Model Based Exposure-Response Analysis of Rivaroxaban to Assess the Adequacy of Current Bioequivalence Limits in New Generic Oral Anticoagulant Drugs

M Gonzalez Sales, L Fang, MJ Kim, and L Zhao

Division of Quantitative Methods and Modeling,
Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, Food and Drug Administration

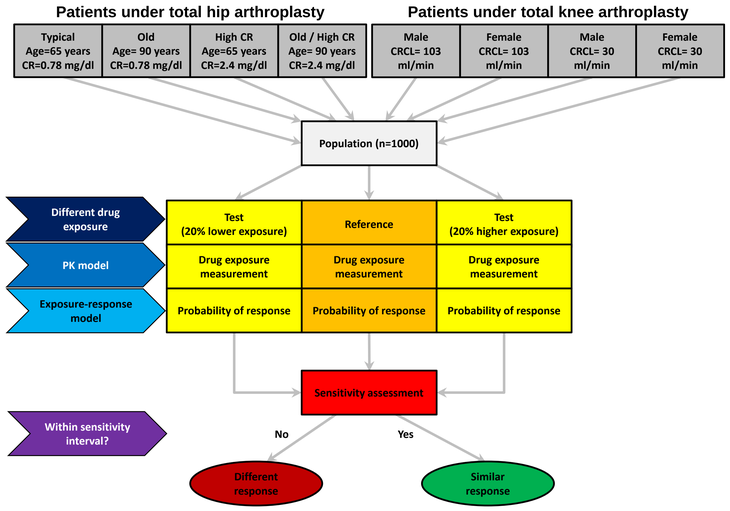
Objective

To assess the performance of currently recommended bioequivalence (BE) assessment criteria for rivaroxaban by exploring its exposure clinical response relationship for major bleeding (MB) risk and prevention of venous thromboembolism (VTE).

Methods

The relationship between rivaroxaban's exposure measurements: minimum concentration at steady state, maximum concentration, average concentration and the area under the concentration time curve (AUC) and clinical outcomes: probability of major bleeding and VTE from a total of 7145 patients under total hip arthroplasty (THA) and total knee arthroplasty (TKA) was modeled using NONMEM. Patients received rivaroxaban oral doses ranging from 2.5 and 40 mg qd or bid for at least 6 days and a maximum of 12 days. Model evaluation was performed using visual predictive check and non-parametric bootstrap (NPB).

Figure 1. Schematics for simulation. Abbreviations: *CR* , serum creatinine; *CRCL*, creatinine clearance

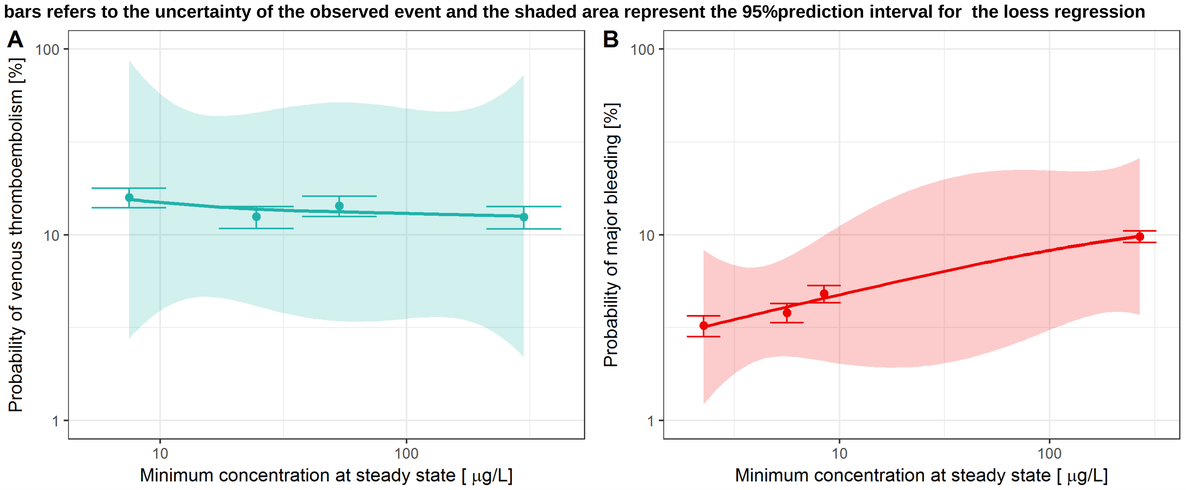


Given the incidence of adverse events reported after the use of other new oral anticoagulants, simulations were undertaken to assess whether or not the current BE limits (80-125%) are appropriate to ensure that generic drugs of rivaroxaban are safe and effective. Special populations including patients that are expected to have a higher rivaroxaban exposure were considered. An extreme scenario of 20% change in AUC was used to simulate an "hypothetical test drug of rivaroxaban". If under this scenario, generic and brand name drug have similar probability of the outcome, safety and efficacy may be expected for generic rivaroxaban products.

Results

A shallow relationship was observed between explored exposure measurements and the probability of VTE. Thus, the relationship was not modelled. For MB a steep relationship was observed.

