

Parenteral Anticoagulants

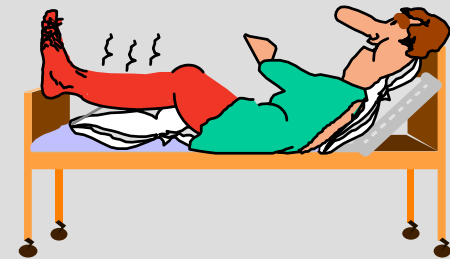
Move Over Heparin-There's a New
Crowd in Town

March 29, 2003

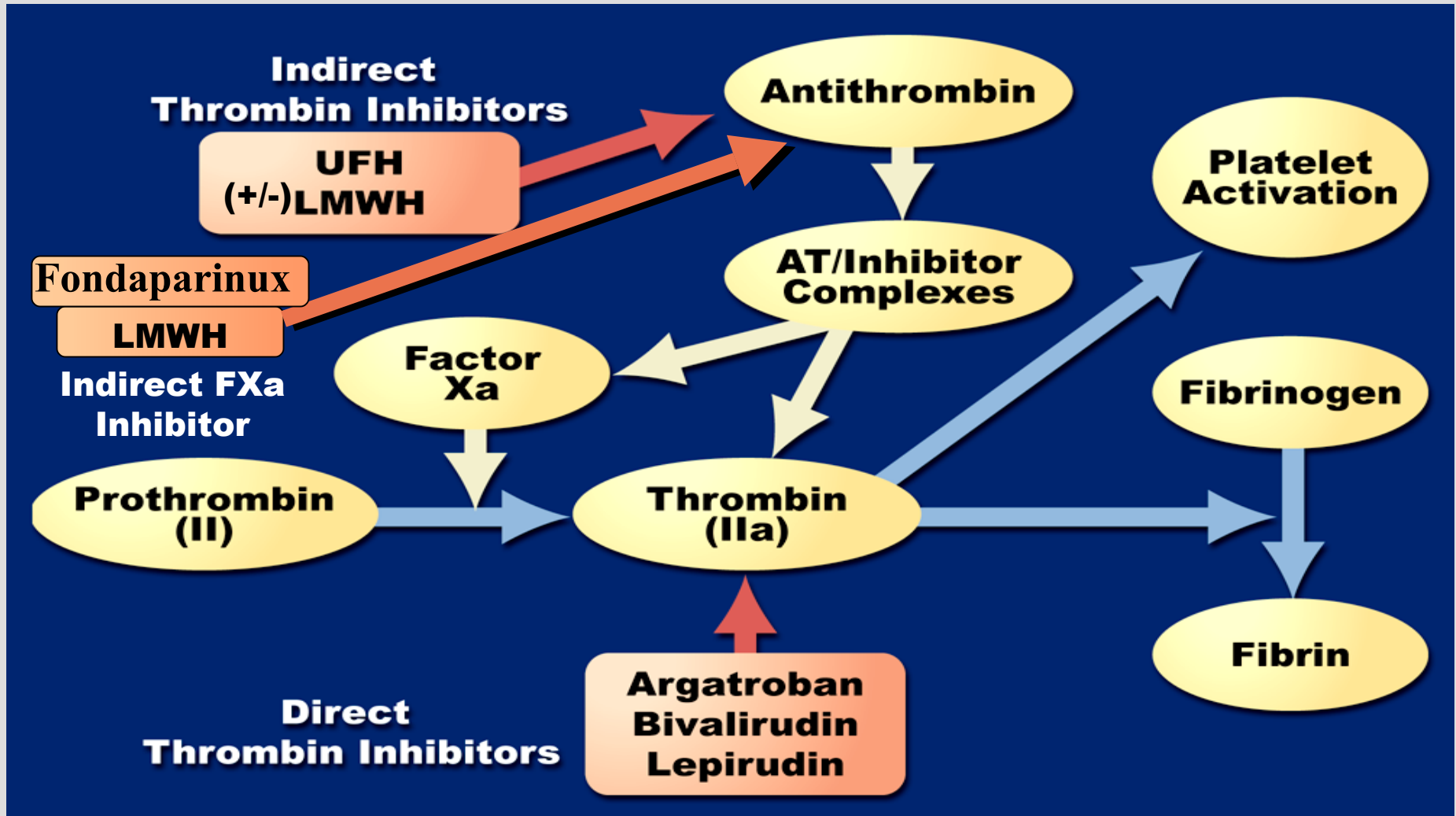
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University of Virginia Health System

