

Direct Thrombin Inhibitors

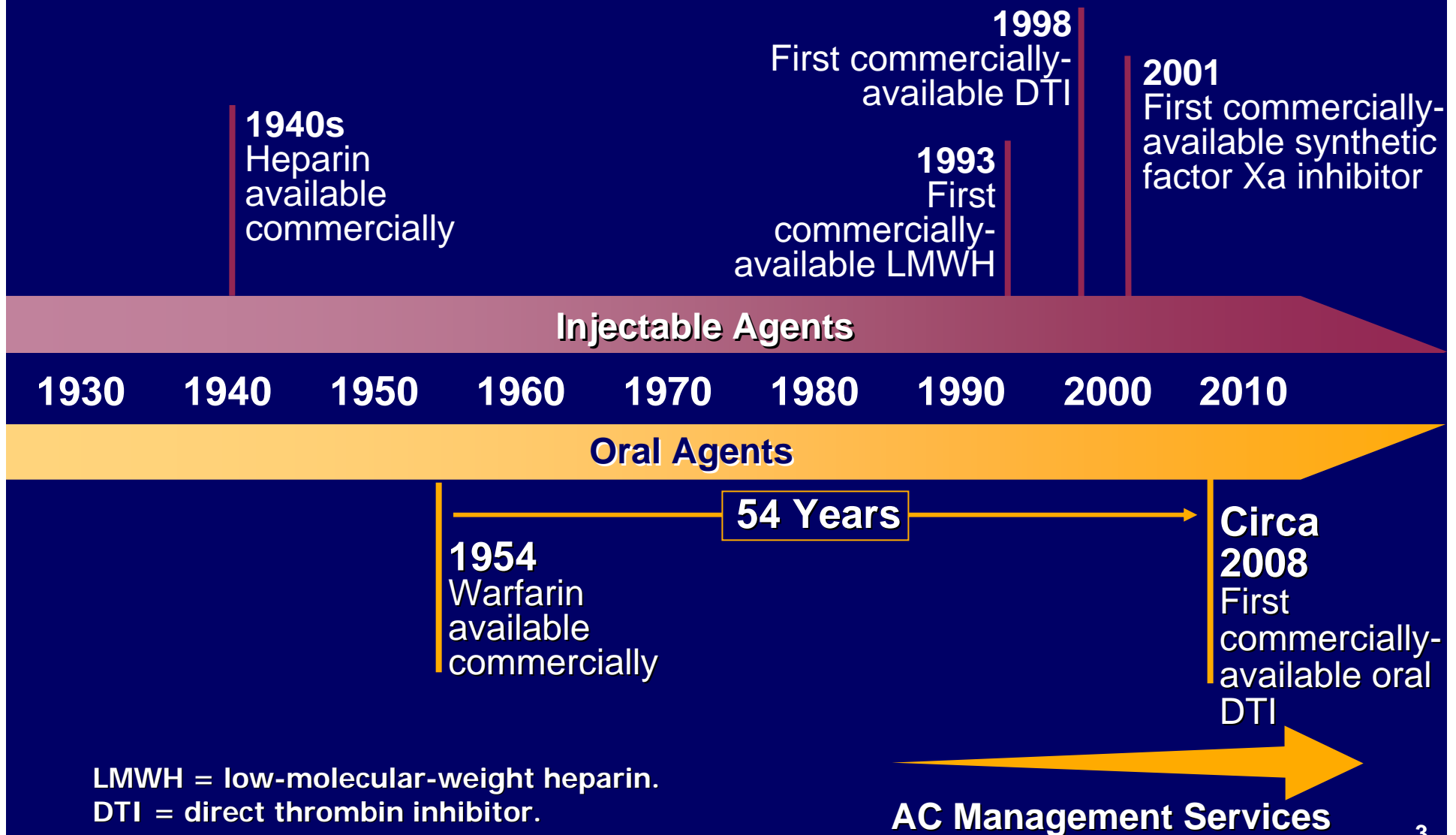
John Fanikos, R.Ph., M.B.A

February 4, 2006

Learning Objectives

- **Compare and contrast:**
 - Pharmacology
 - Pharmacokinetics of the direct thrombin inhibitors with current anticoagulants
- **Evaluate clinical trial data supporting direct thrombin inhibitor use in Heparin Induced Thrombocytopenia**
- **Review the clinical trial data for injectable direct thrombin inhibitors**
- **Review the new oral Direct thrombin inhibitors in development**

Advances in Anticoagulant Therapy in the United States



Injectable Direct Thrombin Inhibitors

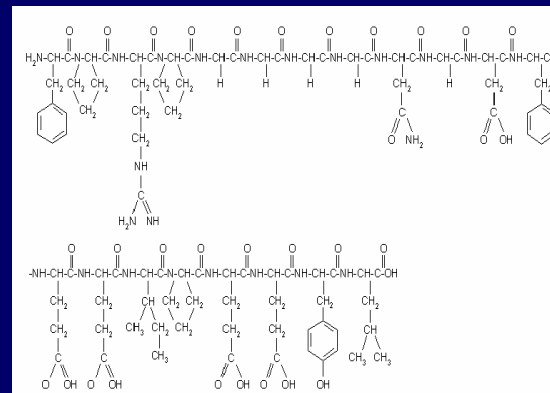
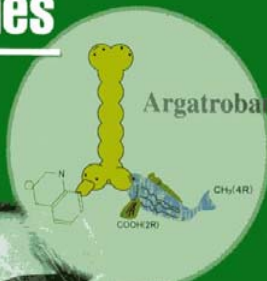
Agent	Approved Indications	Date Approved
Lepirudin (Refludan[®], Hirudin)	Anticoagulation in patients with HIT & associated thromboembolic disease	March 1998
Argatroban (argatroban)	Prophylaxis or treatment of thrombosis in patients with HIT & patients at risk for HIT undergoing PCI	June 2000
Bivalirudin (Angiomax[™], Hirulog)	Patients with unstable angina undergoing PTCA Provisional use with GPI in patients undergoing PCI Patients with/at risk for HIT/HITTS in PCI	December 2000
Desirudin (Iprivask[™])	Prophylaxis of DVT in elective hip replacement surgery	April 2003

HIT = heparin-induced thrombocytopenia; PCI = percutaneous intervention; PTCA = percutaneous transluminal coronary angioplasty, HITTS = heparin-induced thrombocytopenia and thrombosis syndrome

