

Progress of the Direct Oral Anticoagulants in Treatment of Left Ventricular Thrombosis

Jiabin Shi¹, Hua Xiao^{1*}

¹ The First Affiliated Hospital of Chongqing Medical University, Chongqing, China

Email Address

xiaohua197408@163.com (Hua Xiao)

*Correspondence: xiaohua197408@163.com

Received: 26 January 2024; **Accepted:** 12 February 2024; **Published:** 20 February 2024

Abstract:

Left ventricular(LV) thrombosis is a severe complication of several cardiomyopathies that can result in cerebrovascular and peripheral vascular embolism, increasing disability and mortality. Most guidelines recommend using vitamin K antagonists (VKAs) to prevent and treat embolic events in patients with left ventricular thrombus. The introduction of direct oral anticoagulants (DOACs) has provided new treatment options for LV thrombosis. Despite the increasing use of DOACs and the emergence of a growing number of relevant studies in the last two years, their efficacy remains uncertain. Several recent small prospective randomized controlled trials (RCT) have demonstrated that DOACs are non-inferior to the gold standard warfarin in treating patients with LV thrombosis. It is possible that direct oral anticoagulants may replace VKA as the first-line treatment for LV thrombosis in future guidelines. However, prospective randomised data on the optimal treatment of LV thrombosis are still lacking.

Keywords:

Direct Oral Anticoagulant, Left Ventricular Thrombosis, Treatment

1. Introduction

Left ventricular(LV) thrombosis is a significant complication of ischemic and non-ischemic cardiomyopathies due to it is related to an increased risk of stroke and systemic thromboembolism [1]. The causes of LV thrombosis are complex, with acute myocardial infarction (AMI) being the most frequent cause [2]. Despite the significant reduction in the incidence of LV thrombosis since the introduction of thrombolytic therapy and percutaneous coronary intervention (PCI), left ventricular thrombosis still represents a significant threat to human life and health due to its high mortality and disability.

Thrombus formation depends on the Virchow triad, which includes endothelial injury, blood stasis, and hypercoagulability. Blood stasis and hypercoagulability are particularly important in LV thrombosis development and are the theoretical basis for the use of anticoagulants in the treatment of LV thrombosis. The most current

American Heart Association recommends vitamin K antagonists (VKAs) as first-line therapy [3]. However, direct oral anticoagulants (DOACs) are increasingly used in clinical practice due to their advantages of acting on a single target, rapid onset of action, and stable efficacy. The latest European Society of Cardiology (ESC) guidelines for acute coronary syndromes recommend the use of either warfarin or DOACs for the treatment of left ventricular thrombosis after myocardial infarction[4].

Studies on DOACs for the treatment of LV thrombosis have increased over the last few years. However, most of these have been retrospective, and their conclusions have been inconsistent. Recently, several small prospective randomized controlled trials have confirmed that direct oral anticoagulants are not inferior to the gold standard warfarin in treating patients with LV thrombosis. These studies provide hope for future guidelines on the use of direct oral anticoagulants as a first-line treatment for left ventricular thrombosis.

This review examines various aspects of left ventricular thrombosis, including epidemiology, mechanisms, treatment, and current research, with the aim of evaluating the efficacy and safety of DOACs for treating left ventricular thrombosis.