**WHAT DRUGS ARE FDA
APPROVED FOR
ANTICOAGULATION**

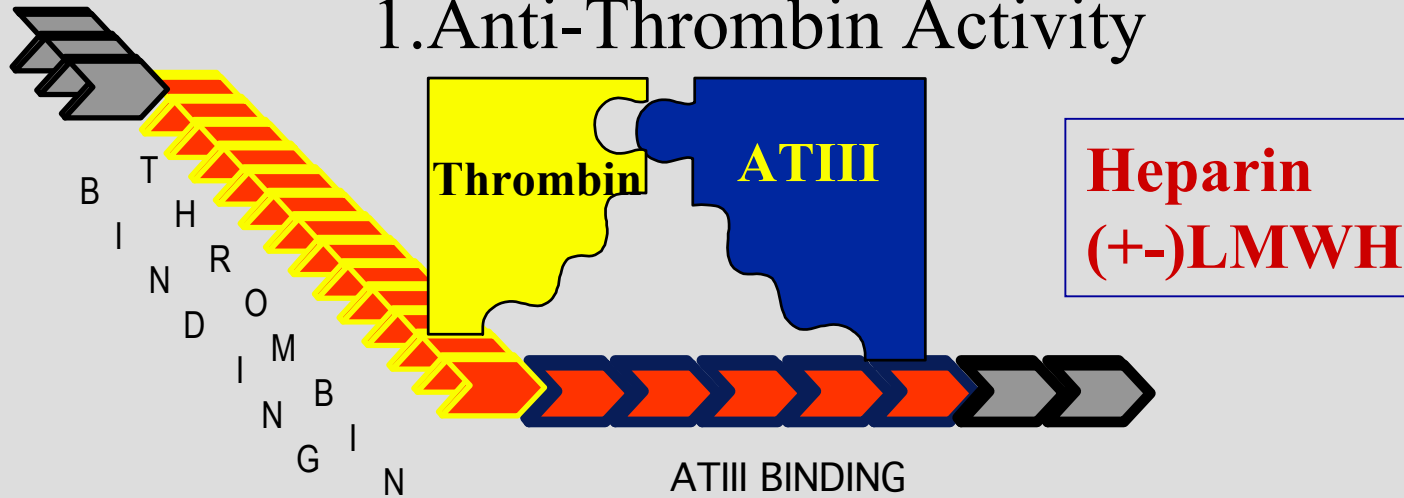


Anticoagulation Schemes



Indirect Inhibition - Requires Antithrombin (ATIII)

1. Anti-Thrombin Activity



2. Anti- Xa Activity



Heparin and Heparin-Based Therapies

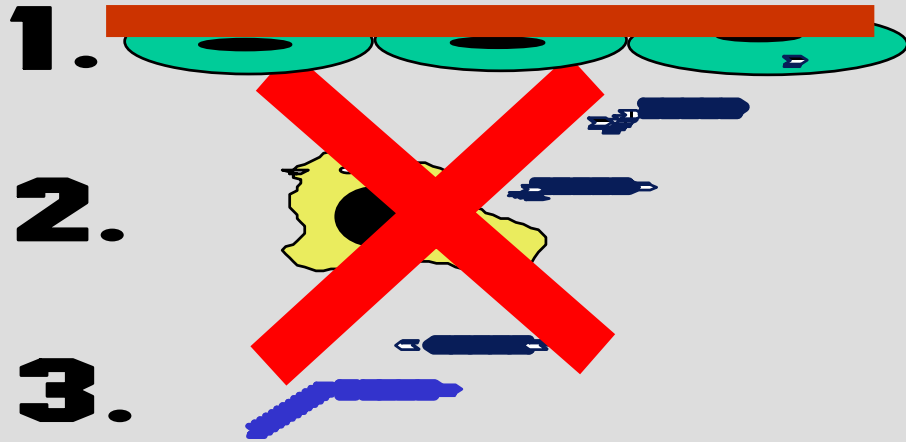
❖ One of the most common parenteral therapies

- ⊙ Approximately 12 million patients receive heparin each year

❖ Two forms of heparin

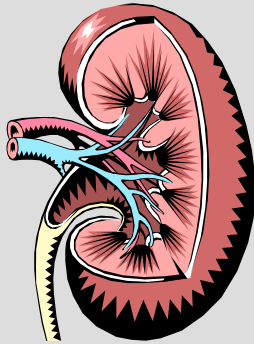
- ⊙ Unfractionated heparin (UFH)
- ⊙ Low-molecular-weight heparin (LMWH)
- ⊙ Chain length influences the anticoagulant profile
 - * Less than 18-saccharides = anti-FXa only
 - * 18 or more saccharides = anti-IIa + anti-Fxa

LMW HEPARIN CLEARANCE



- ◆ Weak Binding to Endothelial cells
- ◆ Limited Binding to Macrophages
- ◆ Weak Binding to Vitronectin

4.



