

No interaction between rivaroxaban – a novel, oral, direct Factor Xa inhibitor – and atorvastatin

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Introduction

- Rivaroxaban is an oral, once-daily, direct Factor Xa (FXa) inhibitor in advanced clinical development for the prevention and treatment of thromboembolic disorders,¹ including stroke prevention in patients with atrial fibrillation and secondary prevention of cardiovascular events in patients with acute coronary syndrome^{2,3}
- Atorvastatin is a synthetic lipid-lowering drug used to treat hypercholesterolaemia and prevent cardiovascular disease. It is currently being investigated for the prevention of atrial fibrillation following cardiothoracic surgery^{4,5}
- Future therapy involving the co-administration of rivaroxaban and atorvastatin is likely in patients with cardiovascular diseases

Objective

- To investigate the effect of steady-state atorvastatin on the safety, pharmacokinetics (PK) and pharmacodynamics (PD) of rivaroxaban. In addition, the effect of rivaroxaban on the PK of atorvastatin was also assessed

Methods

Study design

- In this three-way crossover study, healthy male subjects were randomized to receive rivaroxaban 20 mg alone (day 1 in group A), atorvastatin alone to steady state (10 mg once daily on days 1–3 and 20 mg once daily on days 4–7 in group B), and the combination of both, with rivaroxaban administered on day 7 (group C; Figure 1). There was a washout period of approximately 2 weeks between each study arm

Pharmacokinetic assessments

- The pharmacokinetic profiles of single-dose rivaroxaban alone (day 1, group A) and in the presence of steady-state atorvastatin (day 7, group C) were determined (Figure 1)

