

# **Antithrombotic Therapy Current Status and Future Directions**

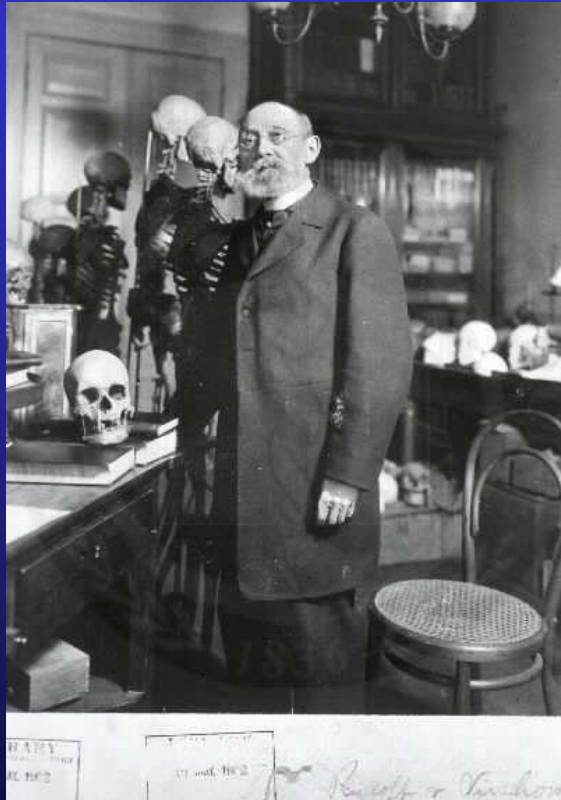
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# Disclosures

<b>Research Support</b>	<b>Wyeth, CSL Behring, Baxter</b>
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<b>Scientific Advisory Board</b>	<b>CSL Behring</b>

- **Epidemiology of VTE**
- **Historical perspective on outcome assessment**
- **Current evidence based treatment recommendations for VTE**
- **Explosion of new compounds**
- **Challenges for the future**

# Clots and thrombosis



Rudolf Virchow (1821-1902)

- autopsy studies that showed clots in legs and lungs of patients who died of pulmonary embolism (1846)
- theory on the pathogenesis of thrombosis (“Virchow’s triad”, 1856)
  - stasis
  - blood components
  - vessel wall

# The burden of the disease

- VTE is the 3rd most common type of cardiovascular disease<sup>1</sup>
- VTE causes over 500,000 deaths in Europe and 300,000 deaths in the United States each year<sup>2,3</sup>
- Annual deaths attributable to VTE are estimated to exceed the combined number of deaths from breast and prostate cancers, AIDS, and traffic accidents<sup>4</sup>
- Total estimated cost for VTE-associated care = EUR 3.1 billion per year<sup>5</sup>

1. Goldhaber SZ. J Am Coll Cardiol. 1992;19:246-7.

2. Cohen AT, et al. Thromb Haemost.2007;98:756-64.

3. Heit JA, et al. Blood. 2005;106: [abstract 910].

4. Fitzmaurice DA, Murray E. BMJ. 2007;334:1017-8.

5. Cohen AT, et al. Poster presented at the ISPOR 8th Annual European Congress; 2005; November 6-8; Florence, Italy.

# Annual Incidence of Venous Thromboembolism

- Symptomatic, objectively confirmed and population based

- F. Anderson et al.  
1991, Arch Intern Med

VTE: 1.07 per 1000  
- 66% first episode  
- DVT : PE = 2 : 1

- M. Nordstrom et al.  
1992, J Intern Med

DVT: 1.6 per 1000

- M. Silverstein et al.  
1998, Arch Int Med

First VTE: 1.17 per 1000

—————> 2 per 1000 per year

# Natural History

## Untreated, symptomatic

- Isolated Calf DVT :  $\pm$  33% extend proximally
- Proximal DVT :  $\pm$  50% symptomatic PE in 3 months
- PE :
  - 26% fatal recurrent PE in 2 weeks
  - 26% non-fatal recurrence

*C. Kearon et al. 2001, Haemostasis and Thrombosis*

# Three Phases in the Evaluation of Antithrombotic Therapies in VTE and Evolution of Outcome Assessment

- **First Phase**                      **1938 – late 1960's**
- **Second Phase**                      **1972 – early 1990's**
- **Third Phase**                      **1992 – 2010**



# First Phase

First use  
of heparin  
in 35 pts  
with VTE.  
Murray and  
Best (1938)

Heparin i.v.  
in 209 VTE  
pts with  
only 3 deaths  
Bauer (1946)

Heparin and  
dicoumarol  
in 329 PE pts  
with one death.  
Allen et al  
(1947)

Heparin i.v.  
and nicoumalone  
vs no treatment  
randomized  
comparison in  
35 PE pts.  
Barritt and Jordan  
(1960)



Survival as major outcome

# Second Phase

**Studies about the appropriate monitoring of APTT and INR, as well as the duration of initial therapy (1972 to early 1990's)**

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**Symptomatic recurrent venous thromboembolism and major bleeding as major outcomes**

# Third Phase

**Studies with LMWH, pentasaccharides, thrombin inhibitors and factor Xa inhibitors.**

**(1992 – approx 2010)**

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**Out of hospital treatment, no laboratory monitoring, ease of use, non-inferiority for efficacy and clinically relevant/non major bleeding as major outcomes.**

**No distinction between initial and long term treatment**

# Treatment Spectrum

Massive VTE (*serious compromise of lung perfusion/impending gangrene*)

- thrombolysis (surgery)

Minimal VTE (*no tendency to extend or re-occur*)

