

# Rivaroxaban for Thromboprophylaxis After Total Knee Arthroplasty

## RECORD3

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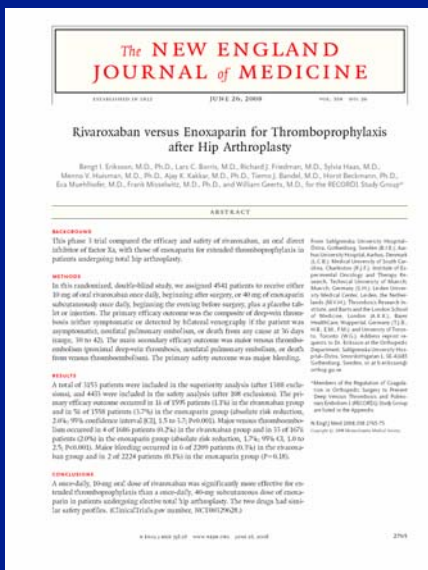
*New England Journal of Medicine* 2008;358:2776–2785

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# Landmark studies RECORD1, 2 and 3 all published in one week in June 2008

## RECORD1



## RECORD2



## RECORD3



Eriksson et al., *N Engl J Med* 2008; 358:2765–2775; Kakkar et al., *Lancet* 2008;372:31–39; Lassen et al., *N Engl J Med* 2008;358:2776–2785

# RECORD3

# New Anticoagulants – The Path From Discovery to Clinical Practice

THE NEW ENGLAND JOURNAL OF MEDICINE

## EDITORIALS



### New Anticoagulants — The Path from Discovery to Clinical Practice

Jens Lohrmann, M.D., and Richard C. Becker, M.D.

For more than half a century, heparin and vitamin K antagonists have defined anticoagulant therapy for the short-term and long-term management, respectively, of thrombotic disorders of the venous system. The history of their development is instructive. In 1922, at the annual meeting of the American Physiological Society, William H. Howell of Johns Hopkins Medical School presented an extraction protocol for isolating heparin preparations. Dicoumarol, a bacterial antagonist of vitamin K in spoiled sweet clover, was recognized as the agent responsible for a fatal hemorrhagic disease in livestock by Karl Link and Wilhelm Schoeffel of the University of Wisconsin. In both cases, decades would pass before heparin and warfarin entered clinical practice, and even today the complex pharmacokinetics, pharmacodynamics, and optimal use of these anticoagulants are causes of uncertainty in the medical community.<sup>1</sup>

Two articles in this issue of the *Journal* describe the results of thromboprophylaxis with an orally active, highly selective, direct inhibitor of factor Xa, rivaroxaban, given at a fixed dose of 10 mg daily, as compared with the results with enoxaparin, a subcutaneously administered, indirect, non-selective factor Xa inhibitor, in patients undergoing major orthopedic surgery. Collectively, more than 7000 patients were included in the Regulation of Coagulation in Orthopedic Surgery to Prevent Deep Venous Thrombosis and Pulmonary Embolism (RECORD1) (ClinicalTrials.gov number, NCT00329626)<sup>2</sup> and RECORD3 (ClinicalTrials.gov number, NCT00561894)<sup>3</sup> studies, with similar results for total hip and total knee arthroplasty, respectively. As compared with enoxaparin, rivaroxaban was associated with significant reductions in

symptomatic and asymptomatic venous thromboembolism and major venous thromboembolism, defined as a composite of proximal deep-vein thrombosis, nonfatal pulmonary embolus, or death related to venous thromboembolism. The frequency of major bleeding and other safety outcomes — including on-treatment bleeding, hemorrhagic wound complications, and hepatic enzyme elevations — was low and did not differ between the study groups.

The favorable observations regarding the use of rivaroxaban raise questions that reach far beyond individual drugs to the overall process of drug development. What are the guiding principles for developing safe, effective, and widely applicable anticoagulants? What properties, characteristics, and outcomes that are discerned through clinical trials will help clinicians to distinguish factor Xa inhibitors from one another should the future offer multiple options?

The environment in which the thrombus occurs is important. Biologic and physiological distinctions among the arterial, venous, and microvascular systems are well known, as are intrinsic patient-specific differences in thromboresistance. Indeed, the regulation of platelet–vessel wall interactions, coagulation proteases, and fibrinolytic systems occurs on the endothelial surface, suggesting that overall hemostatic regulation and the location, extent, and stability of thrombus formation are conditionally based on site-specific differences in endothelial-cell structure, function, and molecular responses to biologic and rheological conditions. The disease state (e.g., cancer) and clinical circumstance (e.g., surgery) exert profound effects on the site of predisposition to thrombo-