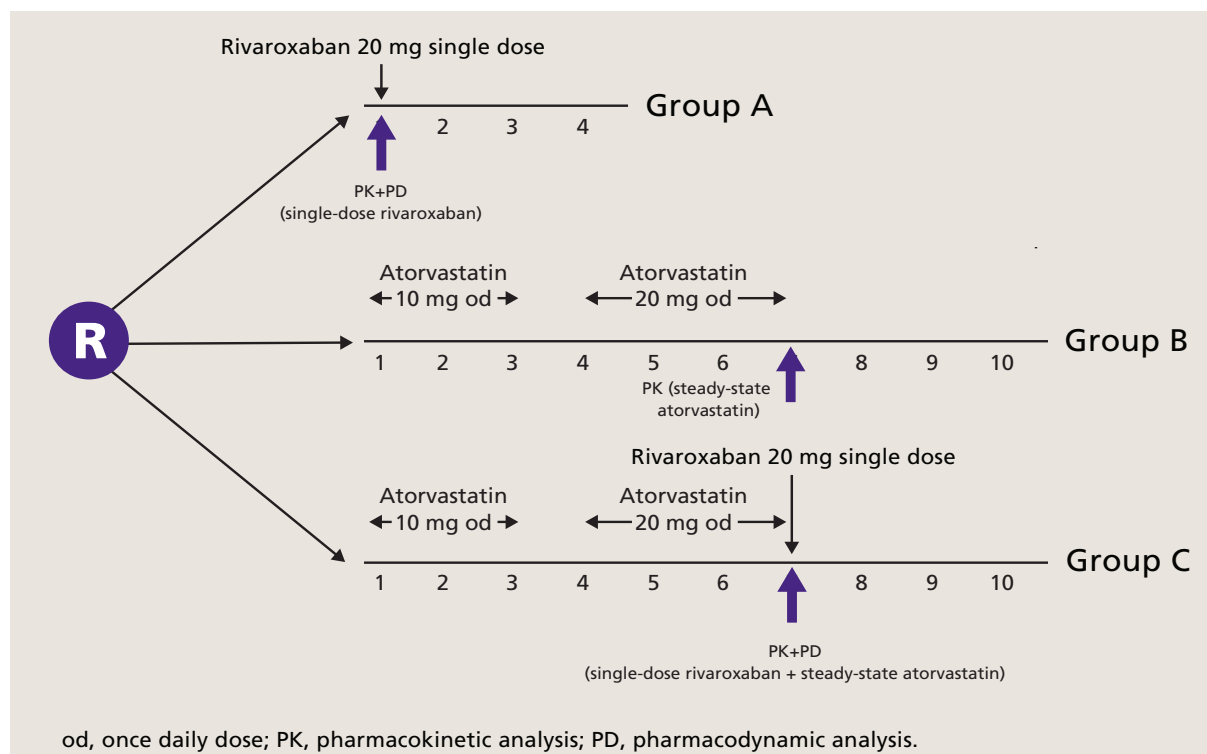


Figure 1. Three-way crossover study design.

- The pharmacokinetic profiles of steady-state atorvastatin alone (day 7, group B) and the effects of single-dose rivaroxaban on the PK of atorvastatin (acid and lactone forms), and its cytochrome P450 3A4-mediated metabolite 2-hydroxy-atorvastatin were also determined (day 7, group C)
- Serial blood samples were collected on days 1–4 in group A; and on days 7–10 in groups B and C

Pharmacodynamic assessments

- The pharmacodynamic effects of single-dose rivaroxaban alone (day 1, group A) and the effects of steady-state atorvastatin on the PD of single-dose rivaroxaban were determined (day 7, group C)
- Inhibition of FXa activity and prolongation of prothrombin time (PT) were determined as described previously⁶

Results

Pharmacokinetics

- Steady-state atorvastatin did not affect the PK of rivaroxaban (Table 1, Figure 2A)

Table 1. Effect of steady-state atorvastatin on the pharmacokinetic parameters of single-dose rivaroxaban 20 mg. Data are geometric means (geometric coefficient of variation) unless otherwise indicated

	Rivaroxaban alone (n=19)	Rivaroxaban + atorvastatin (n=19)	LS-means ratio rivaroxaban + atorvastatin vs rivaroxaban alone (90% CI)
AUC, $\mu\text{g}\cdot\text{h/l}$	1,906 (14.2)	1,884 (23.3)	0.99 (0.91, 1.02)
C_{max} , $\mu\text{g/l}$	247.4 (14.6)	240.8 (21.1)	0.97 (0.80, 1.01)
t_{max} , h ^a	3.0 (0.5–4.0)	3.0 (1.0–4.0)	
CL_{R} , l/h	3.4 (27.1)	3.7 (25.1)	
Ae_{ur} , % ^b	33.3 (7.8)	34.9 (6.0)	
$t_{1/2}$, h	8.0 (45.4)	8.1 (34.3)	

Ae_{ur} , amount of drug excreted via urine; AUC, area under the plasma concentration–time curve; CI, confidence interval; CL_{R} , renal drug clearance; C_{max} , maximum drug concentration in plasma; LS-mean, least-square mean; t_{max} , time to reach maximum drug concentrations; $t_{1/2}$, terminal half-life. ^aMedian (range). ^bArithmetic mean (standard deviation).