- ◆ Kidney major clearance

Favorable LMWH Characteristics

- ◆ **Better bioavailability allowing for predictable anticoagulant effect at a given dose and less need for laboratory monitoring.**
- ◆ **Longer plasma half-life therefore longer dosing interval.**
- ◆ **Less effect on the hemostatic properties of the endothelium and platelets perhaps accounting for decreased hemorrhagic potential.**

Myths Regarding LMWH

1. Never need monitoring - **WRONG**

- ◆ Patients with changing or decreased kidney function must be monitored
- ◆ Very large, very small, and pregnant patients may need dose established by laboratory value

2. Bleeding is not a problem with LMWH - **WRONG!**

- ◆ Treatment dose - bleeding equivalent to heparin
- ◆ LMWH only partially reversible with protamine
- ◆ LMWH have longer $t_{1/2}$ - longer bleeding episodes

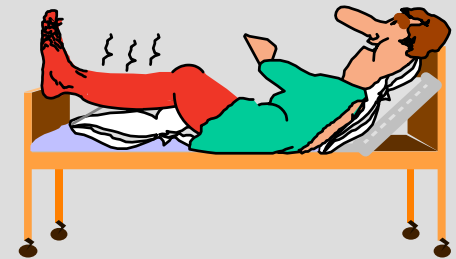
Treatment Of DVT/CAD With LMWH

The Dose

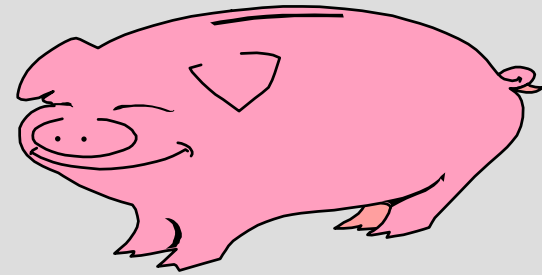
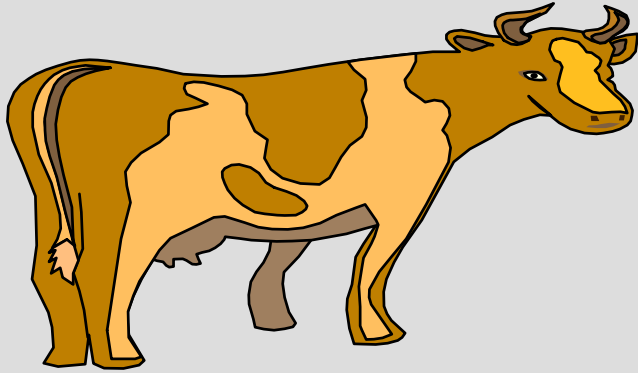
AS OF March 2003:

1. Enoxaparin (Lovenox) 1mg/kg q 12 hrs OR 1.5 mg/kg q24 hrs FDA cleared for treatment DVT and acute coronary syndromes
2. Tinzaparin (Innohep) 175 IU/kg q 24 hrs. FDA cleared for treatment of DVT +/- PE
3. Dalteparin (Fragmin) 100 IU/ kg q 12 hr OR 200 IU/kg q 24hrs FDA cleared for prophylaxis of DVT/PE and acute coronary syndromes

