Antithrombotic Therapy Current Status and Future Directions

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Disclosures

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Employee	No conflicts of interest
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Speakers Bureau	No conflicts of interest
Scientific Advisory Board	CSL Behring

- 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[1]
- VTE causes over 500,000 deaths in Europe and 300,000 deaths in the United States each year[2,3]
- Annual deaths attributable to VTE are estimated to exceed the combined number of deaths from breast and prostate cancers, AIDS, and traffic accidents[4]
- Total estimated cost for VTE-associated care = EUR 3.1 billion per year[5]

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 : ± 33% extend proximally**
- **Proximal DVT : ± 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)

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)

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


25 Gms.
WARFARIN
Abbott
De-Stroy
WATER
SOLUBLE
WARFARIN
RAT
AND MOUSE
KILLER
$1.00 JUST ADD WATER $1.00

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

VKAs

Initial treatment INR 2.0–3.0 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

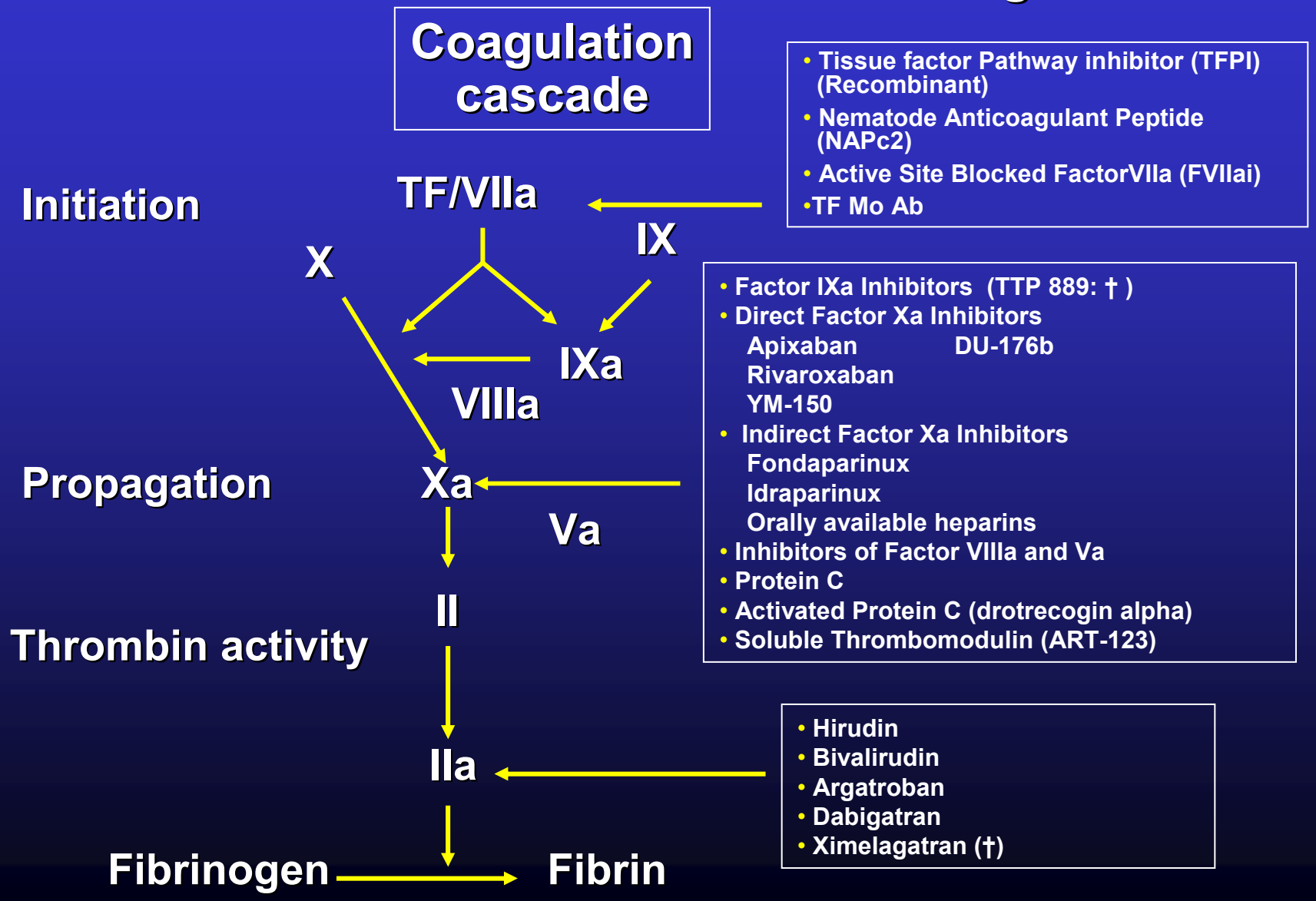
- Initial therapy LMWH/UFH
- Alternatives for LMWH/UFH
- Thrombolytic therapy
- Caval filter
- Ambulation

