Rivaroxaban versus Vitamin K Antagonists (warfarin) based on the triple therapy for left ventricular thrombus after ST-Elevation myocardial infarction

Zhongfan Zhang1 · Daoyuan Si1 · Qian Zhang1 · Ming Qu2 · Miao Yu1 · Zhenya Jiang1 · Delin Li1 · Ping Yang1 · Wenqi Zhang1

Received: 5 June 2021 / Accepted: 13 August 2021 / Published online: 22 August 2021
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Abstract

Background: Left ventricular thrombus (LVT) can complicate ST-Elevation myocardial infarction (STEMI) and is associated with poor outcomes. Conventional triple anticoagulation [Vitamin K Antagonists (VKA) plus dual-antiplatelet therapy (DAPT)] is the first-line therapy for LVT after STEMI. In patients with LVT following STEMI, contemporary data of triple therapy with rivaroxaban are lacking. Methods: We conducted a retrospective cohort study involving 1335 STEMI patients who underwent primary percutaneous coronary intervention (PCI). Among patients who developed LVT after STEMI, we observed differences in efficacy between rivaroxaban plus DAPT therapy and VKA plus DAPT. The time of LVT resolution was also evaluated, as well as net clinical adverse events, and rates of bleeding events. Results: In 1335 patients with STEMI, a total of 77 (5.7%) developed LVT over the follow-up period (median 25.0 months). Of the patients diagnosed with LVT, 31 patients were started on triple therapy with VKA, 33 patients on triple therapy with rivaroxaban. There was a consistent similarity in LVT resolution with rivaroxaban application compared to VKA application during the follow-up period [HR (log-rank test) 1.57 (95% CI 0.89–2.77), \( p = 0.096 \); Adjusted HR 1.70 (95% CI 0.90–3.22), \( p = 0.104 \)]. Triple therapy with rivaroxaban showed quicker resolution than with VKA (6 months: \( p = 0.049 \); 12 months: \( p = 0.044 \); 18 months: \( p = 0.045 \)). Similar risks of ISTH bleeding were not significantly different between the 2 groups [VKA 9.7% vs Rivaroxaban 6.1%, Adjusted HR 0.48 (95% CI 0.73–3.20); \( p = 0.444 \)]. Fewer net adverse clinical events (NACE) were observed in the rivaroxaban group [VKA 58.1% vs Rivaroxaban 24.2%; HR (log-rank test) 0.31 (95% CI 0.14–0.68), \( p = 0.003 \); Adjusted HR 0.23 (95% CI 0.09–0.57), \( p = 0.001 \)]. Conclusion: In the observational study, triple therapy with rivaroxaban has similar and quicker LVT resolution in patients with LVT after STEMI, compared with triple therapy with VKA, and perhaps was associated with a better clinical benefit. Larger sample sizes and randomized controlled trials are needed to confirm this observation.

Keywords

Left ventricular thrombus · Triple therapy · ST-Elevation myocardial infarction · Rivaroxaban

Abbreviations

LVT Left ventricular thrombus
STEMI ST-Elevation myocardial infarction
PCI Percutaneous coronary intervention
VKA Vitamin K Antagonists
TTE Transthoracic echocardiography
WBC White blood cell count
MPV Mean platelet volume
LVEF Left ventricular ejection fraction
LVEDD Left ventricular end-diastolic dimension
LV aneurysm Left ventricular aneurysm
TIMI Thrombolysis in myocardial infarction

Zhongfan Zhang and Daoyuan Si both are the 1st authors.