Figure 2. Exploratory graphical analysis for efficacy (A) and safety (B). Points represents the probability of VTE and MB, respectively. Error bars refers to the uncertainty of the observed event and the shaded area represent the 95%prediction interval for the loess regression



Disclaimer

This poster reflects the views of the authors and should not be construed to represent FDA's views or policies

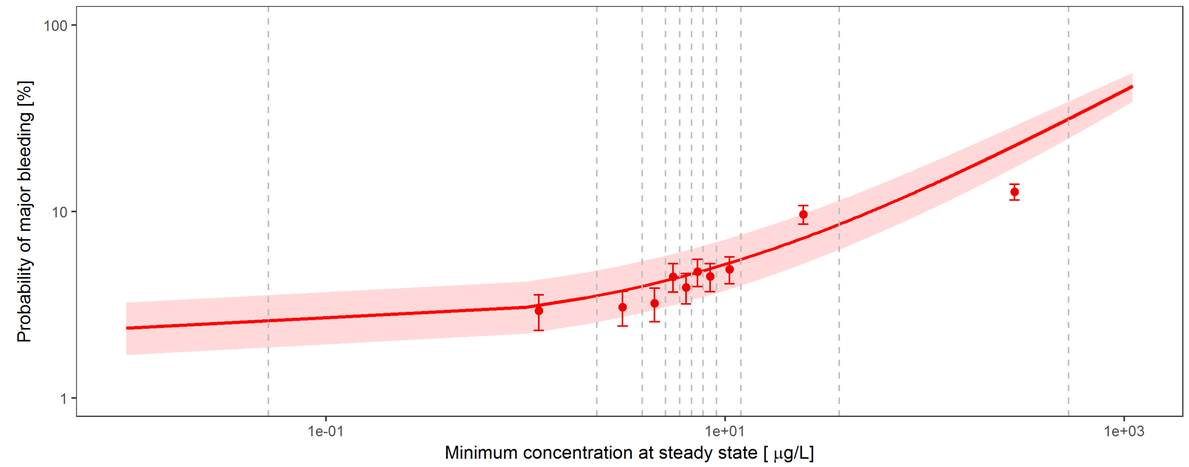
Trough concentrations were found to be a statistically significant predictor of the probability of MB. This relationship was better described using a power function.

Table1. Estimated model parameters and bootstrap results for the exposure-response model of the safety endpoint

	Original dataset	Non-parametric bootstrap (N=825)		
Parameter [unit]	**Typical Value [RSE]**	**Mean**	**95% CI**	
Baseline [%]	2.32 [11.6%]	2.32	1.96	2.84
Power coefficient	0.58 [17.5%]	0.58	0.22	0.77
Inter Study Variability [%CV]				
Baseline	17.4 [52.7 %]	16.7	3.03	30.9

Visual predictive check and non parametric bootstrap confirmed model adequacy.

Figure 3. Visual predictive check of the exposure-response model developed. Points and error bars represent the probability of MB and its uncertainty, respectively. Shaded area represents the 95%prediction interval



Based on the simulations results, the relative risk of MB of a hypothetical test product (with 20% change in AUC) will not statistically differ from brand drug.

Table2. Risk of bleeding (reference product) and relative risk of bleeding (hypothetical products) in THA and TKA subpopulations

Arthroplasty	Subpopulation	Level of exposure	Risk of bleeding (90%CI)	Relative Risk of bleeding (90%CI)
Hip	Age of 65 years and CR of 0.78 mg/dl	Reference	4.64 (2.73; 7.61)	-
		20% lower	4.35 (2.68; 6.97)	0.94 (0.63; 1.41)
		20% higher	4.89 (2.78; 8.20)	1.06 (0.71; 1.56)
	Age of 90 years and CR of 0.78 mg/dl	Reference	7.01 (3.89; 11.2)	-
		20% lower	6.44 (3.70; 10.9)	0.92 (0.66; 1.27)
		20% higher	7.54 (4.06; 12.2)	1.07 (0.79; 1.47)
	Age of 65 years and CR of 2.4 mg/dl	Reference	6.69 (3.70; 10.7)	-
		20% lower	6.15 (3.54; 9.69)	0.92 (0.66; 1.29)
		20% higher	7.18 (3.86; 11.6)	1.07 (0.78; 1.48)
	Age of 90 years and CR of 2.4 mg/dl	Reference	13.1 (8.01; 19.3)	-
		20% lower	11.8 (7.32; 19.3)	0.90 (0.71; 1.14)
		20% higher	14.3 (8.65; 21.2)	1.09 (0.88; 1.36)
Knee	Male with CRCL of 103 ml/min	Reference	3.49 (2.39; 5.81)	-
		20% lower	3.35 (2.38; 5.39)	0.96 (0.60; 1.53)
		20% higher	3.62 (2.40; 6.20)	1.04 (0.66; 1.64)
	Female with CRCL of 103 ml/min	Reference	4.02 (2.48; 6.89)	-
		20% lower	3.81 (2.46; 6.34)	0.95 (0.61; 1.46)
		20% higher	4.21 (2.50; 7.41)	1.05 (0.69; 1.60)
	Male with CRCL of 30 ml/min	Reference	4.00 (2.48; 6.86)	-
		20% lower	3.80 (2.46; 6.31)	0.95 (0.61; 1.47)
		20% higher	4.19 (2.49; 7.37)	1.05 (0.69; 1.60)
	Female with CRCL of 30 ml/min	Reference	4.81 (2.68; 8.33)	-
		20% lower	4.50 (2.64; 7.59)	0.93 (0.63; 1.39)
		20% higher	5.08 (2.72; 9.00)	1.06 (0.72; 1.55)

Conclusions

A generic drug of rivaroxaban passing currently recommended BE assessment is predicted to have similar safety and efficacy profiles to the brand drug in THA and TKA patients.

www.fda.gov