

Pharmacokinetics and pharmacodynamics of rivaroxaban in patients with heart failure

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Introduction

- Patients with heart failure (HF) have an increased risk of thromboembolic events such as deep vein thrombosis (DVT), pulmonary embolism (PE) and stroke, and acute coronary events, associated with increased morbidity and mortality^{1,2}
- These events may be venous or arterial in origin,⁴ and both are likely to contribute to adverse outcomes
- Biomarkers of hypercoagulability, including D-dimer (DD), prothrombin fragment 1.2 (F1.2) and thrombin-antithrombin III complex (TAT) are increased in HF.⁵⁻⁷ The elevated biomarkers are correlated with increased mortality and morbidity, and may be reduced by treatment with the vitamin K antagonist warfarin⁵
- Rivaroxaban is an oral, direct Factor Xa inhibitor that does not require routine coagulation monitoring or dose adjustment, irrespective of age, bodyweight, gender or ethnicity, and has been shown to be safe and effective, when used for the prevention of venous thromboembolism after elective hip or knee replacement surgery
- We have previously reported that rivaroxaban, administered to patients with severe chronic HF, reversed the increase in levels of F1.2, with some evidence of a reduction in the rate of increase of DD and TAT⁸
- Here we report on the pharmacokinetics (PK) and pharmacodynamics (PD) of rivaroxaban in this same patient population

Purpose

- To investigate the PK and PD of rivaroxaban, an oral, direct Factor Xa inhibitor, in subjects with HF

Methods

- This was a randomized, multicentre, phase Ib study in two adult patient cohorts with HF
- Cohort 1 included patients with acute decompensated HF; Cohort 2 included patients with chronic, stable, severe HF (New York Heart Association class III/IV)
 - Patient characteristics and dosing regimens are shown in Table 1
- The study consisted of a screening period (4 days for Cohort 1; 10 days for Cohort 2), followed by a 6-day treatment period, an end of study evaluation on day 7 and a follow-up visit on day 14
- Concurrent HF therapy, i.e. angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and β -blockers was permitted throughout the trial
- Warfarin and other antithrombotic drugs, including platelet aggregation inhibitors, were strictly prohibited at any time. Acetylsalicylic acid at doses of ≤ 100 mg/day was permitted
- The study protocol and amendments were approved by the appropriate institutional review boards and ethics committees, in accordance with the Declaration of Helsinki

Table 1. Patient characteristics and dosing regimens

Cohort	Cohort 1 (n=8)	Cohort 2 (n=18)
Inclusion criteria	Adult patients with: <ul style="list-style-type: none"> Acute decompensated HF Hospitalized for an exacerbation of HF ≤ 12-96 hours before randomization 	Adult patients with: <ul style="list-style-type: none"> Symptomatic HF LVEF $< 40\%$ within 6 months of screening Diagnosis of stable, severe NYHA class III/IV CHF Hospitalized with an HF exacerbation within the last 28-96 days before randomization or <ul style="list-style-type: none"> Who were treated with an intravenous inotropic agent ≤ 180 days, but ≥ 24 hours, before randomization
Exclusion criteria	Subjects who had received: <ul style="list-style-type: none"> PCI or other coronary surgery ≤ 30 days of screening Acute MI at time of screening or severe concomitant disease Renal dysfunction (creatinine clearance < 30 ml/min) Known significant liver disease ALT $> 5 \times$ ULN, or ALT $> 3 \times$ ULN plus total bilirubin $> 2 \times$ ULN) 	
Treatment allocation	<ul style="list-style-type: none"> Open label Patients randomized 2:1 to receive either: <ul style="list-style-type: none"> Oral rivaroxaban 10 mg daily for 6 days (n=6), or Subcutaneous enoxaparin 40 mg daily for 6 days (n=2) 	<ul style="list-style-type: none"> Double blinded Patients randomized 2:1 to receive either: <ul style="list-style-type: none"> Oral rivaroxaban 10 mg daily for 6 days (n=12), or Matching oral placebo daily for the same period (n=6)
Screening period	4 days	10 days

ALT, alanine aminotransferase; CHF, chronic heart failure; HF, heart failure; LVEF, left ventricular ejection fraction, NYHA, New York Heart Association; PCI, percutaneous coronary intervention; ULN, upper limit of normal.

