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An update on new oral anticoagulant drugs

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Disclosures for Henri Bounameaux, MD

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The « old » unspecific anticoagulants

- **Unfractionated heparin UFH and (to some extent) LMWHs**

  Therapeutic index narrow and variability +++ ➔ monitoring +++

  Risk of induced thrombocytopenia ➔ platelet counts

  Continuous iv or 2-3 sc/day

- **Vitamin K antagonists**

  Therapeutic index narrow and variability +++ ➔ monitoring +++

  po but hepatic metabolism + protein binding ➔ interactions +++

➔ Need for increased efficacy/safety/user-friendliness

The ideal anticoagulant drug

- Rapidly inhibits thrombus progression
- Can be administered orally
- Exhibits a large therapeutic margin
- Has predictable pharmacokinetics and dose-response relationship
- Exhibits a low non-specific binding to plasma proteins
- Does not require laboratory monitoring
- Does not need frequent dose adjustments
- Produces few bleeding complications
- Produces few adverse events
- Exhibits few interactions with other drugs and with food

How ideal are LMWH?

- Rapidly inhibits thrombus progression
- Can be administered orally
- Exhibits a large therapeutic margin
- Has predictable pharmacokinetics and dose-response relationship
- Exhibits a low non-specific binding to plasma proteins
- Does not require laboratory monitoring
- Does not need frequent dose adjustments
- Produces few bleeding complications
- Produces few adverse events
- Exhibits few interactions with other drugs and with food
- Are synthetic compounds

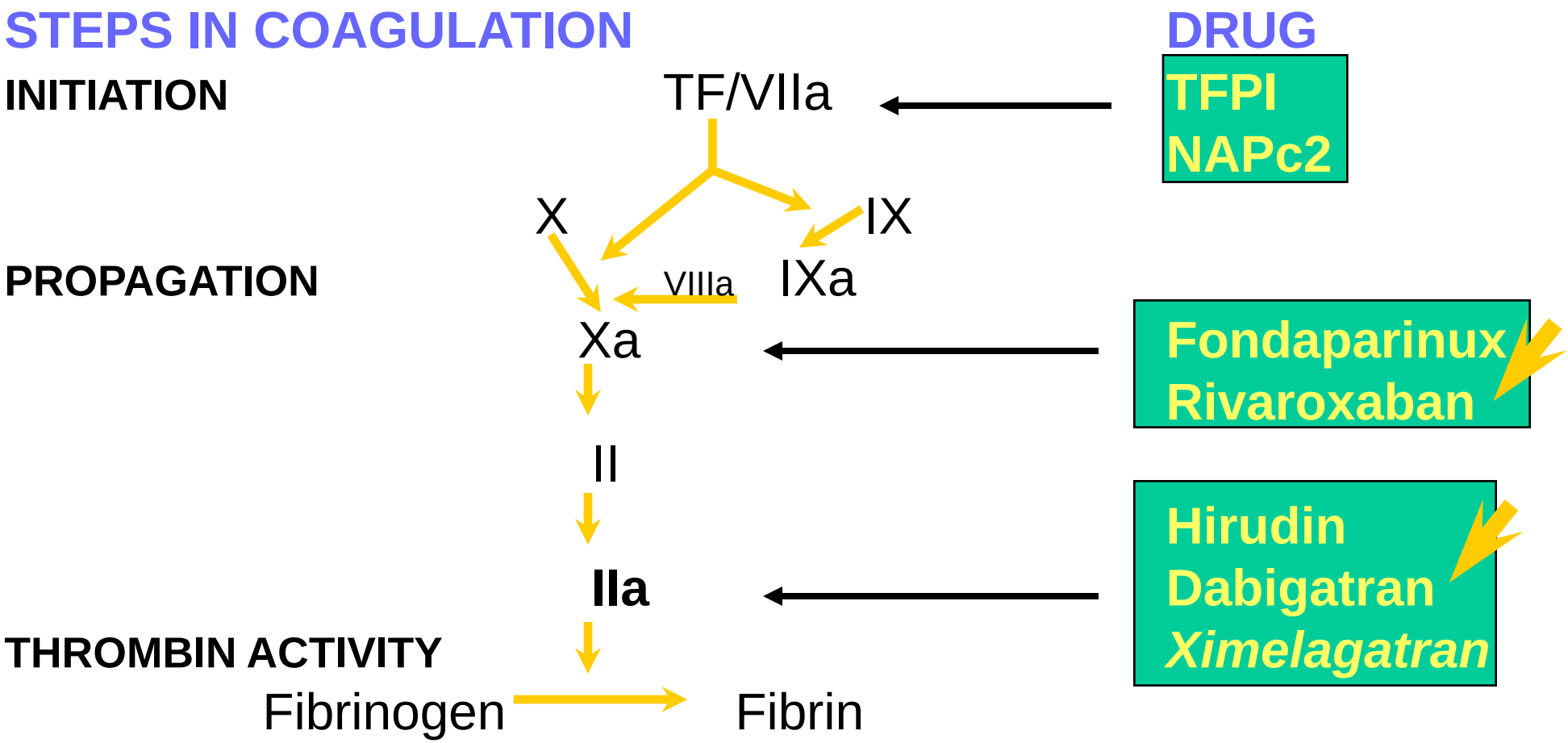
How ideal are VKA?

