Rivaroxaban *versus* Enoxaparin in Non-Major Orthopedic Surgery

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for the **PRO**phylaxis in **NON-M**ajor **O**rthopedic **S**urgery (**PRONOMOS**) investigators

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Background (I)

International Recommendations for trauma and Non-Major Orthopedic Surgery (i.e. excluding hip fracture, total hip or knee replacement)

- **ACCP 2012[1]: "*We suggest no prophylaxis* rather than pharmacologic prophylaxis in patients with isolated lower leg injuries requiring leg immobilization" *(Grade 2B)***

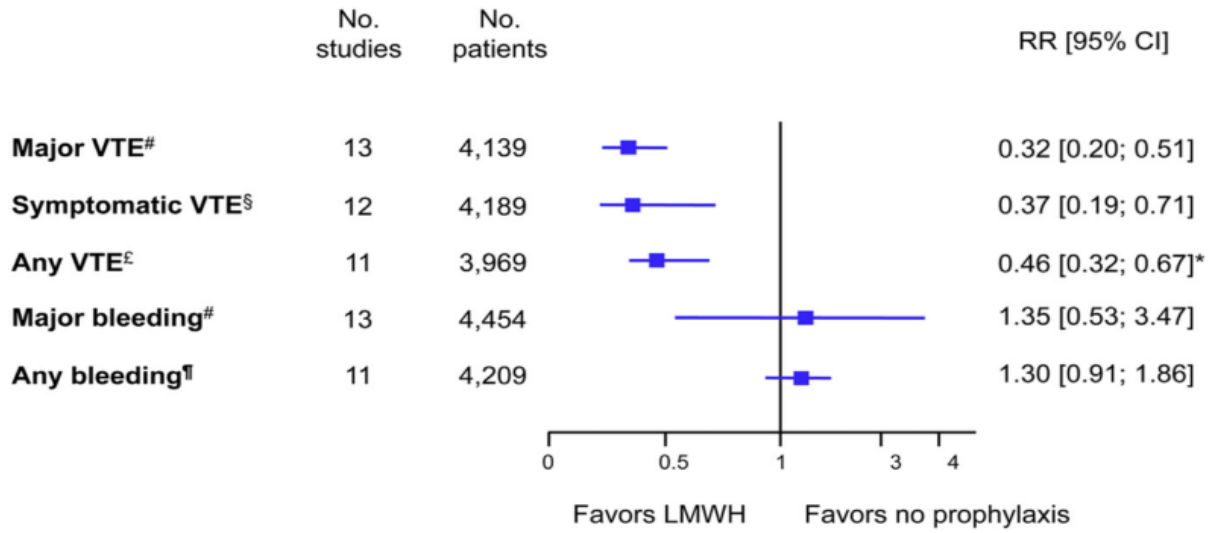
- **Most European guidelines (UK, France, Spain, Austria, Germany…)** suggest **prophylaxis with LMWH** during the period of immobilization in patients with additional risk factors for VTE, after a discussion between the treating physician and the patient on the potential benefits and harms

- **NICE 2018[2]: "*Consider pharmacological* VTE prophylaxis with LMWH or fondaparinux sodium for people with *lower limb immobilization* whose risk of VTE outweighs their risk of bleeding".**

1. Falck-Ytter et al. *Chest.* 2012;141(Suppl 2):278S–325S
2. https://www.nice.org.uk (accessed February 24, 2020)

Background (II)

- **Prophylaxis is supported by a meta-analysis of LMWH *vs* placebo or no treatment in non-major orthopedic surgery with transient reduced mobility**