N ENGL J MED 358:26 www.n engl j med 358:26, 2008

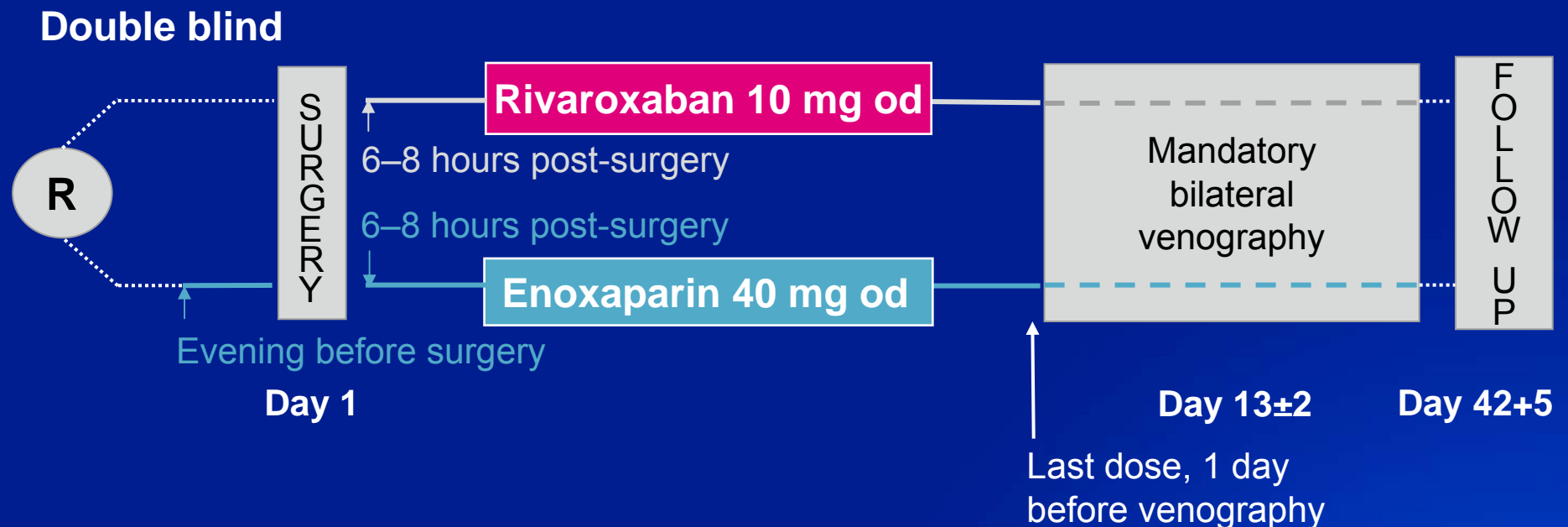
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- ▶ “... rivaroxaban was associated with significant reductions in symptomatic and asymptomatic venous thromboembolism and major venous thromboembolism, ... The frequency of major bleeding and other safety outcomes ... was low and did not differ between the study group”
- ▶ “The path to safer and more effective anticoagulants is paved by scientific knowledge, discovery, due diligence on the part of sponsors working collaboratively with experienced clinicians, and evidence-based translation to patient care and widespread clinical practice”

# Rivaroxaban: the first in a new class of direct Factor Xa inhibitors

- ▶ 10 mg od was selected for investigation in the phase III RECORD programme based on an extensive phase II programme (N=2,857) that evaluated a wide dose range (total daily doses: 5–60 mg)
- ▶ Oral, one tablet, once daily
- ▶ Predictable pharmacokinetics and pharmacodynamics
- ▶ High bioavailability
- ▶ Rapid onset of action
- ▶ Fixed dose
- ▶ No requirement for coagulation monitoring

# RECORD3: study design



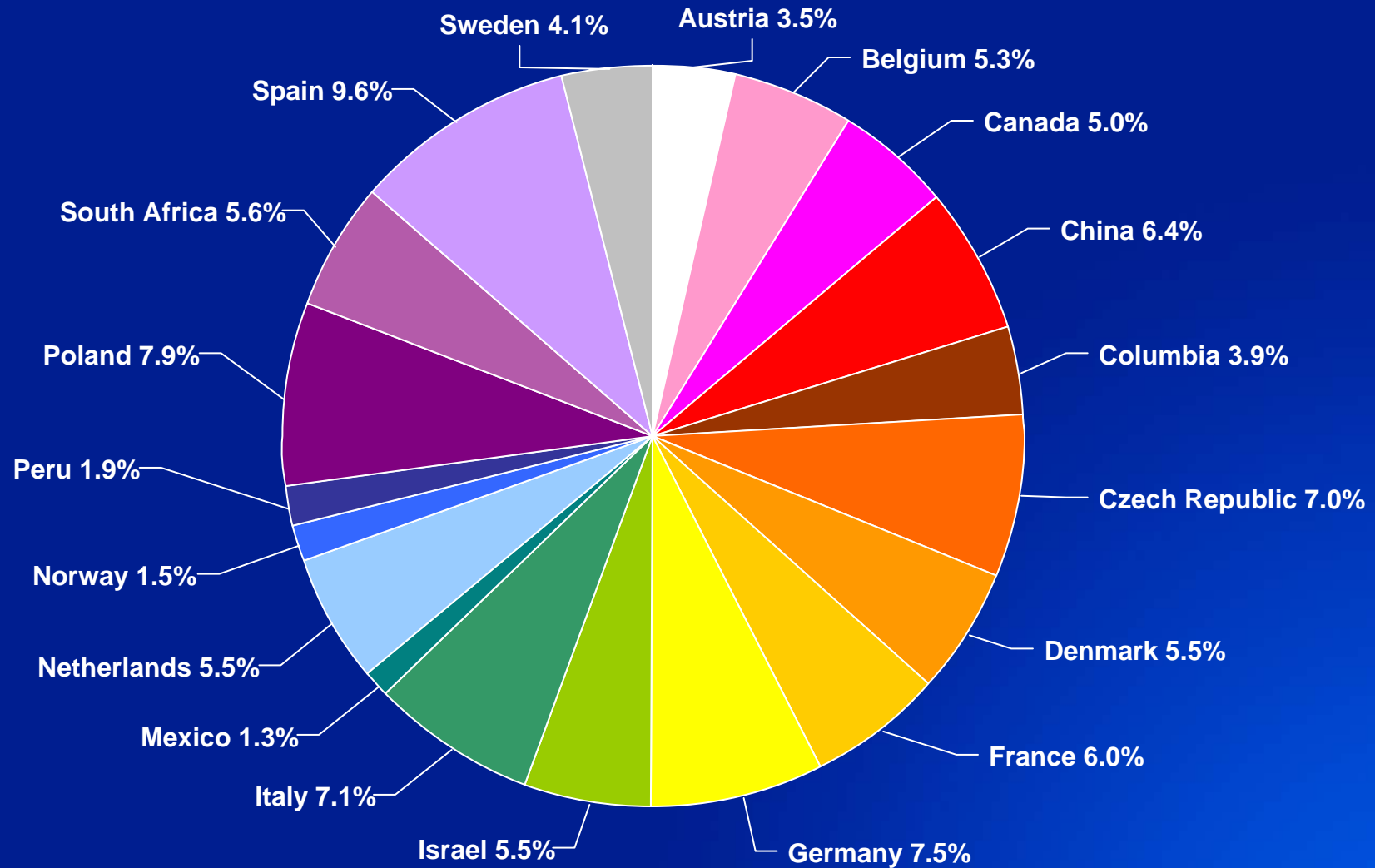
## Inclusion criteria

- ▶ Patients aged  $\geq 18$  years, scheduled to undergo elective, TKR

## 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

# 147 sites worldwide



# Efficacy endpoints

## Primary

- ▶ Total VTE: any DVT, non-fatal PE and all-cause mortality up to day 13+4

## Secondary

- ▶ Major VTE: proximal DVT, non-fatal PE and VTE-related death
- ▶ DVT: any, proximal, distal
- ▶ Symptomatic VTE