**Heparin is CHEAP and
LMWH is convenient-
Why do we need any
other anticoagulants ?**



Source Of Heparin



- **Biologic Product**
- **Variability Lot to Lot**
- **“Refined” to LMWH**

Heparin-Induced Thrombocytopenia and Thrombosis

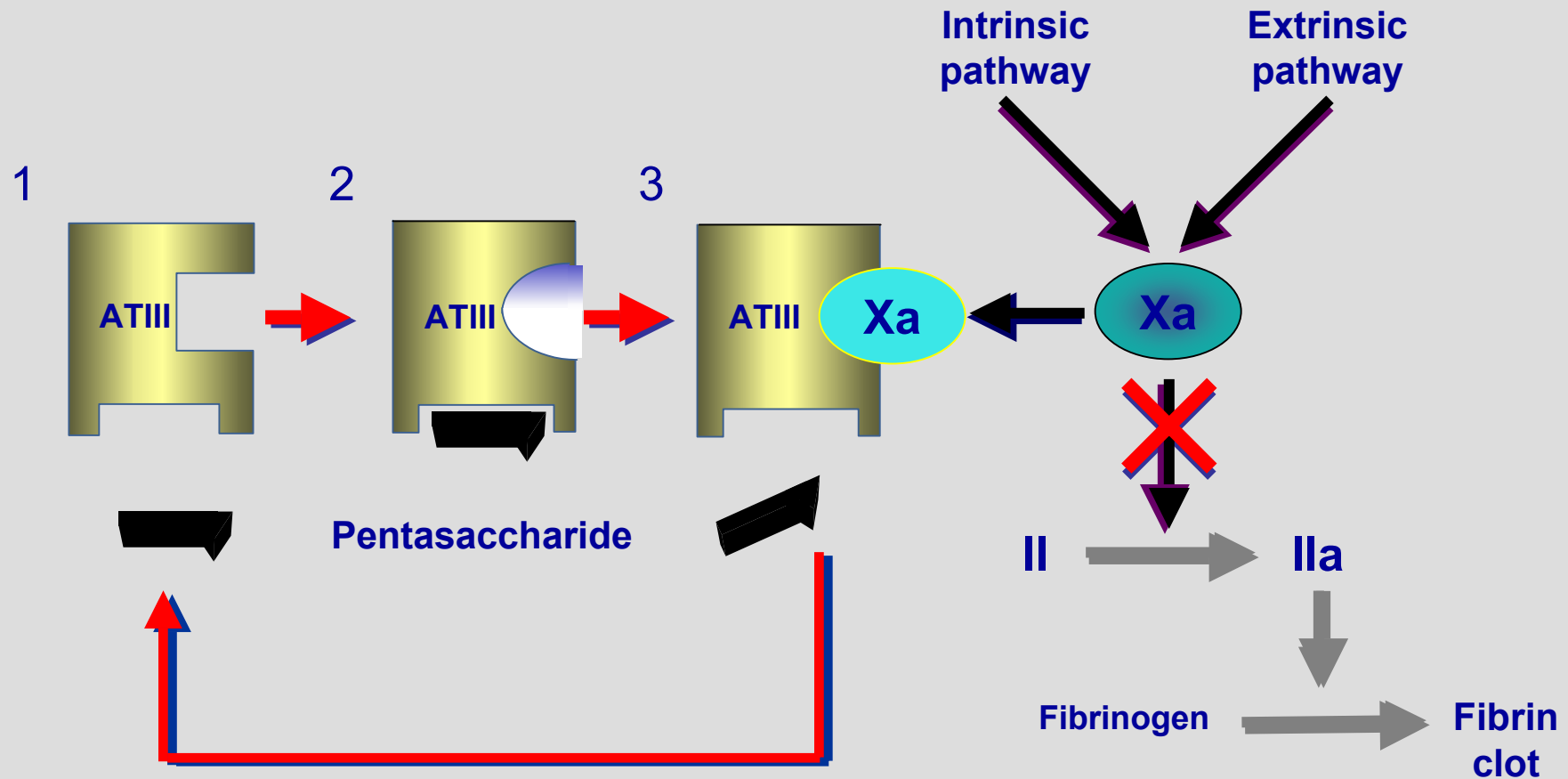
- ❖ **DISASTER-Heparin-associated thrombocytopenia Type II**
 - ✓ Later onset - immune mediated
 - ✓ Reversible ONLY with stopping heparin
 - ✓ IgG directed against PF4-Hep complex on platelet
 - ✓ IgG binds to platelet Fc γ II receptors-promotes activation
 - ✓ Activation induces platelet clumping and fibrin formation
 - ✓ 30-50% thrombosis rate within 30 days

First Synthetic Indirect Inhibition – Pure Anti-Xa Activity



Fondaparinux
Pentasaccharide ONLY

Pentasaccharide (Fondaparinux)



Adapted with permission from Turpie AGG et al. *N Engl J Med*. 2001;344:619.