- Rapidly inhibits thrombus progression
- Can be administered orally
- Exhibits a large therapeutic margin
- Has predictable pharmacokinetics and dose-response relationship
- Exhibits a low non-specific binding to plasma proteins
- Does not require laboratory monitoring
- Does not need frequent dose adjustments
- Produces few bleeding complications
- Produces few adverse events
- Exhibits few interactions with other drugs and with food
- Are synthetic compounds

Comparison of four upcoming novel specific oral anticoagulants

Drug Class	Company	Half-life	Bioavaila-bility	Elimination	Dosage (oral)
Apixaban antiXa	BMS/ Pfizer	8-15	50-85%	25% renal 75% biliary	b.i.d.
Edoxaban anti-Xa	Daïchi-sankyo	10	50%	33% renal 66% biliary	o.d.
Rivaroxaban antiXa	Bayer/ J&J	5-13	>80%	33% renal (unchanged) 33% renal (inactive metabolites) 33% biliary	o.d.
Dabigatran DTI	B-I	14-17	5%	80% renal 20% biliary	b.i.d.

Site of action of new anticoagulants



Adapted from Weitz JI et al. Chest 2001; **119**:95S-107S

Phase III Development of New Anticoagulants

- **Thromboprophylaxis**
  - **Total Hip Replacement**
  - **Total Knee Replacement**
  - Acutely ill hospitalized non-surgical patients
  - Other types of surgical indications
- Treatment of established DVT or PE
- Long-term secondary prevention of VTE
- Prophylaxis of systemic embolization in patients with AF
- Treatment of ACS

The NEW ENGLAND JOURNAL of MEDICINE

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

- Rivaroxaban 10 mg od was compared with enoxaparin in 12,729 patients worldwide

Rivaroxaban versus Enoxaparin for Thromboprophylaxis after Hip Arthroplasty

Bengt I. Eriksson, M.D., Ph.D., Lars C. Borris, M.D., Richard J. Friedman, M.D., Sylvia Haas, M.D., Menno V. Huisman, M.D., Ph.D., Ajay K. Kakkar, M.D., Ph.D., Tiemo J. Bandel, M.D., Horst Beckmann, Ph.D., Eva Muehlhofer, M.D., Frank Misselwitz, M.D., Ph.D., and William Geerts, M.D., for the RECORD1 Study Group*

N Engl J Med 2008;358:2765-75.

Rivaroxaban versus Enoxaparin for Thromboprophylaxis after Total Knee Arthroplasty

Michael R. Lassen, M.D., Walter Ageno, M.D., Lars C. Borris, M.D., Jay R. Lieberman, M.D., Nadia Rosencher, M.D., Tiemo J. Bandel, M.D., Frank Misselwitz, M.D., Ph.D., and Alexander G.G. Turpie, M.D., for the RECORD3 Investigators*

N Engl J Med 2008;358:2776-86.