Structure and Source

Strategies for Creating New Medicines

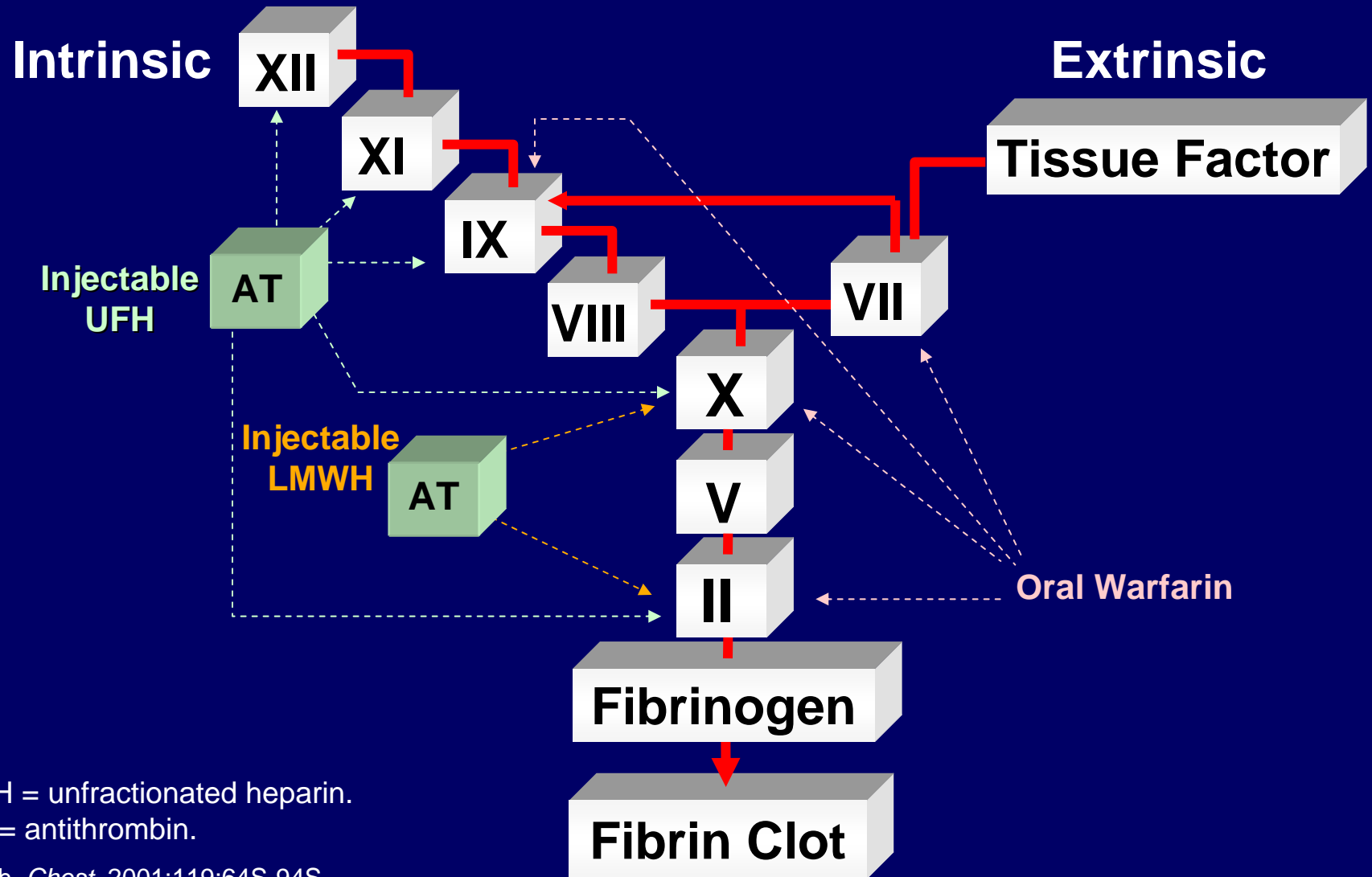
Shosuke Okamoto



Bivalirudin
Synthetic

20 Amino Acids

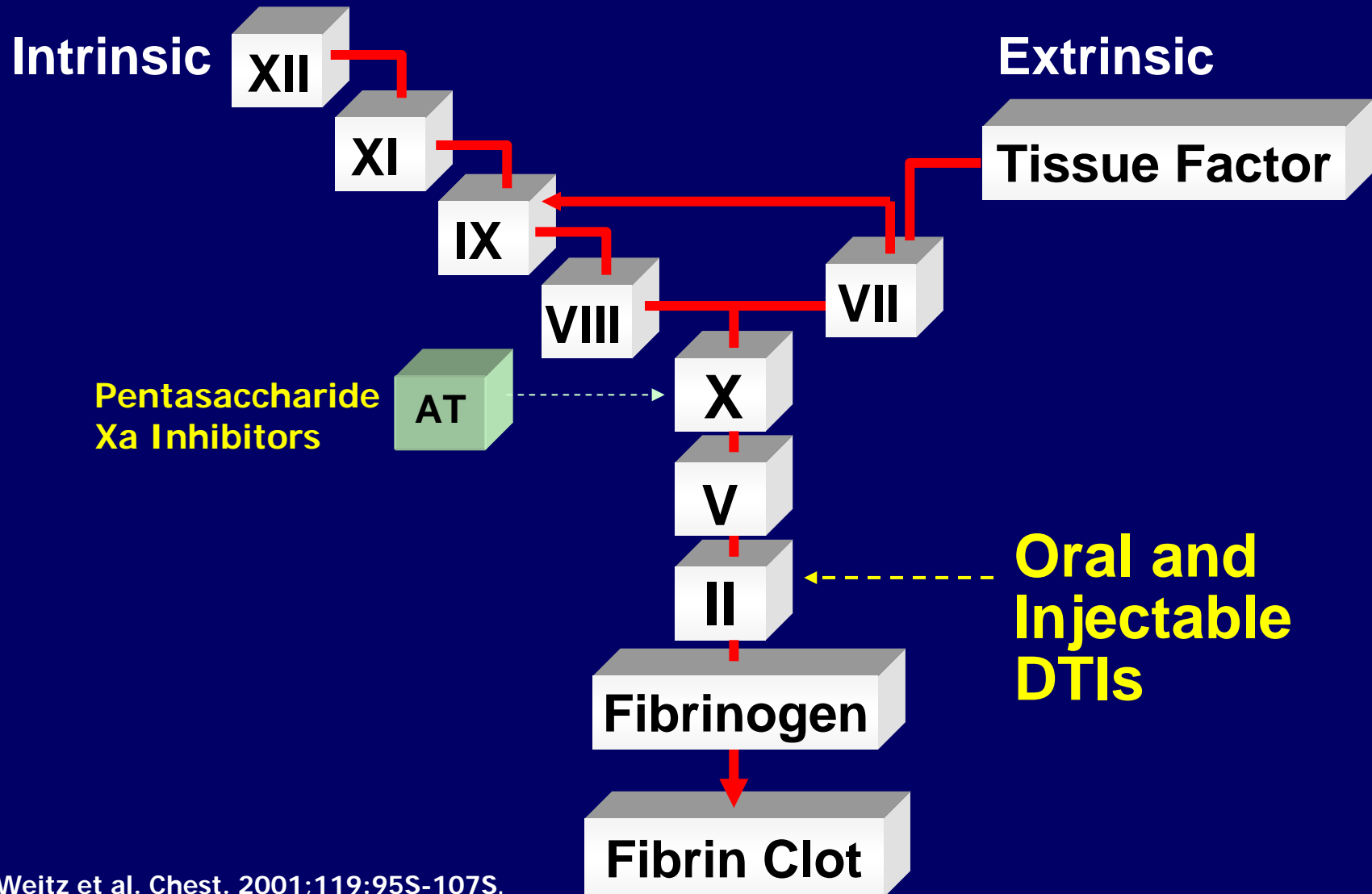
Inhibition of Coagulation Factors by Traditionally-Used Anticoagulants