2. Epidemiology

Although LV thrombus can be found both in ischemic and non-ischemic cardiomyopathies, the majority of LV thrombi form after AMI [2]. In the pre-thrombolytic era, about 30% of individuals with acute anterior wall myocardial infarction developed LV thrombi [5]. With the development of reperfusion and antithrombotic therapies, the incidence of LV thrombosis has significantly decreased. Nevertheless, the incidence of left ventricular thrombus remains high. In the primary PCI era, the prevalence of LV thrombus after acute myocardial infarction distribute widely, ranging from 0.4% to 8.8% [6,7]. A previous meta-analysis, which involved 10,072 individuals, demonstrated that the occurrence of LV thrombosis was 2.7% in patients with STEMI who underwent PCI. The incidence was even higher in cases of anterior wall myocardial infarction, at 9.1%[8]. A high prevalence of LV thrombus 12.2% was found in patients with STEMI in a recent meta-analysis of 2,072 patients with ST-segment elevation myocardial infarction (STEMI) who had a left ventricular thrombus detected by cardiac magnetic resonance imaging (CMR) within 1 month. Among among patients with anterior STEMI and left ventricular ejection fraction (LVEF) <50%, this rate was 19.2%[9]. One of the reasons for this disparity of prevalence is the use of different tools to diagnose left ventricular thrombosis. In clinical practice, transthoracic echocardiography (TTE) is frequently used to screen for LV thrombosis because of its simplicity and low cost. However, CMR is still widely regarded as the gold standard for diagnosing LV Thrombus due to its unparalleled sensitivity and specificity [10]. Studies have shown that CMR has a higher sensitivity than TTE, particularly when it comes to identifying laminar LV mural thrombus and late gadolinium enhancement. Compared to TTE (sensitivity 23%–61%), CMR imaging has higher sensitivity (88%), specificity (99%), and accuracy for detecting LV thrombi[11]. Most of the previous reports diagnosed LV thrombosis by TTE, so we believe that the incidence of LV thrombosis is underestimated.

LV thrombus is strongly related to embolic events, which can increase patient mortality. Research has shown that systemic embolism (SE) occurred in 15 of 92 patients with LV thrombus (16.3%) ,with concomitant LV thrombus after a first AMI,

and that LV thrombus is an independent predictor of SE [12]. A meta-analysis including a total of 11,689 individuals in 11 trials. When comparing the LV thrombus group to the non-LV thrombus group, the results revealed a substantially higher incidence of embolic events. Furthermore, compared to the non-LV thrombus group, the LV thrombus group had a greater long-term death risk [13]. Additionally, several studies have shown that the movement and appearance of left ventricular thrombi seems to correlate with the development of embolism [14,15].

3. Mechanisms

It is generally acknowledged that Virchow triad (including endothelial injury, blood stasis and hypercoagulability) underlies thrombosis. It has a tight connection to the LV thrombus that develops following myocardial infarction [16].

3.1. Endothelial Injury

There is a possibility that the extent of cardiac damage following myocardial infarction is linked to a higher risk of thrombosis [17]. And a study by Acar also showed that patients who developed a LV thrombus after AMI had significantly higher peak levels of troponin-T level and creatine kinase isoenzyme MB (CK-MB) than those who did not develop a thrombus (mean peak levels of troponin-T were 32.63 vs. 18.7 ng/ml, CK-MB were 245.47 vs. 167.37 IU/L) [18]. Also injury to the endothelium causes an inflammatory response, on the other hand, increasing the risk of LV thrombosis.

3.2. Blood Stasis

Blood stasis mainly caused by left ventricular dysfunction. Myocardial infarction is often result in lowed LVEF and/or apical or anterior left ventricular decreased motor function after myocardial infarction due to uneven forces on the ventricular wall, resulting in the formation of abnormal vortex that cause stasis of blood flow [16]. There is evidence that abnormal blood flow patterns due to regional left ventricular dysfunction are strongly associated with thrombosis compared to normal blood flow patterns [19]. Weinsaft et al also found that abnormal apical ventricular wall motion is associated with the occurrence of left ventricular thrombosis [20].

3.3. Hypercoagulability

When myocardial cells are injury, the nitric oxide content on the endocardial surface decreases and the subendocardial collagen is exposed, resulting in the production of a large number of pro-coagulant substances such as erythrocytes, fibrinogen, and platelet particles, and the formation of hypercoagulable state [21]. In addition, after myocardial infarction, local myocardial ischemia and hypoxia triggers an inflammatory response, thus activating the coagulation system. Research has shown that C-reactive protein (CRP), fibrinogen and the ratio of neutrophils to lymphocytes are independent predictors of left ventricular thrombosis after AMI [20], with CRP being of particular importance in this context [22]. This hypercoagulable state after AMI can last for six months or longer [21], thus the risk of developing a LV thrombus is high throughout this period.