* Wenqi Zhang
wenqi@jlu.edu.cn

1 Department of Cardiology, China-Japan Union Hospital of Jilin University, Jilin Provincial Molecular Biology Research Center for Precision Medicine of Major Cardiovascular Disease, Xiantai Street NO.126, Changchun, China

2 Department of Gastroenterology, Endoscopy Center, China-Japan Union Hospital of Jilin University, Changchun, Jilin, China
**Introduction**

Although the prevalence of left ventricular thrombus (LVT) after acute myocardial infarction (AMI) has decreased in modern times due to the generalization and progress of reperfusion therapy used in the early stages of AMI, it continues to complicate the condition of AMI and is associated with a higher incidence of embolism, death, and major adverse cardiovascular events [1–7]. The current view is that LVT mostly formed after ST-Elevation myocardial infarction (STEMI). The first-line therapy recommends conventional triple anticoagulation [Vitamin K Antagonists (VKA) plus dual-antiplatelet therapy (DAPT)] for LVT after STEMI [8–10]. However, the need for dietary restrictions, frequent monitoring, narrow treatment scope, and multiple drug interactions associated with VKA has contributed to an increase in the off-label use of direct oral anticoagulants (DOACs) worldwide. In previous studies on LVT [11–14], DOACs were usually considered as a whole and directly compared with VKA, which may be inappropriate due to the different anticoagulant mechanisms and pathways of DOACs and the different diseases occurring LVT. As one of the most widely used DOACs, the application data of triple therapy with rivaroxaban in the setting of LVT after STEMI are lacking.

The major purposes of this study were to observe differences in efficacy between rivaroxaban plus DAPT therapy and VKA plus DAPT in patients who developed LVT after STEMI. The time of LVT resolution was also evaluated, as well as net clinical adverse events, and rates of bleeding events. Triple therapy with VKA was compared as standard treatment.

**Methods**

**Study population and design**

In this single-center retrospective study, all patients were identified from STEMI patients who underwent primary percutaneous coronary intervention (PCI) in the China-Japan Union Hospital of Jilin University from January 2016 to January 2019. This study flowchart is shown in Fig. 1. STEMI is defined as persistent chest discomfort or other symptoms suggestive of ischemia and ST-segment elevation in at least two contiguous [10]. The exclusion criteria for LVT patients are that (1) using other antithrombotic therapeutic regimens in patients with LVT; (2) hemorrhage or stroke occurred during hospitalization prior to baseline transthoracic echocardiography (TTE); and (3) the quality of TTE was suboptimal, or it was not performed after admission.

**Baseline and data collect**

Baseline characteristics in this study should be clinically and biologically plausible and have been confirmed to be associated with intracardiac thrombosis in previous studies. According to the aforementioned principle, baseline variables are carefully screened, which include age, sex,
hypertension, diabetes mellitus, smoking, white blood cell count (WBC), platelets, mean platelet volume (MPV), fibrinogen, left ventricular ejection fraction (LVEF), left ventricular end-diastolic dimension (LVEDD), left ventricular aneurysm (LV aneurysm), symptom to balloon time, multi-vessel disease, post-PCI TIMI flow grade. All baseline characteristics were collected through the hospital’s medical record system.

**Transthoracic echocardiography**

All patients underwent screening echocardiography on admission and at follow-up. LVT observed by TTE was defined as (1) a high-density echo mass in the left ventricular lumen, which is different from that of the myocardium; (2) Obvious contour towards the cavity; (3) Could be separated from the endocardial layer; (4) exist throughout the cardiac cycle [3]. All TTE images were interpreted by two experienced echocardiographers from the cardiac center. A predesignated third echocardiogram physician was consulted to prevent inconsistencies.

**Antithrombotic therapy**

Triple therapy was defined as DAPT plus oral anticoagulants. DAPT included low-dose aspirin therapy (100 mg/day) and a P2Y12 inhibitor (clopidogrel 75 mg/day). Triple therapy was started when LVT was diagnosed by TTE, and the use of VKA or rivaroxaban was determined by physicians at that time. The dose of rivaroxaban depended on patient-specific factors (i.e., creatinine clearance, bleeding risk, age). According to the ACC/AHA guideline, warfarin dose was titrated to maintain an internationally standardized ratio (INR) goal of 2.0–2.5 [8].

**Endpoints and definitions**

The primary efficacy endpoint was defined as the total resolution of LVT during the follow-up period. The secondary endpoint was a composite of net adverse clinical events (NACE) to assess the net clinical benefit, consisting of all-cause mortality, systemic embolism (SE), re-hospitalization for cardiovascular events, bleeding. SE is defined as abrupt vascular insufficiency with clinical or radiographic evidence. The safe endpoint is bleeding. According to the International Society of Thrombosis and Hemostasis (ISTH) definition [15, 16], all bleeding events are classified as minor, clinically relevant non-major (CRNM), or severe bleeding.