- wait and see

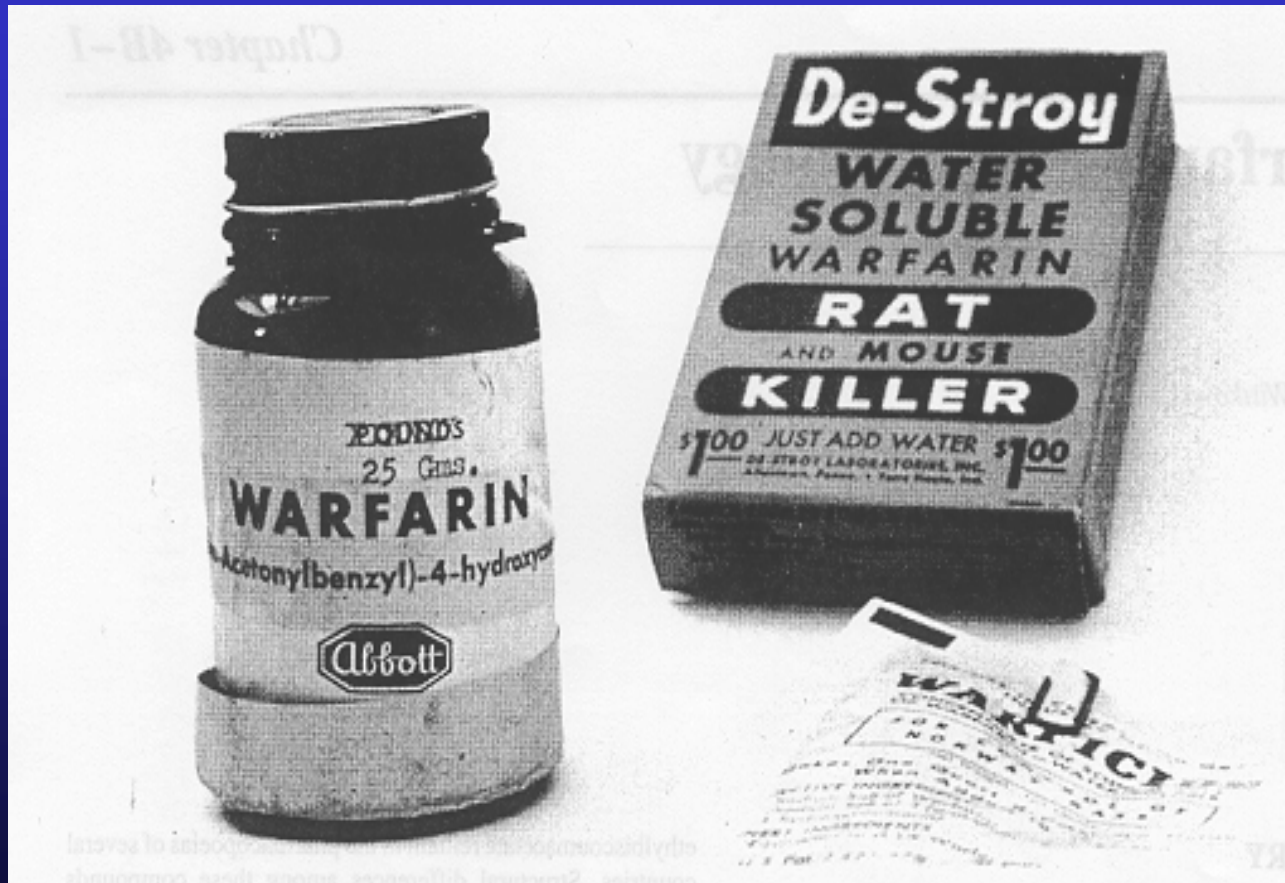
Other VTE

- (LMW) Heparin and VKA

# Heparin 1916–1937



- Discovered 1916
- Maclean
- Human use 1937
- Lancet 1960 – it works!  
(Barrit and Jordan)
- Animal derived
- Side-effects
- Intravenous,  
monitoring, adjustment



# Current evidence-based treatment recommendations for venous thromboembolism

8th ACCP Chest 2008;133, 454-545

# ACCP 2008 Treatment of venous thromboembolism

UFH (i.v., s.c., s.c. fixed doses)  
LMWH  
Fondaparinux  
Thrombolysis



**Initial treatment**

INR 2.0–3.0

VKAs

2.0–3.0 or 1.5–1.9

**Long term-treatment**

**Extended\* treatment**

≥ 5 days

at least 3 months

indefinite\*

\*With re-assessment of the individual risk-benefit at periodic intervals

INR = international normalized ration; LMWH = low-molecular-weight heparin;  
UFH = unfractionated heparin; VKA = vitamin K antagonist.

Kearon C, et al. Chest. 2008;133:454-545.



# Recommendations

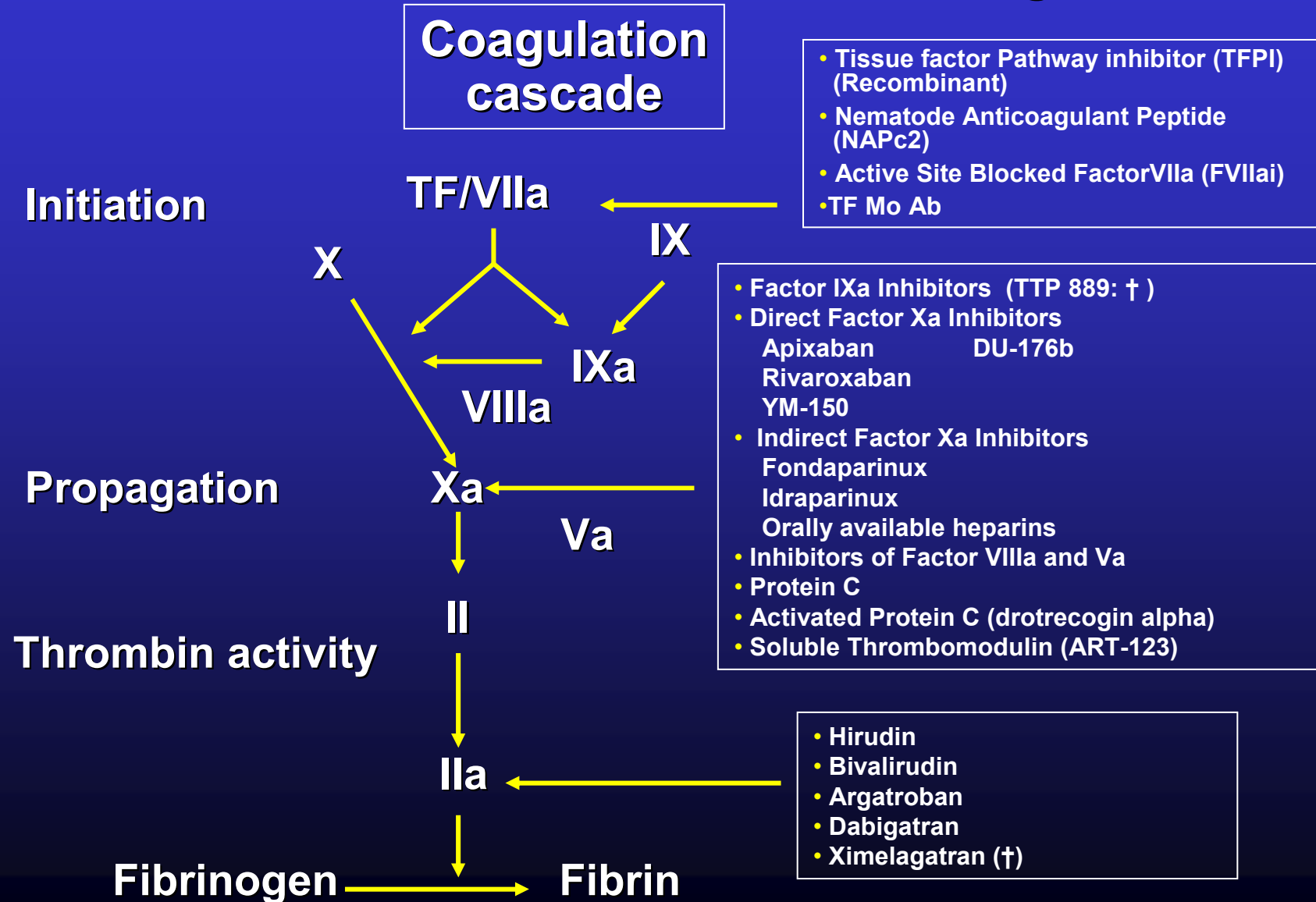
- Initial therapy LMWH/UFH
- Alternatives for LMWH/UFH
- Thrombolytic therapy
- Caval filter
- Ambulation
  
- Start of VKA
- INR intensity
- VKA duration
- Long term treatment in cancer patients
- Compression stockings

# Current problems in the treatment of venous thromboembolism

- **Need for s.c. injections**
- **Monitoring and dose adjustment of vitamin K antagonists**
- **Efficacy excellent, but safety requires improvement (10% bleeding in 3 months)**
- **Optimal duration is unknown**
- **Best treatment in cancer patients**

