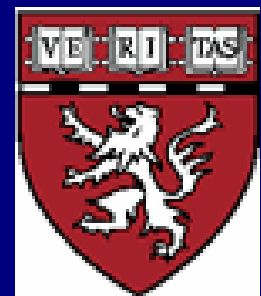


Outpatient Treatment of Venous Thrombosis

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Boston, Massachusetts
February 15, 2007





SWELLING

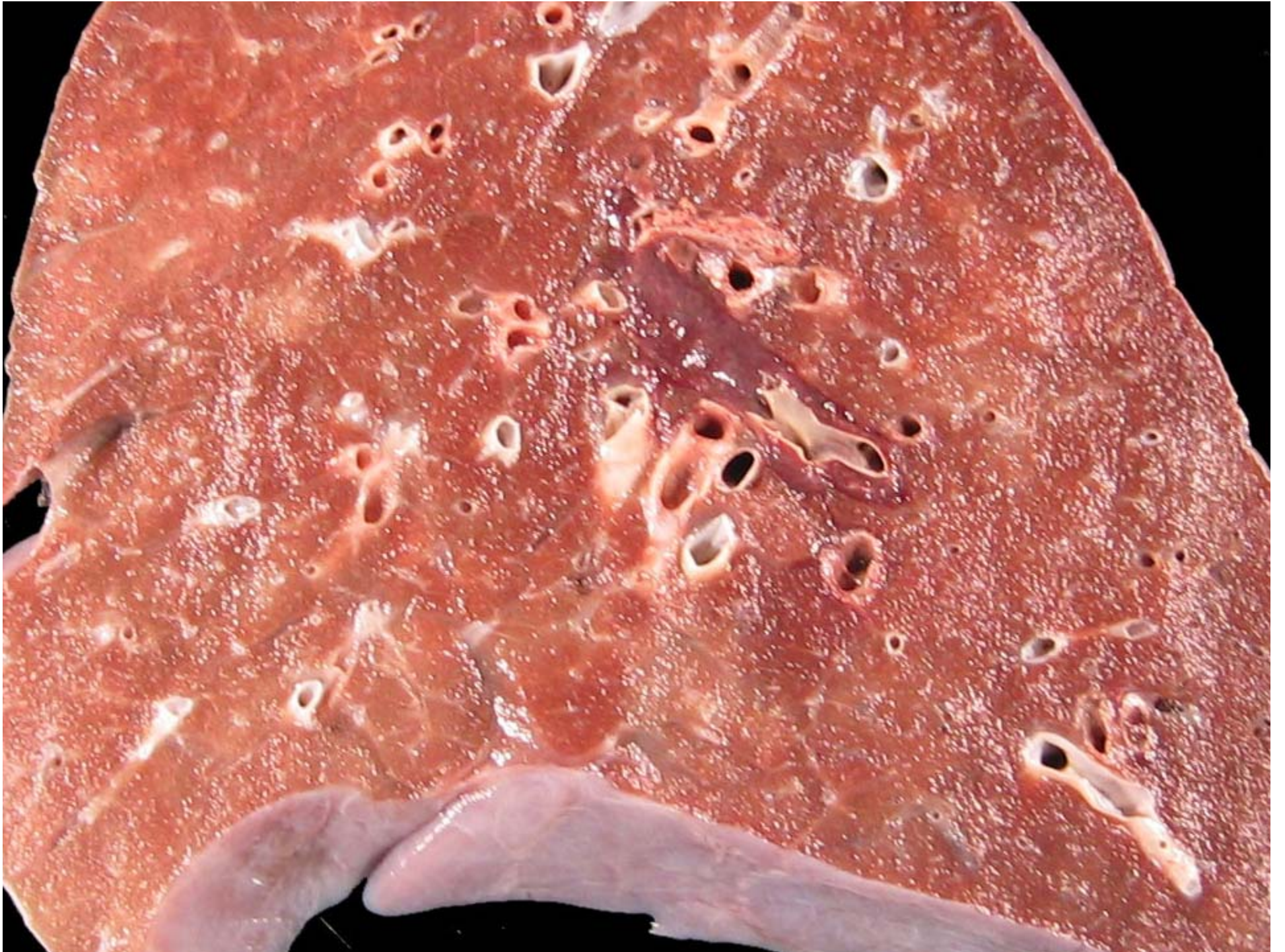
REDNESS

CALF PAIN

**PALPABLE
CORD**

Lower Extremity Ultrasound Positive for DVT





Questions

What is the preferred treatment of patients with acute DVT?