**Statistical analysis**

Normally distributed continuous variables were expressed as the mean±standard deviation (SD), and the t test was used for comparison. Non-normally distributed continuous variables were expressed as the median (quaternary series) [M (Q1–Q3)], and the Mann–Whitney U test is used for comparison. Categorical variables, which are presented as frequencies (percentages), were compared with the Chi-square test or Fisher’s exact test as appropriate.

Time-to-event data are presented as the Kaplan–Meier method, and differences between triple therapy with rivaroxaban and triple therapy with VKA are assessed by the log-rank test. Multivariate Cox regression analyses were used to identify the independent effect of triple therapy by VKA or rivaroxaban on LVT resolution, net adverse clinical events, re-hospitalization for cardiovascular events, bleeding events, all-cause mortality, systemic embolism. Baseline variables that were considered clinically relevant or that associated at univariate analysis (p<0.05) with outcome were entered into multivariate Cox proportional-hazards regression models to adjust analyses, using the method from Thomas Agoritsas [17]. The included variables were carefully chosen, given the number of events available, to ensure parsimony of the final models [18]. Clinically relevant and confounding variables which entered into multivariate Cox proportional-hazards regression models include symptom to balloon time ≥ 12 h, LVEF, post-PCI TIMI flow grade ≤ 2, hypertension, and LV aneurysm. Data analyses were performed using SPSS version 24.0 (IBM Corp, Armonk, NY, USA) and GraphPad Prism 7.00 software (San Diego, California). All p values had a 2-sided significance level of 5%.

**Results**

**Patients**

A total of 77 (5.7%) patients with STEMI were identified to develop LVT. Not surprisingly, of these patients with LVT after STEMI, the majority (91.0%) presented with anterior infarcts (71 patients). The value of fibrinogen is higher in LVT patients (p = 0.002). In terms of echocardiography, LVT patients were significantly lower LVEF than those with no LVT (p<0.001) and tended to have larger LVEDD (p<0.001) (Table 1). More patients with LVT have LV aneurysms (p<0.001). And in the whole cohort study, 30 patients with LVT (39.0%) did not undergo catheter-based revascularization therapy within 12 h of STEMI onset because of late presentation at the hospital, etc. (p<0.001). The post-PCI TIMI flow grade of 6 LVT patients (7.8%) was less than or equal to 2(p = 0.013). Of the patients diagnosed with LVT, 31 patients were started on triple therapy with VKA, among which 7 patients failed to meet the therapeutic target of INR, 33 patients on triple therapy with rivaroxaban, and 13 patients on other therapies due to various reasons. Median duration of triple therapy was 8.5 months.
[interquartile range (IQR) 5.0–17.0 months]. During follow-up, the rates of dropping ASA were 78.8% in the rivaroxaban group and 74.2% in the warfarin group. Within 1 year, the rates of dropping ASA were 69.7% in the rivaroxaban group and 48.4% in the warfarin group. Both triple therapy groups were well matched in terms of baseline characteristics except for Hypertension (\( p = 0.006 \)) and LV aneurysm (\( p = 0.027 \)) (Table 2).

### Thrombus resolution

A reduction of thrombus was observed in 49(76.6%) of 64 patients with triple therapy by VKA or rivaroxaban over the follow-up up period. The time-dependent cumulative total LVT resolution is shown in Fig. 2. 26(78.8%) of 33 patients in the rivaroxaban group and 23(74.2%) of 31 patients in the VKA group had resolution of LVT. There was a consistent similarity in total LVT resolution with rivaroxaban application compared to VKA application [HR (log-rank test) 1.57(95% CI 0.89–2.77), \( p = 0.096 \)].