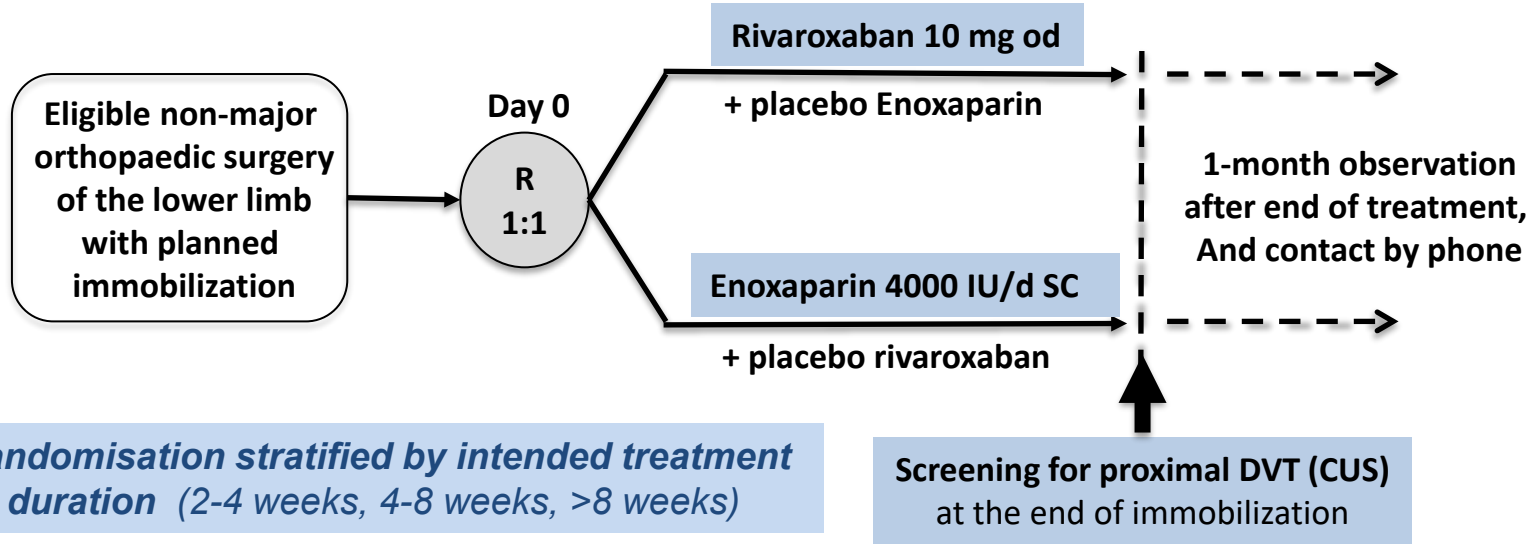
C. Chapelle, N. Rosencher, P. Zufferey, P. Mismetti, M. Cucherat. And S.Laporte, Arthroscopy May Arthroscopy. 2014;30:987–96

Aim of Study

- **Aim**: To compare the effect of rivaroxaban with that of enoxaparin in preventing major venous thromboembolism during immobilization after lower-limb non-major orthopedic surgery
- **Main Inclusion criteria:** Adults undergoing nonmajor orthopedic surgery of the lower limbs and requiring thromboprophylaxis for >2 weeks (investigator's assessment).
- **Primary efficacy endpoint:** **major VTE**, composite of symptomatic distal or proximal DVT, PE or VTE-related death during the treatment period, or asymptomatic **proximal** DVT at the end of treatment (CUS screening)
- **Safety outcomes:** major and clinically relevant non-major bleeding

Study design

International multicentre, interventional, parallel, **randomised, double-blind,** non-inferiority trial



Randomisation stratified by intended treatment duration *(2-4 weeks, 4-8 weeks, >8 weeks)*

Statistics

- It was estimated that a **sample of 4400 patients** would provide 90% power to show noninferiority (two-sided level 5%)
- Noninferiority margin for the upper limit of the 95% CI of the risk ratio was set at 1.30
- A **test for superiority** was planned if rivaroxaban proved noninferior to enoxaparin
- Primary analysis was performed in the intention-to-treat population and in the per-protocol population
- Multiple imputation was used to account for missing data (completed datasets)

Results: Inclusion Period

- Between December 2015 and April 2018, **3604 patients** underwent randomization at 200 sites in 10 countries.

- Slower than expected recruitment led to reaching expiration dates of the study drugs, with prohibitively high replacement costs. The steering committee and sponsor, **unaware of any study results**, decided to **stop enrollment** in April 2018.