- A. LMWH without warfarin
- B. LMWH as a bridge to therapeutic warfarin
- C. Hospitalization with intravenous UFH as a bridge to therapeutic heparin

DVT Treatment

Goals to prevent

- Thrombus extension
- Thrombus embolization
- Early and late thrombus recurrence
- The post-thrombotic syndrome
- Proximal conversion in the case of calf DVT

Goals using thrombolysis to

- Reestablish venous patency

7th ACCP Conference: Antithrombotic Therapy for VTE

For patients with objectively confirmed DVT

- SC LMWH or IV UFH or SC UFH (Grade 1A)
- Initial treatment for acute DVT for at least 5 days (Grade 1C)
- Initiation of VKA together with LMWH or UFH on 1st day and DC heparin when INR is stable and > 2.0 (Grade 1A)

Buller, H. et al. Chest, September 2004; 126(3):401S

Traditional DVT Treatment

Traditional treatment with intravenous unfractionated heparin (UFH)

- Expensive: in the hospital for at least five days
- Inconvenient: immediate hospitalization and frequent blood draws for monitoring; requires IV lines
- Hard to dose correctly: empiric dosing, weight based nomograms suboptimal
 - Absorption of UFH hindered by its suboptimal bioavailability
 - Typically sub-therapeutic 1st few days of administration
 - Followed by excessive anticoagulation due to subsequent release from fat into plasma
- Labor intensive: sleep deprivation of residents, staff

UFH Too Complicated



aPTT

1.5-2.5s

{UFH}

0.2-0.4IU/mL

anti-Xa

0.3-0.7IU/mL

- Even with corrections, dosing UFH remains a challenge
- >300 laboratory methods in use today
- Result: Immense variation in responsiveness to UFH effect
- Dramatic changes in reagents/ instruments over 25 years

Ann Intern Med. 2003;138:720-723.