After multivariate adjustment, triple therapy with rivaroxaban did not present an independent effect on the total LVT resolution, compared with triple therapy with VKA (Adjusted HR 1.70(95% CI 0.90–3.22), \( p = 0.104 \)) (Table 3). When the analysis focused on LVT resolution at different time points during the follow-up period, triple therapy with rivaroxaban showed quicker resolution than with VKA(6 months: \( p = 0.049 \); 12 months: \( p = 0.044 \); 18 months: \( p = 0.045 \)) (Fig. 3).

### Net adverse clinical events

With respect to NACE, rates of NACE were high in all LVT patients (45.4%). NACE occurred in 8(24.2%) of 33 patients in the rivaroxaban group, 18(58.1%) of 31 patients in the VKA group and 9(69.2%) of 13 patients in the other antithrombotic therapies. Cumulative rates of NACE between triple therapy with rivaroxaban and VKA are presented in Fig. 4, and the Significant differences assessed by the log-rank test are shown between the 2 groups [HR (log-rank test) 0.31(95% CI 0.14–0.68), \( p = 0.003 \)].

On multivariable Cox proportional-hazards regression analysis, NACE in the rivaroxaban group, compared with the VKA group, still had a significant reduction (Table 3). Triple therapy with VKA had a higher re-hospitalization rate due to cardiovascular events [VKA 38.7% vs Rivaroxaban 21.2%, Adjusted HR 0.28 (95% CI 0.09–0.83); \( p = 0.022 \)]. Similar risks of ISTH bleeding were recorded in both groups, with no difference between the two groups [VKA 9.7% vs Rivaroxaban 6.1%, Adjusted HR 0.48 (95% CI 0.73–3.20); \( p = 0.444 \)]. These events included gastrointestinal bleeding (\( n = 1 \), VKA group), and gingival bleeding (\( n = 4 \); VKA group, 2; Rivaroxaban group, 2). All bleeding events occurred within the time of triple therapy. No major bleeding

### Table 1 Clinical characteristics in patients with and without left ventricular thrombus

| Characteristics | No LVT \((n = 1258)\) | LVT \((n = 77)\) | \( p \) value |
|-----------------|-----------------------|-----------------|--------------|
| **Baseline characteristics** | | | |
| Male, \( n(\%) \) | 924(73.4) | 59(76.6) | 0.540 |
| Age, years | 62.0(53.0–69.0) | 60.0(53.5–68.5) | 0.594 |
| Hypertension, \( n(\%) \) | 556(44.2) | 26(33.8) | 0.073 |
| Diabetes mellitus, \( n(\%) \) | 236(18.8) | 14(18.2) | 0.900 |
| Current smoker, \( n(\%) \) | 700(55.6) | 41(53.2) | 0.681 |
| **Blood examinations on admission** | | | |
| WBC (\( \times 10^9 \)) | 10.0(8.0–12.0) | 11.0(8.0–13.0) | 0.105 |
| Platelets (\( \times 10^9 \)) | 216.0(181.0–256.0) | 229.0(164.0–266.0) | 0.363 |
| MPV (fl) | 10.0(9.0–10.0) | 10.0(9.0–10.5) | 0.232 |
| Fibrinogen (mg/dl) | 3.0(3.0–4.0) | 4.0(3.0–5.0) | 0.002 |
| **Echocardiography** | | | |
| LVEF, % | 60.0(50.0–65.0) | 41.0(31.0–49.5) | <0.001 |
| LVEDD (mm) | 46.0(42.0–49.0) | 52.0(48.0–58.0) | <0.001 |
| LV aneurysm, \( n(\%) \) | 84(6.7) | 15(19.5) | <0.001 |
| **Procedural characteristics** | | | |
| Symptom to balloon time ≥ 12 h | 291(23.1) | 30(39.0) | <0.001 |
| Multi-vessel disease, \( n(\%) \) | 42(3.9) | 4(5.2) | 0.571 |
| Post-PCI TIMI flow grade ≤ 2, \( n(\%) \) | 29(2.3) | 6(7.8) | 0.013 |

WBC white blood cell count, MPV mean platelet volume, LVEF left ventricular ejection fraction, LVEDD left ventricular end-diastolic dimension, LV aneurysm left ventricular aneurysm, TIMI thrombolysis in myocardial infarction, PCI percutaneous coronary intervention
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1 3 events were seen in the rivaroxaban triple treatment group. It has to be noted that different anticoagulant therapies were not independently associated with SE in this study [VKA 3.0% vs Rivaroxaban 12.9%, Adjusted HR 0.29 (95% CI 0.02–3.13); p = 0.305]. No systemic embolic events occurred in patients within the time of triple therapy with rivaroxaban, with 2 events occurring in patients on VKA. When not in the triple therapy period, 1 event occurred in the rivaroxaban group and 2 events occurred in the VKA group.