4. Treatment

Based on the mechanisms of LV thrombosis described above, current guidelines recommend that anticoagulants are preferred above antiplatelet drugs when treating left ventricular thrombus. The classic anticoagulant is warfarin, which interfering with the synthesis of vitamin K and thus non-specifically inhibits the synthesis of vitamin K-dependent clotting factors to achieve anticoagulation. According to the 2012 guidelines of the American College of Chest Physicians, patients with LV thrombus after anterior wall AMI should receive VKA for 3-6 months in addition to dual antiplatelets therapy [23] (DAPT). According to 2013 American Heart Association (AHA) STEMI guidelines, patients with STEMI who also have anterior apical akinesis or dyskinesis should consider receiving anticoagulation therapy with a vitamin-K antagonism (VKA, such as warfarin) for at least three months [3].

However, warfarin has significant limitations such as being easily affected by food and medicine and requiring regular review of coagulation function. In recent years, direct oral anticoagulants have emerged, providing more choices for anticoagulation therapy. DOAC achieve anticoagulation by acting on a single target and inhibiting activated coagulation factors. This has the advantages of fast onset of action, constant titre, and low risk of bleeding. In 2013, the U.S. Pharmacovigilance Administration approved the use of DOACs for anticoagulation in atrial fibrillation. DOAC has been extended to off-label indications used to treat LV thrombus in clinical practice due to their superior pharmacological and clinical effects.

The 2014 Stroke Guidelines from the AHA/American Stroke Association recommend DOAC as an alternative treatment for patients with ventricular thrombus who occur serious side effects after taking warfarin. A 3-month VKA with a target INR of 2.0–3.0 is advised for patients with ischemic stroke or transient ischemia who have AMI worsened by LV appendage thrombosis. [24] The 2023 ESC Guidelines suggest considering 3-6 months of oral anticoagulant therapy (warfarin or DOAC) as soon as LV thrombus is identified, it is advised to have cardiac magnetic resonance imaging or follow-up echocardiography, and the necessity of concurrent antiplatelet medication should be assessed in light of the total risk of bleeding. [4]

The management of LV thrombosis has been studied and improved over the past decade. However, there are no available guidelines definitively recommend that the best anticoagulation regimen, duration of treatment, or combination of oral anticoagulants and antiplatelet agents for patients with LV thrombosis.

5. Recent Research

Over the past few years, a number of small retrospective observational studies have compared the efficacy of warfarin with the DOACs in the treatment of LV thrombosis. However, these studies have reached inconsistent conclusions. Jones et al [25] in 2021 published a retrospective observational study, it included 101 patients with left ventricular thrombosis, of whom 61 were treated with warfarin and 40 with DOAC, with a median follow-up of 2.2 years, and patients who received DOAC showed a higher and earlier rate of left ventricular thrombosis resolution compared with who received warfarin; and the DOAC group had a better safety profile, with fewer major bleeding events, and no statistically significant difference in the rate of thrombotic event compared to the warfarin group. Robinson et al. [26] arrived at a different conclusion that compared with warfarin, DOACs was associated with a increased risk of stroke and SE. In their multicentre research analysis of 514 patients with LV

thrombosis, 300 received warfarin treatment and 185 received a DOAC. The study showed that 54 thrombotic events were diagnosed during the follow-up, with 17 in the DOAC group and 14 in the warfarin group. The study also found that DOACs treatment was significantly related to a higher risk of SSE compared to warfarin. These trials have confirmed that DOACs have a therapeutic effect on left ventricular thrombosis, but the conclusions about their safety compared with the conventional drug warfarin are vary.

