

Novel Anticoagulants

December 16, 2009

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

Outline

- **Limitations with current anticoagulants**
- **Oral agents moving through clinical trials and early results**
- **Clinical trial programs**
- **Early projections of economic impact**
- **Injectable agents**
- **Future prospects**

Objectives

Following this program, the participant should be able to:

- Identify limitations with existing anticoagulants
- Describe pharmacokinetic and pharmacodynamic benefits of new oral anticoagulants.
- Review recently completed clinical trials and the endpoints achieved
- Project expected cost burden
- Describe new injectable anticoagulants
- Discuss pharmacology of novel anticoagulants completing early pre-clinical trials.

Limitations with Current Anticoagulation Therapy

Agent	Disadvantages
Heparin	<ul style="list-style-type: none">• Parenteral administration• Risk of heparin-induced thrombocytopenia (HIT)• Narrow therapeutic window (low bioavailability, short half-life)
Warfarin	<ul style="list-style-type: none">• Requires frequent monitoring due to:<ul style="list-style-type: none">– Narrow therapeutic window– Unpredictable pharmacology– Multiple drug–drug and food–drug interactions– Increased risk of major and minor bleeds
LMWH	<ul style="list-style-type: none">• Parenteral administration• Risk of heparin-induced thrombocytopenia (HIT)
Indirect Xa Inhibitor (e.g. fondaparinux)	<ul style="list-style-type: none">• Parenteral administration• Long half-life• Limitations related to special patient populations
Direct Thrombin Inhibitors	<ul style="list-style-type: none">• Parenteral administration• Current applications limited to cardiovascular management



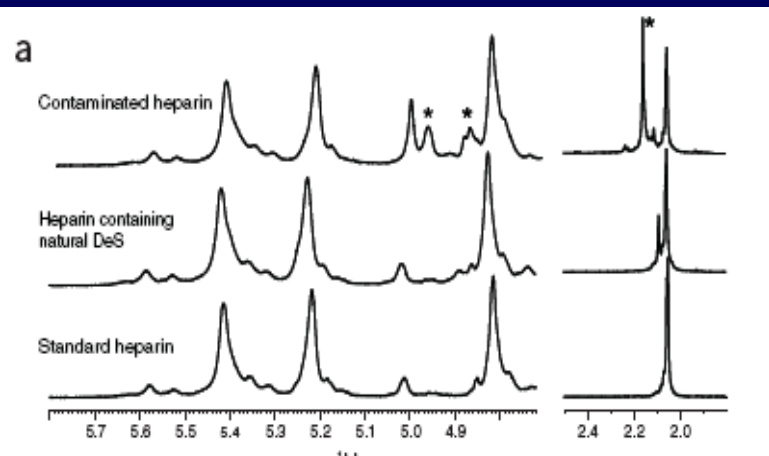
ORIGINAL ARTICLE

Contaminated Heparin Associated
with Adverse Clinical Events and Activation
of the Contact System



nature
biotechnology

Oversulfated chondroitin sulfate is a contaminant in heparin associated with adverse clinical events



THE HEPARIN TRAIL

China's Role In Supply Of Drug Is Under Fire

By GORDON FAIRCLOUGH
AND THOMAS M. BURTON

YUANLOU, China—In a small, damp factory here, blood-smeared men wring pulp from pig intestines, then heat it in concrete vats.

The activity at Yuan Intestine & Casing Factory is the first step in the poorly regulated process of making raw heparin, the main ingredient in a type of blood-thinning medicine that in recent days has come under suspicion in the deaths of four Americans.

More than half the world's heparin comes from China. The chemical is often extracted from pig entrails in small factories—many as rudimentary as this one, which also manufactures sausage casings from intestines. The heparin eventually ends up in drugs used world-wide by patients having surgery or who need dialysis.

Heparin goes through extensive processing in its journey

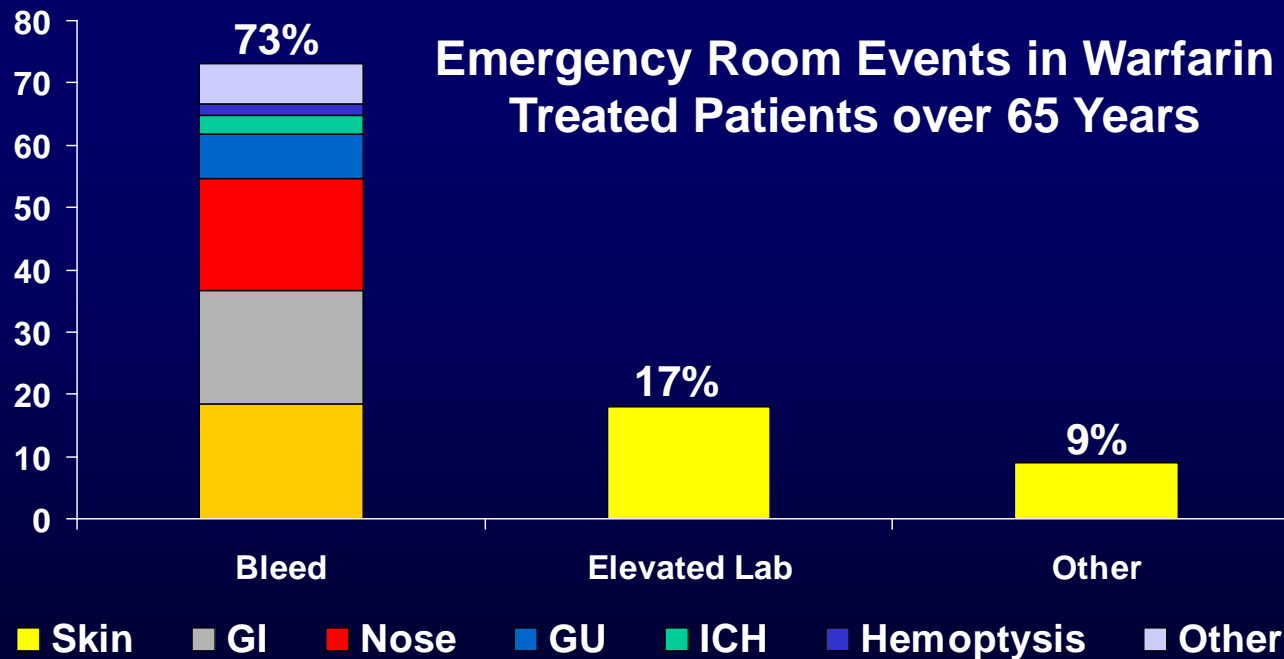
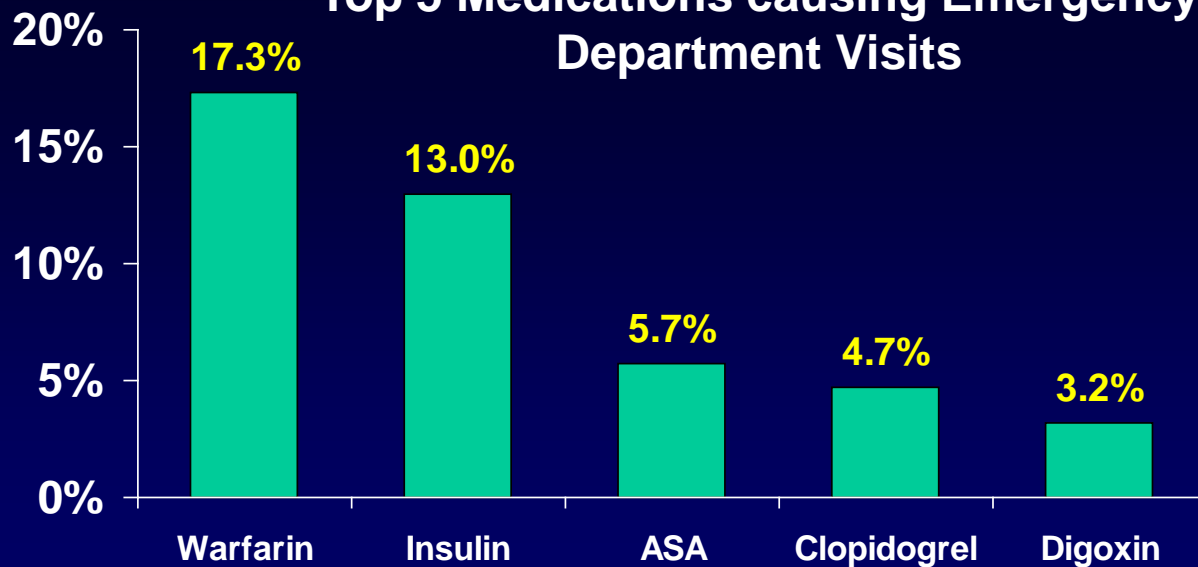
Baxter

Urgent
Product Recall

January 17, 2008

Re: Heparin Sodium Injection 1000 units/mL 10mL Vial
Lot #'s 107054 and 117085

Top 5 Medications causing Emergency Department Visits



Your Guide to Coumadin®/Warfarin Therapy



Oral Anticoagulation Therapy

A Guide to Taking Warfarin

Target

Parenteral agent

Oral agent

Factor IIa (Thrombin)

Desirudin

Ximelagatran

Bivalirudin

Dabigatran

Argatroban

Odiparcil

Factor Xa

Idraparinux

Rivaroxaban

M118

Apixaban

SSR 126517

LY517717

DX-9056a

YM150

Otamixiban

Du-176b

Factor VIIa/TF pathway

Tifacogin (TFPI)

...

