# Anticoagulation for Left Ventricular Thrombosis Post-Myocardial Infarction – Current Recommendations and Future Perspectives

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Abstract
Left ventricular thrombosis (LVT) is one of the most severe complications of acute myocardial infarction (AMI). LVT is commonly associated with an increased risk of cerebral or systemic embolization, which furthermore increases the morbidity and mortality of these patients. Management of LVT implies the administration of anticoagulants to achieve thrombus resolution and reduce the embolic risk. However, in the setting of an AMI, anticoagulants are added to already existing antiplatelet therapy, which increases the bleeding risk for this category of patients. Vitamin K antagonist (VKA) represents the main guideline recommendation for anticoagulation, but its multiple interactions are associated with an increased number of patients who are outside the therapeutic range and low compliance. Early studies that evaluate direct oral anticoagulants (DOAC) as an alternative for VKA show promising results, with reduced strokes and bleeding rates and faster thrombus resolution. Thus, in the near future, DOAC may represent a therapeutic option for treating LVT, but larger studies are needed to validate this approach.

Keywords
Left ventricular thrombosis, vitamin K antagonists, direct oral anticoagulants, anticoagulation, treatment.

Rezumat
Tromboza intraventriculară (TIV) este una dintre cele mai severe complicații ale infarctului miocardic acut (IMA). TIV se asociază în general cu un risc crescut de embolizare sistemică sau cerebrală, ceea ce duce la creșterea morbidității și mortalității la această categorie de pacienți. Managementul TIV constă în administrarea de anticoagulante pentru a obține o rezoluție a trombului și pentru a reduce riscul de evenimente embolice. Cu toate acestea, în contextul unui IMA, adăugarea medicației anticoagulante la terapia antiagregantă deja existent poate crește substanțial riscul de sângerare. Antivitaminele K (AVK) reprezintă principala clasă de anticoagulante recomandată de ghidurile actuale, însă se asociază cu numeroase interacțiuni medicamentoase și complianță redusă a pacienților. Studiile preliminare care au comparat administrarea de anticoagulante orale directe (DOAC), ca alternativă la AVK, au raportat rezultate promițătoare, exprimate printr-o reducere a numărului de evenimentelor embolice și o rezoluție mai rapidă a trombului. Astfel, în viitorul apropiat, DOAC pot reprezenta o opțiune terapeutică pentru tratamentul TIV, dar sunt necesare studii suplimentare pentru a valida această abordare.

Cuvinte cheie
tromboză de ventricul stâng, antagoniști de vitamina K, anticoagulante orale directe, anticoagulare, tratament.

## Introduction

Left ventricular thrombosis (LVT) is one of the most severe complications of acute myocardial infarction (AMI) and other non-ischemic cardiomyopathies with reduced left ventricular ejection fraction (LVEF) [1]. LVT is commonly associated with an increased risk of cerebral or systemic embolization, which furthermore increases the morbidity and mortality of these patients [2].

Although the diagnosis and management of AMIs have advanced substantially, LVT can occur in 3%–9% of patients with transmural myocardial infarction [3]. The main predictors of LVT are represented by the following conditions: anterior myocardial infarction, reduced LVEF, the implication of left ventricular apex, without reference to the affected coronary territory, a large infarct size, left ventricular akinesis or dyskinesis, and severe diastolic dysfunction [1].

Management of LVT implies the administration of anticoagulants to achieve prompt thrombus resolution and to reduce the risk for a stroke or a systemic embolism. However, in the setting of an AMI, anticoagulants are added to already existing dual or single antiplatelet therapy (DAPT/SAPT), which increases the bleeding risk for this category of patients [4].

## Patients and Methods

### 1. Pathophysiology

The mechanism of thrombus formation includes stasis, hypercoagulability, and endothelial lesion (as has been described by Virchow since 1856) and is still valid for LVT, with some particularities for AMI. Through the acute phase of MI, due to hypokinesis/akinesis

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and tissular necrosis, there is a relative stasis of the blood and endocardial inflammation. These processes assure a thrombogenic surface in the LV, promoting the formation of clots. Patients with acute coronary syndrome have increased concentrations of Willebrand factor, prothrombin and fibrinopeptide A, which provide a hypercoagulable state [5] (Figure 1).