All endpoints were adjudicated centrally by independent, blinded committees  
Lassen *et al.*, *N Engl J Med* 2008;358:2776–2785

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# Safety endpoints

## Main

- ▶ Major bleeding starting after the first blinded dose and up to 2 days after last dose ('on-treatment')
  - Bleeding that was fatal, into a critical organ or required re-operation
  - Extra-surgical-site bleeding associated with a drop in hemoglobin  $\geq 2$  g/dL or requiring transfusion of  $\geq 2$  units of blood

## Other

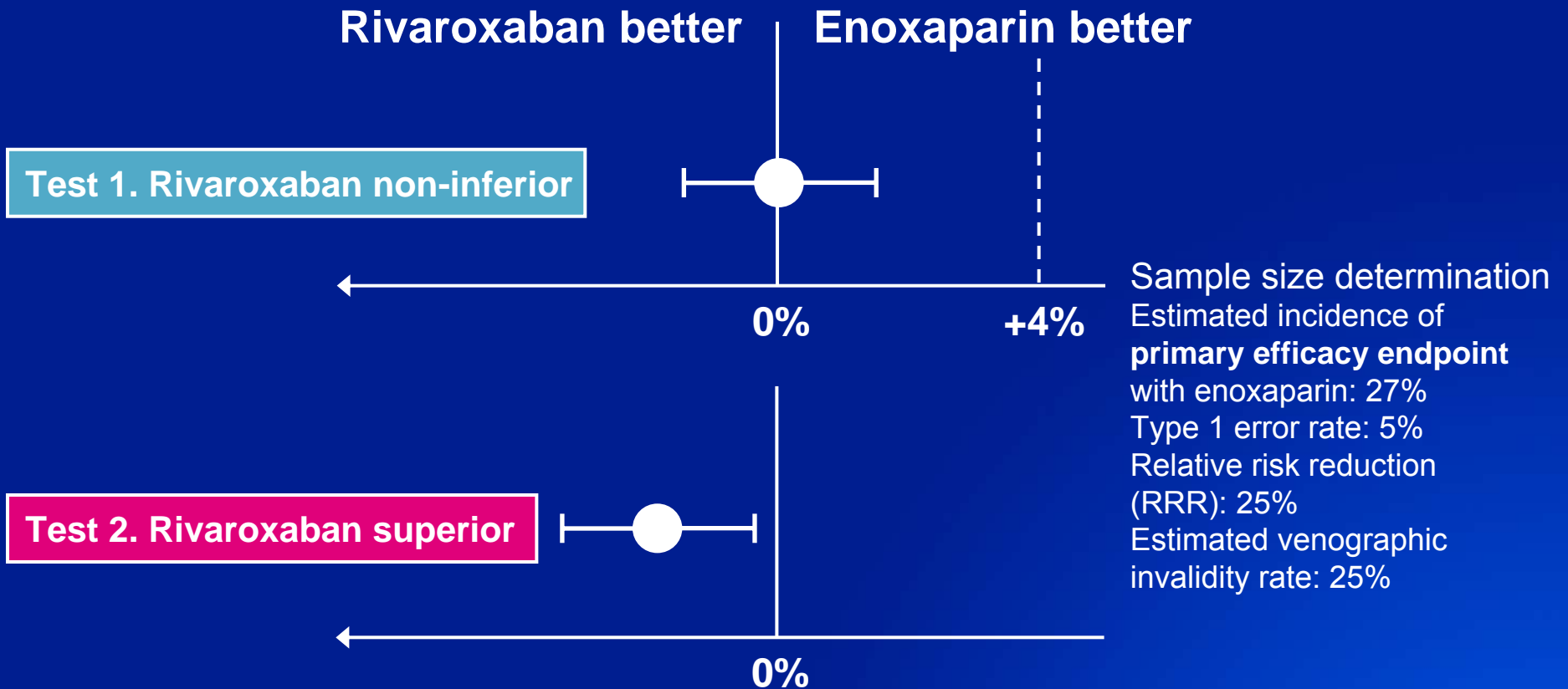
- ▶ Any bleeding on treatment\*
- ▶ Non-major bleeding\*
- ▶ Hemorrhagic wound complications\*#
- ▶ Cardiovascular adverse events
- ▶ Liver enzyme levels

All endpoints were adjudicated centrally by independent, blinded committees; \*Up to 2 days after last dose of study medication; #Composite of excessive wound hematoma and surgical-site bleeding