Several of the trials mentioned above have significant limitations, as they were all small retrospective studies. Significantly, a few recent RCT have consistently concluded that DOACs are not inferior to warfarin for treating LV thrombosis. Abdelnabi [27] conducted a prospective multicenter RCT to evaluate a DOAC for the treatment of LV thrombus after AMI. In this trial, 79 participants were randomized to either warfarin (n = 40) or rivaroxaban (n = 39). The changes in LV thrombus were assessed by TTE at 1, 3, and 6 months after drug administration. The thrombolysis rate in the rivaroxaban group and the warfarin group at 1,3,6 months were 71.79% vs 47.5%, 76.92% vs 67.5%, 87.17% vs 80% , respectively. Additionally, there were no systemic embolic events in the rivaroxaban group, compared with 2 events in the warfarin group (5%). Regarding the incidence of bleeding events, there were 5.1% in the rivaroxaban group and 15% in the warfarin group. A multicentre RCT by Youssef [28] compared the efficacy of apixaban and warfarin for treating LV thrombus after MI. Patients with LV thrombus after anterior wall MI were randomized to receive either apixaban or warfarin to achieve an international normalized ratio (INR) while receiving dual antiplatelet therapy (DAPT). Thrombus resolution rates were lower in the apixaban group than in the warfarin group at 1-month and 3-month, with rates of 40% and 76% compared to 56% and 80%, respectively. However, at the 6-month follow-up endpoint, the apixaban group had a higher resolution rate of 92% compared to 80% in the warfarin group. The statistical analysis showed no significant difference in the rate of LV thrombus dissolution between the two groups ($p < 0.036$). Notably, this study did not report any embolic or haemorrhagic events. Both studies we mentioned diagnosed left ventricular thrombus by TTE, which has limited sensitivity. A current study diagnosed LV thrombosis by contrast-enhanced echocardiography (CE) at baseline and follow-up visit. The study involved 64 patients with left ventricular thrombosis and were administered rivaroxaban either 15mg or 20mg daily, using a microbubble contrast agent (Sonovue) via CE to assess LV thrombus over 12 weeks. The study's findings indicated that 78.1% of LV thrombus dissolution and 95.3% of LV thrombus decreased or dissolved. The rate of serious cardiovascular events was 6.7% [29]. A recent RCT from Jilin University supported the use of low-dose rivaroxaban in addition to DAPT for the prevention of LV thrombosis in patients with anterior STEMI undergoing primary PCI [30]. The study enrolled 279 patients with anterior wall STEMI who met the criteria. All patients underwent PCI for the first time and received aspirin in combination with either tegretol or clopidogrel antiplatelet therapy after surgery. The patients were randomly divided into two groups: 139 patients in the first group received DAPT plus low-dose rivaroxaban for 30 days, whereas 140 patients in the second group received DAPT alone. The study results indicate that within 30 days, the incidence of LVT was significantly lower in the rivaroxaban group (0.7%) compared to the DAPT-only group (8.6%) (HR: 0.08; 95% CI: 0.01-0.62; $P = 0.015$). This suggests that low-dose rivaroxaban can reduce the risk of LVT after AMI. On the other hand, there were no significant differences in safety events between the two groups.

Several small randomized trials have shown that DOAC is not inferior to warfarin in treating LV thrombosis. However, due to the limited sample sizes of these studies, more investigation is required to verify the efficacy and safety of DOAC. Until now, we couldn't definitively say that direct oral anticoagulant will instead of warfarin to be the first choice for the treatment of left ventricular thrombi.

6. Conclusions

Although the incidence of LV thrombosis has declined significantly since the introduction of thrombolytic therapy and percutaneous coronary intervention, treating LV thrombosis remains a clinical challenge. Early diagnosis and initiation of anticoagulation are particularly important in reducing the complications of LV thrombosis. Recent studies have demonstrated the potential role of DOACs in the treatment of LV thrombosis. However, a large number of prospective, multicenter, RCT are still needed to evaluate whether DOACs can replace warfarin as the first-line medicine for the treating LV thrombosis.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