Pharmacokinetic/pharmacodynamic parameters

- Blood samples were taken using a dense sampling approach on day 1 and day 6 for all patients, except those receiving enoxaparin. On days 3-5, a single predose PK sample was taken. Rivaroxaban plasma concentrations were determined by a validated liquid chromatography-mass spectrometry/mass spectrometry method
- Prothrombinase-induced clotting time (PiCT) was examined as an exploratory PD marker. Blood samples for the PiCT assay were collected prior to dosing on day 1 (single dose) and at the end of the treatment period on day 7 (multiple dose, steady state)
- Prothrombin time (PT) was assessed on a STA[®] coagulation analyser (Diagnostica Stago, Asnières-sur-Seine, France) using the STA[®] Néoplastine[®] CI Plus assay kit (Diagnostica Stago). PT results may vary depending on the kit and thromboplastin reagents used; the international normalized ratio conversion is not valid when used with rivaroxaban
- PiCT was measured with the Pefakit[®] PiCT[®] kit (Pentapharm, Basel, Switzerland) using a modified 1-step method that omitted the incubation step
- For each test, the change from baseline (day 1, predose) was calculated and summarized using descriptive statistics

Safety

- Safety was evaluated by monitoring bleeding events and other adverse events (AEs). Incidence, severity and relationship to study drug of AEs were recorded, as were changes in clinical laboratory results (including liver function tests) and vital signs

Results and discussion

- The baseline characteristics of the two treatment groups are listed in Table 2 by cohort; concomitant medications at baseline are detailed in Table 3
- The PK and PD of rivaroxaban were similar in both cohorts, and broadly similar to those previously observed in healthy volunteers⁸
- Rivaroxaban was rapidly absorbed, reaching peak plasma concentrations 1-4 hours after administration, irrespective of cohort
- Plasma concentration-time profiles of rivaroxaban were similar between both cohorts (Figure 1)
- On day 1, rivaroxaban plasma exposure was on average 21% (maximum plasma concentration [C_{max}]) to 23% (area under the plasma concentration-time curve from time of administration up to 24 hours [AUC_{24h}]) higher in Cohort 1 (n=6) than in Cohort 2 (n=12) (Table 4). On day 6, plasma exposure was on average 10% (AUC_{24h}) to 16% (C_{max}) higher in Cohort 1 (n=3) than in Cohort 2 (n=12)
 - Taken together, rivaroxaban clearance appeared to decrease compared with healthy younger subjects,⁸⁻¹⁰ resulting in an increased AUC of approximately 1.8-fold
- Little, if any, accumulation was observed upon multiple dosing
- The half-life ($t_{1/2}$) of rivaroxaban was 7-9 hours, irrespective of cohort
- Rivaroxaban prolonged PT, with peak prolongation occurring 2-4 hours after dosing (Figure 2). The PT versus time profiles of rivaroxaban were comparable between the cohorts and mirrored the plasma concentration-time curve
- The relationship between rivaroxaban plasma concentration and PT was consistent with a linear model and similar in both cohorts (Figure 3)
- Mean PiCT values at baseline were similar in placebo and rivaroxaban patients in Cohort 2 (13.4 \pm 0.7 s vs 14.9 \pm 6.1 s, respectively). After 7 days of treatment, the median change from baseline in patients receiving rivaroxaban and placebo was 3.3 s and -0.4 s, respectively, and the estimated shift in median between the rivaroxaban group and the placebo group was 3.55 s (p=0.007) (Figure 4)