Lancet 2008; 372: 31–39

THE LANCET

Published online May 5, 2009 DOI:10.1016/S0140-6736(09)60734-0

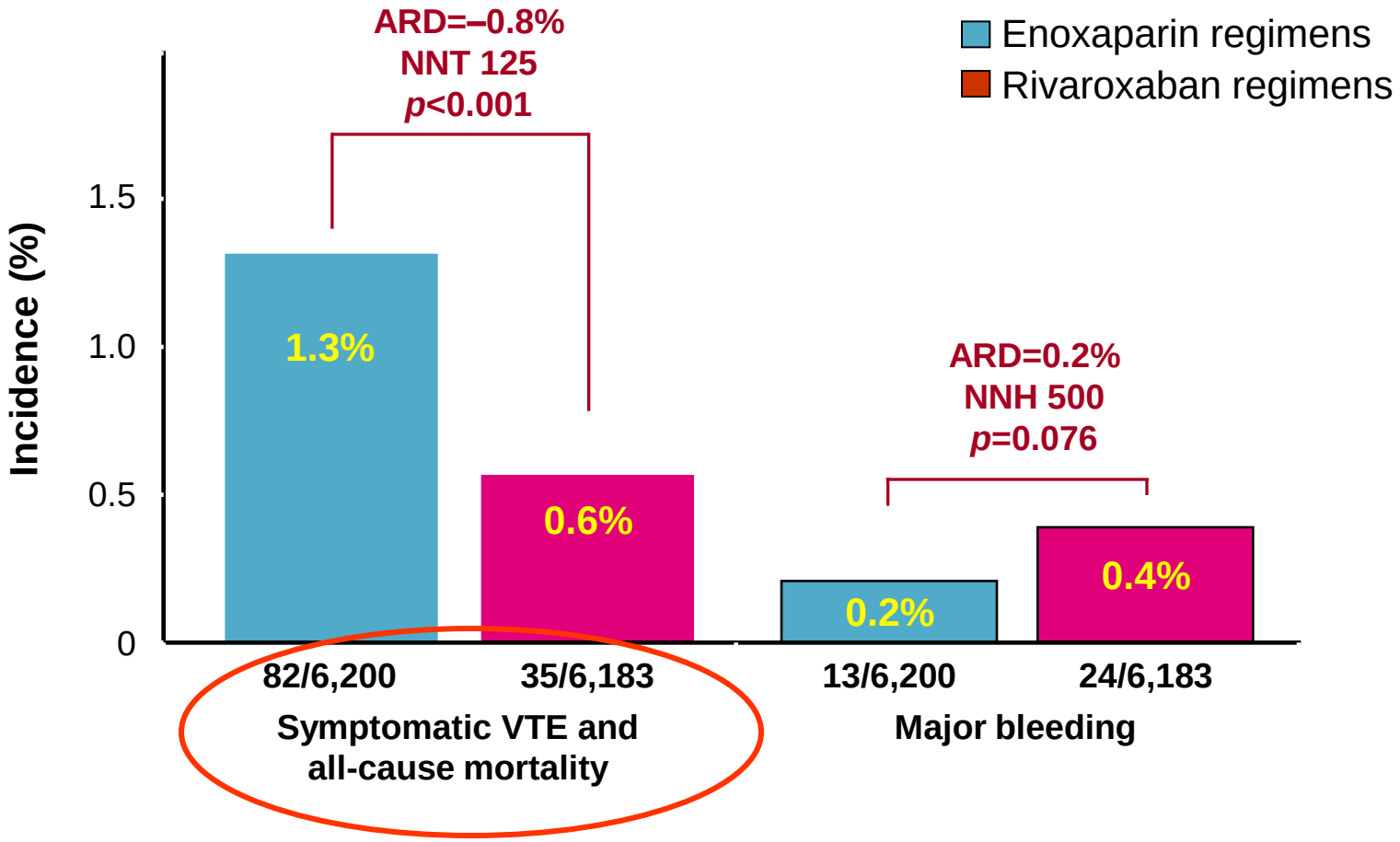
Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial

Ajay K Kakkar, Benjamin Brenner, Ola E Dahl, Bengt I Eriksson, Patrick Mouret, Jim Muntz, Andrea G Soglian, Ákos F Pap, Frank Misselwitz, Sylvia Haas, for the RECORD2 Investigators*

Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial

Alexander G G Turpie, Michael R Lassen, Bruce L Davidson, Kenneth A Bauer, Michael Gent, Louis M Kwong, Fred D Cushner, Paul A Lotke, Scott D Berkowitz, Tiemo J Bandel, Alice Benson, Frank Misselwitz, William D Fisher, for the RECORD4 Investigators*

