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An exploratory study of effectiveness and safety of rivaroxaban in patients with left ventricular thrombus (R-DISSOLVE)

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Abstract

Evidence on the treatment for left ventricular (LV) thrombus is limited and mainly derives from retrospective studies. The aim of R-DISSOLVE was to explore the effectiveness and safety of rivaroxaban in patients with LV thrombus. R-DISSOLVE was a prospective, interventional, single-arm study, conducted from Oct 2020 to June 2022 at Fuwai Hospital, China. Patients with a history of LV thrombus < 3 months and with systemic anticoagulation therapy < 1 month were included. The thrombus was quantitatively confirmed by contrast-enhanced echocardiography (CE) at baseline and follow-up visits. Eligible patients were assigned to rivaroxaban (20 mg once daily or 15 mg if creatinine clearance was between 30 and 49 mL/min) and its concentration was determined by detecting anti-Xa activity. The primary efficacy outcome was the rate of LV thrombus resolution at 12 weeks. The main safety outcome was the composite of ISTH major and clinically relevant non-major bleeding. A total of 64 patients with complete CE results were analyzed for efficacy outcomes. The mean LV ejection fraction was 25.4 ± 9.0%. The dose-response curve of rivaroxaban was satisfactory based on the peak and trough plasma levels and all concentrations were in the recommended treatment range according to NOAC guidelines. The incidence rate of thrombus resolution at 6 weeks was 66.1% (41/62, 95% CI 53.0–77.7%), and of thrombus resolution or reduction was 95.2% (59/62, 95% CI 86.5–99.0%). At 12 weeks, the thrombus resolution rate was 78.1% (50/64, 95% CI 66.0–87.5%) while the rate of thrombus resolution or reduction was 95.3% (61/64, 95% CI 86.9–99.0%). The main safety outcome occurred in 4 of 75 patients (5.3%) (2 ISTH major bleeding and 2 clinically relevant non-major bleeding). In patients with LV thrombus, we reported a high thrombus resolution rate with acceptable safety by rivaroxaban, which could be a potential option for further LV thrombus treatment.

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

Keywords Left ventricular thrombus · Rivaroxaban · Contrast-enhanced echocardiography · Non-vitamin K antagonist oral anticoagulants · Thrombus resolution

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Highlights

- The R-DISSOLVE study prospectively explored rivaroxaban treatment in patients with left ventricular thrombus.
- Contrast-enhanced echocardiography was performed to detect left ventricular thrombus at baseline, 6 weeks, and 12 weeks.
- We reported a high thrombus resolution rate with acceptable safety by rivaroxaban.
- By detecting anti-Xa activity, rivaroxaban met its expected peak and trough plasma levels with an impressive dose-response curve.

Introduction

Left ventricular (LV) thrombus, with an incidence of 4–15%, is mainly secondary to anterior wall myocardial infarction (MI) or dilated cardiomyopathy (DCM) [1]. Patients with LV thrombus experience a 10–22% risk of thromboembolic events within 3 months [2, 3]. Guidelines for MI or stroke recommend patients with LV thrombus be given anticoagulants to reduce the risk of stroke or systemic embolism events [4, 5]. As non-vitamin K antagonist oral anticoagulants (NOACs) come with potentially practical advantages over warfarin, NOACs are increasingly used as off-label anticoagulant therapy in patients with intracardiac thrombi without the necessity for frequent laboratory monitoring. Compared with vitamin K antagonists (VKAs), NOACs were non-inferior in the efficacy and safety for the treatment of LV thrombus in two small randomized clinical trials (RCTs) [6, 7] and several meta-analyses [8–11]. In decades of research, earlier guidelines on anticoagulation for LV thrombus primarily recommended the use of VKAs therapy for 3 months [5, 12], while the latest American Heart Association scientific statement (2022) recommended that NOACs could be a reasonable alternative to warfarin in patients with LV thrombus, based on supportive though insufficiently powered randomized data [13].

To date, LV thrombus is generally confirmed by conventional transthoracic echocardiography (TTE) in both prospective and retrospective clinical trials, which decreases the LV thrombus's detection rate. Compared to TTE, the utilization of contrast-enhanced echocardiography (CE) or cardiac magnetic resonance (CMR) has yielded roughly two- to three-fold sensitivity and accuracy and directly impacted patient treatment or clinical outcomes [14]. The current American Heart Association guidelines for stroke state that in patients with stroke or TIA in the setting of acute MI, it is reasonable to perform advanced cardiac imaging such as CE or CMR to assess for the presence of LV thrombus [12]. However, no studies have investigated the treatment of LV thrombus by CE for detection.

The objective of this study was to explore the efficacy and safety of rivaroxaban in patients with LV thrombus, which was the first prospective study to assess the treatment of LV thrombus by CE. And we hypothesized that LV thrombus could resolve or reduce with the anticoagulant therapy of rivaroxaban for 12 weeks, without increasing the rate of major bleeding.

Methods

R-DISSOLVE study design

R-DISSOLVE (an exploratory study of effectIveneSs and Safety of rivarOxaban in patients with Left VEntricular thrombus, ClinicalTrials.gov: NCT04970381) study was a prospective, interventional, single-arm, open-label study, conducted from October 2020 to June 2022 at Fuwai Hospital, China. This study was approved by the Ethics Committee of Fuwai Hospital (Approval No. 2020-1380, clinical trial Approval No. 2020-ZX49). Patients signed a written informed consent and were required to adhere to a strict study protocol.