- 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



DE EERSTE **ORALE ANTISTOLLING**
ZONDER LABCONTROLE

Pradaxa
dabigatran etexilaat

Transforming anticoagulation

Classical Pathway of the Evaluation of New Antithrombotics

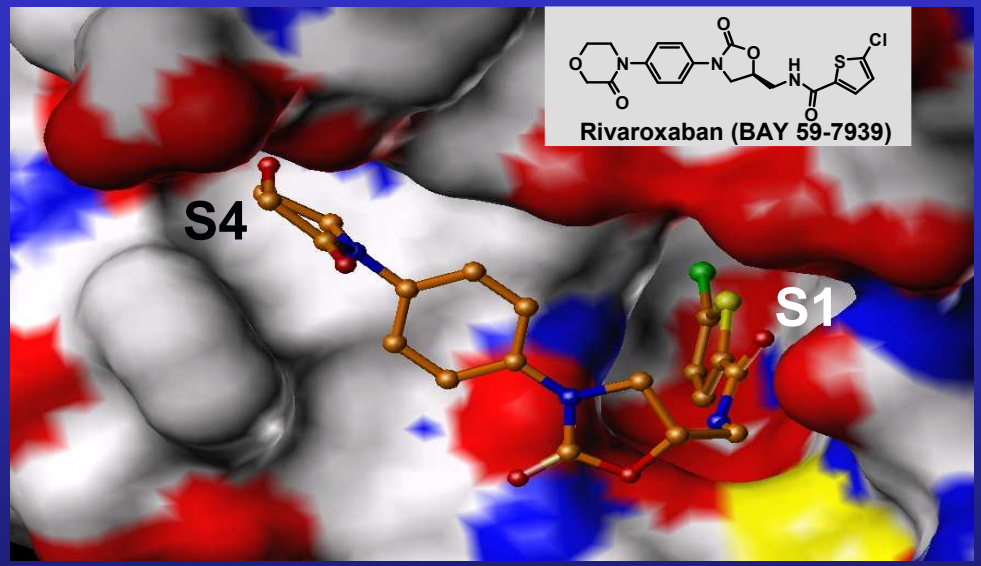
- **First : orthopaedic surgery**
- **Second: treatment of established venous thrombosis**
- **Third : atrial fibrillation acute coronary syndromes**

Human Factor Xa/rivaroxaban complex

X-ray crystal structure

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

- Selective for Factor Xa (K_i = 0.4±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 | RECORD 2 | RECORD 3

The NEW ENGLAND JOURNAL of MEDICINE

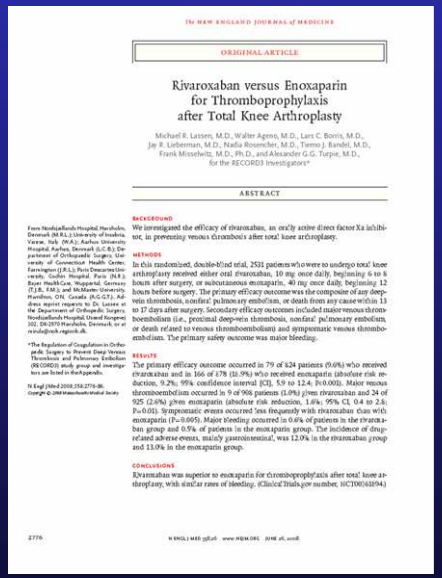
Rivaroxaban versus Enoxaparin for Thromboprophylaxis after Hip Arthroplasty

THE LANCET

Articles

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

The NEW ENGLAND JOURNAL of MEDICINE



ORIGINAL ARTICLE

Rivaroxaban versus Enoxaparin for Thromboprophylaxis after Total Knee Arthroplasty