Table 2. Demographic and baseline characteristics

	Cohort 1		Cohort 2		Total (N=26)
	Enoxaparin 40 mg (n=2)	Rivaroxaban 10 mg (n=6)	Placebo (n=6)	Rivaroxaban 10 mg (n=12)	
Race, n (%)					
White	1 (50)	4 (67)	6 (100)	7 (58)	18 (69)
Black	1 (50)	2 (33)	0	5 (42)	8 (31)
Sex, n (%)					
Male	1 (50)	5 (83)	4 (67)	9 (75)	19 (73)
Female	1 (50)	1 (17)	2 (33)	3 (25)	7 (27)
Age (years)					
Mean (SD)	48.0 (11.31)	52.5 (13.16)	64.3 (12.60)	58.9 (15.86)	57.8 (14.40)
Range	(40-56)	(39-72)	(39-72)	(25-87)	(25-87)
Baseline weight (kg)					
Mean (SD)	90.0 (7.07)	98.8 (27.84)	80.2 (22.95)	94.2 (25.52)	91.7 (24.41)
Range	(85-95)	(57-134)	(51-115)	(54-132)	(51-134)
Heart failure aetiology, n (%)					
Hypertensive	1 (50)	1 (17)	0	1 (8)	3 (12)
Idiopathic	0	1 (17)	1 (17)	3 (25)	5 (19)
Ischaemic	0	2 (33)	4 (67)	4 (33)	10 (38)
Other	1 (50)	2 (33)	1 (17)	4 (33)	8 (31)
Ejection fraction (%)					
Mean (SD)	17.0 (4.24)	22.3 (6.59)	21.7 (6.83)	20.8 (3.89)	21.0 (5.22)
Range	(14-20)	(15-31)	(10-30)	(15-29)	(10-31)
NYHA class, n (%)					
III	2 (100)	6 (100)	6 (100)	9 (75)	23 (88)
IV	0	0	0	3 (25)	3 (12)
Calculated creatinine clearance, n (%)					
30-50 ml/min	0	0	3 (50)	3 (25)	6 (23)
50-80 ml/min	0	2 (33)	2 (33)	2 (17)	6 (23)
>80 ml/min	1 (50)	3 (50)	1 (17)	7 (58)	12 (46)
Missing	1 (50)	1 (17)	0	0	2 (8)

NYHA, New York Heart Association; SD, standard deviation.

Table 3. Baseline concomitant medications

Medication class, n (%)	Cohort 1		Cohort 2		Total (N=26)
	Enoxaparin 40 mg (n=2)	Rivaroxaban 10 mg (n=6)	Placebo (n=6)	Rivaroxaban 10 mg (n=12)	
ACE inhibitor	2 (100)	6 (100)	4 (67)	7 (58)	19 (73)
ARB	0	0	1 (17)	4 (33)	5 (19)
β -blocker	2 (100)	6 (100)	6 (100)	12 (100)	26 (100)
Other vasodilators (nitrates/nitride)	1 (50)	1 (17)	1 (17)	1 (8)	4 (15)
Aldosterone antagonist	0	4 (67)	2 (33)	2 (17)	8 (31)
Loop or thiazide diuretic	2 (100)	6 (100)	4 (67)	12 (100)	24 (92)
Digitalis	2 (100)	3 (50)	1 (17)	3 (25)	9 (35)
Amiodarone	1 (50)	0	0	0	1 (4)
Lipid-lowering medications/statins	2 (100)	4 (67)	5 (83)	6 (50)	17 (65)
Antiplatelet medications	2 (100)	6 (100)	6 (100)	11 (92)	25 (96)

Note: Percentages were calculated with the number of patients in each group as denominator. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker. Implantable cardioverter defibrillator and biventricular pacemaker were inserted in 14 (4 in Cohort 1, and 10 in Cohort 2), and 7 (2 in Cohort 1, and 5 in Cohort 2) subjects, respectively.