### Discussion

To our knowledge, this was the first comparative study assessing the potential role of triple therapy with rivaroxaban on the influence of LVT among patients with STEMI who underwent PCI. The major findings of this observational study are: (1) the prevalence of LVT in STEMI patients

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Table 2  Clinical characteristics in patients with LVT who received triple anticoagulation (Rivaroxaban/Warfarin)

| Characteristics                        | Warfarin (n = 31) | Rivaroxaban (n = 33) | p value |
|----------------------------------------|------------------|----------------------|---------|
| **Baseline characteristics**           |                  |                      |         |
| Male, n(%)                             | 23(74.2)         | 24(72.7)             | 0.894   |
| Age, years                             | 61.3±9.0         | 60.3±14.7            | 0.730   |
| Hypertension, n(%)                     | 11(33.5)         | 23(69.7)             | 0.006   |
| Diabetes mellitus, n(%)                | 5(16.1)          | 10(30.3)             | 0.181   |
| Current smoker, n(%)                   | 17(54.8)         | 11(33.3)             | 0.083   |
| Atrial fibrillation, n(%)              | 0(0)             | 0(0)                 |         |
| **Blood examinations on admission**    |                  |                      |         |
| WBC (×10^9)                            | 11.0(8.0–13.0)   | 11.4(8.4–14.0)       | 0.914   |
| Platelets (×10^9)                      | 229.0(154.0–304.0) | 258.0(193.5–307.5) | 0.405   |
| MPV (fl)                               | 10(9.0–11.0)     | 9.6(9.0–10.7)        | 0.416   |
| Fibrinogen (mg/dl)                     | 4.0(3.0–6.0)     | 4.0(3.0–4.0)         | 0.213   |
| Creatinine clearance<sup>a</sup>, mL/min |                  |                      |         |
| ≤15                                    | 0(0)             | 0(0)                 |         |
| 15–29                                  | 0(0)             | 0(0)                 |         |
| 30–59                                  | 1(3.2)           | 1(3.0)               |         |
| 60–89                                  | 9(29.0)          | 8(24.2)              |         |
| 90–119                                 | 11(35.5)         | 11(33.3)             |         |
| ≥120                                   | 10(32.3)         | 13(39.4)             |         |
| **Echocardiography**                   |                  |                      |         |
| LVEF, %                                | 41.4±10.8        | 42.9±13.1            | 0.614   |
| LVEDD (mm)                             | 52.5±6.5         | 51.1±7.4             | 0.437   |
| LV aneurysm, n(%)                      | 11(35.5)         | 4(12.1)              | 0.027   |
| **Procedural characteristics**         |                  |                      |         |
| Symptom to balloon time ≥ 12 h         | 12(38.7)         | 15(45.5)             | 0.585   |
| Multivessel disease, n(%)              | 3(9.7)           | 1(3.0)               | 0.272   |
| Post-PCI TIMI flow grade ≤ 2, n(%)     | 2(6.5)           | 3(9.1)               | 0.694   |

Abbreviations as in Table 1

<sup>a</sup>Creatinine clearance was estimated with the Cockcroft-Gault formula
underwent PCI at our center was 5.7%; (2) Low LVEF, large LVEDD, LV aneurysm, high fibrinogen, delayed revascularization, and the poor blood flow after revascularization are relevant factors for LVT; (3) there were similar and quicker resolutions of LVT in the triple therapy with rivaroxaban compared to patients treated with VKA; (4) the incidence of bleeding was similar in both triple therapy; (5) triple therapy with rivaroxaban had less net adverse clinical events (NACE) during the follow-up period, compared with VKA group.