Factor VIIai

...

Factor IXa

Factor IXa Aptamer

TTP889

Protein C Pathway

Protein C

...

ART123 (thrombomodulin)

...

Factor Xa/Factor IIa

Hexadecasaccharide
(SR 123781A)

...

Bemiparin (ultra LMWH)

...

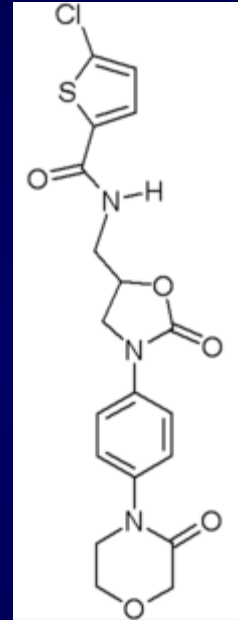
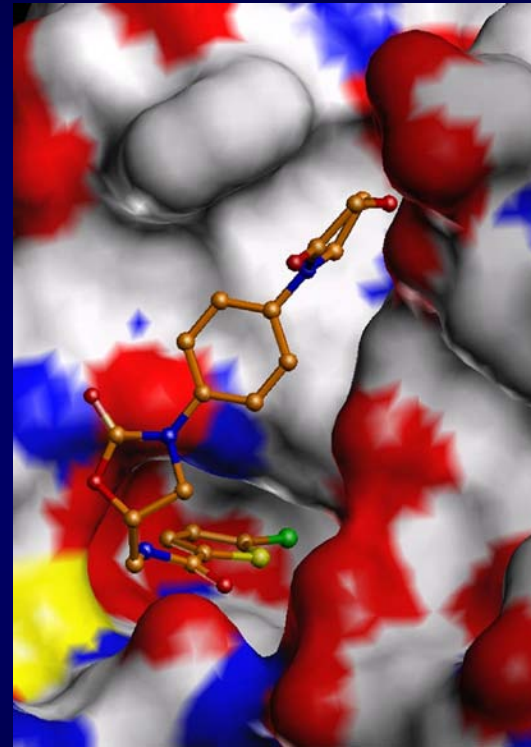
New Oral Anticoagulants

Drug	Target	Oral Dosing	Coagulation Monitoring	Half Life (h)	Renal Clearance (%)	Interactions
Rivaroxaban	Factor Xa	Fixed, Once daily or Twice daily	No	9.0	65	Potent CYP3A4 inhibitors
Apixiban	Factor Xa	Fixed, Twice daily	No	9-14	25	Potent CYP3A4 inhibitors
Dabigatran	Factor IIa (Thrombin)	Fixed, Once daily or Twice daily	No	14-17	100	Proton Pump Inhibitors

Rivaroxaban: An Oral Direct Factor Xa Inhibitor

- Direct, specific, competitive Factor Xa inhibitor
- Inhibits free and fibrin-bound Factor Xa activity and prothrombinase activity
- Does not directly inhibit thrombin, but inhibits thrombin generation via direct inhibition of Factor Xa activity
- Rapid onset within 2-4 hours
- High bioavailability of > 80%
- No observed effects on agonist-induced platelet aggregation
- Does not require a cofactor such as antithrombin
- No dosage adjustment for gender, age, extreme body weight
- No interaction with aspirin, enoxaparin, digoxin, naproxen, ranitidine, or antacids
- Approved in Canada

Xarelto[®]



Perzborn E. J Thromb Haemost 2005.

Kubitza D., J Clin Pharmacol 2007.

Eikelboom JE. Thromb Haemostasis 2009

Gulseth GP. Am Soc Health-Syst Pharm 2008

RECORD Phase III Trials: VTE Prophylaxis

RECORD 1

HIP replacement

Rivaroxaban 10 mg od
for 31–39 days

VS

enoxaparin 40 mg od
for 5 weeks

N=4,541

RECORD 2

HIP replacement

Rivaroxaban 10 mg od
for 31–39 days

VS

enoxaparin 40 mg od
for 10–14 days then
oral placebo

N=2,509

RECORD 3

KNEE replacement

Rivaroxaban 10 mg od
for 10–14 days

VS

enoxaparin 40 mg od
for 10–14 days

N=2,531

RECORD 4

KNEE replacement

Rivaroxaban 10 mg od
for 10–14 days

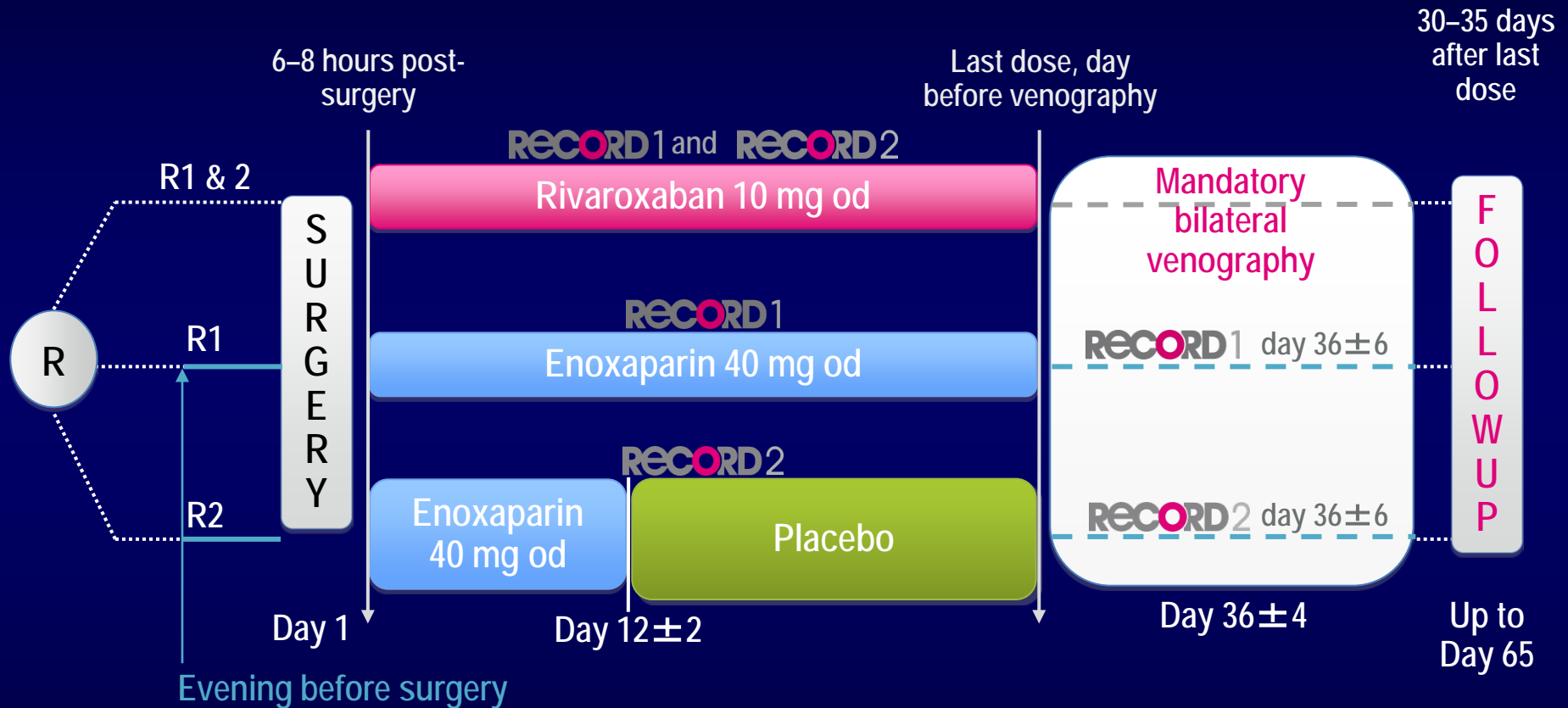
VS

enoxaparin 30 mg bid
for 10–14 days

N=3,148

- ▶ Same efficacy and safety outcomes
- ▶ Same independent, blinded committee adjudicated all outcomes
- ▶ 12,729 patients randomized