# New Anticoagulants

## Drug



DE EERSTE ORALE ANTISTOLLING  
ZONDER LABCONTROLE



**Pradaxa**  
dabigatran etexaat

*Transforming anticoagulation*

# Classical Pathway of the Evaluation of New Antithrombotics

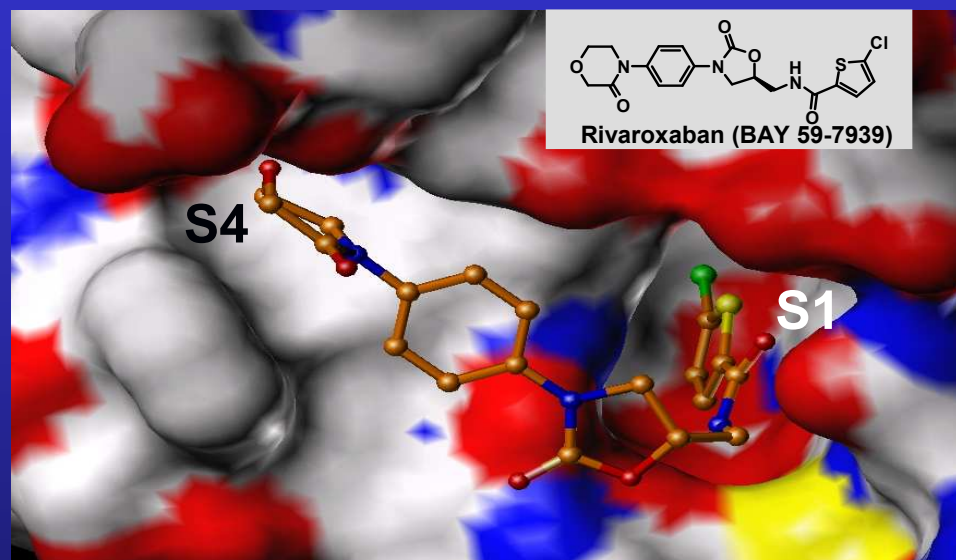
- **First** : orthopaedic surgery
- **Second:** treatment of established venous thrombosis
- **Third** : atrial fibrillation  
acute coronary syndromes

# Human Factor Xa/rivaroxaban complex

## X-ray crystal structure

Roehrig *et al.*, *J Med Chem* 2005

- Selective for Factor Xa ( $K_i = 0.4 \pm 0.02$ )
  - No effects on Factor VIIa, Factor IXa, Factor XIa, kallikrein, thrombin, activated protein C, plasmin, tPA, urokinase, trypsin, chymotrypsin ( $IC_{50} > 20,000$ -fold)
- Inhibits:
  - Free Factor Xa
  - Prothrombinase activity
  - Fibrin-bound Factor Xa
- Does not require a cofactor
- No direct effect on thrombin
- No direct effect on agonist-induced platelet aggregation



# RECORD 1, 2 and 3 publications

## RECORD 1



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 26, 2008 VOL 358, NO 26

### Rivaroxaban versus Enoxaparin for Thromboprophylaxis after Hip Arthroplasty

Bengt I. Eriksson, M.D., Ph.D., Lars C. Erikss, M.D., Richard J. Friedman, M.D., Sylvia Haas, M.D., Marco V. Hauman, M.D., Ph.D., Aja K. Kakkar, M.D., Ph.D., Tienne J. Bandet, M.D., Hans Beckmann, Ph.D., Eva Mannhalter, M.D., Frank Mozzoni, M.D., Ph.D., and William Geerts, M.D. for the RECORD1 Study Group\*

**ABSTRACT**

**BACKGROUND:** This phase 3 trial compared the efficacy and safety of rivaroxaban, an oral direct inhibitor of factor Xa, with those of enoxaparin for extended thromboprophylaxis in patients undergoing total hip arthroplasty.

**METHODS:** In this randomized, double-blind study, we assigned 4143 patients to receive either 10 mg of rivaroxaban once daily, beginning after surgery, or 40 mg of enoxaparin subcutaneously once daily, beginning the evening before surgery, plus a placebo control at discretion. The primary efficacy outcome was the composite of deep-vein thrombosis (either asymptomatic or detected by bilateral ultrasonography if the patient was asymptomatic), isolated pulmonary embolism, or death from any cause at 30 days (range, 30 to 42). The main secondary efficacy outcome was major venous thromboembolism (proximal deep-vein thrombosis, isolated pulmonary embolism, or death from venous thromboembolism). The primary safety outcome was major bleeding.

**RESULTS:** A total of 1331 patients were included in the superiority analysis (after 1188 cancellations) and 4410 were included in the safety analysis (after 206 cancellations). The primary efficacy outcome occurred in 14.4 of 1599 patients (1.7%) in the rivaroxaban group and in 16.4 of 1793 patients (1.7%) in the enoxaparin group (absolute risk reduction, 2.0%; 95% confidence interval [CI], 1.5 to 2.5; P<0.0001). Major venous thromboembolism occurred in 4.4 of 1699 patients (0.7%) in the rivaroxaban group and in 11.1 of 1722 patients (2.0%) in the enoxaparin group (absolute risk reduction, 1.7%; 95% CI, 1.0 to 2.5; P<0.0001). Major bleeding occurred in 6.0 of 2209 patients (0.7%) in the rivaroxaban group and in 2.4 of 2224 patients (0.7%) in the enoxaparin group (7–13.8%).

**CONCLUSIONS:** A once-daily, 10-mg oral dose of rivaroxaban was significantly more effective for extended thromboprophylaxis than a once-daily, 40-mg subcutaneous dose of enoxaparin in patients undergoing elective total hip arthroplasty. The two drugs had similar safety profiles. (ClinicalTrials.gov number, NCT00279628.)

*N Engl J Med* 2008; 358:2765–2775. www.n engl j med.com June 26, 2008 2765

## RECORD 2



Articles

### Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial

Aja K. Kakkar, Benjamin Bevilacqua, John Doherty, Emma Papan, Patrick Mounis, Jim Mounis, Andrew Clayton, Alan Flap, Frank Mozzoni, Tienne J. Bandet, Lars C. Eriksson, Bengt Eriksson

**Summary**

**Background:** The risk of venous thromboembolism is high after total hip arthroplasty and could persist after hospital discharge. Our aim was to compare the use of rivaroxaban for extended thromboprophylaxis with short-term thromboprophylaxis with enoxaparin.

**Methods:** 2509 patients scheduled to undergo elective total hip arthroplasty were randomised, stratified according to centre, with computer-generated randomisation code, to receive oral rivaroxaban 10 mg once daily for 35–39 days (with placebo injection for 10–14 days, n=1252), or enoxaparin 40 mg once daily subcutaneously for 10–14 days (with placebo tablet for 20 days, n=1257). The primary efficacy outcome was the composite of deep-vein thrombosis (asymptomatic or asymptomatic detected by ultrasound, isolated pulmonary embolism, or death from any cause) within 30 to 42 days. Secondary efficacy outcomes included major venous thromboembolism (proximal deep-vein thrombosis, isolated pulmonary embolism, or death from venous thromboembolism), and major bleeding. Rivaroxaban was more effective than enoxaparin in reducing the risk of venous thromboembolism and major bleeding. Rivaroxaban was also associated with a lower rate of hospital readmission. Rivaroxaban was not associated with a higher rate of mortality.

**Interpretation:** Extended thromboprophylaxis with rivaroxaban was significantly more effective than short-term enoxaparin plus placebo for the prevention of venous thromboembolism, including symptomatic events, in patients undergoing total hip arthroplasty.