Total treatment duration pool
Primary efficacy analysis in RECORD 1- 4



p-values analyzed using a Cox regression model; **s**afety population, n=12,383

Turpie AG et al ASH Abstract 2008

VTE Prevention in orthopaedic surgery
Phase III – studies with Dabigatran

2,101 Patients

TKR

Europe / South Africa / Australia

Eriksson BI JTH 2007

2,615 Patients

TKR

North-America

Ginsberg J J Arthr 2009

3,494 Patients

THR

Europe / South Africa / Australia

Erikson BI Lancet 2007

Pooled Analysis Major VTE and VTE-Related Death

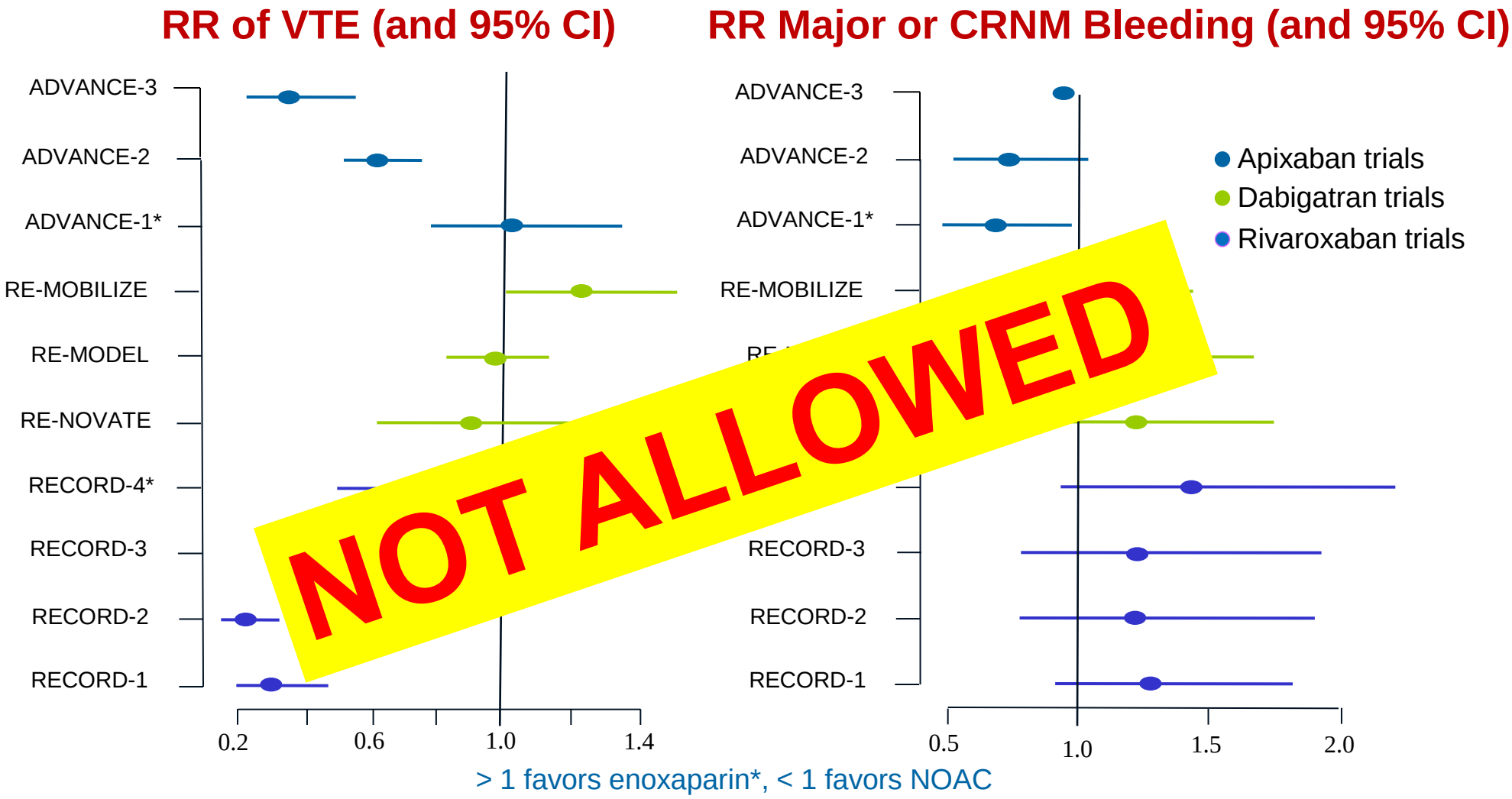
Study	Dabigatran 150 mg	Dabigatran 220 mg	Enoxaparin
RE-NOVATE* (THR)	4.3%	3.1%	3.9% (40 mg od)
RE-MODEL** (TKR)	3.8%	2.6%	3.5% (40 mg od)
RE-MOBILIZE*** (TKR)	3.0%	3.4%	2.2% (60 mg od)
Pooled	**3.8%**	**3.0%**	**3.3%**
Absolute risk difference	**0.5**	**-0.2**	
(Dabigatran – Enoxaparin) [95% CI]	**[-0.6 to 1.6]**	**[-1.3 to 0.9]**	

