The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Rivaroxaban or Enoxaparin in Nonmajor Orthopedic Surgery

C. Marc Samama, M.D., Silvy Laporte, Ph.D., Nadia Rosencher, M.D., Philippe Girard, M.D., Juan Llau, M.D., Patrick Mouret, M.D., William Fisher, M.D., Javier Martínez-Martín, M.D, Daniel Duverger, M.D., Béatrice Deygas, M.Sc., Emilie Presles, M.Sc., Michel Cucherat, M.D., and Patrick Mismetti, M.D., for the PRONOMOS Investigators*

Background

- Nonmajor orthopedic surgery of the lower limbs, that results in transient reduced mobility, places patients at risk for venous thromboembolism.
- There is a lack of consensus on the use of thromboprophylaxis in patients undergoing nonmajor orthopedic surgery.
- European guidelines recommend a personalized strategy of prophylaxis with low-molecular weight heparin.
- There are no evidence on the efficacy and safety of direct oral anticoagulants for the thromboprophylaxis in patients undergoing nonmajor orthopedic surgery.

AIM of the study

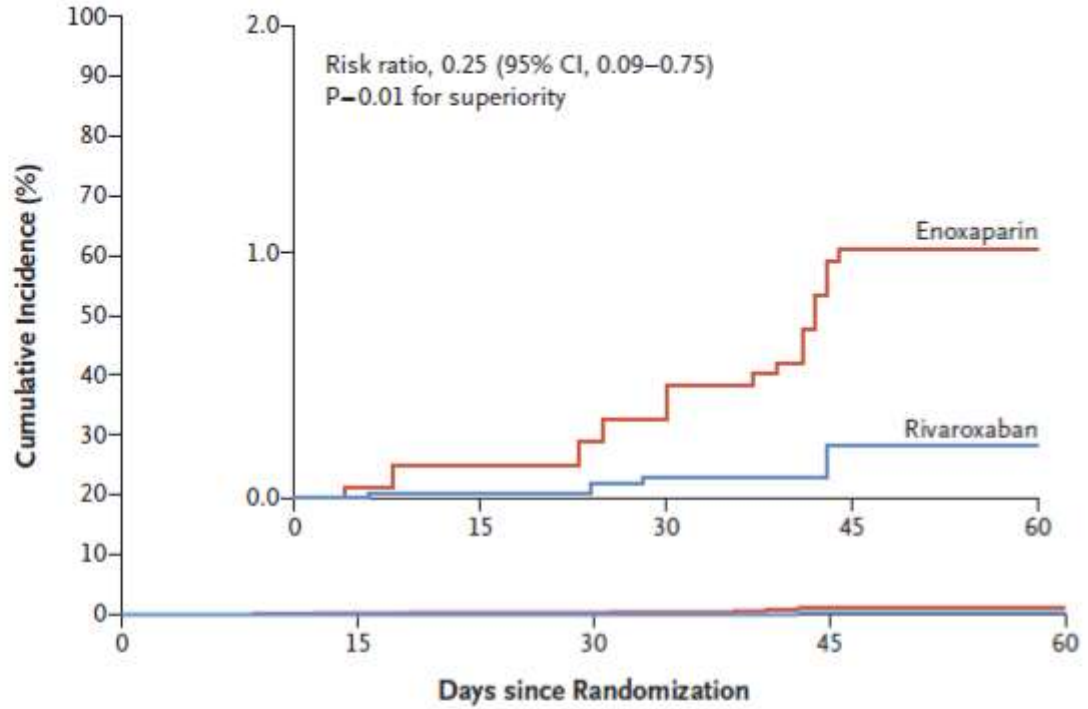
Aim of the Prophylaxis in Nonmajor Orthopaedic Surgery (PRONOMOS) trial is to compare the effect of rivaroxaban with that of enoxaparin in the prevention of major venous thromboembolism after lower-limb nonmajor orthopedic surgery.

Methods

- International, parallel-group, randomized, double-blind, noninferiority trial.
- Adults who had been admitted to the hospital to undergo nonmajor orthopedic surgery in the lower limbs and who received thromboprophylaxis for at least 2 weeks (according to the investigator's assessment of the patient's venous thromboembolic risk) were included.
- Two arms of treatment:
- rivaroxaban 10 mg/ daily
- Enoxaparin 4000 IU /daily
- Primary efficacy outcome: a composite of symptomatic distal or proximal deep-vein thrombosis, pulmonary embolism, or venous thromboembolism–related death during the treatment period or asymptomatic proximal deep-vein thrombosis at the end of treatment.
- Safety outcome: major bleeding and nonmajor clinically relevant bleeding.

