

## Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Lassen MR, Ageno W, Borris LC, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. *N Engl J Med* 2008;358:2776-86.

Online supplement

**Table I.** Adverse events (safety population; n=2459)

	<b>Rivaroxaban 10 mg once daily (n=1220)</b>	<b>Enoxaparin) 40 mg once daily (n=1239)</b>
<b>Adverse events (including deep vein thrombosis, pulmonary embolism, and bleeding events)</b>		
Total adverse events	803 (65.8)	882 (71.2)
Serious treatment-emergent events	90 (7.4)	110 (8.9)
Serious drug-related treatment-emergent events	26 (2.1)	19 (1.5)
Adverse events leading to medication discontinuation	39 (3.2)	56 (4.5)
Death	0	6 (0.5)
<b>Treatment-emergent adverse events with an incidence of <math>\geq 3\%</math> or difference of 10 or more events*</b>		
Any system organ class	776 (63.6)	844 (68.1)
Blood and lymphatic system disorders	50 (4.1)	60 (4.8)
Anemia	38 (3.1)	48 (3.9)
Cardiac disorders	57 (4.7)	51 (4.1)
Gastrointestinal disorders	301 (24.7)	334 (27.0)
Constipation	79 (6.5)	67 (5.4)
Diarrhea	18 (1.5)	34 (2.7)
Nausea	124 (10.2)	127 (10.3)
Vomiting	129 (10.6)	161 (13.0)
General disorders and administration-site conditions	161 (13.2)	197 (15.9)
Edema peripheral	48 (3.9)	37 (3.0)
Pyrexia	83 (6.8)	115 (9.3)
Infections and infestations	67 (5.5)	74 (6.0)
Injury, poisoning, and procedural complications	172 (14.1)	166 (13.4)
Procedural pain	44 (3.6)	47 (3.8)
Investigations	124 (10.2)	135 (10.9)
Gamma-glutamyltransferase increased	19 (1.6)	33 (2.7)
Metabolism and nutrition	30 (2.5)	50 (4.0)
Musculoskeletal and connective tissue disorders	71 (5.8)	69 (5.6)
Nervous system disorders	72 (5.9)	93 (7.5)
Headache	16 (1.3)	30 (2.4)
Psychiatric disorders	95 (7.8)	92 (7.4)
Insomnia	49 (4.0)	52 (4.2)
Renal and urinary disorders	45 (3.7)	55 (4.4)
Respiratory, thoracic, and mediastinal disorders	31 (2.5)	38 (3.1)
Skin and subcutaneous tissue disorders	92 (7.5)	100 (8.1)
Vascular disorders	203 (16.6)	290 (23.4)
Deep vein thrombosis	123 (10.1)	196 (15.8)
Hematoma	12 (1.0)	27 (2.2)
<b>Serious treatment-emergent adverse events with an incidence of <math>\geq 0.2\%*</math></b>		
Arthritis infective	3 (0.2)	0
Pneumonia	1 (0.1)	4 (0.3)
Wound infection	3 (0.2)	3 (0.2)
Post-procedural hemorrhage	4 (0.3)	0
Wound secretion	3 (0.2)	1 (0.1)
Alanine aminotransferase increased	7 (0.6)	4 (0.3)
Aspartate aminotransferase increased	4 (0.3)	3 (0.2)

Blood bilirubin increased	3 (0.2)	0
Hemarthrosis	1 (0.1)	3 (0.2)
Dyspnea	0	3 (0.2)
Pulmonary embolism	0	5 (0.4)
Deep vein thrombosis	20 (1.6)	40 (3.2)
Hematoma	2 (0.2)	4 (0.3)
Wound hemorrhage	3 (0.2)	3 (0.2)
<b>Serious drug-related treatment-emergent adverse events with an incidence of <math>\geq 0.2\%</math>*</b>		
Post-procedural hemorrhage	4 (0.3)	0
Alanine aminotransferase increased	4 (0.3)	2 (0.2)
Aspartate aminotransferase increased	3 (0.2)	2 (0.2)
Wound hemorrhage	2 (0.2)	3 (0.2)

Data are n (%). \*According to MedRA, descending frequency.