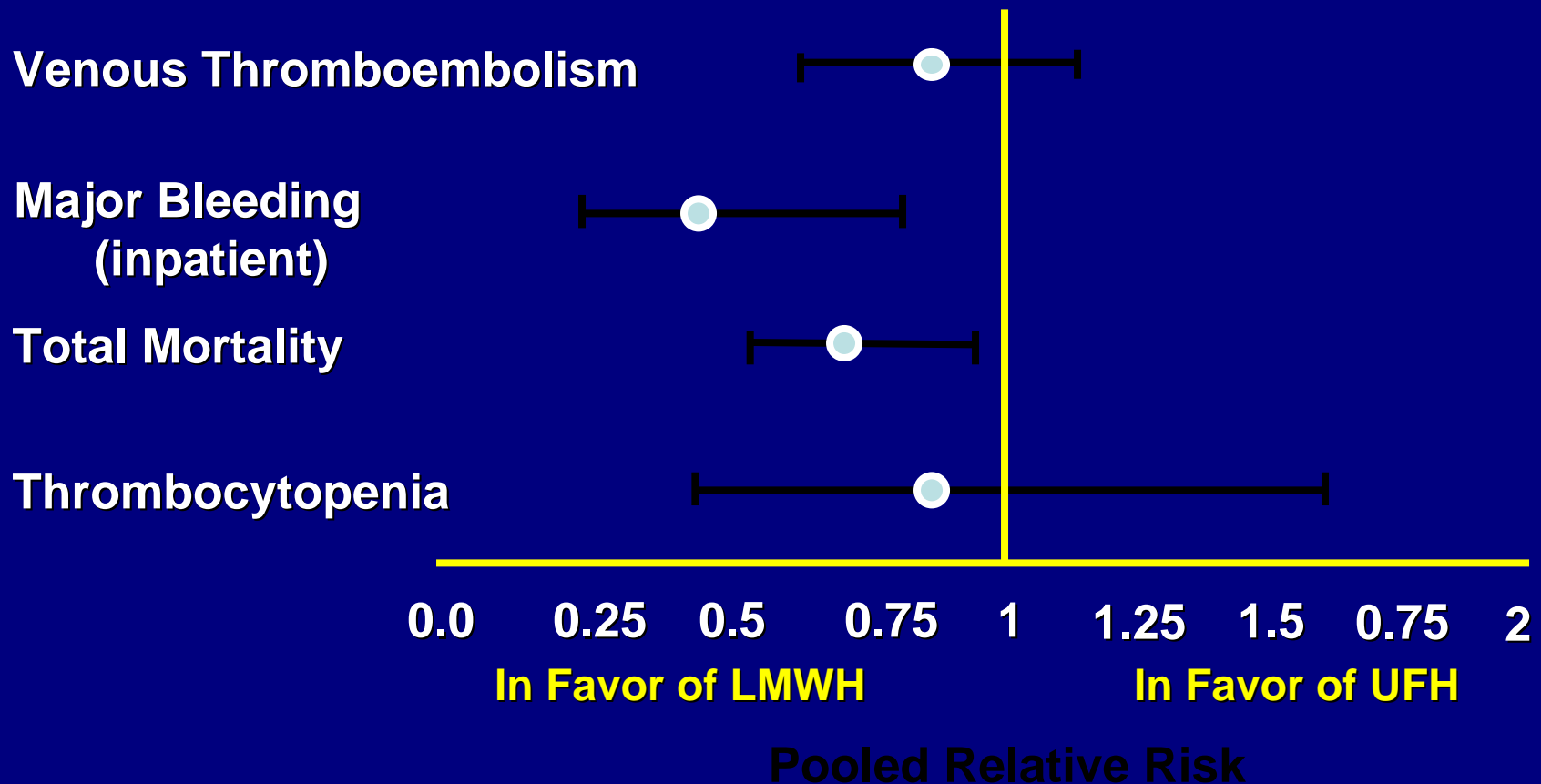
LMWH Easy To Use

Advantages of LMWH

- More predictable anticoagulant response
 - Longer half-life
 - Better bioavailability at lower doses
 - More predictable weight-based dose response
 - Avoids blood tests to adjust heparin
- Hemorrhage less likely
- No need to monitor activated Partial Thromboplastin Time (aPTT)
- SC administration
- Lower incidence of heparin induced thrombocytopenia with thrombosis

LMWH vs. UFH

Acute Treatment of VTE



Arch Intern Med. 2000;160:181-187.

DVT Trials with LMWH

	Levine et al.		Koopman et al.	
	Enoxaparin (n=247)	UFH (n=253)	Nadroparin (n=202)	UFH (n=198)
Recurrent TE	5.3%	6.7%	6.9%	8.6%
Major Bleeding	0.5%	2.0%	2.0%	1.2%
Death	6.9%	8.0%	4.0%	6.3%
Hospital (days)	1.1 days	6.5 days	2.7 days	8.1 days

NEJM 1996;334:677-681. NEJM 1996;334:681-687.

Treatment of DVT: The Evidence for LMWH versus UFH

LMWH dosed by weight has been shown to be at least as effective and safe by 11 randomized controlled trials with follow-up ≥ 3 months

- 30% decreased mortality
- Mortality benefit in patients with cancer, with absolute risk reduction of 0.75%
- 40% decreased major bleeding
- 1/3rd decreased rate of thrombocytopenia
- Less frequent thrombotic events