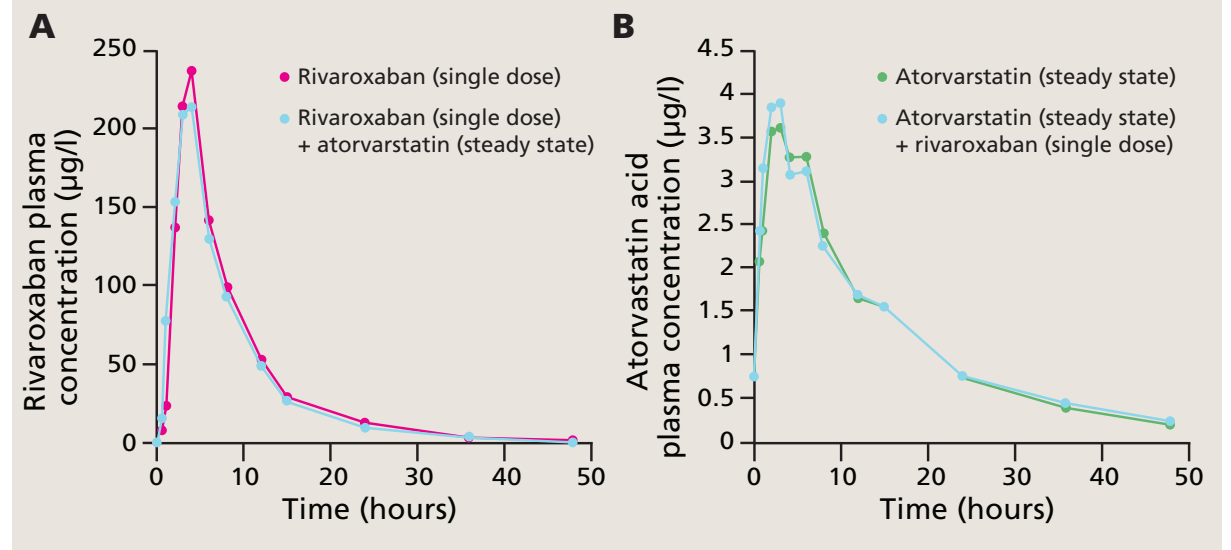


Figure 2. Plasma concentration–time profile of (A) single-dose rivaroxaban 20 mg with and without steady-state atorvastatin in healthy male subjects, and (B) steady-state atorvastatin following administration of steady-state atorvastatin with and without single-dose rivaroxaban 20 mg (geometric means; n=19).

- Rivaroxaban did not affect the PK of steady-state atorvastatin and atorvastatin-lactone or its cytochrome P450 3A4-mediated metabolite 2-hydroxy-atorvastatin (Figure 2B; Table 2)

Table 2. Effect of single-dose rivaroxaban 20 mg on the pharmacokinetic parameters of atorvastatin and atorvastatin-lactone, and its cytochrome P450 3A4-mediated metabolite 2-hydroxy-atorvastatin in healthy males. Data are geometric means (geometric coefficient of variation) unless otherwise indicated

Analyte	Parameter	Atorvastatin alone (n=19)	Atorvastatin + rivaroxaban (n=19)	LS-means ratio rivaroxaban + atorvastatin vs atorvastatin alone (90% CI)
Atorvastatin	AUC, $\mu\text{g}\cdot\text{h/l}$	47.4 (45.5)	47.5 (54.5)	1.01 (0.93, 1.01)
	C_{max} , $\mu\text{g/l}$	4.7 (50.8)	4.9 (64.2)	1.03 (0.88, 1.20)
	t_{max} , h ^a	2.0 (0.5–6.0)	2.0 (0.5–3.0)	
	$t_{1/2}$, h ^b	12.6 (26.7)	13.1 (32.7)	
Atorvastatin-lactone	AUC, $\mu\text{g}\cdot\text{h/l}$	33.4 (41.4)	33.6 (39.4)	1.01 (0.92, 1.11)
	C_{max} , $\mu\text{g/l}$	2.5 (42.1)	2.6 (42.7)	1.06 (0.94, 1.20)
	t_{max} , h ^a	3.0 (1.0–8.0)	3.0 (1.0–4.0)	
	$t_{1/2}$, h ^b	13.3 (22.9)	13.8 (24.0)	
2-hydroxy-atorvastatin	AUC, $\mu\text{g}\cdot\text{h/l}$	28.8 (37.1)	29.0 (40.2)	1.01 (0.94, 1.09)
	C_{max} , $\mu\text{g/l}$	2.4 (40.7)	2.4 (36.0)	1.00 (0.90, 1.11)
	t_{max} , h ^a	4.0 (1.0–6.0)	4.0 (1.0–6.0)	
	$t_{1/2}$, h ^b	13.6 (25.1)	14.6 (27.0)	

AUC, area under the plasma concentration–time curve; CI, confidence interval; C_{max} , maximum drug concentration in plasma; LS-mean, least-square mean; t_{max} , time to reach maximum drug concentrations; $t_{1/2}$, terminal half-life. ^aMedian (range). ^bArithmetic mean (standard deviation).