RECORD1 and 2 Study Design



Inclusion criteria

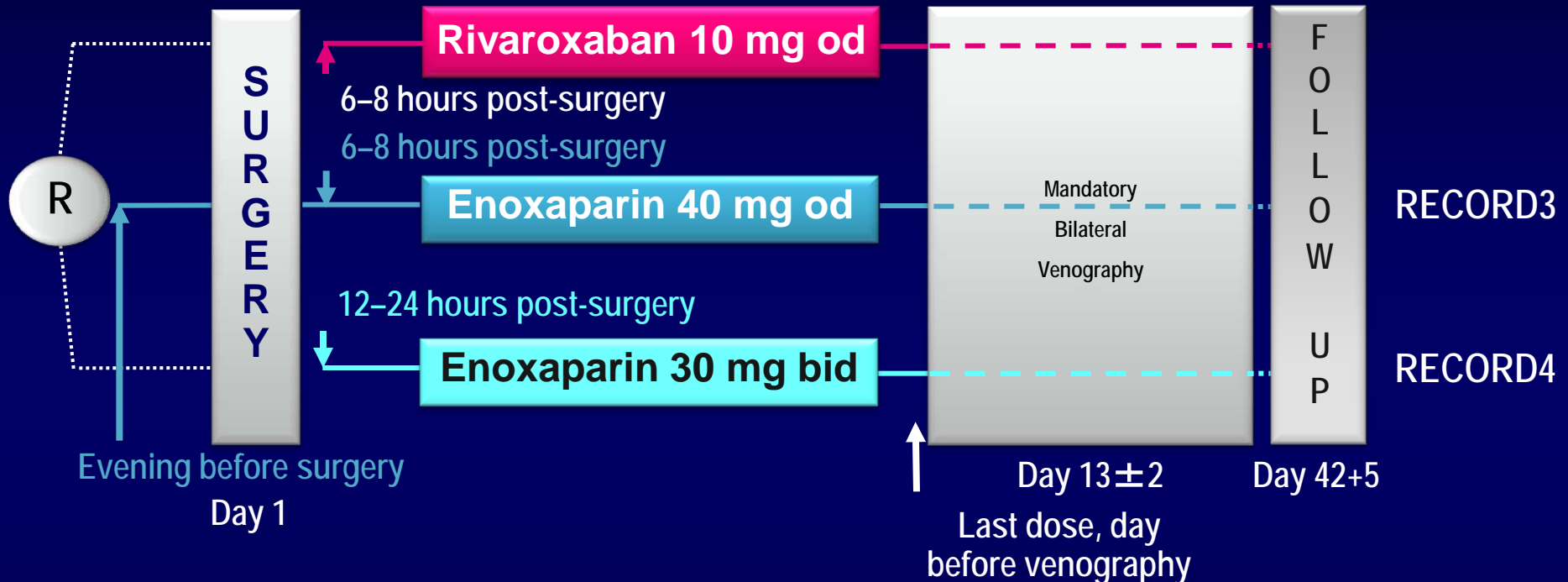
- ▶ Patients aged ≥ 18 years, scheduled to undergo elective, total knee replacement surgery

Major exclusion criteria

- ▶ Active bleeding or high risk of bleeding
- ▶ Significant liver disease
- ▶ Anticoagulant therapy that could not be stopped
- ▶ Use of HIV-protease inhibitors

RECORD3 and 4 Study Design

Double blind



Inclusion criteria

- ▶ Patients aged ≥ 18 years, scheduled to undergo elective, total knee replacement surgery

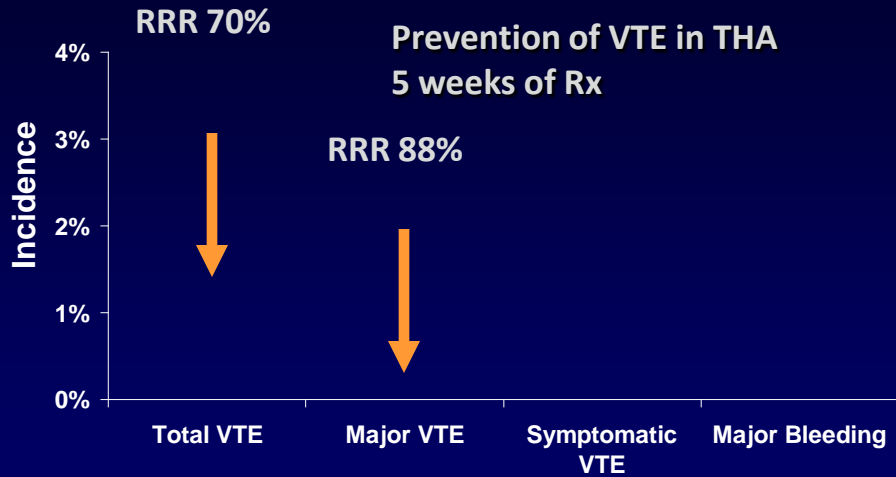
Major exclusion criteria

- ▶ Active bleeding or high risk of bleeding
 - ▶ Significant liver disease
- ▶ Anticoagulant therapy that could not be stopped
 - ▶ Use of HIV-protease inhibitors

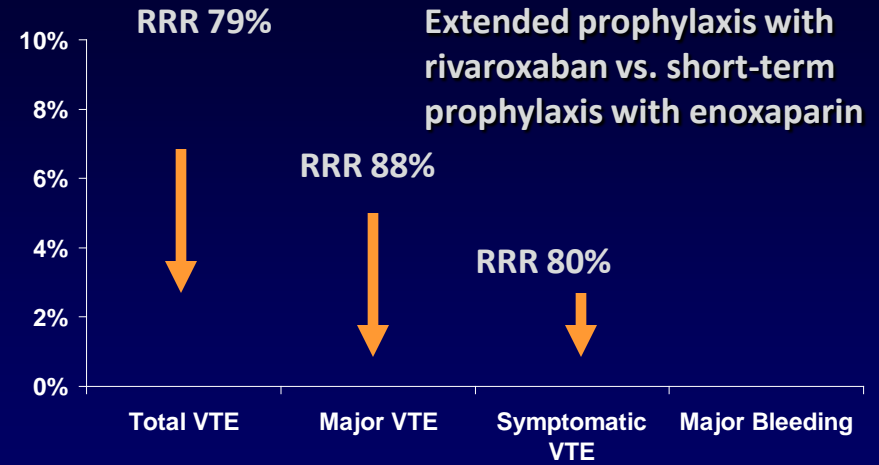
bid, twice daily; od, once daily; R, randomization

Lassen *et al.*, *N Engl J Med* 2008; Turpie *EFORT* 2008

RECORD1



RECORD2

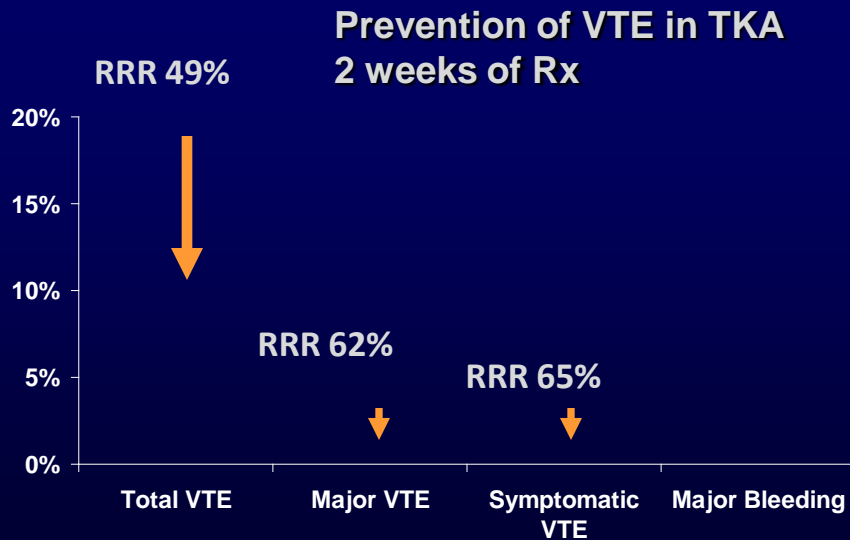


Eriksson BI et al. N Engl J Med 2008; 358:2765-2775.

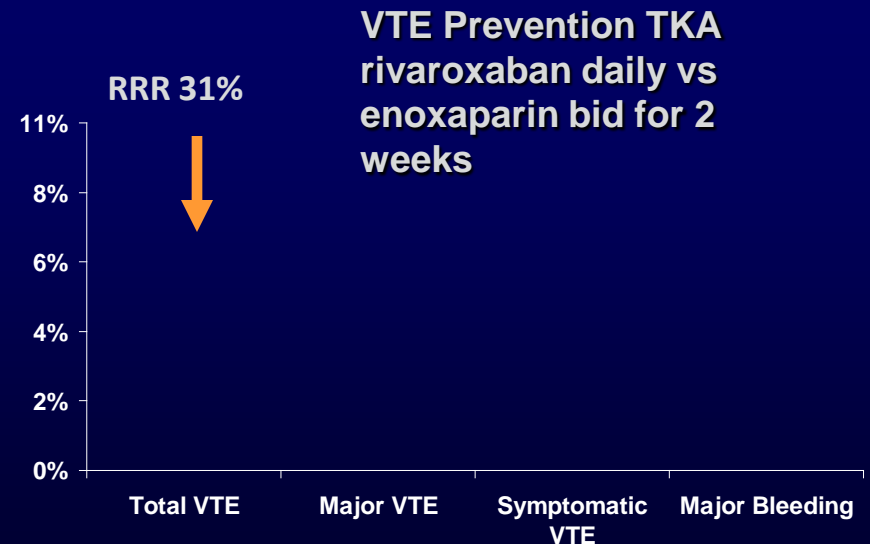
■ Enoxaparin 40 mg QD
■ Rivaroxaban 10 mg QD

Kakkar AK et al., Lancet 2008;372:31-39

RECORD3








RECORD4



Lassen MR et al. N Engl J Med 2008; 358:2776-2786.

Turpie AGG, et al. Lancet 2009;373:1673-1680.