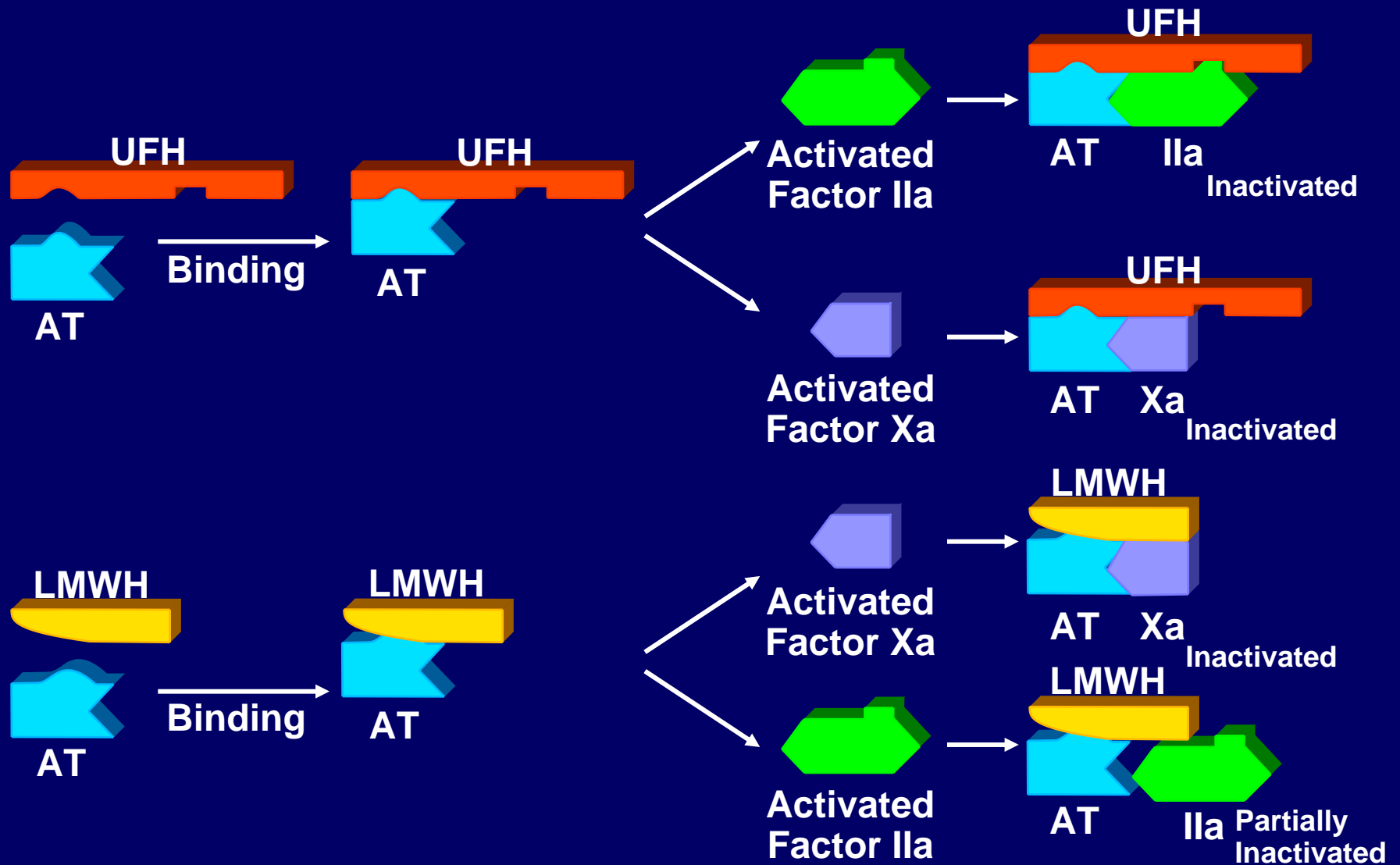
UFH = unfractionated heparin.
AT = antithrombin.

Hirsh. *Chest*. 2001;119:64S-94S.

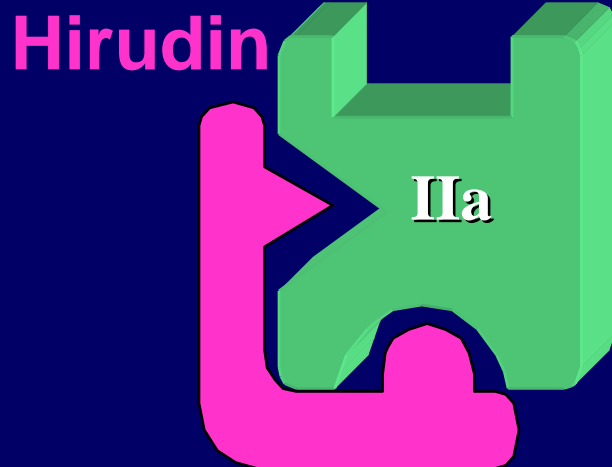
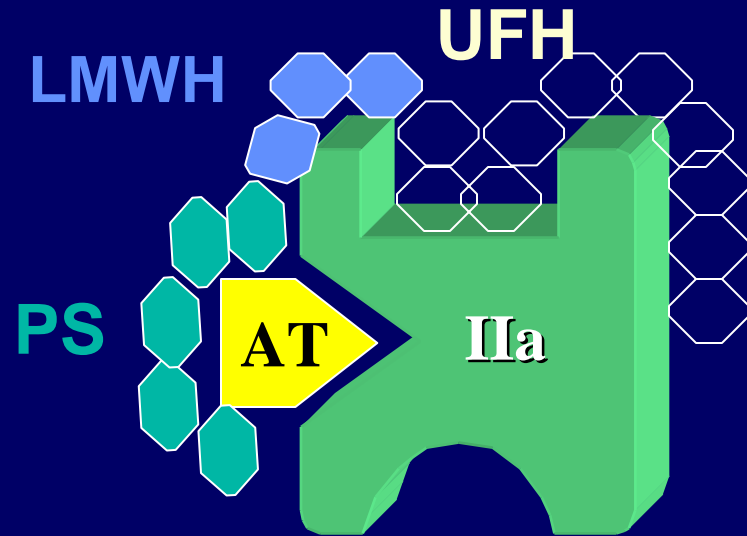
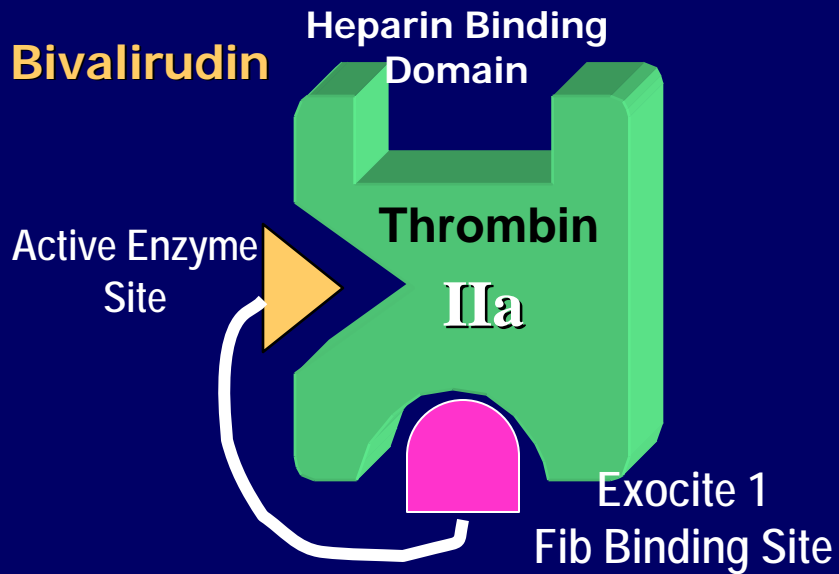
Inhibition of Coagulation Cascade by New Anticoagulants