* Eriksson et al. *Lancet* 2007;370:949
** Eriksson et al *JTH* 2007; 5:2178-85
*** Ginsberg et al *J Arthroplasty* 2009;24:1-9

Pooled Analysis Bleeding Events

	Dabigatran etexilate		Enoxaparin
	150 mg N=2737	220 mg N=2682	N=2716
Major Bleeding Event	**1.1%**	**1.4%**	**1.4%**
95% CI	**(0.7 , 1.4)**	**(1.0, 1.9)**	**(1.0, 2.0)**

Cross Trial Comparisons: Forest Plots



CRNM = clinically relevant non-major

*vs. enoxaparin 30 mg bid (all other 40 mg od)

Phase III Development of New Anticoagulants

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Anticoagulant treatment for VTE :

Summary recommendations of the 8th ACCP Consensus

8th ACCP Guidelines: Kearon C et al. Chest 2008; 133:454S-545S

sq LMWH
iv or sq UFH
sq Fondaparinux
All : 1A

≧ 5 days 1A

at l

Vitamin K Ant
(INR

In patients who receive long-term anticoagulant treatment, the risk-benefit ratio of continuing such treatment should be reassessed periodically 1C

valuate for long-term 1C
if no CI opt for long-term 1A
if less monitoring low INR 1A

Initial treatment

Secondary prophylaxis

EINSTEIN-DVT Study:

Non-monitored rivaroxaban 15 mg bid (3w), followed by 20 mg od vs enoxaparin/INR-monitored VKA

	Rivaroxaban (n=1731)	**Enoxaparin/VKA (n=1718)**
Symptomatic recurrent VTE	36 (2.1%) HR 0.68 (0.44-1.04) p<0.0001 for non inferiority	51 (3.0%)
Major bleeding	14 (0.8%) NS	20 (1.2%)
Major or NMCR bleeding	139 (8.1%) HR 0.97 (0.78-1.22) P=0.77	138 (8.1%)
Net clinical benefit	51 (2.9%) HR 0.67 (0.47-0.95)	73 (4.2%)

Büller HR et al. ESC (Stockholm Proceedings, 2010 (Aug. 31))
Hotline 3 abstracts session (Abstr. 3770)

Main efficacy and safety results of EINSTEIN-EXT

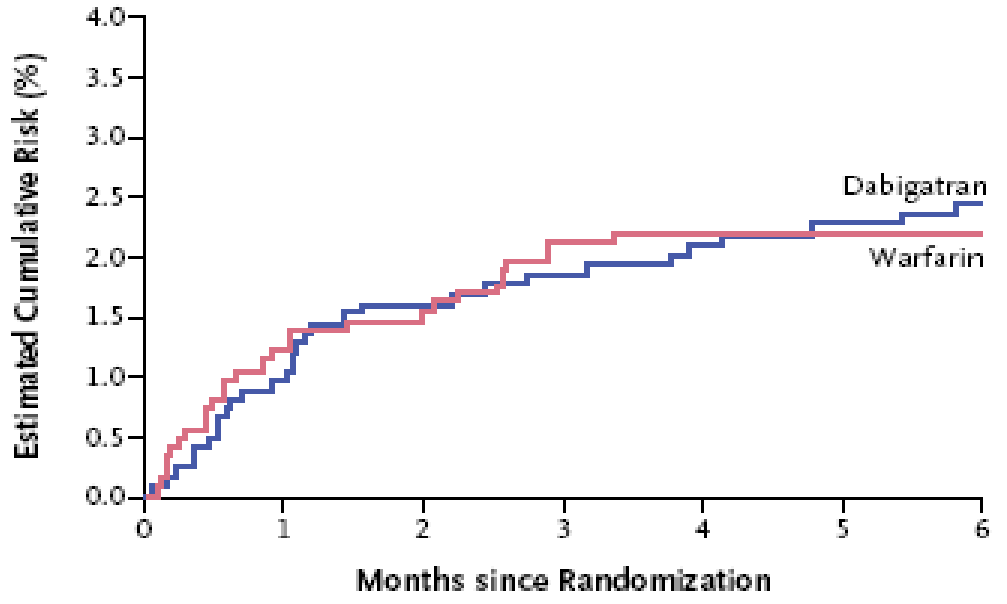
Rivaroxaban 20 mg od vs placebo for secondary VTE prevention

