

World Congress of Cardiology 2006

Barcelona, Spain 2-6 September 2006

Symposium “Antithrombotic therapy in atrial fibrillation” – Room Mumbai (Zone 1)

September 4th 2006, 08:30-10:00

New developments in pentasaccharides in atrial fibrillation

Raffaele De Caterina MD, PhD

**“G. D’Annunzio” University - Chieti and
CNR Institute of Clinical Physiology, Pisa, Italy**

September 4th 2006, 09:14-09:36, 16 min + 6 min discussion



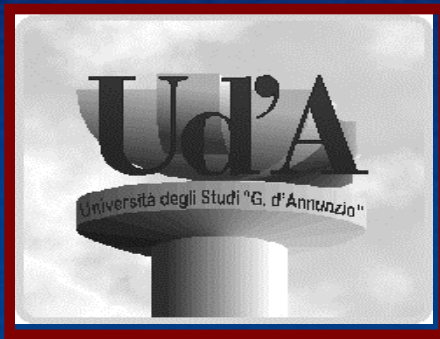
World Congress of Cardiology 2006

Barcelona, Spain 2-6 September 2006

Symposium "Antithrombotic therapy in atrial fibrillation" – Room Mumbai (Zone 1)

September 4th 2006, 08:30-10:00

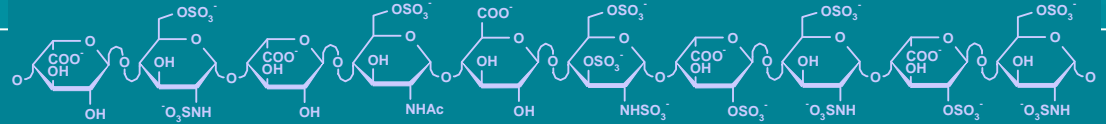
New developments in pentasaccharides in atrial fibrillation



Raffaele De Caterina MD, PhD
"G. D'Annunzio" University - Chieti and
CNR Institute of Clinical Physiology, Pisa, Italy

September 4th 2006, 09:14-09:36

Heparin binds to antithrombin and reinforces its anticoagulant activity



Coagulation/Thrombosis trigger

Factor X

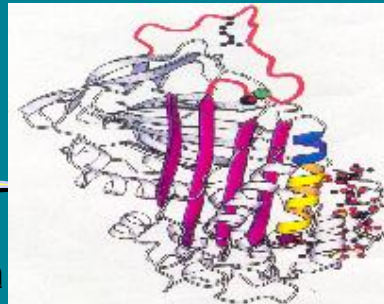
Factor Xa

Prothrombin
(Factor II)

Thrombin
(Factor IIa)

Fibrinogen

Fibrin Clot
(thrombosis)

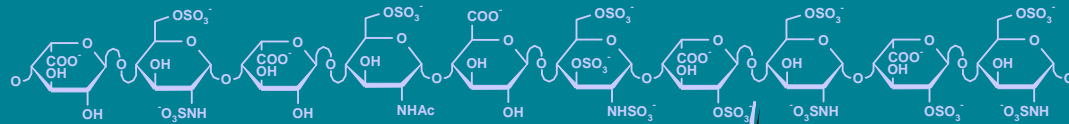


Heparin

Antithrombin



Heparin binds to antithrombin and reinforces its anticoagulant activity



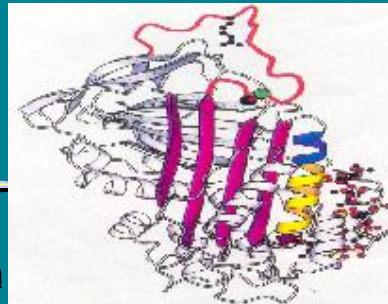
LMWH

Coagulation/Thrombosis trigger

Factor X



Factor Xa



Antithrombin



Prothrombin (Factor II)



Thrombin (Factor IIa)



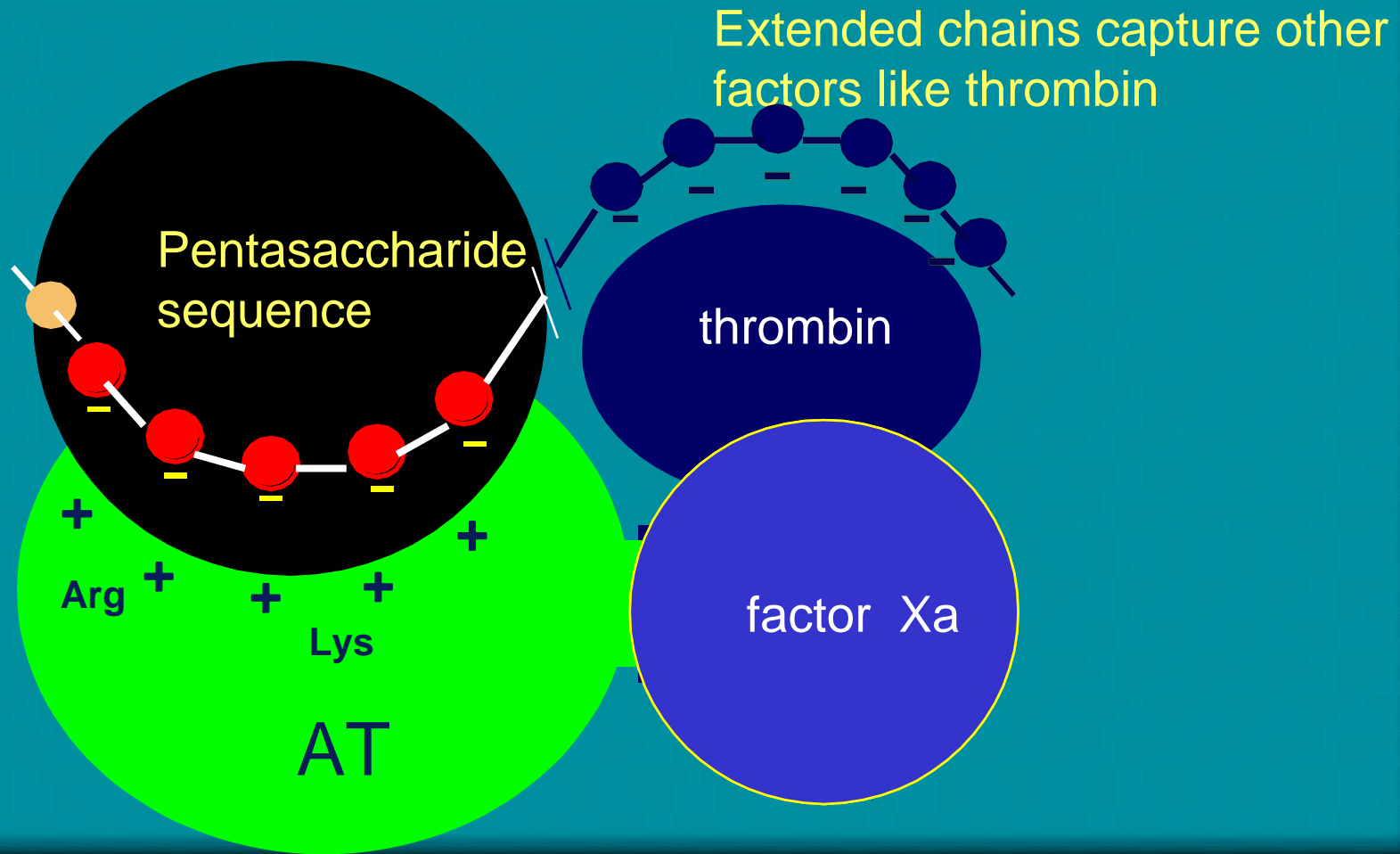
Fibrinogen



Fibrin Clot (thrombosis)