Rivaroxaban Clinical Development Program

Trial	Indication	Trial design	Notes
 RECORD	VTE prevention in major orthopedic surgery	>11,000 patients Hip replacement or knee replacement Vs standard prophylaxis (enoxaparin)	Approved in Canada; EU pending; FDA Advisory Committee March '09
 MAGELLAN	VTE prevention in medically ill	Vs standard prophylaxis (enoxaparin)	Late start
 ROCKET AF	Stroke Prevention in Atrial Fibrillation	~14,000 patients Non-inferiority vs standard therapy (warfarin)	2010
 EINSTEIN	VTE treatment	~7,500 patients Vs standard therapy	2010
 ATLAS ACS TIMI 46	Acute Coronary Syndromes	~3,500 patients	2012

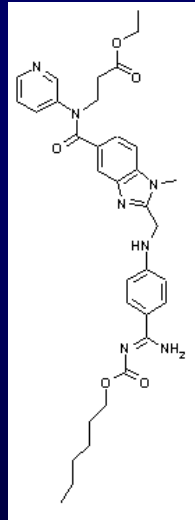
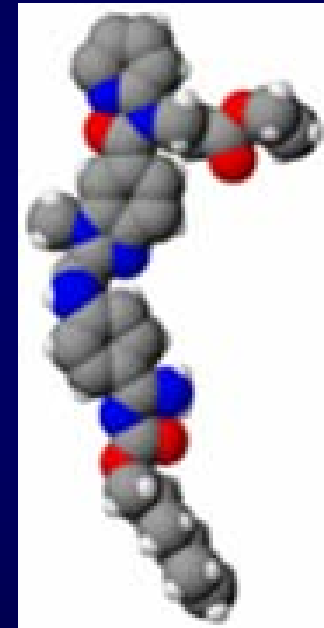
Links to FDA documents:

- ▶ **FDA Rivaroxaban Documents.**
- ▶ http://www.fda.gov/ohrms/dockets/ac/09/briefing/2009-4418b1-03-Johnson_Johnson.pdf
- ▶ <http://www.fda.gov/ohrms/dockets/ac/09/briefing/2009-4418b1-01-FDA.pdf>
- ▶ <http://www.fda.gov/ohrms/dockets/ac/09/briefing/2009-4418b1-02-FDA-Errata.pdf>

Dabigatran Etexilate: An Oral Direct Thrombin Inhibitor

- Specific, competitive, reversible univalent thrombin inhibitor
- Inhibits free and fibrin-bound thrombin activity
- Pro-Drug rapidly converted to active form
- Rapid onset within 2 hours
- Low bioavailability, 3.5-5%
- Half life 12-17 hours
- Renal clearance as glucuronic acid conjugate
- Cytochrome P450 system isoenzymes are not involved with metabolism, no induction or inhibition.
- Prolongs aPTT in a non-linear fashion
- Approved in Europe

Rendix,
Pradaxa®



Baetz BE. Pharmacotherapy 2008.

Perzborn E. J Thromb Haemost 2005.

Kubitza D., J Clin Pharmacol 2007.

Eikelboom JE. Thromb Haemostasis 2009.

Study Design: Phase III Trials

	RE-MOBILIZE	RE-MODEL	RE-NOVATE
Target Population	TKR	TKR	THR
Dabigatran Dose	150 & 220 mg	150 & 220 mg	150 & 220 mg
1 st Dose	6 to 12 hours post-op	1 to 4 hours post-op	1 to 4 hours post-op
Enoxaparin Dose	30 mg Twice daily*	40 mg Daily†	40 mg Daily†
Treatment Duration	12 to 15 days	6 to 10 days	28 to 35 days
Primary Endpoint	Total VTE + all-cause mortality	Total VTE + all-cause mortality	Total VTE + all-cause mortality
Non-inferiority margin	9.2 %	9.2%	7.7%

*Commenced 12-24 h post surgery; †Commenced evening before surgery.

Major VTE and VTE-Related Death

Study	Dabigatran 150 mg	Dabigatran 220 mg	Enoxaparin
RE-NOVATE* (THR)	4.3%	3.1%	3.9%
RE-MODEL (TKR)	3.8%	2.6%	3.5%
RE-MOBILIZE (TKR)	3.0%	3.4%	2.2%
Pooled	3.8%	3.0%	3.3%
Absolute risk difference	0.5	-0.2	
(Dabigatran – Enoxaparin)			
[95% CI]	[-0.6 to 1.6]	[-1.3 to 0.9]	

*RE-NOVATE adjudicated by a different committee than RE-MODEL and RE-MOBILIZE

Eriksson BI et al. Lancet 2007;370:949-56

Eriksson BI et al. J Thromb Haemost 2007;5:2178-2185

RE-MOBILIZE Writing Committee J Arthroplasty 2009;24(1):1-9.

RE-MOBILIZE: Elective Total Knee Replacement

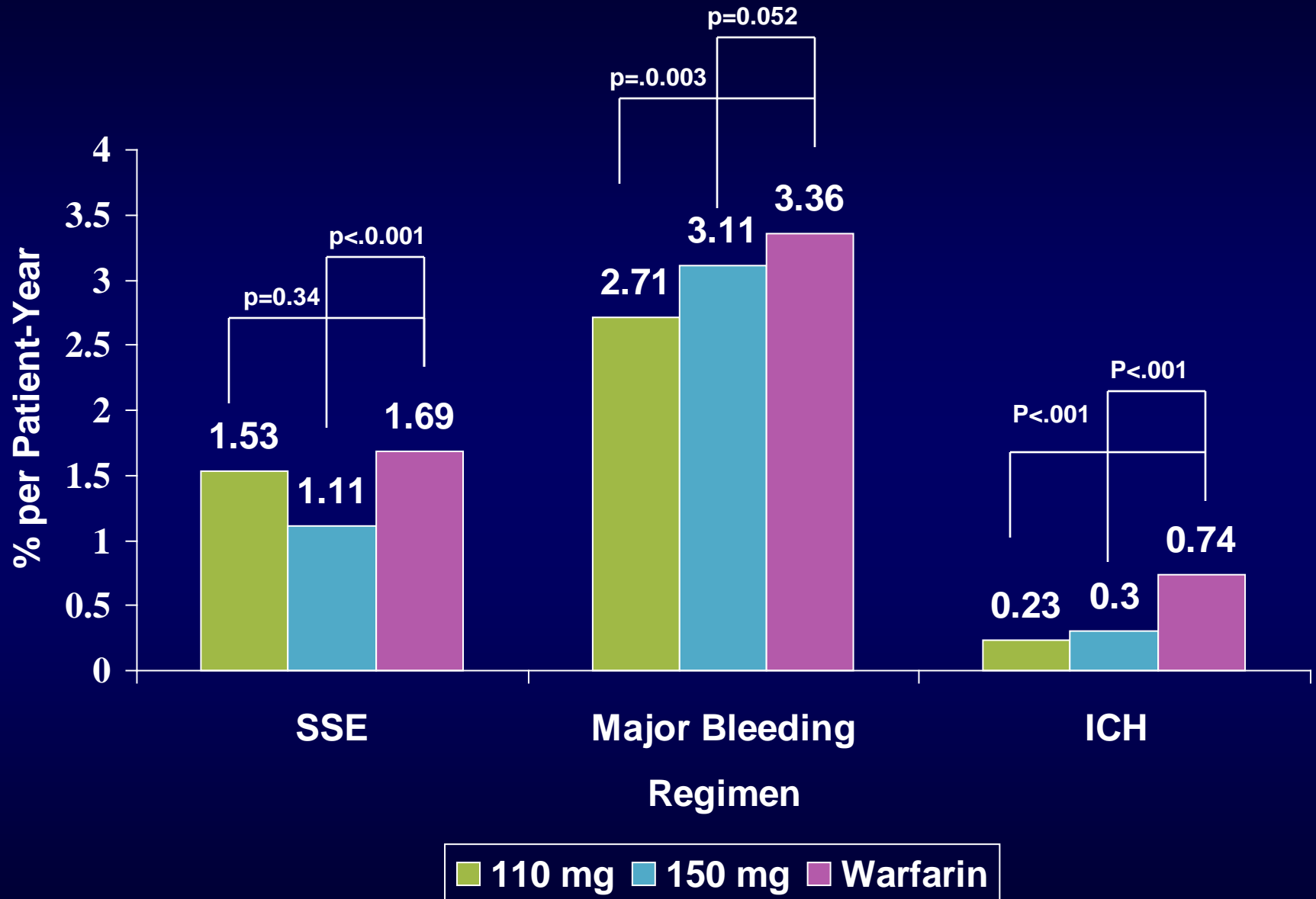
	Dabigatran 150 mg QD (n=871)	Dabigatran 220 mg QD (n=857)	Enoxaparin 30 mg Twice Daily (n=868)
All VTE and Mortality	33.7%	31.1%	25.3%
Distal DVT	30.5%	27.6%	23.0%
Proximal DVT	3.1%	2.3%	1.6%
Non Fatal PE	0.0%	1.0%	0.8%
Major Bleeding	0.6%	0.6%	1.4%