Mean treatment period: 190 days	Rivaroxaban (n=602)	Placebo (n=594)	
Symptomatic recurrent VTE	8 (1.3%) HR 0.18 (0.09-0.39) p<0.0001	42 (7.1%)	**NNT 17**
Major bleeding	4 (0.7%) p=0.106	0	**NNH 143**
Major or CRNM bleeding	36 (6.0%) HR 5.2 (2.3-11.7) p<0.001	7 (1.2%)	**NNH 21**

Büller HR et al. ASH Proceedings, 2009 (Dec. 8)
Late breaking abstracts session

Main efficacy and safety results of RE-COVER

Non-monitored Dabigatran 150 mg bid vs INR-monitored warfarin in acute VTE



No. at Risk							
Dabigatran	1274	1238	1221	1203	1192	1181	1024
Warfarin	1265	1215	1204	1194	1187	1174	998

Figure 1. Cumulative Risk of Recurrent Venous Thromboembolism or Related Death during 6 Months of Treatment among Patients Randomly Assigned to Dabigatran or Warfarin.

Major bleeding (%)

W 1.9%

D 1.6%

HR 0.82 (0.45-1.48)

Major or CRNM bleeding (%)

W 8.8%

D 5.6%

HR 0.63 (0.47-0.83)

Schulman S et al. NEJM 2009; 361: 361:2342-52

Design of the studies with the new oral anticoagulants in established VTE (all vs. warfarin)

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target	Thrombin	Factor Xa	Factor Xa	Factor Xa
Study acronym	RE-COVER	EINSTEIN	AMPLIFY	HOKUSAI
Study design	DB, R, NI	O, R, NI	DB, R, NI	DB, R, NI
Dosage	150 mg bid	15 mg bid (21d) then 20 mg od	10 mg bid (7d) then 5 mg bid	60 mg od
Initial UFH/LMWH	Mandatory (≥ 5d)	Optional (max. 48h)	Optional (max. 36h)	Mandatory (5-12d)

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Dabigatran versus Warfarin in Patients with Atrial Fibrillation

Stuart J. Connolly, M.D., Michael D. Ezekowitz, M.B., Ch.B., D.Phil., Salim Yusuf, F.R.C.P.C., D.Phil., John Eikelboom, M.D., Jonas Oldgren, M.D., Ph.D., Amit Parekh, M.D., Janice Pogue, M.Sc., Paul A. Reilly, Ph.D., Ellison Themeles, B.A., Jeanne Varrone, M.D., Susan Wang, Ph.D., Marco Alings, M.D., Ph.D., Denis Xavier, M.D., Jun Zhu, M.D., Rafael Diaz, M.D., Basil S. Lewis, M.D., Harald Darius, M.D., Hans-Christoph Diener, M.D., Ph.D., Campbell D. Joyner, M.D., Lars Wallentin, M.D., Ph.D., and the RE-LY Steering Committee and Investigators*