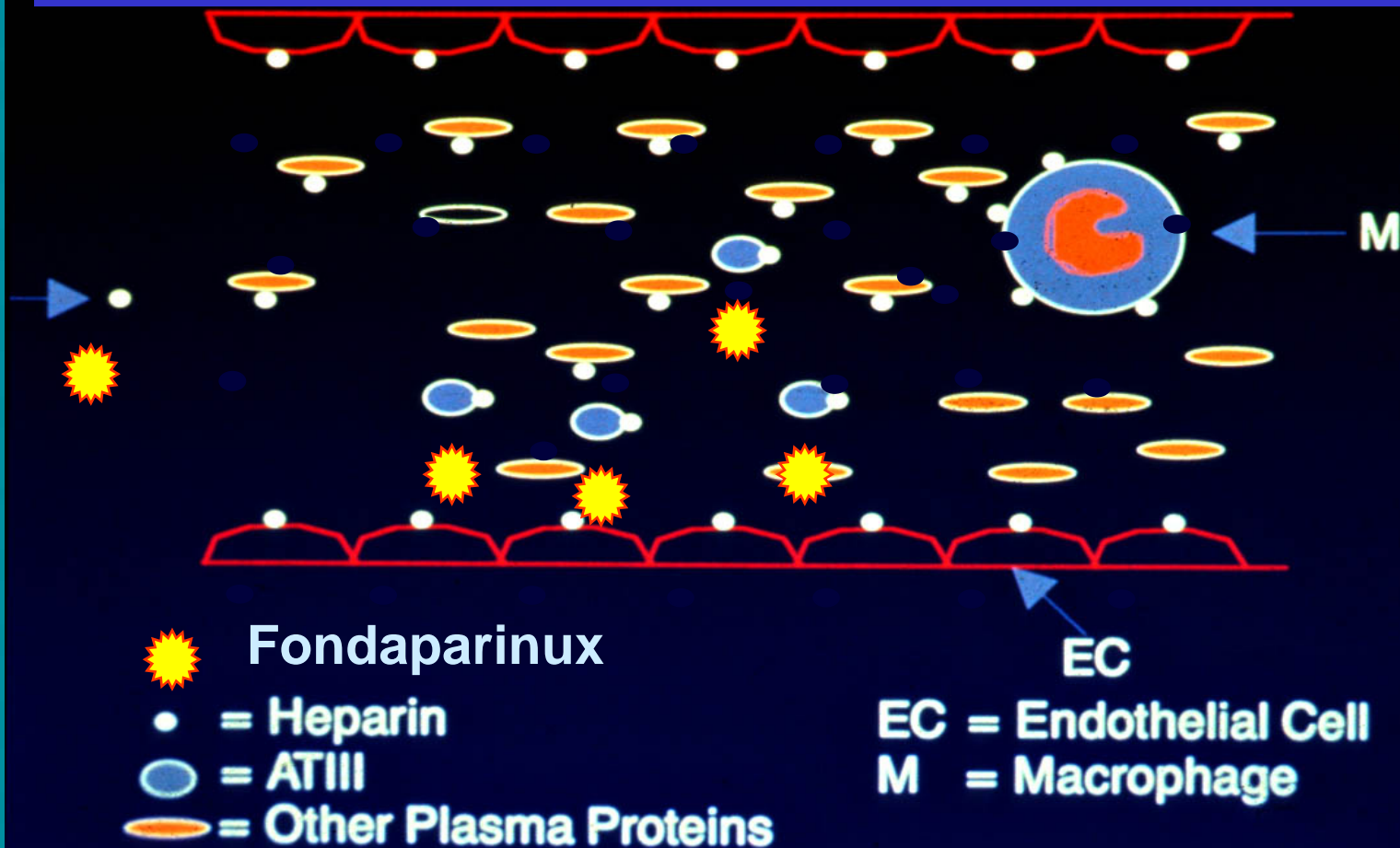


Mechanism of action of heparins and heparin-derived pentasaccharides

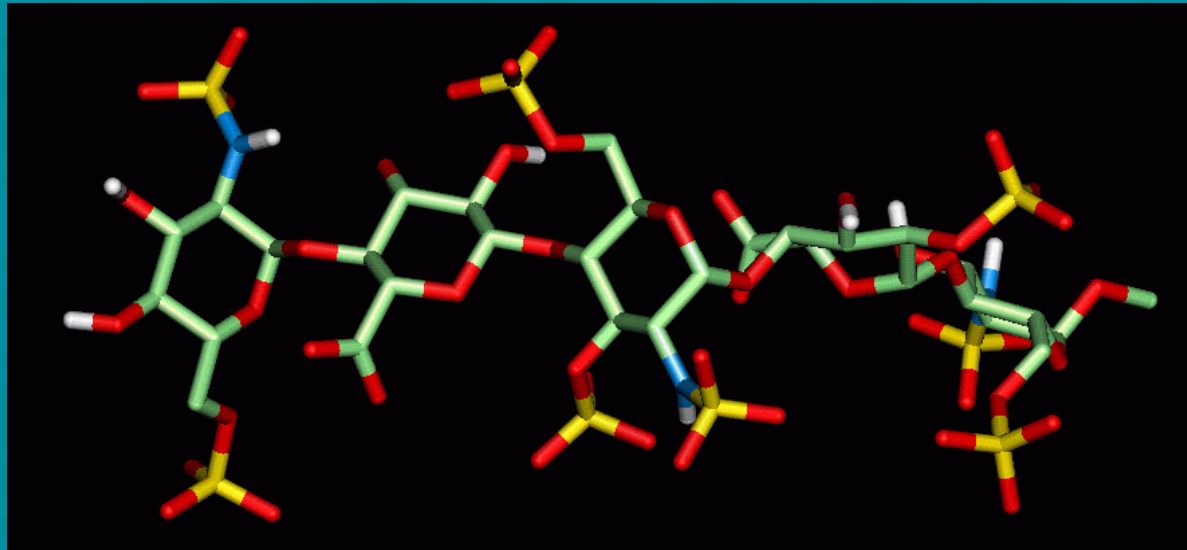


NON-SPECIFIC PROTEIN BINDING OF HEPARIN

SPECIFIC BINDING OF FONDAPARIINUX



Fondaparinux: the first in a new series of synthetic and selective factor Xa inhibitors

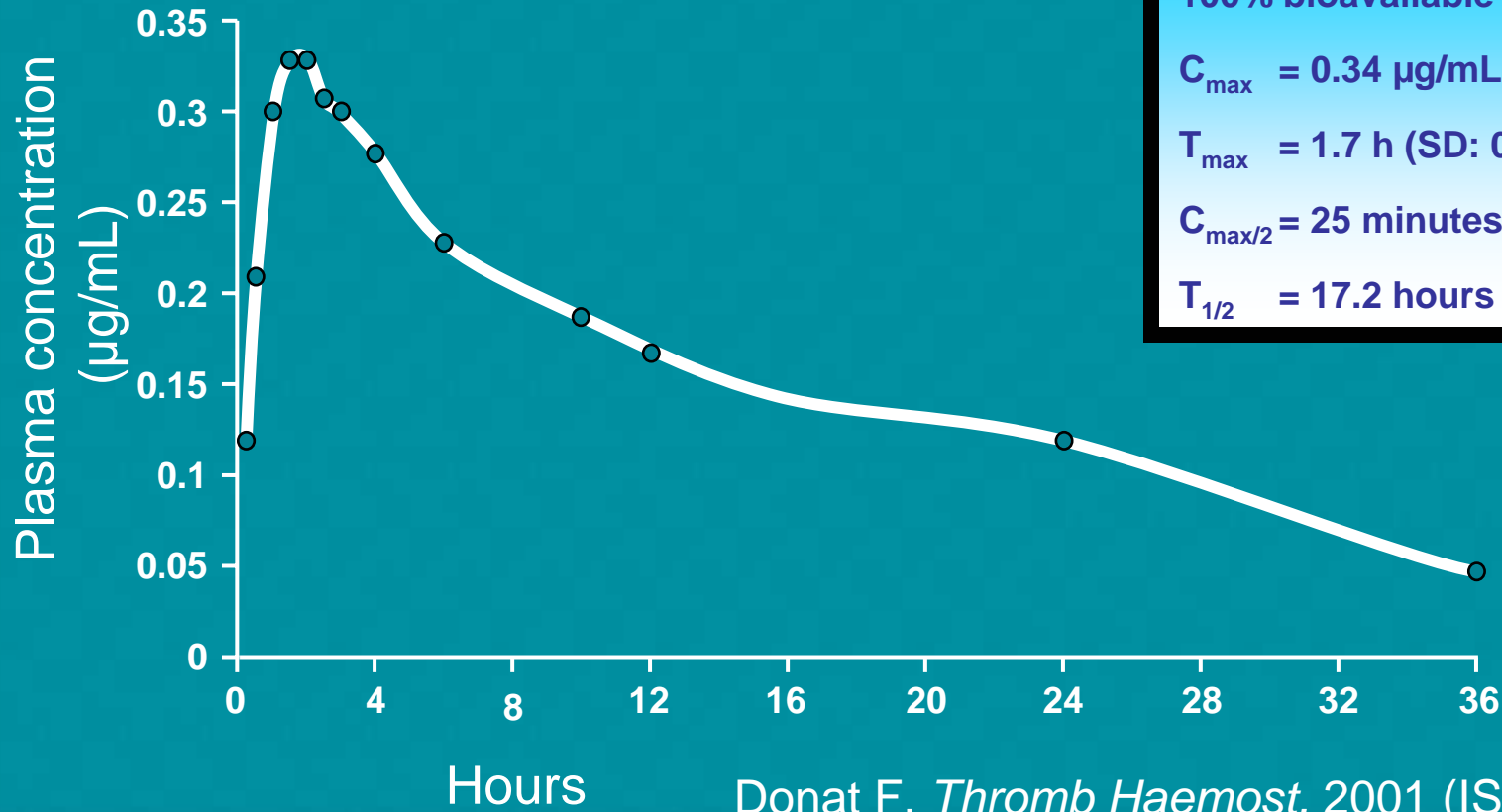


● Total chemical synthesis

- Highly selective against FXa
- Predictable and dose-dependent anticoagulant effect
- Only parenteral administration
- Renal clearance