Safety: Major Bleeding Events

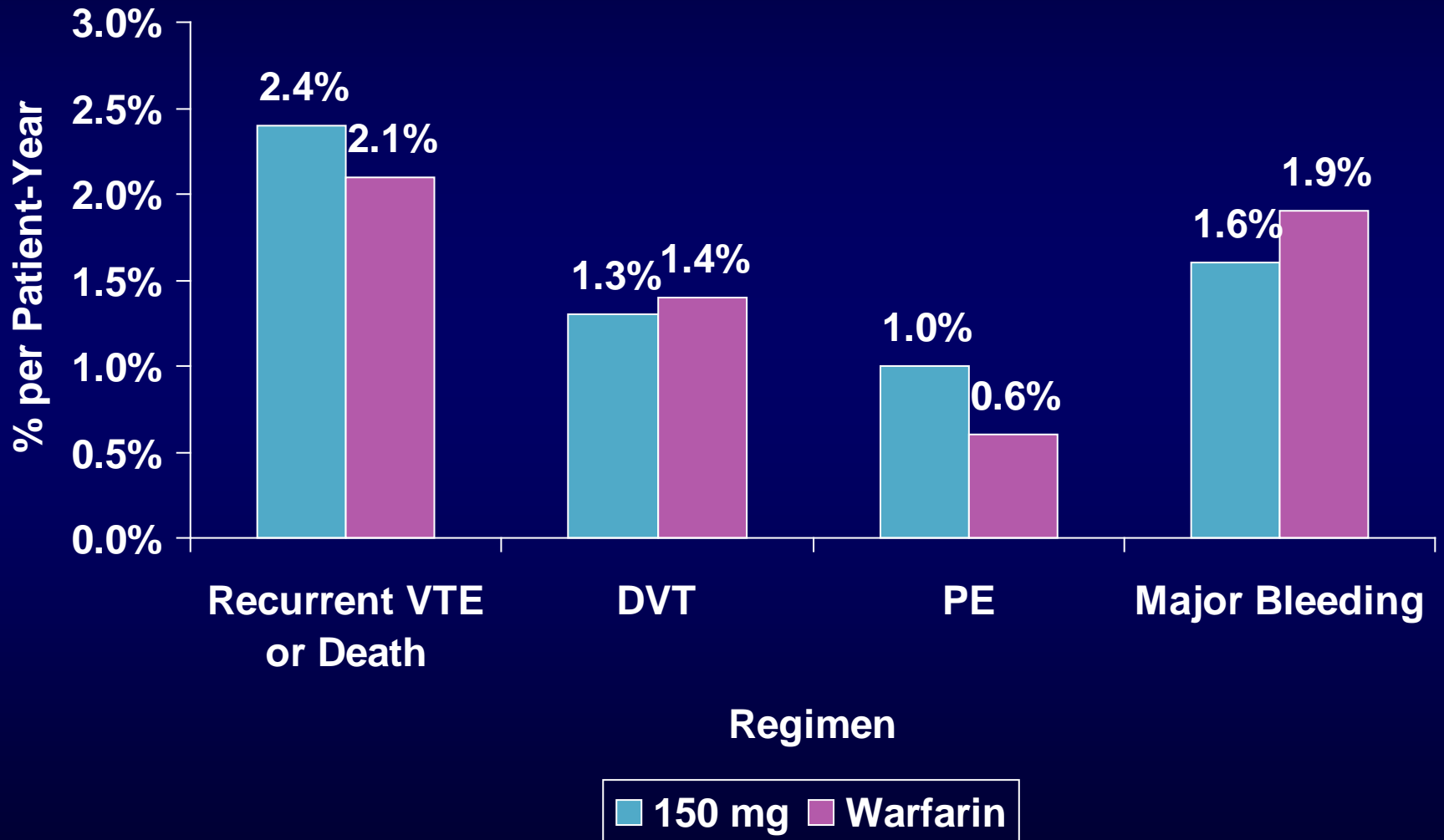
	Dabigatran		Enoxaparin
	150 mg	220 mg	
	N=2737	N=2682	N=2716
Major Bleeding Event n (%)	29 (1.1)	38 (1.4)	39 (1.4)

- All bleeding events adjudicated by the same independent adjudication committee in all three studies
- Results consistent across all three studies with no statistically significant differences for any of the bleeding outcomes

RE-LY Trial



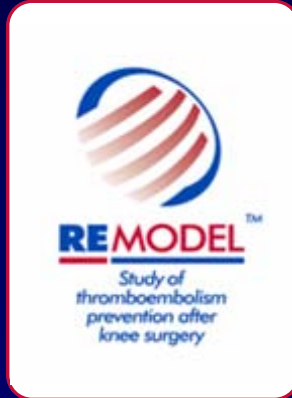
RE-COVER Trial



Schulman S, et al. N Engl J Med 361:2342-2352.

RE-VOLUTION - Trial Program

Primary VTE Prevention (completed)



Secondary Prevention in ACS—Phase II



Acute VTE Treatment



Secondary VTE Prevention



Stroke Prevention in Atrial Fibrillation

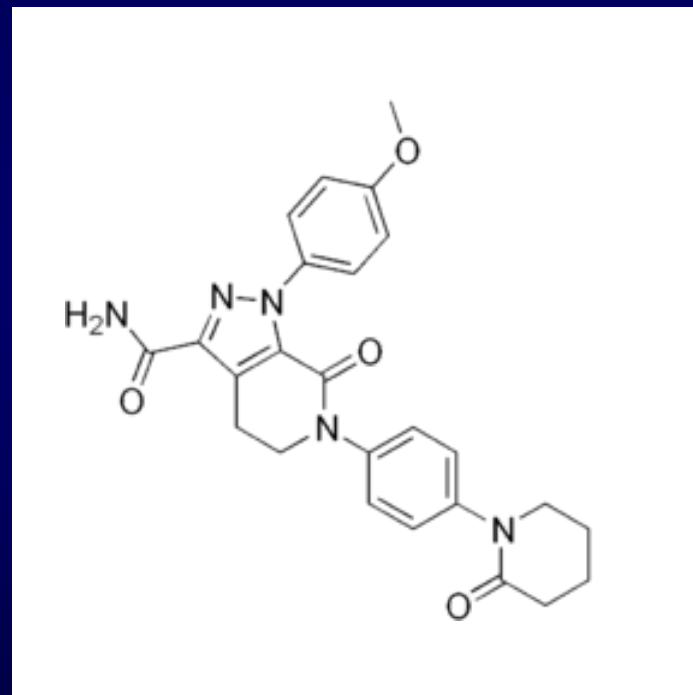


More than 34,000 patients involved

Apixaban: An Oral Direct Factor Xa Inhibitor

- Direct, reversible Factor Xa inhibitor
- Rapid onset, peak within 3 hours
- Bioavailability of 51-85%
- Small volume of distribution (16-25 liters)
- Long half life, slightly longer in elderly (15 hours)
- Multiple elimination pathways
 - 25% renal
 - 75% biliary
- Metabolism via CYP3A4, SULT1AA pathways
- Major metabolite phenol sulfate conjugate
- Follow-up to Razaxaban (halted due to high bleeding)

BMS-562247



Frost C. J Thromb Haemost 2007.
Kubitza D., J Clin Pharmacol 2007.
Eikelboom JE. Thromb Haemostasis 2009