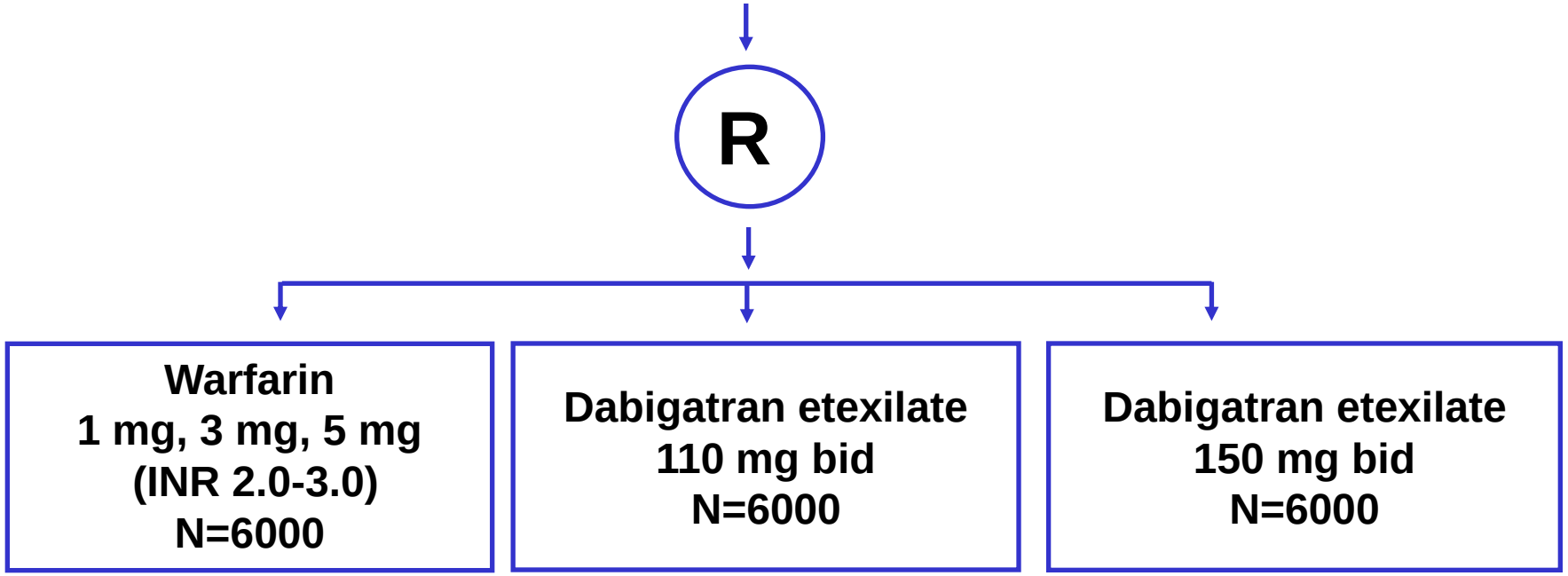
This article (10.1056/NEJMoa0905561) was published on August 30, 2009, at NEJM.org.

N Engl J Med 2009;361.