Herbert , *Cardiovasc Drug Rev*, 1997
Van Boeckel, *Angew Chem Int Ed Engl*, 1993

Fondaparinux pharmacokinetic profile



100% bioavailable

C_{\max} = 0.34 µg/mL (SD: 0.04)

T_{\max} = 1.7 h (SD: 0.4)

$C_{\max/2}$ = 25 minutes

$T_{1/2}$ = 17.2 hours (SD: 3.2)

Donat F, *Thromb Haemost*, 2001 (ISTH Abstract)

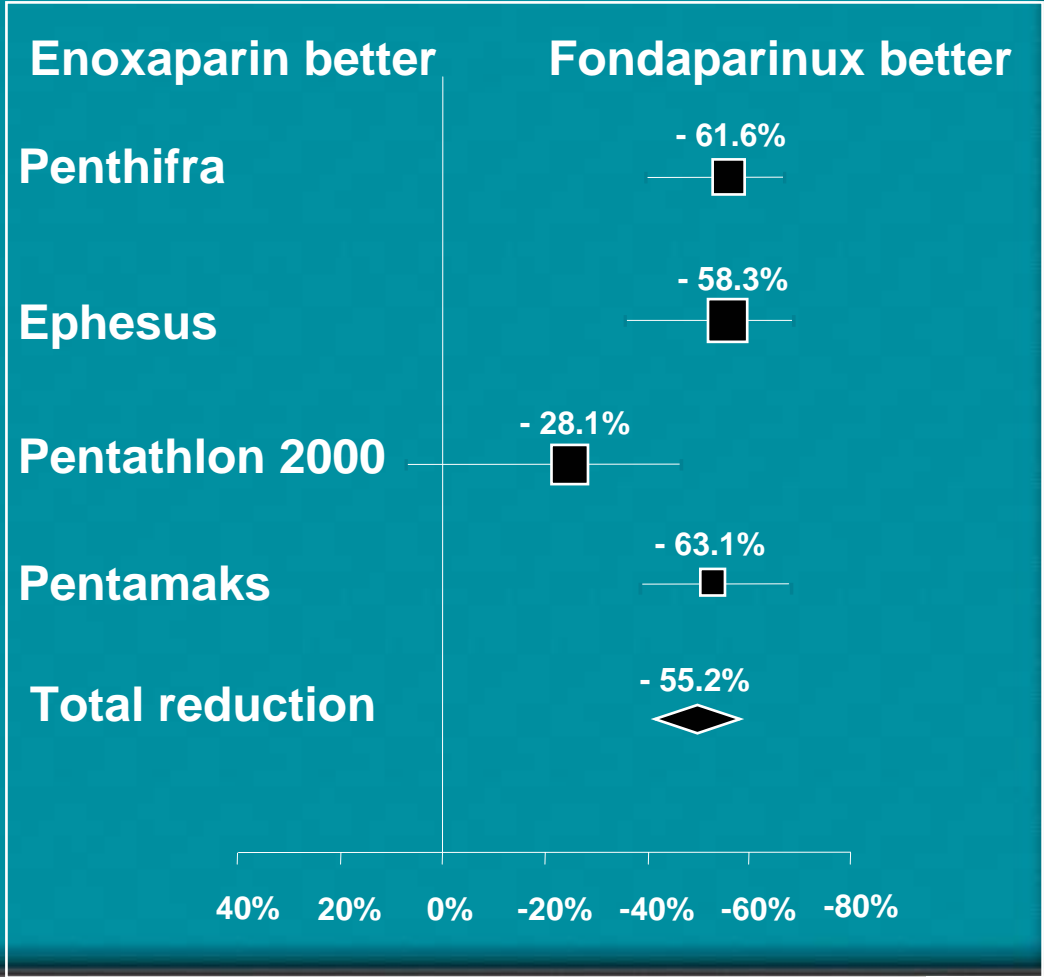
Fondaparinux : phase III studies in major orthopaedic surgery

| | |
|-------------------------|---|
| PENTHIFRA: | Hip fracture (Europe, South America, Oceania) 1,711 patients |
| EPHESUS: | Hip replacement (Europe) 2,309 patients |
| PENTATHLON 2000: | Hip replacement (North America, Oceania) 2,275 patients |
| PENTAMAKS: | Major knee surgery (North America) 1049 patients |

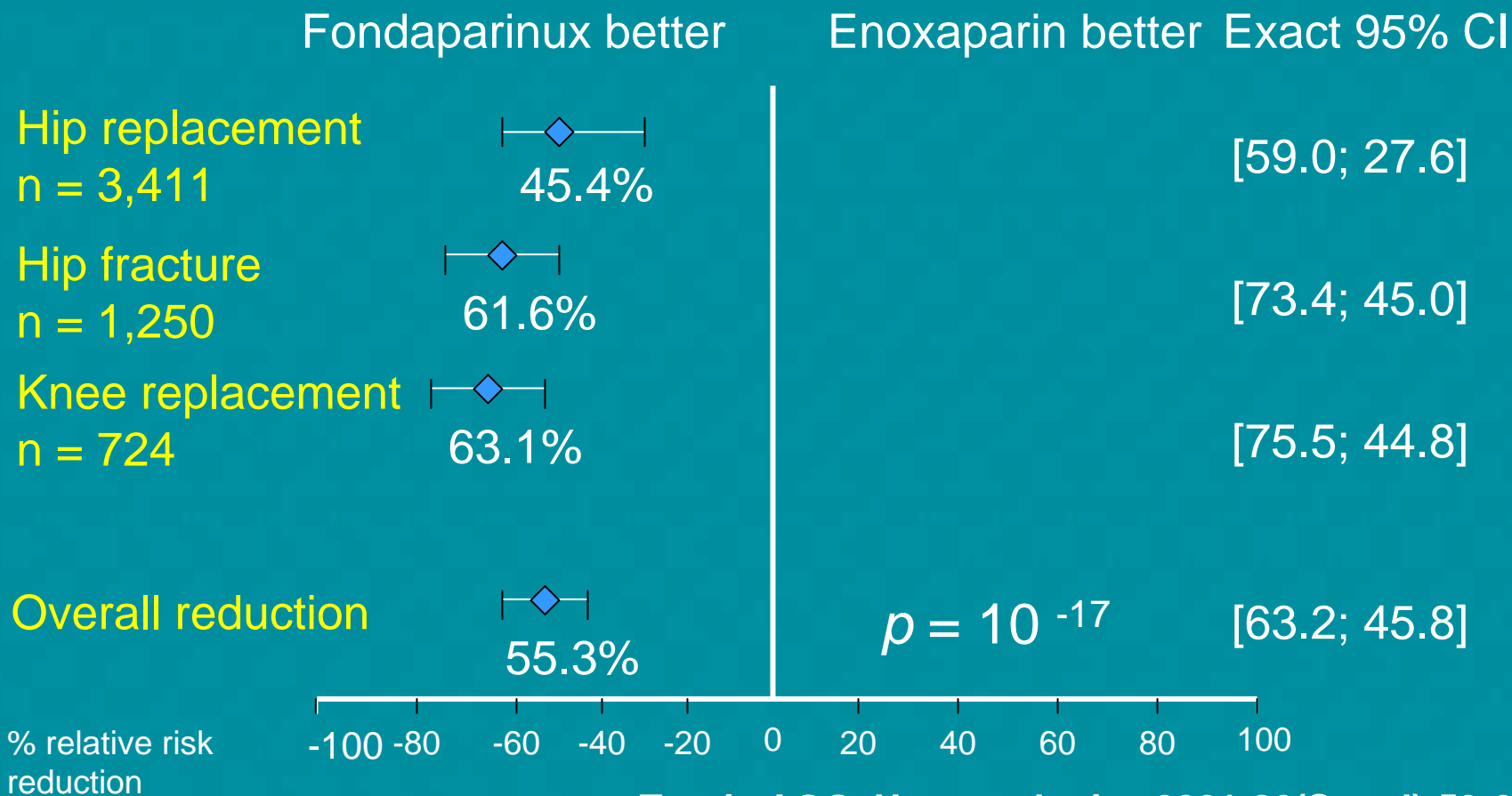
Fondaparinux: meta-analysis of four studies in major orthopedic surgery

RRR of VTE: 55.2 %
p < 0.001

Turpie, *Arch Intern Med*, 2002



Overall efficacy of Fondaparinux vs enoxaparin: % reduction per type of surgery and overall



Turpie AGG, Haematologica 2001;86(Suppl):59-62.