**Funding:** Bayer HealthCare AG, Johnson & Johnson Pharmaceutical Research and Development LLC.

**Introduction**

Patients undergoing total hip arthroplasty are at a high risk of venous thromboembolism (VTE) because of the duration of hospital stay and the extent of surgery. The incidence of VTE after total hip arthroplasty is 20–30% within 30 days of surgery, with a mortality rate of 10–15%.<sup>1,2</sup> The risk of VTE is highest in the first 72 h after surgery.<sup>3,4</sup>

Current guidelines recommend pharmacological prophylaxis for a minimum of 10–14 days, and up to 35 days after surgery.<sup>5</sup> Despite evidence from meta-analyses indicating that extended thromboprophylaxis after elective hip arthroplasty reduces the frequency of venous thromboembolism,<sup>6–8</sup> it is not clear what dose of enoxaparin, or what duration of enoxaparin prophylaxis, is best. In a large prospective randomised trial, extended pharmacological prophylaxis with intravenous unfractionated heparin or subcutaneous enoxaparin was associated with a lower rate of VTE than short-term prophylaxis with intravenous unfractionated heparin or subcutaneous enoxaparin. However, the risk of major bleeding was not significantly different between the two groups.

## RECORD 3



ORIGINAL ARTICLE

### Rivaroxaban versus Enoxaparin for Thromboprophylaxis after Total Knee Arthroplasty

Michael R. Lassen, M.D., Walter Ageno, M.D., Lars C. Erikss, M.D., Jørgen R. Lassen, M.D., Nadia Rosendorfer, M.D., Tienne J. Bandet, M.D., Frank Mozzoni, M.D., Ph.D., and Alexander G.G. Turpie, M.D., for the RECORD3 Investigators\*

**ABSTRACT**

**BACKGROUND:** We investigated the efficacy of rivaroxaban, an orally active direct factor Xa inhibitor, in preventing venous thrombosis after total knee arthroplasty.

**METHODS:** In this randomized, double-blind trial, 3203 patients who were to undergo total knee arthroplasty received either oral rivaroxaban, 10 mg once daily, beginning 6 to 8 hours after surgery, or subcutaneous enoxaparin, 40 mg once daily, beginning 12 hours before surgery. The primary efficacy outcome was the composite of any deep-vein thrombosis, isolated pulmonary embolism, or death from any cause within 13 to 27 days after surgery. Secondary efficacy outcomes included major venous thromboembolism (i.e., proximal deep-vein thrombosis, isolated pulmonary embolism, or death related to venous thromboembolism) and symptomatic venous thromboembolism. The primary safety outcome was major bleeding.

**RESULTS:** The primary efficacy outcome occurred in 7.9 of 424 patients (9.0%) who received rivaroxaban and in 16.4 of 1778 patients (9.9%) who received enoxaparin (absolute risk reduction, 2.0%; 95% confidence interval [CI], 1.5 to 2.4; P<0.0001). Major venous thromboembolism occurred in 3.9 of 424 patients (1.0%) given rivaroxaban and 2.4 of 1778 patients (0.7%) given enoxaparin (absolute risk reduction, 1.5%; 95% CI, 0.4 to 2.6; P=0.02). Symptomatic events occurred less frequently with rivaroxaban than with enoxaparin (7.4 vs 9.6%). Major bleeding occurred in 6.4% of patients in the rivaroxaban group and 6.9% of patients in the enoxaparin group. The incidence of drug-related adverse events, mainly gastrointestinal, was 12.0% in the rivaroxaban group and 11.9% in the enoxaparin group.

**CONCLUSIONS:** Rivaroxaban was superior to enoxaparin for thromboprophylaxis after total knee arthroplasty, with similar rates of bleeding. (ClinicalTrials.gov number, NCT00281601.)

*N Engl J Med* 2008; 358:2776–2785. www.n engl j med.com June 26, 2008 2776

Eriksson et al., *N Engl J Med* 2008; 358:2765–2775; Kakkar et al., *Lancet* 2008;372:29–37; Lassen et al., *N Engl J Med* 2008;358:2776–2785

# RECORD: phase III programme for VTE prevention

- Rivaroxaban 10 mg once daily investigated
- Same study design and efficacy and safety outcomes
  - Randomized, active-comparator-controlled, parallel-group, double-blind, double-dummy
- Same independent, blinded adjudication committees

