**EDUCATIONAL SESSION ABSTRACT**
**2010 ASHP Midyear Clinical Meeting**
**Anaheim, California**

**239-1**

# Is Warfarin Dosing by Strict Nomogram Okay?

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With the increasing role of pharmacists managing antithrombotic therapy combined with Joint Commission requirements, many departments of pharmacy have looked to develop warfarin nomograms to assist in dosing. This presentation will clearly show why nomograms that are "rigid" in their dosing approach are neither safe nor effective for patient care. Instead, it is recommended to develop warfarin guidelines that streamline patient care practices and provide some standardization to warfarin dosing.

**Learning Objectives:**

1. Through the use of an interactive case study, determine if dosing warfarin by a strict nomogram is appropriate for routine patient care.
2. List the Joint Commission requirements for anticoagulation "protocols."
3. Describe the critical elements of an effective warfarin guideline.

**Self-Assessment Questions:** (True or False)

1. Strict warfarin nomograms are appropriate for all patients in all situations.
2. Joint Commission requires adoption of a strict warfarin nomogram.
3. Assuring optimal warfarin follow up after discharge is a recommended element as part of a warfarin guideline.

**Answers**: 1. (F); 2. (F); 3. (T)

## Debates and Pearls in Antithrombotic Therapy: Practical Insights for Patient Care

Monday, December 6, 2010
2:00 PM – 5:00 PM

## Disclosures

The Program Chair and presenters for this continuing pharmacy education activity report no relevant financial relationships except:

- Paul P. Dobesh - sanofi-aventis consultant; Received research grants from Eli Lilly and AstraZeneca
- Michael P. Gulseth - Johnson and Johnson stockholder; Ortho McNeil Janssen and sanofi-aventis consultant; Speaker's Bureau member for sanofi-aventis, GlaxoSmithKline, and Eisai
- Maureen Smythe - GlaxoSmithKline Speaker's Bureau Member

## Is Warfarin Dosing by Strict Nomogram Okay?

Michael P. Gulseth
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## Question 1

- For those of you who work at facilities that allow pharmacists to manage warfarin, how would you describe your warfarin nomogram/protocol?
  - A. Strict; pharmacist must contact the physician to vary
  - B. Loose with the ability for the pharmacist to vary as needed for clinical reasons
  - C. Our pharmacists are allowed to manage warfarin with no official protocol

## JT, how would you manage under a strict "nomogram/protocol?"

- CC-JT is a 69 yowf admitted on 8/30/10 with an infected (MRSA) right prosthetic knee; she is 66" and 140 kg
- HPI-She has a complicated orthopedic history, but she is currently admitted to remove knee hardware/cement and to start 6 weeks of IV antibiotics in conjunction with placement of antibiotic impregnated spacers.

## Past Medical History

- Gout
- Hypertension
- Diabetes mellitus
- Peripheral neuropathy
- Morbid obesity
- Anemia
- Vitamin D deficiency
- Hemorrhoids
- Bilateral TKA in 2005
- Patellar fracture with failed internal fixation 2/2009
- 2 stage repair involving an extensor mechanism allograft and reimplantation of her total knee hardware

## Impression/Plan

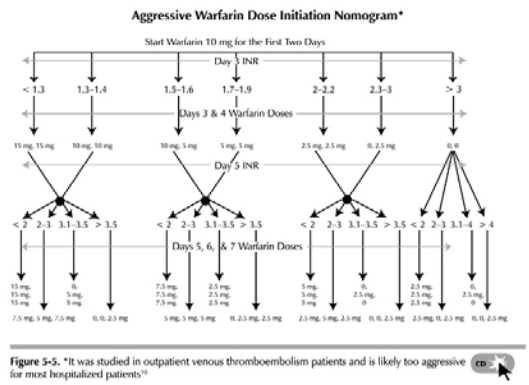
- Removed knee hardware/cement
- Patient was started on short term gentamicin along with long term vancomycin/rifampin
- Patient was started on DVT prophylaxis with enoxaparin 40 mg sc q24h transitioning to warfarin
- Pharmacy is asked to manage the anticoagulation and antibiotics
  - We will focus on the anticoagulation issues

## Hospital Course/Warfarin Dosing

- 8/30-successful surgery, rifampin started, INR-1.35
- 8/31-BP very unstable, on norepinephrine (NE), wound C/D/I, INR 1.27, warfarin 2.5 mg, enoxaparin started
- 9/1-INR 1.28, warfarin 2.5 mg
- 9/2-INR 1.37, hgb good, off NE, warfarin 5 mg
- 9/3-INR 1.88, warfarin 2.5 mg, patient transferred to floor
- 9/4-INR 2.11, warfarin 2.5 mg, enoxaparin stopped
- 9/5-INR 2.03, warfarin 2.5 mg

## Question #2

- On 9/6, the INR is 1.57, what should be done with the warfarin dosing now?
  - A. Continue 2.5 mg
  - B. Increase dose to 5 mg
  - C. Increase dose to 7.5 mg
  - D. Increase dose to 10 mg




Kovacs MJ, et. al. *Ann Intern Med.* 2003; 138: 714-719.

| 5-mg Warfarin Nomogram | | |
|---|---|---|
| Day | INR | Dosage |
| 1 | | 5.0 mg |
| 2 | < 1.5<br>1.5 - 1.9<br>2.0 - 2.5<br>>2.5 | 5.0 mg<br>2.5 mg<br>1.0 - 2.5 mg<br>0.0 |
| 3 | < 1.5<br>1.5 - 1.9<br>2.0 - 2.5<br>2.5 - 3.0<br>> 3.0 | 5.0 - 10.0 mg<br>2.5 - 5.0 mg<br>0.0 - 2.5 mg<br>0.0 - 2.5 mg<br>0.0 |
| 4 | < 1.5<br>1.5 - 1.9<br>2.0 - 3.0<br>> 3.0 | 10.0 mg<br>5.0 - 7.5 mg<br>0.0 - 5.0 mg<br>0.0 |
| 5 | < 1.5<br>1.5 - 1.9<br>2.0 - 3.0<br>> 3.0 | 10.0 mg<br>7.5 - 10.0 mg<br>0.0 - 5.0 mg<br>0.0 |
| 6 | < 1.5<br>1.5 - 1.9<br>2.0 - 3.0<br>> 3.0 | 7.5 - 12.5 mg<br>5.0 - 10.0 mg<br>0.0 - 7.5 mg<br>0.0 |

Harrison L, et. al. *Ann Intern Med.* 1997; 126: 133-136.

Crowther MA, et. al. *Ann Intern Med.* August 15, 1997 127:332-333

Crowther MA, et. al. *Arch Intern Med.* 1999; 159: 46-48.

## International Warfarin Pharmacogenomics Consortium

- Mathematical equation that does account for age, size, genotype, race, enzyme inducers, and amiodarone
  - Predicts 43% of warfarin's variability ($R^2$) for the studied population
  - With an enzyme inducer in the equation and unknown genotypes, it calculates a weekly dose of 61 mg/week

*N Engl J Med.* 2009; 360: 753-64.

## So what does Joint Commission actually require with the NPSG?

- "Use approved protocols for the initiation and maintenance of anticoagulant therapy."
  - This must have a measure of success
  - But what is an "approved protocol" when it comes to warfarin?

http://www.jointcommission.org/NR/rdonlyres/868C9E07-037F-433D-8858-0D5FAA4322F2/0/July2010NPSGs_Scoring_HAP2.pdf Accessed 9-22-10.

## To clarify this point, a surveyor in AJHP recently stated:

- "A physician can simply write 'Implement warfarin protocol,' meaning the protocol that has been approved by the medical staff, and then people follow the protocol."
- "The typical protocol that does not pass muster is one that allows physicians to order whatever dosage of warfarin they want."
- "The Joint Commission expects the pharmacist to follow a protocol."

Rich DS. *Am J Health-Syst Pharm. 2010; 67:144-7.*

## To clarify this point, a surveyor in AJHP recently stated:

- "I have seen certain cases in which the physicians turn over dosing responsibility to the pharmacy, which has some 'experts' in anticoagulation therapy who make dosage adjustments on the basis of individual experience and knowledge. That situation is not acceptable. The pharmacists must agree among themselves to follow a single protocol for best practices."

Rich DS. *Am J Health-Syst Pharm. 2010; 67:144-7.*

## Let's step back a minute……

- We just demonstrated with that case why one nomogram/protocol does not work for every patient
  - If we used it "blindly," we would have:
    - Overdosed her to start (with both the regular 5/10 mg nomograms and the genomic equation)
    - No clear guidance on how to handle the medication interaction and the recovery from her acute illness
    - Had no appreciation of her bleeding vs. thrombosis risk
    - When any tool is reported in the literature, it is critical to understand the population on which it was studied
      - Is it really appropriate to initiate an acutely ill critical care patient on an estimated maintenance dose?
      - What about the delay in rifampin enzyme induction?

## Clarification

- A recent commentary on this topic appeared in AJHP stating these and other concerns:
  - Wittkowsky AK, et. al. Am J Health Syst Pharm. 2010 67: 1554-1556.
- This led to a clarification response from the same surveyor

## Clarification

- "As I stated in the presentation on which this article was based and subsequent presentations, the Joint Commission's interpretation of the term *protocol* for this specific NPSG requirement includes not only the more-rigid preprinted order sheets, dosing nomograms, and standing orders but also clinical practice guidelines, critical pathways, and medical staff policies. Thus, the recommendation of Wittkowsky et al. to use warfarin dosing guidelines is acceptable under this NPSG requirement."
- Moral of the story:
  - Implement warfarin guidelines that standardize care practices, and even some dosing, but they should not be "rigid" regarding dosing

Rich DS. Am J Health Syst Pharm. 2010 67: 1557.

## Question #2

- On 9/6, the INR is 1.57, what should be done with the warfarin dosing now?
  - A. Continue 2.5 mg
  - B. Increase dose to 5 mg
  - C. Increase dose to 7.5 mg
  - D. Increase dose to 10 mg

## Question #3

- How much warfarin each day do you think JT was stabilized on?
  - A. 2.5 mg po daily
  - B. 5 mg po daily
  - C. 7.5 mg po daily
  - D. 15 mg po daily

## Conclusion

- In my opinion, based on the available evidence and managing thousands of warfarin patients, is that a strict warfarin dosing nomogram/protocol is NOT okay
- Instead, implement warfarin guidelines that:
  - Develop an individual treatment plan for each patient
  - Obtain INR values on a daily basis unless stable
  - Evaluate the dosing of warfarin daily and readjust based on INR values, patient clinical status, and hospital care guidelines (can include dosing guidance to help with standardization)
  - Address critical INRs quickly
  - Monitor patients for signs of bleeding and new thrombosis
  - Assure all transitional care issues are addressed

Wittkowsky AK, et. al. Am J Health Syst Pharm 2010 67: 1554-1556.

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**239-2**

# Is Genetic Testing for Warfarin Useful After a Patient Starts Therapy?

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The Human Genome Project has opened a new era of being able to better tailor medication use to an individual patient's genetic profile. Warfarin has been one of the most studied agents, in this regard, due to its narrow therapeutic index. Despite the advances in understanding how genetics affect warfarin response, very few labs can perform these tests in a timely fashion. Further, even when run in a timely fashion, no data exists from well controlled trials showing they improve outcomes. Until further data become available, genetic testing to aid in warfarin dosing cannot be recommended both due to the lack of clear benefit and since some of the information is likely not helpful in not available when commencing therapy.

**Learning Objectives:**

1. Through the use of an interactive case study, determine if delayed warfarin genotyping is effecting in improving patient care.
2. Describe the effects of variations of CYP2C9 and VCORC1 on warfarin metabolism and sensitivity.
3. Describe the results of the one well controlled trial that has done prospective genotyping.

**Self-Assessment Questions:** (True or False)

1. Warfarin genotyping is most helpful if the results are delayed until after warfarin being started.
2. VCORC1 variations lead to slower warfarin metabolism.
3. The Anderson trial did not show a clear benefit to prospectively genotyping new warfarin patients.

**Answers**: 1. (F); 2. (F); 3. (T)

# Is Genetic Testing for Warfarin Useful After a Patient Starts Therapy?

Michael P. Gulseth
Program Director for Anticoagulation Services
Sanford USD Medical Center
Sioux Falls, SD

## Question 1

- Based on your current understanding of the evidence, do you believe that genotyping patients on warfarin can help improve outcomes?
  - A. Yes
  - B. No

## Question 2

- How many of you work in institutions where genotyping for warfarin is readily available (within 24 hours)?
  - A. Yes, it is readily available
  - B. No, it is not readily available

## Let's take the recent Sanford case of DS

- DS is an 80 yowm admitted on 7/1/2009 with an atrial fibrillation with a rapid ventricular response; he is 70" and 73 kg
- HPI-He had been noticing some recent "fluttering" of his heart, and today when it happened he felt very weak and nearly passed out. In the emergency room, he had a heart rate of 150, and since his other vitals were stable, he was admitted on rate control therapy (diltiazem).

## Past Medical History

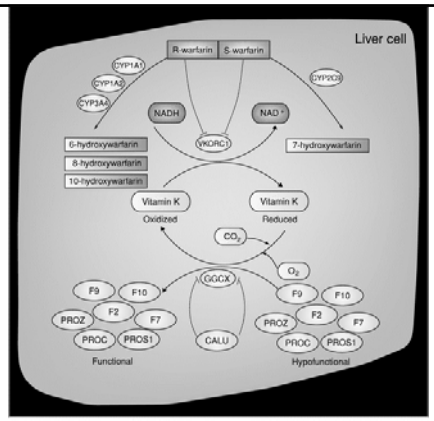
- Hypertension
- Diabetes mellitus
- BPH
- THA in 2005
- History of CAD with bypass surgery 10 years ago

## Impression/Plan

- His heart rate is rapidly controlled with IV diltiazem; a future cardioversion is planned as a clot is visualized on TEE
- He is started on anticoagulation with heparin and warfarin
  - The physician elects to do all of the anticoagulation management himself
  - He orders a warfarin genotype panel
    - This takes at lease 2-3 days for us to get back and is sent out to Mayo in Rochester, MN

## Question 3

- So if you cannot rapidly "turn around" the test, like in this case, do you believe this possibly affects the utility of the test?
  - A. Yes
  - B. No
- By the way, this is a "loaded" question and the point of the presentation




Voora D, et. al. *Pharmacogenomics.* 2005; 6(5): 503-513.

## Overview of CYP2C9 genetic variation

- Wild type allele is deemed CYP2C9 *1
- 50 variations of this allele have been described
  - CYP2C9 *2 and *3 mutations are known to affect warfarin dosing
- It has been linked to increased risk of bleeding events during the initiation period

Voora D, et. al. *Pharmacogenomics.* 2005; 6(5): 503-513.

## Enzymatic activity of different CYP2C9 variants on warfarin

| | | | |
|---|---|---|---|
| *CYP2C9* *2 | 430C > T | Arg144Cys | An approximately 50% decrease of the maximum rate of metabolism (*V*max) and 30–50% lower turnover (kcat) of *S*-warfarin |
| *CYP2C9* *3 | 1075A > C | Ile359Leu | Markedly higher *K*m and lower intrinsic clearance with an approximately 90% decrease of *S*-warfarin |
| *CYP2C9* *5 | 1080C > G | Asp360Glu | Decrease: intrinsic clearance of warfarin approximately 10% of wild type |

Adapted from Yin T, Miyata T. *Thrombosis Research* (2007); 120: 1-10.

## VKOR1

- VKOR stands for vitamin K epoxide reductase (VKOR)
  - Target of warfarin
  - Encoded by VKOR1 gene
    - Vitamin K epoxide reductase complex subunit 1

## VCOR1 and warfarin dosing

- Most studied issues are:
  - 1173C>T
    - Located in intron 1
    - "T" mutation is associated with increased warfarin sensitivity
  - -1639G>A
    - Located in the VKOR 1 promoter
    - "A" mutation is associated with increased warfarin sensitivity
  - 5 major haplotypes that can be broken into a "high dose (B)" and "low dose (A)" warfarin groups
    - Both of the above mutations are part of the low dose haplotype groups

Adapted from Yin T, Miyata T. *Thrombosis Research* (2007); 120: 1-10.