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

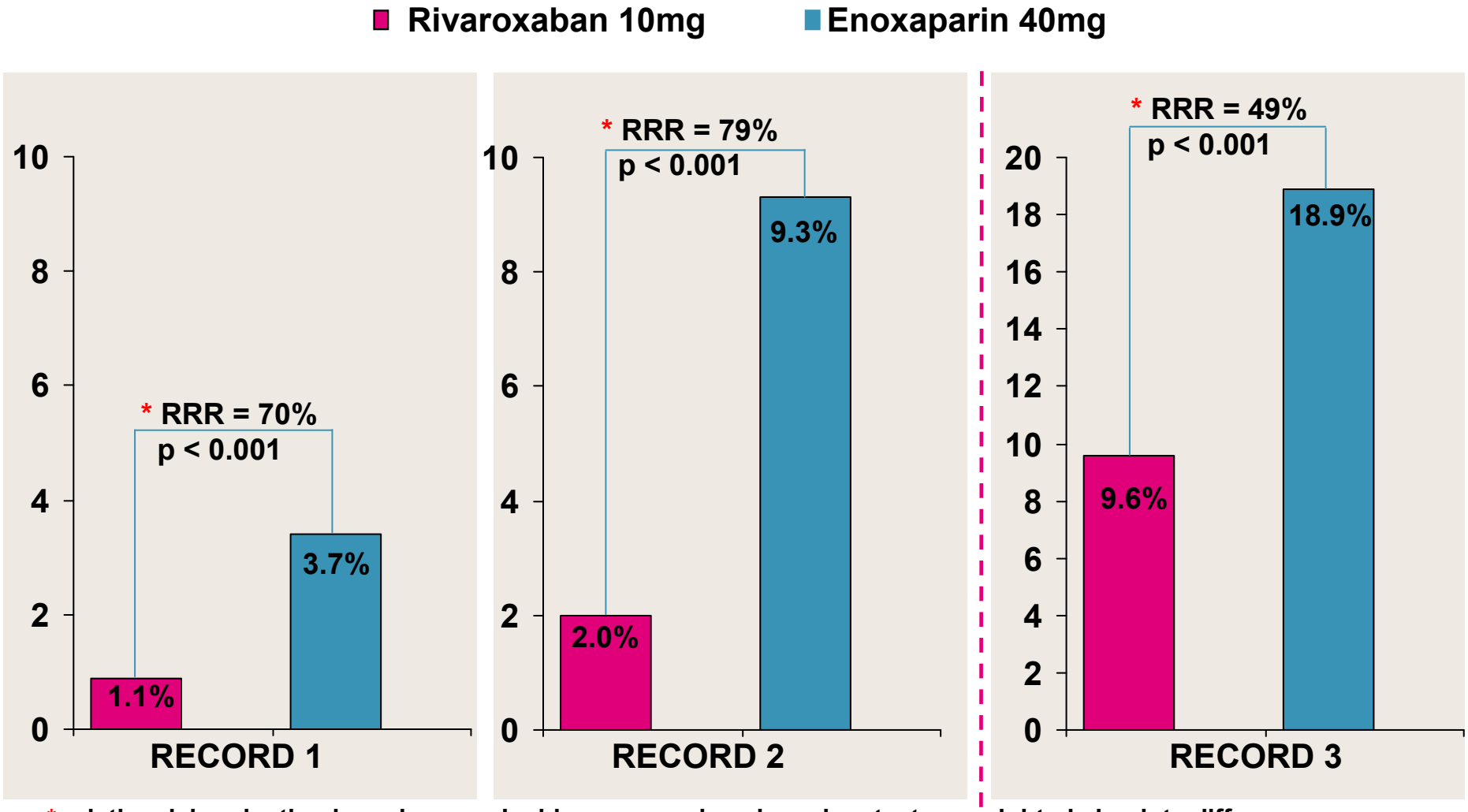
- Rivaroxaban 10 mg once daily investigated
- Same study design and efficacy and safety outcomes
  - Randomized, active-comparator-controlled, parallel-group, double-blind, double-dummy
- Same independent, blinded adjudication committees

RECORD 1	RECORD 2	RECORD 3	RECORD 4
HIP replacement	**HIP replacement**	**KNEE replacement**	**KNEE replacement**
Rivaroxaban 10 mg od for 5 weeks vs enoxaparin 40 mg od for 5 weeks	Rivaroxaban 10 mg od for 5 weeks vs enoxaparin 40 mg od for 10–14 days then oral placebo	Rivaroxaban 10 mg od for 10–14 days vs enoxaparin 40 mg od for 10–14 days	Rivaroxaban 10 mg od for 10–14 days vs enoxaparin 30 mg bid for 10–14 days
N=4,541	**N=2,509**	**N=2,531**	**N=3,148**

RECORD

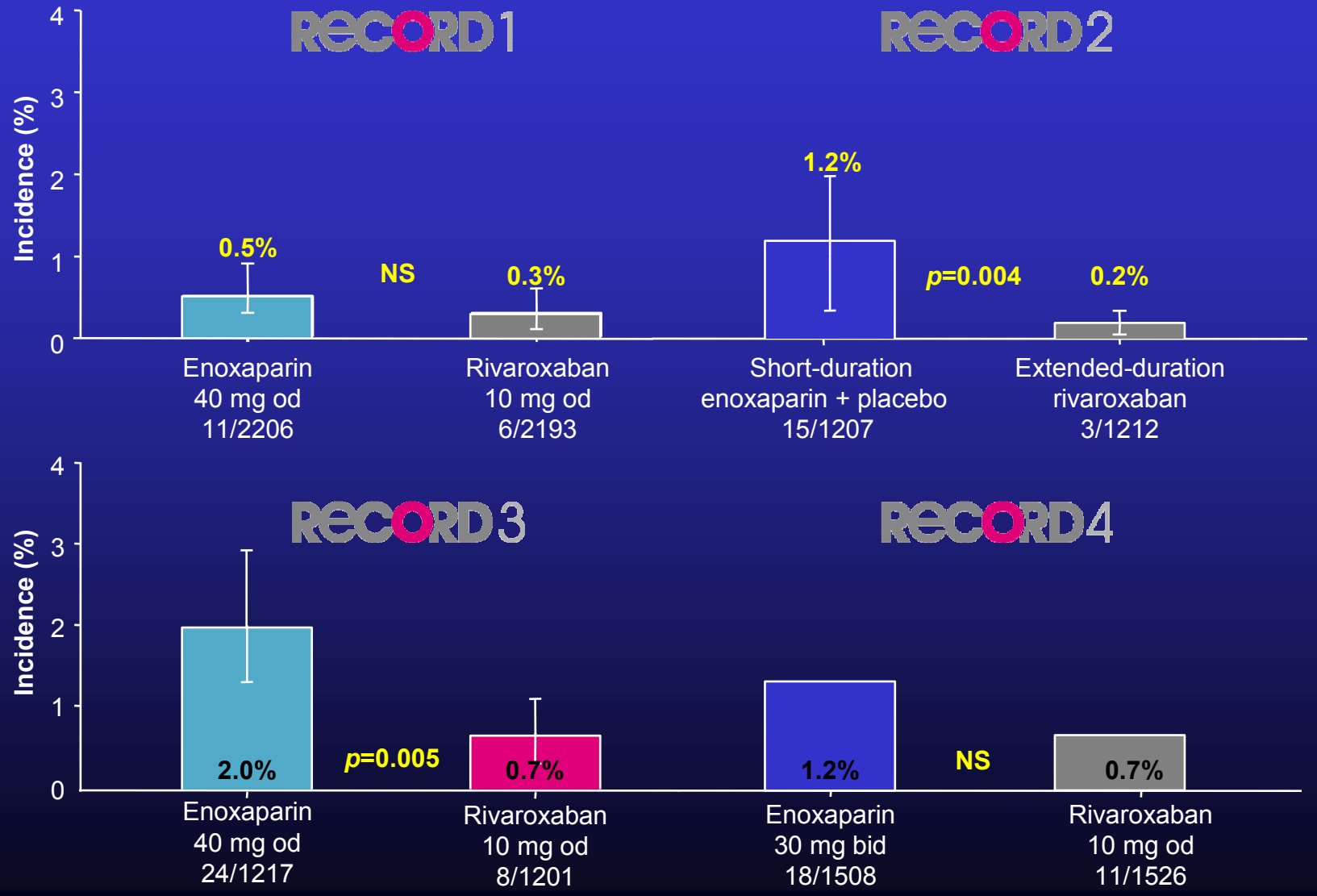
REgulation of Coagulation in major Orthopaedic surgery reducing the Risk of DVT and PE