Patient population and treatment regimens

We consecutively enrolled patients who were aged 18 years or older with evidence of LV thrombus identified by either TTE, computer tomography (CT), or CMR imaging within three months and received systemic oral anticoagulation treatment for less than one month. The major exclusion criteria were contraindications to anticoagulation therapy such as severe renal or liver dysfunction, and a history of hemorrhagic stroke or major bleeding within 1 month. Details of inclusion and exclusion criteria were listed in the Supplementary material online (Table S1). Included patients were assigned to a standard dose of rivaroxaban 20 mg once daily (OD). Patients were considered to be administered reduced dosing (15 mg OD), for whom were on dual antiplatelet agents, or with creatinine clearance (CrCl) of 30-50mL/min. Additionally, to assess the peak and trough plasma levels of rivaroxaban, we measured the levels of anti-factor Xa (anti-Xa) at 7 timepoints (blank baseline, before/2–4 h after medication on the fourth day of rivaroxaban treatment, before/2–4 h after medication at 6 weeks and 12 weeks separately).

Patients who were on short-time anticoagulants were switched to rivaroxaban therapy according to guidelines

before or within 12 h after baseline CE measurement. All medications according to the recommendation of guidelines for the treatment of underlying diseases were encouraged. The investigators took extreme precautions to avoid any sort of drugs that were potent inhibitors of either P-glycoprotein or cytochrome P3A4. When an invasive intervention was needed, rivaroxaban was restarted afterward as soon as possible.

Outcome assessment

Thrombus assessment was quantitatively performed via CE with the use of a microbubble contrast agent (Sonovue) at baseline, 6-week, and 12-week follow-up visits. LV thrombus was defined as an abnormal echo mass in the LV cavity, which was distinguishable from the internal structures such as the LV endocardium, papillary muscles, trabeculae, or tendons. Multiple apical orientations (two-, three-, and four-chamber views) were required to assess the thrombus and its largest diameter and thickness were recorded. The two largest thrombi were chosen if a patient had more than two. The predefined criteria of thrombus outcome were defined according to the left atrial thrombus assessment [15]: (a) resolved: no thrombus was detectable on the CE; (b) reduced: the diameter or thickness of the thrombus reduced by > 15%; (c) enlarged: the diameter or thickness of the thrombus increased by > 15%; (d) unchanged: the change of the diameter or thickness of the thrombus was ≤ 15%. To ensure the uniformity of the assessment, a specialized echocardiographer (Prof. Quan) was required to conduct CE in accordance with echocardiographic guidelines [16, 17]. Two independent, highly qualified echocardiographic observers who were not involved in the study were invited to assess the LV thrombus while blinded to the treatment status. Digitally archived contrast-enhanced echocardiograms were quantified in a core lab, blinded to patient characteristics.

The primary endpoint of this study was the incidence rate of thrombus resolution at 12 weeks confirmed by CE. The secondary efficacy outcomes included the categories of thrombus outcomes at follow-ups (the resolved or reduced rate at 12 weeks, the unchanged or enlarged rate at 12 weeks, the resolution rate at 6 weeks, the resolved or reduced rate at 6 weeks, the unchanged or enlarged rate at 6 weeks). The main safety outcome was the composite of the International Society on Thrombosis and Haemostasis criteria (ISTH) major bleeding and clinically relevant non-major bleeding. We also recorded major cardiovascular events defined as a composite of embolism events and all-cause death. Adverse events were collected as well according to the Food and Drug Administration regulation. Patients were scheduled for follow-up visits at this center at 6 weeks and 12 weeks and reported details on all current medications at each visit such as drug name, dosage, frequency, and duration. In addition, investigators examined prescription data from electronic medical records to assess patient adherence. 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 according to the 2018 European Heart Rhythm Association Practical Guide on the use of NOACs. An additional clinic or telephone follow-up visit was conducted at 6 months to collect events and anticoagulant use.

Statistics analysis

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 [18]. 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 [19]. To investigate any significant interactions in more detail, we then ran corresponding pairwise comparisons using the *emmeans* function in R [20]. Additionally, the multi-rater Fleiss kappa coefficient (κ) statistics were used to evaluate the coefficient of agreement among echo-raters [21]. Poor (κ < 0.20), fair (0.20–0.40), moderate (0.40–0.60), good (0.60–0.80), and excellent (0.80–1.00) agreement levels were assessed. 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).

Results

Patient population and baseline characteristics

Between 1 October 2020 to 30 June 2022, 75 patients who received at least one dose of rivaroxaban were included in

the safety population (Fig. 1). Nine patients were excluded and the reasons were as follows: 5 patients withdrew consent, 1 patient had heart transplantation, 1 patient had suspected rivaroxaban allergy, and 2 patients were not suitable to use rivaroxaban. Before the first follow-up, 2 patients died, hence, a total of 64 patients with CE results at follow-up visits were analyzed for efficacy outcomes. At 6 weeks, 62 patients had complete follow-up data while 2 out of 64 patients were unable to come to the hospital during the epidemic period.