## Incidence of these SNPs

| Ethnicity | Patients with *VKORC1* Haplotype (%) A/A | A/B | B/B | %) *2/*3 | *3/*3 |
|---|---|---|---|---|---|
| Caucasian | 7.3–36.8 | 46.9–55.6 | 12.7–42.0 | 0–5.6 | 0–16.8[b] |
| African American | 0–22.0 | 14.8–20.8 | 79.3–84.6 | 0 | 0–1.5[b] |
| Japanese | 83.3 | 16.1 | 0.72 | NA | 1.0 |
| Chinese/Malay/East Indian | 75.4–86.2/34.4/10.5 | 14.3/46.9/5.3 | 1.2–13.0/6.3/63.2 | NA | 1.8–12.0[b] |
| Hispanic | 27.0–38.0 | NA | 57.0–71.0 | NA | 1.0–2.0[b] |
| Other or not reported | NA | NA | NA | 0.8 | 0.8 |
| Caucasian and African American | 48.9 | 40.2 | 10.9 | 1.2–4.3 | 0 |

[a]Combined *1/*2 and *2/*2.
[b]Combined *1/*3 and *2/*3.
[c]Combined *1/*2 and *1/*3.
[d]NA = not applicable.

Gulseth MP, et. al. *Am J Health-Syst Pharm.* 2009; 66:123-33

## Influence on warfarin dose

Table 2. Estimated Warfarin Dosages at Stable INRs Stratified by *CYP2C9* Genotype and *VKORC1* Haplotype

| | *CYP2C9* Genotype | | | | | |
|---|---|---|---|---|---|---|
| | Rapid Metabolism, | Intermediate Metabolism, | Poor Metabolism | | | |
| VKORC Haplotype | *1/*1 | *1/*2 | *1/*3 | *2/*2 | *2/*3 | *3/*3 |
| High dose (BB) | 6.7 | 5.4 | 4.5 | 4.4 | 3.6 | 3.0 |
| Medium dose (AB) | 4.8 | 3.9 | 3.2 | 3.2 | 2.6 | 2.2 |
| Low dose (AA) | 3.5 | 2.8 | 2.3 | 2.3 | 1.9 | 1.6 |

Data are daily doses (mg).

Limdi NA, e. al. *Pharmacotherapy* 2008;28(9):1084–1097.

## So is delayed testing helpful?

- VCORC1
  - Very unlikely, as it is likely driven by variations in mRNA levels
    - -1639G>A is the likely offender in the promoter region
      - See Wang D, et. al. Blood Cells, Molecules, and Diseases; 43: 119–128.
    - One study showed that a warfarin refinement algorithm, including VCORC1, was not any better than one without; day 4 INR became more critical
      - See Millican, E.A. et al. *Blood* ;110: 1511–1515 .
    - Yet another study deriving algorithms on day 4 or 5 of therapy only shows an improvement of 12-17% over a clinical algorithm
      - See Lenzini, P. et. al. *Clin Pharmacol Ther.* 87; 572-8.

## So is delayed testing helpful?

- CYP2C9
  - Since this will affect warfarin clearance and ½ life, maybe it is helpful
  - Effect shows up “later” than VCORC1
    - See Schwarz UI, et. al. *N Engl J Med* 2008;358:999-1008.
  - Has been linked with bleeding
  - However, no data yet to prove this concept and it has been found to be a lesser determinant of warfarin variability than VCORC1

Gulseth MP, et. al. *Am J Health-Syst Pharm.* 2009; 66:123-33

## Anderson JL, et. al.

- Consenting patients (n=206) randomized to pharmacogenetic guided or standard dosing
  - Genetic dosing used regression equation including cyp2C9 genotype, VKOR1 C1173T, age, sex, and weight
  - Standard used empirical protocol
- INR done on days 0,3, 5, 8, 21, 60, and 90
- Patients followed 3 months
- Open label

Anderson JL, et. al. *Circulation. 2007; 116:* 2563-2570.

## Results

- No difference in primary endpoint of percentage of out of range INRs (30.7% genetic and 33.1% control)
- No difference in adverse events
- Genetic dosing more accurately predicted stable doses and resulted in smaller and fewer dose adjustments
- Subset analysis found more benefit in wild type/multiple variant carriers

Anderson JL, et. al. *Circulation. 2007; 116:* 2563-2570.

## Question 3

- So if you cannot rapidly "turn around" the test, like in this case, do you believe this possibly affects the utility of the test?

A. Yes
B. No

## Conclusion

- Genomic information for warfarin is likely most helpful prior to therapy initiation
  - Delay likely decreases some utility
- Further, prospective genotyping has not been proven to improve "hard" outcomes in any well controlled, prospective trials
- Until large prospective trials demonstrate a benefit, rigorous INR monitoring should be the norm, not genetic testing
  - These are currently being conducted

Gulseth MP, et. al. *Am J Health-Syst Pharm*. 2009; 66:123-33

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**239-3**

# Pearls From the World of Antithrombotic Bridging

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When the risk of thrombosis is high, interruptions or absence of anticoagulation therapy may not be desired. Because of the delay in onset for warfarin activity, the addition of a rapid onset anticoagulant to bridge the gap is a frequent management strategy. In many settings, approaches to bridging lack supporting clinical trial guidance. Pharmacists involved in the management of anticoagulants can provide a key role in guiding the use of a bridging anticoagulant if warrented. This presentation will develop insights and skills for implementing a anticoagulation bridge in patients requiring warfarin therapy.

**Learning Objectives:**

1. Discuss reasons to use, or not use, bridging therapy for antithrombotic regimens.
2. Discuss the use of thrombosis risk assessment scores to determine the need for bridging regimens.
3. Describe issues to consider in developing a anticoagulation plan when a invasive procedure is planned.

**Self-Assessment Questions:** (True or False)

1. The use of a bridging regimen should weigh the risk of an acute thromboembolic event to the potential risk for increased bleeding.
2. The CHADs scoring system is a tool to assess the risk of a cardioembolic stroke
3. A LMWH should be stopped 24 hours in advance of a major surgical procedure that is associated with a high risk for bleeding.

**Answers:** 1. (T); 2. (T); 3. (T)

# Pearls From the World of Antithrombotic Bridging

William Dager, Pharm.D., BCPS (AQ Cardiology)
FCSHP, FCCP, FCCM, FASHP

Pharmacist Specialist : U C Davis Medical Center
Clinical Professor of Pharmacy, UC San Francisco School of Pharmacy
Clinical Professor of Medicine, UC Davis School of Medicine
Clinical Professor of Pharmacy, Touro School of Pharmacy

## Could you tell me the *bridging* dose of enoxaparin:

- My patient has AF and we want to do a procedure.
- The warfarin is on hold
- He has a DVT and we need to do a LP
- She had a PE and is now post-op
- Is 200kg
- Has a cardiac valve and recent GI bleed
- He has a history of HIT

## Why do we bridge?

- Risk of thromboembolism remains high
- Need to cover/anticoagulate "now" until:
  - Warfarin is again therapeutic
  - Risk or immediate concerns for thrombosis is gone
- Just Because

- What is the price:
  - Drug costs
  - Bleeding

## What do we use to bridge

- Unfractionated heparin
  - Is a loading dose necessary
  - Can we just start a infusion (no bolus)
- LMWH/Fondaparinux
- Aspirin
- Heparin-induced thrombocytopenia?
  - Acute: DTI/Fondaparinux
  - History of: > 100 days since? Fondaparinux?
  - How long?

## New Anticoagulants

- No shot
- Age, Drug interactions, Coverage
- Can increase the INR
- Cost (Short term vs long term therapy)
- As a bridge to warfarin: Will 2 PO's be off the radar?
- What dose?
- Assuring/Measuring if effects are gone by procedure?

## How Long do we bridge

- Until warfarin is therapeutic again
  - Is a INR of 1.8 adequate?
  - INR ↑→ ↓↓ Factor VII > ↓ Factor II
    - Thus, a INR of 2.2 on day 1 of therapy may not reflect full anticoagulation
  - INR ↓→ ↑↑ Factor VII > ↑ Factor II
    - Thus, a INR of 1.8 after holding 1-2 days may still be anticoagulated
  - Is a ↓ INR of 1.8 more anticoagulated than a ↑ INR of 2.2?
- Until bleeding occurs

## AF: Considerations for Bridging

- Having a Stroke on my watch is a very bad thing!
- Thrombus typically develops in the cardiac chamber
  - ◆Aspirin?
  - ◆LMWH: What dose?
  - ◆UFH: Do I need to bolus? aPTT target?
- Is the patient in sinus rhythm?
- What is the risk for bleeding?
  - ◆Any critical issues?

## Atrial Fibrillation: Bridging
## What is the risk for a thrombembolic event?
## CHADS2 Score

**High Risk**

- **Poor LV Function**
- **Hx multiple CVA**
- **Immediately post ablation**
- **"Smoke" or thrombus on ECHO**
- **ACCP Risk Factors:**
  - **Heart Failure, HTN, DM, >75**

**1 Pt: CHF, HTN, Age > 75, DM**
**2 Pt: Stroke or TIA**

| Pt | Adj Risk (1.5 x ↑ Rate/Pt) |
|---|---|
| 0 | 1.9 Rate per 100 pt-yrs |
| 1 | 2.8 |
| 2 | 4.0 |
| 3 | 5.9 |
| 4 | 8.5 |
| 5 | 12.5 |
| 6 | 18.2 |

Gage B et al *JAMA*. 2001;285: 2864-2870

## $CHA_2DS_2VASc$

| Stroke Risk factor | Points |
|---|---|
| **C**ongestive heart failure | = 1 |
| **H**ypertension | = 1 |
| **A**ge ≥75 years of age | = 2 |
| **D**iabetes | = 1 |
| Prior **S**troke/TIA/systemic embolus | = 2 |
| **V**ascular Disease (prior MI, PAD or aortic plaque) | =1 |
| **A**ge 65-74 | = 1 |
| Sex category (female) | = 1 |

Recommended antithrombotic Tx:
**Score -**
**>1: Oral anticoagulation (VKA INR 2-3)**
**= 1: Either oral antithrombotic therapy (INR 2-3) - preferred, or aspirin 75-325mg/day**
**= 0: No anticoagulation therapy (preferred), or aspirin 75-325mg daily**

**The $CHA_2DS_2VASc$ identifies a lower risk population. The impact of the approach over the $CHADS_2$ has not been determined**

Lip GY, et al. Chest 2010;137:263-272.

## Major Hemorrhage in AF: $HEMORR_2HAGES$

- **H**epatic or Renal Dz
- **E**thanol abuse
- **M**alignancy
- **Older (> 75)**
- **R**educed Plt Count / function
- **R**ebleeding risk (2 pt)
- **Hypertension** (uncontrolled)
- **A**nemia
- **G**enetic factors (CYP 2C9 polymorphisms)
- **E**xcessive fall risk
- **Stroke**

| Pt | Adjusted Risk Bleeds/100 pt years |
|---|---|
| 0 | 1.9 |
| 1 | 2.5 |
| 2 | 5.3 |
| 3 | 8.4 |
| 4 | 10.4 |
| ≥ 5 | 12.3 |
| Any Score | 18.2 |

Gage et al: Am Heart J 2006;151:713-9

## Atrial Fibrillation: LMWH or UFH RCT's

- Stroke: 14 day recurrent stroke rate
- AF but no warfarin
- (CHEST 2008: Bridge for high risk patients)

| HAEST | Dalteparin 100 u/kg BID | ASA 160mg/day | OR |
|---|---|---|---|
| | 8.5% | 7.5% | 1.1 (0.6-2.2) |
| Saxena | UFH 12,500 BID | No UFH | |
| | 2.3% | 4.9% | 0.5 (0.3-0.8) |

HAEST: Lancet 2000; Saxena Stroke 2001

## VTE – (DVT/PE): Considerations for Bridging

- Suspected VTE (Scans pending)
- New VTE and transitioning to warfarin
  - ◆What INR is OK to stop
  - ◆5 days of parenteral therapy (in target range)
- History of a VTE
  - ◆Recent
  - ◆> 6 months
  - ◆Repeat event vs single "provoked" event
  - ◆Hypercoagulable condition present

Most experiences from observational trials

## Cardiac Valves: What do we use to bridge?

- **Location**
  - Mitral vs Aortic vs Tricuspid
  - Heart Failure: ↑ Turbulence in the region
- **Type of Valve**
  - Porcine
  - Mechanical (Old or New)
- **How many times has the Valve been replaced**
- **Stroke, Atrial Fibrillation, Endocarditis present?**
- **Any thrombus on the valve?**
- **What dose of LMWH or UFH?**

## Developing a anticoagulation plan when a invasive procedure is planned

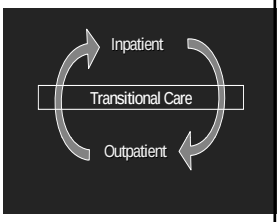
- **Bridge Pre-OP and Post Op?**
  - What is the procedure, when?
- **Anticoagulation needs assessment**
  - Indication
  - Risk for thrombosis vs changes in bleeding risks
  - Change in anticoagulation goals
  - Return to OR
- **Advance plan for management**
  - Epidural Catheter
  - Alternative anticoagulant than typically used
  - Laboratory values prior to procedure

## When to hold/restart bridge therapy

- **Stopping prior to procedure**
  - **Depends on the location and bleeding risk**
  - **UFH: D/C 4-6 hr prior**
  - **LMWH: D/C 24 hr prior**
  - **Fondaparinux: D/C 36hr or more**
- **Restarting:**
  - **Develop final plan after the procedure**
  - **Assess bleeding (Drains, epidural catheter etc)**
  - **Laboratory values**
  - **LMWH: Peak effect 4 hr post dose**
  - **UFH: Bolus, or no bolus prior to starting a infusion**

## Continuity of Care

**Transitional Care**
**-Home therapy**
**-Successful Implementation**




**Availability/Outpatient Coverage (Clerical Support)**
**•Adequate clinician follow-up**
**•Ability to self provide therapy, Phone at home**
**• No significant bleeding risk**
**• Rapid follow up immediately post discharge: AC Referral**

**EDUCATIONAL SESSION ABSTRACT**
**2010 ASHP Midyear Clinical Meeting**
**Anaheim, California**

**239-4**

# How Long Should LMWH be Used for DVT Prophylaxis in Medical Patients

Dager, W.E.
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As the duration of hospital stay decreases, and risk of venous thromboembolism (VTE) extends after discharge, concerns for preventing thrombotic events may extend into the outpatient setting. Because VTE in many situations is preventable, the approach to prevention using low molecular-weight heparin (LMWH) for pharmacological prophylaxis is commonly undertaken, especially in the inpatient setting. The benefits of continued VTE prophylaxis after hospital discharge for medical patients with prolonged risk of a VTE are unclear. Pharmacists involved in the management of anticoagulants are in a position to risk assess and facilitate completion of anticoagulation management plans, including the use of prophylactic regimens. This presentation will develop insights and skills for assessing and assisting in the use of prophylactic anticoagulation regimens to prevent VTE in the medical patient population.

**Learning Objectives:**

1. Discuss the role of the pharmacist in initiating a LMWH for VTE prophylaxis in medical patients.
2. Describe which medical patients most likely to, or not to, benefit from prolonged VTE prophylaxis.
3. Describe how to assure prophylaxis using a LMWH can be implemented in the outpatient setting.