Efficacy: Total VTE (primary endpoint)



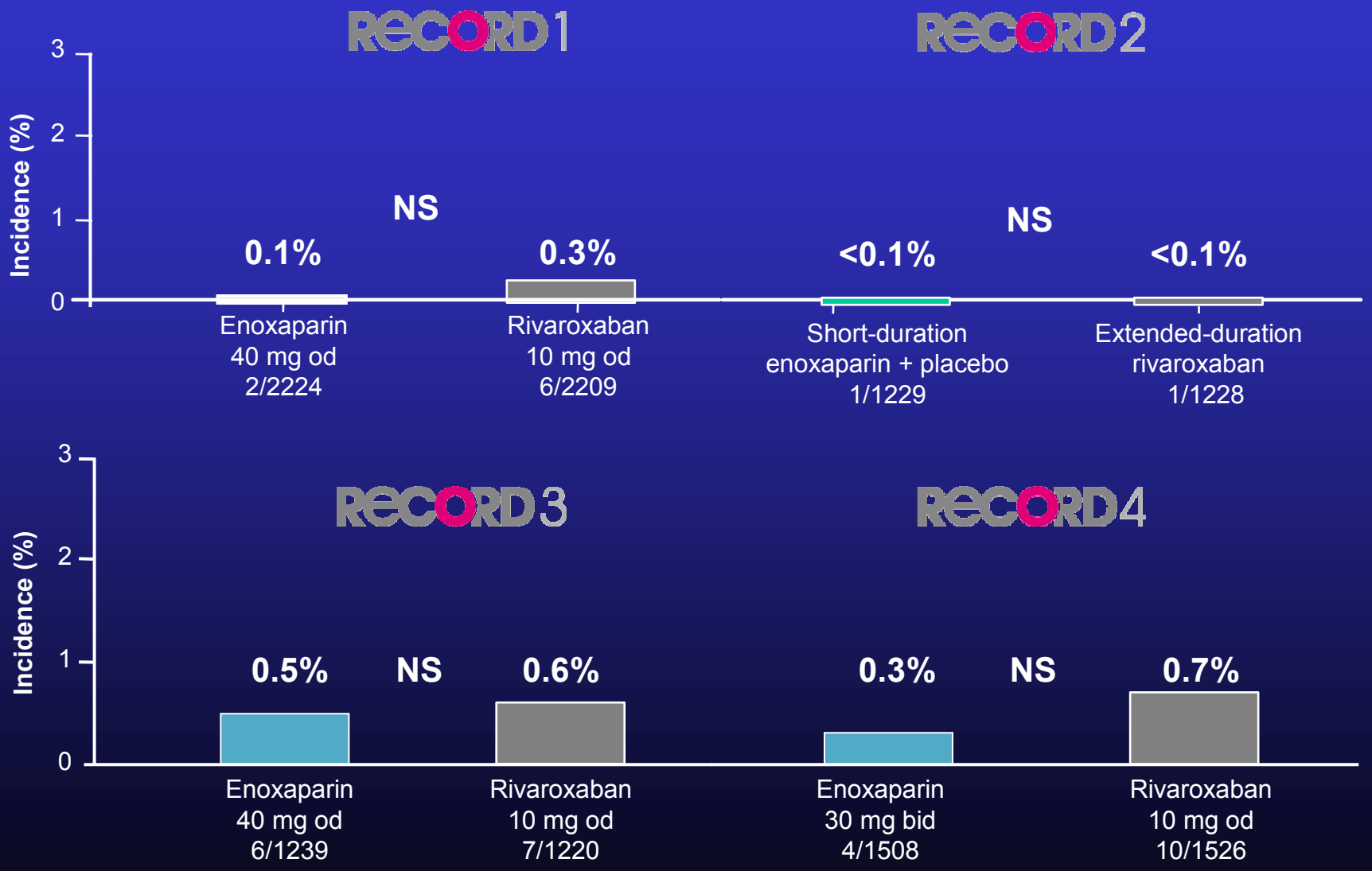
* relative risk reduction based on raw Incidences; p-values based on test on weighted absolute differences