Fondaparinux development

| Indication | Area | Study |
|----------------------------|---|---------------------|
| DVT prophylaxis | High-risk abdominal surgery | PEGASUS |
| DVT Therapy | DVT | REMBRANDT |
| DVT Therapy | DVT, PE | MATISSE(DVT-PE) |
| ACS Therapy ACS Therapy | AMI after thrombolysis Unstable angina | PENTALYSE PENTUA |
| ACS Therapy | non-ST ACS and STEMI | MICHELANGELO |



OASIS 5-MICHELANGELO

Patients with NSTEMI ACS, Chest discomfort < 24 hours

2 of 3: Age > 60, ST Segment Δ, ↑ cardiac markers

ASA, Clop, GP IIb/IIIa, planned Cath/PCI as per local practice

Exclude

- Age < 21
- Any contra-ind to Enox
- Hem stroke < 12 mo.
- Creat > 3 mg/dL/265 umol/L



Randomize

Fondaparinux 2.5 mg sc once

N=20,000

Enoxaparin 1 mg/kg sc twice

PCI < 6 h: IV Fonda 2.5 mg without IIb/IIIa, 0 with IIb/IIIa
PCI > 6 h: IV Fonda 2.5 mg with and 5.0 mg without IIb/IIIa

PCI < 6 h, No additional UFH
PCI > 6 h, IV UFH
 With IIb/IIIa 65 U/kg
 Without IIb/IIIa 100 U/kg

Outcomes

Primary: **Efficacy:** Death, MI, refractory ischemia at 9 days

Safety: Major bleeding at 9 days

Risk benefit: Death, MI, refractory ischemia, major bleeds 9 days

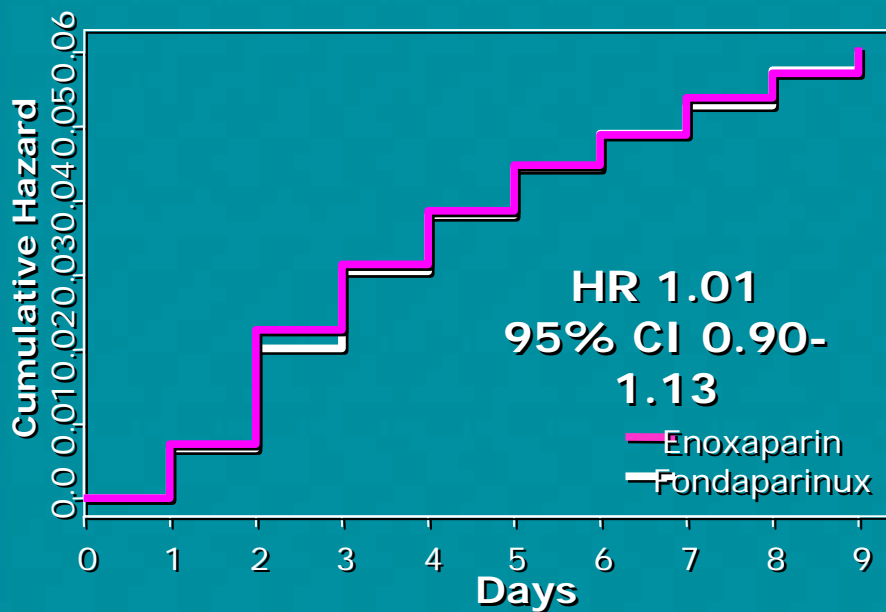
Secondary: Above & each component separately at day 30 & 6 months