## RECORD 1

### HIP replacement

Rivaroxaban 10 mg od  
for 5 weeks

vs

enoxaparin 40 mg od  
for 5 weeks

**N=4,541**

## RECORD 2

### HIP replacement

Rivaroxaban 10 mg od  
for 5 weeks

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

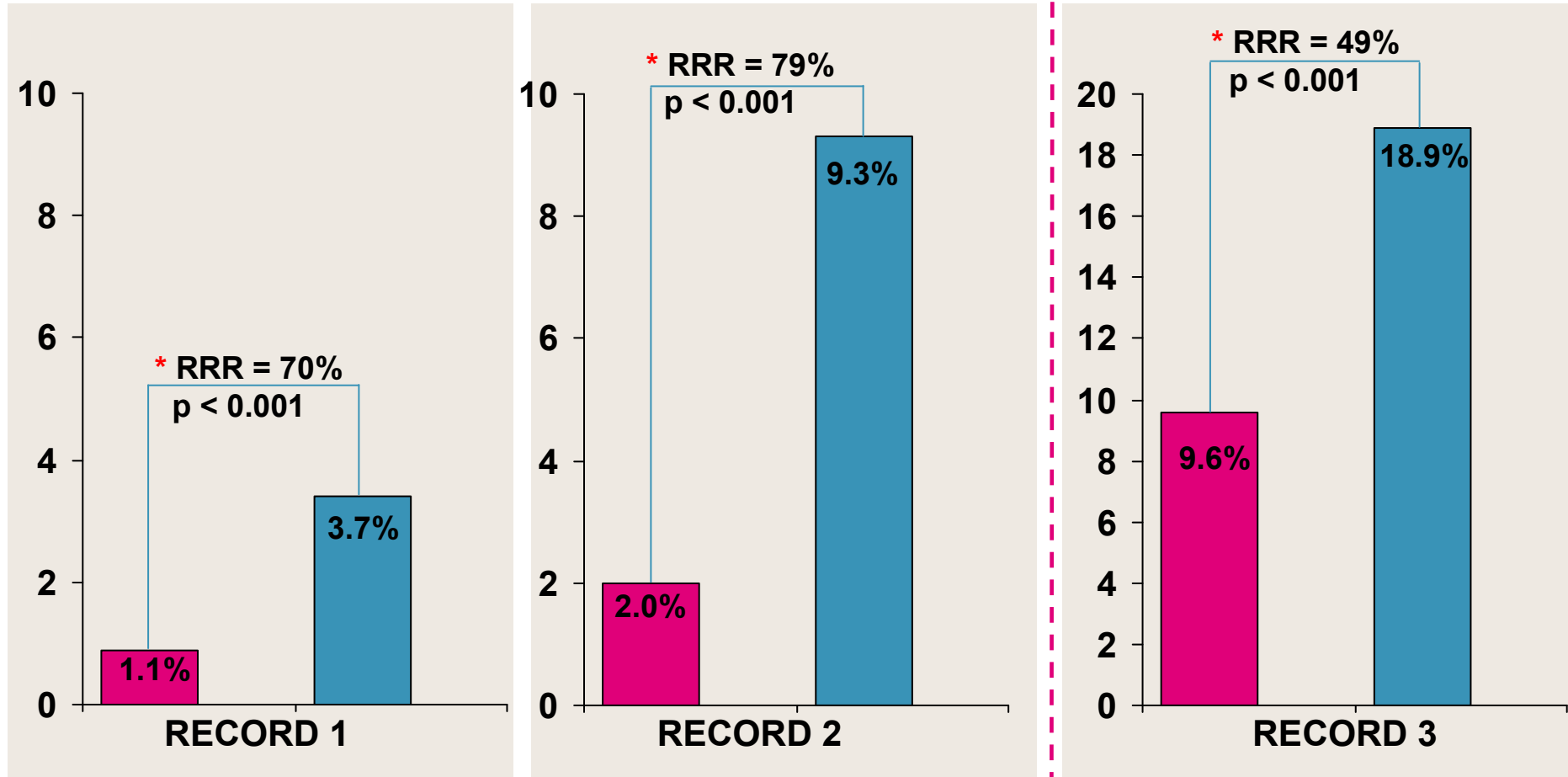
**N=3,148**



# RECORD **RE**gulation of **C**oagulation in major **O**rthopaedic surgery reducing the **R**isk of **D**VT and PE

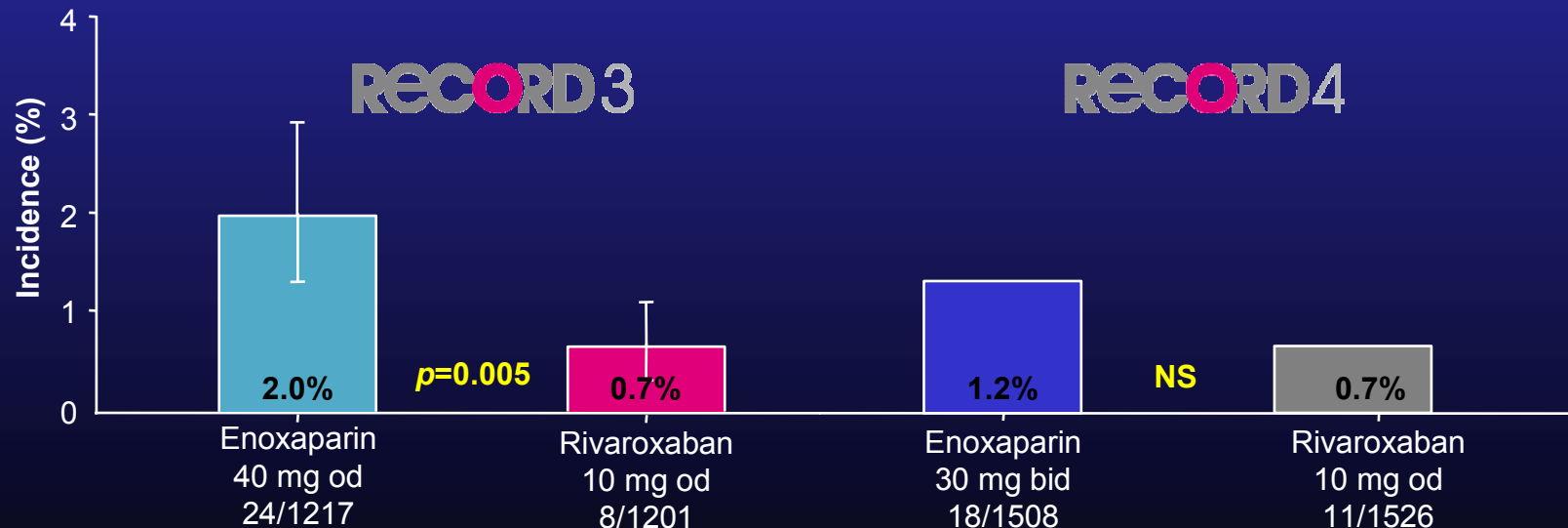
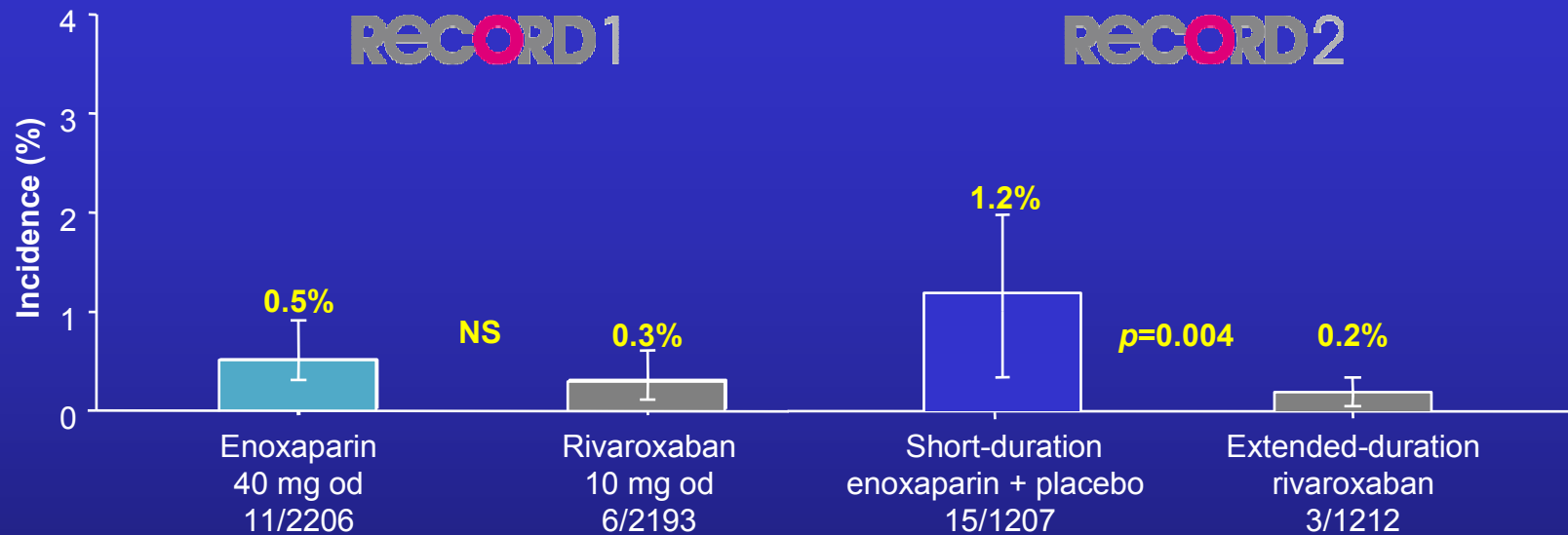
## Efficacy: Total VTE (primary endpoint)

■ Rivaroxaban 10mg      ■ Enoxaparin 40mg



\* relative risk reduction based on raw Incidences; p-values based on test on weighted absolute differences