Symptomatic VTE: summary



Safety population who underwent surgery
RECORD1, n=4399; RECORD2, n=2419; RECORD3, n=2418; RECORD4, n=3034

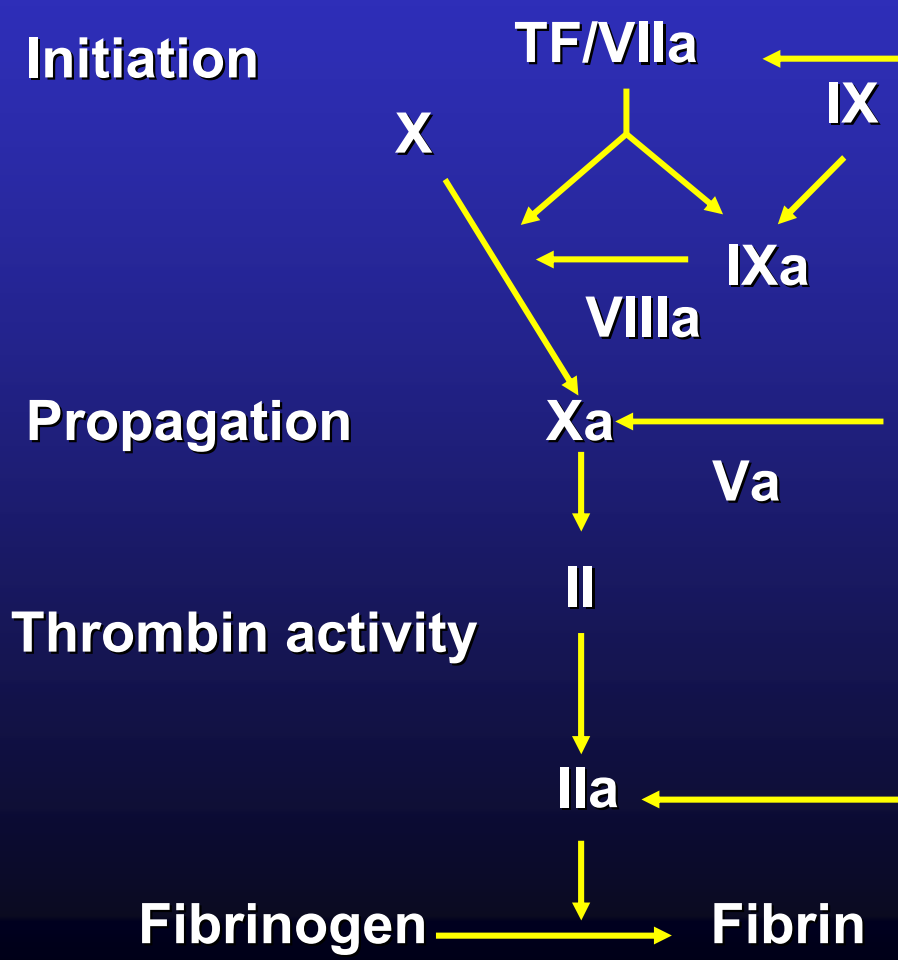
Major bleeding: summary



Rivaroxaban ongoing

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

New Anticoagulants



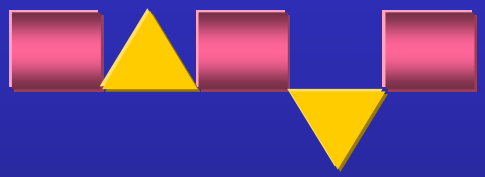
Drug

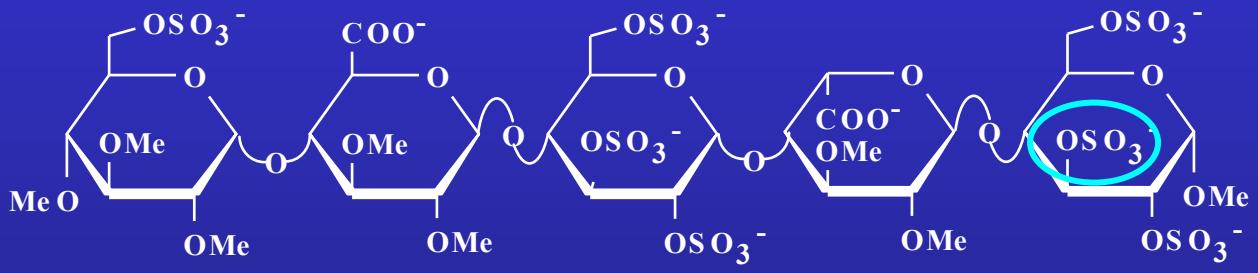
- Tissue factor Pathway inhibitor (TFPI) (Recombinant)
- Nematode Anticoagulant Peptide (NAPc2)
- Active Site Blocked FactorVIIa (FVIIai)
- TF Mo Ab

- Factor IXa Inhibitors (TTP 889: †)
- Direct Factor Xa Inhibitors
  - Apixaban
  - DU-176b
  - Rivaroxaban
  - LY 517717 (†)
  - YM-150
- Indirect Factor Xa Inhibitors
  - Fondaparinux
  - Idraparinux
  - Orally available heparins
- Inhibitors of Factor VIIIa and Va
- Protein C
- Activated Protein C (drotrecogin alpha)
- Soluble Thrombomodulin (ART-123)