Hypothesis: First test non-inferiority, then test superiority

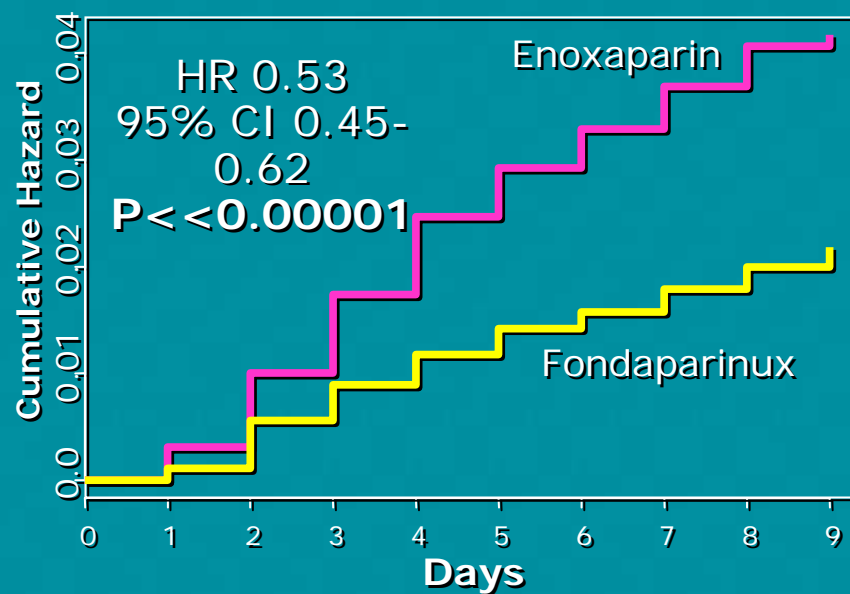


Results

Death/MI/recurrent
ischemia: 9 Days

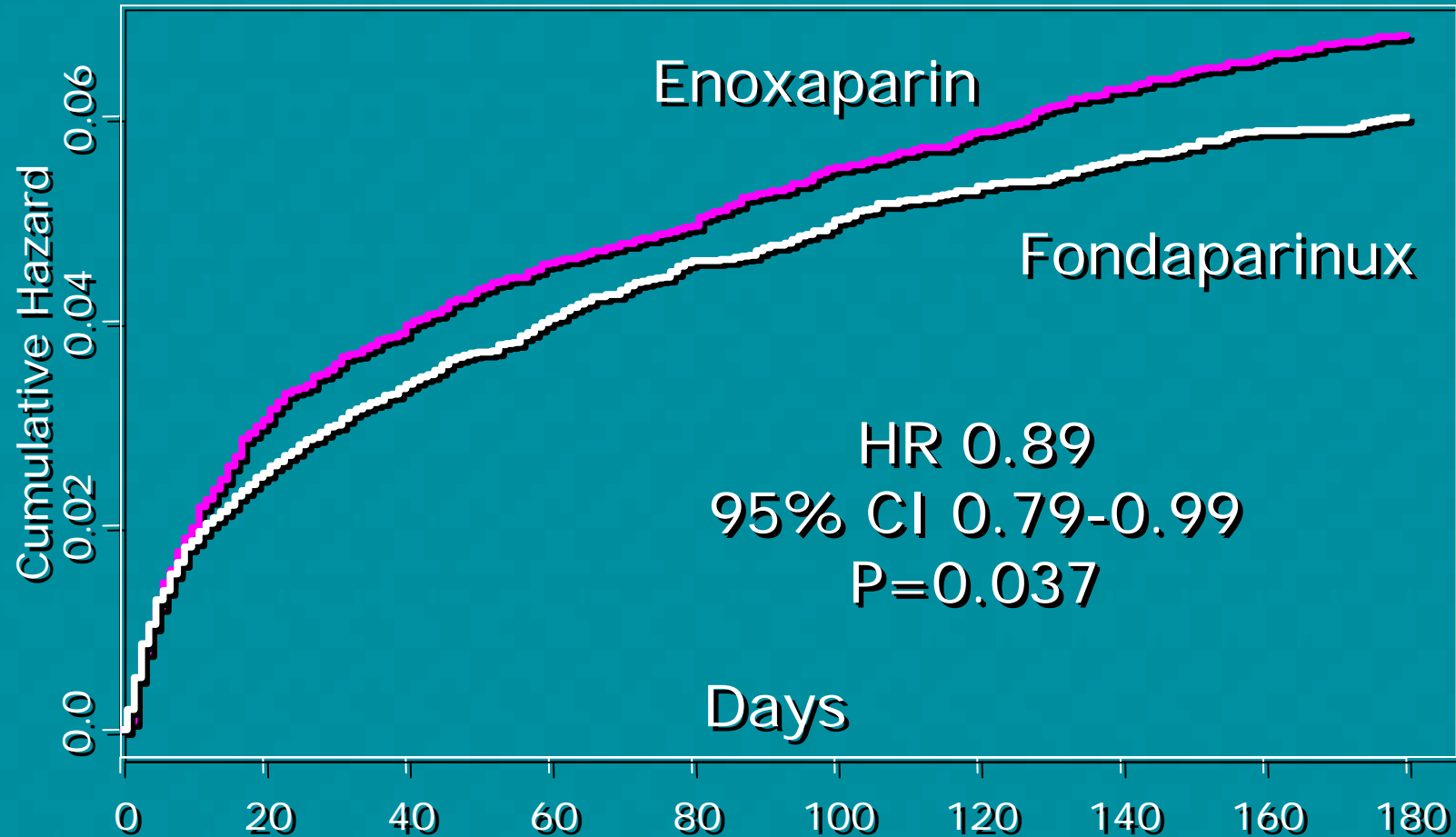


Major Bleeding:
9 Days



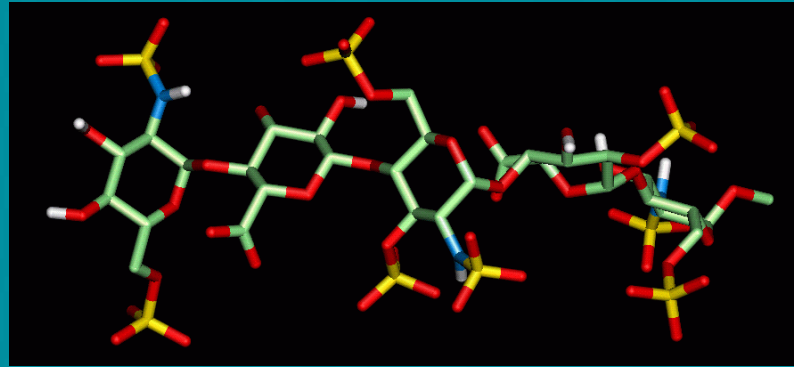
S. Yusuf & S. R. Mehta, CA, 1332

Mortality at 6 Months



S. Yusuf & S. R. Mehta, CA, 1332

Fondaparinux



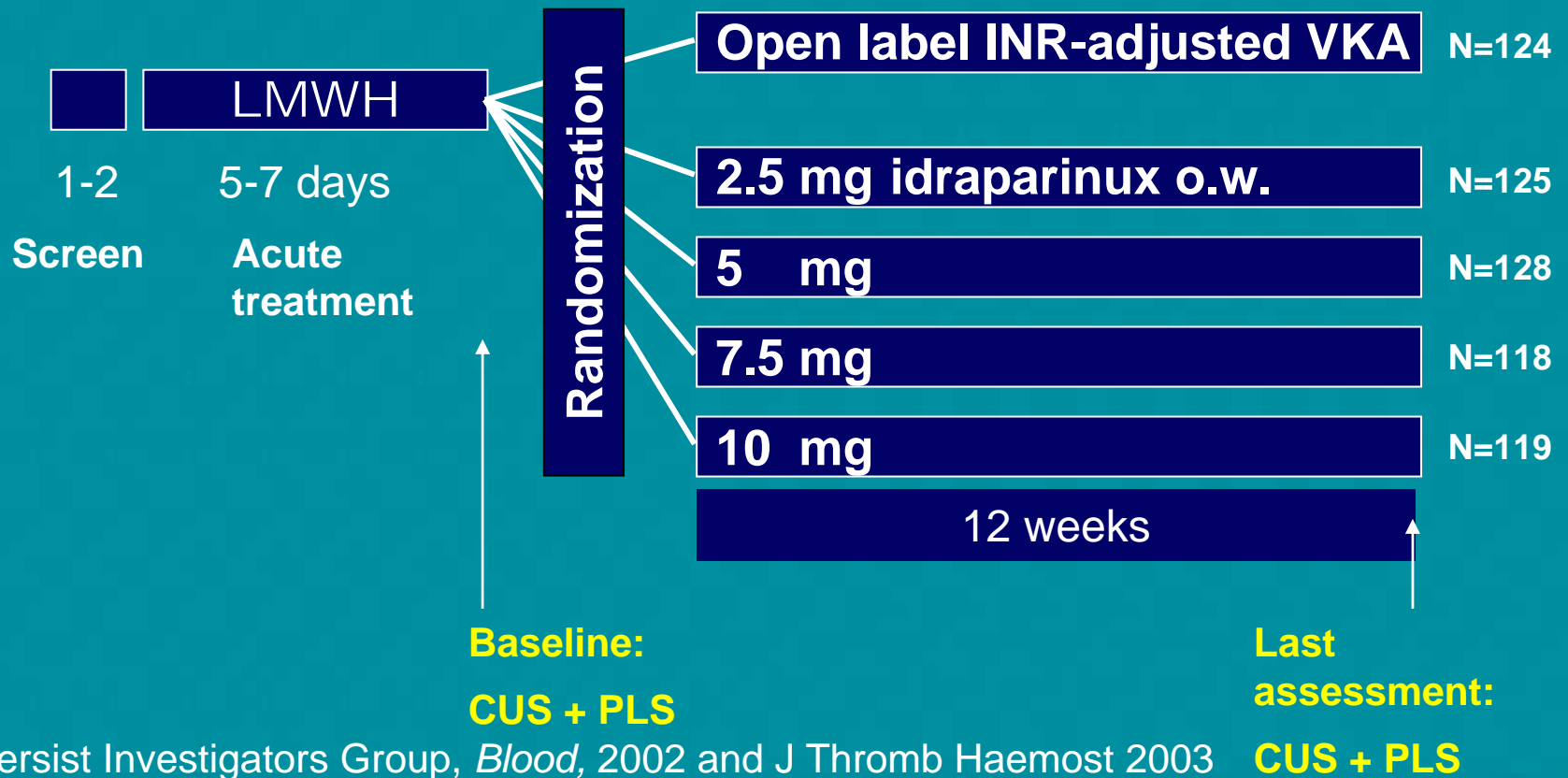
Chemical modification
by replacement of N-sulphated groups
and methylation of hydroxylated groups

Idraparinux

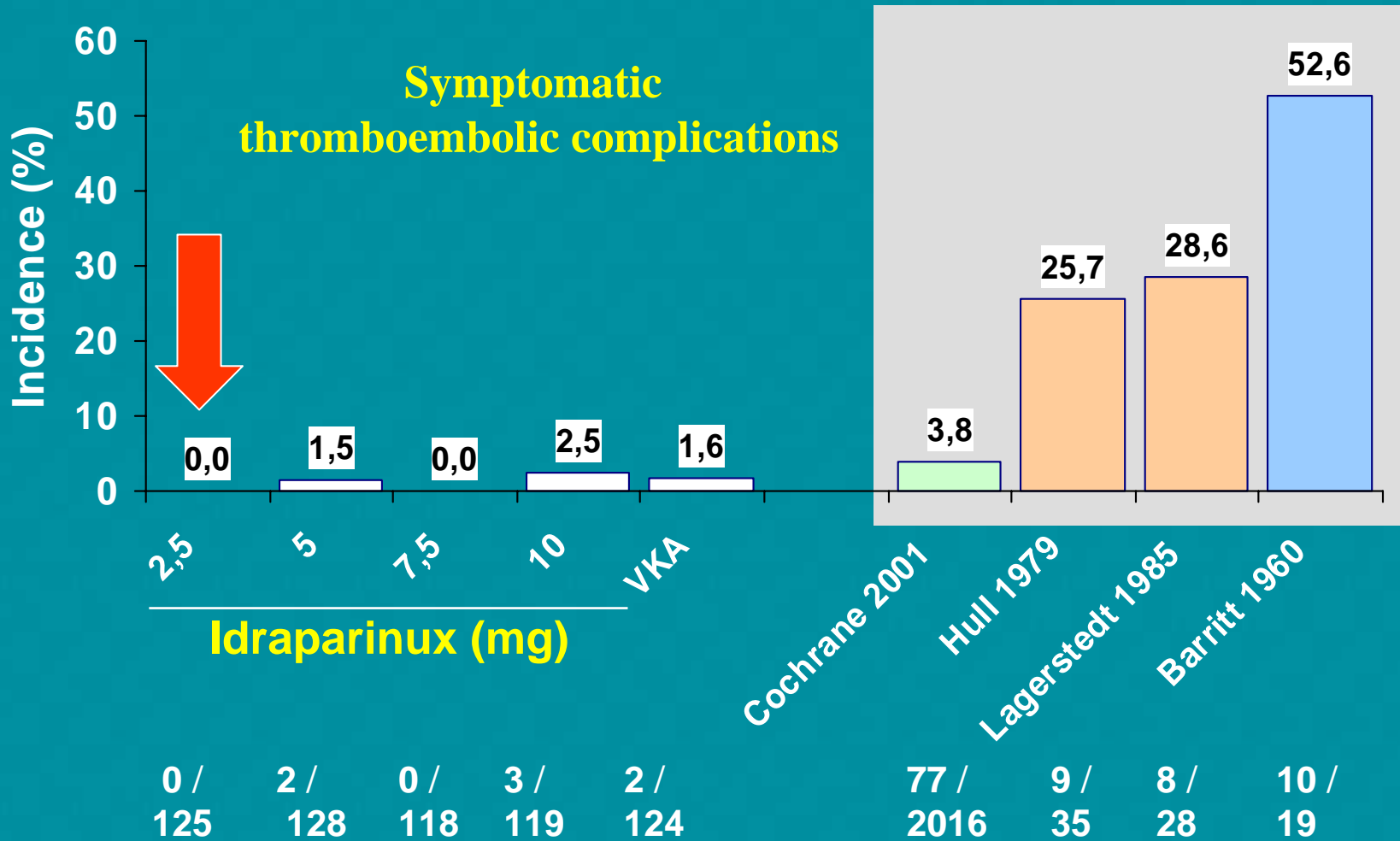
(O-methyl, O-sulphate
Pentasaccharide)

- High affinity for antithrombin
- Half-life = 120 h
- Administration once weekly

PERSIST: A dose-finding study with idraparinux in the secondary prophylaxis of DVT

