

The Effect of Rivaroxaban on Biomarkers of Hypercoagulability in Patients with Chronic Heart Failure

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Introduction

- ◆ Patients with heart failure (HF) are at increased risk of thromboembolic events such as deep vein thrombosis, pulmonary embolism, and stroke, which are associated with increased morbidity and mortality^{1,2}
- ◆ Intracoronary thrombosis can be arterial (platelet-rich) or venous (fibrin-rich) in origin, and can worsen HF by causing myocardial ischemia and increasing the rates of acute coronary events and sudden death.^{3,4} Prevention of these thromboembolic events may lead to an improvement in patient outcomes⁴
- ◆ D-dimer (DD), prothrombin fragment 1.2 (F1.2), and thrombin-antithrombin III complex (TAT) are biomarkers of hypercoagulability that are increased in HF.^{5,6} This increase in hypercoagulability biomarkers is associated with increased mortality and morbidity, but may be reduced by the vitamin K antagonist (VKA), warfarin⁶
- ◆ Currently, VKAs are the mainstay of oral anticoagulant therapy; however, they have multiple food and drug interactions and require patients to undergo regular coagulation monitoring and dose adjustments
- ◆ New oral anticoagulants are being developed that may avoid many of the problems associated with VKA use
- ◆ Rivaroxaban is an oral, direct Factor Xa inhibitor that does not require routine coagulation monitoring or dose adjustment, irrespective of age, body weight, gender, or ethnicity for prevention of venous thromboembolism after major orthopaedic surgery. The effects of rivaroxaban in patients with HF have not been extensively studied
- ◆ Currently, patients with chronic HF (CHF) are being enrolled in the further rivaroxaban clinical trials: MAGELLAN, ROCKET, and ATLAS ACS TIMI 51. Up to 30% of patients enrolled in these trials may have HF

Objective

- ◆ To examine the effect of rivaroxaban (in addition to concurrent CHF therapy) on the circulating concentrations of DD, F1.2, and TAT in subjects with New York Heart Association (NYHA) class III/IV CHF

Methods

- ◆ This was a randomized, double-blind, multicenter, phase Ib study
- ◆ The study protocol and amendments were approved by an institutional review board
- ◆ Subjects were considered for inclusion in the study if aged ≥ 18 years, with symptomatic CHF and a left ventricular ejection fraction (LVEF) $< 40\%$ within 6 months of screening
- ◆ Subjects were also required to have a diagnosis of stable, severe NYHA class III/IV CHF and have been hospitalized with an HF exacerbation within the last 28–180 days before randomization, or have been treated with an intravenous inotropic agent within 180 days, but no less than 24 hours, before randomization
- ◆ Use of warfarin, other antithrombotic drugs, and thienopyridines was prohibited within 30 days before randomization and during the study
- ◆ Patients were randomly assigned 2:1 in a double-blind manner to receive either rivaroxaban (10 mg) or placebo once daily for 6 days in addition to concurrent HF therapy, i.e. angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, plus β -blockers
- ◆ Biomarker levels were determined using commercially available enzyme immunoassays. TAT and F1.2 levels were determined by the Enzygnost TAT[®] and Enzygnost F1+2[®] kits (Dade Behring, Marburg, Germany); DD levels were measured using the Asserachrom D-Dimer kit (Diagnostica Stago, Asnières-sur-Seine, France)
- ◆ Blood samples for the analysis of biomarkers were obtained before administration of blinded study medication (day 1) and up to 24 hours after the last dose (day 7)
- ◆ For each test, the change from baseline (day 1, predose) was calculated and summarized using descriptive statistics
- ◆ Analysis of variance (ANOVA) was used to compare the difference in change from baseline between rivaroxaban and placebo groups. The data are presented as mean \pm standard error of the mean

Results

- ◆ The baseline characteristics of the two treatment groups are listed in Table 1:
 - Twelve subjects received rivaroxaban and six received placebo
 - Mean age of subjects was 61 years
 - 27% were female
 - Mean LVEF was 21%
- ◆ There were discrepancies in age, race, and gender between the two treatment groups; however, this was a small randomized study – more balanced numbers would be expected if the study population was larger
- ◆ In subjects receiving rivaroxaban, the mean concentration of F1.2 decreased by 2.7 ± 0.9 ng/mL over 7 days, compared with an increase of 11.6 ± 4.2 ng/mL in subjects receiving placebo, an absolute difference of 14.3 ± 3.3 ng/mL ($p=0.0009$) (Figure 1A)
- ◆ A trend toward a reduction in the rate of increase was seen for DD and TAT in subjects receiving rivaroxaban (Figure 1B and C, respectively)

