Quantitative Benefit–Risk Assessment of Rivaroxaban for the Prevention of Venous Thromboembolism

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Introduction: Venous thromboembolism (VTE) is a common complication after hip or knee replacement and is associated with significant morbidity and mortality. Anticoagulants reduce the risk of these complications, but can also result in increased bleeding, thus requiring an assessment of benefit–risk. *Patients and Methods:* To obtain more precise estimates of treatment effects on low frequency events, data were pooled from 4 phase 3 randomized clinical trials (RECORD1–4) of rivaroxaban vs enoxaparin regimens (or enoxaparin/placebo combination in 1 study) for the prevention of deep vein thrombosis (DVT) and pulmonary embolism (PE) in total hip and knee replacement. Although the studies were designed to answer slightly different questions and differed in treatment duration and comparator dose, pooling was supported by similar study designs, identical endpoints, identical event ascertainment methods, and the same independent central blinded adjudication committees. Benefit–risk was assessed by comparing the excess number of outcome events for benefits vs that for harms ('risks'), occurring over the treatment period. Excess number of events was defined as the number of events in a hypothetical population of 10,000 patients treated with enoxaparin minus the number of events in such a population treated with rivaroxaban. A positive value indicates that fewer events occur in the population treated with rivaroxaban. The analysis was undertaken for several clinically comparable pairs of composite benefit and harm outcomes: total VTE (any DVT, non-fatal PE, or death from any cause) vs major and clinically relevant non-major (CRNM) bleeding; major VTE (proximal DVT, non-fatal PE, or VTE-related death) vs major bleeding; and symptomatic VTE/all-cause mortality vs major bleeding. For each pair, pooled Mantel–Haenszel weighted risk differences were used to compute the excess number of benefit and harm events, and the difference between excess numbers of events was used to evaluate net clinical benefit (NCB; Table). In all calculations, benefits and risks were weighted equally. An additional

assessment was performed using all treatment-emergent serious adverse events (SAEs) as reported by investigators. *Results:* Rixaroxaban is associated with statistically significantly fewer total VTE, major VTE, and symptomatic VTE/all-cause mortality events than enoxaparin, whereas enoxaparin is associated with a smaller number of different bleeding events, although no bleeding endpoints, other than the composite of major + CRNM bleeding, were statistically significantly different. In each pairwise comparison, the excess number of bleeding events is less than the excess number of VTE-related events by a factor ranging from 4 to 10 (Table). Enoxaparin was also associated with an excess of 194 treatment-emergent SAEs compared with rivaroxaban out of 10,000 patients. In all cases, there is a positive NCB for rivaroxaban vs enoxaparin with 95% confidence intervals (CIs) excluding 0, suggesting that the benefits of rivaroxaban exceed the risks when compared with enoxaparin. *Conclusions:* This quantitative benefit–risk approach provides a comparison of interventions in clinically relevant population terms. Using the net clinical benefit approach, for a variety of endpoints defining benefits and harms, the benefit–risk profile for rivaroxaban is consistently improved compared with enoxaparin for patients after elective hip and knee replacement.

Table: Pairwise NCB calculations

	Number (#) of events (in 10,000 patients)				*Excess # of events†*		*NCB (difference in excess # of events)*	
	Rivaroxaban (R)		*Enoxaparin (E)*		*(E - R)*			
*Outcome**	*N*	*95% CI*	*N*	*95% CI*	*N*	*95% CI*	*N*	*95% CI*
Total VTE	426	(364, 488)	943	(853, 1032)	504	(399, 608)	440	(320, 560)
Major and CRNM bleeding	319	(274, 363)	255	(215, 295)	-64	(-123, -5)		
Major VTE	68	(44, 93)	274	(226, 321)	205	(153, 257)	187	(132, 243)
Major bleeding	39	(23, 55)	21	(9, 33)	-18	(-37, 1)		
Symptomatic VTE & all-cause mortality	57	(38, 77)	132	(103, 161)	76	(42, 110)	58	(19, 97)
Major bleeding	39	(23, 55)	21	(9, 33)	-18	(-37, 1)		
Any treatment-emergent SAE	657	(594, 720)	852	(781, 923)	194	(101, 287)		

* Total and major VTE are based on modified intent-to-treat population. Symptomatic VTE, all-cause deaths, bleeding events, and SAEs are based on safety population. Efficacy events are based on treatment duration period and bleeding events on treatment-emergent period.
† Mantel–Haenszel weighted difference.

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