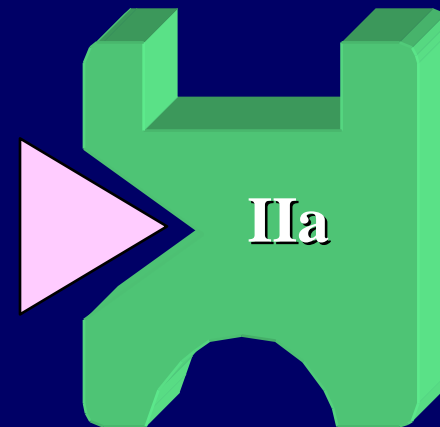
Mechanism of Action of UFH and LMWH



Thrombin Binding Sites



Argatroban
Melagatran
Ximelagatran
Dabigatran



Direct Thrombin Inhibitors

- Inhibition of thrombin independent of Antithrombin
- Can inhibit clot-bound thrombin
- No direct effect on platelet function
- No immune thrombocytopenia
- No reversal agent or “antidote” available

Pharmacokinetics & Pharmacodynamics

Characteristic	Lepirudin	Argatroban	Bivalirudin
FDA Approval for HIT	Yes	Yes	No
Molecular Weight (daltons)	6979	526	2180
HIT cross antigenicity (%)	No	No	No
Administration	SC, IV	IV	IV
Elimination	Renal	Hepatic	Renal
Half Life	1.3 hours 2.0 hours (SC)	39-51 minutes	10-24 minutes
Fe (%)	35 %		
t _{max} ^c (hours)	No Data	1-3	1-2
Binding	Irreversible	Reversible	Reversible
Monitoring Test	aPTT/ECT	aPTT/ACT	aPTT/ACT
Effects INR	No	Yes	Yes
Pregnancy Category	B	B	B



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Lepirudin: Design of Clinical Trials

- Prospective, intent-to-treat analysis with a historical control group
- Inclusion criteria:
 - ◆ Clinical diagnosis of HIT based on platelet counts with or without new Thromboembolic complications during heparin treatment
 - AND
 - ◆ Laboratory confirmation of the presence of HIT antibodies (caused a treatment delay of 1.5 to 1.9 days)
- Patients with severe renal dysfunction were enrolled in HAT-2, but were excluded from HAT-1

HAT-1 Treatment Groups

	HITT	HITT with Lysis	HIT	CABG
Dose Bolus	0.4 mg/kg	0.2 mg/kg	None	0.25 mg/kg, 5 mg
Infusion	0.15 mg/kg/h	0.1 mg/kg/h	0.1 mg/kg/h	None
No.	51	5	18	8
Age	60	41	61	72
Duration	10	9	15	9
*Medical	47 %	80%	67%	25%
Ortho	24 %		6%	13%
Trauma	8 %		0%	0
CSS	2 %		11%	100%
Other	25%	20%	17%	0%

*Patient may have > 1 disease

A. Greinacher. Circulation 1999; 99:73-80

HAT-2 Treatment Groups

	HITT	HITT with lysis	HIT
Dose			
Bolus	0.4 mg/kg	0.2 mg/kg	None
Infusion	0.15 mg/kg/h	0.1 mg/kg/h	0.1 mg/kg/h
No.	64	4	43
Age	56	44	42
Duration	10	9	15
*Medical	51 %	50%	35%
Ortho	15 %		14%
Trauma	14 %	25%	5%
CSS	3 %		9%
Other	17%	25%	37%

*Patients may have >1 disease

A. Greinacher. Circulation 1999;100:587-93

HAT-1 and HAT-2 Endpoints

Response Criteria:

Increase in platelets \geq 30% of nadir value to $>10^9$ on Day 9

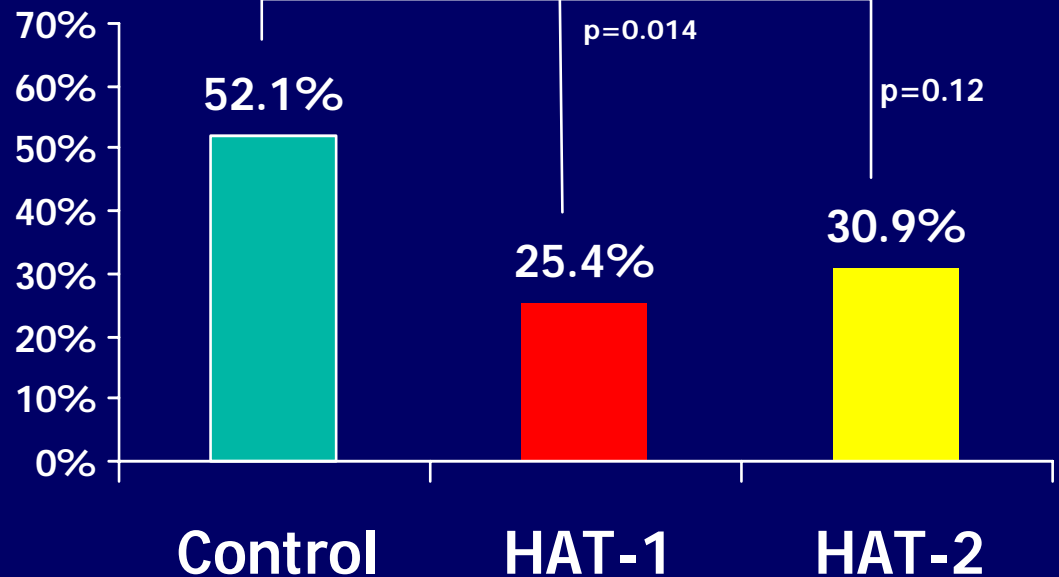
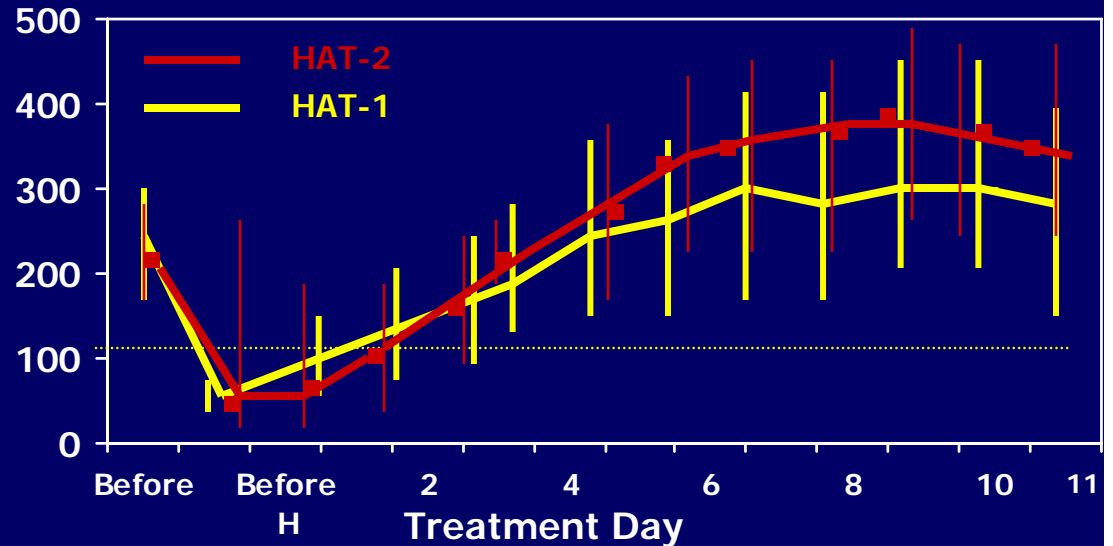
Cumulative incidence of combined endpoint;

Death,

Limb amputation,

New Thromboembolic Event

Time Course to Platelet Recovery



Lepirudin Dosing

- Goal: aPTT 1.5-2.5 x Control
- aPTT 4-6 hr (Longer in Renal Insufficiency)
- Bolus: 0.4 mg/kg (up to 110 kg)
- Infusion: 0.15 mg/kg/hr

CrCl (ml/min)	% Standard Infusion rate	Rate
>60		0.15 mg/kg/hr
45-60	50%	0.075 mg/kg/hr
30-44	30%	0.045 mg/kg/hr
15-29	15%	0.0225 mg/kg/hr
<15	(Not recommended)	0.01-0.015 mg/kg/hr ?