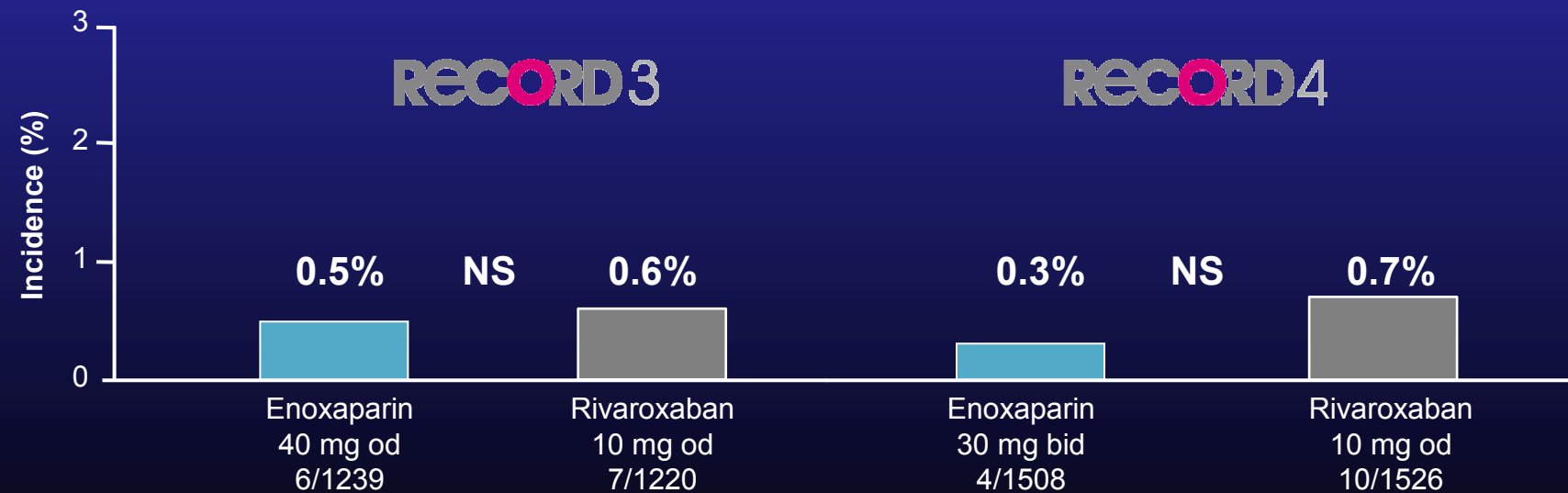
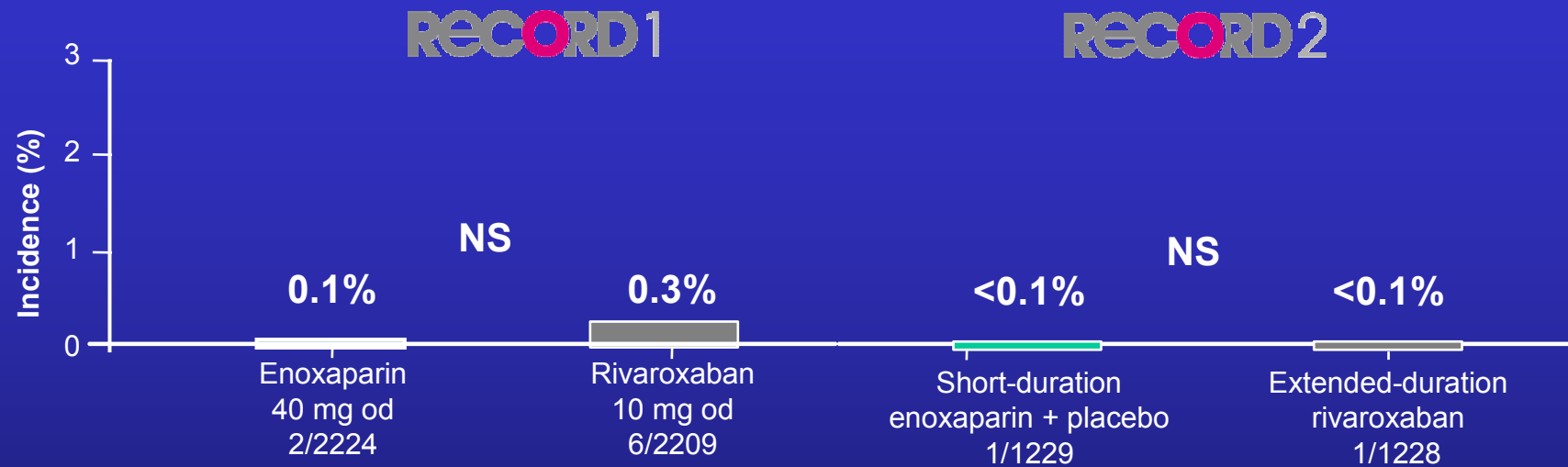
# Symptomatic VTE: summary



