160 (CABG, heparin given)
- 3/27 131 (after CABG)
- 4/2 12! (patient notes swelling began 2 days ago in her right arm where a PICC line was)

Current Hospital Medications

- Doccusate sodium 100 mg po hs
- Aspirin 325 mg po daily
- Amiodarone 200 mg po twice daily
- Furosemide 40 mg po daily
- Metformin 1 gram po daily
- KCL 20 mEq po daily
- Insulin glargine 20 units sc daily
- Paroxetine 20 mg po daily
- Famotidine 20 mg po twice daily
- Metoprolol succinate 75 mg po daily

Question for the Audience/Panel

- Which medication is the most likely cause in this case?
  a) Heparin
  b) Eptifibatide
  c) Insulin glargine
  d) Furosemide

4/2 Hematology Consult

- Determines the most likely cause of thrombocytopenia is heparin
- Orders heparin dependent antibody test
  - Send out at SMMC; results in 2 days
- Orders bilateral upper and lower extremity ultrasound
  - DVT confirmed right arm by ultrasound
  - D-dimer is 31,300

Question for the Audience/Panel

- What agent would you pick to manage the HIT at this point?
  a) Argatroban
  b) Lepirudin
  c) Bivalirudin
  d) Fondaparinux

Question for the Audience/Panel

- What target aptt would you use?
  a) Institutional heparin guideline
  b) 1.5-3 X baseline aptt
  c) 1.5-2 X baseline aptt
  d) 2-3X baseline aptt

Hospital Course

- Argatroban started by pharmacy and dosed at 2 mcg/kg/min on 4/2/08
  - Pharmacy pick target aptt of 40-80 based on baseline of 26, but try to keep the APTT over 50 based on history
  - APPT quickly stabilizes at around 55 with no needed dose adjustments
- 4/3-platelets 12
- 4/4-heparin dependent antibody strongly positive, platelets 16

Hospital Course

- 4/5-platelets 17
- 4/6-platelets 28
- 4/7-platelets 27
  - Concern expressed by the attending MD if the argatroban is therapeutic (swelling in the arm has gotten worse) and asks pharmacy to attempt to try to keep the appt closer to 3 times baseline, around 75 seconds
  - Aptt was 56, and drip is turned up to 2.25 mcg/kg/min

Hospital Course

- 4/8: plt 41, aptt 54, 64
  - Argat. 2.5 mcg/kg/min
- 4/9: plt 40, aptt 47-58
  - Argat. 2.5 mcg/kg/min
- 4/10: plt 44, aptt 55
  - Argat. 2.5 mcg/kg/min
- 4/11: plt 27, aptt 51-53
  - Argat. 3 mcg/kg/min
- 4/12: plt 40, aptt 52-58
  - Argat. 4.5 mcg/kg/min
  - Left lower extremity DVT found
  - MD asks to keep aptt over 75

Question for the Panel

- Is this clinical raising of the goal aptt appropriate?
- Any other critical issues that a pharmacist should consider?

Hospital Course

- 4/13: plt 36, aptt 61-68
  - Argat. 8.5 mcg/kg/min
- 4/14: plt 43, aptt 68-76
  - Argat. 10 mcg/kg/min
- 4/15: plt 40, aptt 70
  - Argat. 10 mcg/kg/min
- 4/16: plt 40, aptt 79, 82
  - Argat. 10 mcg/kg/min
- 4/17: plt 35, aptt 81
  - Argat. 10 mcg/kg/min
  - INR 3.8
- 4/18: plt 42, aptt 79
  - Argat. 10 mcg/kg/min
- 4/19: plt 38, aptt 66-72
  - Argat. 12 mcg/kg/min
- 4/20: plt 39, aptt 65-78
  - Argat. 13 mcg/kg/min
  - ACT 313, INR 3.5