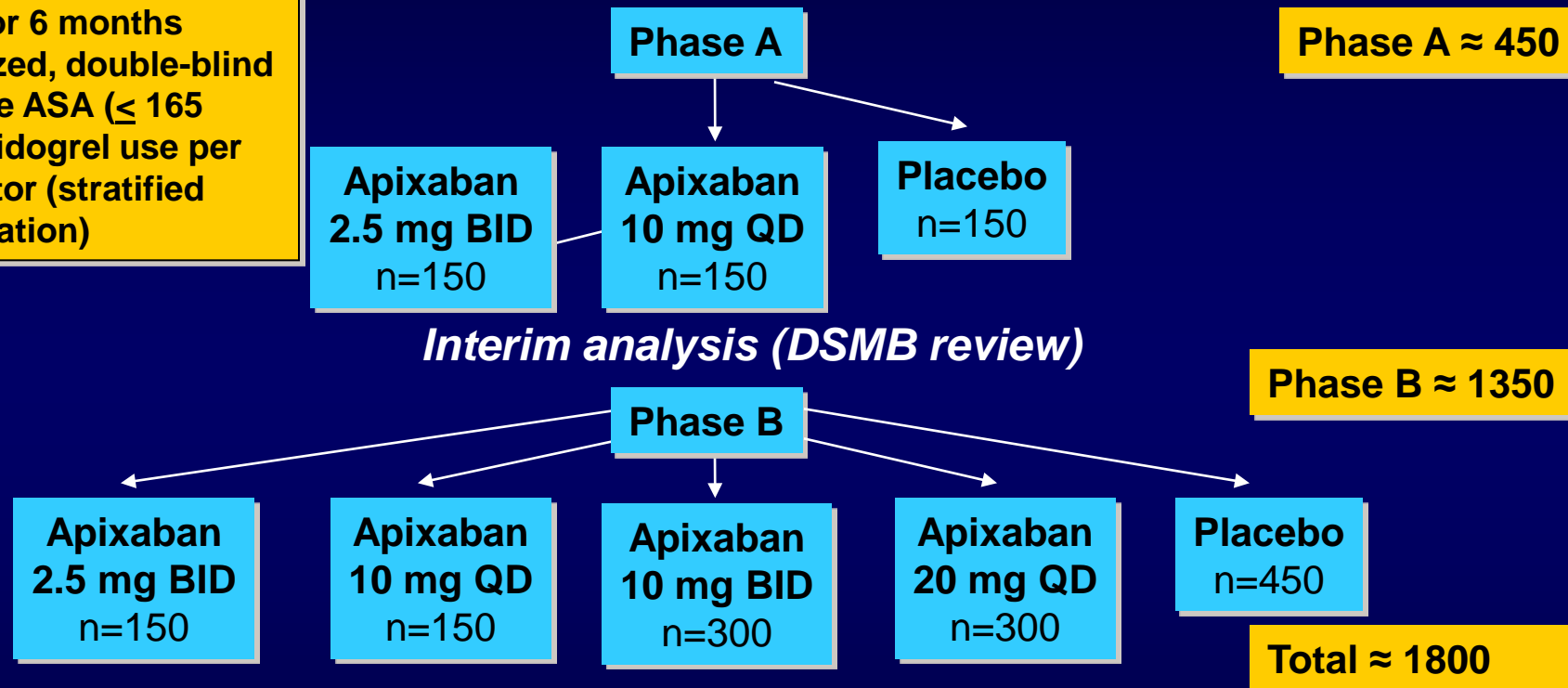
Apixaban Phase II Studies

APROPOS CV185010 completed	Phase II dose-ranging study (2.5 mg BID vs 5 mg QD vs 5 mg BID vs 10 mg QD vs 10 mg BID vs 20 mg QD vs Enoxaparin vs Warfarin) for VTE prevention in patients undergoing total knee replacement.
BOTTICELLI CV185017 completed	Phase II dose-ranging study (5 mg BID vs 10 mg BID vs 20 mg QD) for treatment of DVT
ADVOCATE CV185027 ongoing	Phase II pilot study (5 mg QD vs Placebo) for VTE prevention in patients with advanced cancer
APPRAISE-1 CV185023 completed	Phase II study (2.5 mg BID vs 10 mg QD vs 10 mg BID vs 20 mg QD vs Placebo) in patients with recent acute coronary syndromes

APPRAISE-1

Recent ACS patients (n=1,715)
≤7 days and at least one risk factor

Treated for 6 months
Randomized, double-blind
All receive ASA (≤ 165 mg), clopidogrel use per investigator (stratified randomization)



•Efficacy endpoint: major CV events (death, non fatal MI, severe recurrent ischemia & stroke)

- 2.5 mg Relative Risk Reduction 27%
- 10 mg Relative Risk Reduction 39%

•Safety endpoint: major bleeding (ISTH)

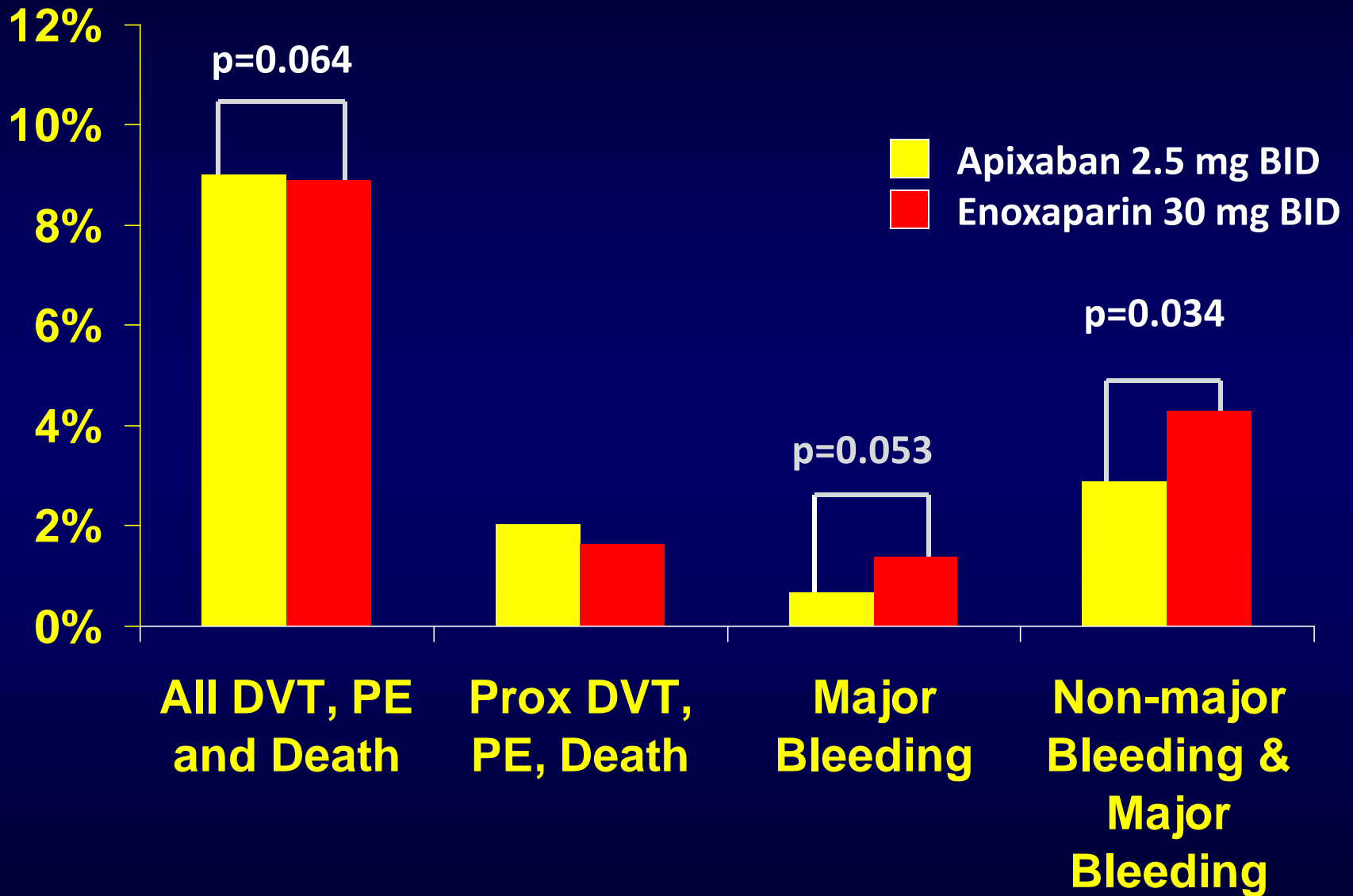
- 2.5 mg 5.7%
- 10 mg 7.9%
- 3% Placebo

Presented European Society of
Cardiology Meeting, Munich 2008

Apixaban Phase 3 VTE Prevention

ADVANCE-1 CV185034	VTE prevention after knee replacement surgery (N = 3000) <ul style="list-style-type: none">• 2.5 mg Twice daily for 12d vs. enoxaparin 30mg BID
ADVANCE-2 CV185047	VTE prevention after knee replacement surgery (N = 3000) <ul style="list-style-type: none">• 12d vs. enoxaparin 40mg QD
ADVANCE-3 CV185035	VTE prevention after hip replacement surgery (N=4000) <ul style="list-style-type: none">• 35d vs. enoxaparin 40mg QD
ADOPT CV185036	VTE prevention in acutely ill medical patients (N=6500) <ul style="list-style-type: none">• 30d vs. ~6d enoxaparin 40mg QD followed by placebo post-discharge

ADVANCE-1



Apixaban Phase 3 VTE Treatment

**AMPLIFY
CV185056**

Treatment of subjects with confirmed symptomatic proximal DVT or PE (N=5,000)

- 6 month treatment with 5 mg BID apixaban (after 1 week at 10 mg BID) vs. warfarin titrated to INR 2-3 (after initiation with enoxaparin 1 mg/kg BID)

**AMPLIFY-EXT
CV185057**

Extended treatment of subjects with DVT/PE who have completed standard anticoagulant therapy (N=2,400)

- One year treatment with 2.5 or 5 mg BID apixaban vs. placebo

Apixaban Phase 3

Stroke Prevention in Atrial Fibrillation

ARISTOTLE CV185030	Stroke prevention in patients with atrial fibrillation (N=15,000) <ul style="list-style-type: none">• Treatment for up to two years with 5 mg BID apixaban vs. warfarin (INR 2 -3)
AVERROES CV185048	Stroke prevention in patients with atrial fibrillation not able to receive warfarin (N=5,600) <ul style="list-style-type: none">• Treatment for up to two years with 5 mg BID apixaban vs. aspirin

“Real World” Anticoagulant Related Costs

	Drug Cost per month	AMS Labor month	Lab Testing (4 INRs)	Total
+Warfarin 5mg	11.66	39.60	292.00	\$343.26
+ Enoxaparin 40 mg	998.83	0.00	0.00	\$998.83
*Rivaroxaban 10 mg	487.50	0.00	0.00	\$487.50