References

- [1] Velangi, P. S.; Choo, C.; Chen, K. A. et al. Long-Term Embolic Outcomes After Detection of Left Ventricular Thrombus by Late Gadolinium Enhancement Cardiovascular Magnetic Resonance Imaging: A Matched Cohort Study. *Circ Cardiovasc Imaging*, 2019, 12(11), e009723.
- [2] Massussi, M.; Scotti, A.; Lip, G. et al. Left ventricular thrombosis: new perspectives on an old problem. *Eur Heart J Cardiovasc Pharmacother*, 2021, 7(2), 158-167.
- [3] O'Gara, P.T.; Kushner, F.G.; Ascheim, D.D. et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*, 2013, 127(4), e362-425.
- [4] Byrne, R.A.; Rossello, X.; Coughlan, J.J. et al. 2023 ESC Guidelines for the management of acute coronary syndromes. *Eur Heart J*, 2023, 44(38), 3720-3826.
- [5] Kupper, A.J.; Verheugt, F.W.; Peels, C. H. et al. Left ventricular thrombus incidence and behavior studied by serial two-dimensional echocardiography in acute anterior myocardial infarction: left ventricular wall motion, systemic embolism and oral anticoagulation. *J Am Coll Cardiol*, 1989, 13(7), 1514-20.
- [6] Ram, P.; Shah, M.; Sirinvaravong, N. et al. Left ventricular thrombosis in acute anterior myocardial infarction: Evaluation of hospital mortality, thromboembolism, and bleeding. *Clin Cardiol*, 2018, 41(10), 1289-1296.

- [7] Delewi, R.; Nijveldt, R.; Hirsch, A.et al. Left ventricular thrombus formation after acute myocardial infarction as assessed by cardiovascular magnetic resonance imaging. *Eur J Radiol*, 2012, 81(12), 3900-4.
- [8] Robinson, A.A.; Jain, A.; Gentry, M.et al. Left ventricular thrombi after STEMI in the primary PCI era: A systematic review and meta-analysis. *Int J Cardiol*, 2016, 221, 554-9.
- [9] Bulluck, H.; Chan, M.; Paradies, V.et al. Incidence and predictors of left ventricular thrombus by cardiovascular magnetic resonance in acute ST-segment elevation myocardial infarction treated by primary percutaneous coronary intervention: a meta-analysis. *J Cardiovasc Magn Reson*, 2018, 20(1), 72.
- [10] Srichai, M.B.; Junor, C.; Rodriguez, L. L.et al. Clinical, imaging, and pathological characteristics of left ventricular thrombus: a comparison of contrast-enhanced magnetic resonance imaging, transthoracic echocardiography, and transesophageal echocardiography with surgical or pathological validation. *Am Heart J*, 2006, 152(1), 75-84.
- [11] Roifman, I.; Connelly, K.A.; Wright, G. A.et al. Echocardiography vs. Cardiac Magnetic Resonance Imaging for the Diagnosis of Left Ventricular Thrombus: A Systematic Review. *Can J Cardiol*, 2015, 31(6), 785-91.
- [12] Maniwa, N.; Fujino, M.; Nakai, M.et al. Anticoagulation combined with antiplatelet therapy in patients with left ventricular thrombus after first acute myocardial infarction. *Eur Heart J*, 2018, 39(3), 201-208.
- [13] Chen, P.F.; Tang, L.; Yi, J. L.et al. The prognostic effect of left ventricular thrombus formation after acute myocardial infarction in the contemporary era of primary percutaneous coronary intervention: A meta-analysis. *Eur J Intern Med*, 2020, 73, 43-50.
- [14] Stratton, J.R.; Resnick, A.D. Increased embolic risk in patients with left ventricular thrombi. *Circulation*, 1987, 75(5), 1004-11.
- [15] Meltzer, R.S.; Visser, C.A.; Fuster, V. Intracardiac thrombi and systemic embolization. *Ann Intern Med*, 1986, 104(5), 689-98.
- [16] Camaj, A.; Fuster, V.; Giustino, G.et al. Left Ventricular Thrombus Following Acute Myocardial Infarction: JACC State-of-the-Art Review. *J Am Coll Cardiol*, 2022, 79(10), 1010-1022.
- [17] Hashmi, K.A.; Saeed, H.Y.; Ahmed, J.et al. Left Ventricular Thrombus Formation in Acute Anterior Wall Myocardial Infarction: A Comparison Between Thrombolized and Non-Thrombolized Patients. *Cureus*, 2020, 12(7), e9090.
- [18] Acar, Z.; Ziyrek, M.; Korkmaz, L.et al. Mean platelet volume at admission is a determinant of left ventricular thrombus formation after primary percutaneous coronary intervention for first anterior wall myocardial infarction. *Acta Cardiol*, 2014, 69(6), 603-9.
- [19] Delemarre, B.J.; Visser, C.A.; Bot, H.et al. Prediction of apical thrombus formation in acute myocardial infarction based on left ventricular spatial flow pattern. *J Am Coll Cardiol*, 1990, 15(2), 355-60.