In the R-DISSOLVE study, patients with LV thrombus were approximately 50 years old and 64 (85.3%) patients were male. The main underlying etiology was ischemic cardiomyopathy (ICM) (n = 30, 40.0%), while 38.7% (n = 29) and 21.3% (n = 16) of the rest had a diagnosis of DCM or other cardiovascular diseases. A total of 14 (18.7%) patients were given oral anticoagulants with a median duration of 5.5 d before entering into the trial, while 9 (12.0%) patients had received rivaroxaban with a range of duration from 1 to 14 d. Baseline data were shown in Table 1 and Table S2.

According to CE measurements at baseline, patients had a left ventricular ejection fraction (LVEF) with a median level of 24 (20, 31) %. In terms of the thrombus outcome, there was excellent overall agreement among echocardiographers (Fleiss' $\kappa = 0.836$, $p < 0.001$). As for rivaroxaban treatment, 42 (56.0%) patients were given 20 mg OD, 31 (41.3%) patients were administered 15 mg OD, and 2 (2.7%) patients were with 10 mg OD (1 was on dual antiplatelet agents and 1 had nasal bleeding with clopidogrel). Ten patients (13.3%) were given antiplatelet therapy at the same time. During the period of follow-up visits, 7 patients adjusted the dose because of decreased renal function or clinically relevant non-major bleeding events.

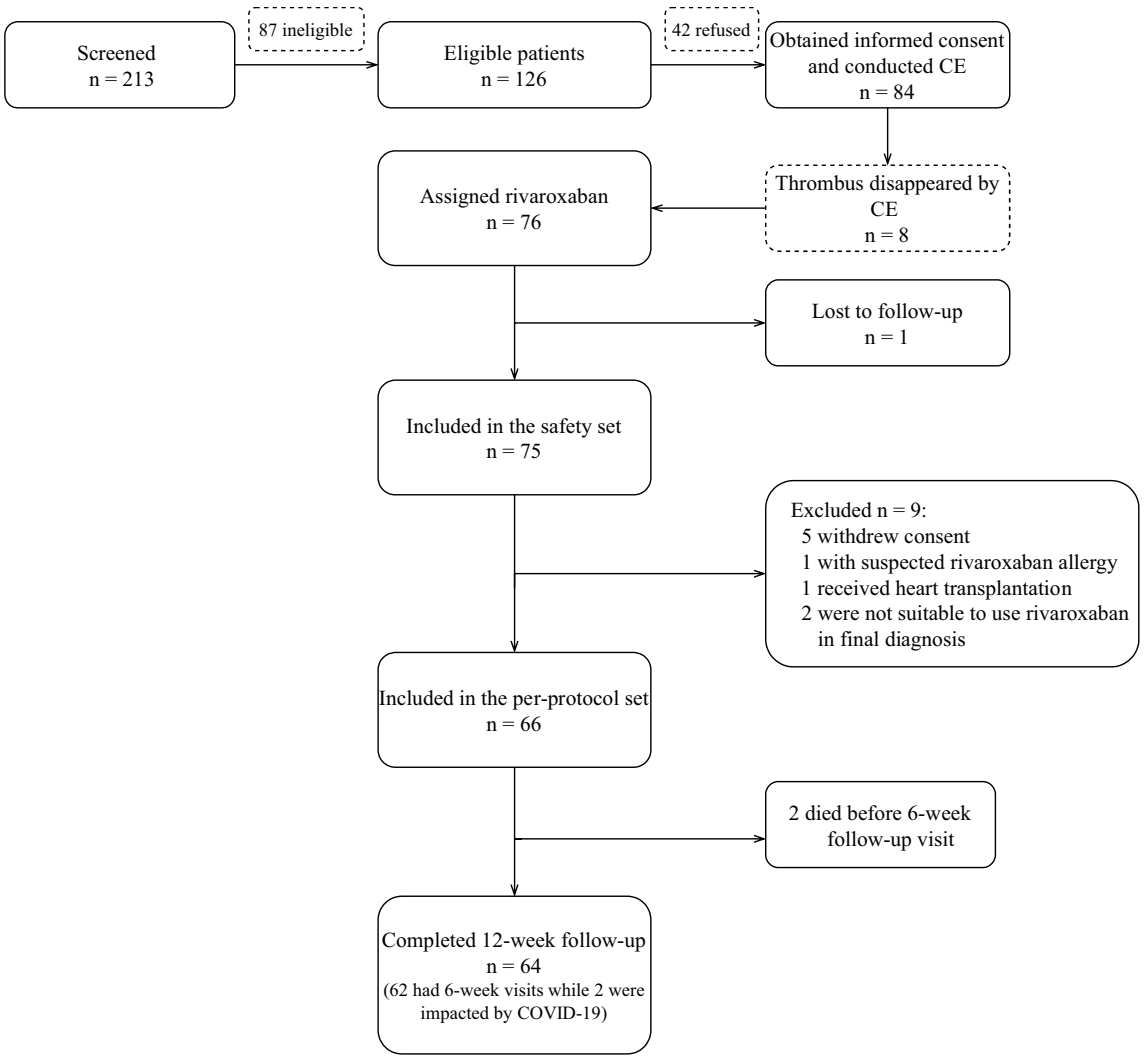

Fig. 1 Study patient flow diagram. *CE* contrast-enhanced echocardiography, *COVID-19* coronavirus disease 2019