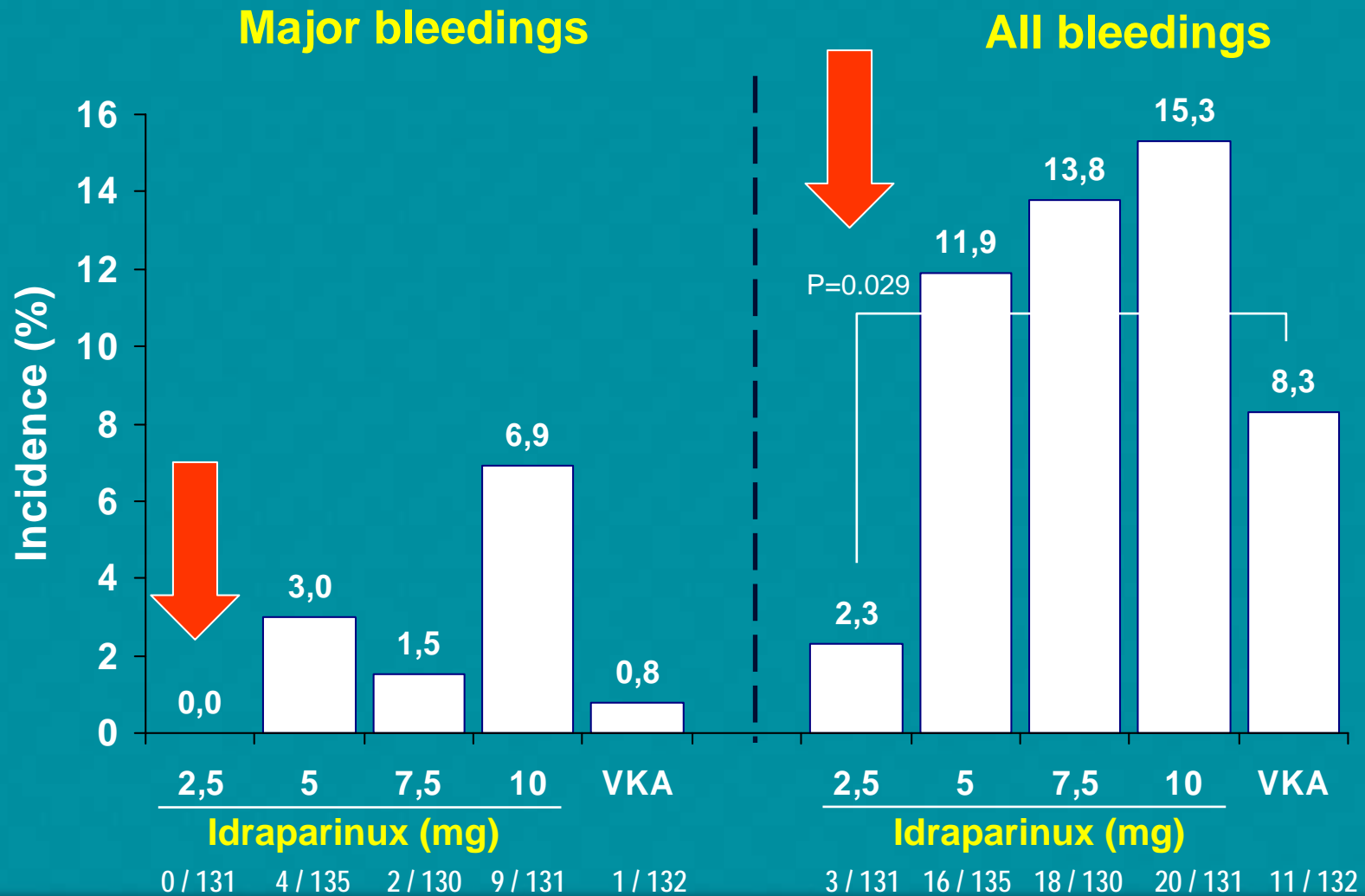


PERSIST: Efficacy profile



The Persist Investigators Group, *Blood*, 2002 and *J Thromb Haemost* 2003

PERSIST Study: Tolerability profile



Idraparinux Van Gogh Program



Van Gogh programme

Open label

Protocol EFC 3484: PE

idraparinux, 13 wks

idraparinux, 26 weeks

1100 patients

(LMW)H/VKA, 13 wks

(LMW)H/VKA, 26 weeks

1100 patients

Protocol EFC 3491: DVT

idraparinux, 13 wks

idraparinux, 26 weeks

1450 patients

(LMW)H/VKA, 13 wks

(LMW)H/VKA, 26 weeks

1450 patients

Eligible from outside these studies

(LMW)H/VKA, 26 weeks

double blind

Protocol EFC 5135: EXTension

Idraparinux
6 months

Placebo
6 months

**600 patients
per treatment group**

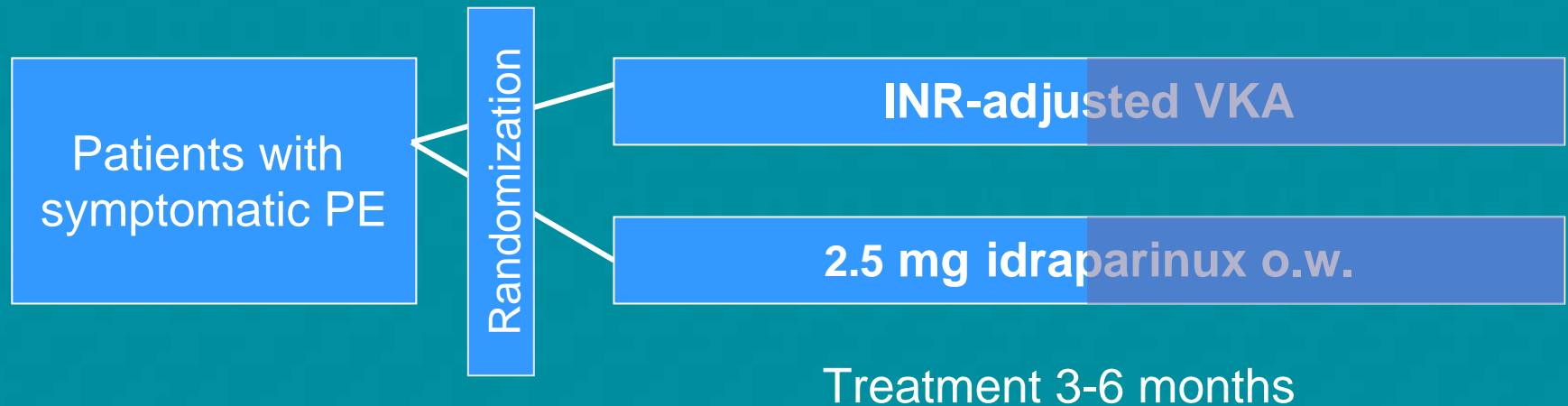
Safety
observation
period

3 months ↑

Final
contact

R

Idraparinux sodium (SanOrg34006) Phase III van Gogh-PE



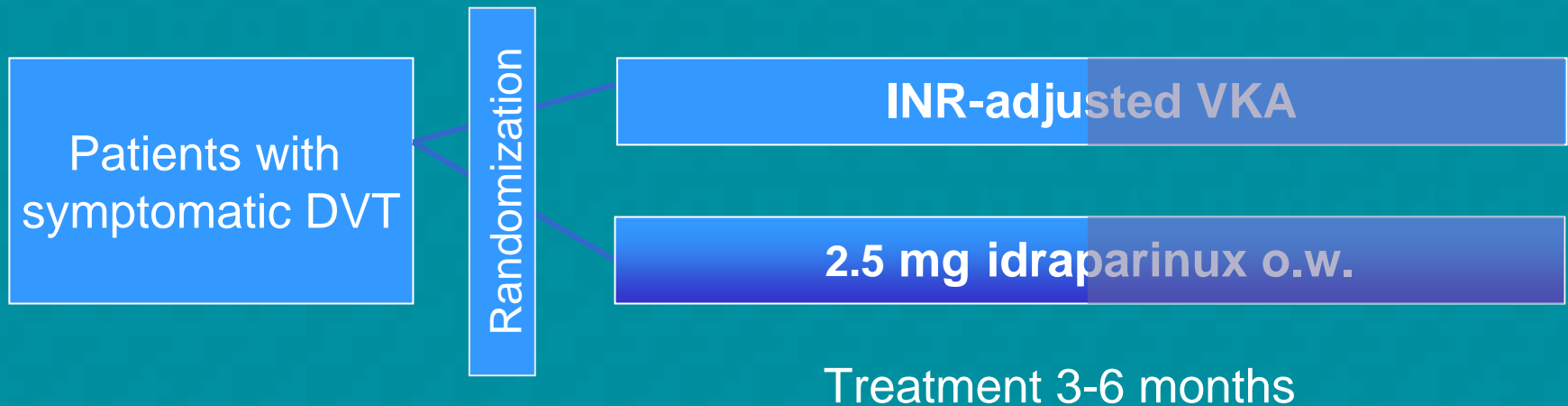
N=2,200; 1,100 patients per group

Open-label

EFFICACY: Symptomatic thromboembolic complications

SAFETY: All bleeding

Idraparin sodium (SanOrg34006) Phase III van Gogh-DVT



N=2,200; 1,100 patients per group

Open-label

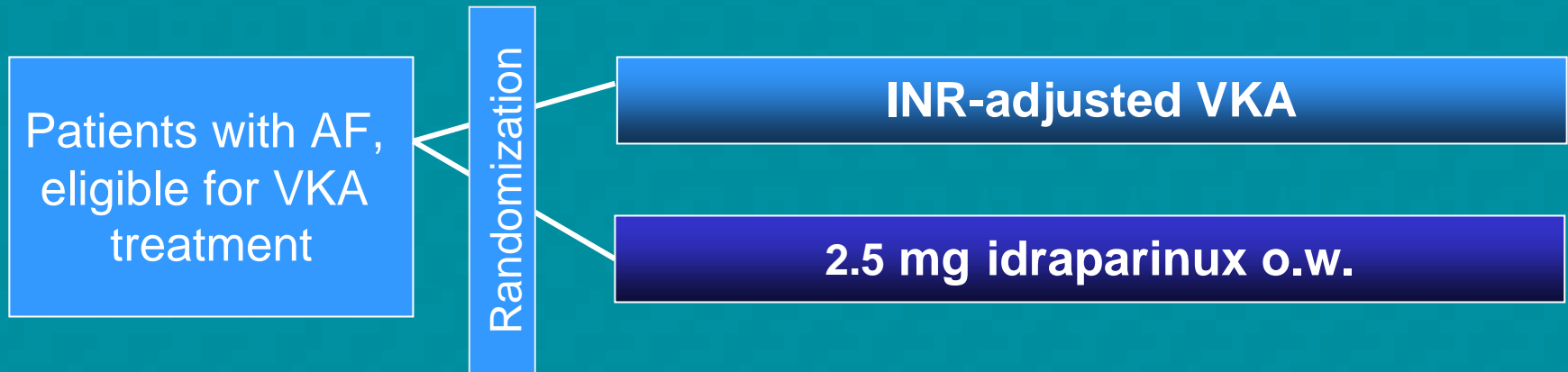
EFFICACY: Symptomatic thromboembolic complications

SAFETY: All bleeding

Van Gogh Program - Status

- All Van Gogh results will be shown in *ASH*, December 2006

Idraparinux sodium (SanOrg34006) Phase III Amadeus AF



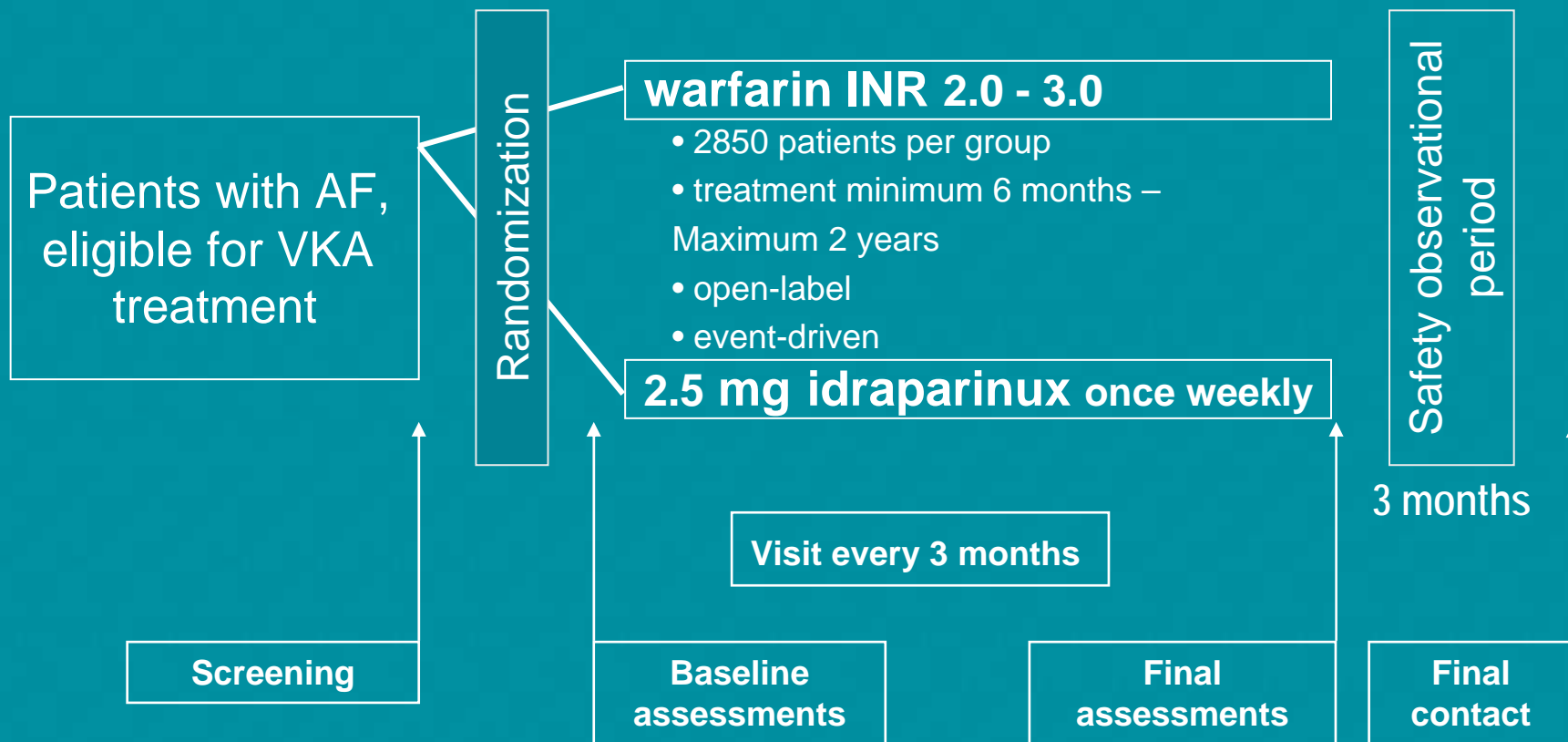