N Engl J Med 2009;361:1139-51

RE-LY® – study design

Atrial fibrillation with ≥ 1 risk factor
Absence of contraindications



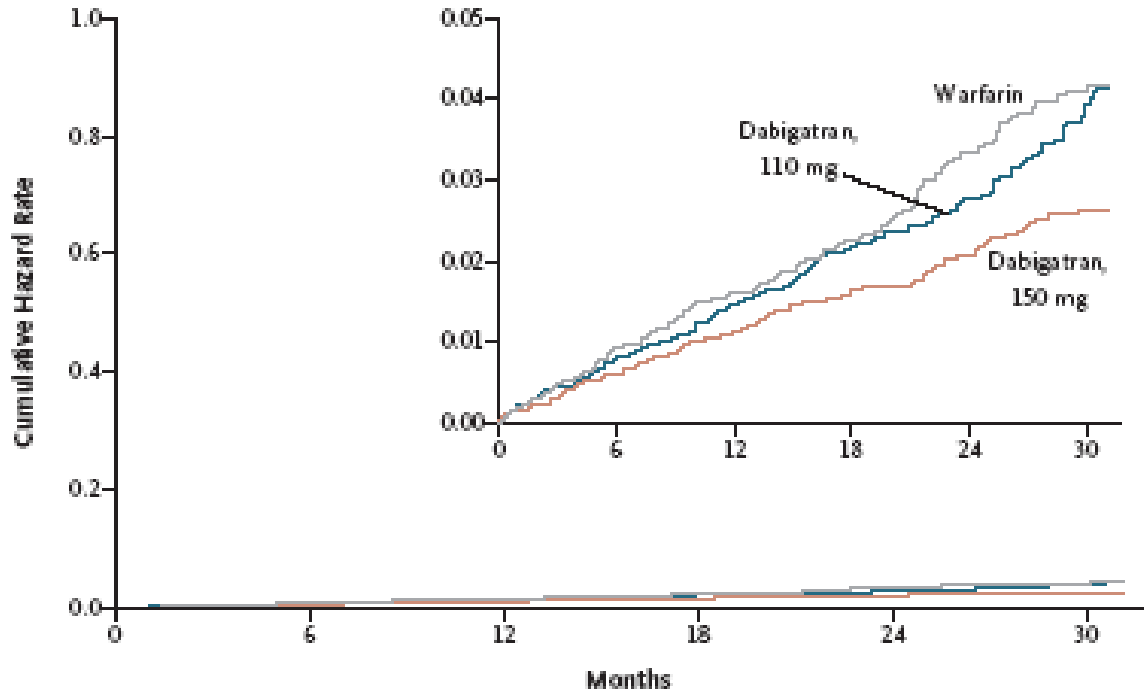
Open

Double-blinded

Connolly SJ et al. N Engl J Med 2009;361:1139-51.

Main efficacy and safety results of **RE-LY**

Dabigatran 110 or 150 mg bid vs INR monitored warfarin in AF



No. at Risk

Warfarin	6022	5862	5718	4593	2890	1322
Dabigatran, 110 mg	6015	5862	5710	4593	2945	1385
Dabigatran, 150 mg	6076	5939	5779	4682	3044	1429

Figure 1. Cumulative Hazard Rates for the Primary Outcome of Stroke or Systemic Embolism, According to Treatment Group.

Major bleeding (%/year)

W	3.36
D110	2.71*
D150	3.11**

*p=0.003
** NS

Connolly SJ et al. N Engl J Med 2009;361:1139-51.

Adverse events and discontinuations

Table 4. Discontinuation of the Study Drug, Adverse Events, and Liver Function According to Treatment Group.*

Variable	Dabigatran, 110 mg (N = 6015)	Dabigatran, 150 mg (N = 6076)	Warfarin (N = 6022)
	number of patients (percent)		
Study-drug discontinuation			
Discontinued at 1 yr†	862 (15)	935 (16)	608 (10)
Discontinued at 2 yr†	1161 (21)	1211 (21)	902 (17)
Reason for discontinuation			
Patient's decision	440 (7.3)	474 (7.8)	375 (6.2)
Outcome event	192 (3.2)	164 (2.7)	130 (2.2)
Serious adverse event‡	163 (2.7)	166 (2.7)	105 (1.7)
Gastrointestinal symptoms§	134 (2.2)	130 (2.1)	38 (0.6)
Gastrointestinal bleeding	58 (1.0)	80 (1.3)	54 (0.9)
Adverse events¶			
Dyspepsia‡	707 (11.8)	688 (11.3)	348 (5.8)

Connolly SJ et al. N Engl J Med 2009;361:1139-51.

The ideal anticoagulant drug

RIVA	DABI	
▶	▶	Rapidly inhibits thrombus progression
▶	▶	Can be administered orally
▶	▶	Exhibits a large therapeutic margin
▶	▶	Has predictable pharmacokinetics and dose-response relation
▶	▶	Exhibits a low non-specific binding to plasma proteins
▶	▶	Does not require laboratory monitoring
▶	▶	Does not need frequent dose adjustments
▶	▶	Produces few bleeding complications
?	?	Produces few adverse events
▶	▶	Exhibits few interactions with other drugs and with food

Conclusions (I)

- **New oral anticoagulants**: specific towards Xa or IIa

  Therapeutic index broader and low variability ➔ **No monitoring**

  No risk of induced thrombocytopenia ➔ **No platelet counts**

  Oral (once or twice daily)

  Potential to replace LMWH and VKA

- **In EU: Rivaroxaban and dabigatran marketed for VTE prevention after THR, TKR / MOS**

New compounds: new adverse effects? Liver toxicity killed Ximelagatran

New compounds: dabigatran, rivaroxaban, apixaban, edoxaban in Phase III studies

➔ We have entered a new era

Conclusions (II): New problems ?

- Exhibit interactions with other drugs (and VKA ?)
- Can be associated with hepatotoxicity (ximelagatran)
- May be associated with decreased compliance (?)
- Cannot be monitored (« do not need be monitored »)
- Cannot be antagonized (need ? Ongoing studies)

Thank you for your kind attention