A composite of net adverse clinical events (NACE) consisting of all-cause mortality, SE, re-hospitalization for cardiovascular events, bleeding. HR hazard ratio, CI confidence interval
anticoagulant mechanisms and pathways of DOACs and the different diseases occurring LVT. To the best of our knowledge, there are no published studies regarding triple therapy with single DOACs versus VKA in patients with LVT following STEMI. As one of the most widely used DOACs, the application data of rivaroxaban for LVT after STEMI are limited and warrant continued investigation. Meanwhile, several landmark trials [19, 20] have shown rivaroxaban was non-inferior in efficacy, compared to VKA, in preventing thromboembolism for atrial fibrillation (AF). Rivaroxaban also appears to have a positive effect in the treatment of left atrial appendage thrombosis [21]. The formation of LVT is pathologically similar to the formation of left atrial appendage thrombosis, occurring in a low-flow setting. Given the efficacy of rivaroxaban in the prevention of atrial fibrillation thromboembolism and for treatment of left atrial appendage thrombosis, it is reasonable to extrapolate its efficacy to LVT treatment.

The rate of LVT resolution during treatment is one of the most concerned problems. Previous case studies and reviews have demonstrated the efficacy and safety of DOACs in patients with LVT after AMI [22–25]. Based on previous case studies and reviews of DOACs for LVT after AMI, Daniel Jones et al. [13] demonstrated that LVT resolution was quicker in the DOACs group than in the VKA group (1 year 82 vs 64.4%, p = 0.0018). However, in their study, all DOACs were analyzed as a whole, and anti-thrombotic regimens vary, which may be inaccurate to determine the effect of various DOACs on LVT after AMI. In the present study, only rivaroxaban was used as the DOACs, and triple therapy was the only antithrombotic regimen. When LVT resolution rates were analyzed throughout the follow-up period, triple therapy with rivaroxaban versus VKA was found to have similar resolution rates. Given the long follow-up time of this study, similar LVT resolution between the two groups is understandable. The difference became apparent when we analyzed the resolution of the two groups at different time points, whether at 6, 12, or 18 months, rivaroxaban had a quicker resolution than VKA, which supports the efficacy of rivaroxaban, as compared with warfarin, was favorable. Meanwhile, we also note that the resolution rate of LVT in the triple therapy of VKA in our center seems to be low, compared with other studies [11–13]. When focusing on this, it is found that this may be related to the INR compliance rate and LV aneurysm in the triple therapy with VKA. Among patients receiving triple treatment with VKA, LV aneurysms occurred at a higher rate, and 7 patients (22.5%) failed to meet the therapeutic target of INR, which may affect the resolution rate of LVT.

Persistent LVT is another problem worth focusing on. The recent guidelines recommended a short-duration triple therapy (Up to 6 months) in patients with residual thrombus [10]. The guidelines also acknowledged the lack of prospective RCT data in this area. Meanwhile, most evidence that formed the basis of the current guideline was from an earlier era before contemporary expedited reperfusion strategies with primary PCI or a fibrinolysis pharmacoinvasive strategy delivered within STEMI systems of care [26–28]. For the treatment of persistent LVT over 6 months, clinicians continued to face uncertainty in decision-making [29]. In our center, the rates of LVT resolution, within 6 months, were 42.4% in the rivaroxaban group and 19.4% in the warfarin group. There was considerable anxiety with cessation of the powerful antithrombotic therapy in the presence of a persistent thrombus. In this dilemma, some centers, after fully considering the risks and benefits of chronic anticoagulation, adopted the strategy of long-term triple therapy under close follow-up (Table 4) [1, 12, 14, 30–33]. In our center, we also adopted a long-term triple therapy strategy with close follow-up until LVT resolution, unless the physician judged that the patient cannot continue triple therapy due to increased bleeding risk, bleeding events, or other factors. The median duration of triple therapy was 8.5 months (IQR 5.0–17.0 months). Throughout the follow-up period, the rate of bleeding remained relatively low, and a relatively