Table 1 Baseline characteristics of patients with LV thrombus

	N = 75
Demographic	
Age, y	50.3 ± 14.3
Male, n (%)	64 (85.3)
BMI, kg/m^2	24.5 ± 3.1
Presenting diagnosis, n (%)	
ICM	30 (40.0)
DCM	29 (38.7)
Others[†]	16 (21.3)
Treatment, n (%)	
Rivaroxaban	
20 mg OD	42 (56.0)
15 mg OD[§]	33 (44.0)
Antiplatelet therapy	10 (13.3)
Creatinine clearance, n (%)	
< 50 mL/min	10 (13.3)
≥ 50 mL/min	65 (86.7)
Previous therapy	
Oral anticoagulation therapy, n (%)	14 (18.7)
Duration, d	5.5 (3, 11)
CE measurements	
Left atrial diameter, mm	45.1 ± 5.6
Left ventricular end-diastolic diameter, mm	65.4 ± 8.5
LVEF (Simpson's methods), %	24 (20, 31)
Ventricular aneurysm, n (%)	22 (29.3)
Protuberant or mobile thrombi, n (%)	32 (42.7)
Number of thrombi, n (%)	
1	48 (64.0)
≥ 2	27 (36.0)
Size of thrombi, mm [Median (IQR)]	
Diameter	24.0 (17.5, 35.5)
Thickness	10.0 (7.0, 13.5)

Variables are presented as n (%), mean ± SD, and median (IQR)

LV left ventricular, *SD* standard deviation, *IQR* interquartile range, *BMI* body mass index, *ICM* ischemic cardiomyopathy, *DCM* dilated cardiomyopathy, *CE* contrast-enhanced echocardiography, *LVEF* left ventricular ejection fraction

[†]Other diagnoses included hypertensive heart disease (n = 5), inflammatory cardiomyopathy (n = 2), heart failure (n = 2), restrictive cardiomyopathy (n = 2), hypertrophic cardiomyopathy (n = 1, as follows), alcoholic cardiomyopathy, noncompaction of ventricular myocardium, chemotherapy-induced cardiomyopathy, and valvular heart disease

[§]A total of 31 (41.3%) patients were administered 15 mg OD, while 2 (2.7%) patients were with 10 mg OD

Efficacy outcome

The primary efficacy outcome of thrombus resolution at 12 weeks was 78.1% (50/64, 95% CI 66.0–87.5%), whereas the rate of thrombus reduced or resolved was 95.3% (61/64, 95% CI 86.9–99.0) and of thrombus unchanged or enlarged was 4.7% (3/64, 95% CI 1.0–13.1). At 6 weeks, 66.1% (41/62, 95% CI 53.0–77.7%) of the patients had complete thrombus resolution, 95.2% (59/62, 95% CI 86.5–99.0) had a reduced or resolved thrombus, and 4.8% (3/62, 95% CI 1.0–13.5) had unchanged thrombus (Table 2). The median time of thrombus resolved was 45 (42–51) d and the time of unresolved was 84 (82–87) d. Figure 2 showed the images of LV thrombus at baseline and follow-up visits.

Safety outcome

Bleeding

In the safety population, the main safety outcome occurred in 4 (5.3%) patients at 12 weeks (Table 3). Two (2.7%) patients had major bleeding: one patient occurred hemorrhage in the right eye and the other had pulmonary bleeding. Clinically relevant non-major bleeding events occurred in 2 (2.7%) patients—one patient had severe nasal bleeding while the other had hemoptysis and his fecal occult blood test (FOBT) was positive. Moreover, there were 19 (25.3%) patients with minor bleeding—1 patient had nasal bleeding, 1 patient had subcutaneous petechiae, and 17 patients with positive FOBT. All 17 patients had performed a second FOBT in 3–5 days which showed a negative result. No major bleeding or clinically relevant non-major bleeding events were recorded by either patients with or without thrombus resolution during the 12-week to 6-month period.

Major cardiovascular events and adverse events

The rate of major cardiovascular events was 6.7% (5/75 the safety set population) during the 12-week follow-up visit, of which 3 (4.0%) patients experienced a stroke/embolism event in the hospital − 2 (2.7%) patients had suspicious TIA and 1 (1.3%) patient occurred pulmonary embolism (Table 3). Two (2.7%) deaths for unknown reasons were reported after discharge.

There were 9 (12.0%) patients with adverse events. One patient who experienced skin eruption (3 h after administering rivaroxaban) discontinued rivaroxaban since its first use. The rest 8 (10.7%) patients reported rehospitalization during a 12-week follow-up (4 patients were hospitalized for acute heart failure, 2 patients were for palpitation, 1 patient was for prolonged hospitalization, and 1 patient was for planned heart transplantation). Between the 12-week and the 6-month follow-ups, neither significant cardiovascular events nor adverse events were documented by telephone interviews or clinic visits, regardless of the thrombus outcome.

Table 2 LV thrombus resolution confirmed by CE at 6 weeks and 12 weeks

	Total N	N thrombus resolved	%	95% CI
At 6 weeks				
Complete thrombus resolution at 6 weeks	62	41	66.1	53.0–77.7
Resolved or reduced thrombus at 6 weeks	62	59	95.2	86.5–99.0
Unchanged or enlarged thrombus at 6 weeks	62	3	4.8	1.0–13.5
At 12 weeks				
Complete thrombus resolution at 12 weeks	64	50	78.1	66.0–87.5
Resolved or reduced thrombus at 12 weeks	64	61	95.3	86.9–99.0
Unchanged or enlarged thrombus at 12 weeks	64	3	4.7	1.0–13.1

LV left ventricular, *CE* contrast-enhanced echocardiography

Further analysis

Factors related to thrombus resolution at baseline

Eleven variables were statistically significant in the univariable analysis (Table S3), including the history of chronic kidney disease, rivaroxaban dosages, antiplatelet therapy, LVEF, thrombus diameter, ventricular aneurysms, regional wall motion abnormality, hemoglobin, creatinine, alanine transaminase, and total bilirubin measurements.