LMWH was cost-effective versus UFH

- Early discharge or outpatient treatment

Outpatient DVT Treatment

LMWHs

Economic Analysis Results

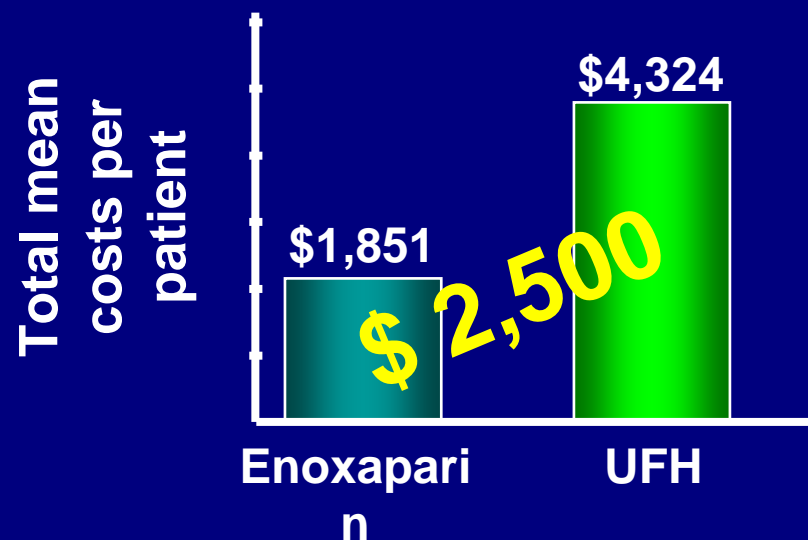
<u>Author</u>	<u>Outpatient Triage</u>
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Levine (1996)	49%
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Koopman (1996)	36%
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Harrison (1998)	79%
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Wells (1998)	83%
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NEJM 1996;334:677-681. NEJM 1996;334:681-687. Arch Intern Med 1998;158:2001. Arch Intern Med 1998;158:1809.

JMCP 2000;6:298-304.

Fondaparinux FDA Approval for Treatment DVT/PE (May 28, 2004)

Clinical Pharmacology: Selective Binder to ATIII

- Does not inactivate thrombin
- No known effect on platelet function
- No affect on bleeding time or fibrinolytic activity