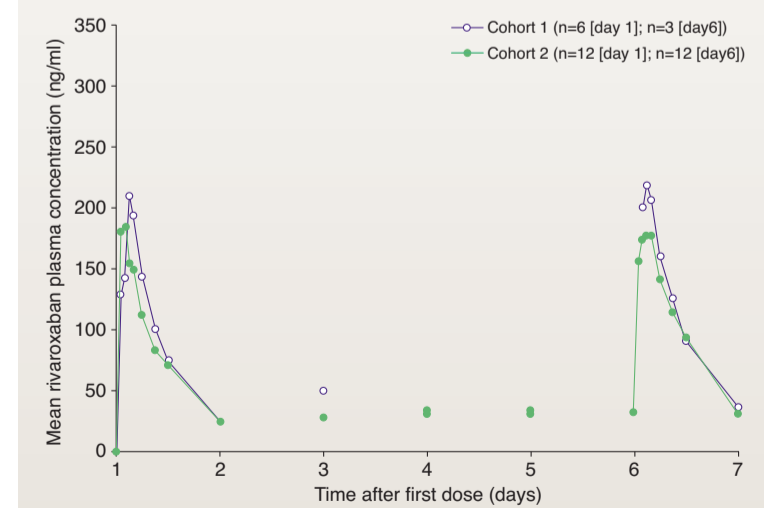


Figure 1. Mean plasma concentration-time profiles of rivaroxaban

- Rivaroxaban appeared safe and well tolerated, consistent with previously reported data.⁶ No patient discontinued the study because of an AE. No liver-related laboratory abnormalities were observed during the study in subjects receiving rivaroxaban
- Twelve (46.2%) patients reported ≥ 1 treatment-emergent AE during the study (Table 5); none was considered to be study drug related

Table 4. Descriptive statistics of rivaroxaban pharmacokinetic parameters

	Cohort 1			Cohort 2		
	n	Mean \pm SD	Median	n	Mean \pm SD	Median
Day 1						
T_{max} , h	5	-	3.22 (1.08-4.00)	11	-	1.05 (1.00-5.98)
C_{max} , ng/ml	5	238 \pm 88.5	229	11	197 \pm 73.9	175
AUC_{24h} , ng-h/ml	5	2,184 \pm 779	1,699	10	1,770 \pm 372	1,740
$AUC_{0-\infty}$, ng-h/ml	5	2,547 \pm 1,125	1,933	11	2,127 \pm 462	2,288
$t_{1/2}$, h	6	6.93 \pm 2.53	6.26	12	8.64 \pm 2.86	8.24
Day 6						
T_{max} , h	3	-	2.92 (1.12-3.00)	12	-	1.92 (0.98-4.00)
C_{max} , ng/ml	3	27.3 \pm 11.2	23.4	12	28.6 \pm 17.1	23.8
C_{min} , ng/ml	3	25.1 \pm 55.6	25.9	12	216 \pm 82.8	190
AUC_{24h} , ng-h/ml	3	2,609 \pm 668	2,603	12	2,369 \pm 741	2,366
$t_{1/2}$, h	6	7.04 \pm 2.56	5.95	12	7.95 \pm 1.88	7.43
Accumulation index*	2	0.785-1.22 [†]		11	1.23 \pm 0.210	1.30
C_{avg} , ng/ml	3	110 \pm 25.9	108	12	98.1 \pm 29.4	98.4
CL/F, l/h	3	4.01 \pm 1.06	3.84	12	4.55 \pm 1.22	4.24

* AUC_{24h} (day 6) divided by AUC_{24h} (day 1); [†]range. AUC, area under the plasma concentration-time curve; AUC_{0-∞}, until infinity; AUC_{24h}, time zero to 24 hours; C_{avg} , average plasma concentration over dosing interval; CL/F, apparent clearance; C_{max} , maximum plasma concentration; C_{min} , dosing interval; PK, pharmacokinetic; SD, standard deviation; $t_{1/2}$, half-life; T_{max} , time to reach C_{max} .

