Table 1 Demographic characteristics of simulated patients and corresponding dosing regimens

ID	Age (years)	BW (kg)	LBM [a] (kg)	SCr (mg/dL)	CrCl [b] (mL/min)	Dose regimen
1	55	70	55	1.03	80	20 mg q24h
2	55	70	55	2.07	40	15 mg q24h
3	75	70	55	0.79	80	20 mg q24h
4	75	70	55	1.58	40	15 mg q24h

Abbreviations: LBM, lean body mass; BW, total body weight; SCr, serum creatinine; CrCl, creatinine clearance.

[a] Calculated lean body mass (LBM) in [kg]. for males:

$$LBM\left(kg\right)=1.10\cdot\left(weight\left(kg\right)\right)-128\cdot\left(\frac{weight\left(kg\right)}{height\left(cm\right)}\right)^{2}$$; for females:

$$LBM\left(kg\right)=1.07\cdot\left(weight\left(kg\right)\right)-148\cdot\left(\frac{weight\left(kg\right)}{height\left(cm\right)}\right)^{2}.$$

[b] Calculated creatinine clearance by Cockcroft-Gault formula in [mL/min].

$$CrCl\left(mL/min\right)=\frac{\left(140-age\left(years\right)\right)\cdot\left(weight\left(kg\right)\right)}{72\cdot SCr\left(mg/dL\right)}\cdot 0.85$$ (for female).

Table 2 Population pharmacokinetic/pharmacodynamic (PK/PD) parameter estimates used in the Monte Carlo simulation

PK and PD parameter (units) and formula			BSV (%)
PK			
C_p (mg/L)	=	$\frac{k_a \cdot F \cdot DOSE}{V \cdot \left(k_a - \frac{CL}{V}\right)} \cdot \left[\left(\frac{1-e^{\frac{-CL}{V}\cdot n\cdot\tau}}{1-e^{\frac{-CL}{V}\cdot\tau}} \cdot e^{\frac{-CL}{V}\cdot t}\right) - \left(\frac{1-e^{-k_a\cdot n\cdot\tau}}{1-e^{-k_a\cdot\tau}} \cdot e^{-k_a\cdot t}\right)\right]$	
k_a (/h)	=	1.16	/
CL/F (L/h)	=	6.10·(1-0.011·[age-65]-0.194·[SCr-1.09])	35.2
V/F (L)	=	79.7·(1-0.00133·[age-65]+0.0118·[LBM-57.5])	17.6
WSV (%)		47.9	/
FXa activity			
$FXa(\%)$	=	$E_0 \cdot \left(1 - \frac{E_{max} \cdot C_p}{EC_{50} + C_p}\right)$	
E_0 (%)	=	104 [a]	16.61
E_{max} (%)	=	107	/
EC_{50} (μg/L)	=	760	5.97
WSV (%)		10.1	/
PT			
PT (s)	=	$PT_0 + slope \cdot C_p^{1-exponent\cdot C_p}$	
PT_0 (s)	=	11.40·(1-0.000192·[CrCl-76])	22.6
slope	=	0.0426	/
exponent	=	0.0000551·(1+0.0174·[CrCl-76])	4.42
WSV (%)		12.9	/

Abbreviations: BSV, between-subject variability; CL/F, apparent oral clearance; CrCl, creatinine clearance; FXa, factor Xa; k_a, absorption rate constant; PK, pharmacokinetics; PT, prothrombin time; V/F, volume of distribution; WSV, within-subject variability.

[a] E_0 was reported to be affected by age moderately, but parameter estimate was not shown in the literature.

Notes: data is from Girgis IG, Patel MR, Peters GR, et al. J Clin Pharmacol, 2014, 54 (8): 917-27.