**Self-Assessment Questions:** (True or False)

1. Risk factors for extending VTE prophylaxis in medical patients include length of hospital stay and presence of adequate VTE prophylaxis in the inpatient setting.
2. LMWH have been shown in clinical trials to be superior agents in most medical patients requiring extended VTE prophylaxis.
3. The pharmacist should consider the ability of the patient to receive and inject a LMWH for VTE prophylaxis.

**Answers:** 1. (T); 2. (F); 3. (T)

# How Long Should LMWH be Used for DVT Prophylaxis in Medical Patients

William Dager, Pharm.D., BCPS (AQ Cardiology)
FCSHP, FCCP, FCCM, FASHP

Pharmacist Specialist : U C Davis Medical Center
Clinical Professor of Pharmacy, UC San Francisco School of Pharmacy
Clinical Professor of Medicine, UC Davis School of Medicine
Clinical Professor of Pharmacy, Touro School of Pharmacy

## The pharmacist in entering, verifying, risk assessing or monitoring for VTE prophylaxis

- What agent should be used?
  - Risk of VTE vs bleeding (HgB, Plt, other agents)
  - Allergy
  - Formulary
- What dose should be given?
  - Wt, Age
  - Scr

## The pharmacist responsible for monitoring the patient may consider:

- Is prophylaxis ordered?
- Is the dose currently correct?
- Labs: Hgb, Scr, Plt
- Bleeding
- How long?

- A physician is calling to request how long my patient should receive prophylaxis.
- They are concerned because:
  - Several recent re-admissions with VTE
  - Patient recently died of a PE after discharge
  - Recent article
  - Materials recently provided to me suggested the use of prolonged prophylaxis

## What should we consider when determining the duration of VTE prophylaxis?

- How long are risk factors present?
- Was inpatient prophylaxis provided?
- What adverse risk factors are present?
  - **Bleeding**
  - **HIT**
  - **Costs (Hospitalization/Event to Drug)**
- What is the duration of responsibility?

## What will be the patients situation to go the distance

- Where will the patient be?
  - ICU, Floor, Nursing Home, Home (sweet) Home
- What is available to the patient and the setting?
  - Prescription benefit coverage/Medicare/out-of-pocket expenses
  - Anticoagulant agent choice and availability
  - Patient and caregiver training and education
- What data supports longer prophylaxis?
  - **Few studies of prolonged prophylaxis**

## Risk Factors for VTE in *Hospitalized* Patients

| Conditions | Clinical Characteristics |
|---|---|
| Acute infectious disease | Previous VTE |
| Congestive heart failure* | Older age (especially >75 years) |
| Acute myocardial infarction | Recent surgery or trauma |
| Acute respiratory disease | Immobility or paresis |
| Stroke | Obesity (BMI >30)± |
| Rheumatic disease (e.g., acute arthritis) | Central venous catheterization |
| Inflammatory Bowel Disease | Inherited or acquired thrombophilia |
| | Varicose veins |
| | Estrogen therapy |

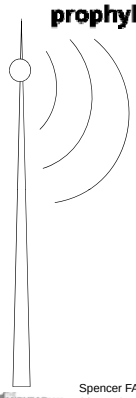
* Congestive heart failure is defined as New York Heart Association class III or IV disease
± BMI is the weight in kg divided by the square of height in meters

Francis CW. *N. Engl.J.Med.* 2007; 356:1438-44.

## Preventing VTE In Long Term Care

- Incidence and effective prophylaxis not well studied
- VTE risk is a growing concern; symptoms likely to be 'silent'
- Risk of bleeding poses a significant barrier
- Economic burden and aging of Americans – not well studied

## Signals suggesting prolonged need for prophylaxis?



Age: 38% are over 65, 24% are 75 or older

Use of prophylaxis is increasing!
Regulators, payers are watching

Length of Hospital stay is getting shorter!
Rehabilitation in the home is increasing

Most VTE events occur after discharge
26% occur in inpatients
74% in outpatients

Spencer FA et al. *Arch Intern Med.* 2007; 167:1471-5; DeFrances CJ et al.*Adv Data.* 2007; 385:1-19; DeFrances CJ et al.2006 National Hospital Discharge Survey. July 30, 2008.

## What agent would you recommend?

- Now
- Long Term plans

How does a LMWH fit in here?

## Arguments for LMWH?

- Ease of use
  - Given less frequently each day
  - No monitoring
- Warfarin is a pain to do
- Less HIT
- Less bleeding
- The physician wants it
- Just because (and everybody else is doing it)

## VTE Prophylaxis in Medical Patients: 2008 ACCP Guidelines

| Admission VTE Risk Factor | Recommended Prophylaxis | Grade |
|---|---|---|
| CHF, severe respiratory disease | LMWH<br>LDUH<br>Fondaparinux | 1A |
| OR confined to bed with at least 1 additional risk factor:<br>• active cancer<br>• previous VTE<br>• sepsis or critical care setting<br>• acute neurologic disease<br>• inflammatory bowel disease | LMWH<br>LDUH<br>Fondaparinux | 1A |
| Patients with risk factors BUT have a contraindication to anticoagulant | Mechanical: GCS or IPC | 1A |

## DVT Prophylaxis trials in medically ill

| | Regimen | VTE (DVT/PE) | Post trial VTE (Tx) |
|---|---|---|---|
| PRIME<br>N=959 | UFH 5K TID x 7<br>Enox 40d x 7 | 1.4% 0.2% | Not assessed |
| PRINCE<br>N=665 | UFH 5K TID x 10<br>Enox 40d x 10 | CHF Resp<br>16.1% 5.9%<br>9.7% 7.1% | Not Assessed |
| MEDENOX<br>N=1102 | Placebo x 6-14d<br>Enox 20/40 x6-14d | 15% (0.7/0.7)<br>15% / 5.5%*(1/ 0.3 0/0) | N=9 |
| PREVENT<br>N=3706 | Placebo<br>Dalt 5Kd x14 | 5.0% (0.63/0.23)<br>2.8% (0.28/0.28) | N=5 |
| ARTEMIS<br>N=849 | Placebo x 6-14d<br>Fonda 2.5d x 6 -14d | 10.5% (1.2% fatal PE)<br>5.6% (p=0.29) (0 PE) | N=10 |

## EXCLAIM Trial

- Medical patients randomized to extended post-hospital VTE prophylaxis for approx. 1 month using LMWH or placebo after initial ~10 day course
- Controversial - study design amended
  - Lower rate of VTE than anticipated at interim analysis
  - Began recruiting higher-risk for VTE patients
  - Results should not be generalized to entire patient population

Hull RD et al. *Ann Intern Med.* 2010;153:8-18.

## EXCLAIM Trial: Results

Extended duration LMWH x 28 days
LMWH: n=2975 vs. placebo, n=2988

- Reduced VTE incidence with extended prophylaxis (absolute risk difference favored enoxaparin, -1.53%)
- *Significant, but clinically small number, experienced bleeding* (absolute risk difference favored placebo, 0.53%)
- Benefits restricted to patients >75 years of age, women, and acutely ill medical patients with level 1 immobility

Hull RD et al. *Ann Intern Med.* 2010;153:8-18.

## Thromboembolism in Malignancy

- Annual incidence of VTE in all patients: 117 in 100,000
- Annual incidence of VTE in patients with cancer: 1 in 200
- Cancer increases risk of thrombosis 4.1-fold
- 15% of cancer patients develop venous or arterial thrombosis
- Chemotherapy increases risk of thrombosis 6.5-fold
- Additive risk factors: surgery, radiation therapy, central venous catheters, other antitumor and supportive therapies

Decreased Platelet Counts from chemotherapy
3-6 x increase in bleeding with warfarin

Green KB, Silverstein RL. Hematol Oncol Clin North Am. 1996;10:499-530; Silverstein MD et al. Arch Intern Med. 1998;158:585-593; Heit JA et al. Arch Intern Med. 2000;160:809-815; Lee AYY, Levine MN. Circulation. 2003;107:I17-21.

## Prolonged "Prophylaxis" in HIT

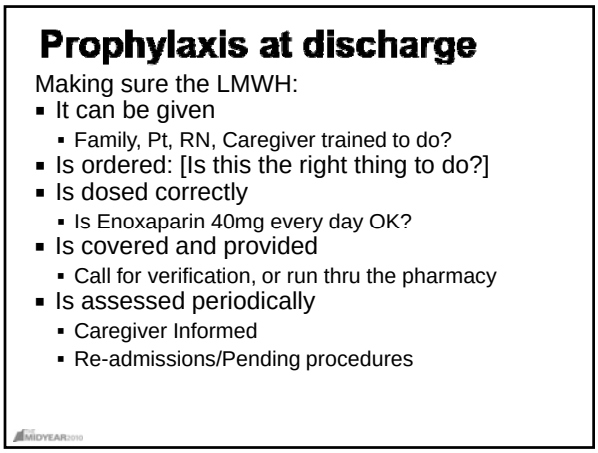
- Risk of VTE prolonged – may need as outpatient
- Was it truly HIT?
- LMWH is contraindicated
- Fondaparinux is a option

## CT is a 75yo male, 155kg admitted for acute decompensated heart failure

- PMH: COPD, HF, History of DVT
- Scr 2.6
- EF = 20%

- Day 3 of admission: Patient still not walking much, and the physician is inquiring about sending him out on a LMWH

How would you respond?



**EDUCATIONAL SESSION ABSTRACT**
**2010 ASHP Midyear Clinical Meeting**
**Anaheim, California**

**239-5**

# Therapeutic Debate: Is Anticoagulation Intensity Monitoring Needed for Therapeutic Heparin?

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Unfractionated heparin has a narrow therapeutic range requiring accurate dosing to avoid the development of recurrent thromboembolism or hemorrhagic complications. Several laboratory tests are available to monitor heparin therapy including whole blood clotting time, activated partial thromboplastin time (aPTT), and activated clotting time (ACT). The aPTT is the most widely used method where the therapeutic range for aPTT is traditionally considered 1.5–2.5 times the mean normal control value. Drawbacks to using aPTT levels to monitor heparin have been recognized and include poor correlation with blood heparin concentration, varying response to laboratory equipment and reagents, and the responsiveness of aPTT to biological factors independent of heparin activity. Recent studies have employed fixed weight based heparin regimens for the treatment of acute venous thromboembolism with reduced or omitted aPTT monitoring. Since these heparin regimens lack FDA approval and alternative agents exists, their role in thrombosis treatment is a source of debate.

**Learning Objectives:**

1. Critically evaluate the laboratory and clinical data that supports the heparin therapeutic range using the aPTT and the anti-factor Xa level.
2. Identify limitations associated aPTT and anti-factor Xa monitoring.
3. Explain reasons for wide spread aPTT use and performance measures in hospitals.
4. Describe rationale that support use of a fixed weight based unfractionated heparin regimen in venous thromboembolism.
5. Identify clinical outcomes that support aPTT monitoring and the successful deliver of anticoagulant therapy.

**Self-Assessment Questions:**

1. (True or False) Data to support the lower limit of APTT therapeutic range is based on animal studies, post-hoc & pooled analysis.

2. The aPTT can be impacted by;
    a. Blood sampling technique and materials.
    b. Laboratory reagents and equipment.
    c. Patient factors like age and weight.
    d. All of the above.
3. The aPTT is a globally accepted testing method because;
    a. Data supports a strong relationship between high aPTT and bleeding in VTE.
    b. It is a sophisticated test.
    c. It has continued to be improved over time.
    d. There is clinical satisfaction among users.
4. A fixed dose weight based unfractionated heparin regimen in venous thromboembolism:
    a. Routinely places patients in an optimal therapeutic aPTT range.
    b. Is statistically non-inferior to weight based low molecular weight heparin therapy.
    c. Was associated with a low incidence or recurrent venous thromboembolism and bleeding.
    d. All of the above.
5. (True or False) For patients presenting to an Emergency Department with venous thromboembolism, early attainment of a therapeutic aPTT value with unfractionated heparin is associated with a lower in-hospital mortality.

**Answers**: 1. (T); 2. d; 3. d; 4. c; 5. (T)

# Therapeutic Debate: Is Anticoagulation Intensity Monitoring Needed for Therapeutic Heparin? Yes

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## Disclosures

- Speakers Bureau
  - None
- Consultant
  - None
- Board of Directors
  - North American Thrombosis Forum (NATF)
- Family
  - Dad (James) CVS
  - Brother (Paul) Boehringer-Ingleheim

## Outline

- Recent history and reminders.
- Discuss coagulation tests.
- Performance with existing tests.
- Data support coagulation testing
  - Outcomes
- Limitations of fixed dose regimens

## Objectives

- Cover the strengths and weakness associated with UFH coagulation tests.
- Provide performance measures with existing tests.
- Identify the limitations with fixed dose UFH regimens.
- Identify settings where UFH laboratory monitoring is important.

## Audience Polling: Which anticoagulant did the FDA recall in 2008?

- A. Clopidogrel (Plavix)
- B. Dalteparin (Fragmin)
- C. Enoxaparin (Lovenox)
- D. Heparin
- E. Warfarin (Coumadin, Jantoven)

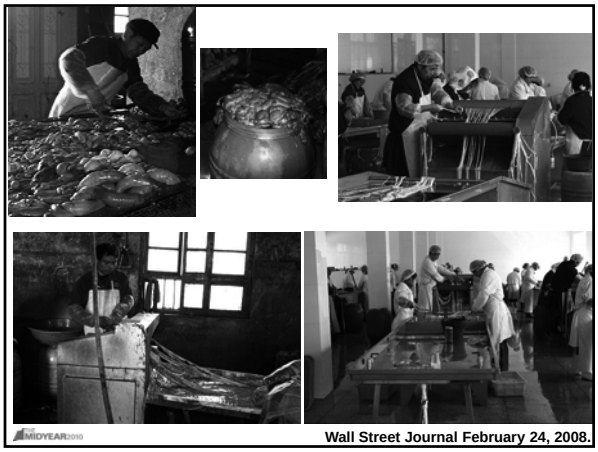
## Heparin Recall

Jan 17th, 2008

- 01/09/08: Centers for Disease Control report to FDA small clusters of allergic events in MO dialysis centers.
- 01/16: FDA inspects Baxter facility in Cherry Hill, NJ.
  - 9 Lot numbers implicated
- 01/17: Baxter issues limited recall.
- 2/11: FDA press conference announces 350 events and 4 deaths
- 02/18: FDA announces comprehensive inspection of Changzhou SPL (China) facility.
- 02/28: Baxter issues recalls all heparin injection single and multi dose vials.
  - 50% of US supply.

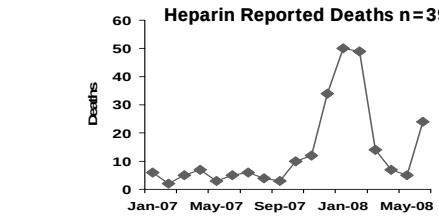

Baxter

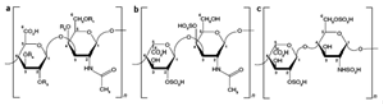
Urgent Product Recall



Wall Street Journal February 24, 2008.

## Heparin Aftermath



Chondroitin Dermatan Heparin

http://energycommerce.house.gov

http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm184502.htm.

## Changes in the USP Heparin Monograph and Implications for Clinicians

**"This may particularly impact those clinicians who use large, weight-adjusted, fixed doses of heparin for the treatment of acute venous thromboembolism."**

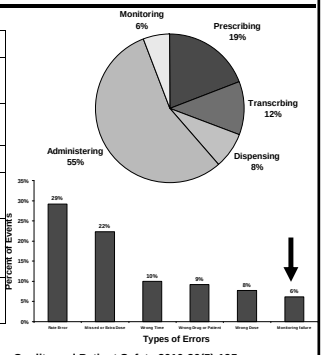
Smythe MA et al. Pharmacotherapy 2010;30(5):428.