After adjusting the significant variables in the univariable analysis and additional potential factors (e.g., presenting diagnosis, baseline D-dimer levels), seven variables remained in the multivariable Cox model (Table 4). They were listed as follows: a history of chronic kidney disease, LVEF, thrombus diameter, ventricular aneurysm, anti-Xa (C-peak) level, platelet count, and creatinine clearance. As stated in the univariable analysis, lower LVEF and smaller thrombi were linked to a greater likelihood of thrombus resolution, whereas the adjusted model showed no significant differences in the ventricular aneurysm and history of chronic kidney disease. Likewise, as evidenced by the HRs of anti-Xa (C-peak) level and platelet count being close to 1.00, there was no association between the two factors and thrombus resolution. In addition, we spilt variables of interest into subgroups based on the LV thrombus resolution of 65.8% in patients with NOACs [8]. Details were shown in the Supplementary material, Fig. S1.

Key laboratory parameters during follow-ups

When testing the concentration of anti-Xa on the fourth day of rivaroxaban treatment, the mean C-trough level was 44 (30, 54) ng/mL while the C-peak level was 185 (115, 260) ng/mL (in comparison to the expected concentrations of rivaroxaban in patients treated for stroke prevention: C-trough 44 (12, 127) ng/mL, C-peak 249 (184, 243) ng/mL [22]). Figure 3 showed the levels of coagulation parameters (anti-Xa, Fibrin monomer (FM), D-dimer, and fibrin degradation products (FDP)) with corresponding standard errors across time for each group. In measuring the level of anti-Xa of each patient at 7 timepoints, the main effects of time in anti-Xa remained significant ($P = 0.0021$) while no significant difference was found between the thrombus resolution and unresolution group. Additionally, both the peak and trough concentrations of anti-Xa met the expected reference level at either 6 weeks or 12 weeks. The time effects in D-dimer at baseline-to-6week and baseline-to-12week remained significant (estimated effect (β) = − 1.27, standard error = 0.25, $P < 0.0001$ and $\beta = -1.31$, standard error = 0.25, $P < 0.0001$; respectively). The main effects of time in FDP and FM also remained significant ($P < 0.0001$, $P < 0.0001$; respectively). D-dimer levels between the thrombus resolution and unresolution groups differed significantly at 6 weeks ($P = 0.03$) but not at baseline ($P = 0.89$) or 12 weeks ($P = 0.06$). Furthermore, there were no remarkable differences in the FDP levels between the two groups at baseline, 6 weeks, and 12 weeks.

Discussion

This prospective trial was the first one that assessed the treatment of LV thrombus by CE and explored the effectiveness and safety of rivaroxaban in patients with LV thrombus for 12 weeks of anticoagulation therapy. R-DISSOLVE showed that the complete thrombus resolution was 78.1% and the resolved or reduced thrombus was in 95.3% of patients within 12 weeks, combined with a 2.7% rate of major bleeding, indicating that rivaroxaban could be a potential option for the treatment of LV thrombus irrespective of underlying etiologies.

R-DISSOLVE demonstrated a high rate of thrombus resolution, particularly the rate of resolution or reduction at both 6 weeks and 12 weeks. The findings may be attributed to the careful supervision under strict and standard management across the entire trial, indicating great compliance and adherence to treatment. And our inclusion criteria determined that