Pentasaccharide versus LMWHs

	Pentasaccharide	LMWHs
Biologic effect ¹	Selective and specific inhibition of factor Xa	Multitargeted activity; inhibition of factor IIa, Xa, IXa
Effect of therapeutic doses on aPTT ¹	None	Modest
HIT response ¹	Not observed Resistant to PF4	Cross-reactivity when heparin is positive for PF4
Platelets ¹	No effect on function or aggregation	Some effect on function and aggregation
Bioavailability (SC route) ¹	100%	High SC availability
Half-life	15–18 h ¹ Allows qd injection in all indications	~4 h ² Requires injections bid in some indications

¹Walenga JM et al. *Thromb Res.* 1997;86:1–36; ²Hirsh J et al. *Chest.* 2001;119:64S.

Indirect Thrombin and/or FXa Inhibitors

	Heparin	LMWH*	Fondaparinux (Arixtra)
Product	Biologic-beef or pork source	Modified Heparin short/active chain	Synthetic Pentasaccharide
FDA	Grandfathered	Prophylaxis/ treatment DVT/PE or coronary syndromes	Prophylaxis only knee/hip replacement or hip fracture
MW	Varies 7-20,000	Varies 4-7,000	1780
Action	Equal anti IIa and anti-Xa activity	Anti Xa:IIa varies 2:1-4:1	Pure anti-Xa

*Indications and characteristics vary for three available products

Indirect Thrombin and/or FXa Inhibitors

Heparin

LMWH*

Fondaparinux (Arixtra)

T 1/2

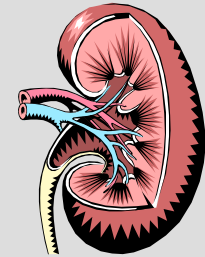
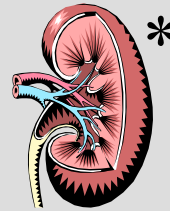
Varies by dose
1-4 hours average

12-24 hours*

17-24 hours

Excretion

Endothelium



Δ T 1/2

Higher dose
longer t 1/2

Kidney disease

Kidney disease

Reversible

Protamine

Protamine*
minimal

NO

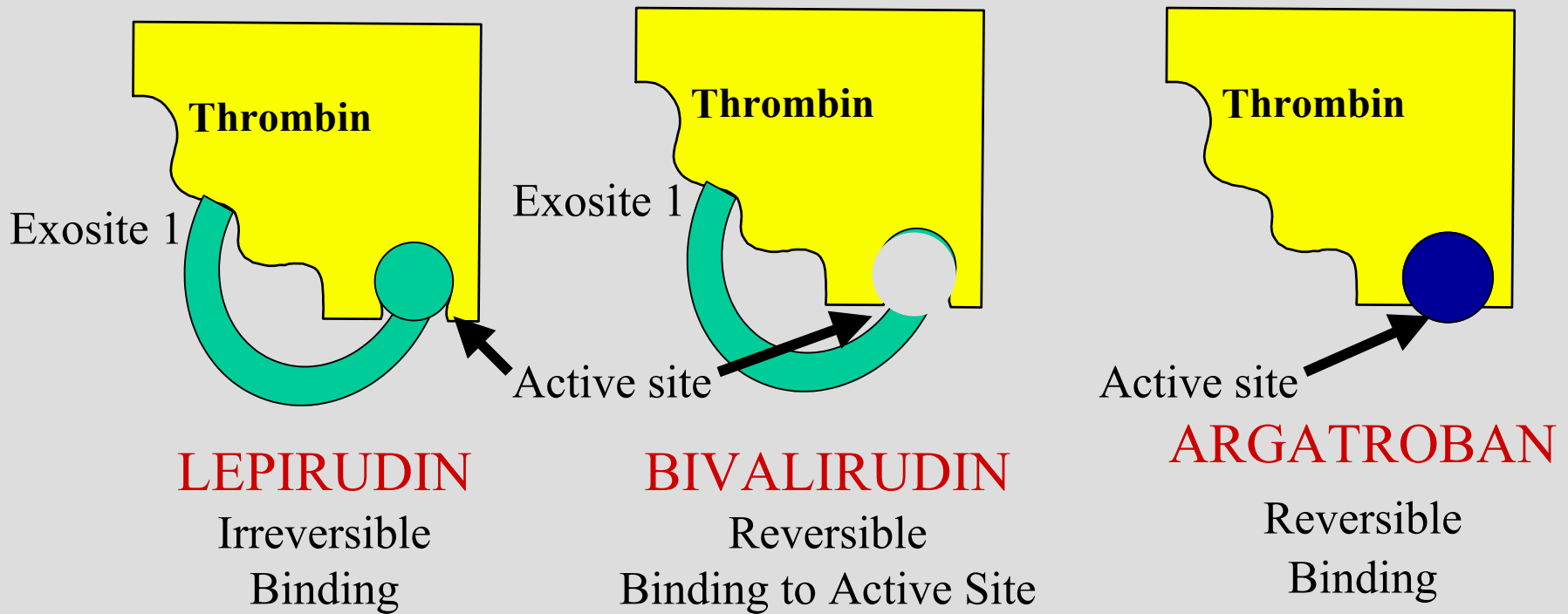
*Indications and characteristics vary for three available products