## FDA Public Health Alert: Change In Heparin USP Monograph-10/01/09

- Healthcare providers should be aware of the potency change for heparin and the possible clinical effects of this decrease in potency.
- Manufacturers will label their new products in a manner that will help healthcare providers differentiate them from the old products.
- There will be simultaneous availability of heparin manufactured to meet the "old" and "new" USP monograph, with potential differences in potency.
- Consider the potential potency variation when administering heparin.
- The potency change may require more frequent or intensive aPTT or ACT monitoring.

## Harmful Medication Errors Involving Heparins

| Event | Total |
|---|---|
| All Medication Errors and Near Misses | 284,383 |
| Heparin Errors and Near Misses | 10,359 |
| Harm from Heparin | 275 |
| Heparin Reports as Percent of All Reports | 3.6% |
| Harmful Errors from Heparin as Percent of All Reports | 0.1% |
| Percent of Heparin Reports Resulting in Harm | 2.7% |

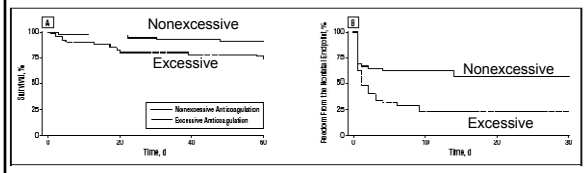


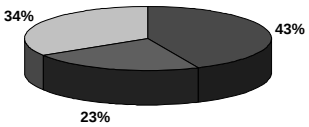

Grissinger MC et al. Joint Commission Journal on Quality and Patient Safety 2010;36(5):195.
Fanikos J et al. Am J Cardiol 2004; 94:532-535.

## Effect of Excessive Anticoagulation on Mortality

Survival

Freedom from Stroke, MI, Hypotension, Critical anemia, surgical/angiographic intervention




Warfarin Heparin Bridge Heparin alone

Koo, S. Arch Intern Med 2004;164:1557-60

Landefeld CS et al. Am J Med 1993;95:315-328.

## Classification of Therapeutic Monitoring Goals

- Primary Method-titration to a clear, measurable, physiologic response.
- Secondary Method-titration to a secondary physiologic response that correlates to with the primary response (aPTT, ACT, PT).
- Tertiary Method- titration to a given concentration of drug, called the targeted concentration strategy.
  - Heparin assays (functional, chemical, neutralizing).
    - Antifactor Xa Test

Olson JD et al. Arch Pathol Lab Med 1998;122:782-798

## aPTT: Why question these methods ?

- Prolongation of the aPTT by itself does not necessarily mean the blood is effectively anticoagulated.
- Degree of prolongation of the aPTT in response to clinical effective concentration of the drug varies among different aPTT methods.
- Degree of antithrombotic effect is for heparin and other anticoagulants is different at the same degree of prolongation of the aPTT.
  - Lack of concordance = excessive bleeding
- Several groups recommend that a therapeutic range be determined relative to the plasma concentration.

Olson JD et al. Arch Pathol Lab Med 1998;122:782.

## Publications on aPTT Limitations

| Author | Title |
|---|---|
| Chiu HM et al. Blood 1977 | Relationship between the anticoagulant and antithrombotic effects of heparin in experimental venous thrombosis |
| Bill-Edwards P. et al. Archives of Intern Med 1993 | Establishing a therapeutic range for heparin therapy |
| Baker BA et al. Archives of Intern Med 1997 | Inability of the activated partial thromboplastin time to predict heparin levels. Time to reassess guidelines for heparin assays |
| International Society on Thrombosis and Haemostasis Posted 2001 | Limitations on the laboratory monitoring of heparin therapy. Scientific and Standardization Committee Communications |
| Raschke R et al. Ann Intern Med 2003 | Suboptimal monitoring and dosing of unfractionated heparin in comparative studies with low molecular weight heparin |

## Pharmacy Publications on aPTT Limitations

| Author | Title |
|---|---|
| Smythe MA et al. Pharmacotherapy 1999 | Heparin monitoring: The Confusion Continues |
| Francis JL et al. Pharmacotherapy 2004 | Challenges in Variation and Responsiveness of Unfractionated Heparin |
| Bussey H et al. Pharmacotherapy 2004 | Heparin Overview and Issue. |
| Dobesh P. Pharmacotherapy 2004 | Unfractionated Heparin Dosing Nomograms: Road Maps to Where? |
| Spinler S et al. Ann Pharmacotherapy 2005 | Anticoagulation Monitoring Part 2. Unfractionated Heparin and Low-Molecular-Weight Heparin |

**...it is now apparent that laboratories must determine the appropriate therapeutic range for their own aPTT system used to monitor heparin therapy".**

| Consensus Recommendations Monitoring with the Activated Partial Thromboplastin Time (aPTT) |
|---|
| The therapeutic range of UFH for the aPTT reagent-instrument system should determined with each change in reagent (lot number or manufacturer) or instrument.<br>This may be accomplished by<br>a. Comparison of ex vivo specimens with an appropriately validated heparin assay (anti-factor Xa or protamine sulfate neutralization).<br>b. Comparison of an ex vivo specimens to a previously calibrated aPTT, using a method to control for reagent drift. (Level 3) |
| **Consensus Recommendations For Manufacturers and Pharmacists** |
| Manufacturers should provide the heparin responsiveness of reagents to be used for aPTT (Level 3) |
| A hospital pharmacy should supply heparin of a single manufacturer and lot number for therapy. When the lot must change, the laboratory should be notified to reevaluate the therapeutic range of the test(s) being monitored. |
| Pharmceutical heparin should be calibrated against an international standard (preferably the WHO standard) using an anti-factor Xa assay (Level 2) |

Adapted from Olson JD et al. Arch Pathol Lab Med 1998;122:782-798.
Brill-Edwards P, et al. Ann Intern Med 1993:119:1404-109.

## Are there better tests?
## Antifactor Xa heparin activity

- 625 bed teaching hospital
- 268 patients
  - 87% arterial
  - 13% venous
- UFH on ideal weight
- Monitored by either HA or aPTT over 96 hours.
- HA assay costs $4.37 more per patient.

| Unfractionated Heparin Dosage Adjustment Protocol Using Antifactor Xa HA for Monitoring | | |
|---|---|---|
| HA result (U/ml) | Response | Next HA Level |
| 0.00–0.09 | Bolus 25 U/kg; increase infusion by 3 U/kg/hr | 6 hrs |
| 0.10–0.19 | Increase infusion by 2 U/kg/hr | 6 hrs |
| 0.20–0.29 | Increase infusion by 1 U/kg/hr | Next A.M. |
| 0.30–0.69 | No change | Next A.M. |
| 0.70–0.79 | Decrease infusion by 1 U/kg/hr | Next A.M. |
| 0.80–0.89 | Stop infusion for 1 hr, then decrease by 2 U/kg/ hr | 6 hrs |
| 0.90–0.99 | Stop infusion for 1 hr, then decrease by 3 U/kg/hr | 6 hrs |
| 1.00–1.09 | Stop infusion for 2 hrs, then decrease by 4 U/kg/hr | 6 hrs |
| > 1.10 | Stop infusion for 2 hrs, then decrease by 5 U/kg/hr | 6 hrs |

Rosborough TK. Pharmacotherapy 1999;19(6):760–766.

## Are there better tests?
## Antifactor Xa heparin activity

| UFH Treatment Characteristics and Outcomes of Patients Monitored by HA aPTT | | | |
|---|---|---|---|
| | HA Group (n=137) | aPTT Group (n=131) | p Value |
| Hours of therapy | 75 (46–104) | 62 (36–88) | 0.02 |
| Average U/hr | 1120 (920–1310) | 1120 (950–1280) | 0.66 |
| U/ideal weight/hr | 18 (16–20) | 18 (16–20) | 0.37 |
| AUC-HA (U) | 0.51 (0.40–0.62) | 0.50 (0.40–0.60) | 0.47 |
| AUC-aPTT (sec) | 82 (61–103) | 81 (64–98) | 0.25 |
| Therapeutic HA (%) | 67 (53–81) | 67 (50–84) | 0.22 |
| Therapeutic aPTT (%) | 33 (14–52) | 38 (20–56) | 0.03 |
| Sensitivity index | 0 (–28–28) | 0 (–26–26) | 0.78 |
| Monitoring tests/24 hrs | 1.46 (1.25–1.68) | 1.68 (1.39–1.97) | <0.0001 |
| Dosage changes/24 hrs | 0.46 (0.19–0.72) | 0.84 (0.53–1.15) | <0.0001 |

Rosborough TK. Pharmacotherapy 1999;19(6):760–766.

## Weight based Heparin Protocol using Antifactor Xa Monitoring

- 50 consecutive patients on UFH
- Bolus 26 U/kg,
  - Contrast w/ ACCP loading dose of 80 U/kg
- IV Infusion @ 15 U/kg/hr
  - Contrast w/ various trials listed at 18 U/kg/hr
- Heparin Anti-Xa Levels q6 hrs & post each rate change.
- Heparin Anti-Xa Targets: 0.3 – 0.7 U/ml.

| Anti-Xa Conc. (U/ml) | Repeat Heparin Bolus Dose | Infusion Adjustment |
|---|---|---|
| <0.20 | 26 U/kg | Increase by 4 U/kg/hr |
| 0.20 – 0.29 | None | Increase by 2 U/kg/hr |
| 0.30 – 0.70 | None | No Change |
| 0.71 – 0.80 | None | Decrease by 1 U/kg/hr |
| 0.81 – 0.99 | None | Decrease by 2 U/kg/hr |
| ≥ 1.00 | None | Interrupt for 1 hr, then decrease by 3 U/kg/hr |

ML Smith & LE Wheeler, Am J Health-System Pharmacy 2010; 67(5):371

## College of American Pathologists

### Consensus Recommendations: Monitoring by Target Concentration

1. The target concentration strategy may be used to monitor unfractionated heparin therapy (Level 1).
2. The heparin used for the calibration of the assay should be linked to an approved international standard heparin, preferably the WHO standard (Level 2).
3. Monitoring heparin by target concentration should be considered when
   1. Heparin dose is elevated (>50%) above that needed to produce the expected activated partial thromboplastin time (aPTT) effect, particularly when treating venous thromboembolic disease (Level 1).
   2. The baseline aPTT (or activated clotting time) is prolonged by lupus anticoagulants, contact factor deficiency, or oral anticoagulant effect. The optimal method of monitoring unfractionated heparin in other acquired coagulopathies remains unclear (Level 2).
   3. A non specific (lupus-type) anticoagulant is present even with normal aPTT (Level 3).

Adapted from Olson JD et al. Arch Pathol Lab Med 1998;122:782-798.

## Antifactor Xa heparin Assay: Strengths and Weaknesses

- Chromogenic assay
  - Chromogen substrate specific to Factor Xa
  - Non-clotting assay with or without added AT
  - One or two stage assay

**Chromogenic assay PROS:**
- Not affected by
  - LA or coag factor deficiencies
  - elevated FVIII or Fibrinogen
  - platelet assoc phospholipids (PF4)
- Requires fewer tests and dose adjustments

**Chromogenic assay CONS:**
- Relatively expensive vs. aPTT
- Affected by added & patient's AT level
- Therapeutic effectiveness is relatively unstudied in comparison to PTT
- Resources
- Protocols
- Comfort

## Why do we still use aPTT ?

- Logical appeal of a physiologic measurement
- Introduced 1950s, accepted test since 1960s
- Clinical satisfaction
- Low cost
- Ease
- Speed/Turnaround
- Lack of a suitable alternative

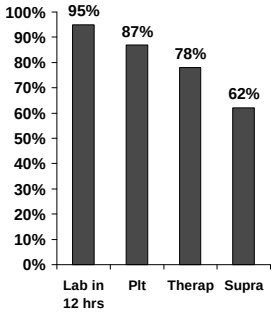
Francis JF et al. Pharmacotherapy 2004;24(8 Pt 2):108S–119S.

## Audience Polling:

- FR is a 62 year old male (80kg) presenting with suspected PE. He is started on weight based UFH infusion therapy.
- What percent of North American hospitals would be able to provide an aPTT result in <12 hours?
  - A. 20%
  - B. 40%
  - C. 60%
  - D. 80%
  - E. 95%

## Heparin Monitoring and Patient Safety

- "Real world" setting.
- 140 US and Canadian hospitals.
  - 30% teaching, 70 community
- 3431 inpatients receiving heparin ≥ 3 days.
- Endpoints
  - Heparin Dose.
  - Monitoring within 12 hours of the first dose aPTT, Anti-Xa.
  - Therapeutic value within 24 hours.
  - ≤ 1 supratherapeutic levels with 72 hours.
  - Platelet count with 72 hours.



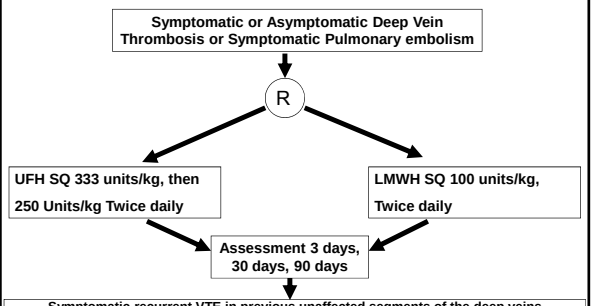

Valenstein PN. Arch Pathol Lab Med 2004;128:397-402

## Audience Polling:

- FR is a 62 year old male (80kg) presenting in the ED with suspected PE.
- The most important step in determining this patient's outcome is:

- A. Lab testing (d-Dimer, troponin, BNP, pro-BNP, echocardiography) for screening, diagnosis and risk stratification.
- B. Confirming PE diagnosis with an objective study (CT, MRI, lung perfusion scan).
- C. Early initiation of parenteral anticoagulation.
- D. Achieving a therapeutic aPTT within 24 hours with IV UFH.

## FIDO STUDY DESIGN




Kearon C et al. JAMA 2006;296:935-942

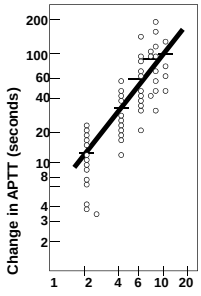
## FIDO Caveats

- Trial lacked statistical power.
- Targeted enrollment would not have proven noninferiority.
- Lower (3%-4%) than predicted (6%) frequency of VTE recurrence in both trial groups.
- Only 55% of patients reached and maintained a therapeutic target INR range of 2.0 to 3.0.
- Over 80% of the patients presented with DVT alone.
- The study consisted primarily of outpatients.
- Alternative FDA approved regimens.
- Patients with VTE who require UFH infusion and in whom intravenous access proves difficult.
- In resource-poor settings, with no anticoagulant other than UFH, and where intravenous infusions is impractical.

SZ Goldhaber. Ann Intern Med 2006;145(12):929-930.