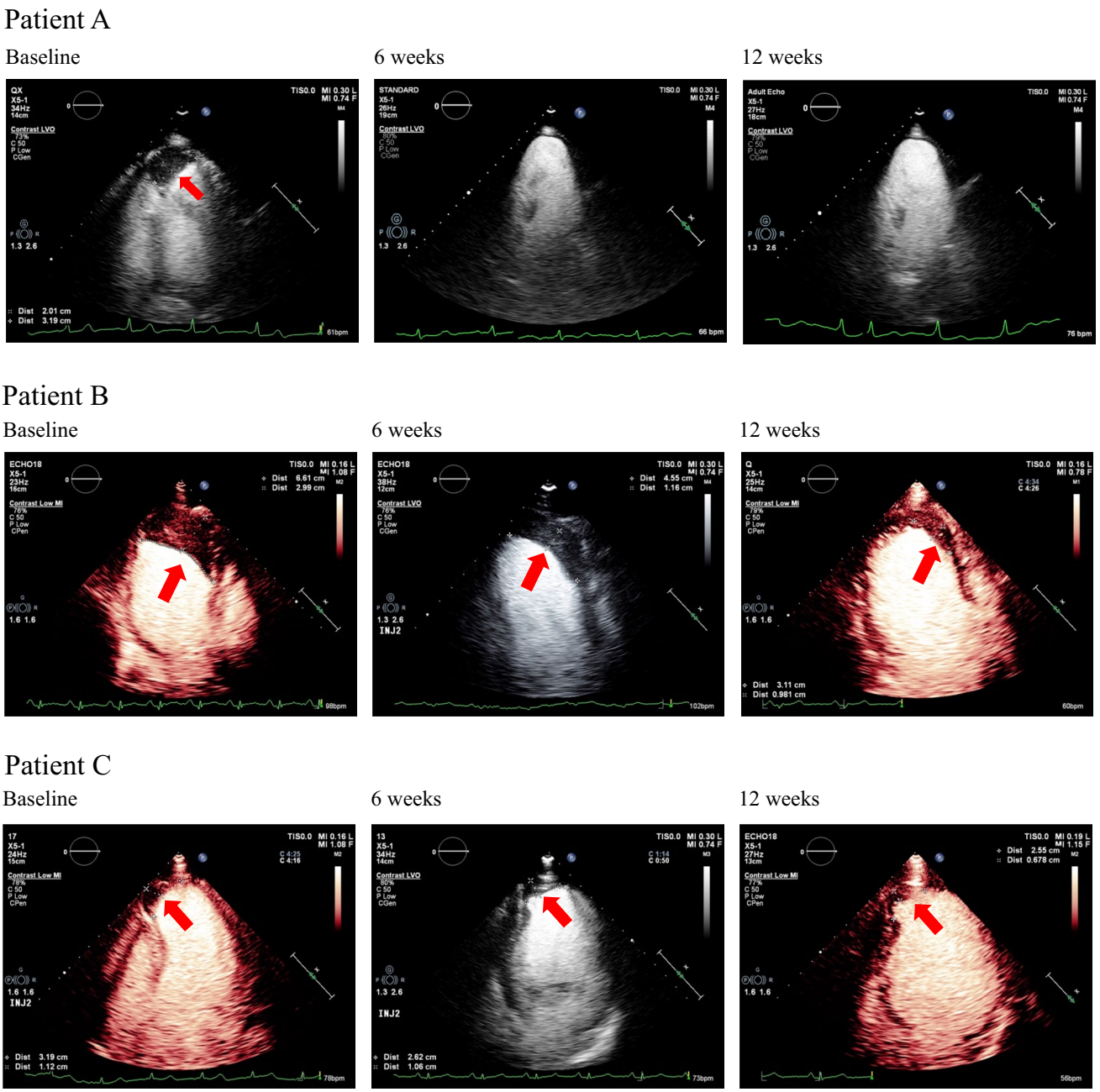

Fig. 2 Patient examples of CE images. Patient A had the thrombus resolution at 6 weeks and 12 weeks, compared to LV thrombus (red arrows) at baseline. Patient B had the thrombus reduced at 6 weeks and 12 weeks, compared to LV thrombus (red arrows) at baseline. Patient C had the thrombus unchanged at 6 weeks and 12 weeks, compared to LV thrombus (red arrows) at baseline. *LV* left ventricular, *CE* contrast-enhanced echocardiography

patients enrolled in the trial had fairly fresh thrombi without long-term anticoagulation, which could result in a higher likelihood of resolution compared to those calcified or organized thrombi. The CE verification of the thrombus resolution not only at baseline but also at each following clinic visit was another notable feature of this trial. As TTE has a low specificity or sensitivity, it is advisable to administer CE or CMR to increase sensitivity in patients in whom there is a concern for LV thrombus [13]. CE as a relatively inexpensive tool, estimated the size of the LV thrombus accurately, showing a non-developing structure with a clear boundary, which is of great value in finding the small thrombus. The concept that CE impacted cardiac diagnosis was validated by Kurt et al., who enrolled 632 consecutive patients who received CE. They discovered that the number of suspected thrombi declined from 35 patients to just 1 patient following

Table 3 Safety outcomes at 12-week follow-up [N = 75]

	N	%
Main safety outcome	4	5.3
Major bleeding	2	2.7
Clinically relevant non-major bleeding	2	2.7
Major cardiovascular events	5	6.7
Stroke/embolism	3	4.0
All-cause death	2	2.7
Adverse events	8	10.7
Allergy causing rivaroxaban discontinuation	1	1.3
Rehospitalization[†]	7	9.3

[†]Hospitalization due to congestive heart failure and arrhythmia

Table 4 Adjusted variables related to thrombus resolution by multivariable Cox regression

	HR (95%CI)	P value
History of chronic kidney diseases	2.61 (0.90–7.55)	0.077
Anti-Xa (C-peak)[†]	1.00 (0.99–1.00)	0.012
Creatinine clearance	0.99 (0.97–1.00)	0.011
Platelet count	0.99 (0.99–1.00)	0.022
Diameter of thrombi	0.97 (0.95–1.00)	0.017
LVEF (Simpson's methods)	0.95 (0.91–0.99)	0.006
Ventricular aneurysm	0.54 (0.25–1.16)	0.115

HR hazard ratio, *CI* confidence interval, *LVEF* left ventricular ejection fraction

[†]The level of anti-Xa is measured on the fourth day of rivaroxaban treatment. The time of C-peak refers to the time of 2–4 h after medication

contrast use. In a cohort study, LV thrombus was confirmed in 20 (61%) of 33 patients with suspected thrombus, and in 14 out of 123 patients for whom TTE results were deemed inconclusive for LV thrombus identification. Moreover, the researchers declared that CE could not only improve the detection of LV thrombus but alter antithrombotic therapy in 68% of patients with confirmed LV thrombus. The utilization of CE in the R-DISSOLVE study led to a higher diagnostic yield for detecting LV thrombus with more accuracy and assisted clinics in patient management decisions such as the duration of anticoagulation.