Table 3 Remedial dosing recommendations for patients with atrial fibrillation

Delayed time (h)	Dose recommendations and strategies [a] based on		
	Concentration	Factor Xa activity	Prothrombin time
20 mg q24h (55 years, CrCl 80 mL/min)			
0-1	20-20 [B/EHRA]	20-20 [B/EHRA]	20-20 [B/EHRA]
1-2	20-20 [B/EHRA]	20-20 [B/EHRA]	20-20 [B/EHRA] / 10-20 [C]
2-3	20-20 [B/EHRA] / 10-20 [C]	20-20 [B/EHRA]	20-20 [B/EHRA] /10-20 [C]
3-4	10-20 [C] / 20-20 [B/EHRA]	20-20 [B/EHRA]	10-20 [C] /20-20 [B/EHRA] /20-10 [D]
4-5	10-20 [C]	20-20 [B/EHRA]	10-20 [C]
5-6	10-20 [C]	20-20 [B/EHRA] /10-20 [C]	10-20 [C]
6-7	10-20 [C]	10-20 [C] /20-20 [B/EHRA]	10-20 [C]
7-8	10-20 [C]	10-20 [C]	10-20 [C]
8-10	10-20 [C]	10-20 [C]	10-20 [C] /20-10 [D]
10-12	10-20 [C]	10-20 [C]	10-20 [C] /20-10 [D]
12-14	10-20 [C] /20-10 [D]	10-20 [C] /20-10 [D]	20-10 [D] /10-20 [C]
14-16	20-10 [D] /10-20 [C]	10-20 [C] /20-10 [D]	20-10 [D]
16-18	20-10 [D]	20-10 [D]	20-10 [D]
18-20	20-10 [D] / 0-20 [A/EHRA]	0-20 [A/EHRA] /20-10 [D]	20-10 [D] /10-20 [C]
20-22	0-20 [A/EHRA]	0-20 [A/EHRA]	0-20 [A/EHRA] /20-10 [D]
20-24	0-20 [A/EHRA]	0-20 [A/EHRA]	0-20 [A/EHRA]
20 mg q24h (75 years, CrCl 80 mL/min)			
0-2	20-20 [B/EHRA]	20-20 [B/EHRA]	20-20 [B/EHRA]

Table 3 (continued)

Delayed time (h)	Dose recommendations and strategies [a] based on		
	Concentration	Factor Xa activity	Prothrombin time
2-3	20-20 [B/EHRA] / 10-20 [C]	20-20 [B/EHRA]	20-20 [B/EHRA] /10-20 [C]
3-4	10-20 [C] / 20-20 [B/EHRA]	20-20 [B/EHRA]	10-20 [C] /20-20 [B/EHRA] / 20-10 [D]
4-5	10-20 [C]	20-20 [B/EHRA] / 10-20 [C]	10-20 [C] /20-20 [B/EHRA]
5-6	10-20 [C]	20-20 [B/EHRA] / 10-20 [C]	10-20 [C]
6-7	10-20 [C]	10-20 [C] /20-20 [B/EHRA]	10-20 [C]
7-10	10-20 [C]	10-20 [C]	10-20 [C]
10-12	10-20 [C]	10-20 [C]	10-20 [C] /20-10 [D]
12-14	10-20 [C] /20-10 [D]	10-20 [C] /20-10 [D]	10-20 [C] /20-10 [D]
14-16	20-10 [D] /10-20 [C]	10-20 [C] /20-10 [D]	20-10 [D] /10-20 [C]
16-18	20-10 [D]	20-10 [D] /10-20 [C]	20-10 [D]
18-20	20-10 [D] /0-20 [A/EHRA]	20-10 [D] /10-20 [C] / 0-20 [A/EHRA]	20-10 [D] /10-20 [C]
20-22	0-20 [A/EHRA]	0-20 [A/EHRA]	0-20 [A/EHRA] /20-10 [D] /10-20 [C]
22-24	0-20 [A/EHRA]	0-20 [A/EHRA]	0-20 [A/EHRA]
15 mg q24h (55 years, CrCl 40 mL/min)			
0-2	15-15 [B/EHRA]	15-15 [B/EHRA]	15-15 [B/EHRA] /7.5-15 [C]
2-3	15-15 [B/EHRA] / 7.5-15 [C]	15-15 [B/EHRA]	15-15 [B/EHRA] /7.5-15 [C] / 15-7.5 [D]

Table 3 (continued)