Results

- 3604 patients randomized: 1809 patients were assigned to receive rivaroxaban, and 1795 to receive enoxaparin.
- Major venous thromboembolism occurred in 4 of 1661 patients (0.2%) in the rivaroxaban group and in 18 of 1640 patients (1.1%) in the enoxaparin group ($P<0.001$ for noninferiority; $P = 0.01$ for superiority).
- The incidence of bleeding did not differ significantly between the rivaroxaban group and the enoxaparin group (1.1% and 1.0%, respectively, for major bleeding or nonmajor clinically relevant bleeding; 0.6% and 0.7%, respectively, for major bleeding).



No. at Risk, According to Intended Treatment Period

2 Wk to 1 mo					
Enoxaparin	1070	636	15	5	—
Rivaroxaban	1082	679	16	5	—
>1 Mo to 2 mo					
Enoxaparin	674	639	604	79	4
Rivaroxaban	677	644	617	78	7
>2 Mo					
Enoxaparin	51	45	44	42	34
Rivaroxaban	50	48	47	47	41

Figure 1. Kaplan–Meier Analysis of the Primary Composite Efficacy Outcome.

Table 2. Primary Outcome of Venous Thromboembolism (Fatal or Nonfatal).

Outcome	Rivaroxaban (N=1809)	Enoxaparin (N=1795)	Risk Ratio (95% CI)*
	no. of patients with event/total no. of patients (%)		
Venous thromboembolism	4/1661 (0.2)	18/1640 (1.1)	0.25 (0.09–0.75)
Primary outcome, stratified according to intended duration of thromboprophylaxis			
2 Wk to 1 mo	2/1016 (0.2)	3/993 (0.3)	—
>1 Mo to 2 mo	2/599 (0.3)	15/605 (2.5)	—
>2 Mo	0/46	0/42	—
Components of the primary outcome			
Symptomatic venous thromboembolism	3/1756 (0.2)	11/1737 (0.6)	0.28 (0.08–1.00)
Distal deep-vein thrombosis†	3/1756 (0.2)	5/1737 (0.3)	—
Proximal deep-vein thrombosis†	0/1756	5/1737 (0.3)	—
Pulmonary embolism	0/1756	1/1737 (0.1)	—
Venous thromboembolism–related death	0/1756	0/1737	—
Asymptomatic proximal deep-vein thrombosis	1/1661 (0.1)	7/1637 (0.4)	—
Major venous thromboembolism‡	1/1661 (0.1)	13/1640 (0.8)	0.12 (0.02–0.84)

* The primary efficacy outcome of venous thromboembolism was a composite of symptomatic distal or proximal deep-vein thrombosis, pulmonary embolism, or venous thromboembolism–related death throughout the treatment period or asymptomatic proximal deep-vein thrombosis at the end of treatment. The risk ratios were estimated by multiple imputation, and marginal estimates are reported.

† Among the 13 patients with symptomatic deep-vein thromboses, 9 patients had an event on the day of compression ultrasonography at the end of immobilization (Table S5).

‡ Major venous thromboembolism was defined as pulmonary embolism or proximal deep-vein thrombosis.

Table 3. Secondary Outcomes.*

Outcome	Rivaroxaban (N = 1809)	Enoxaparin (N = 1795)	Risk Ratio (95% CI)	P Value
	no. of patients with event/total no. of patients (%)			
Major bleeding or nonmajor clinically relevant bleeding	19/1757 (1.1)	18/1739 (1.0)	1.04 (0.55–2.00)	0.89
Major bleeding	10/1757 (0.6)	12/1739 (0.7)	0.81 (0.35–1.88)	0.62
Nonmajor clinically relevant bleeding	9/1757 (0.5)	6/1739 (0.3)	1.48 (0.52–4.17)	0.46
Overt thrombocytopenia	1/1756 (0.1)	0/1737	3.06 (0.13–70.85)	0.48
Death from any cause	0/1756	1/1737 (0.1)	0.63 (0.17–2.36)	0.49
Net clinical benefit†	14/1668 (0.8)	30/1643 (1.8)	0.48 (0.26–0.90)	—

* The analyses of secondary outcomes were for adjudicated events. Major bleeding was defined as fatal, critical, or clinically overt bleeding or bleeding at the surgical site leading to intervention.[11] Risk ratios were estimated with the use of multiple imputation, and marginal estimates are reported.

† Net clinical benefit was assessed in a post hoc analysis that compared the composite of venous thromboembolism or major bleeding between groups. Because this was a post hoc analysis, no statistical test was performed.

Conclusions

- Treatment with rivaroxaban was associated with a 75% lower risk of major venous thromboembolism through the end of treatment than enoxaparin (0.2% vs. 1.1%).
- The use of rivaroxaban was not associated with a higher incidence of major bleeding or other bleeding events.
- These results, if confirmed in larger studies, could modify the current recommendation of the international guidelines by extending the use of thromboprophylaxis also in patients undergoing nonmajor orthopedic surgery.