Treatment 6-24 months

open-label

EFFICACY: All strokes and non-CNS embolism

SAFETY: All bleeding

Study design AF - Phase III (AMADEUS)



✓ Primary efficacy outcome: fatal and non fatal stroke (ischemic or hemorrhagic) and non CNS systemic embolism

✓ Primary safety outcome: any clinically relevant bleeding

Amadeus results

- To be presented at the next AHA Scientific Sessions, Chicago 2006
- Status
 - Study discontinued mid July by Steering Committee (following DSMB recommendation) because of excess major bleeding
 - Analysis on going
- Efficacy on thromboembolic events likely demonstrated, but risk/benefit ratio unfavorable



Biotinylated Idraparinux

SSR 126517



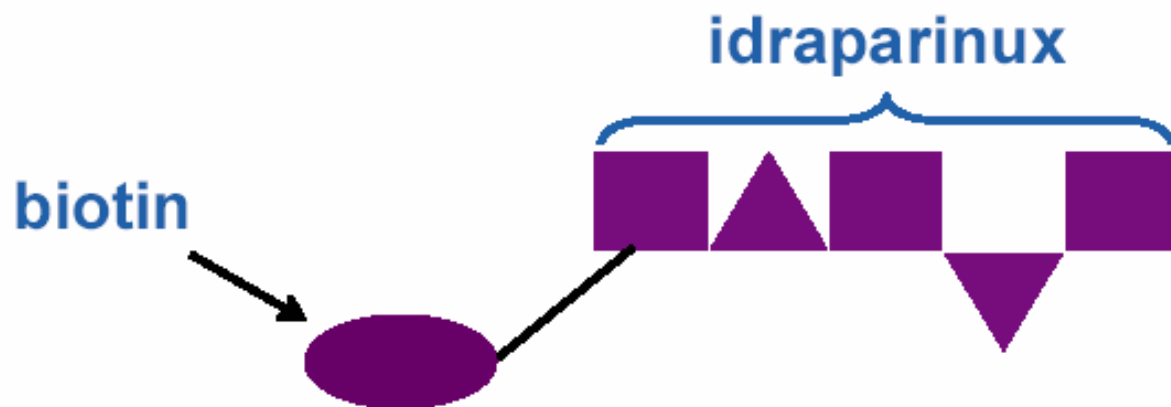
Concept of biotinylated long-acting penta-saccharide as a neutralizable anticoagulant drug ^(1/4)

- To introduce a « hook » on the compound to allow immediate « fishing » and rapid elimination in case of unpredictable increased bleeding

On condition that

- The « hook » should not impair the pentasaccharide/ATIII interaction
- The « hook » should not impair the interaction of the pentasaccharide/ATIII complex with factor Xa
- The « hook » should allow quick and efficient « fishing »

Concept of biotinylated long-acting penta-saccharide as a neutralizable anticoagulant drug (2/4)



Concept of biotinylated long-acting penta-saccharide as a neutralizable anticoagulant drug (3/4)