Argatroban: Design of Clinical Trials

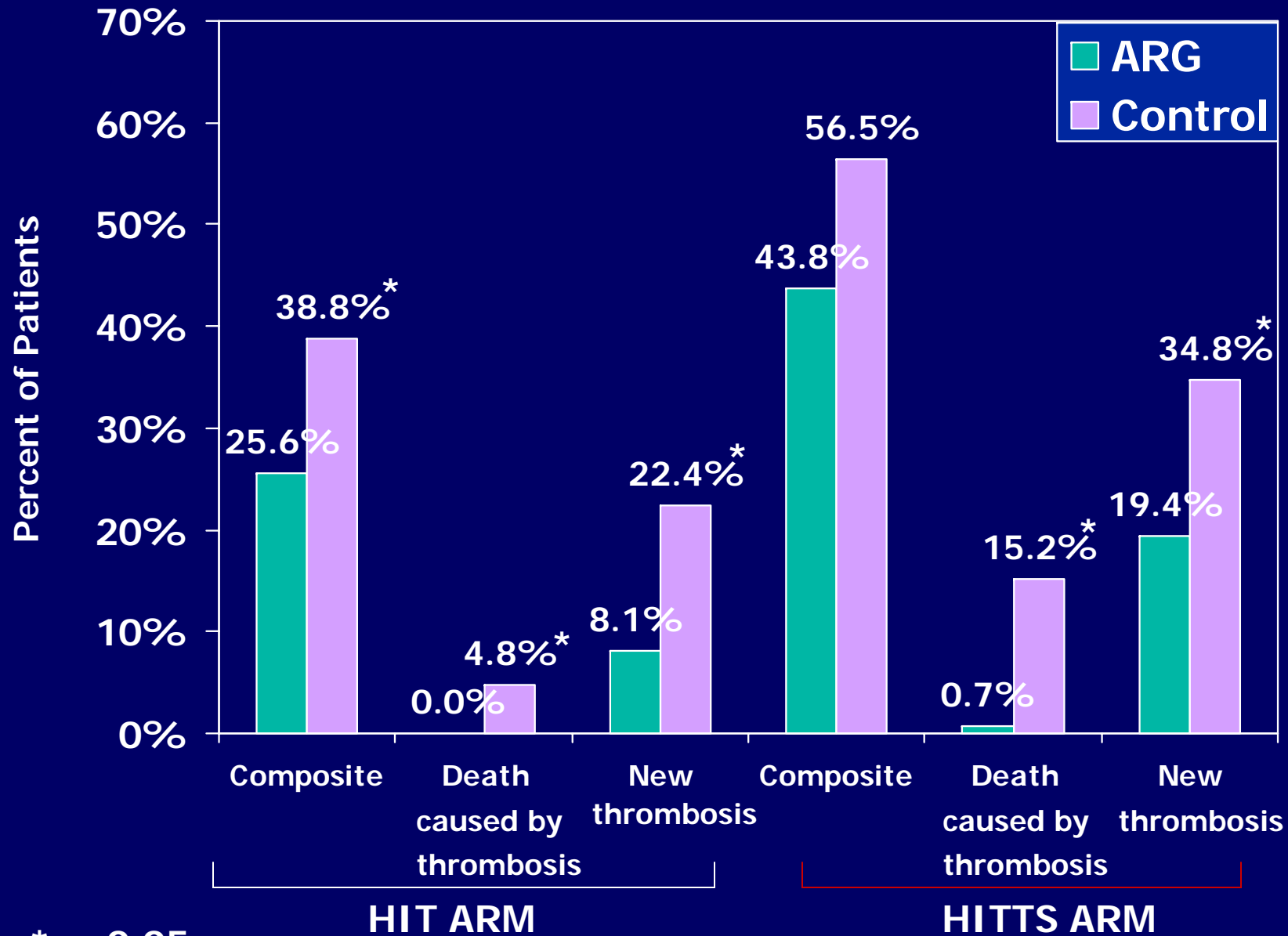
- Prospective, historically controlled
- Inclusion criteria—acute HIT not required
 - ◆ Thrombocytopenia ($<100,000/\text{mm}^3$)
OR
 - ◆ A 50% reduction from preheparin platelet counts with no alternate explanation
OR
 - ◆ Prior history of positive HIT antibody even in the absence of thrombocytopenia or heparin challenge
- Laboratory confirmation not required
- Study began at initiation of therapy
 - ◆ No pretreatment study period

ARG 911 Treatment Group

	HIT Control	HIT ARG	HITT Control	HITT ARG
No.	147	160	46	144
Age	66±12.3	61.3±13.5*	65.7±10.9	61.5±12.7*
Weight (Kg)	80±22.8	78.9±18.6	83.8±24.7	83.0±20.5
Test Positive	81 %	50%*	65%	65%
Platelets x 10 ⁹ /L (Baseline)	111	82	94	66
Circulatory Disease	86%	100%	94%	100%

*P_≤0.05 vs Control group

ARG 911 Efficacy Analysis vs. Controls



*p < 0.05

ARG 915 Treatment Group

	HIT Control	HIT ARG	HITT Control	HITT ARG
No.	139	189	46	229
Age	66±12	64±15	66±11	64±14
Weight (Kg)	81±22	79±22	84±25	82±21
Platelets x 10⁹/L (Baseline)	123±72	84±66	106±83	88±83