Delayed time (h)	Dose recommendations and strategies [a] based on		
	Concentration	Factor Xa activity	Prothrombin time
3-4	7.5-15 [C] /15-15 [B/EHRA]	15-15 [B/EHRA]	7.5-15 [C] /15-15 [B/EHRA] / 15-7.5 [D]
4-5	7.5-15 [C]	15-15 [B/EHRA]	7.5-15 [C]/15-7.5 [D]
5-6	7.5-15 [C]	15-15 [B/EHRA]	7.5-15 [C]
6-8	7.5-15 [C]	15-15 [B/EHRA] / 7.5-15 [C]	7.5-15 [C]
8-10	7.5-15 [C]	7.5-15 [C]	7.5-15 [C]
10-12	7.5-15 [C]	7.5-15 [C]	7.5-15 [C] /15-7.5 [D]
12-14	7.5-15 [C] /15-7.5 [D]	7.5-15 [C]	15-7.5 [D] /7.5-15 [C]
14-16	15-7.5 [D] /7.5-15 [C]	7.5-15 [C] /15-7.5 [D]	15-7.5 [D]
16-18	15-7.5 [D]	15-7.5 [D] /7.5-15 [C]	15-7.5 [D]
18-20	15-7.5 [D]	15-7.5 [D] /0-15 [A/EHRA] /7.5-15 [C]	15-7.5 [D]
20-22	0-15 [A/EHRA]	0-15 [A/EHRA]	0-15 [A/EHRA] /15-7.5 [D] / 7.5-15 [C] /22.5-0 [E]
22-24	0-15 [A/EHRA]	0-15 [A/EHRA]	0-15 [A/EHRA]
15 mg q24h (75 years, CrCl 40 mL/min)			
0-2	15-15 [B/EHRA]	15-15 [B/EHRA]	15-15 [B/EHRA]
2-3	15-15 [B/EHRA] / 7.5-15 [C]	15-15 [B/EHRA]	15-15 [B/EHRA] /7.5-15 [C]
3-4	15-15 [B/EHRA] / 7.5-15 [C]	15-15 [B/EHRA]	7.5-15 [C] /15-15 [B/EHRA] / 15-7.5 [D]
4-5	7.5-15 [C] / 15-15 [B/EHRA]	15-15 [B/EHRA]	7.5-15 [C] /15-15 [B/EHRA]

Table 3 (continued)

Delayed time (h)	Dose recommendations and strategies [a] based on		
	Concentration	Factor Xa activity	Prothrombin time
5-6	7.5-15 [C]	15-15 [B/EHRA]	7.5-15 [C] /15-7.5 [D] / 15-15 [B/EHRA]
6-8	7.5-15 [C]	15-15 [B/EHRA] / 7.5-15 [C]	7.5-15 [C]
8-12	7.5-15 [C]	7.5-15 [C]	7.5-15 [C]
12-14	7.5-15 [C]	7.5-15 [C]	7.5-15 [C] /15-7.5 [D]
14-16	7.5-15 [C] /15-7.5 [D]	7.5-15 [C] /15-7.5 [D]	15-7.5 [D] /7.5-15 [C]
16-18	15-7.5 [D] /7.5-15 [C]	15-7.5 [D] /7.5-15 [C]	15-7.5 [D]
18-20	15-7.5 [D] /7.5-15 [C]	15-7.5 [D] /7.5-15 [C]	15-7.5 [D] /7.5-15 [C]
20-22	0-15 [A/EHRA] / 15-7.5 [D] /7.5-15 [C]	0-15 [A/EHRA] / 15-7.5 [D] /7.5-15 [C]	/15-7.5 [D] /0-15 [A/EHRA] / 7.5-15 [C] /22.5 [E]
22-24	0-15 [A/EHRA]	0-15 [A/EHRA]	0-15 [A/EHRA]

Abbreviations: CrCl, creatinine clearance; EHRA, European Heart Rhythm Association.

[a] "Dose recommendations and strategies" are expressed as "dose taken immediately" – "dose taken at next scheduled time" [dosing strategy].

Notes: Simulated patients were assumed to take multiple rivaroxaban doses regularly and have reached steady state. Six strategies are:

A) skip the delayed dose, and administrate the regular dose at the next scheduled time, and then resume the regular dosing regimen;

B) administrate a regular dose immediately, followed by a regular dose at the next scheduled time, and then resume the regular dosing regimen;

C) administrate a half dose immediately followed by a regular dose at the next scheduled time, and then resume the regular dosing regimen;

D) administrate a regular dose immediately followed by a half dose at the next scheduled time, and then resume the regular dosing regimen;

E) administrate one and a half regular doses immediately and skip a dose at the next scheduled time, and then resume the regular dosing regimen;

F) administrate double doses and skip a dose at the next scheduled time, and then resume the regular dosing regimen. EHRA guide: administrate the forgotten dose when it`s less than 12 h later; otherwise skipped the dose and took and next scheduled dose.