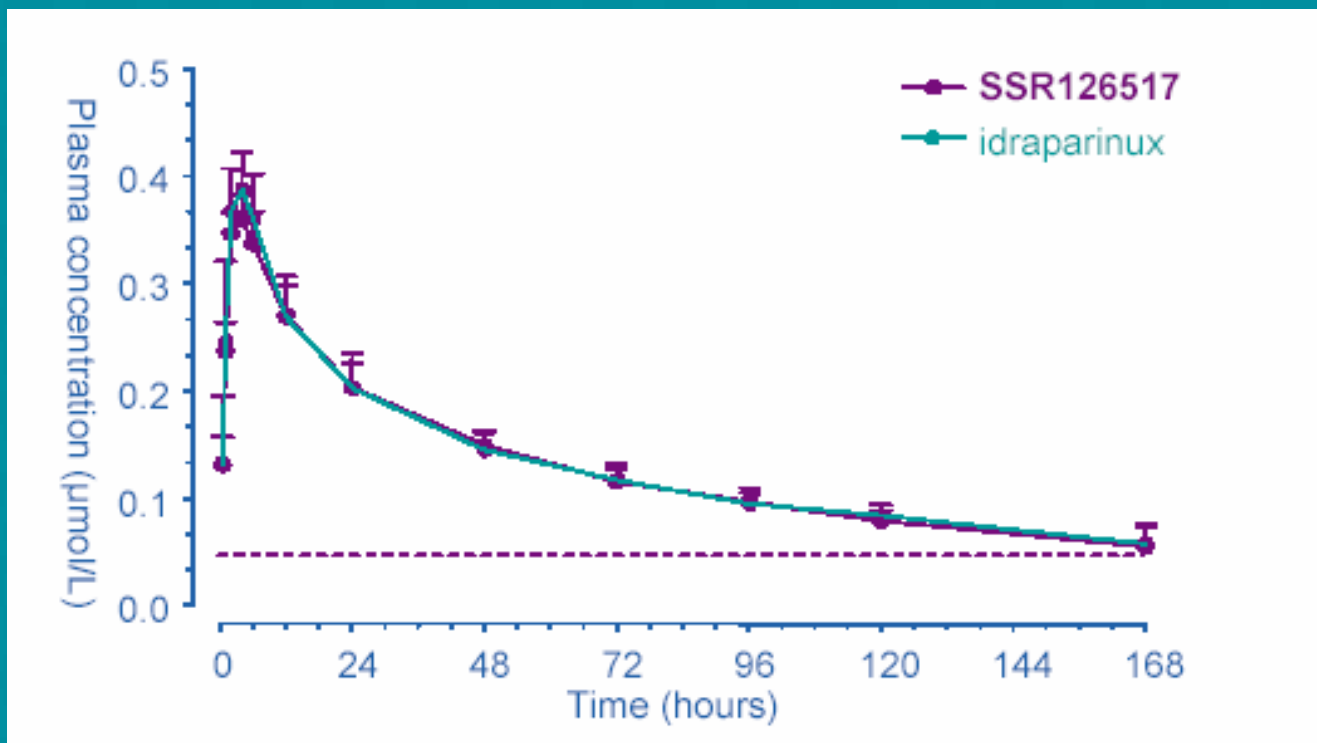
- A synthetic long-acting pentasaccharide carrying a biotin moiety
 - Same oligosaccharidic sequence as idraparinux
 - Same anticoagulant activity as idraparinux in vitro
 - High affinity for antithrombin III
 - Strong and specific inhibition of factor Xa
 - No HIT* reaction expected
 - Same pharmacokinetic properties as idraparinux
 - Long lasting effects
 - One subcutaneous administration per week
 - Same antithrombotic activity as idraparinux
 - Prevention of venous thrombosis
 - Low hemorrhagic effect
 - Biotin (vit H) covalently bound to idraparinux
 - Strong and specific affinity for avidin (neutralizing agent)

*HIT = Heparin-
Induced
Thrombocytopenia



PK comparison SSR126517 (biotinylated idraparinux) vs. Idraparinux in humans

Mean (SD) plasma concentrations of SSR126517 and idraparinux after a single s.c. dose of 3.0 and 2.5 mg, respectively, in molar units (parallel groups / n=12 per group) - Pharmacokinetic profiles of both compounds after a single s.c. equimolar dose are superimposable



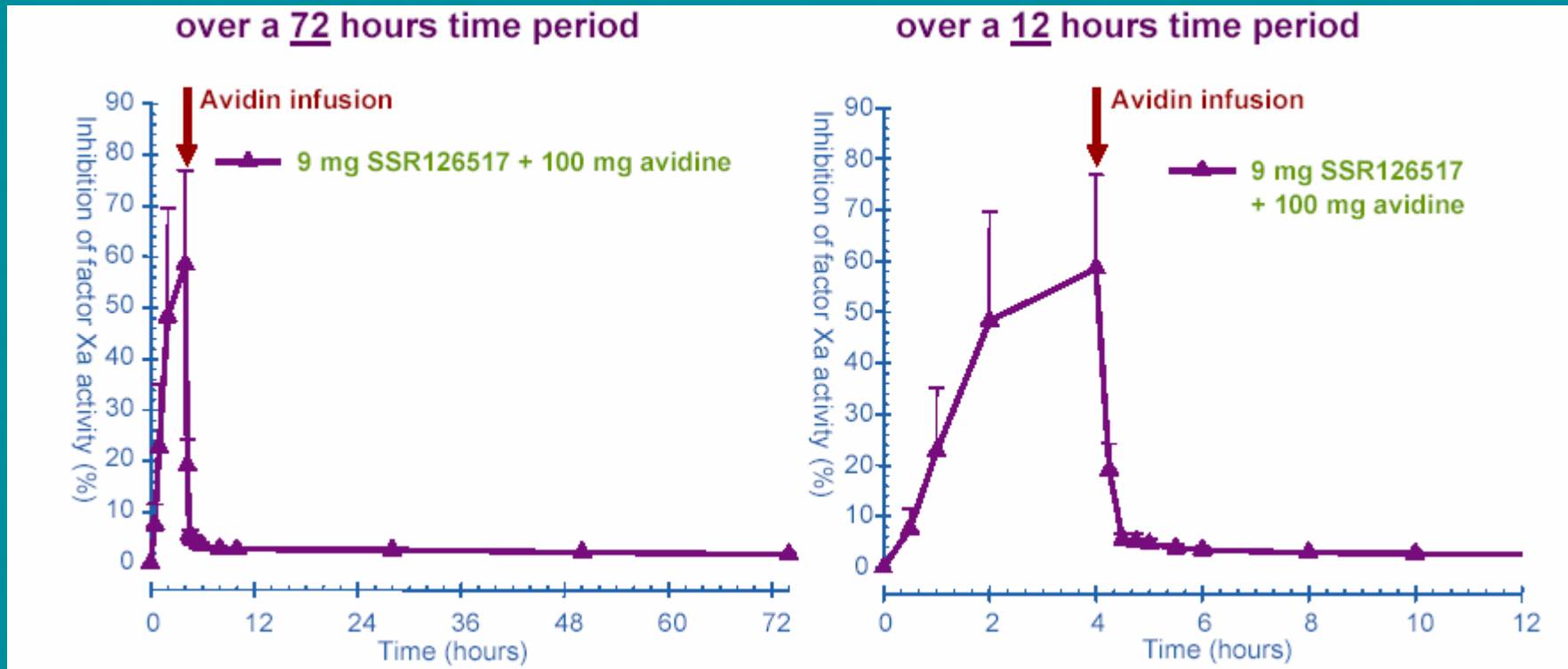
Concept of biotinylated long-acting penta-saccharide as a neutralizable anticoagulant drug (4/4)

- An injectable protein for neutralization
- Avidin binds to biotin with very strong affinity
- Affinity for biotin 10^{-15} M
- No other ligand described
- Avidin is devoid of any pharmacological effects
- No pro-thrombotic effect to counteract the antithrombotic activity
- Avidin is rapidly eliminated after IV injection
- $T_{1/2} = 2$ min in rats
- Injection of avidin results in a quick elimination of bound biotinylated idraparinux from the circulation



Anti-Xa PD profiles in humans

Mean (SD) inhibition of factor Xa activity of SSR126517 after administration of SSR126571 followed by an IV infusion of avidin 4 hours later (n=6)



After infusion of avidin, a rapid and large neutralization of factor Xa activity is observed at all dose combinations - No evidence of a rebound

Rationale for development of biotinylated idraparinux

- Bridging with idraparinux development
 - Phase III in VTE with idraparinux
 - Van Gogh program
 - Bioequipotency study with idraparinux (EFC5945)
 - 700 patients
 - Treatments: 3mg – 3 months
 - To be started Q1 2006
- Clinical study in patients with pulmonary embolism and DVT (EFC6034)
 - 3,200 patients
 - Treatment: 3mg – 3 months
 - Double blind versus warfarin
 - To be started Q2 2006