## Nomograms

- Multiple regression developed to explain variance in UFH doses.
- Whole body weight, sex, symptom onset, smoking.[1]
  - $R^2 = 0.78$
- Weight, sex, age, clinical diagnosis, and Thromboplastin reagent.[2]
  - $R^2 = 0.52$ For Age and Weight
  - $R^2 = 0.43$ For Weight (DVT)
  - $R^2 = 0.20$ For Weight (CAD)




1. Cipolle RJ et al. Clin Pharmacol Ther 1981;29(1):387-393.
2. White RH et al. Arch Intern Med 1997;157:2468-2472.

## Outcomes: Failure to Achieve Adequate aPTT

| Study | Diagnosis | Outcome | Relative Risk |
|---|---|---|---|
| Hull R, et al (NEJM 1986) | DVT | Recurrent VTE | 15.0 |
| Basu D, et al. (NEJM 1972) | DVT | Recurrent VTE | 10.7 |
| Turpie AG, et al (NEJM 1989) | AMI | LV thrombus | 22.2 |
| Kaplan K, et al. (Am J Cardiol 1987) | AMI | Recurrent MI, Ischemia | 6.0 |
| Camilleri, et al. (Arch Mal Coeur Vaiss) | AMI | Recurrent MI, Ischemia | 13.3 |

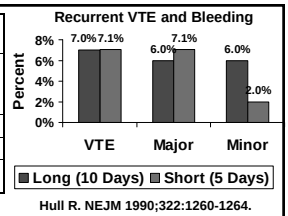
Eikelboom JW et al. Thromb Haemost 2006:547-552

## Heparin Studies in VTE

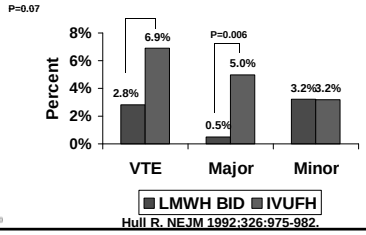
| Author | Title |
|---|---|
| Hull RD et al NEJM 186 | Continuous Intravenous Heparin Compared with Intermittent Subcutaneous Heparin in the Initial Treatment of Proximal Thrombosis |
| Hull RD et al NEM 1990 | Heparin for 5 Days as Compared with 10 Days in the Initial Treatment of Proximal Venous Thrombosis |
| Hull RD et al | Subcutaneous Low-Molecular-Weight Heparin Compared with Continuous Intravenous Heparin in the Treatment of Proximal-Vein Thrombosis |

| Group | Frequency of Recurrent VTE | | P Value |
|---|---|---|---|
| | aPTT Response < Lower limit | aPTT Response ≥ Lower Limit | |
| SQ | 27.8% | 4.4% | 0.04 |
| IV | 17.6% | 0 % | 0.02 |
| All patients | 24.5% | 1.6% | <0.001 |

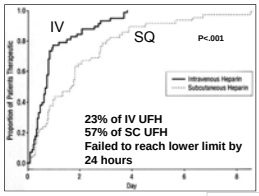
Hull R. NEJM 1986;315:1109-1114.

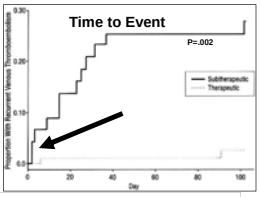



Hull R. NEJM 1990;322:1260-1264.

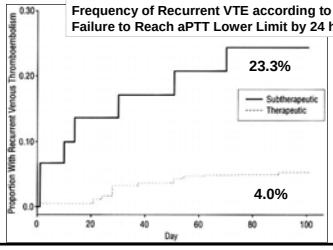



Hull R. NEJM 1992;326:975-982.



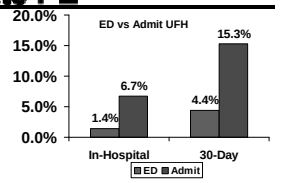

Hull R et al. Arch Intern Med 1997;157:2562-2568.

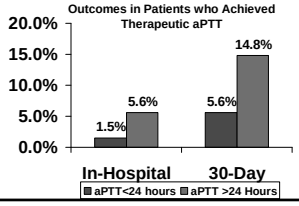



## Early Anticoagulation Reduces Mortality in Acute PE

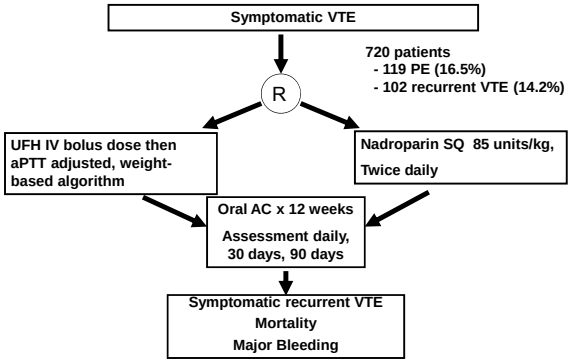
- Single center tertiary care ED.
- 400 adult patients diagnosed with acute PE.
- Primary Endpoints
  - % of patients achieving a therapeutic aPTT with 24 hours.
  - In-hospital and 30 day mortality.

Smith SB et al. CHEST 2010;137(6):1382-1390




## Galilei Study




Galilei Investigators. Arch Intern Med 2004;164:1077-1083.

## Galilei Investigators: UFH Dosing

| Weight | IV Bolus (Units) | SQ Dose (Units) |
|---|---|---|
| < 50kg | 4,000 | 12,500 |
| 50-70kg | 5,000 | 15,000 |
| >70kg | 6,000 | 17,500 |

| Step Dose |
|---|
| 10,000 units |
| 12,500 units |
| 15,000 units |
| 17,500 units |
| 21,250 units |
| 25,000 units |
| 30,000 units |

| aPTT | Regimen |
|---|---|
| <120 | |
| <50 | One step up |
| 50-90 | Same |
| 91-120 | One step down |
| >120 Withhold, perform aPTT after 6 hours, then: | |
| <50 | Same step |
| 50-90 | One step down |
| 91-120 | Two Steps down |
| >120 | Withhold |

Galilei Investigators. Arch Intern Med 2004;164:1077-1083.

## Galilei Investigators: Results

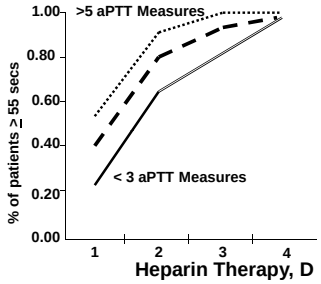
| | UFH (n=360) | LMWH (n=360) |
|---|---|---|
| Recurrent VTE | 15 (4.2%) | 14 (3.9%) |
| Major Bleeding | 4 (1.1) | 3 (0.8) |

| | |
|---|---|
| Mean UFH Dose Day 1 | 36,500±5,300 units |
| Mean Dose Day 2 | 30,500±10,800 units |
| Therapeutic Day 1 | 73.1% |
| Therapeutic Day 2 | 88.1% |
| No dosing changes | 6.4% |
| 1 Dose Change | 9.7% |
| 2 Dose changes | 16.1% |
| >2 Dose changes | 67.7% |

Galilei Investigators. Arch Intern Med 2004;164:1077-1083.

## Challenges to the Effective use of UFH

- Retrospective study (n=311).
  - Stroke, VTE, PAO.
- Major hemorrhage 4.8%.
- 29% with therapeutic aPTT at next measure.
  - 7% therapeutic for 4 sequential days.
- 54% had at least 1 interruption in UFH infusion.
- 20% met current guidelines for VTE.




Hylek E. et al. Arch Intern Med.2003;163:621-627.

## Conclusions

- Existing coagulation tests have limitations.
  - "…this is as good as it gets."
- Following National consensus statements and guidelines will reduce variability.
- Limitations with fixed dose, unmonitored UFH regimens.
- Clinical trials support;
  - Early initiation, rapid achievement of therapeutic levels.
- Therapeutic monitoring provides ranges
  - Target or goal to shoot for.
  - Improve outcomes

## Therapeutic Debate: Is Anticoagulation Intensity Monitoring Needed for Therapeutic Heparin?

No

Maureen A. Smythe, Pharm.D., FCCP
Department of Pharmaceutical Services
Beaumont Hospital, Royal Oak, MI
Professor (Clinical), Pharmacy Practice
Wayne State University
Detroit, MI

## Objective

- To critically evaluate the data to support the heparin therapeutic range using the aPTT and the anti-factor Xa level

## Audience Poll

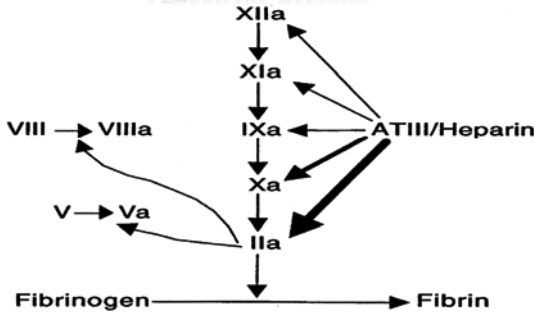
At your institution which of the following best describes how heparin infusion therapy is monitored ?

A. aPTT – range 1.5 – 2.5 x baseline

B. aPTT- range corresponds to heparin anti-Xa level of 0.3 – 0.7 units/ml

C. aPTT – different range than stated in A and B

D. Heparin anti-Xa level




Chest 2001; 119: 64s-94s

## Heterogeneity of Heparin

- molecular weight ranges from 5,000 – 30,000
- only 1/3 of molecules have AT III activity
- anticoagulant activity influenced by chain length
- clearance of heparin influenced by molecular size
- accumulation of lower molecular weight
- binds to many proteins, concentrations of these proteins vary

## History of the aPTT Therapeutic Range

- Prospective trial of value of monitoring heparin infusion therapy ( 234 patients)
- Adjusted to maintain aPTT 1.5 – 2.5 control
- mean aPTT lower in those with recurrence (n =5) however mean aPTT in first 24 hours was sub-therapeutic in both groups

New Engl J Med 1972; 287:324-327

## History of the aPTT Therapeutic Range

- 1977 – Chiu et al.
- rabbit model of thrombosis
- found marked prevention of thrombus extension with heparin levels of 0.4 – 0.5 u/ml by protamine sulfate titration
- Some prevention of thrombus extension with heparin level of 0.2 u/ml (aPTT ratio of 1.5 x baseline)
- Bleeding increased with increasing heparin level

Blood 1977; 49(2): 171-184.

## aPTT Reagent Sensitivity Comparison

| | Actin FSL | Actin FS | Actin | Pathrombin SL |
|---|---|---|---|---|
| Overall Sensitivity to F IX, XI, XII | | | | |
| Heparin sensitivity | | | | |
| Lupus anticoagulant sensitivity | | | | |

Extremely Sensitive | Highly Sensitive | Sensitive | Somewhat Sensitive

## Many Factors affect aPTT!

**Pre-Analytic Variables**
- Sample timing
- Site of sample
- Concentration of citrate
- Sample handling
  - Centrifugation
  - Processing time

**Analytic Variables**
- aPTT reagent
- Laboratory instrument

**Other Variables**
- Weight, age, gender
- Clotting factor deficiencies
- ↑ fibrinogen and factor VIII
- AT deficiency
- Liver disease
- Warfarin
- Lupus anticoagulants
- Specific factor inhibitors
- DIC

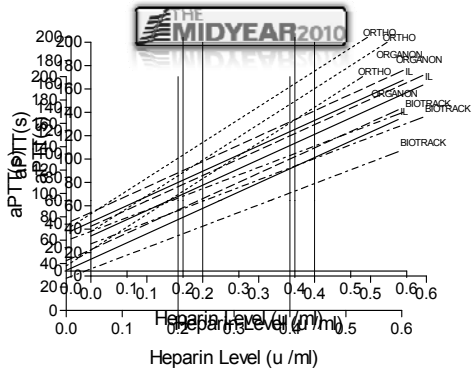
stable aPTTs within a patient can be difficult to achieve

Pharmacotherapy 2004; 24 (8 Pt 2): 108s-119s
Arch Pathol Lab Med 1998; 122: 782-798

## ACCP Recommendations: Heparin Monitoring

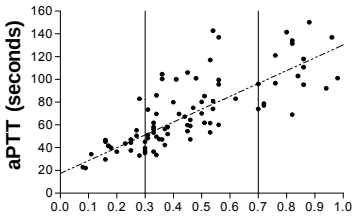
| Time-Line | Recommendations – aPTT |
|---|---|
| 1986 | 1.5 – 2 x control, Grade A |
| 1989 | 1.5 – 2 x control, Grade A |
| 1992 | 1.5 – 2.5 x control, Grade A |
| 1995 | heparin level of 0.2 – 0.4 units/ml, Grade A |
| 1998 | heparin level of 0.2 – 0.4 units/ml PST or 0.3 – 0.6 units/ml anti-factor Xa, Grade 1A |
| 2001 | heparin level of 0.2 – 0.4 units/ml PST or 0.3 – 0.6 IU/ml by anti-Xa, Grade 1C+ |
| 2004 | heparin level of 0.3 – 0.7 units/ml anti-factor Xa, Grade 1C+ |
| 2008 | heparin level of 0.3 – 0.7 units/ml anti-factor Xa, Grade 1C |

PST = protamine sulfate titration




Adapted from Ann Int Med 1993; 119; 104-109

## Establishing a Heparin Concentration Derived aPTT Therapeutic Range




The aPTT therapeutic range should be adapted to the responsiveness of the reagent & coagulometer used

Chest 2008; 133: 141s-159s

## Patient Case

- FR is a 62 year old male (80kg) hospitalized patient with PE on weight based heparin infusion therapy
- Currently on day 2 of therapy, rate: 1700 units/hour
- aPTT therapeutic range is 42-87 sec. (anti-Xa level of 0.3 – 0-.7 units/ml)
- aPTT returns as 68 seconds, heparin anti-Xa run returns at 0.3 units/ml

## Patient Case

The pharmacist should….

A) Increase the dose of heparin

B) Repeat the anti-Xa level

C) No change in dose

D) Contact pharmacy and lab and tell them the hospital therapeutic range doesn't work

## Anti-factor Xa Levels –Equivalent to 0.2 – 0.4 u/ml by Protamine Titration

| | |
|---|---|
| Levine et al. 1994: | 0.35 – 0.67 u /ml |
| Kitchen et al. 1996: | 0.29 – 0.47 u /ml |
| Baker et al. 1997 | 0.3 – 0.6 u /ml |
| Theaker et al. 1997 | 0. 25 – 0.38 u /ml |
| | 0.28 – 0.49 u /ml |
| | 0.27 – 0.52 u /ml |
| | 0.26 – 0.44 u /ml |
| | 0.33 – 0.45 u /ml |
| | 0.29 – 0.49 u/ml |
| Taylor et al. 1999 | 0.25 – 0.45 u /ml |

Chest 2002; 121 (1): 303-304.

## Are there better tests for heparin monitoring? Anti Xa

**CAP CG2-B and CG2-C 2007 Survey Data**

| Survey | Hep Conc* | Assay | # Labs | Mean | CV | High | Low |
|---|---|---|---|---|---|---|---|
| CG2-12 | 0.25 | 1 | 42 | 0.19 | 26.8 | 0.3 | .07 |
| CG2-12 | 0.25 | 2 | 60 | 0.09 | 51.5 | 0.2 | 0 |
| CG2-07 | 0.3 – 0.7 | 1 | 41 | 0.46 | 21.4 | 0.64 | 0.2 |
| CG2-07 | 0.3 – 0.7 | 2 | 64 | 0.38 | 12.6 | 0.5 | 0.27 |

* units/ml, 1 chromogenic anti-Xa, 2 Diag Stago Rota Anti-Xa,

## Heparin Dosage Adjustment Decisions

Heparin concentration derived aPTT range vs heparin conc.

How often do clinical decisions to adjust heparin based on aPTT results agree with those based on heparin concentrations ?

Answer:
only 47 – 82 % of the time

Am J Clin Pathol; 2001; 115: 148-155, Arch Int Med 1997; 157: 2475-2479, Ann Pharmacother 2003; 37: 794-798

## The Therapeutic Range for Heparin

- ACCP and CAP recommend a heparin concentration derived aPTT therapeutic range of 0.3 – 0.7 u/ml by anti-factor Xa
- data to support the lower limit is based on animal studies, post-hoc & pooled analysis
- studies showing relationship between low aPTT value and VTE recurrence involve initial heparin doses ≤ 30,000 units/day and do not use weight based heparin regimens
- no good data to support relationship between high aPTT and bleeding in VTE
- the recommended range has never been prospectively evaluated

Chest 2004; 126: 401s – 428s, Arch Pathol Lab Med 1998; 122: 782-798

## Excessive Anticoagulation: a reason to monitor?

- Excessive anticoagulation is bad, but doesn't support that monitoring would make a difference
- 13 heparin patients with 2 consecutive elevated aPTTs
  - No outcomes directly linked to excessive UFH alone
  - Were baseline groups really similar?