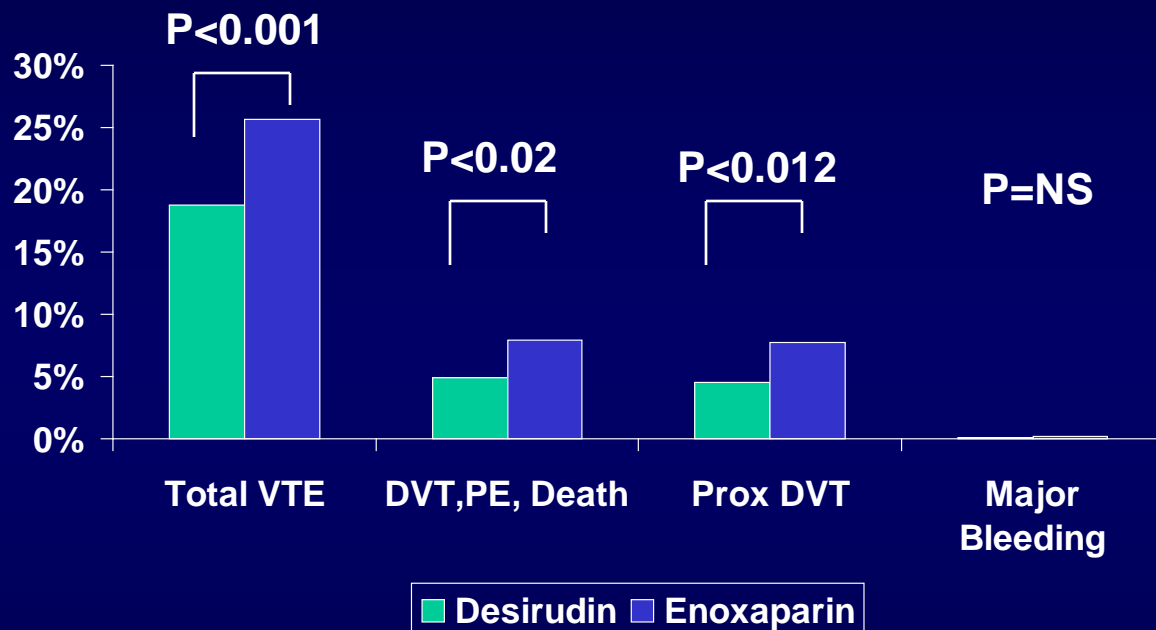
AMS = Anticoagulation Management Services

+ Drugstore.Com pricing

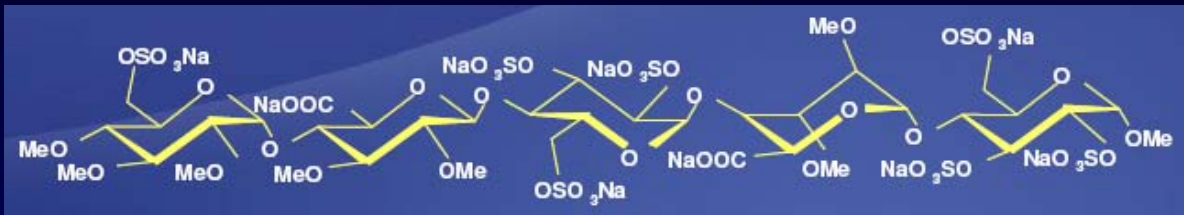
***Canadian dollars adjusted to U.S.**

Desirudin (Ipravask™)

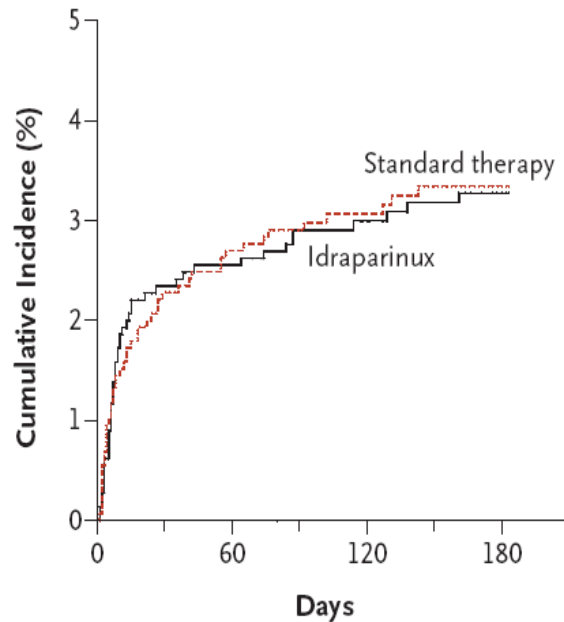
- 65 Amino acid chain
- Derived from medicinal leech
- Approved in US April 2003 for VTE prevention in THA
- Administered via subcutaneous injection
- Soon to be launched in the US late 2009



Idraparinux-Long Acting Factor Xa Inhibitor



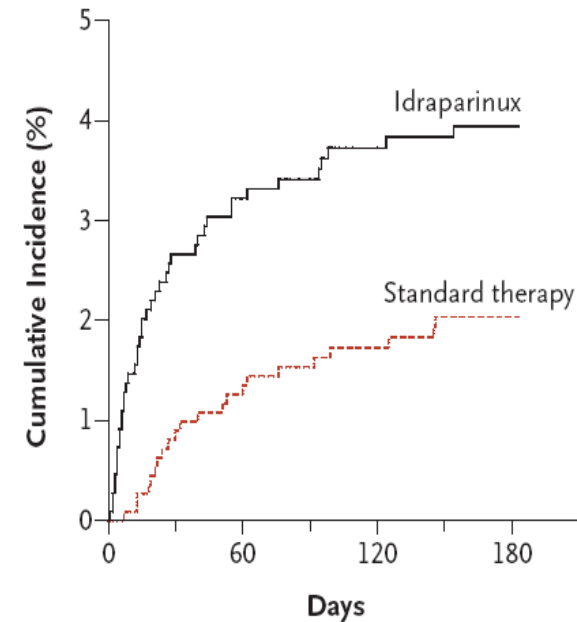
A DVT Study



No. at Risk

Idraparinux	1452	1395	1050	1034
Standard therapy	1452	1389	1067	1054

B PE Study



No. at Risk

Idraparinux	1095	1029	906	897
Standard therapy	1120	1083	965	950

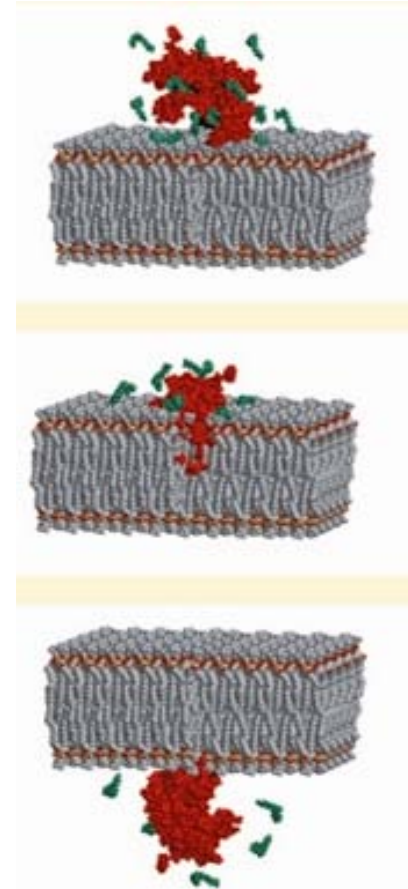
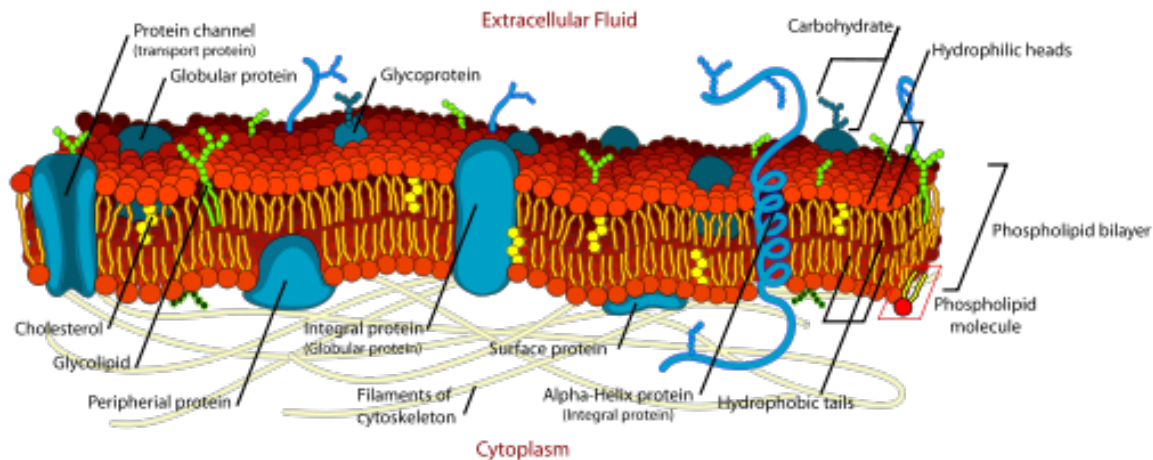
Cumulative Incidence of venous thromboemboli events