Results: Main Baseline Characteristics and Treatment Duration

Characteristic	Rivaroxaban (N=1809)	Enoxaparin (N=1795)
Age — median (IQR)	41 years (29–54)	41 years (29–54)
Male sex	66.0%	64.0%
Body mass index - median (IQR)	26.3 (23.7–29.4)	26.3 (23.6–29.3)
Intended treatment duration		
• From 2 weeks to 1 month	1082 (59.8%)	1070 (59.6%)
• More than 1 month to 2 months	677 (37.4%)	674 (37.5%)
• More than 2 months — no. (%)	50 (2.8%)	51 (2.8%)

Results: Main Types of Surgery

	Rivaroxaban (N=1809)	Enoxaparin (N=1795)
Duration of surgery — median (IQR)	60 min (40–85)	60 min (40–88)
• Ligament repair of the knee	673 (37.2%)	660 (36.8%)
• Ankle fracture	286 (15.8%)	257 (14.3%)
• Knee arthroscopy	156 (8.6%)	167 (9.3%)
• Tibial osteotomy	113 (6.2%)	119 (6.6%)
• Tibial fracture	99 (5.5%)	93 (5.2%)
• Achilles' tendon repair	85 (4.7%)	100 (5.6%)

In fact, more than 20 types of surgery (arthrodesis, femur and tibial plateau fracture…….)

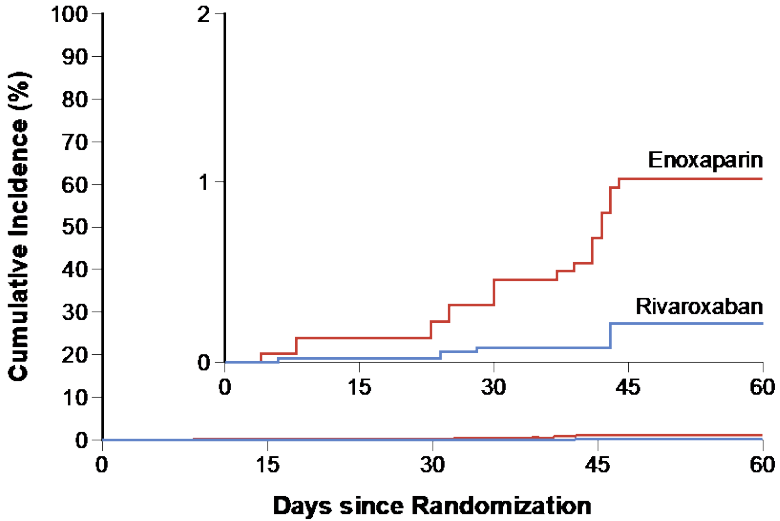
Results: Primary Efficacy Outcome

	Rivaroxaban (N=1809)	Enoxaparin (N=1795)	Risk Ratio (95% CI)
Venous thromboembolism	**4/1661 (0.2%)**	**18/1640 (1.1%)**	**0.25 (0.09 to 0.75)**
• **Symptomatic VTE**	**3/1756 (0.2%)**	**11/1737 (0.6%)**	**0.28 (0.08 to 1.00)**
Distal DVT	3	5	–
Proximal DVT	0	5	–
PE	0	1	–
VTE-related deaths	0	0	–
• **Asymptomatic proximal DVT**	**1/1661 (0.1%)**	**7/1637 (0.4%)**	**–**