| Study          | Design   | Patients                  | Triple therapy for LVT (%) | Triple therapy duration                      |
|----------------|----------|---------------------------|----------------------------|---------------------------------------------|
| Lattuca [1]    | Single center | Patients diagnosed with LVT | 35.2                      | Median: 508 days (IQR 115–986 days)         |
| Iqbal [14]     | Single center | Patients diagnosed with LVT | 38                        | Mean: 677 ± 568 days                        |
| Maniwa [30]    | Single center | AMI                       | 38                        | Median: 6.6 months (IQR 1.9–12.9 months)    |
| Cambronero [31] | Single center | AMI                       | 100                       | ≥ 6 months until LVT resolution              |
| Meurin [32]    | Multi-center | Anterior AMI              | 96.2                      | ≥ 6 months until LVT resolution              |
| Robinson [12]  | Multi-center | Patients diagnosed with LVT | 12.5                      | Median: 418 days (IQR 139–927 days)         |
| Khoury [33]    | Single center | AMI                       | 100                       | ≥ 3 months until LVT resolution (Mean follow-up period: 677 ± 568 days) |

LVT left ventricular thrombus, AMI acute myocardial infarction, IQR interquartile range
high rate of LVT resolution was observed. Several contemporary studies also indicated that a prolonged anticoagulation therapy was independently associated with a reduced risk of MACE in LVT patients (Median duration of triple therapy: 508 days, IQR 115–986 days) [1], and appropriated that anti-coagulation therapy might decrease the incidence of embolic events without increasing the incidence of bleeding events in patients with first AMI complicated by LV thrombus (Median duration of triple therapy: 6.6 months, IQR 1.9–12.9 months) [30]. Therefore, after fully evaluating the risks and benefits of prolonging triple therapy, it could be considered to give long-term triple therapy to such a population at high risk of thromboembolism.

The clinical issue associated with LVT is the increased risk of SE, with the incidence of embolization complications in LVT patients ranging from 10 to 35% [3, 27]. In the present study, the incidence (11.3%) on VKA plus DAPT appears consistent with earlier publications. The incidence (3.3%) on rivaroxaban plus DAPT was lower than previous studies on DOACs [12, 13]. The study published by Daniel A Jones et al. [13] showed that in the treatment of LVT, no difference in rates of SE was seen between VKA group and DOACs group in patients with LVT after AMI. However, Austin A. Robinson et al. [12] published an observational study of 514 patients with LVT (all indications) showed the use of DOACs was significantly associated with systemic embolism compared with VKA. There may be several possible reasons for the inconsistent results of these studies: (1) The diseases included in the same studies were different, and the treatment after the occurrence of LVT in a certain disease was not analyzed separately. (2) All DOACs were analyzed as a whole, without considering the different mechanisms and pathways of action of DOACs, as well as the differences in efficacy and side effects; (3) There were different antithrombotic treatment regimens in these same studies, some were given triple therapy (anti-coagulant+ DAPT), some were given double therapy (anti-coagulation+antiplatelet therapy), and some were given only anticoagulant therapy, which may lead to an imprecise assessment of the pros and cons of treatment options. Although these studies reflect some of the advantages and disadvantages of DOACs as a whole in the treatment of LVT, more precise studies are worth continuing. Rivaroxaban was the only DOACs that were focused on in this study. Previous studies have demonstrated the superior performance of the triple therapy given rivaroxaban in reducing cardiovascular events in patients with atrial fibrillation and ACS [20, 34]. In the present study, in patients with LVT after STEMI, the triple therapy given rivaroxaban also had a lower incidence of SE than the triple therapy given VKA (3.0 vs 12.9%), but it was not statistically significant. This may be related to the relatively small sample size in our study. According to previous studies on rivaroxaban, we tend to think that rivaroxaban has a positive effect on SE in patients with LVT after STEMI, which needs to be confirmed in larger clinical trials.