- Hirudin
- Bivalirudin
- Argatroban
- Dabigatran
- Ximelagatran (†)

Idraparinux: once-weekly anticoagulant





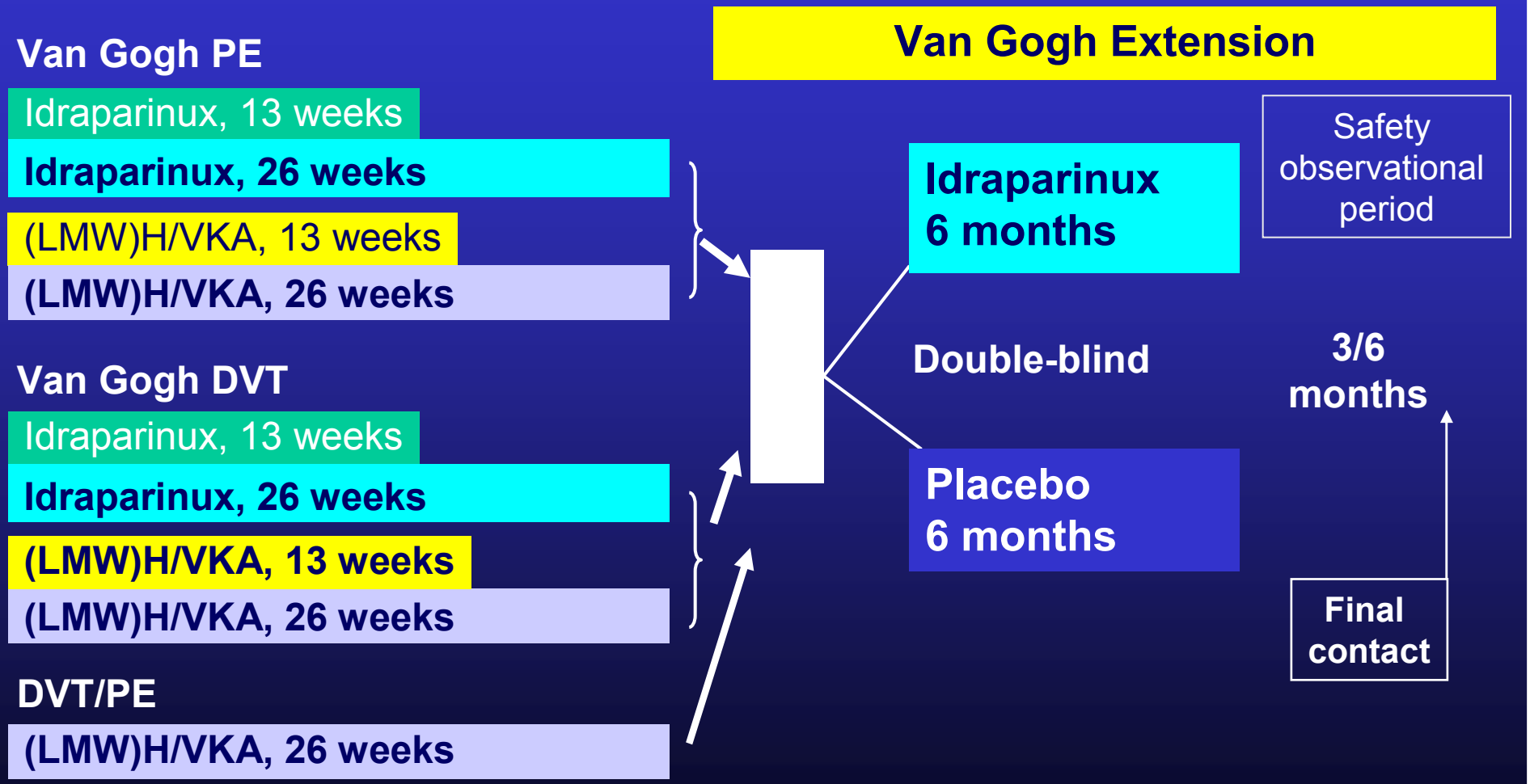
Sulfate group on H block

Long half-life

Once weekly administration

Herbert JM, et al. Blood. 1998;91:4197-205.

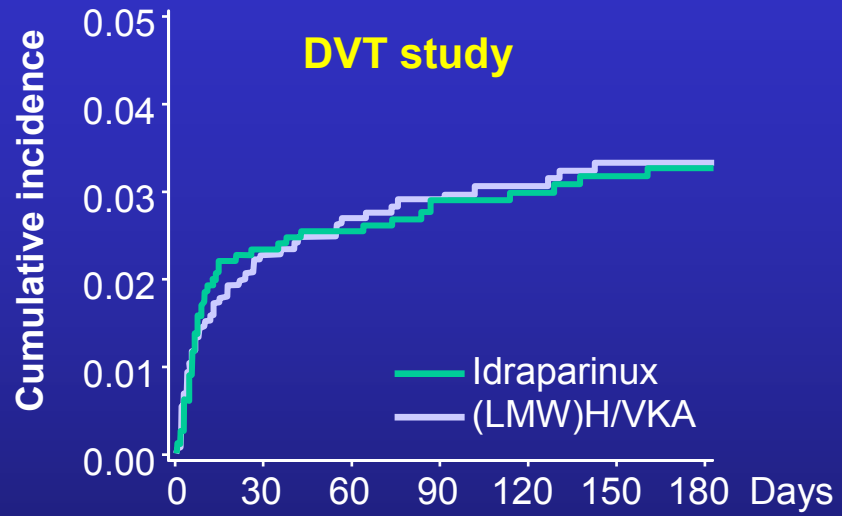
Idraparinux for VTE treatment Phase III programme – Van Gogh