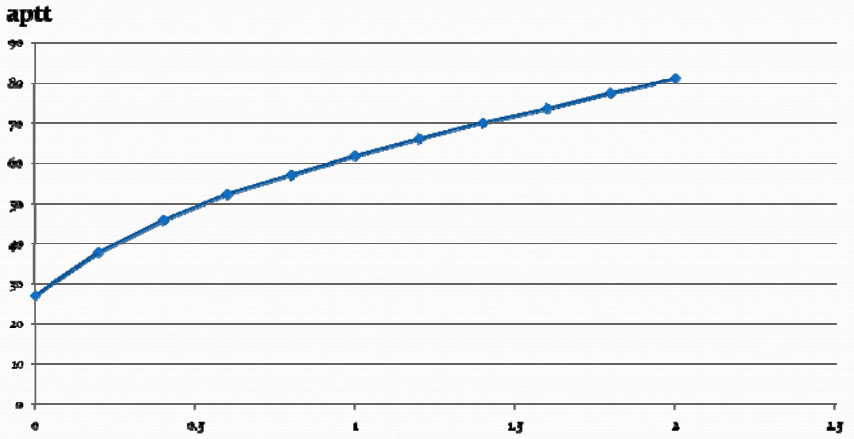
Question for the Audience/Panel

- With the patient doing well clinically, would you have made any changes to the argatroban infusion at this point?

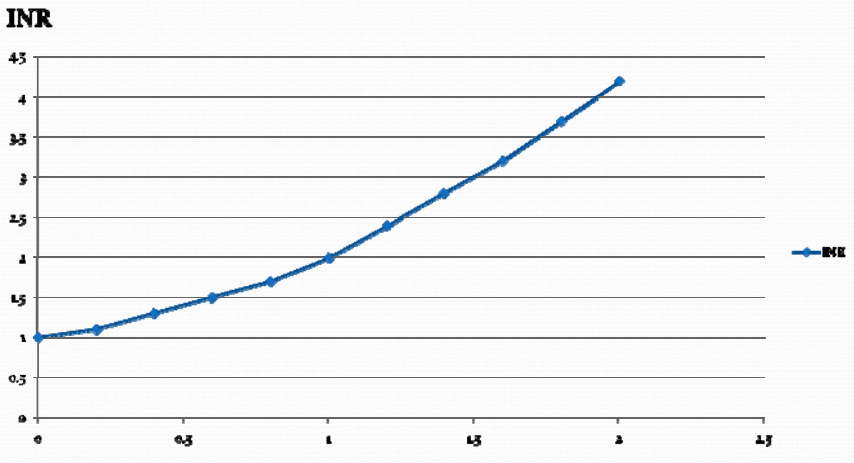
Hospital Course

- 4/21: plt 45, aptt 58-71
  - Argat. 15.5 mcg/kg/min
- 4/22: plt 43, aptt 75-83
  - Argat. 15.5 mcg/kg/min
- 4/23: plt 43, aptt 78-86
  - Argat. 15.5 mcg/kg/min
- 4/24: plt 42, aptt 83
  - Argat. 15.5 mcg/kg/min
  - In vitro study completed
- 4/25: plt 42, aptt 82
  - Argat. 15.5 mcg/kg/min
  - In vitro study completed
  - INR-4.3
  - Decision made to watch INR closely

In Vitro Study Results



In Vitro Study Results



Hospital course

- 4/26: plt 50, aptt 76
  - Argat. 15.5 mcg/kg/min
  - INR-4.4
- 4/27: plt 56, aptt 78-86
  - Argat. 15.5 mcg/kg/min
  - INR-4.3
- 4/28: plt 63, aptt 90
  - Argat. 15 mcg/kg/min
  - INR 5.1
  - Warfarin started; 3 mg
- 4/29: plt 77, aptt 132
  - Warfarin 3 mg given again
  - INR 1.1
  - Argatroban dc'd; fondaparinux 7.5 mg sc q 24 hours started
- 4/30: plt 85, aptt 29
  - Patient discharged on warfarin 5 mg po daily and fondaparinux 7.5 sc q 24 hours, INR 1.2

Question for the Audience/Panel

- Do you agree with the discharge plan? If not, what else needs to be done?
- How would you handle this transition in care to assure no patient harm occurs?
- What are critical education items for this patient that you would cover with her?

Outpatient follow up

- Patient has daily INR checked again on Friday, 5/1 as an outpatient
  - INR is now 2.8, platelets at 150
- Can the fondaparinux be discontinued?
- How long would you recommend warfarin treatment in this case?

Conclusion

- Pharmacists can make a huge difference in caring for complicated anticoagulation cases
- As demonstrated in this case, we can:
  - Help identify HIT
  - Manage and monitor DTI's
  - Think about issues with meds often overlooked by the MDS
  - Transition a patient to alternative anticoagulants and warfarin
  - Arrange seamless outpatient care and excellent patient education