Modern use of more aggressive antithrombotic therapy resulted in a decrease in the incidence of LV thrombus development after ST-elevation acute myocardial infarction (STEMI) from 20% to 5%. LV thrombus can develop even 24 hours after an AMI. Patients in whom a mural thrombus forms early (48 to 72 hours from MI) present an increased mortality rate caused by the complications of a large infarction (rupture, shock, ventricular tachyarrhythmia), rather than embolization from LV thrombus [5]. Resolution of LV thrombus can occur spontaneously, but it usually requires anticoagulant therapy. Complete or rapid resolution is less frequent for patients with dyskinesia or apical aneurysm, compared with those with apical akinesia [6].

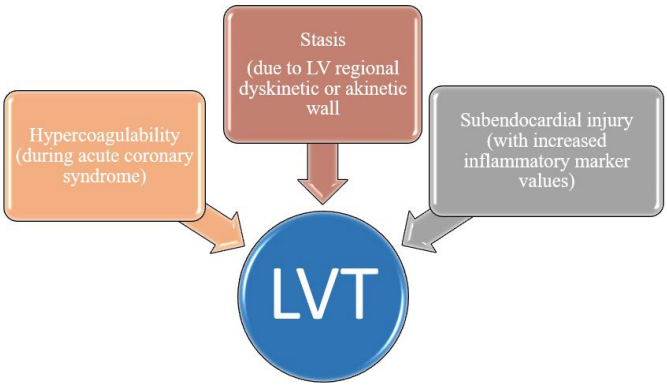


Figure 1 - Virchow's triad adapted for left ventricular thrombosis (LVT) (modified after Delewi, et al.[5]).

**2. Diagnostic Modalities**

Transthoracic echocardiography (TTE) is the technique most often used for LVT diagnosis, as it is widely used to rule out post-MI mechanical complications and evaluate post-infarction LV structure and function. LV thrombus on echocardiography is defined as an echo-dense mass separate from the endocardium with well-defined edges, frequently adjoining a hypokinetic, akinetic or aneurysmal myocardium that is seen from at least two views [7]. The diagnostic efficiency is influenced by image quality, in order to exclude artefacts and rule out trabeculae and false tendons [3]. To decrease the potential of false-positive diagnoses of thrombus, field-depth and gain settings should be additionally adjusted, together with the use of different carrier frequencies and with transducers in various orientations and positions [5]. Figure 2 exemplifies the echocardiographic aspect of apical septal wall left ventricle thrombus.

To improve detection of LVT, contrast echocardiography can be used as it ameliorates the view of the endocardial edge [7,8]. Intravenous echo contrast during TTE enhances the quality, sensitivity (64% vs 35% in contrast versus non-contrast echo), and specificity (82% vs 92% in contrast vs non-contrast echo) for LV thrombus visualization through decrease the hazy image of left ventricular apex [3]. The diagnostic accuracy of TTE it is largely improved, from 82% to 92%, when using ultrasound contrast agents [9].

Currently, transoesophageal echocardiography (TOE) represents the gold standard for the detection of thrombi and atrial masses in the left atrial appendage. However, TOE it is not that efficient in the detection of LV thrombus, due to the relative distance and the anterior orientation of the left ventricular apex (LVA) compared with the transducer, which makes it difficult to visualize [5]. The best incidence in visualizing the LVA is achieved by using a midesophageal long-axis view with slight retroflexion of the probe, which enables a proper visualisation of an existing thrombus. However, TOE is usually preferred in the case of patients with a bad transthoracic echocardiographic window [10]. Real-time, three-dimensional echocardiography (RT3DE) represents a full volume data set obtained by collecting cutting plains in all directions and provides better assessment and comprehension of cardiac structures. This technique enables a better visualisation of the LVT and its attachment to the LV wall by rotating and cropping the collected volumetric data. From the data set obtained by RT3DE, the tomographic planes can be re-aligned, reducing the potential for overlooking and not diagnosing small apical thrombi [9,11].