Monitoring: PT, PTT, BT Unsuitable

- Anti-Factor Xa activity assay using Fondaparinux

Overdosage: No Known Antidote

- ↑ hemorrhage risk with ↑ renal impairment

Fondaparinux

Matisse PE

- At least as effective and safe as UFH for initial treatment of PE

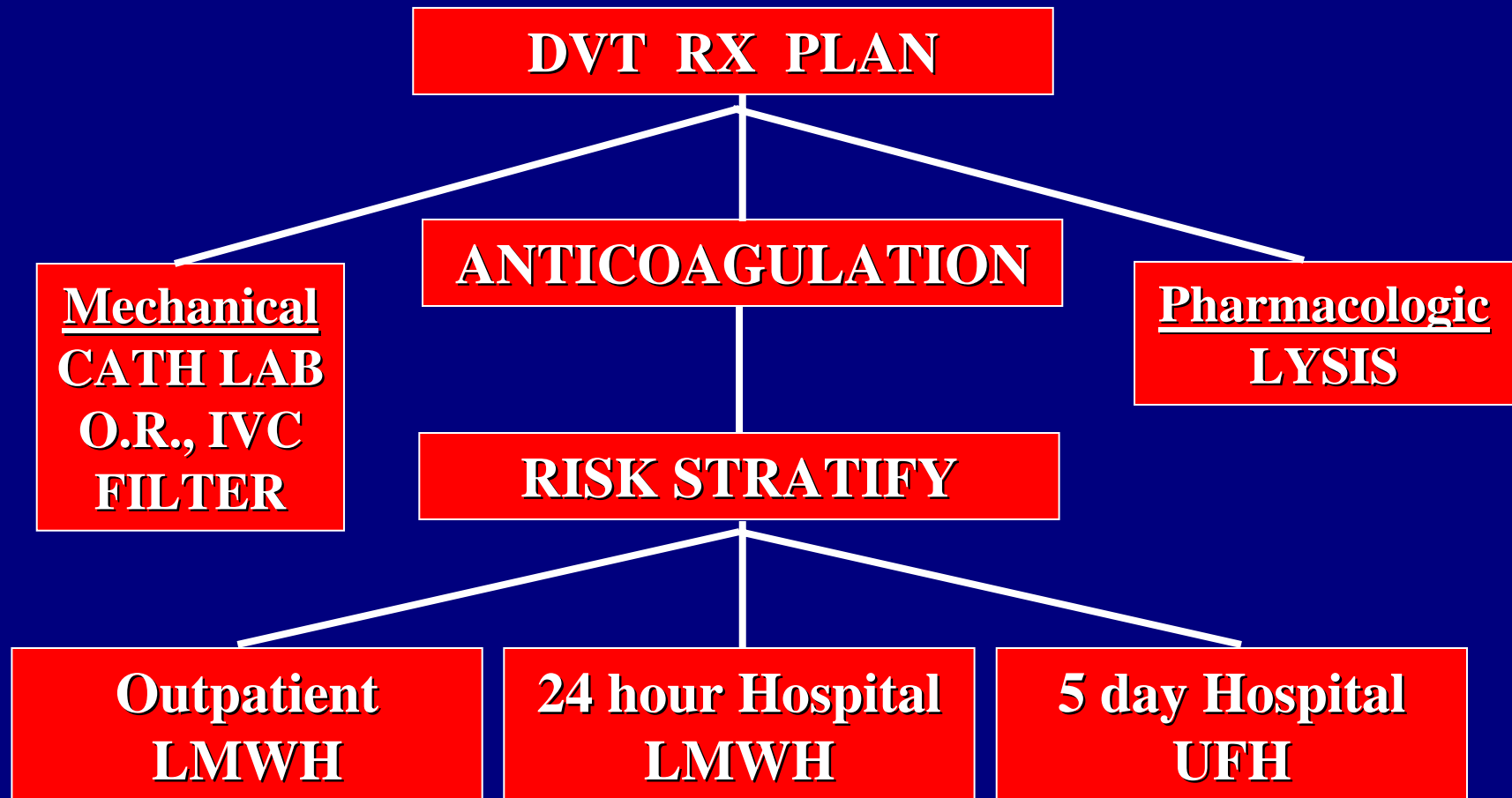
Matisse DVT

- At least as effective and safe as LMWH for DVT

Advantage

- Once daily fixed-dose SQ injection

DVT/PE Management Strategies



Questions

True or False.

Outpatient treatment of DVT has been associated with a lower mortality and risk of complications at lower cost than inpatient treatment of DVT.

Outpatient Treatment of Acute DVT with LMWH

ASHP Therapeutic Position Statement on the Use of LMWHs
for Adult Outpatient Treatment

- As safe and effective as traditional inpatient therapy with UFH
- Often more cost effective than traditional inpatient therapy
- Associated with greater patient satisfaction

Am J Health-Sys Pharm, Sept 2004, 61: 1950

Developed through the ASHP Commission on Therapeutics

Inpatient versus Outpatient Treatment of DVT

Factors to consider a limited short stay in the hospital despite eligibility for outpatient management

- Pregnancy (fetal viability, high risk)
- Need for patient and family education
- Concerns about patient falling, bleeding, or somehow unable to manage

Not Suitable for Outpatient RX

- Homeless/Phoneless
- Impaired (mentally, hearing, alcohol or IV drug use)
- Unsupervised blind
- Bleeding
- Other co-morbid complications that would affect treatment
- Obese, Renal Failure?

Questions

What is the preferred drug treatment of patients with cancer and acute DVT?