To date, no studies have reported anti-Xa activity in the treatment of LV thrombus and we conducted the measurements for the first time in the trial. Measurement of rivaroxaban anticoagulant activity was desirable in the assessment of anticoagulant effect as well as in special clinical settings such as bleeding or suspected overdose. Guidelines recommended that anti-Xa assays can provide a quantitative measure of rivaroxaban concentration [22, 23]. In terms of rivaroxaban, anti-Xa activity is linear over a wide range of drug levels. The concentration of rivaroxaban is determined by detecting anti-Xa activity. The dose-response curve of rivaroxaban in the current trial was satisfactory at different time points and the main effects of time in anti-Xa remained significant whereas no significant difference was observed between the thrombus resolution and unresolved group. Furthermore, according to guidelines for laboratory assessment of direct oral anticoagulants, rivaroxaban reached the peak and trough plasma levels that were expected [22]. A systematic review suggested that anti-Xa should be regarded as the best alternative to gauge rivaroxaban's anticoagulant activity and determine if it is currently clinically relevant below, within, or above levels of on-therapy medication [24].

Given the inherent disadvantages of warfarin, rivaroxaban provides various practical benefits as well as comparable anticoagulation in the treatment of multiple cardiovascular diseases. Patients with venous thromboembolism were recommended to take NOACs rather than VKAs, according to the 2020 American Society of Hematology (ASH) guidelines [25]. In the X-TRA which was a prospective, single-arm study to explore NOAC rivaroxaban for the resolution of left atrial thrombus in patients with non-valvular atrial fibrillation, the complete thrombus resolution rate was 41.5% with rivaroxaban anticoagulation for 6–8 weeks, while the rate of thrombus resolved or reduced was 60.4% [15], and the use of rivaroxaban for LV thrombus also achieved a greater result in the R-DISSOLVE study. In terms of LV thrombus resolution, numerous meta-analyses or retrospective studies were conducted, otherwise yielded inconsistent findings. In most of the studies, no statistical difference was observed in the comparison of NOACs vs. warfarin [11, 26–30]. Burmeister et al. collected 11 retrospective studies with 2153 patients (33% with NOACs and 63% with warfarin) and concluded that LV thrombus resolution was significantly higher in NOACs compared with VKAs [31]. In a small RCT comparing the use of apixaban and warfarin, it found that 16/17 patients receiving apixaban treatment experienced LV thrombus resolution within a 3-month follow-up, compared to 14/15 patients receiving warfarin [32], of which, the rate of resolution by apixaban was higher than that by rivaroxaban in the finding of R-DISSOLVE. Another prospective trial reported that 39 patients with LV thrombus were randomly assigned to rivaroxaban while 40 patients were with warfarin. At 1 month, the thrombus resolution rate in the rivaroxaban group (71.8%) was considerably greater than that in the warfarin group (47.5%), and no embolic events occurred in the rivaroxaban group. Due to the relatively small patient population and absence of a highly accurate assessment of LV thrombus, the sensitivity and externality of this randomized trial were limited even though it provided good evidence for the treatment of LV thrombus [7].

As rivaroxaban is a direct inhibitor of factor Xa, it possesses the possibility to cause or aggravate acute severe