**Table II.** Pre-specified sensitivity analyses for the primary efficacy outcome

<b>Randomized population</b>	<b>No. (percent)</b>	<b>Absolute difference (percent) (95% confidence intervals)</b>
Observed cases*		
Rivaroxaban (n=1254)	85 (6.8)	-6.62 (-8.94 to -4.31)
Enoxaparin (n=1277)	171 (13.4)	
Realistic scenario <sup>†</sup>		
Rivaroxaban (n=1254)	122 (9.7)	-8.43 (-11.07 to -5.79)
Enoxaparin (n=1277)	232 (18.2)	
Best-case scenario <sup>‡</sup>		
Rivaroxaban (n=1254)	79 (6.3)	-6.71 (-8.98 to -4.45)
Enoxaparin (n=1277)	166 (13.0)	
Pessimistic scenario <sup>§</sup>		
Rivaroxaban (n=1254)	509 (40.6)	-3.56 (-7.33 to 0.20)
Enoxaparin (n=1277)	565 (44.2)	

\*Patients with inadequate assessment of thromboembolism were included regardless of venography or symptomatic event/death time window.

<sup>†</sup>Within a geographic region, patients with inadequate assessment of thromboembolism were assumed to have the same risk for asymptomatic deep vein thrombosis as those with adequate assessment belonging to the same medication group.

<sup>‡</sup>All patients with inadequate assessment of thromboembolism were assumed to be event-free.

<sup>§</sup>All patients with inadequate assessment of thromboembolism were assumed to have an event.

**Table III.** Analysis of primary efficacy endpoint (adjudicated), regardless of venography/symptomatic event/death time window (population: randomized patients who have evaluable bilateral venography [adjudicated] or a confirmed symptomatic event/death)

Endpoint	Medication group	Point estimate (%)	95% exact confidence interval	Mantel–Haenszel weighted difference to enoxaparin	
				Point estimate (%)	95% confidence interval
Primary efficacy endpoint	Rivaroxaban	85/834 (10.19)	8.22 to 12.45	–8.86	–12.15 to –5.57
	Enoxaparin	171/888 (19.26)	16.71 to 22.01	–	–

Confidence intervals for proportions were calculated using exact methods.

Confidence intervals for weighted differences were calculated using asymptotic methods, with weights based upon sample sizes per strata (geographic region). Rate=number of events/number at risk, where number of events=number of patients with the event reported/number at risk=number of patients in reference population

**Table IV.** Analysis of primary efficacy endpoint, regardless of venography/symptomatic event/death time window and including evaluable investigator assessments if adjudicated assessment is non-evaluable (population see footnote)

Endpoint	Medication group	Point estimate (%)	95% exact confidence interval	Mantel–Haenszel weighted difference to enoxaparin	
				Point estimate (%)	95% confidence interval
Primary efficacy endpoint	Rivaroxaban	114/980 (11.63)	9.69 to 13.81	–8.05	–11.20 to –4.91
	Enoxaparin	200/1013 (19.74)	17.33 to 22.33	–	–

Population based on: randomized patients who have evaluable bilateral venography (adjudicated) or confirmed symptomatic event/death. Plus, randomized patients excluded from above who have evaluable bilateral venography/ultrasonography as performed by the investigator or a symptomatic event/death, provided the symptomatic event was not adjudicated to be a non-event by the venous thromboembolism committee.

Confidence intervals for proportions were calculated using exact methods. Confidence intervals for weighted differences were calculated using asymptotic methods, with weights based upon sample sizes per strata (geographic region). Rate=number of events/number at risk, where number of events=number of patients with the event reported/number at risk=number of patients in reference population.