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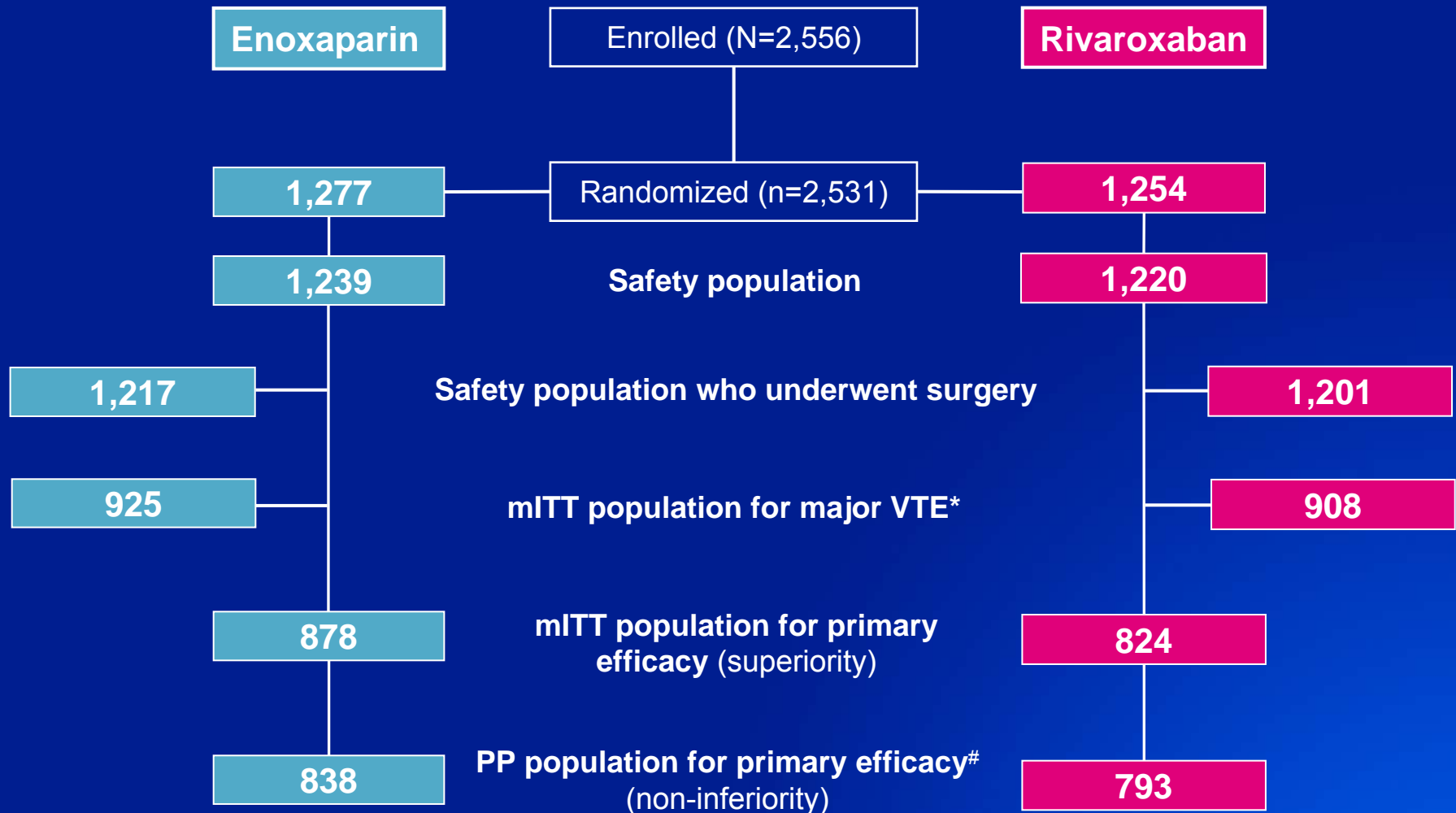
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# Statistical analysis of the primary efficacy endpoint



Absolute risk difference  $\pm$  95% confidence interval  
between rivaroxaban and enoxaparin (delta)

# Study flow



\*Patients may be valid for major VTE analysis if only proximal veins were assessed;  
 #patients could have more than one protocol violation

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# Reasons for exclusion

<b>n %</b>	<b>Enoxaparin 40 mg od</b>	<b>Rivaroxaban 10 mg od</b>
Randomized	1,277	1,254
No intake of study medication	38	34
Valid for safety analysis	1,239 <b>97.0%</b>	1,220 <b>97.3%</b>
Inadequate assessment of thromboembolism	339 <b>26.5%</b>	376 <b>30.0%</b>
– Venography not performed	166	156
– Unilateral venography	69	82
– Indeterminate/non-evaluable venography	96	131
– Not in time window*	8	7
Planned surgery not performed	22	19
Valid for mITT population	878 <b>68.8%</b>	824 <b>65.7%</b>

\*The time window for a valid venography was day 13±4, unless a positive finding was detected earlier