Safety population who underwent surgery

RECORD1, n=4399; RECORD2, n=2419; RECORD3, n=2418; RECORD4, n=3034

# Major bleeding: summary

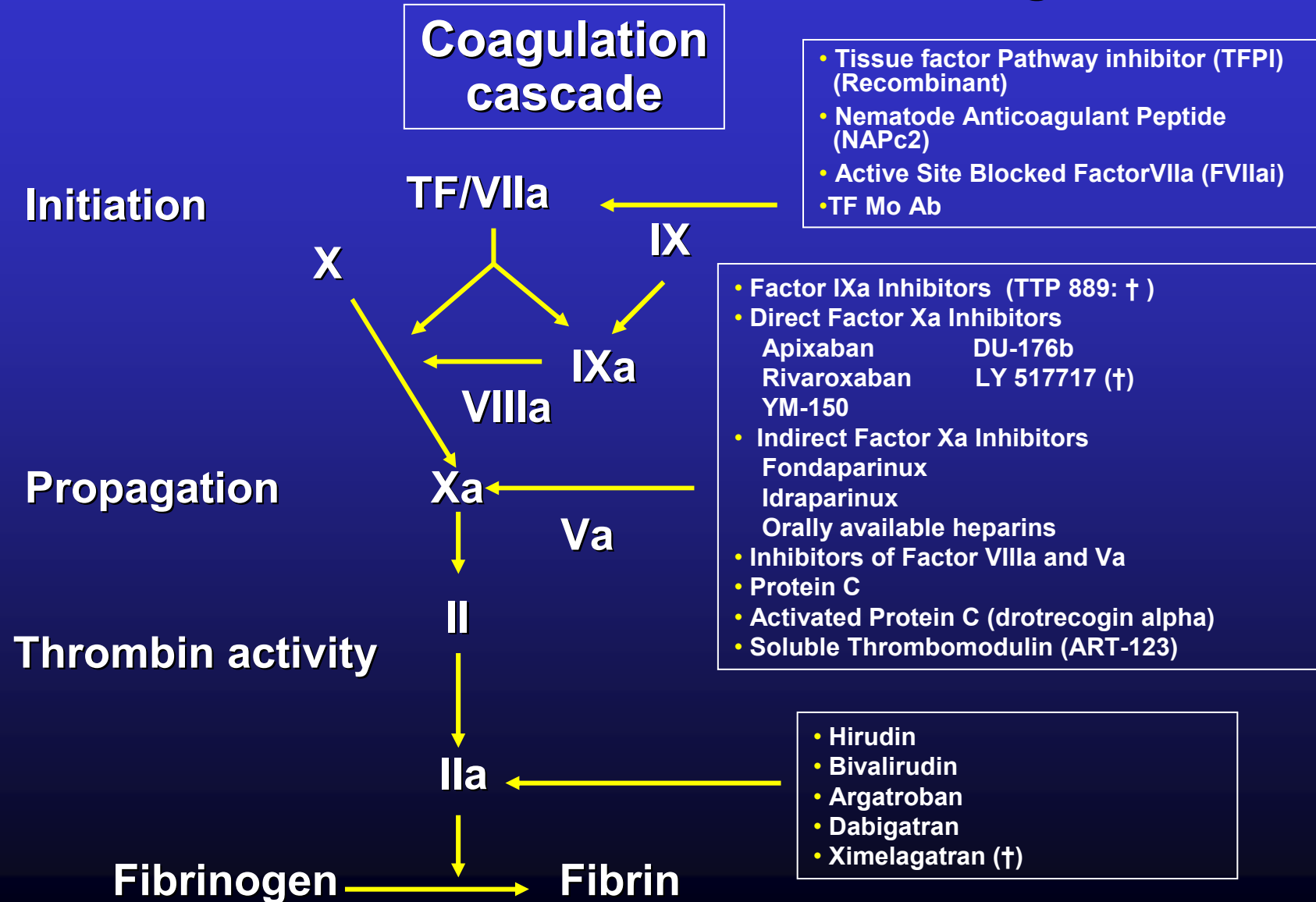


# Rivaroxaban ongoing

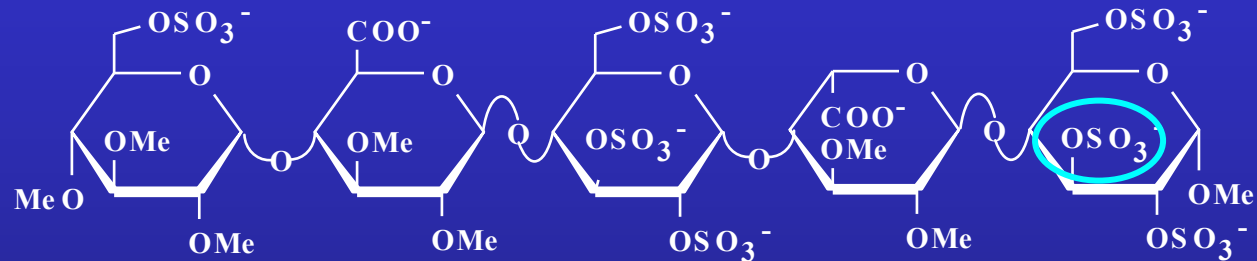
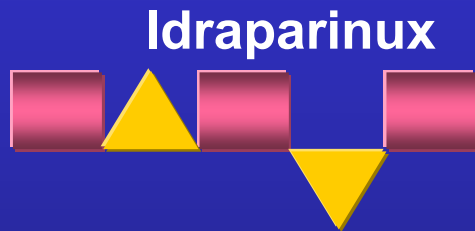
- **Prevention VTE in elective knee and elective hip surgery (Record program)** **Phase III**
- **Treatment of VTE (Einstein program)** **Phase II**
- **Artrial fibrillation** **Phase II**
- **Acute conorary syndrome (ATLAS-TIMI)** **Phase II**

# New Anticoagulants

## Drug



# Idraparinux: once-weekly anticoagulant



Sulfate group on H block

Long half-life

Once weekly administration

# Idraparinux for VTE treatment Phase III programme – Van Gogh

## Van Gogh PE

Idraparinux, 13 weeks

Idraparinux, 26 weeks

(LMW)H/VKA, 13 weeks

(LMW)H/VKA, 26 weeks

## Van Gogh DVT

Idraparinux, 13 weeks

Idraparinux, 26 weeks

(LMW)H/VKA, 13 weeks

(LMW)H/VKA, 26 weeks

## DVT/PE

(LMW)H/VKA, 26 weeks

## Van Gogh Extension

Idraparinux  
6 months

Double-blind

Placebo  
6 months

Safety  
observational  
period

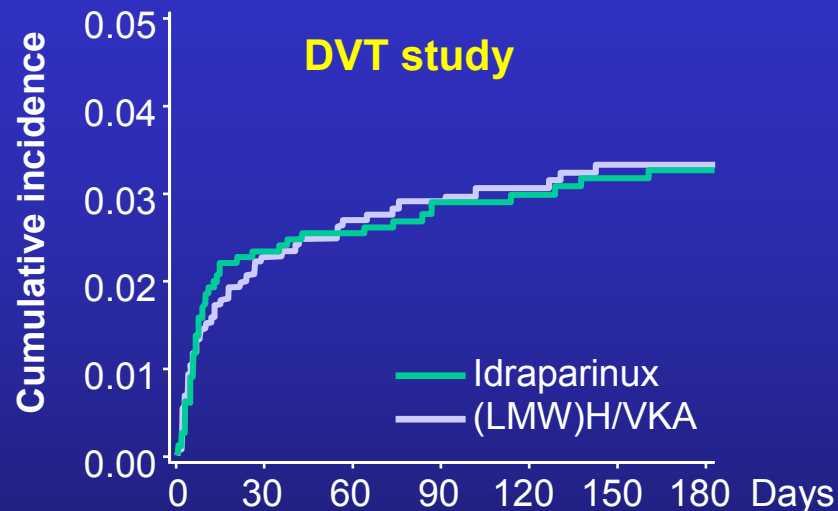
3/6  
months

Final  
contact

(LMW)H = (low-molecular-weight) heparin; VKA =  
vitamin K antagonist.

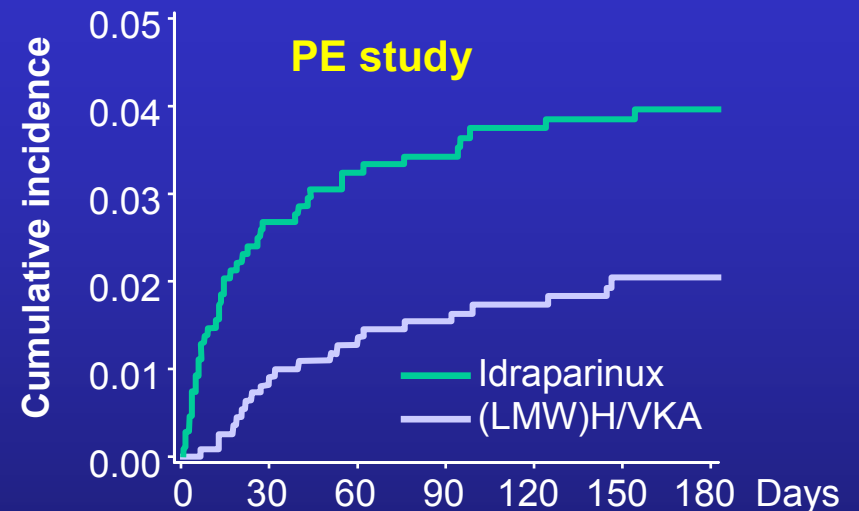
Buller et al. *NEJM* 2007;357:1094-1104.  
Buller et al. *NEJM* 2007;357:1105-1112.

# Possible reasons for different results for efficacy for DVT vs PE



Number at risk:

Idraparinux	1,452	1,408	1,395	1,381	1,050	1,043	1,034
(LMW)H/VKA	1,452	1,409	1,389	1,378	1,067	1,057	1,054



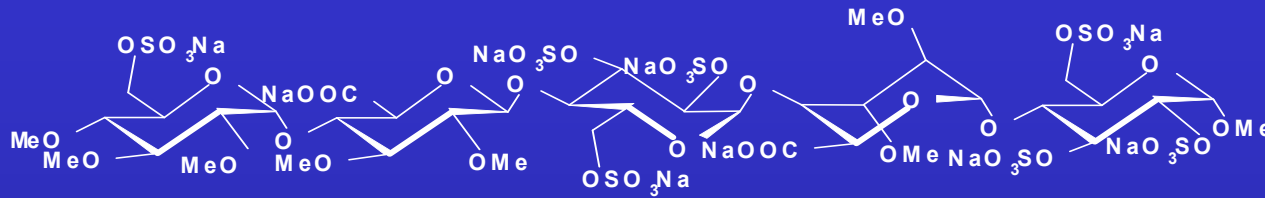
Number at risk:

Idraparinux	1,095	1,050	1,029	1,016	906	904	897
(LMW)H/VKA	1,120	1,098	1,083	1,074	965	954	950