Contrast-enhanced cardiac magnetic resonance (CE-CMR) has a superior sensitivity and specificity (88% and 99%) to TTE (23% and 96%) or TOE (40% and 96%) for detection of LVT [8]. Therefore, CMR represents the gold standard in diagnosis and evaluating the location, size and existence of LVT. Furthermore, almost one one-third of LVTs diagnosed by CMR were visible on TTE [3]. To better assess the risk of developing thrombus and to better diagnose this condition, Bulluck et al. developed an algorithm which integrates the clinical setting, together with TTE and CMR imaging [12], as described in Figure 3.

**3. Pharmacological Management**

Management of LVT focuses on the administration of anticoagulant drugs in order to prevent systemic embolization, to inhibit further thrombus formation, and to promote thrombus resolution. The American College of Cardiology Foundation/American Heart Association (ACC/AHA) STEMI Guidelines from 2013 and the AHA/American Stroke Association Guidelines on stroke prevention from 2014 both recommend vitamin K antagonist (VKA) therapy for up to 3 months for patients with LVT after STEMI [13,14]. Furthermore, VKA could be administered in the context of stroke and STEMI, when there is a high risk of LVT formation, even though it has not yet been diagnosed [14]. All guidelines recommend echocardiographic evaluation at least 3 months after LVT diagnosis to assess thrombus resolution. The 2017 European Society of Cardiology (ESC) STEMI guidelines recommend a longer period of anticoagulant therapy, up to 6 months, with repeated imaging follow-up but without specifying the type of anticoagulant [15]. All guideline recommendations for pharmacological management of LVT are resumed in Table 1.

**4. Vitamin K antagonist therapy for LVT**

VKAs were the central component of anticoagulation for more than half a century before the development of direct oral anticoagulants

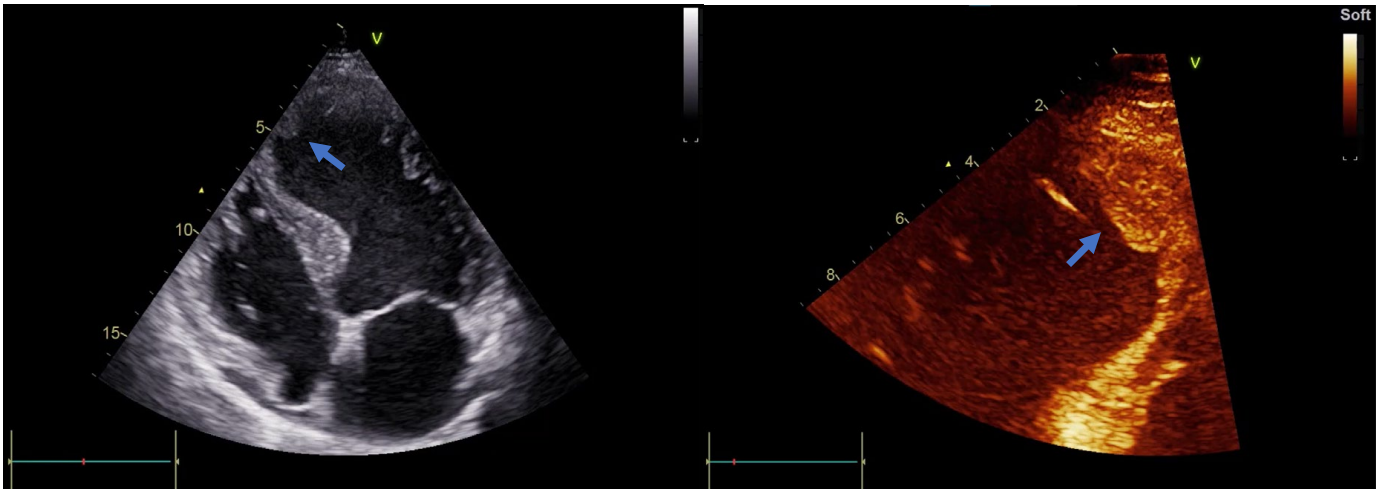


Figure 2 - Transthoracic echocardiography of the left ventricle. Thrombus (*arrows*) attached to the apical septal wall in a patient with ischemic cardiomyopathy.