Indirect Thrombin and/or FXa Inhibitors

	Heparin	LMWH*	Fondaparinux (Arixtra)
Monitor	aPTT	Anti-Xa assay	Anti-Xa assay
Effects PT	Minimal	No	No
Route adm	IV or SQ	SQ	SQ
Bleeding	+++	++	++

*Indications and characteristics vary for three available products


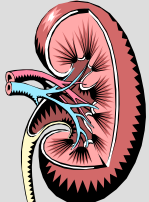
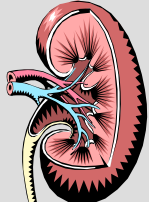
Direct Thrombin Inhibitors



Direct Thrombin Inhibitors

	Argatroban	Lepirudin (Refludan)	Bivalirudin (Angiomax)
Product	Synthetic arginine analogue	Recombinant protein	Synthetic peptide
FDA	Approved HITT/ PTCA	Approved HITT	Approved PTCA
MW	506	6979	2180
Action	Direct anti-IIa Reversible binding Irreversible inhibition	Direct anti-IIa Irreversible inhibition	Direct anti-IIa Reversible inhibition

Direct Thrombin Inhibitors

	Argatroban	Lepirudin	Bivalirudin
T 1/2	39-51 min	1.5 hrs	25 min
Excretion			
Δ T 1/2	Liver disease-hours	Kidney disease 52 hr	Kidney disease 57min-3.5hr
Reversible	NO	NO	NO

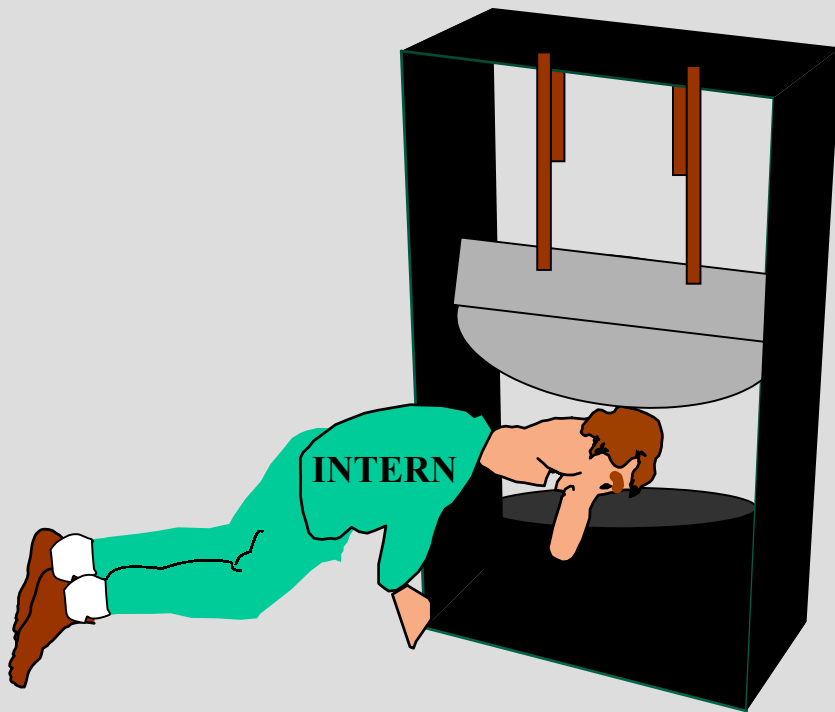
Direct Thrombin Inhibitors

	Argatroban	Lepirudin	Bivalirudin
Monitor	aPTT 1.5-3.0	aPTT 1.5-2.5	ACT 250-350
Effects PT	YES	YES	YES
Route adm	IV	IV	IV
Bleeding	++	+++	++

Direct Thrombin Inhibitors

- ❖ Do **NOT** require cofactor for activity-direct inhibitor
- ❖ Do **NOT** bind to endothelium or other proteins
- ❖ **DO** inhibit clot bound thrombin
- ❖ Do **NOT** cause thrombocytopenia
- ❖ No known drug interactions
- ❖ **ARE NOT REVERSIBLE BY PROTAMINE OR BLOOD PRODUCTS**

Treatment Pitfalls - Famous Last Words!