- [20] Ertem, A.G.; Ozcelik, F.; Kasapkara, H. A.et al. Neutrophil Lymphocyte Ratio as a Predictor of Left Ventricular Apical Thrombus in Patients with Myocardial Infarction. *Korean Circ J*, 2016, 46(6), 768-773.
- [21] Stein, B.; Fuster, V. Antithrombotic therapy in acute myocardial infarction: prevention of venous, left ventricular and coronary artery thromboembolism. *Am J Cardiol*, 1989, 64(4), 33B-40B.
- [22] Lechner, I.; Reindl, M.; Tiller, C.et al. Association between inflammation and left ventricular thrombus formation following ST-elevation myocardial infarction. *Int J Cardiol*, 2022, 361, 1-6, .
- [23] Holbrook, A.; Schulman, S.; Witt, D. M.et al. Evidence-based management of anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*, 2012, 141(2) Suppl, e152S-e184S.
- [24] Kernan, W.N.; Ovbiagele, B.; Black, H. R.et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*, 2014, 45(7), 2160-236.
- [25] Jones, D.A.; Wright, P.; Alizadeh, M. A.et al. The use of novel oral anticoagulants compared to vitamin K antagonists (warfarin) in patients with left ventricular thrombus after acute myocardial infarction. *Eur Heart J Cardiovasc Pharmacother*, 2021, 7(5), 398-404.
- [26] Robinson, A.A.; Trankle, C.R.; Eubanks, G.et al. Off-label Use of Direct Oral Anticoagulants Compared With Warfarin for Left Ventricular Thrombi. *JAMA Cardiol*, 2020, 5(6), 685-692.
- [27] Abdelnabi, M.; Saleh, Y.; Fareed, A.et al. Comparative Study of Oral Anticoagulation in Left Ventricular Thrombi (No-LVT Trial). *J Am Coll Cardiol*, 2021, 77(12), 1590-1592.
- [28] Youssef, A.A.; Alrefae, M.A.; Khalil, H. H.et al. Apixaban in Patients With Post-Myocardial Infarction Left Ventricular Thrombus: A Randomized Clinical Trial. *CJC Open*, 2023, 5(3), 191-199.
- [29] Yang, Q.l Quan, X.; Zhang, Y.et al. An exploratory study of effectiveness and safety of rivaroxaban in patients with left ventricular thrombus (R-DISSOLVE). *J Thromb Thrombolysis*, 2023, 55(4), 649-659.
- [30] Zhang, Z.; Si, D.; Zhang, Q.et al. Prophylactic Rivaroxaban Therapy for Left Ventricular Thrombus After Anterior ST-Segment Elevation Myocardial Infarction. *JACC Cardiovasc Interv*, 2022, 15(8), 861-872.



© 2024 by the author(s); licensee International Technology and Science Publications (ITS), this work for open access publication is under the Creative Commons Attribution International License (CC BY 4.0). (<http://creativecommons.org/licenses/by/4.0/>)