- A. LMWH without warfarin
- B. LMWH as a bridge to therapeutic warfarin

VTE and Cancer: LMWH Monotherapy VS. Warfarin

Enoxaparin 1.5 mg / kg / day; N = 138

	<u>Enoxaparin</u>	<u>Warfarin</u>
	<u>(N = 67)</u>	<u>(N = 71)</u>
Clotting	2	3
Bleeding	5	12

Meyer G, et al. Arch Intern Med 2002; 162: 1729-1735

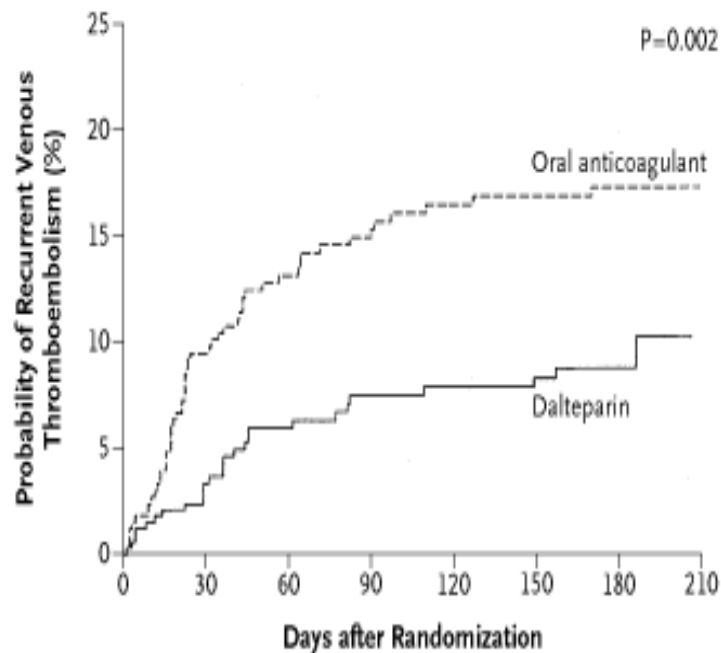
CLOT Trial

- Dalteparin monotherapy for 6 months was more effective (8.8% vs. 17% recurrence) and safer (3.6% vs. 5.6% bleeds) than warfarin in 672 cancer patients with DVT.
- Dalteparin dose: 200 u/kg daily 1st month, then 150 u/kg daily.

Agnes Lee, et al. NEJM July 10, 2003

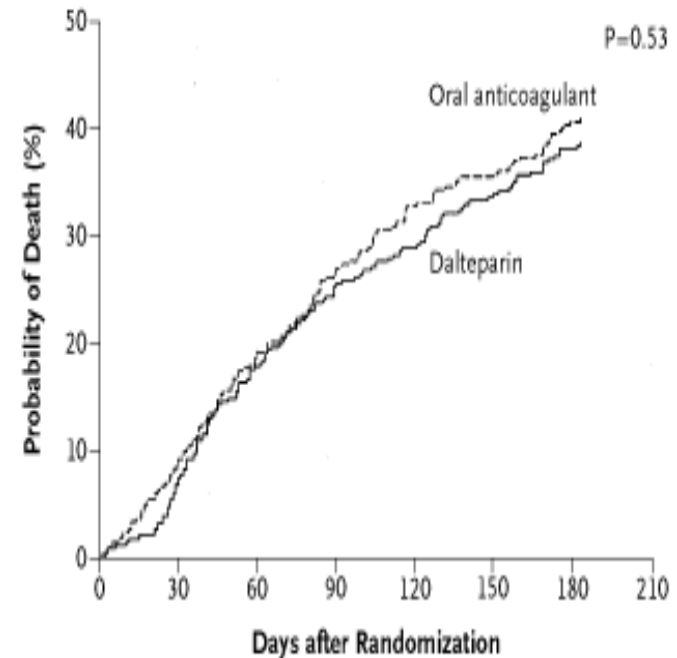
The Clot Trial

Probability of Recurrent VTE



No. at Risk							
Dalteparin	336	301	264	235	227	210	164
Oral anticoagulant	336	280	242	221	200	194	154