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

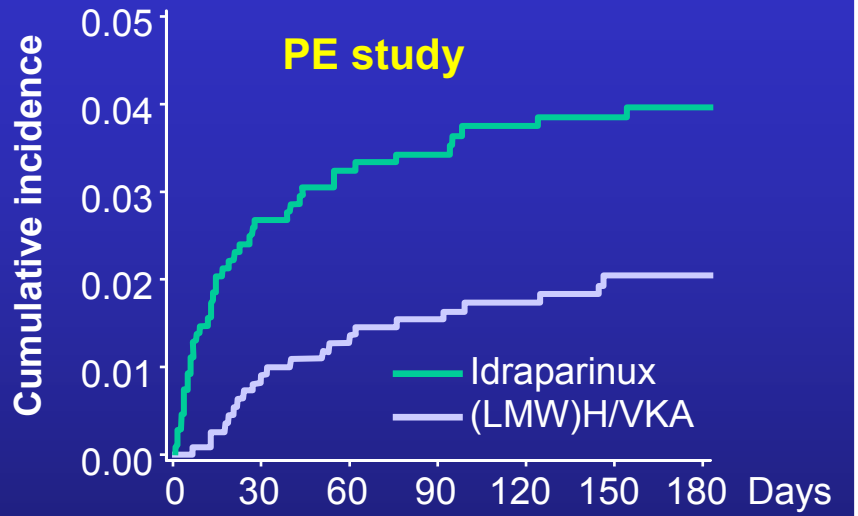
Buller et al. *NEJM* 2007;357:1094-1104.
Buller et al. *NEJM* 2007;357:1105-1112.

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

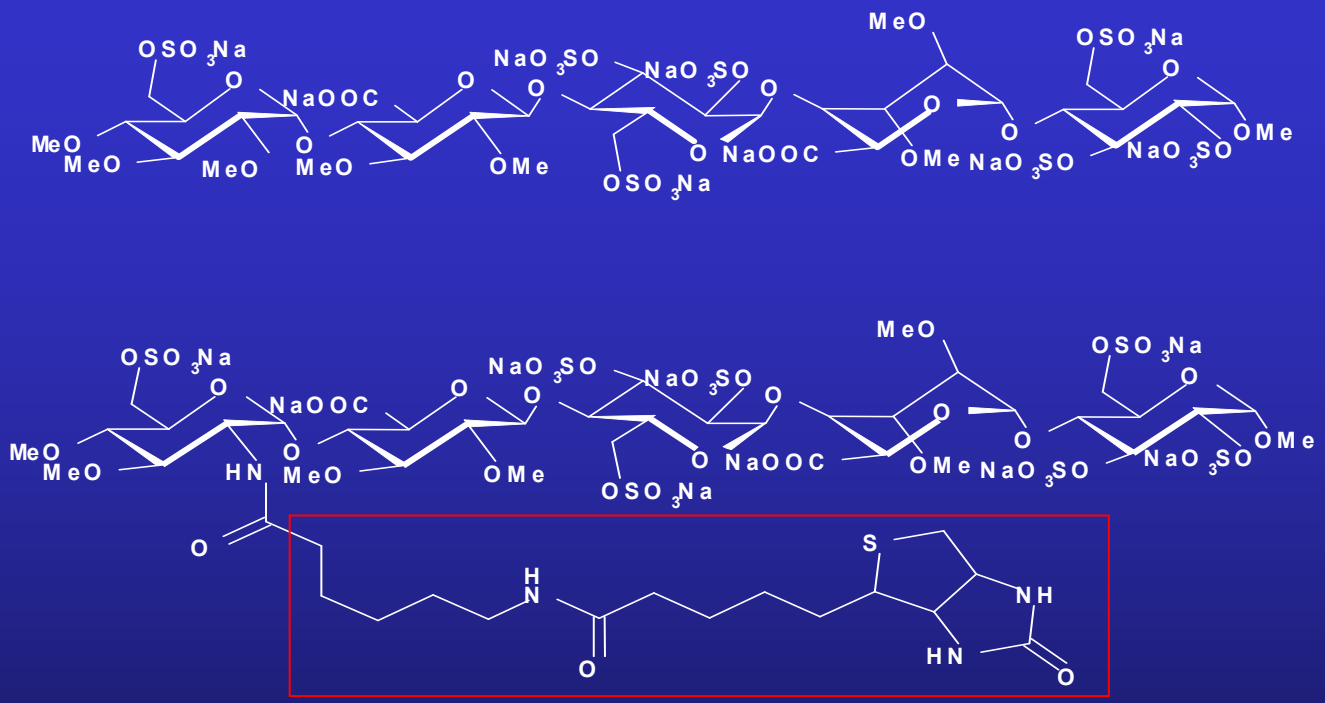


Number at risk:

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



Biotin arm with spacer

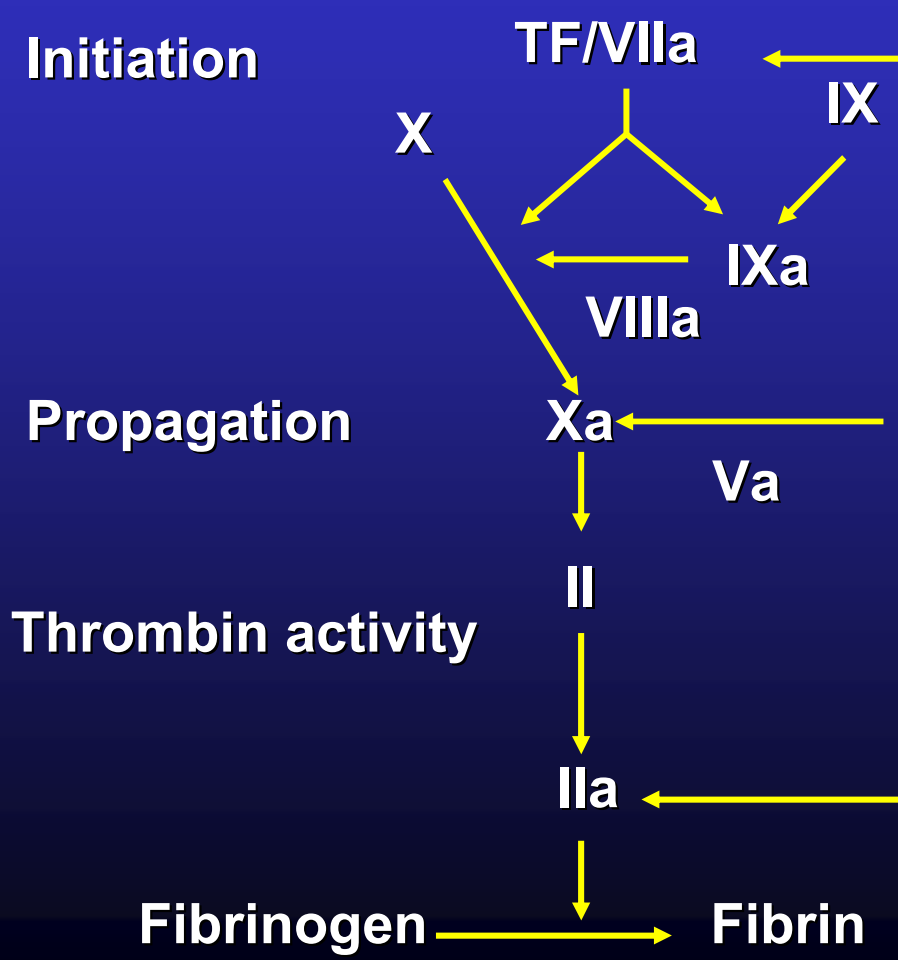
Biotinylated idraparinux (SSR126517E)

- **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**

Biotinylated Idraparinux ongoing

- Prevention VTE — no studies
- Treatment of VTE
  - Equinox (DVT) — bioequipotency
  - Cassiopea (PE) — Phase III
- Atrial fibrillation
  - Borealis — Phase III

New Anticoagulants



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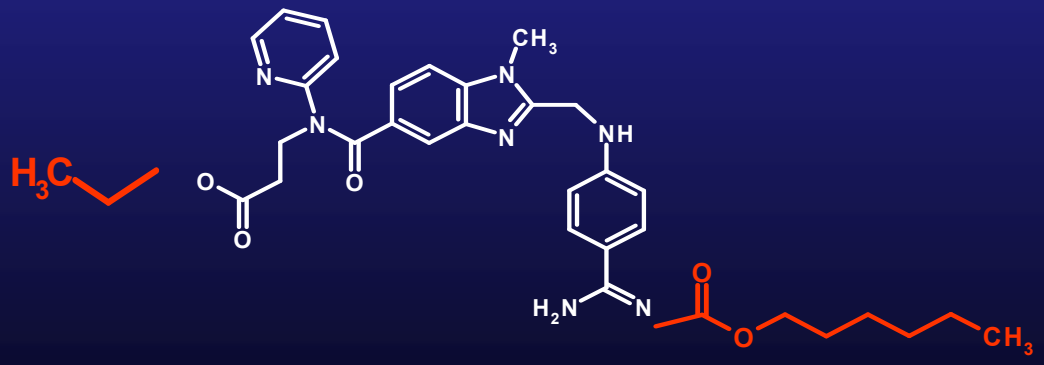
Dabigatran Etexilate

- An oral, small molecule, reversible, direct thrombin inhibitor
- Prodrug: dabigatran etexilate
- Absolute bioavailability ~6.5 %[1]
- Half life 14-17 hours [1]
- 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	40.5	36.4	37.7
(TKR; 6-10 d; EU)	1.3	1.5	1.3
RE-MOBILIZE	33.7	31.1	25.3
(TKR; 12-15 d; NA)	0.6	0.6	1.4
RE-NOVATE	8.7	6.0	6.7
(THR; 28-35d; EU)	1.3	2.0	1.6

Caprini, ISTH, 2007; Eriksson, ASH, 2006

Dabigatran etexilate ongoing

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

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**