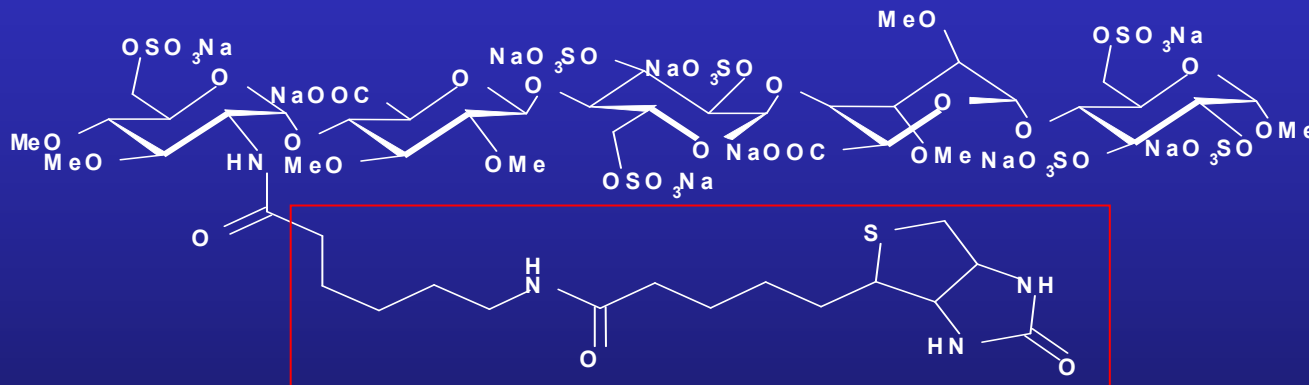
- Lower risk patients, or different burden of thromboembolism
- Failure to receive idraparinux and/or missed injections
- Diagnostic suspicion bias
- Pharmacokinetics and/or pharmacodynamics of idraparinux
- Chance



# Biotinylated idraparinux : Structure and product profile



Idraparin sodium  
(SR34006)



Biotinylated  
idraparinux  
(SSR126517E)

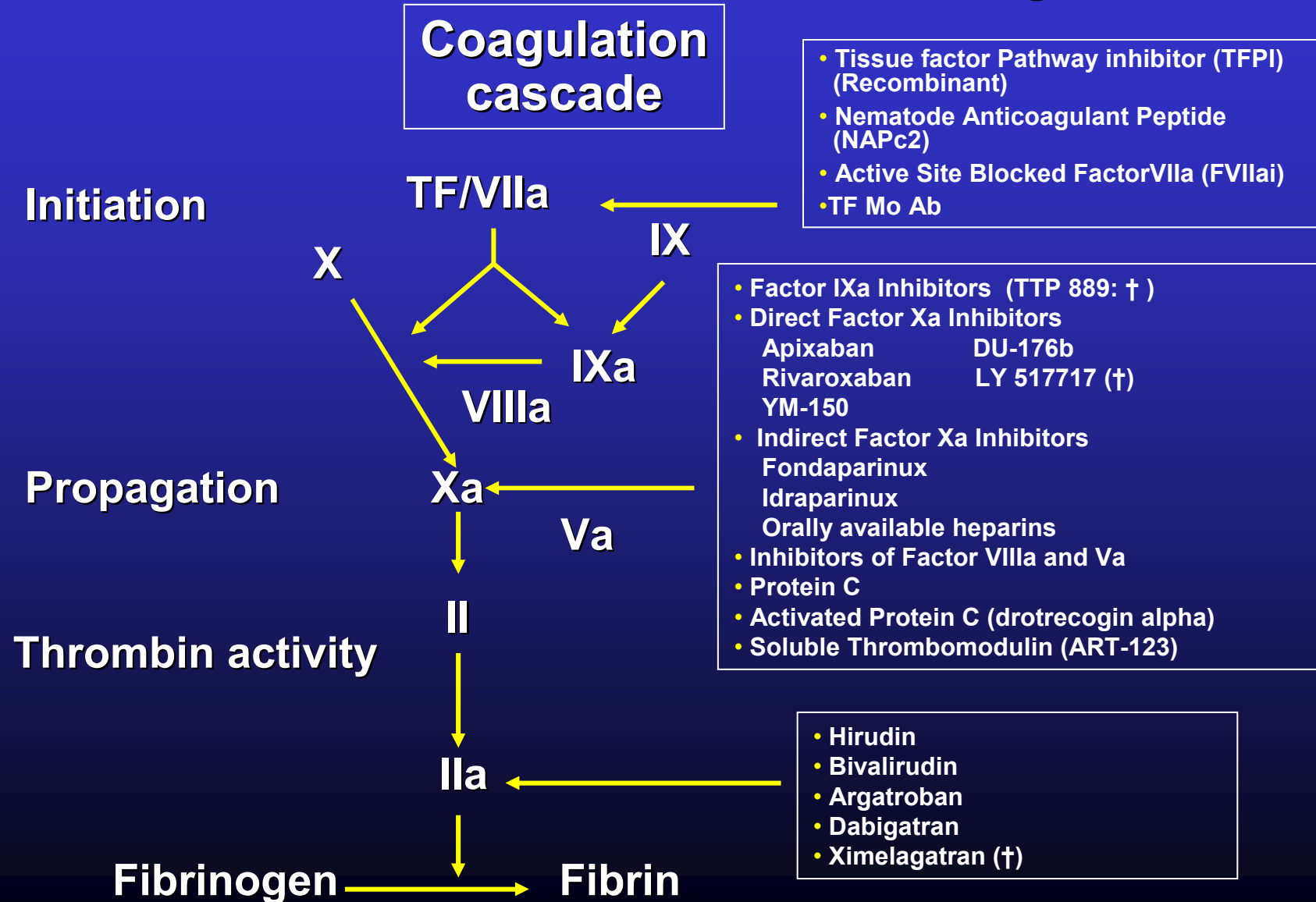
Biotin arm with spacer

- Idraparinux active moiety responsible for pharmacological activity for both molecules
- Biotinylated part allows neutralization by avidin (extracted from white part of eggs)
- Bioequipotency of 3 mg biotinylated idraparinux with 2.5 mg idraparinux after a single injection



# New Anticoagulants

## Drug



# Dabigatran Etexilate

- An oral, small molecule, reversible, direct thrombin inhibitor
- Prodrug: dabigatran etexilate
- Absolute bioavailability ~6.5 %<sup>1</sup>
- Half life 14-17 hours <sup>1</sup>
- Renal excretion 80%



Dabigatran **etexilate**

1. Stangier et al *British Journal of Clinical Pharmacology* 2007

# Dabigatran, a new oral direct thrombin inhibitor in development

## Results of RE-MODEL, RE-MOBILIZE, and RE-NOVATE trials

Endpoint	Dabigatran (150 mg)	Dabigatran (220 mg)	Enoxaparin (40 mg/30 mg bid)
VTE+/-Mortality (%)			
Major bleeding (%)			
RE-MODEL (TKR; 6-10 d; EU)	40.5 1.3	36.4 1.5	37.7 1.3
RE-MOBILIZE (TKR; 12-15 d; NA)	33.7 0.6	31.1 0.6	25.3 1.4
RE-NOVATE (THR; 28-35d; EU)	8.7 1.3	6.0 2.0	6.7 1.6

# Dabigatran etexilate ongoing

- **Prevention VTE in elective hip/knee  
(Renovate; Remobilize)** **Phase III**
- **Treatment of VTE  
(Recover; Remedy)** **Phase III**
- **Atrial fibrillation  
(Rely)** **Phase III**

# Challenges for venous thromboembolism treatment

## - 2020 -

- **Studying all new antithrombotic agents**
- **Improving facilities for out of hospital treatment/monitoring**
- **Better stratification for who should be treated long term**
- **Single drug treatment**
- **Heparin and vitamin K antagonists will play minor role. Challenges for compliance and monitoring**





# Conclusions

- **Real explosion of compounds**
- **Some major failures**
- **Some will definitely survive**
- **There is life after warfarin and heparin**