ARG 915: Outcomes vs Historical Controls

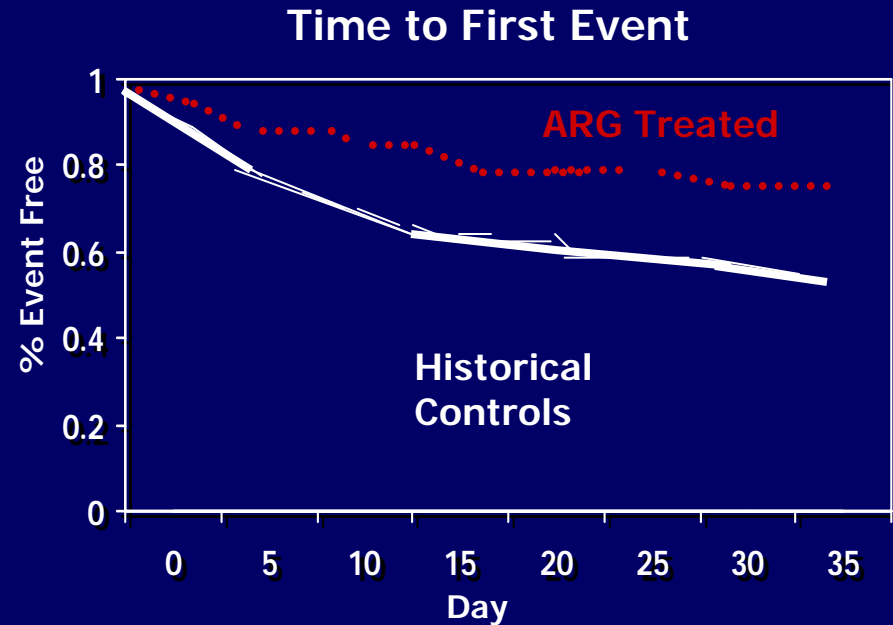
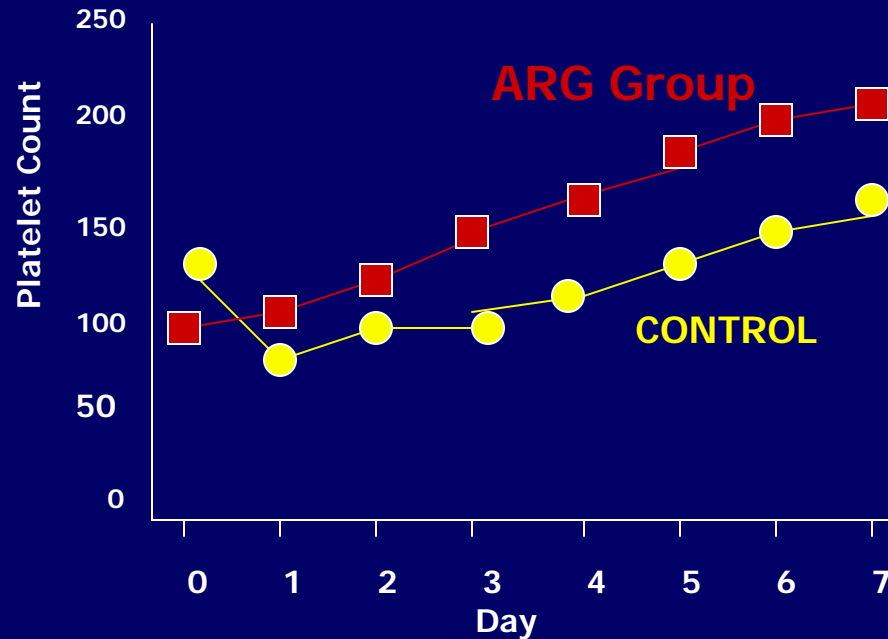
Parameter	Isolated HIT			HIT with Thrombosis		
	Control (n=139)	Argatroban (n=189)	P	Control (n=46)	Argatroban (n=229)	p
Composite*	54 (38.8)	53 (28.0)	.04	26 (56.5)	95 (41.5)	.07
Death (all)	29 (20.9)	36 (19.0)	.78	13 (28.3)	53 (23.1)	.45
Death by thrombosis	6 (4.3)	1 (0.5)	.04	7 (15.2)	6 (2.6)	.002
Amputation	4 (2.9)	8 (4.2)	.57	5 (10.9)	34 (14.8)	.64
Any new thrombosis	32 (23)	11 (5.8)	<.001	16 (34.8)	30 (13.1)	<.001

Values are n (%)

*All cause death, all cause amputation, or new thrombosis with 37 days

Lewis BE. Arch Int Med 2003;163:1849-1856

ARG 915: Outcomes vs Historical Controls



Isolated HIT

HIT with Thrombosis

Outcome*	Control (n=139)	Argatroban (n=189)	P	Control (n=46)	Argatroban (n=229)	p
Major Bleeding	12 (8.6)	10 (5.3)	.27	1 (2.2)	14 (6.1)	.48
Minor Bleeding	57 (41.0)	59 (31.2)	.08	19 (41.3)	87 (38.0)	.74

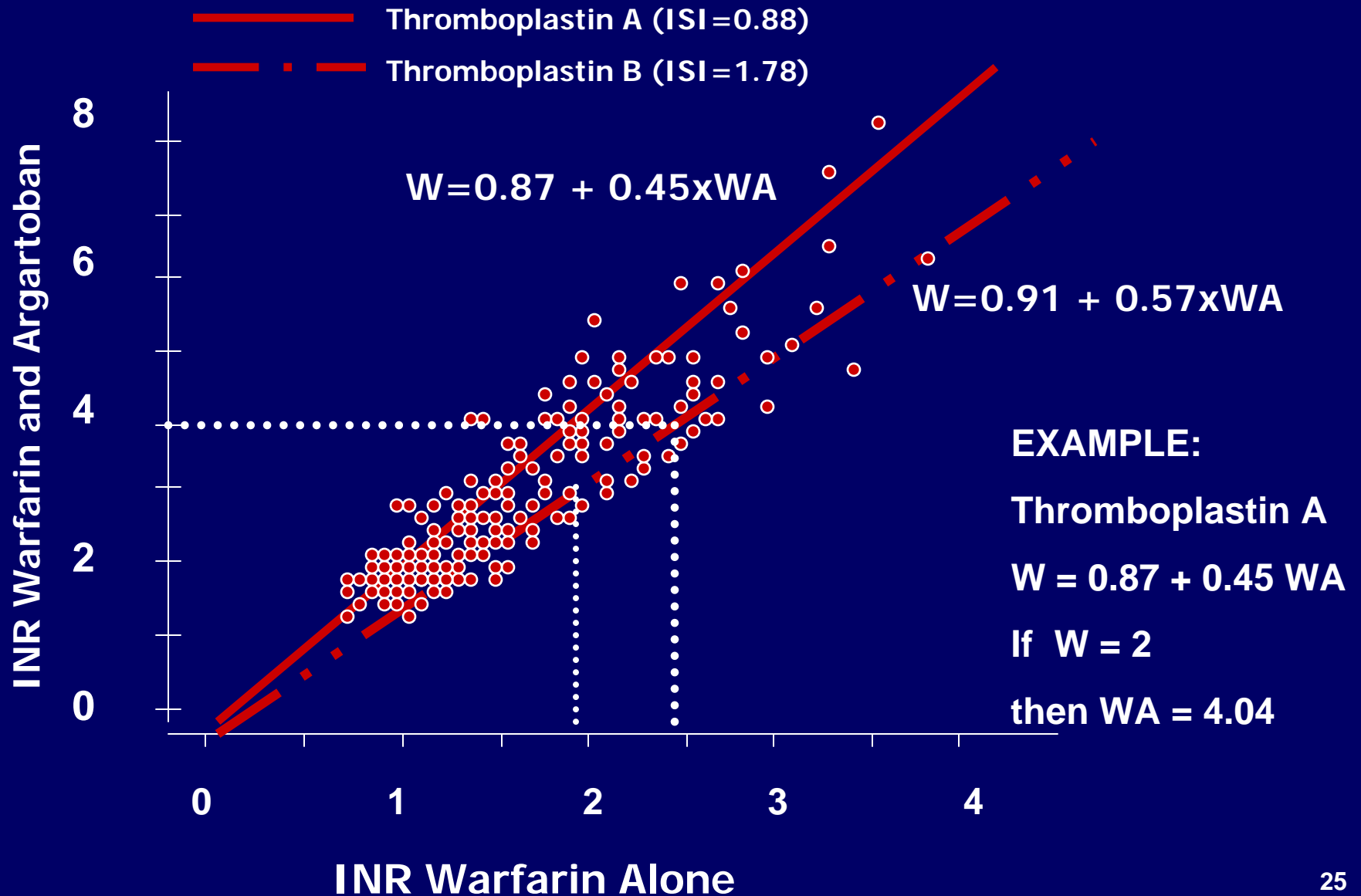
Values are n (%)

*Patients with more than one events are counted once.