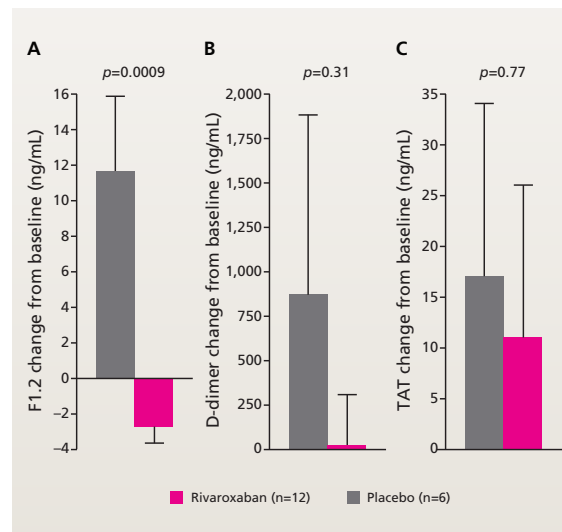


Figure 1. Effects of rivaroxaban 10 mg once daily for 7 days versus placebo on the levels of biomarkers of coagulation activation in subjects with stable chronic heart failure (mean \pm standard error of the mean change from baseline): (A) prothrombin fragment 1.2 (F1.2); (B) D-dimer; (C) thrombin-antithrombin III complex (TAT).

Table 1. Demographic and baseline characteristics

	Rivaroxaban 10 mg (n=12)	Placebo (n=6)
Race, n (%)		
White	7 (58)	6 (100)
Black	5 (42)	0
Sex, n (%)		
Male	9 (75)	4 (67)
Female	3 (25)	2 (33)
Age (years)		
Mean (SD)	58.9 (15.86)	64.3 (12.60)
Median	59.5	68.0
Range	(25–87)	(39–72)
Baseline weight (kg)		
Mean (SD)	94.2 (25.52)	80.2 (22.95)
Median	102.5	82.0
Range	(54–132)	(51–115)
Baseline height (cm)		
Mean (SD)	173.9 (9.05)	165.5 (10.45)
Median	175.0	164.0
Range	(157–185)	(152–183)
Baseline body mass index (kg/m²)		
Mean (SD)	31.3 (8.69)	29.0 (6.76)
Median	33.8	27.4
Range	(17–46)	(20–40)
Heart failure etiology, n (%)		
Hypertensive	1 (8)	0
Idiopathic	3 (25)	1 (17)
Ischemic	4 (33)	4 (67)
Other	4 (33)	1 (17)
Ejection fraction (%)		
Mean (SD)	20.8 (3.89)	21.7 (6.83)
Median	20.0	22.5
Range	(15–29)	(10–30)

SD, standard deviation.

- ◆ The incidence of adverse events was similar between rivaroxaban and placebo groups (Table 2). Rivaroxaban appeared to be well tolerated

Table 2. Treatment-emergent adverse events

	Rivaroxaban 10 mg (n=12)	Placebo (n=6)
Total no. of subjects with adverse events	4	3
Cardiac disorders	1	1
Cardiac failure	0	0
Cardiac failure congestive	1	1
Gastrointestinal disorders	1	1
Diarrhea	0	0
Nausea	0	1
Rectal hemorrhage	1	0
Stomach discomfort	0	0
General disorders and administration-site conditions	0	0
Pain	0	0
Infections and infestations	0	0
Nasopharyngitis	0	0
Injury, poisoning, and procedural complications	1	0
Fall	1	0
Investigations	1	0
Blood creatinine increased	1	0
Hemoglobin decreased	1	0
Metabolism and nutrition disorders	0	0
Hyperglycemia	0	0
Musculoskeletal and connective tissue disorders	0	2
Flank pain	0	1
Muscular weakness	0	1
Trismus	0	1
Nervous system disorders	0	0
Headache	0	0
Respiratory, thoracic, and mediastinal disorders	1	0
Cough	1	0

One subject may have experienced more than one event within a category. Numbers in bold refer to the number of subjects, whereas non-bold numbers refer to the number of adverse events recorded in each category.

Conclusions

- ◆ In patients with severe CHF, *in vivo* markers of hypercoagulability appear to increase over time
- ◆ Rivaroxaban reversed this trend for F1.2 with attenuation of DD and TAT
- ◆ Rivaroxaban decreased levels of hypercoagulability biomarkers that are associated with increased thrombosis-related mortality
- ◆ These data warrant further studies of rivaroxaban in HF
- ◆ If further observations in late-phase clinical trials are consistent with these findings, this raises the possibility that anticoagulation with rivaroxaban may potentially provide additional clinical benefit in patients with HF

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Disclosure of Conflict of Interest

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