The main disadvantage of continuous anticoagulation is the increased risk of bleeding. The incidence of adverse outcomes, such as death, stroke, and reinfarction, was higher in patients with bleeding events [35]. Especially in the patients taking antiplatelet agents plus VKA, anticoagulation is associated with an increased risk of bleeding [36]. Several studies [37, 38] have reported that triple therapy with VKA has 3–4 times higher risk of major bleeding than antiplatelet therapy alone or single oral anticoagulant. Andrade et al. [38] conducted a systematic review and meta-analysis of the risk of bleeding in patients receiving triple therapy with VKA after PCI. In their analysis, the rates of major bleeding with DAPT plus VKA were, at 30 days and 6 months, significantly higher than the DAPT. In the WOEST trial [39], 12.3% of patients receiving triple therapy with VKA had moderate and severe bleeding events within 1 year, significantly higher than those receiving the dual therapy. However, the results observed in the current studies of rivaroxaban are different. In the PIONEER AF-PCI trial with non-valvular AF patients who had undergone PCI [20], the rate of bleeding on triple therapy with rivaroxaban was significantly lower than triple therapy with VKA (18.0 vs. 26.7%). In the ATLAS ACS 2-TIMI 51 trial among STEMI patients[34], triple therapy with rivaroxaban reduced the primary efficacy endpoint of cardiovascular death, myocardial infarction, or stroke, but the rate of fatal hemorrhage was not significantly increased (0.2 vs. 0.1%, p=0.51). In the present study, similar bleeding risks were documented between the two groups, and showed no difference. But when focusing on NACE consisting of bleeding, all-cause mortality, SE, re-hospitalization for cardiovascular events, we found that NACE were lower in triple therapy with rivaroxaban during the follow-up period, compared with triple therapy with VKA. These results are reassuring, because they indicated that the increase in bleeding seen does not offset the benefit of reduction in vascular events, which suggested that triple therapy with rivaroxaban may have a better net clinical benefit for patients with LVT after STEMI.

Limitations

First, this was a retrospective clinical study from a large tertiary referral center. Unappreciated or immeasurable confounding variables could have affected the results, although we have carefully screened and adjusted the variables based on previous studies [17, 18]. Second, due to the condition of STEMI patients, the diagnosis of LVT was mainly based on echocardiography in this study, which may have lower detection sensitivity and specificity compared with other imaging
method. Third, the main limitations of this study are the small sample size and non-randomness, albeit this study including the largest number of patients treated with triple therapy with rivaroxaban for assessing LVT after STEMI so far. Therefore, our results should be considered exploratory rather than definitive. Given the complication and poor outcomes of LVT after STEMI, we believe a large randomized controlled study is clearly necessary, although this may be difficult given the relatively low incidence of LVT among patients with STEMI in modern times. A randomized trial regarding the short-term efficacy of triple therapy with rivaroxaban versus VKA in patients with LVT following STEMI is underway (NCT03764241) and may provide new insights on this issue hopefully.

Conclusion

This observational study provides moderate evidence evaluating the efficacy of triple therapy with rivaroxaban used in LVT after STEMI, which indicates triple therapy with rivaroxaban had similar and quicker LVT resolution in patients with LVT after STEMI, compared with triple therapy with VKA, and perhaps was accompanied with a better clinical benefit. Larger sample sizes and randomized controlled trials are needed to confirm this observation.

Acknowledgements

None.

Author contributions ZZ, DS, and WZ conceived and designed the study. ZZ and QZ collected and analyzed data, performed the literature search. ZZ and MY drafted the manuscript. DS and WZ interpreted the data and made a critical revision to the manuscript. MQ, MY, ZJ, DL contributed to data collection and performed the literature search. WZ provided consultation, participated in the coordination of the manuscript. All authors read and approved the final manuscript.

Funding

This work was supported by grants from Science and technology project of Jilin Provincial Department of Education (JJKH20190062KJ) and Science and Technology of Jilin Province (20180520054HJ and 20200801076GH).

Data availability

The datasets used and/or analyzed in this study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest The authors have no conflict of interest to disclose.

Ethical approval This retrospective study was reviewed and approved by the ethical review board of China-Japan Union Hospital of Jilin University. All procedures performed in this study involving human participants were in accordance with the ethical standards of the institution and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent to participate The written informed consent was obtained from each participant on admission.

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