Arch Int Med 2004; 1557-1560

## Early Anticoagulation Decreases Mortality

- 400 acute PE patients, timing of anticoagulation evaluated in relation to patient outcomes
- Heparin in ED independent predictor of 30 day mortality
- Therapeutic aPTT in 24 hrs not an independent predictor of 30 day mortality
  - Was weight based heparin dosing really used?
  - Different baseline's
  - Those therapeutic within 24 hours more likely to have heparin in ED

Chest 2010; 137:1382-1389

## Do You Need To Monitor UFH ?

- Randomized, open-label, multicenter, noninferiority trial
- 708 pts with acute VTE → weight based SC heparin BID
  → weight based SC LMWH BID
- Pts with Scr > 2.3 mg/dl excluded, no weight exclusion
- Fixed dose UFH: dose 1: 333 units/kg, then 250 units/kg q 12 hrs, not monitored!
- LMWH: dalteparin or enoxaparin 100 IU/kg q 12 hrs

JAMA 2006; 296 (8): 935-942

## Do You Need To Monitor UFH ?

- Heparins for at least 5 days & until INR > 2 x 2 days
- Warfarin started on day one
- UFH patients: aPTT 6 hrs post dose on day 3
- Recurrent VTE and major bleeding assessed
  - 1˚ efficacy endpoint: recurrent VTE at 3 months
  - 1˚ safety endpoint: bleeding within 10 days of randomization
- Sample size: 824 pts to have 95% probability of detecting a 5% ↑ in thrombosis with UFH

JAMA 2006; 296 (8): 935-942

## Do You Need To Monitor UFH?

- Trial stopped early
- 68% outpatients at diagnosis
- In UFH group none of VTE recurrences were in those with aPTT < 60 seconds day 3
- Recurrent VTE within 10 days: 1 in UFH and 2 in LMWH
- 121 patients with aPTT > 85 seconds; no major bleeding

| | Heparin N = 345 | LMWH N = 352 |
|---|---|---|
| duration | 6.3 days | 7.1 days |
| Recurrent VTE | 3.8% | 3.4% |
| Major Bleeding | 1.1% | 1.4% |
| Death (3 months) | 5.2% | 6.3% |

JAMA 2006; 296 (8): 935-942

* None of above differences significant

## Patient Case

- FR is a 62 year old male (80kg) hospitalized patient with PE on weight based heparin infusion therapy
- Currently on day 2 of therapy, rate: 1700 units/hour
- aPTT therapeutic range is 42-87 sec. (anti-Xa level of 0.3 – 0-.7 units/ml)
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## Patient Case

The pharmacist should….

A) Increase the dose of heparin

B) Repeat the anti-Xa level

C) No change in dose

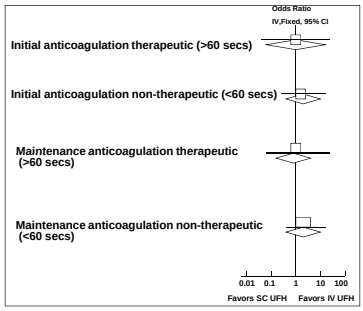
D) Contact pharmacy and lab and tell them the hospital therapeutic range doesn't work

## Counterpoint

| Outcome | SC UFH | | IV UFH | |
|---|---|---|---|---|
| | Correlation to initial aPTT | Correlation to Maintenance aPTT | Correlation to initial aPTT | Correlation to Maintenance aPTT |
| Recurrent DVT at 3 months | NS | NA | NS | NA |
| New PE during UFH treatment | NS | NS | NS | NS |
| DVT Resolution at end of UFH treatment | NS | P<0.0001 | NS | p-=0.0268 |
| Major Bleeding During UFH treatment | NS | NS | NS | NS |
| Minor Bleeding during UFH Treatment | P<0.001 | P=0.0132 | P=0.0023 | NS |

Vardi M et al. Thromb Haemost 2009;102:879-886

## Counterpoint




From Vardi M et al. Thromb Haemost 2009;102:879-886

## EMPEROR Registry

- **Two independent studies reported an increase in mortality in patients where therapeutic anticoagulation was delayed.**
- **Outcomes study in patients diagnosed with acute PE**
- **n=1,880 patients**
- **All cause in-hospital mortality 3.4%**
- **All cause 30 day mortality 5.4%**
- **Therapeutic anticoagulation started in the ED in 84% patients.**
- **In 60% of fatal cases therapeutic anticoagulation was never achieved.**

Kline J, et al. In press. J Amer Coll Card

## ACCP Levels of Evidence

| Grade of Recommendation | Benefit vs Risk and Burdens | Methodologic Quality of Evidence |
|---|---|---|
| **Grade 1A** Strong recommendation, high-quality evidence. | Desirable effects clearly outweigh undesirable effects, or vice versa. | Consistent evidence from RCTs without important limitations or exceptionally strong evidence from observational studies. |
| **Grade 1C** Strong recommendation, low or very low-quality evidence. | Desirable effects clearly outweigh undesirable effects, or vice versa. | Evidence for at least one critical outcome from observational studies, case series, or from RCTs with serious flaws or indirect evidence. |

## ACCP Recommendations VTE Treatment

- Fixed dose SC UFH
  - 333 units/kg followed by 250 units/kg BID, level 1A
- Weight based heparin or 5000 unit bolus& 1300 units/hour infusion titrated to aPTT prolongation that = heparin anti-factor Xa level – level 1C

Chest 2008; 133: 454s- 545s

## Heparin Monitoring…

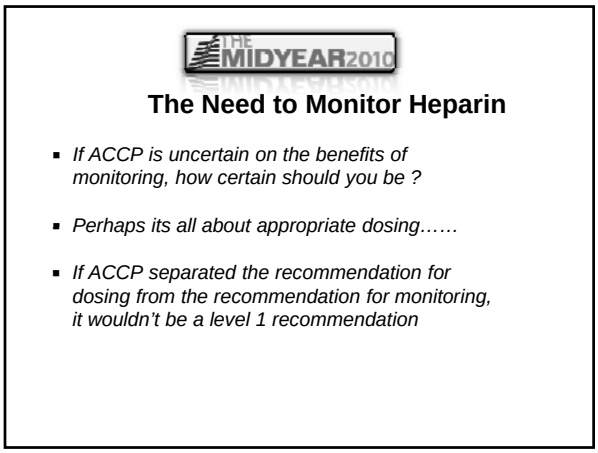
- "it is likely ALTHOUGH UNPROVEN that adjusting the dose of heparin in pts according to the intensity of its anticoagulant effect improves outcomes"[1]
- "no correlation between the "heparin" anticoagulation level and the major clinical outcomes was found…"[2]

Thromb Haemost 2006; 96: 547-52.
Thromb Haemost 2009; 102: 879-886.

## ACCP Recommendations

- "when patients are treated with an initial heparin infusion of at least 1250units/hour (corresponding to 30,000 units/day) or 18 units/kg/hr, it is uncertain if adjustment of heparin dose in response to aPTT or heparin levels improves efficacy or safety"

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



**EDUCATIONAL SESSION ABSTRACT**
**2010 ASHP Midyear Clinical Meeting**
**Anaheim, California**

**239-6**

# Therapeutic Debate: What is the Appropriate Heparin Regimen for DVT Prophylaxis in the Medically Ill, 5000 Units Subcutaneously Q8H or Q12H? Q8H Argument

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Venous thromboembolism (VTE), a serious disease that encompasses both deep-vein thrombosis and pulmonary embolism, continues to be a significant cause of morbidity and mortality in the US. In the absence of prophylaxis, the incidence of objectively confirmed, hospital-acquired DVT is approximately 10–30% among medically ill patients. Studies in acutely ill medical patients have demonstrated that VTE prophylaxis with unfractionated heparin (UFH), low-molecular-weight heparin), and fondaparinux can reduce the incidence of VTE by approximately 50% without a significant increase in bleeding.

The use of UFH for VTE prophylaxis in medically ill patients remains high. There has been significant controversy over the optimal dosing of UFH for VTE prophylaxis in hospitalized medically ill patients (5000 units twice daily vs. three times daily). The ACCP guidelines do not recommend a specific dosing frequency for UFH, however, current International Union of Angiology guidelines specify a three times daily regimen for medical patients at high-risk of VTE. Trials suggesting a possible benefit of UFH twice-daily in medically ill patients have serious trial design flaws limiting their application in clinical practice. The only well-conducted trials of twice daily UFH in medical ill patients demonstrate a non-significant difference between UFH and no prophylaxis. To the contrary, UFH three times daily has consistently demonstrated a significant reduction in VTE events in medically ill patients. Therefore, when UFH is used for VTE prophylaxis in medically ill patients, a three times daily regimen should be utilized.

# Therapeutic Debate: What is the Appropriate Heparin Regimen for DVT Prophylaxis in the Medically Ill, 5000 Units Subcutaneously Q8H or Q12H? Q8H Argument

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## Relevant Disclosures

- Consulting fees / honoraria: None
- Speaker's bureau: None
- Ownership / partnership / principal: None
- Research grants: None
- Salary: None

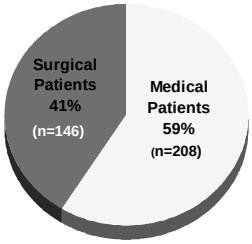
## Risk Factors for VTE
### ACCP - CHEST 2008

- Increasing age
- Prolonged Immobility, stroke, paralysis
- Previous VTE
- Cancer and its treatment
- Major surgery (abdomen, pelvis)
- Trauma
- Obesity
- Varicose veins
- Cardiac dysfunction
- Central venous catheters
- Inflammatory bowel disease
- Nephrotic syndrome
- Pregnancy
- Estrogen use
- Smoking

Geerts WH. *Chest*. 2008;133(suppl):381S-453S.

## VTE Is Most Common In Patients Hospitalized for Medical Illness

DVT, PE, or Both in Hospitalized Patients

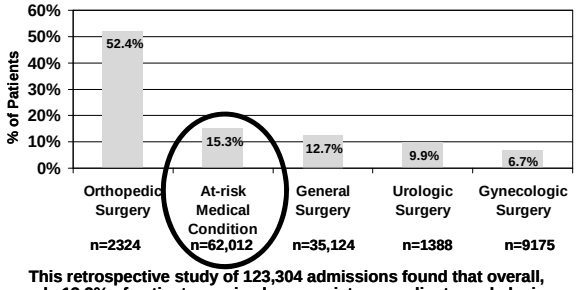



Surgical patients included those receiving general, orthopedic, thoracic, or cardiac surgery services.

Medical patients included those receiving general medicine or medical oncology services.

Goldhaber SZ et al. *Chest* 2000;118:1680-1684.

## Compliance With ACCP Prophylaxis Guidelines Is Low in All Patient Groups




**This retrospective study of 123,304 admissions found that overall, only 13.3% of patients received appropriate, compliant prophylaxis.**

Yu H-T et al. *Am J Health-Syst Pharm*. 2007;64:69-76.
Geerts WH et al. *Chest*. 2001;119:123S-175S.

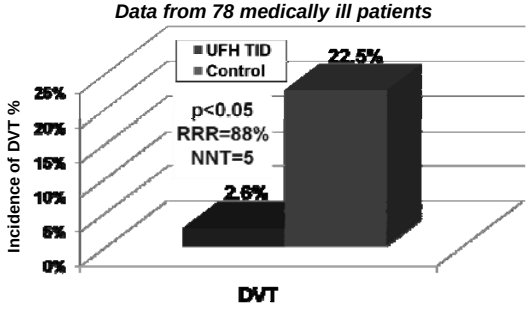
## UFH Three Times Daily
### Prophylaxis in Medically Ill Patients

- UFH 5,000 tid vs. Control
  - Elective surgery (n=226)
  - Hip fracture surgery (n=46)
  - Medically ill (n=78)
- All patients were over 40 years old
- DVT detected by $^{125}$I – Fibrinogen scanning

Gallus AS, et al. *N Engl J Med* 1973;288:545-551.

## UFH Three Times Daily
### Prophylaxis in Medically Ill Patients

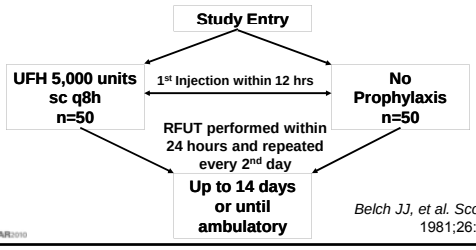
*Data from 78 medically ill patients*




Gallus AS, et al. *N Engl J Med* 1973;288:545-551.

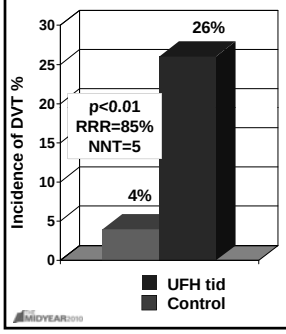
## UFH Three Times Daily
### Prophylaxis in Medically Ill Patients

- **Objective: To determine if low-dose UFH reduces the frequency of DVT in medical patients**
- **Patients 40-80 years old with HF and/or chest infection**




*Belch JJ, et al. Scott Med J* 1981;26:115-117.

## UFH Three Times Daily
### Prophylaxis in Medically Ill Patients



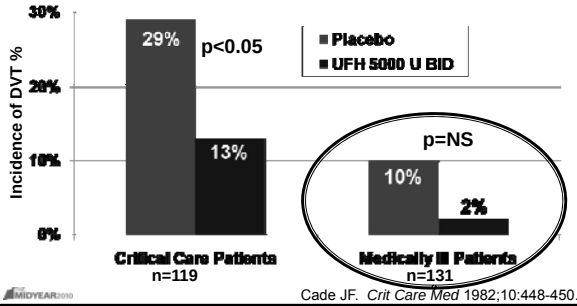

- **Bruising: 20% of patients receiving UFH tid**
- **No difference in hemoglobin from entry to completion of the trial in the heparin group**

Belch JJ, et al. *Scott Med J* 1981;26:115-117.

## UFH Twice Daily
### Prophylaxis In Medically Ill Patients

*Randomized double-blinded study*

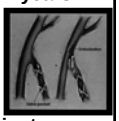
**DVT identified by $^{125}$I-fibrinogen scanning**




Cade JF. *Crit Care Med* 1982;10:448-450.

## UFH Twice Daily vs. Control
### *Heparin Prophylaxis Study Group*

- **19,751 patients screened at 6 hospitals over 4 years (11,693 were randomized)**
  - **n = 5,776 randomized UFH 5,000 SC BID**
  - **n = 5,917 randomized to control group**

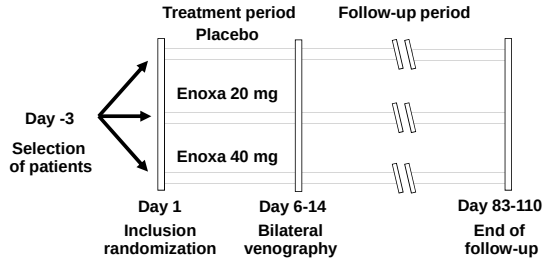


- **Post-mortem examinations for evaluable patients:**
  - **63.8% of UFH patients (n = 194)**
  - **56.8% of control patients (n =189)**

**No significant difference between UFH or placebo upon necropsy in the occurrence of either PE (primary endpoint), 7.7% vs. 8.5% or VTE, 49% vs. 49.2%**

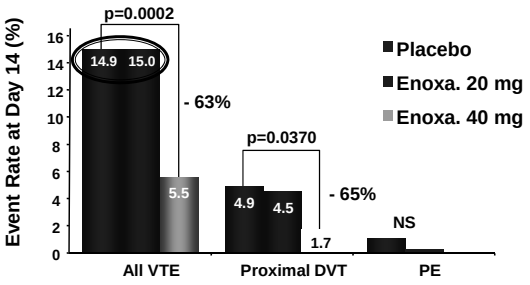
Gårdlund B. *Lancet* 1996;347:1357-61.

## MEDENOX Study Design




Samama M et al. *N Engl J Med* 1999;341:793-800.