Multiple imputation, $P_{non\text{-}inferiory}<0.001$ $P_{superiority}=0.01$

Results: Primary Efficacy Outcome

Kaplan Meier analysis



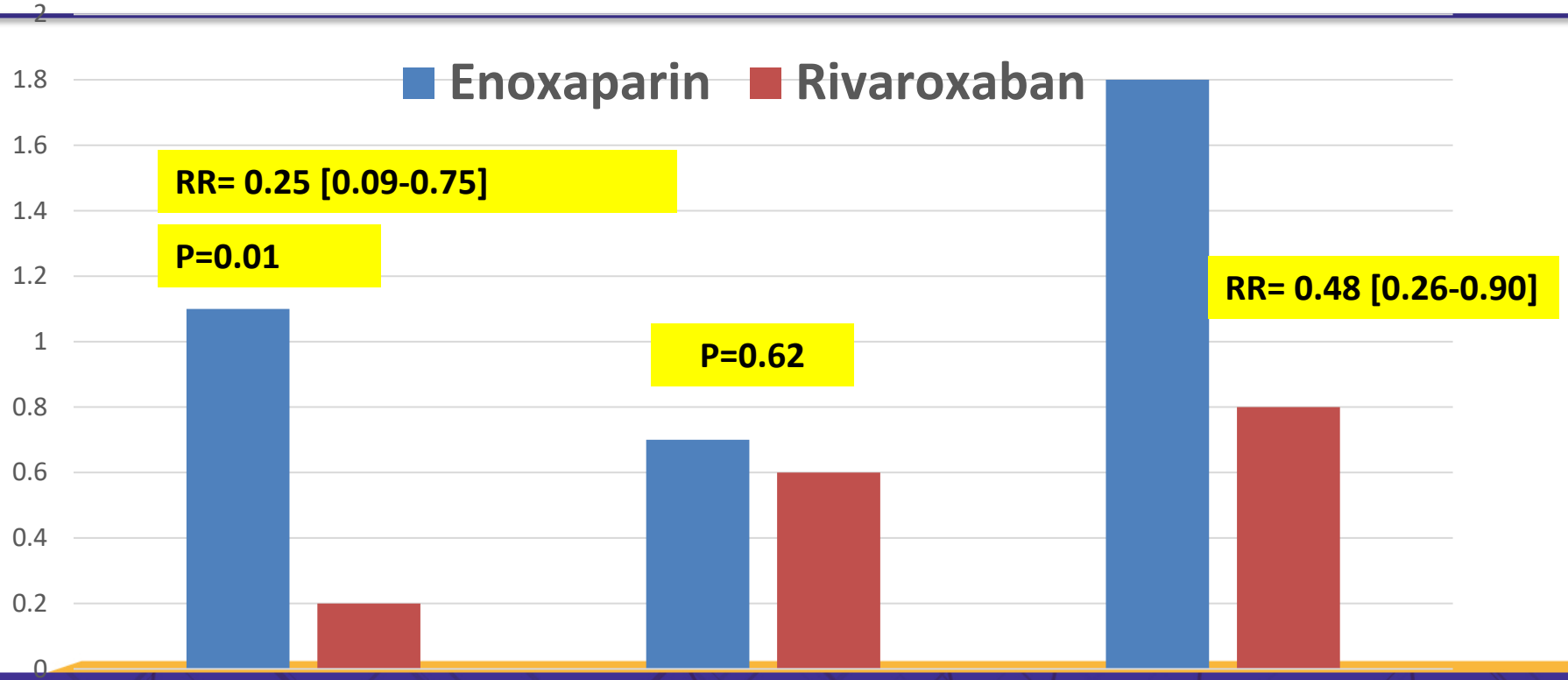
2 weeks to 1 month					
Rivaroxaban	1082	679	16	5	
Enoxaparin	1070	636	15	5	
More than 1 month to 2 months					
Rivaroxaban	677	644	617	78	7
Enoxaparin	674	639	604	79	4
More than 2 months					
Rivaroxaban	50	48	47	47	41
Enoxaparin	51	45	44	42	34

Results: Secondary Outcomes

Outcome (ISTH definition)	Rivaroxaban (N=1809)	Enoxaparin (N=1795)	Risk Ratio (95% CI)*
Safety population - N	1757	1739	
Major plus nonmajor clinically relevant bleeding	19 (**1.1**%)	18 (**1.0**%)	**1.04** (0.55 to 2.00)
Major bleeding	10 (**0.6**%)	12 (**0.7**%)	**0.81** (0.35 to 1.88)
Nonmajor clinically relevant bleeding	9 (**0.5**%)	6 (**0.3**%)	**1.48** (0.52 to 4.17)
All-cause death	0	1 (**0.1**%)	**0.63** (0.17 to 2.36)
Net clinical benefit VTE + Major Bleeding	14/1668 (**0.8**%)	30/1643 (**1.8**%)	**0.48** (0.26 to 0.90)

*No significant difference

Conclusions: Main Results (%)



Conclusions

- Oral rivaroxaban was superior to subcutaneous enoxaparin in preventing venous thromboembolism in patients undergoing non-major orthopedic surgery with a period of immobilization.
- There was no significant difference with rivaroxaban versus enoxaparin in the rate of major bleeding.
- In patients deemed at risk, rivaroxaban could replace LMWH to prevent VTE during postoperative reduced mobility after non-major orthopedic surgery

Full article available online at nejm.org

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Patients	
Investigators	200 centers and 10 countries
Steering Committee	Charles Marc Samama (chair), Nadia Rosencher (co-chair), Patrick Mismetti, Silvy Laporte, Juan Llau, Patrick Mouret, William Fisher
Data Monitoring Committee	Michel Cucherat (Chair), Alain Sautet, Annick Steib
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