- The amount of unchanged rivaroxaban excreted in the urine was similar when rivaroxaban was administered alone (33.4%) and with steady-state atorvastatin (34.9%)

Pharmacodynamics

- Rivaroxaban alone inhibited FXa activity by a maximum of 56% and prolonged PT by 1.74 times baseline (Figure 3)
- Atorvastatin alone did not affect FXa activity or PT
- Steady-state atorvastatin did not affect rivaroxaban-mediated inhibition of FXa activity and prolongation of PT (Figure 3)

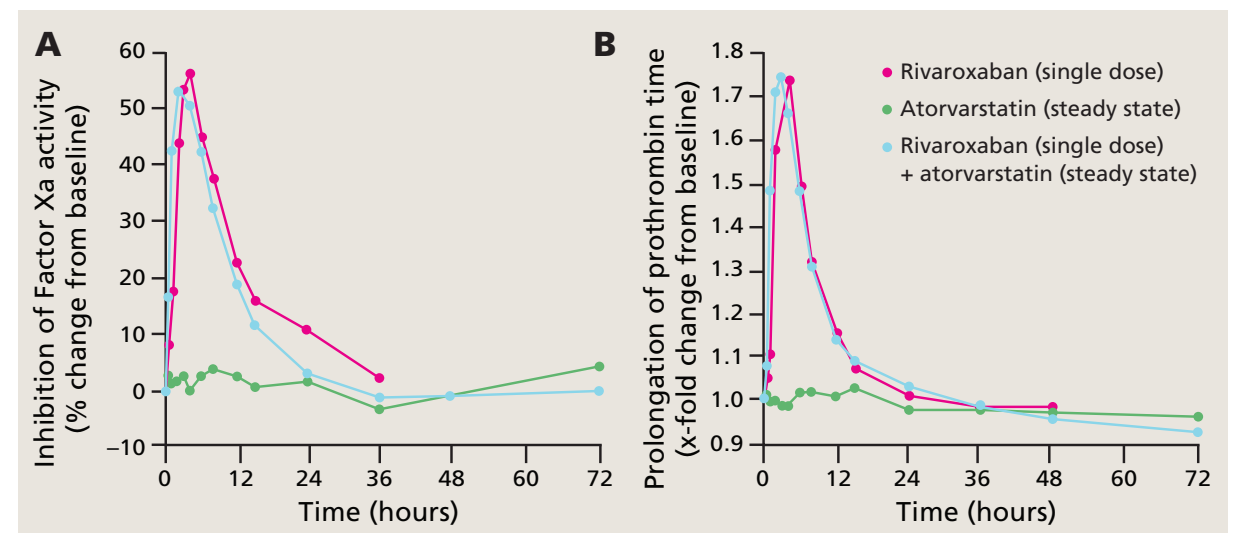


Figure 3. Effect of single-dose rivaroxaban 20 mg alone, steady-state atorvastatin alone, and single-dose rivaroxaban in combination with steady-state atorvastatin on (A) inhibition of Factor Xa activity, and (B) prolongation of prothrombin time in healthy male subjects (median values; n=19).

Safety and tolerability

- Rivaroxaban was well tolerated alone and in combination with steady-state atorvastatin. There was no evidence of relevant changes in laboratory parameters, vital signs or ECG parameters attributable to rivaroxaban

Conclusions

- The tolerability, PK and PD of rivaroxaban were not affected by co-administration with steady-state atorvastatin
- The PK of atorvastatin were not affected by co-administration with rivaroxaban
- These results suggest that rivaroxaban may be co-administered with atorvastatin in patients with cardiovascular diseases

References and disclosures

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