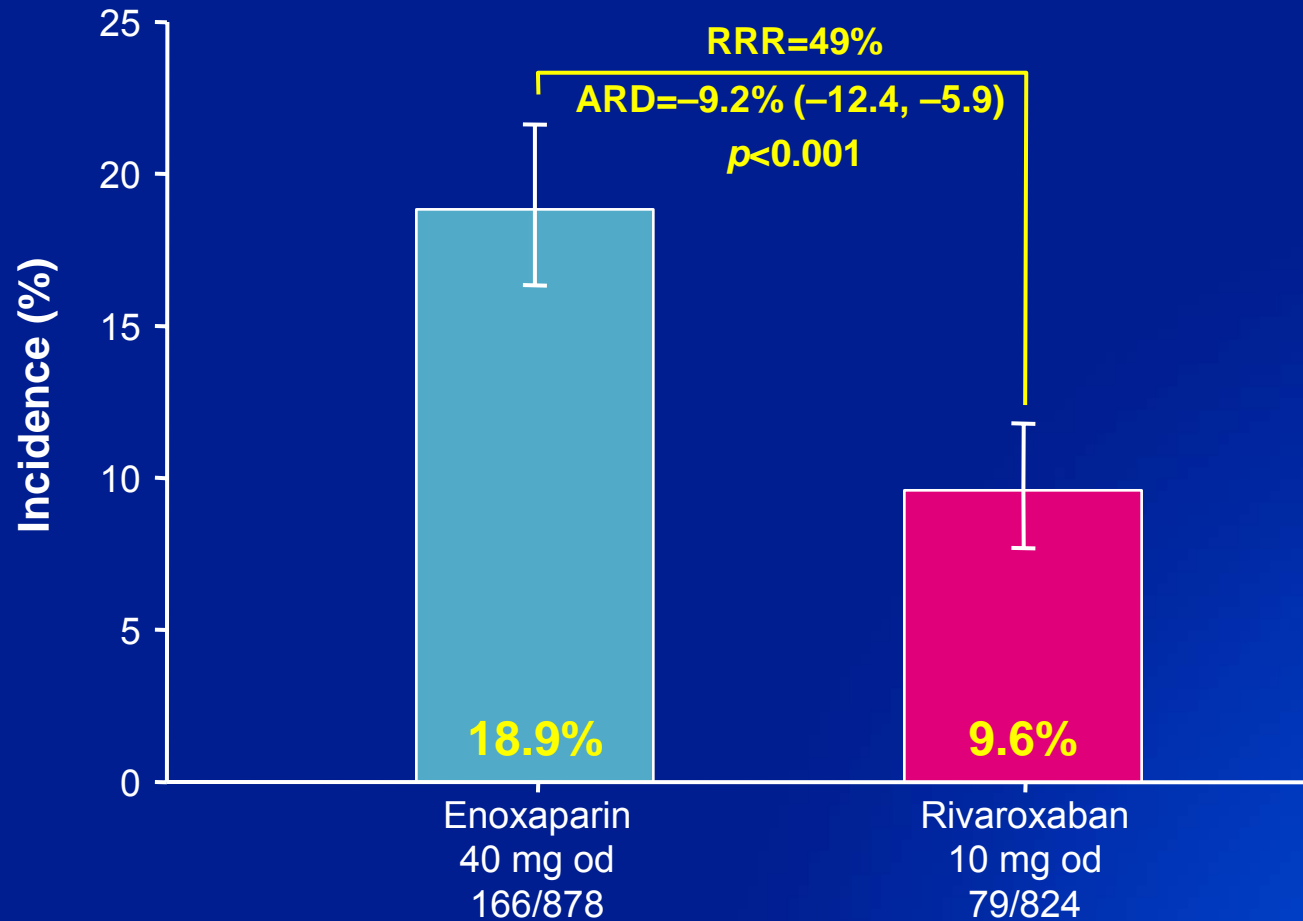
# Patient demographics

	Enoxaparin 40 mg od (n=1,239)		Rivaroxaban 10 mg od (n=1,220)	
Female, n %	821	<b>66.3%</b>	857	<b>70.2%*</b>
Age#, years (range)	67.6	(30–90)	67.6	(28–91)
Weight#, kg (range)	81.2	(41–157)	80.1	(45–150)
Body mass index#, kg/m <sup>2</sup> (range)	29.8	(16.0–54.3)	29.5	(16.3–51.1)
Race, n %				
– Caucasian	997	<b>80.5%</b>	1,000	<b>82.0%</b>
– Asian	82		76	
– Hispanic	54		46	
– Black	13		15	
– Other/data missing	93		83	
History of VTE, n %	42	<b>3.4%</b>	48	<b>3.9%</b>

\*Significantly different between rivaroxaban and enoxaparin groups ( $p=0.033$ ); #mean values

# Primary efficacy endpoint

## Total VTE



ARD (with 95% CI); mITT population, n=1,702

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# Primary efficacy endpoint: individual components

n % (95% CI)	Enoxaparin 40 mg od (n=878)		Rivaroxaban 10 mg od (n=824)		p- value
Primary efficacy endpoint	166	<b>18.9%</b> (16.4, 21.7)	79	<b>9.6%</b> (7.7, 11.8)	<0.001
All-cause mortality	2	<b>0.2%</b> (0.0, 0.8)	0	<b>0</b> (0.0, 0.5)	
Non-fatal PE	4	<b>0.5%</b> (0.1, 1.2)	0	<b>0</b> (0.0, 0.3)	
DVT	160	<b>18.2%</b> (15.7, 20.9)	79	<b>9.6%</b> (7.7, 11.8)	
– Proximal only	20	<b>2.3%</b> (1.4, 3.5)	9	<b>1.1%</b> (0.5, 2.1)	
– Distal only	140	<b>15.9%</b> (13.6, 18.5)	70	<b>8.5%</b> (6.7, 10.6)	

