An Exploratory Study of Effectiveness and Safety of Rivaroxaban in Patients With Left Ventricular Thrombus

Study Protocol and Statistical Analysis Plan

(Sep 10, 2020)

Trial registration This study was registered at ClinicalTrials.gov as NCT 04970381.

Study Protocol

Study design

This study was a prospective, single-center, open, single-arm observational clinical study.

Ethics approval

For the study, documented approval from the appropriate independent ethics committees/institutional review boards was obtained for the participating center before the start of the study according to good clinical practice and local laws, regulations, and organizations.

Patient population

Consecutive patients aged 18–75 years with left ventricular (LV) thrombus confirmed by surface ultrasound within three months were eligible for study participation. Major exclusion criteria were contraindications to anticoagulation and current anticoagulant therapy. Complete inclusion and exclusion criteria were listed in *Table 1*.

Table 1 Inclusion and exclusion criteria

Inclusion criteria	**Exclusion criteria**
Age ≥18 years old	LV thrombus exists > 3 months (old thrombus)
Newly found LV thrombus ≤ 3 months by surface ultrasound before enrollment, and the underlying disease was not limited	Has contraindications to anticoagulant therapy with rivaroxaban
The standard anticoagulation treatment < 4 weeks before enrollment, with no antiplatelet drugs or only a single antiplatelet drug	A history of acute pulmonary embolism or deep vein thrombosis within 3 weeks, requiring intensive anticoagulation therapy
Patients voluntarily join the study and sign the informed consent form of the study.	A history of hemorrhagic stroke within 4 weeks; -Malignant and benign heart tumors
	Dual antiplatelet therapy such as aspirin and P2Y12 receptor antagonist or other antiplatelet agents must be retained
	Severe liver and kidney dysfunction, alanine aminotransferase > 3 times the upper limit and total bilirubin > 2 times the upper limit, creatinine clearance rate < 15ml/min/1.73m2
	A history of major bleeding, intracranial hemorrhage, or active bleeding within 1 month
	Hematological diseases, hemoglobin < 100g/L, platelets < 880×109/L
	Pregnancy status, planned pregnancy, and lactating women
	Life expectancy was less than 1 year
	Has been included in other clinical studies
	Other situations which were not suitable for participation considered by investigators

Note: In patients with LV thrombus complicated with hemorrhagic stroke ≥ 4 weeks or recent ischemic stroke/transient ischemic attack, the investigators decided whether anticoagulation therapy can be given according to the specific situation.

Study treatments

The enrolled patients were assigned to a standard dose of rivaroxaban 20 mg qd (it can be reduced to 10-15 mg qd depending on the patient's condition and renal function) after the confirmation of LV thrombus by contrast-enhanced echocardiography.

Study endpoints

The primary endpoint of this study was the LV thrombus resolution rate at 12 weeks confirmed on contrast-enhanced echocardiography.

The secondary endpoint events:

1) the LV thrombus resolution rate at 6 weeks, the LV thrombus resolution or reducing rate at 6 weeks, the LV thrombus unchanging or increasing rate at 6 weeks, the LV thrombus resolution or reducing rate at 12 weeks, and the LV thrombus unchanging or increasing rate at 12 weeks. (disappearance of thrombus as an indicator of resolution rate, >15% reduction in thrombus length or thickness measured by ultrasonography as an indicator of reduction rate, ⩽15% variation in length or thickness as an indicator of unchanged rate, and >15% increase in length or thickness as an indicator of increasing rate)

2) incidence of the composite of stroke, systemic embolism, myocardial infarction,and cardiovascular death during follow-up

3) major bleeding according to the International Society on Thrombosis and Haemostasis [ISTH] criteria and clinically related non-major hemorrhage events during follow-up.

An adverse event was any adverse medical event, including an exacerbation of a pre-existing condition or abnormal laboratory findings on clinical examination of a subject on medication, which was not necessarily related to such treatment. A serious adverse event can be fatal, life-threatening, requiring hospitalization or prolongation of an ongoing hospital stay, resulting in persistent or significant disability/incapacity, and it was any adverse medical event that represents a significant risk of congenital

anomalies/birth defects and/or other clinically significant serious events.

Study procedures

First of all, for patients with LV thrombus (regardless of the type of fundamental disease) confirmed by surface ultrasound within three months, who met the inclusion criteria and did not meet the exclusion criteria, informed consent was signed. Blood routine, biochemical and coagulation tests were required to complete, and baseline contrast-enhanced echocardiography was evaluated. Secondly, a standard dose of rivaroxaban 20 mg qd (it can be reduced to 10-15 mg qd depending on the patient's condition and renal function) was administered to the enrolled patients. Then, at 6 and 12 weeks, hematological parameters such as routine blood tests, liver and kidney function, coagulation, and other hematological parameters were re-examined. At the same time, contrast-enhanced echocardiography was also performed and thrombus size, anticoagulant use, and endpoint events were documented as well. After 12 weeks, the investigator decided on the follow-up treatment plan according to the patient's condition. Clinic or telephone follow-up visits were conducted at 6 months to collect events and anticoagulant use. During the entire study, patients were educated about anticoagulation and bleeding observation, informed about the importance of maintaining treatment compliance and notified about the management of bleeding in the presence of bleeding according to the EHRA 2018 NOACs clinical guidelines.

Statistics Analysis Plan

Patients who received at least one dose of rivaroxaban were included in the safety set population. Patients who completed treatment and follow-up visits were included in the primary analysis set which was used for evaluating efficacy outcomes.

Normally distributed continuous data were presented as mean and standard deviation (SD) while non-normally distributed continuous data by the median and interquartile range (IQR), and the dichotomous data were computed using frequency and percentage. The rates and their 95% confidence intervals (CIs) were calculated for the primary endpoint and the secondary endpoints. The hazard ratio (HR)was estimated with or without adjustment for covariates using Cox regression models. Significant variables in the univariate analysis and other variables of interest were included in the subgroups to investigate the potential influences on the resolution of the thrombus, where continuous variables were dichotomized based on the median value. A forest plot was created to display subgroup analysis. To test for changes in diffusion data across different time points of thrombus resolved vs. thrombus unresolved (including reduced, unchanged, and enlarged thrombus), linear mixed models were tested using the *lme* function in R. To investigate any significant interactions in more detail, we then ran corresponding pairwise comparisons using the *emmeans* function in R. Comparisons were regarded as two-sided, and statistical significance was determined by the P value of 0.05. All analyses were scheduled for completion with R version 3.5.1 (The R Project for Statistical Computing, Vienna, Austria).