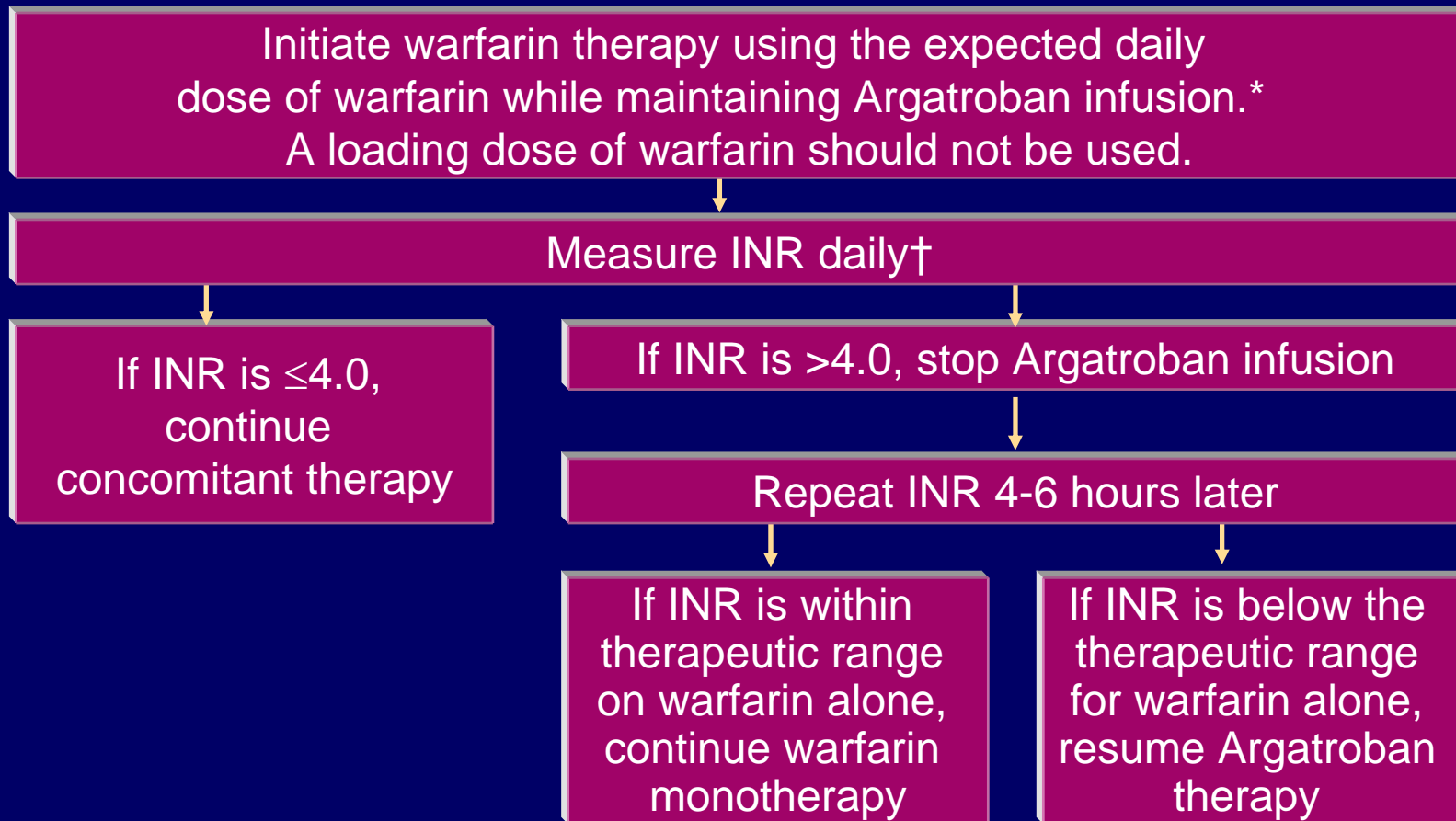
Argatroban: Dosing

- Dose: 2 mcg/kg/min
- Max: 10 mcg/kg/min
- Reduce to 25% in hepatic failure
- aPTT
 - ◆ Goal: 1.5 - 3 x control
 - ◆ Check at 4-6 hours
 - ◆ Longer in Elderly, Hepatic Failure

Argatroban: False Positive INR



Conversion to Oral Anticoagulant Therapy



* For Argatroban infusion at ≤ 2 mcg/kg/min, the INR on monotherapy may be estimated from the INR on cotherapy (see prescribing information).

† If the dose of Argatroban > 2 mcg/kg/min, temporarily reduce to a dose of 2 mcg/kg/min 4-6 hours prior to measuring the INR.

Event Rate by Anticoagulant

	UFH	Warfarin	LMWH	Argatroban	Lepirudin	Total
Total*	86 (66.2%)	28 (21.5%)	12 (9.2%)	2 (1.5%)	2 (1.5%)	130 (100%)
Total No. of Patients Treated	67,190	30,553	10,205	65	72	77,688¶
Event rate per 1,000 patients	1.27	0.92	1.18	30.8	27.8	1.67
Events Rate per 10,000 patient days	1.14	0.877	0.160	0.027	0.027	1.72
Event Rate per 100,000 doses dispensed	20.0	24.0	15.9	429.2	153.8	25.7

*Some patients received more than one anticoagulant

Argatroban in PCI n=91

Multi-center open labeled

- Dosing: Bolus 350 mcg/kg Infusion 25 mcg/kg/min
- Target ACT: 300-450 sec
- Post procedure: 2.5-5 mcg/kg/min aPTT < 100 (1.5-3 control)

Parameter	Argatroban N/total %	Historical N/total %	P value
Acute procedural Success	110/112 (98%)	5352/5676 (94%)	0.06
Major Bleeding	2/112 (1.8%)	29/939 (3.1%)	1.00

AT-BAT Trial: Bivalirudin in PCI

- Prospective, multi-center, single arm, open label study to evaluate safety and efficacy of patients undergoing PCI with HIT or HITTS involving 52 patients.
- Inclusion Criteria
 - ◆ Thrombocytopenia ($<100,000/\text{mm}^3$) OR
 - ◆ Thrombocytopenia ($<150,000/\text{mm}^3$) from preheparin platelet counts OR
 - ◆ Prior history of positive HIT antibody even in the absence of thrombocytopenia or heparin challenge or venous thrombosis
 - ◆ HITT: Thrombocytopenia and arterial or venous thrombosis
- Treatments: 1.0mg/kg bolus followed by 2.5mg/kg/hr or 0.75mg/kg bolus followed by 1.75 mg/kg/hr infusion.
- Results: 1 case of major bleeding
 - ◆ 98% procedural success (TIMI 3 flow)