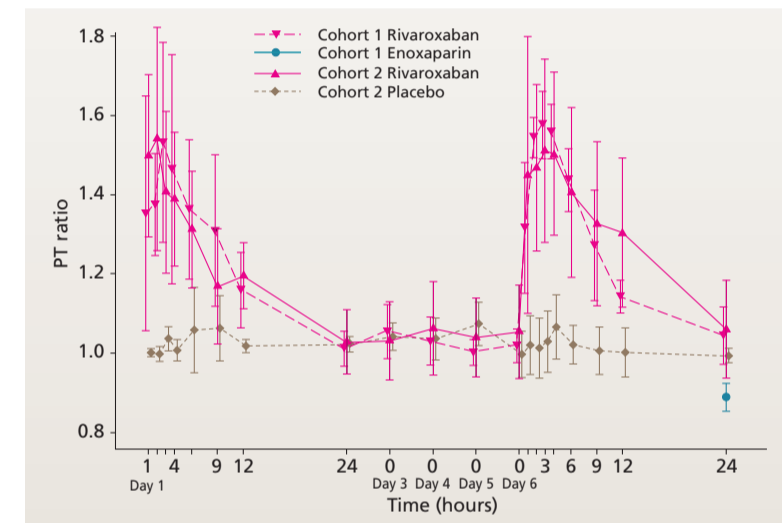


Figure 2. Mean (\pm standard deviation) prothrombin time (PT)-time profiles - relative change from baseline values.

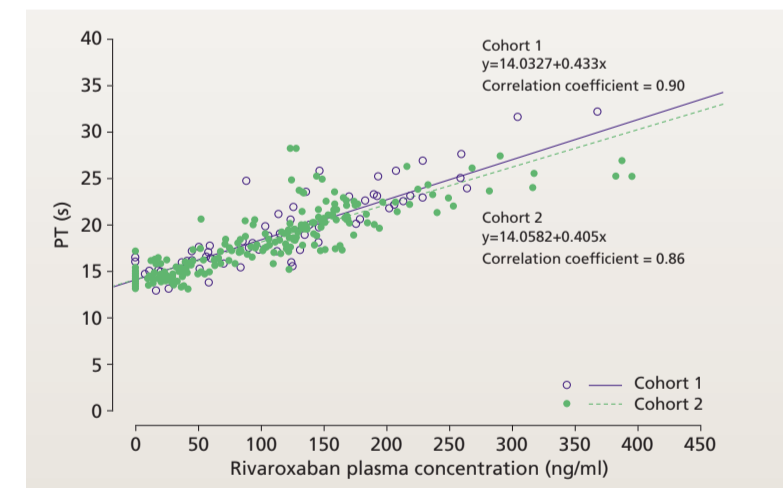


Figure 3. Relationship between rivaroxaban plasma concentration and prothrombin time (PT).

- Treatment-emergent AE rates were similar between the rivaroxaban and placebo/enoxaparin treatment groups. One Cohort 2 patient receiving rivaroxaban experienced on-treatment rectal bleeding and subsequently died of worsening HF 26 days after the last dose of study drug; however, neither event was considered to be study drug related
- The primary limitations of this study are the small study population (which likely contributed to the observed discrepancies in baseline and demographic characteristics and the relatively high variability in PK parameters), and differing trial designs between Cohort 1 (open label, placebo-controlled) and Cohort 2 (double-blinded, enoxaparin-controlled). Hence caution should be used when comparing the study cohorts
- There were discrepancies in age, race and gender between the two treatment groups - more balanced numbers would be expected if the study population were larger
 - It was challenging to recruit patients for this study, particularly for Cohort 1, since most patients with acute decompensated HF will receive intravenous anticoagulants on admission

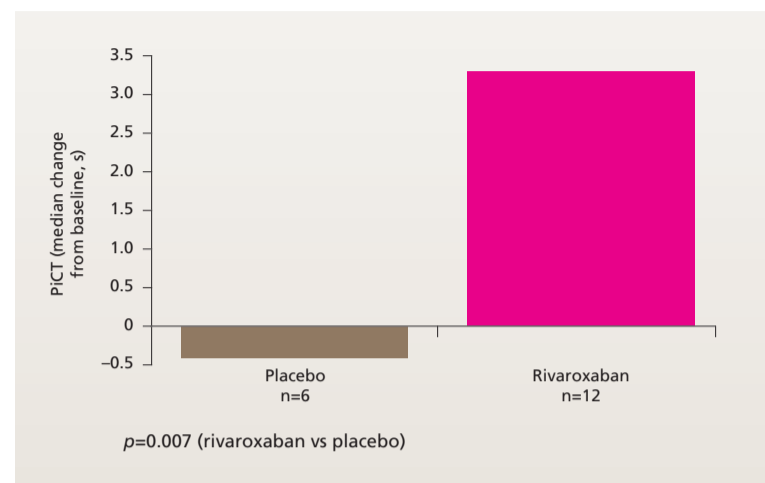


Figure 4. Median change in prothrombinase-induced clotting time (PiCT) in Cohort 2 patients (day 7 minus baseline levels).