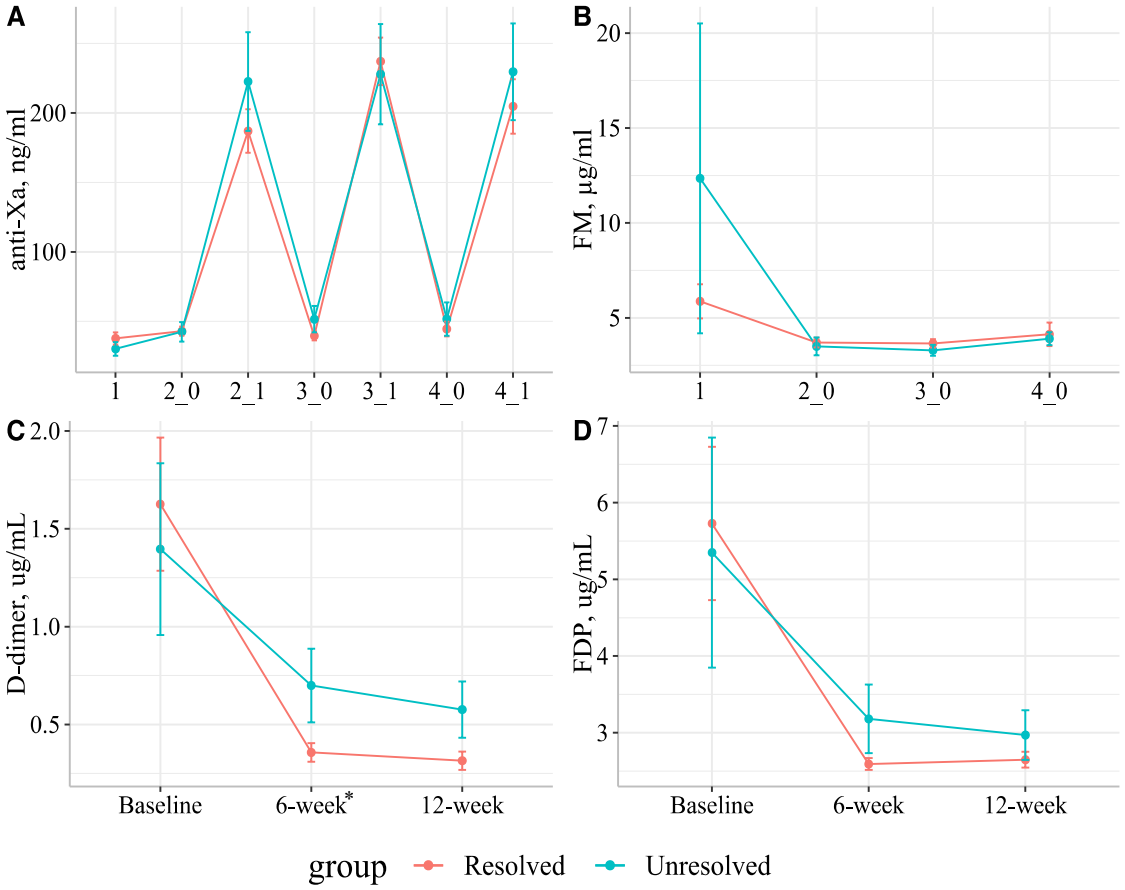

Fig. 3 Levels of biomarkers (y-axis) across time points (x-axis) between the thrombus resolved group (orange) and the thrombus unresolved group (green). *The level of D-dimer at 6 weeks shows a significant difference in the two groups. Error bars indicate standard error. In the measurements of anti-Xa (**A**) and FM (**B**), the timepoint of "1" refers to the blank baseline level, "2" refers to the level testing on the fourth day of rivaroxaban treatment, "3" refers to the level testing at 6 weeks, "4" refers to the level testing at 12 weeks, "_0" refers to the time before medication, and "_1" refers to 2–4 h after medication. (**C**) and (**D**) show the trend of D-dimer levels and FDP levels at baseline, 6 weeks, and 12 weeks. *FM* Fibrin monomer, *FDP* fibrin degradation products

bleeding, which is problematic to manage given that there is no specific reversal agent. Hence, it is essential to pay close attention to the incidence of bleeding episodes. According to an updated meta-analysis comprising 21 studies with 3057 patients (824 NOACs and 2233 VKAs), no significant difference was noted in safety in the treatment of LV thrombus between NOACs and VKAs treatment, while analyzing only four prospective trials, NOAC use was associated with a 71% lower risk of bleeding than VKA use [13]. Chen et al. conducted a meta-analysis of thirteen retrospective studies and summarized that the rate of clinically relevant bleeding events was lower in the group that took NOACs than warfarin [33]. In a retrospective cohort study, NOACs use was also associated with a lower risk of bleeding, whereas 37 (27.6%) bleeding that required hospitalization in the NOACs group occurred [28]. According to the R-DISSOLVE outcomes, 4 (5.3%) patients reported ISTH major bleeding and clinically relevant non-major bleeding events, indicating a relatively low rate of bleeding.

In R-DISSOLVE, patients with DCM showed a higher resolution than those with ICM, which had a slow blood flow in an enlarged LV and impaired endothelial function. Given the pathological conditions (e.g., heart development, pump failure, blood stasis, and hypercoagulability) that were associated with activation of the anticoagulation and fibrinolysis system, patients who were hospitalized with reduced LVEF were more likely to develop a new onset LV thrombus, which was easier to resolve than those calcified ones. Hofer et al. reported that 51.9% of patients with thrombus resolution had LVEF < 50% [34]. According to our findings, the median LVEF was 24 and 65.6% of patients had an LVEF of less than 30%. The subgroup results further supported that patients with reduced LVEF experienced a greater thrombus resolution after adhering to standardized anticoagulation, showing that patients with LVEF levels of

less than 24% performed better resolution than those with an LVEF of more than 24%.

The main limitation of the study is the absence of a control group, thus we are unable to compare rivaroxaban with warfarin head-to-head. Second, due to the study's open-label design, selection bias could not be avoided. Patients were more likely to participate in the study if they preferred to use rivaroxaban without monitoring frequently. However, the echocardiographic observers were blinded to the treatment status since patient expectations for the course of treatment could influence how it turned out. Additionally, due to the impact of the coronavirus disease pandemic, the sample was quite small and a comparatively high proportion of patients failed to complete their follow-up visits.

Overall, rivaroxaban is considered to be a reasonable option in patients with LV thrombus, according to this study and currently available data. Large RCTs are required and two prospective trials compared rivaroxaban to warfarin (rivaroxaban versus warfarin: NCT03764241, NCT04970576) are in progress, which will provide definitive evidence on this topic.

Conclusion

R-DISSOLVE provided valuable insights into the use of the CE and rivaroxaban in the assessment and treatment of LV thrombus, presenting a finding that patients receiving rivaroxaban experienced a relatively high thrombus resolution after 6 to 12 weeks of anticoagulation therapy, along with a low rate of major bleeding or major cardiovascular event. Large randomized controlled studies are required to generalize our findings.

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Data availability The data used to support the findings of this study are available from the corresponding author upon request.

Declarations

Conflict of interest The authors have indicated that they have no other conflict of interest regarding the content of this article.

Ethical approval This study was approved by the Ethics Committee of Fuwai Hospital (Approval No. 2020-1380).

Consent to participate Patients signed a written informed consent and were required to adhere to a strict study protocol.

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