The van Gogh Investigators. N Engl J Med 2007;357:1094-104₃₃

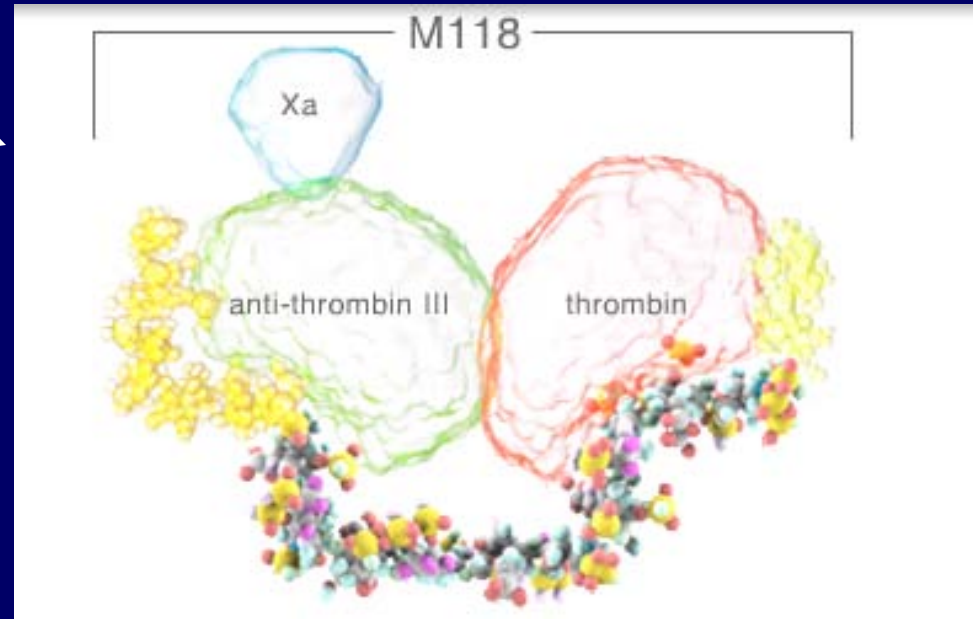
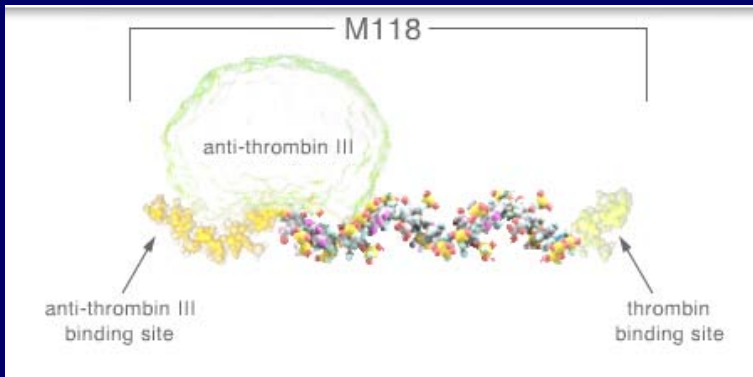
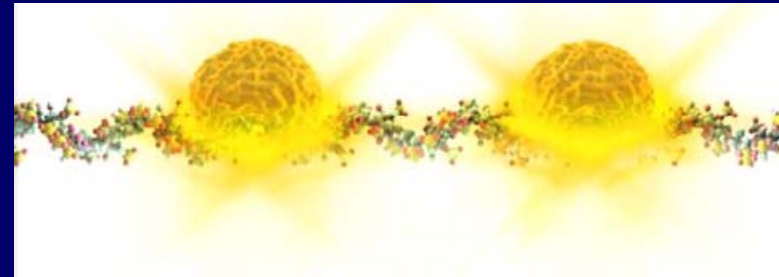
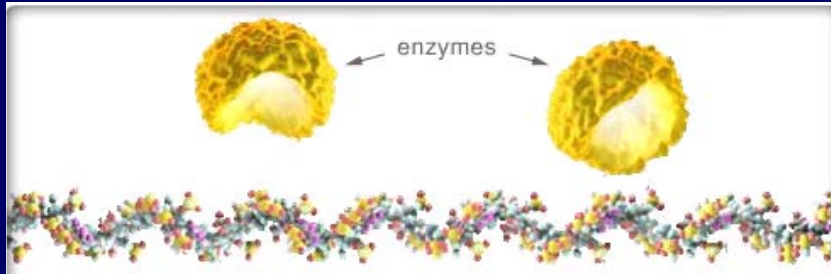
The Amadeus Investigators. Lancet 2008;371:315-321

Oral Heparin

- Combining unfractionated heparin with the carrier molecule: Sodium N-(8 [2-hydroxybenzoyl]amino) caprylate, or SNAC
- Markedly increased the gastrointestinal absorption

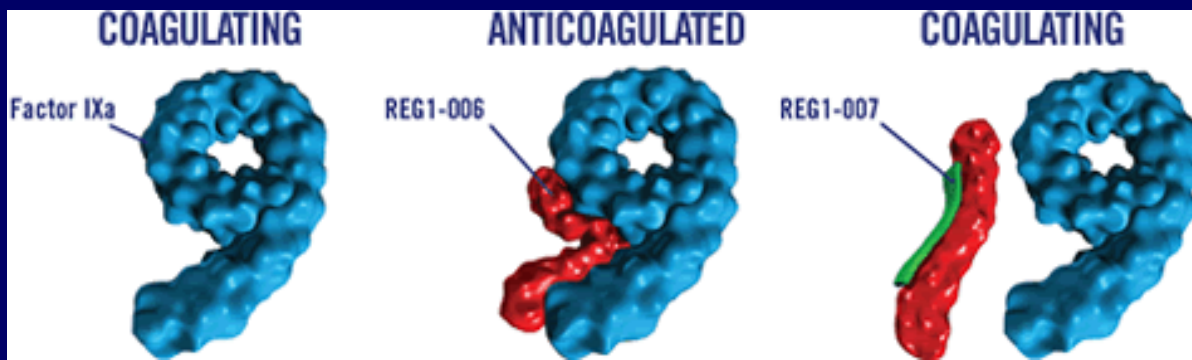
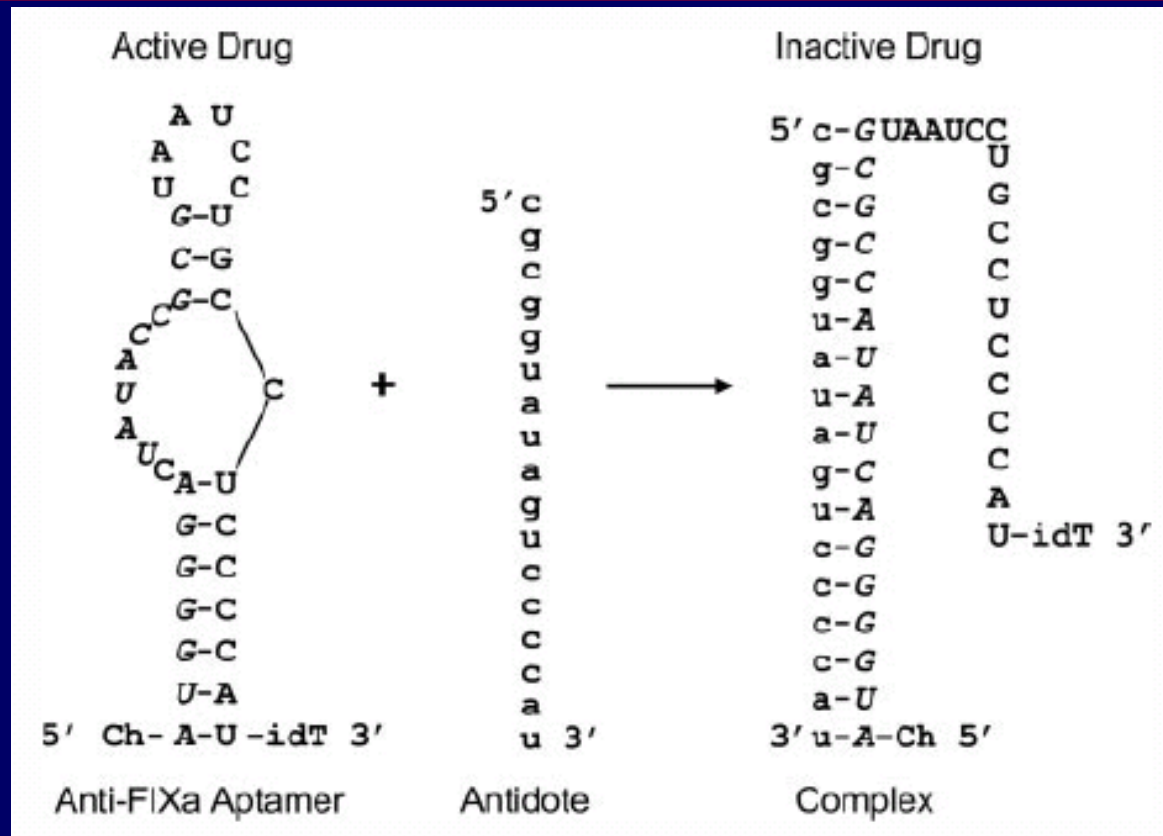


M118-Momenta, Inc



REG1 Anticoagulation System

- Comprised of an aptamer-based anticoagulant
- RB006, & its matched antidote, RB007



Summary

- Novel agents are available in Europe and Canada and under FDA review in the U.S.
- Each offers pharmacodynamic advantages over existing agents.
- Clinical trial results show comparable performance to existing agents.
 - Underlying disease still remains
- The \$ impact to patients, insurers, providers remains a question.
- More molecules are in early “discovery”.
- Patients and patience will reveal long term benefits.