Table 5. Treatment-emergent adverse events

Body system or organ class	Cohort 1		Cohort 2		Rivaroxaban Total (n=18)	Total (N=26)
	Enoxaparin 40 mg (n=2)	Rivaroxaban 10 mg (n=6)	Placebo (n=6)	Rivaroxaban 10 mg (n=12)		
Dictionary-derived term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total number of patients with adverse events	1 (50.0)	4 (66.7)	3 (50.0)	4 (33.3)	8 (44.4)	12 (46.2)
Cardiac disorders	0	1 (16.7)	1 (16.7)	1 (8.3)	2 (11.1)	3 (11.5)
Cardiac failure	0	1 (16.7)	0	0	1 (5.6)	1 (3.8)
Cardiac failure congestive	0	0	1 (16.7)	1 (8.3)	1 (5.6)	2 (7.7)
Gastrointestinal disorders	0	1 (16.7)	1 (16.7)	1 (8.3)	2 (11.1)	3 (11.5)
Diarrhoea	0	1 (16.7)	0	0	1 (5.6)	1 (3.8)
Nausea	0	0	1 (16.7)	0	1 (5.6)	1 (3.8)
Rectal haemorrhage	0	0	0	1 (8.3)	1 (5.6)	1 (3.8)
Stomach discomfort	0	1 (16.7)	0	0	1 (5.6)	1 (3.8)
General disorders and administration-site conditions	1 (50.0)	0	0	0	0	1 (3.8)
Pain	1 (50.0)	0	0	0	0	1 (3.8)
Infections and infestations	0	1 (16.7)	0	0	1 (5.6)	1 (3.8)
Nasopharyngitis	0	1 (16.7)	0	0	1 (5.6)	1 (3.8)
Injury, poisoning and procedural complications	0	0	0	1 (8.3)	1 (5.6)	1 (3.8)
Fall	0	0	0	1 (8.3)	1 (5.6)	1 (3.8)
Investigations	0	0	0	1 (8.3)	1 (5.6)	1 (3.8)
Blood creatinine increased	0	0	0	1 (8.3)	1 (5.6)	1 (3.8)
Haemoglobin decreased	0	0	0	1 (8.3)	1 (5.6)	1 (3.8)
Metabolism and nutrition disorders	0	1 (16.7)	0	0	1 (5.6)	1 (3.8)
Hyperglycaemia	0	1 (16.7)	0	0	1 (5.6)	1 (3.8)
Musculoskeletal and connective tissue disorders	0	0	2 (33.3)	0	0	2 (7.7)
Flank pain	0	0	1 (16.7)	0	0	1 (3.8)
Muscular weakness	0	0	1 (16.7)	0	0	1 (3.8)
Trismus	0	0	1 (16.7)	0	0	1 (3.8)
Nervous system disorders	1 (50.0)	2 (33.3)	0	0	2 (11.1)	3 (11.5)
Headache	1 (50.0)	2 (33.3)	0	0	2 (11.1)	3 (11.5)
Respiratory, thoracic and mediastinal disorders	0	0	0	1 (8.3)	1 (5.6)	1 (3.8)
Cough	0	0	0	1 (8.3)	1 (5.6)	1 (3.8)

Rivaroxaban total includes all patients who received rivaroxaban from Cohort 1 and Cohort 2.

Conclusions

- Rivaroxaban exhibited similar predictable PK and PD profiles in both acutely decompensated and stable HF patients

- Since thromboembolic events such as PE, DVT or acute coronary events often occur in patients with chronic HF, and contribute to the high mortality and morbidity rates in such patients, further studies investigating the efficacy and safety of anticoagulation with rivaroxaban in patients with HF are warranted

References

- Freudenberger RS *et al.* *Circulation*