## MEDENOX Study Results

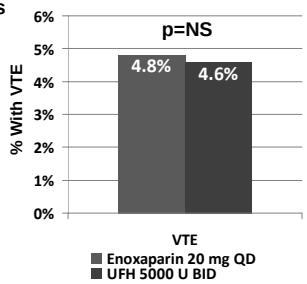



Samama M et al. *N Engl J Med* 1999;341:793-800.

## UFH Twice Daily vs. Enoxaparin

***Enoxaparin in Medicine Study Group***

- 439 Medically ill patients
  - Age 83 years
  - Heart failure = 19.6%
  - Chest infection = 24.4%
  - Ischemic stroke = 8.7%
  - Cancer 6.8%
- Parallel group study
  - Enoxaparin 20 mg QD
  - UFH 5000 U BID
- Results
  - Difference: p=NS
  - Equivalents: p=0.0005




Bergma J-F, et al. *Thromb Haemost* 1996;76:529-534.

## Low Dose UFH: BID vs. TID
## Meta-Analysis in Medically Ill Patients

| | LDUH BID | LDUH TID | *p-value* |
|---|---|---|---|
| **VTE Events*** | | | |
| DVT | 5.40 | 3.01 | *0.42* |
| PE | 1.50 | 0.53 | *0.09* |
| DVT/PE | 5.41 | 3.46 | *0.87* |
| Proximal+PE | 2.34 | 0.86 | *0.05* |
| | | | NNT=68 |
| **Bleeding Events*** | | | |
| Minor bleeding | 0.18 | 0.14 | *0.83* |
| Major bleeding | 0.35 | 0.96 | *< 0.001* |
| | | | NNH=164 |

* = events per 1000 patient days

**n = 7978 patients in 12 randomized trials comparing low dose UFH bid or tid to placebo or control**

King CS et al. *Chest* 2007;131:507-516.

## Guideline Recommendations

- ACCP remains noncommittal
  - 2001 specific for BID or TID
  - 2004 and 2008 simply state LDUH
- International Consensus Statement (Guidelines According to Scientific Evidence)
  - "For acutely ill medical patients prophylaxis with ***LDUH 5000 IU TID*** or LMWH are ***Grade A recommendations***."

Geerts WH, et al. *Chest* 2001;119:132S-175S.
Geerts WH, et al. *Chest* 2004;126:338S-400S.
Geerts WH, et al. *Chest* 2008;133:381S-453S.
Nicholaides AN, et al. *Int Angiol* 2006;25:101-161.

## Audience Response Question

**Which one of the following statements is TRUE regarding UFH for VTE prophylaxis in medically ill patients?**

| | |
|---|---|
| Green | UFH 5000 U twice daily has demonstrated equal efficacy to UFH 5000 U three time daily in trials |
| Red | UFH 5000 U three times daily has consistently demonstrated benefit over no prophylaxis |
| Yellow | UFH 5000 U twice daily has consistently demonstrated benefit over no prophylaxis |
| Blue | All of the above |

## Audience Response Question

**Which one of the following statements is TRUE regarding Dr. Nutescu's motivation to use UFH twice daily for VTE prophylaxis in medically ill patients?**

| | |
|---|---|
| Green | Dr. Nutescu is on the payroll of the nursing union and wants to be sure less injections are given. |
| Red | Dr. Nutescu does not really care about her patients and likes to watch a PE in progress. |
| Yellow | Dr. Nutescu likes to see how much she can twist the data and manipulate an audience. |
| Blue | Dr. Nutescu is just a hag with nothing better to do than argue ridiculous issues. |

# Rebuttal Slides

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## VTE Prevention in Medically Ill Patients
### *UFH 5000 units twice daily - Evidence*

| Trial | N | Outcome | UFH | Control | p-value |
|---|---|---|---|---|---|
| Cade (1982) | 131 | DVT | 2% | 10% | NS |
| Gardlund (1996) | 11,693 | VTE | 49% | 49% | NS |
| Halkin (1982) | 1102 | Mortality | 7.8% | 10.9% | <0.05 |
| Ibarra-Perez (1988) | 192 | DVT | 2.6% | 26.1% | <0.05 |

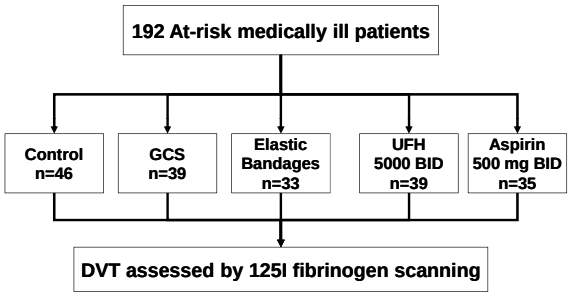
Cade JF. *Crit Care Med* 1982;10:448-50.
Gårdlund B. *Lancet* 1996;347:1357-61.
Halkin H, et al. *Ann Intern Med* 1982;96:561-65.
Ibarra-Perez C, et al. *Angiology* 1988;39:505-13.

## UFH Twice Daily
### Prophylaxis in Medically Ill Patients

- UFH 5000 BID vs. no prophylaxis
- Primary outcome of mortality
  - 7.8% with UFH BID vs. 10.9% with nothing; p=0.025
- Study design issues
  - Open label trial
  - Randomized by medical record number
    - Even numbers given UFH
    - Odd numbers given nothing
  - Physician determined contraindications
    - 25% with nothing and 32% with UFH (p<0.05)
    - Mortality in excluded patients
      - 12.7% with nothing vs. 14.4% with UFH (p<0.05)
- "Randomization was based on the hospital record number and therefore was subject to recruitment bias."

Halkin H, et al. *Ann Intern Med* 1982;96:561-565.
Geerts WH, et al. *Chest* 2004;126:338S-400S.

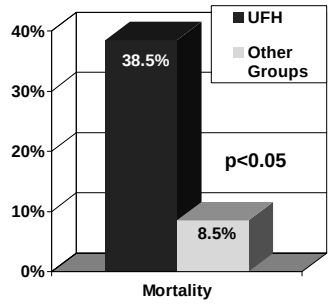
## UFH Twice Daily
### Prophylaxis in Medically Ill Patients




Ibarra-Pérez C, et al. *Angiology* 1988;39:505-513.

## UFH Twice Daily
### Prophylaxis in Medically Ill Patients

- Incidence of DVT
  - Control = 26% (12/46)
  - GCS = 0% (0/39)
    - p<0.0003 vs. control
  - EB = 12% (4/33)
    - p=0.10 vs. control
  - UFH BID = 2.6% (1/39)
    - p<0.0022 vs. control
  - Aspirin = 5.7% (2/35)
    - p<0.0148 vs. control
- No differences between any of the active groups




Ibarra-Pérez C, et al. *Angiology* 1988;39:505-513.

## UFH BID vs. TID Meta-Analysis

- Variety of different methods for detecting DVT
- Variety of different methods for defining bleeding
- Used all of the Cade and colleagues data
- Most of BID data from Gårdlund study
  - Sensitivity analysis when removed (BID vs. TID)
    - DVT: 6.71% vs. 3.01%; p=0.004; NNT=27
    - DVT+PE: 6.71% vs. 3.46%; p=0.0029; NNT=31
    - Major Bleeding: 0.88% vs. 0.96%; p=0.71; NNH=1250
- NOT A SINGLE HEAD-TO-HEAD STUDY IN THE ANALYSIS
  - Some studies vs. control or placebo
  - Some studies vs. other active treatments

King CS et al. *Chest* 2007;131:507-516.

# BID vs TID Heparin in Medical Patients: Searching for the "Truth"

Edith A. Nutescu, Pharm.D., FCCP.
Clinical Professor
Department of Pharmacy Practice & Center for Pharmacoeconomic Research
The University of Illinois at Chicago
College of Pharmacy & Medical Center

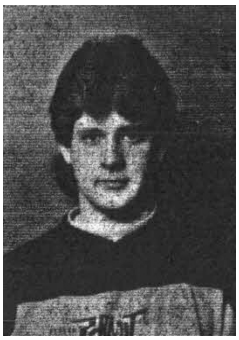
## Patient Case 1

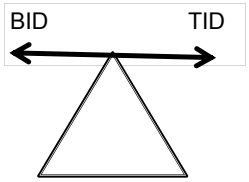
- 83 y/o female admitted with urosepsis
  - Wt 47Kg, Ht 5'6"
  - PMH: PUD, HTN, DJD, CVA (L side paresis)
  - Meds: Pantoprazole, Metoprolol, Salsalate, Tramadol, Clopidogrel
  - Labs: H/H: 9.1/29 , CrCL 38mL/min
  - She lives in assisted living; has limited mobility due to her hx of CVA

## Patient Case 1

- The following is an appropriate VTE prophylaxis option for this patient:
- A. UFH 5,000 units SC bid
- B. UFH 5,000 units SC tid
- C. Generic Enoxaparin 40mg SC daily
- D. None of the above
- E. Unsure

## Dr. Dobesh's "Thoughts"



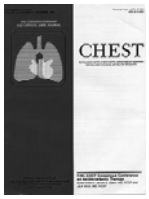



## Outline

- Current State of The Art
- UFH bid versus placebo
- UFH tid versus placebo
- UFH bid versus LMWH
- UFH tid versus LMWH
- Evidence based to Practice Points

## ACCP Recommendations

- **In acutely ill medical patients** who have been admitted to the hospital with
  - congestive heart failure
  - severe respiratory disease
  - confined to bed and have one or more additional risk factors
    - active cancer
    - previous VTE
    - sepsis
    - acute neurological disease
    - inflammatory bowel disease
- **Recommend prophylaxis**
  - LDUH (Grade 1A) or
  - LMWH (Grade 1A) or
  - Fondaparinux (Grade 1A)



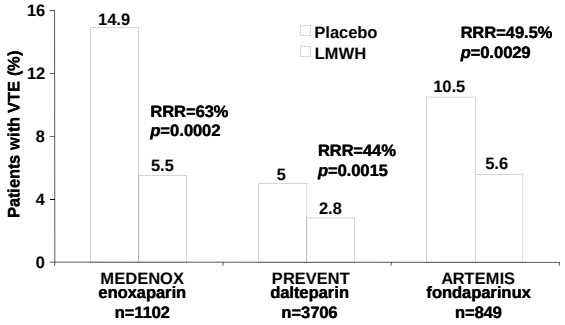

Geerts WH. *Chest*. 2008; 133;381-453

## What is the Risk of VTE in Hospitalized Patients ?

| Patient Group | DVT Prevalence, % |
|---|---|
| Medical patients | 10-20 |
| General surgery | 15-40 |
| Major gynecologic surgery | 15-40 |
| Major urologic surgery | 15-40 |
| Neurosurgery | 15-40 |
| Stroke | 20-50 |
| Hip or knee arthroplasty, Hip fracture surgery | 40-60 |
| Major trauma | 40-80 |
| Spinal cord injury | 60-80 |
| Critical care patients | 10-80 |

Geerts WH. *Chest.* 2008; 133;381-453

## VTE Prophylaxis: Medical Patients
### *LMWH vs Placebo Trials*




Samama MM, et al. *N Engl J Med.* 1999;341:793-800.
Leizorovicz A, et al. *Circulation.* 2004;110:874-879.
Cohen AT, et al. *BMJ.* 2006;332:325-329.

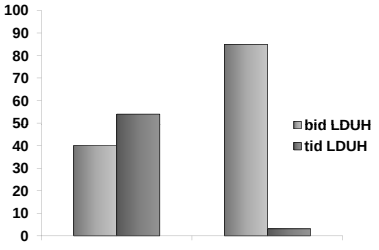
8

## Levels of Thromboembolism Risk & Recommended Thromboprophylaxis in Hospitalized Patients

| Levels of Risk | Approximate DVT Risk Without Thromboprophylaxis, %† | Suggested Thromboprophylaxis Options‡ |
|---|---|---|
| Low risk | | |
| Minor surgery in mobile patients<br>Medical patients who are fully mobile | < 10 | No specific thromboprophylaxis<br>Early and "aggressive" ambulation |
| Moderate risk | | |
| Most general, open gynecologic or urologic surgery patients<br>Medical patients, bed rest or sick | 10–40 | LMWH (at recommended doses), LDUH bid or tid, fondaparinux |
| Moderate VTE risk plus high bleeding risk | | Mechanical thromboprophylaxis§ |
| High risk | | |
| Hip or knee arthroplasty, HFS<br>Major trauma, SCI | 40–80 | LMWH (at recommended doses), fondaparinux, oral vitamin K antagonist (INR 2-3) |
| High VTE risk plus high bleeding risk | | Mechanical thromboprophylaxis§ |

Geerts WH. *Chest.* 2008; 133;381-453

## IMPROVE registry
### (International Medical Prevention Registry on Venous Thromboembolism 2007)




IMPROVE
International Medical Prevention Registry on Venous Thromboembolism

Tapson VF, Decousus H, Pini M et al. *Chest.* 2007 132:936–945.

## VTE PROPHYLAXIS: UFH BID vs CONTROL

| Therapy | n | Dx | End Points | Results (%) | | *p*- Value |
|---|---|---|---|---|---|---|
| | | | | UFH | Control | |
| 1. Warlow.,1973 (5000 U bid vs control) | 146 | MI | VTE by RFUT | 3.2 | 17.2 | <0.025 |
| 2. Gelmer, 1980 (5000 U bid vs control) | 104 | AIS | VTE by microspheres | 2 | 23 | < 0.001 |
| 3. Cade, 1982 (5000 U bid vs placebo) | 119 | ICU | VTE by RFUT | 13 | 29 | < 0.05 |
| 4. Halkin, 1982 (5000 U bid vs control) | 1358 | ICU | Mortality | 7.8 | 10.9 | 0.025 |
| 5. Zawilska, 1989 (5000 U bid vs control) | 103 | AMI | VTE by RFUT | 4 | 19 | < 0.05 |
| 6. Gardlund, 1996 (5000 U bid vs control) | 11,693 | Infection | Non fatal VTE | 36 | 61 | 0.0012 |

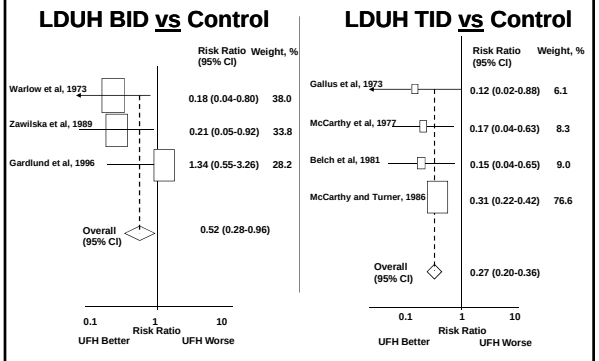
1. A randomized double-blind trial
2. A randomized open-label trial
3. A randomized double-blind trial
4. A non-randomized , open label trial
5. A randomized double-blind trial
6. A randomized, open label, multicenter trial

## VTE PROPHYLAXIS: UFH TID vs CONTROL

| Therapy | n | Dx | End Points | Results (%) | | *p*- Value |
|---|---|---|---|---|---|---|
| | | | | UFH | Control | |
| 1. Gallus, 1973 (5000 U SC tid vs control) | 350 | MI | VTE by RFUT | 2.6 | 22.5 | < 0.05 |
| 2. McCarthy,1977 (5000 U SC tid vs control) | 32 | AIS | VTE by RFUT | 2 | 12 | < 0.01 |
| 3. Belch, 1981 (5000 U SC tid vs control) | 100 | CHF +/- chest Infection | VTE by RFUT | 4 | 26 | < 0.01 |
| 4. McCarthy & Turner, 1986 (5000 U tid vs control) | 305 | AIS | VTE by RFUT | 22.2 | 72.7 | < 0.05 |

1. A randomized, open label trial
2. A randomized, open label trial
3. A randomized , double-blind trial
4. A randomized, open label, multicenter trial