IND Oral DTIs

Characteristic	Ximelagatran Melagatran	Dabigatran
Route of Administration	Oral Intravenous Subcutaneous	Oral
Plasma Half Life	3-5 Hours (PO) 2-3 Hours (IV/SC)	12 Hours
Main Site of Clearance	Kidney	Kidney
Monitoring	None	None

DTIs Compared with Control therapy in ACS

Study	Therapy	No.	DTI	Control	Endpoints	Efficacy	Bleeding
DTI Trialist Group	ACS ± PCI	35,970	Hirudin Bivalirudin Argatroban Egagatran	UFH	Death or MI @ 30D	DTI 7.4% UFH 8.2% p=0.001	1.9% 2.3% p<0.001
HERO-2	STEMI	17,073	Bivalirudin	UFH	Death @30D	Bival 10.8% UFH 10.9%	0.7% 0.5%
REPLACE-2	PCI	6,010	Bivalirudin	UFH	Death, MI, Urgent TVR, bleeding	Bival 9.2% UFH 10.0%	2.4% 4.1% p<0.001

DTIs for Post-op VTE Prophylaxis

Study	Therapy	No.	DTI	Control	Endpoints	Efficacy	Bleed Events
Colwell et al.	THR	1838	Ximelagatran 24mg BID x 7-12 days	Enoxapa rin	Proximal DVT± PE	Xi 3.6% Enox 1.2 (p<0.05)	0.8% 0.9%
Francis et al	TKR	680	Ximelagatran 24 BID x 7-12 days	Warfarin	Total VTE	Xi 24mg 19.2% Warf 25.7%	1.7% 0.9%
EXULT A	TKR	1851	Ximelagatran 24 & 36mg BID x 7-12 days	Warfarin	Total VTE or Death	Xi 36mg 20.3% (p=.003) Xi 24mg 24.9% Warf 27.6%	0.8% 0.8% 0.7%
METHRO III	THR/TKR	2,788	Melagatran SC, Ximelagatran 24mg BID x 8-11 days	Enoxapa rin	Total VTE	Mel/Xi 31% Warf 27.3%	1.4% 1.7%
BISTRO II	THR	1,973	Dabigatran 50mg 150mg 225 mg 300 mg	Enoxapa rin	Total VTE	50mg 28.5% 150mg 17.4% 225 mg 13.1% 300 mg 16.6% (p=0.007-0.04) Enox 24.0%	0.3% 4.1% 3.8% 4.7% 2.0%

VTE Treatment and Secondary Prevention

Study	Disease	No.	DTI	Control	Endpoints	Efficacy	Bleed Events
THRIVE	Acute DVT	2489	Ximelagatran 36 mg BID x 6 mos	Enoxaparin-Warfarin	Recurrent VTE	Ximelgatran 2.1% Enox/Warfarin 2.0%	1.3% 2.2%
THRIVE III	VTE	1233	Ximelagatran 24 mg BID x 18 mos	Placebo	Recurrent VTE	Ximelgatran 2.8% Placebo 12.6% (p<0.001)	1.1% 1.3%

Ximelagatran—Liver Enzyme Elevations

BioCentury, THE BERNSTEIN REPORT ON BIOBUSINESS

SEPTEMBER 13, 2004

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Product Development

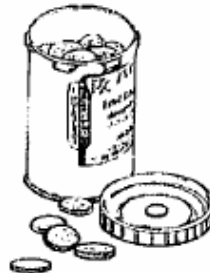
Exanta strikes out

**By Steve Usdin
Washington Editor**

AstraZeneca plc conducted a clinical development program in over 30,000 patients and persuaded European regulators to allow Exanta ximelagatran on the market. But last week, the company only managed to persuade one voting participant in an FDA advisory committee meeting to support the use of Exanta for any indication.

On Friday, the Cardiovascular and Renal Drugs Advisory Committee and its consultants voted 11-1 and 10-1 with one abstention, respectively, that AstraZeneca failed to demonstrate a favorable risk-benefit ratio for two long-term indications for Exanta: prevention of stroke and other thromboembolic complications associated with atrial fibrillation, and long-term secondary prevention of venous thromboembolism (VTE) after standard treatment of an episode of acute VTE.

The panel also unanimously rejected one short-term indication: prevention of VTE in patients undergoing knee replacement surgery.



over-dosing.

Indeed, an entire industry has developed to monitor coagulation levels in warfarin patients, and failure to adequately manage the drug is a leading cause of malpractice litigation.

Exanta is an oral small molecule direct thrombin inhibitor. The compound is a prodrug of melagatran, a non-marketed compound.

AZN has touted Exanta as a major breakthrough: a direct thrombin inhibitor that can be safely administered in a fixed oral dose without coagulation monitoring. But doubts about safety, as well as the ability to manage safe use of the drug, led to its downfall before the committee.

In the past, the company has acknowledged but downplayed the significance of data indicating that it causes elevated liver enzyme levels in a small proportion of patients. But a new safety concern, the possibility that Exanta damages the heart, emerged with the release of data for last week's meeting. This appeared to tip the balance for most committee members against allowing Exanta onto the market for even the short-term use to prevent blood clots in patients undergoing knee replacement surgery.

TKR surgery

SPORTIF III Investigators Lancet 2003; 362: 1691-1698

Albers GW. JAMA 2005; 293:690-698

DTI Trials in Progress

- ACUITY-Bivalirudin \pm GP IIb/IIIa vs Enoxaparin \pm GP IIb/IIIa
- Study of Bivalirudin in Infants under 6 with Thrombosis
- Evaluation of Argatroban in Pediatric Patients
- Bivalirudin in Patients with HIT/HITTS undergoing Off Pump CABG
- UFH vs Lepirudin Flushes in Preventing Blockages in Venous Access Devices
- RENOVATE: A randomized double blind trial to investigate the safety of 2 different regimens of Dabigatran for 28-35 days in THR
- REMODEL: A study of 2 different Dabigatran dose regimens vs Enoxaparin after knee surgery

Features of Current and IND Anticoagulants

	UFH	LMWH	Warfarin	Pentasaccharide Xa Inhibitors	Injectable DTIs	Oral DTIs
Administration Route	IV	SC	Oral	SC	IV or SC	Oral
Narrow Therapeutic Index	No	No	Yes	No	Yes	No
Fixed Dosing (no titration)	No	Yes	No	Yes	Yes*	Yes
Coagulation Monitoring	Yes	No	Yes	No	No [†]	No
Risk of HIT	Yes	Yes	No	No	No	No
Reversibility with antidote	Yes	Yes	Yes	No	No	No
Half-life	Short: 0.4-2.5 hrs	Long: 4-7 hrs	Long: 20-60 hrs	Long: 17-21 hrs	Short: 2.5 -5 hrs	Short: 2.5-5 hrs

*Except in patients with renal or hepatic impairment.

[†]Argatroban uses an activated partial thromboplastin time (aPPT).

Features of Current and IND Anticoagulants (cont)

	UFH	LMWH	Warfarin	Pentasaccharide Xa Inhibitors	Injectable DTIs	Oral DTIs
Predictable PK/PD	No	Yes	No	Yes	Yes	Yes
Rapid Onset/Offset	Yes	Yes	No	Yes	Yes	Yes
CYP450 Interaction	No	No	Yes	No	No	No
Food Interactions	No	No	Yes	No	No	No
Clinically-Significant Drug Interactions	No	No	Yes	No	No	—

PK/PD = pharmacokinetics/pharmacodynamics.