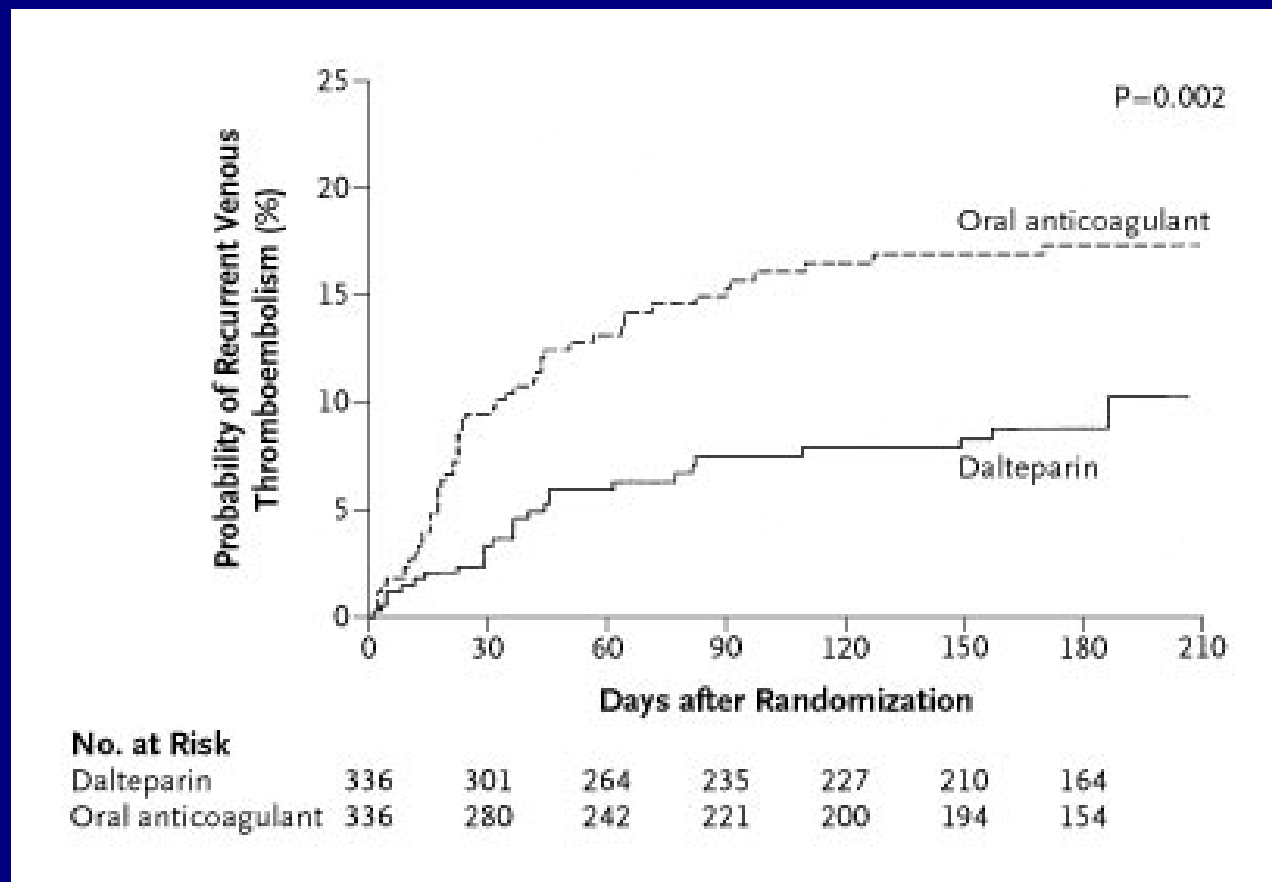
Probability of Death



No. at Risk							
Dalteparin	336	310	274	248	237	220	206
Oral anticoagulant	336	301	268	240	220	211	194

Lee AYY et al. NEJM 2003;349:146-153

LMWH Monotherapy Reduces Recurrence in Patients with VTE and Cancer (N = 676)



NEJM 2003; 349:146-153

Summary and Conclusions

- DVT occurs frequently
- Public awareness is increasing
- LMWH offers many advantages over UFH
- Prescribe LMWH without warfarin for cancer patients
- LMWH home treatment is easy, safe, and cost effective.
- Be aware of dose adjustments for elderly, obese, and renally impaired patients

Modern Treatment of VTE

For acute DVT

- LMWH SC once or twice daily over UFH on outpatient basis if possible; on inpatient basis if necessary with abbreviated hospital stay