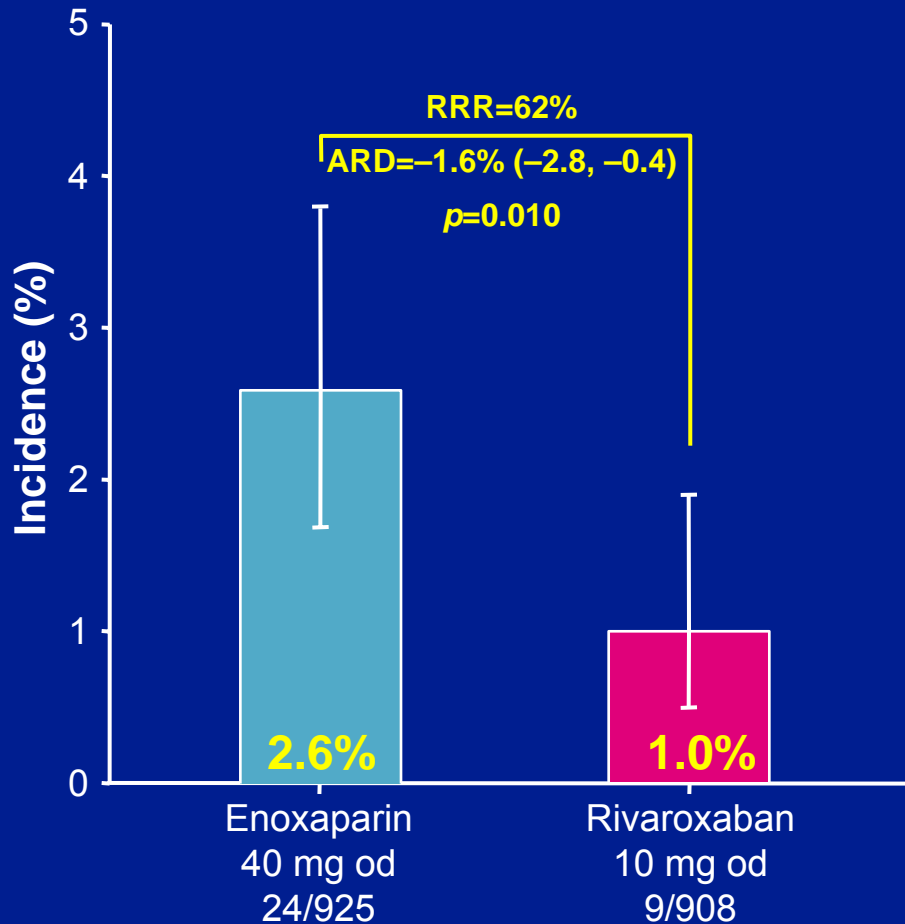
mITT population, n=1,702

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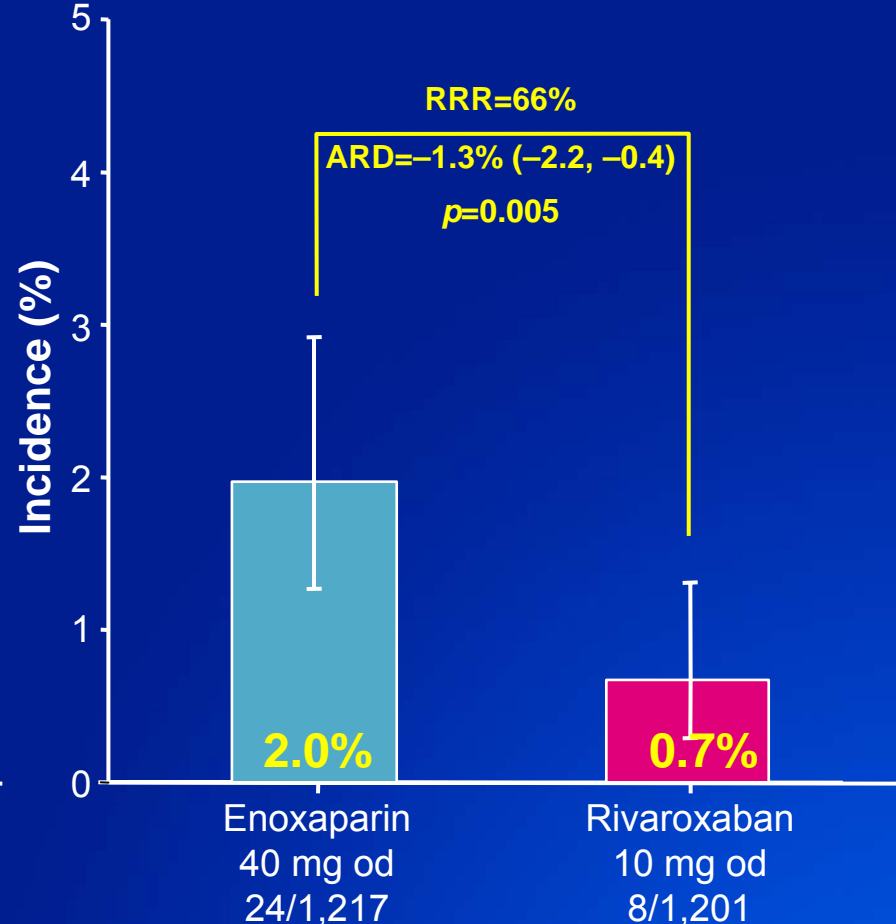
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# Secondary efficacy endpoints