I'll just reverse the drug if he bleeds...

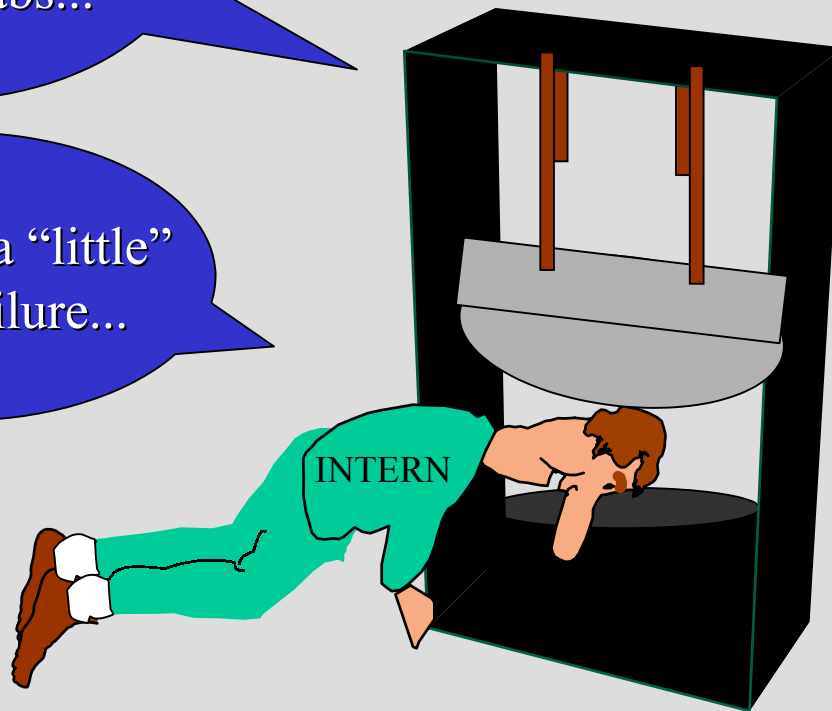
Are Direct Thrombin Inhibitors Reversible?



Treatment Pitfalls - Famous Last Words!

I'm sure the lepirudin is therapeutic-no need to check labs...

He just had a "little" kidney failure...



- Lepirudin accumulates rapidly in patients with renal insufficiency- $t_{1/2}$ increases
- 40% of patients on lepirudin will develop antibodies to the drug within 5-10 days
- Antibodies SLOW clearance - $t_{1/2}$ prolongs to hours
- Follow aPTT at least BID - STOP/DECREASE dose if aPTT begins to rise
- Start warfarin within 24-48 hours - hopefully warfarin will be therapeutic before antibodies develop

Recommended Dosing Guidelines for Argatroban

HIT Patients

**Initiate at
2 $\mu\text{g}/\text{kg}/\text{min}$**



**Titrate until
steady-state aPTT
is 1.5-3.0 times
baseline value**

**HIT Patients with
Renal Impairment**

**No dosage
adjustment required**

**HIT Patients with
Hepatic Impairment**

**Initiate at
0.5 $\mu\text{g}/\text{kg}/\text{min}$**



**Titrate until
steady-state aPTT
is 1.5-3.0 times
baseline value**

Recommended Dosing Guidelines for Lepirudin

HIT Patients

Initiate at
0.4 mg/kg bolus
0.15mg/kg/hr



Titrate until
steady-state aPTT
is 1.5-3.0 times
baseline value*

HIT Patients with Renal Impairment

If creatinine 1.5-2.0
Use 1/2 the bolus
and infusion rate



Titrate until
steady-state aPTT
is 1.5-3.0 times
baseline value

HIT Patients with Hepatic Impairment

No change in dose

Recommended Dosing Guidelines for Bivalirudin

PTCA Patients

Initiate at
1 mg/kg bolus
2.5mg/kg/hr
initial 4-hr infusion
0.2mg/kg/hr next
20 hours