## Meta-Analysis in Medical Patients




Wein L et al. *Arch Intern Med* 2007; 167:1476-1486

## LDUH BID vs TID Meta-Analysis in Medical Patients

**N = 7978 patients in 12 randomized trials comparing LDUH bid or tid to placebo or control**

| | LDUH BID | LDUH TID | *p-value* |
|---|---|---|---|
| **VTE Events*** | | | |
| DVT | 5.40 | 3.01 | *0.42* |
| PE | 1.50 | 0.53 | *0.09* |
| DVT/PE | 5.41 | 3.46 | *0.87* |
| Proximal+PE | 2.34 | 0.86 | *0.05* |
| **Bleeding Events*** | | | |
| Minor bleeding | 0.18 | 0.14 | *0.83* |
| Major bleeding | 0.35 | 0.96 | *< 0.001* |

*** = events per 1000 patient days**

King CS et al. *Chest* 2007; 131:507-516

## VTE PROPHYLAXIS: UFH BID vs LMWH

| Therapy | n | Dx | End Points | Results (%) | | p-Value |
|---|---|---|---|---|---|---|
| | | | | LDUH | LMWH | |
| 1. Turpie, 1992 (Danaparoid 750 U bid) | 87 | AIS | VTE by RFUT (proximal) | 11.9 | 4.4 | › 0.02 |
| 2. Dumas,1994 (Danaparoid 1250 U bid) | 179 | AIS | VTE by RFUT | 19.8 | 14.6 | 0.329 |
| 3. Bergmann & Neuhart, 1996 (Enoxaparin 20 mg daily) | 439 | Acute medical ill (Elderly) | VTE by RFUT | 4.8 | 4.6 | NS |
| 4. Sherman, 2007 (Enoxaparin 40 mg daily) | 1762 | AIS | Composite of asx and sx DVT / PE | 18 | 10 | 0.0001 |

1. A randomized double-blind trial
2. A randomized double-blind trial
3. A randomized double-blind, multicenter
4. A randomized, open label, multicenter trial

## The efficacy and safety of enoxaparin versus unfractionated heparin for the prevention of venous thromboembolism after acute ischaemic stroke (PREVAIL Study): an open-label randomised comparison

| | Enoxaparin (n=666) | Unfractionated heparin (n=669) | Relative risk (95% CI)* | p† | Difference (95% CI) |
|---|---|---|---|---|---|
| VTE | 68 (10%) | 121 (18%) | 0·57 (0·44–0·76) | 0·0001 | −7·9% (−11·6 to −4·2) |
| PE‡ | 1 (<1%) | 6 (1%) | 0·17 (0·02–1·39) | 0·059 | −0·7% (−1·5 to 0·0) |
| Symptomatic VTE | 2 (<1%) | 7 (1%) | 0·29 (0·06–1·38) | 0·096 | −0·7% (−1·6 to 0·1) |
| Symptomatic DVT | 1 (<1%) | 4 (1%) | 0·25 (0·03–2·24) | 0·18 | −0·4% (−1·1 to 0·2) |
| Asymptomatic DVT§ | 66 (10%) | 114 (17%) | 0·57 (0·43–0·75) | <0·0001 | −7·1% (−10·8 to −3·5) |
| All DVT | 67 (10%) | 118 (18%) | 0·57 (0·43–0·75) | <0·0001 | −7·6% (−11·3 to −3·9) |
| Proximal | 30 (5%) | 64 (10%) | 0·47 (0·31–0·72) | 0·0003 | −5·1% (−7·8 to −2·3) |
| Distal | 44 (7%) | 85 (13%) | 0·52 (0·37–0·74) | 0·0002 | −6·1% (−9·2 to −2·9) |
| Proximal and distal¶ | 7 (1%) | 31 (5%) | 0·23 (0·10–0·51) | <0·0001 | −3·6% (−5·4 to −1·8) |

Data are number (%) unless otherwise indicated. DVT=deep vein thrombosis. PE=pulmonary embolism. VTE=venous thromboembolism. The individual numbers of events for each endpoint do not always add up to the total number because patients might have had more than one type of event. *Enoxaparin versus unfractionated heparin. †Adjusted for National Institutes of Health Stroke Scale score stratification for VTE, but unadjusted for other criteria. ‡Three PE events were fatal (one with enoxaparin and two with unfractionated heparin). §Confirmed by ultrasound: five of 66 (8%) enoxaparin, nine of 114 (8%) unfractionated heparin; confirmed by venography: 61/66 (92%) enoxaparin, 104/114 (91%) unfractionated heparin. ¶Events also counted in proximal DVT and distal DVT.

Table 2: Incidence of venous thromboembolic events up to day 14 in the efficacy group

Sherman DG et al., *Lancet* 2007;369:1347-55

## PREVAIL Study: *Safety Outcomes*

| | Enoxaparin (n=877) | Unfractionated heparin (n=872) | Relative risk (95% CI) | p* | Difference (95% CI) |
|---|---|---|---|---|---|
| Bleeding at end of treatment + 48 h | | | | | |
| Total† | 69 (8%) | 70 (8%) | 0·98 (0·71–1·35) | 0·90 | −0·2% (−3·7% to 2·4) |
| Symptomatic intracranial haemorrhage | 4 (1%) | 6 (1%) | 0·66 (0·19–2·34) | 0·55 | −0·2% (−0·9% to 0·5) |
| Death of patient with symptomatic intracranial haemorrhage | 3 (<1%) | 4 (1%) | .. | .. | −0·1% (−0·7% to 0·5) |
| Major extracranial haemorrhage‡ | 7 (1%) | 0 | .. | 0·015 | 0·8% (0·2% to 1·4) |
| Resulting in death | 2 (<1%) | 0 | .. | .. | 0·2% (−0·1% to 0·5) |
| Drop of haemoglobin >30 g/L | 7 (1%) | 0 | .. | .. | 0·8% (0·2% to 1·4) |
| Transfusion of ≥2 units of blood | 5 (1%) | 0 | .. | .. | 0·6% (0·1% to 1·1) |
| Clinically important haemorrhage | 11 (1%) | 6 (1%) | 1·82 (0·68–4·91) | 0·23 | 0·6% (−0·4% to 1·5) |
| Death of patient with clinically important haemorrhage§ | 5 (1%) | 4 (1%) | 1·24 (0·33–4·65) | 1·0 | 0·1% (−0·6% to 0·8) |
| Minor extracranial haemorrhage¶ | 42 (5%) | 48 (6%) | 0·87 (0·58–1·30) | 0·50 | −0·7% (−2·8% to 1·4) |
| All-cause mortality up to day 14 | 48 (6%) | 45 (5%) | 1·12‖ (0·75–1·69) | 0·58** | .. |
| All-cause mortality up to day 90 | 100 (12%) | 103 (12%) | 1·01‖ (0·77–1·33) | 0·96** | .. |

Data are number (%) unless otherwise indicated. *Fisher's exact test if n=5 in one group. †Some patients had more than one bleeding event. ‡There were gastrointestinal bleeding, one surgical stoma of tracheostomy, one duodenal ulcer haemorrhage, one haematuria, and one haemoglobin decrease. §Defined as the composite of major extracranial and symptomatic intracranial haemorrhages. ¶All intracranial haemorrhages were regarded as major. ‖Hazard ratio. **Log-rank test.

Table 5: Safety outcomes

Sherman DG et al., *Lancet* 2007;369:1347-55

## VTE PROPHYLAXIS: UFH TID vs LMWH

| Therapy | n | Dx | End Points | Results (%) | | p-Value |
|---|---|---|---|---|---|---|
| | | | | LDUH | LMWH | |
| 1. Harenberg, 1990 (1,500U LMWH QD) | 166 | Medical | VTE by RFUT | 4.5 | 3.6 | › 0.05 |
| 2. Lechler et al., 1996 (Enoxaprin 40 mg daily) | 959 | Medical | VTE | 1.4 | 0.2 | 0.123 |
| 3. Hillbom et al, 2002 (Enoxaparin 40 mg daily) | 212 | AIS | VTE, death | 49.1 | 37.7 | 0.127 |
| 4. Kleber et al., 2003 (Enoxaparin 40 mg daily) | 451 | CHF & severe resp dz | VTE | 10.4 | 8.4 | 0.146 |
| | | | | | | |

1. A randomized double-blind trial
2. A randomized double-blind, multicenter trial
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## LDUH Dose related with HIT ??

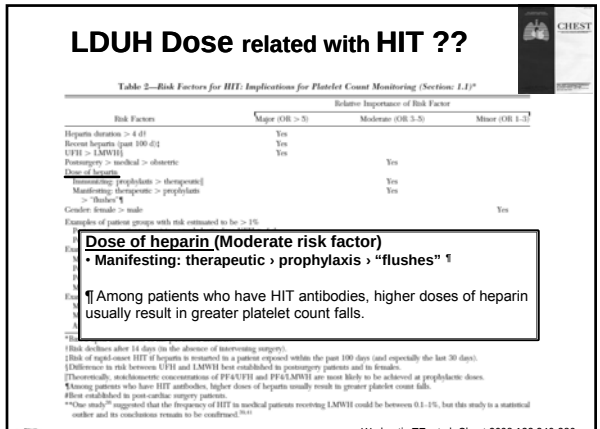


*Table 2—Risk Factors for HIT: Implications for Platelet Count Monitoring (Section: 1.1)**

| Risk Factors | Relative Importance of Risk Factor: Major (OR > 5) | Moderate (OR 5–5) | Minor (OR 1–3) |
|---|---|---|---|
| Heparin duration > 4 d† | Yes | | |
| Recent heparin (past 100 d)‡ | Yes | | |
| UFH > LMWH§ | Yes | | |
| Postsurgery > medical > obstetric | | Yes | |
| Dose of heparin | | | |
| Immunologic [prophylaxis > therapeutic] | | Yes | |
| Manifesting: therapeutic > prophylaxis > "flushes"¶ | | Yes | |
| Gender: female > male | | | Yes |
| Examples of patient groups with risk estimated to be > 1% | | | |

**Dose of heparin (Moderate risk factor)**
- **Manifesting: therapeutic › prophylaxis › "flushes" ¶**

¶ Among patients who have HIT antibodies, higher doses of heparin usually result in greater platelet count falls.

†Risk declines after 14 days (in the absence of intervening surgery).
‡Risk of rapid-onset HIT if heparin is restarted in a patient exposed within the past 100 days (and especially the last 30 days).
§Difference in risk between UFH and LMWH best established in postsurgery patients and in females.
[Theoretically, stoichiometric concentrations of PF4/UFH and PF4/LMWH are most likely to be achieved at prophylactic doses.
¶Among patients who have HIT antibodies, higher doses of heparin usually result in greater platelet count falls.
#Best established in post-cardiac surgery patients.
**One study[20] suggested that the frequency of HIT in medical patients receiving LMWH could be between 0.1–1%, but this study is a statistical outlier and its conclusions remain to be confirmed.[20,41]

Warkentin TE, et al. Chest 2008;133;340-380

## VTE Risk Without Prophylaxis in Surgical Patients & Medical Patients

| | Calf DVT | Proximal DVT | Clinical PE | Fatal PE | VTE Prophylaxis |
|---|---|---|---|---|---|
| Low Risk | 2% | 0.4% | 0.2% | <0.01% | Early mobilization |
| **Moderate Risk** | **10-12%<br>10-19%** | **2-4%** | **1-2%<br>1-1.2%** | **0.1-0.4%<br>0.1-1.2%** | **LDUH(q12),** LMWH, GCS, or IPC |
| Higher Risk | 20-40% | 4-8%<br>**5%** | 2-4% | 0.4-1%<br>**0.1-1.2%** | **LDUH(q8h),** LMWH, or IPC |
| Highest Risk | 40-80% | 10-20% | 4-10% | 0.2-5% | LDUH + IPC/GCS, oral VKA, LMWH, fondaparinux |

Geerts WH. *Chest.* 2008; 133;381-453
Mahan CE et al. *Intern Emerg Med* 2010. 5:299-306.

## Risk Stratification: A Better Approach ?

Comorbid conditions and additional risk factors in medical patients at risk for VTE

| Comorbid conditions in medical patients at risk for VTE | | |
|---|---|---|
| CHF | Respiratory failure | |
| Cancer | Infection | |
| **Additional risk factors for VTE** | | |
| Restricted mobility | Varicose veins | Age >40 years |
| ICU admission | Chronic lung disease | Obesity |
| Inflammatory bowel disease | Surgery | Smoking |
| Prior history of VTE (DVT or PE) | | |

*CHF* congestive heart failure; *ICU* intensive care unit; VTE, venous thromboembolism


Geerts WH. *Chest.* 2008; 133;381-453

## Advantages of LDUH bid vs. tid for VTE Prophylaxis in Medical Patients

| | UFH bid | UFH tid |
|---|---|---|
| **Risk of bleeding** | Lower | Higher |
| **Risk of HIT** | Lower | Higher |
| **Nursing time** | Lower | Higher |
| **Patient acceptance** | Higher | Lower |
| **Cost** | Higher | Lower |

## Patient Case 1

- 83 y/o female admitted with urosepsis
  - Wt 47Kg, Ht 5'6"
  - PMH: PUD, HTN, DJD, CVA (L side paresis)
  - Meds: Pantoprazole, Metoprolol, Salsalate, Tramadol, Clopidogrel
  - Labs: H/H: 9.1/29 , CrCL 38mL/min
  - She lives in assisted living; has limited mobility due to her hx of CVA

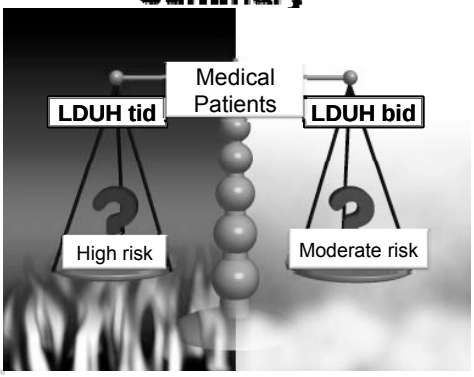
## Patient Case 1

- The Following Is an Appropriate VTE Prophylaxis Option for this patient:
  - A. UFH 5,000 units SC bid
  - B. UFH 5,000 units SC tid
  - C. Generic Enoxaparin 40mg SC daily
  - D. None of the above
  - E. Unsure

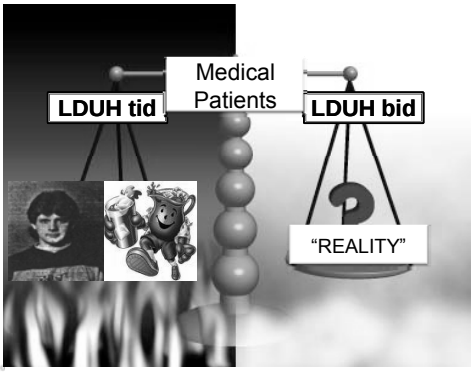
## Conclusion (The "Truth")

- Lack of Head to Head Trials = "Lack of quality evidence"
- Both bid and tid demonstrated efficacy vs placebo
- No "Evidence Based" Guideline Support
  - Beware of "industry funding" for "expert guidelines"
- TJC/CMS VTE core measures do not support tid vs bid
- Unfair to compare data across trials
  - Apples ≠ Oranges
- Recent/Better designed LMWH trials even in higher risk patient (i.e. PREVAIL - stroke) used bid as comparator
  - Why use a suboptimal dose as comparator if tid is "supposedly" the standard ? ☺ Do the Europeans know something we don't ?
- Higher bleeding risk with tid
- Higher Cost and patient discomfort with tid
- How about looking at the patient and risk assessing ?

## Summary




## "KOOL-AID" SUMMARY




## Summary Points

SUBTITLE

No Head to Head Trials
No Guideline Support
Both bid and tid > placebo
Unfair comparison of apples and oranges
Better designed LMWH trials (i.e. PREVAIL) used bid as comparator
Higher bleeding risk
Higher Cost