## Major VTE



## Symptomatic VTE

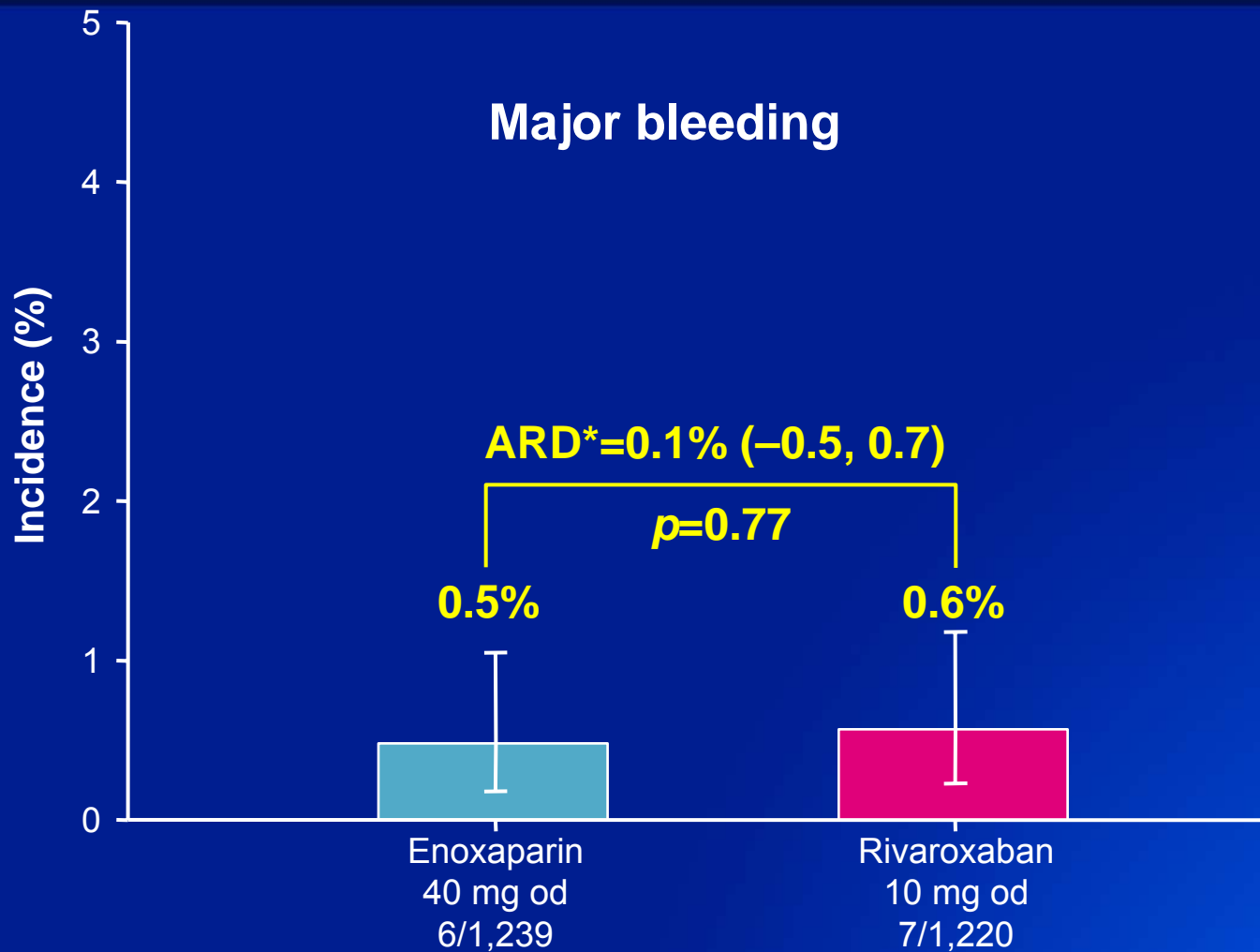


MITT population valid for major VTE, n=1,833 and symptomatic VTE in safety population who underwent surgery, n=2,418

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# Main safety endpoint



On-treatment major bleeding; \*unweighted ARD (with 95% CI); safety population, n=2,459

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# Safety: components of bleeding

n %	Enoxaparin 40 mg od (n=1,239)	Rivaroxaban 10 mg od (n=1,220)
Any bleeding	60 4.8%	60 4.9%
Major bleeding*	6 0.5%	7 0.6%
Fatal	0	0
Into a critical organ	1	0
Leading to re-operation	4	5
Leading to fall in hemoglobin <sup>‡</sup>	0	1
Leading to transfusion of ≥2 units of blood <sup>‡</sup>	0	1
Hemorrhagic spinal puncture	1	1 <sup>#</sup>
Non-major bleeding	54 4.4%	53 4.3%
Clinically relevant non-major bleeding	28 2.3%	33 2.7%
– Hemorrhagic wound complications <sup>§</sup>	24 1.9%	25 2.0%
Other non-major bleeding	31 2.5%	22 1.8%

On-treatment bleeding; \*major bleeding events could qualify for more than one subcategory;  
<sup>#</sup>event occurred before intake of first rivaroxaban dose; <sup>‡</sup>extra-surgical-site bleeding;  
<sup>§</sup>composite of excessive wound hematoma and surgical-site bleeding; safety population, n=2,459

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# Adverse events

<b>n %</b>	<b>Enoxaparin 40 mg od (n=1,239)</b>		<b>Rivaroxaban 10 mg od (n=1,220)</b>	
<b>Any adverse event</b>	882	<b>71.2%</b>	803	<b>65.8%</b>
On treatment	844	<b>68.1%</b>	776	<b>63.6%</b>
During follow-up	148	<b>11.9%</b>	129	<b>10.6%</b>
<b>Cardiovascular adverse events</b>	9	<b>0.7%</b>	4	<b>0.3%</b>
On treatment	3	<b>0.2%</b>	4	<b>0.3%</b>
During follow-up*	6 <sup>#</sup>	<b>0.5%</b>	0	<b>0</b>
<b>Wound-related infections</b>	11	<b>0.9%</b>	7	<b>0.6%</b>
On treatment	11	<b>0.9%</b>	7	<b>0.6%</b>
During follow-up	1	<b>0.1%</b>	0	<b>0</b>
<b>Death</b>	6	<b>0.5%</b>	0	<b>0</b>

\*Events occurring more than 1 day after the last intake of study drug; safety population, n=2,459

<sup>#</sup>One patient had two events

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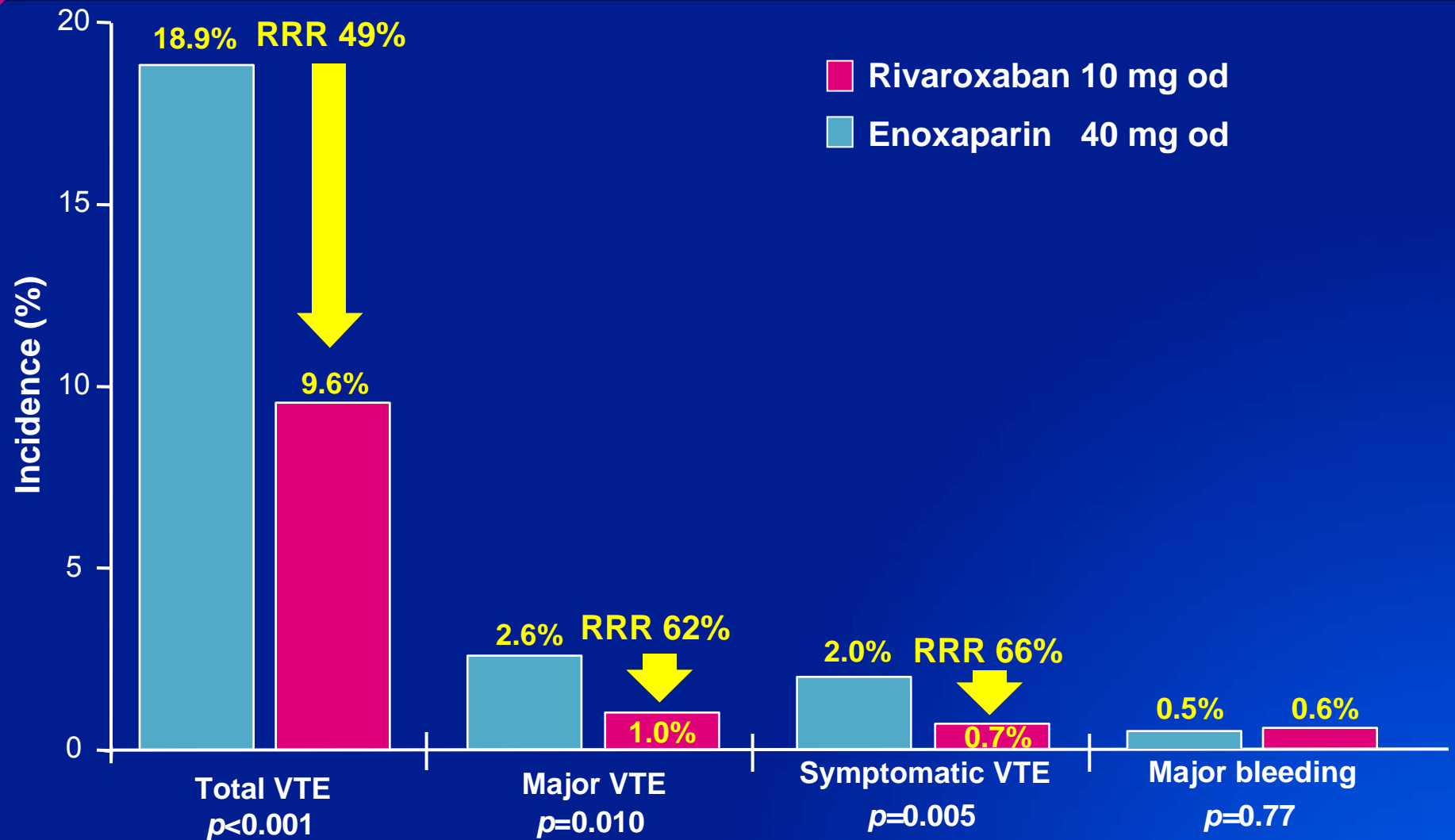
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# Liver function tests