ACT goal 300 sec

PTCA Patients

GFR 30-59
20% reduction dose
GFR 10-29
60% reduction dose
Dialysis patients
90% reduction dose



Adjust to ACT
300s

PTCA Patients

No change in dose

Guidelines for Conversion to Oral Anticoagulant Therapy While on Argatroban or Lepirudin

Initiate warfarin therapy using the expected daily dose of warfarin while maintaining Argatroban/lepirudin infusion. A loading dose of warfarin should not be used

Measure INR daily

**If INR is ≤ 4.0 ,
continue concomitant therapy**

**If INR is > 4.0 ,
stop anti-thrombin drug infusion**

Repeat INR 4-6 hours later

If INR is within therapeutic range on warfarin alone, continue warfarin monotherapy

If INR is below the therapeutic range for warfarin alone, resume antithrombin drug therapy

Recommended Dosing Guidelines for Fondaparinux

Prophylaxis Hip & Knee

Hip Fracture

Initiate at
2.5 mg SQ
DAILY

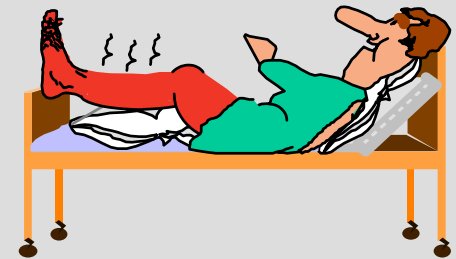
Start 6-8 hr
Post - operatively
Continue
7-9 days

Renal Impairment

Decrease Dose
For Renal

Contraindicated if
Creatinine
Clearance <30cc/hr

**WHAT OTHER DRUGS
ARE IN THE
PIPELINE?**



Other Drugs in Development

✕ ORAL Direct Thrombin Inhibitor

- ✓ **Melagatron (EXANTA) – planned FDA submission 2003**
- ✓ **Primarily Inactive - ~ 10% converted to active form by enzyme found in several tissues including gut**
- ✓ **Anticoagulant effect onset ~ 3 hour; Lasts ~12 hour**
- ✓ **No known food or drug interactions**
- ✓ **NOT reversible**

Other Drugs in Development

⊗ Inhibitors of FVIIa /Tissue Factor (TF) Complex

- ✓ **Tissue Factor Pathway Inhibitor**-binds Xa & then binds and inhibits FVIIa/Tissue Factor complex(Phase III)
- ✓ **Active-site blocked Factor VIIa** - competes for TF
- ✓ **Nematode Anticoagulant Peptide**-binds FX/Xa and complex inhibits FVIIa (Phase II)

Other Drugs in Development

↔ Inhibitors of Propagation of Coagulation

✓ Factor IXa Inhibitors

- ✓ Active Site blocked FIXa-competes with FIXa for FVIII binding
- ✓ Antibody against FIX/FIXa- inhibits factor IX activity (Phase 1)

Other Drugs in Development

↔ Inhibitors of Propagation of Coagulation

✓ Factor Xa Inhibitors

✓ Direct FXa inhibitors- directly inactivate FXa

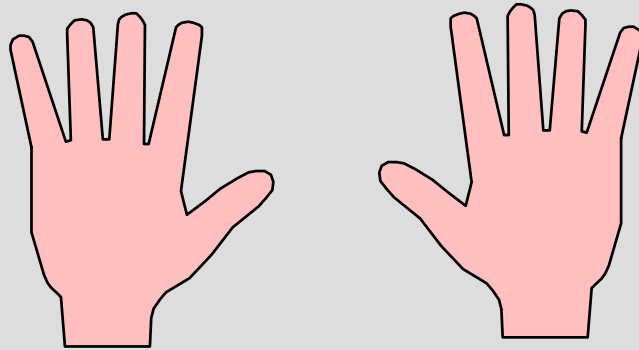
✓ Oral FXa Inhibitor

Other Drugs in Development

↔ Inhibitors of Propagation of Coagulation

✓ Inhibitors of Factors Va and VIIIa

- ✓ **Activated Protein C** - directly inactivates FV/FVIII - APPROVED for sepsis
- ✓ **Protein C** - converted to aPC (Phase II)
- ✓ **Soluble Thrombomodulin** - binds thrombin and activates Protein C (Phase II)



Tune in again for more
- Cascade of Caveats -
during the next COAG HOUR