n/N %	Enoxaparin 40 mg od	Rivaroxaban 10 mg od
ALT >3×ULN		
On treatment*	20/1,156 <b>1.7%</b>	20/1,150 <b>1.7%</b>
During follow-up	2/1,054 <b>0.2%</b>	5/1,052 <b>0.5%</b>
ALT >3×ULN + bilirubin >2×ULN		
On treatment*	0/1,174 <b>0.0%</b>	2 <sup>#</sup> /1,159 <b>0.2%</b>
During follow-up	0/1,051 <b>0.0%</b>	0/1,053 <b>0.0%</b>

\*From first intake of study drug up to 2 days after the last intake of study drug; <sup>#</sup>Normalized with continued treatment

# RECORD3: summary



## RECORD3: conclusions

- ▶ RECORD3 found that in patients undergoing TKR rivaroxaban (10 mg od for 10–14 days), an orally effective direct factor Xa inhibitor, given in a fixed, once-daily dose regimen without coagulation monitoring, was superior to enoxaparin (40 mg od for 10–14 days) in preventing venous thrombosis, with similar rates of bleeding

# Thank you to the patients, their relatives, the study nurses, and...

**Independent Central Adjudication Committee:** M Levine; **Venous Thromboembolic Event Adjudication Committee:** H Eriksson, G Sandgren, J Wallin; **Cardiovascular Adverse Event Adjudication Committee:** JP Bassand, C Bode, T Lüscher; **Bleeding Event Adjudication Committee:** U Angeras, A Falk, M Prins; **Data Safety and Monitoring Board:** H Bounameaux, S Dittmar (sponsor contact), D Larray, W Lehmacher (independent statistician), A Leizorovicz; **Study sponsor Statistical Analysis:** A Benson; **Study Management:** A Duszczyszyn; **Medical Expert:** M Lederman; **Investigators, Austria:** J Hochreiter, G Labek, R Windhager, P Zenz; **Belgium:** T Borms, C Brabants, P Gunst, W Henkes, H Mortelet, E Vandermeersch, D Vanlommel, B Willems; **Canada:** F Abuzgaya, D Armstrong, E Dessouki, C Dobson, S Dolan, P Grosso, G Jasey, J Naude, E Wai, P Zalzal; **China:** T Chen, H Lv, Y Wang, Q Yang, B Zeng, H Zhang; **Colombia:** B Aguilera, R Botero, A Reyes; **Czech Republic:** I Kofranek, K Koudela, M Krbec, P Kubat, J Kubes, J Sedivy, O Stano, O Vins; **Denmark:** OA Borgwardt, P Joergensen, MR Lassen, G Lausten, S Mikkelsen; **France:** M Carles, P Chaussis, JM Debue, E Eisenberg, C Forestier, JP Franceschi, G Hennion, T Lazard, D Lugrin, P Macaire, X Maschino, Y Matuszczak, JP Moulinie, A Peron; **Germany:** W Birkner, J Eulert, HM Fritsche, A Halder, T Horacek, F Kleinfeld, R Krauspe, A Kurth, P Mouret, B Muehlbauer, H Schmelz; **Israel:** V Benkovich, B Brenner, S Dekel, M Elias, N Halperin, D Hendel, U Martinowitz, M Nyska, I Otremski; **Italy:** B Borghi, P Cherubino, G Davi, G Della Rocca, G Fanelli, P Grossi, M Gusso, R Landolfi, R Masei, G Melis, R Nardacchione, P Parise; **Mexico:** E Berumen Nafarr, E Gomez Sanchez, R Inigo Pavlovich; **The Netherlands:** CN Dijk, PA Nolte, HM Schuller, R Slappendel, JJJ Van der List, CCPM Verheyen, HM Vis; **Norway :** K Al-Dekany, K Griegel, RE Roenning, P Stahl, O Talsnes; **Peru:** F Arrieta, R Cotrina, L Merzthal, E Pastor; **Poland:** A Bednarek, J Blacha, A Gusta, J Kruczyski, K Kwiatkowsk, P Madyk, S Mazurkiewi, T Niedwiedzki, J Skowronski, M Synder; **South Africa:** U Dhanjee, J Diedericks, J Engelbrecht, F Greeff, B Jacobson, S Moodley, H Myburgh, R Routier, O Van der Spuy, L Van Zyl; **Spain:** R Canosa Sevillano, A Delgado, JL Diaz Almodovar, F Gomar, X Granero, R Lecumberri Villamedi, A Navarro Quiles, R Otero Fernandez, L Peidro Garces, Á Salvador; **Sweden:** L Ahnfelt, B Edshage, BI Eriksson, M Flondell, H Laestander, S Lind, B Paulsson, A Wykman