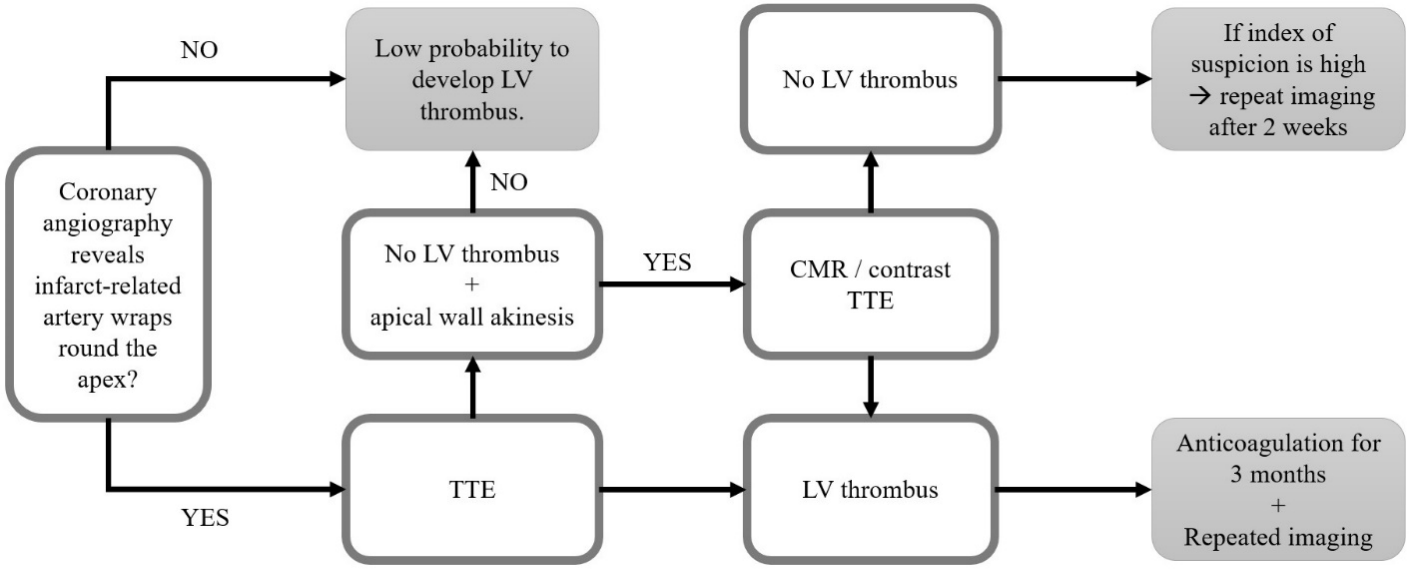


Figure 3 - Algorithm for the diagnosis of LVT in reperfused STEMI patients. Abbreviations: LV – left ventricle, TTE – transthoracic echocardiography, CMR – cardiac magnetic resonance imaging (adapted after Bulluck, et al.[12])

(DOACs). VKAs inhibit the reactivation of vitamin K1 by blocking the enzyme vitamin K epoxide reductase, thus stopping the synthesis of coagulation factors (II, VII, IX, X), and additionally they can inhibit anticoagulant proteins S and C. Warfarin is the most used VKA drug. The efficiency of VKAs in the management of LVT thrombus has been proven in multiple studies, and they have become the primary choice of anticoagulant in both European and American Guidelines [13,15]. Administration of VKA should initially be administered together with parenteral anticoagulation until an optimal antithrombotic status is reached [19]. The target international normalized ratio (INR) for patients with LVT has been reported to be 2.5 (range 2–3). The duration of anticoagulation varies from 3 to 6 months and should be adjusted according to the thrombus resolution and general bleeding risk. The main consensus is that anticoagulation can be stopped after the resolution has been confirmed by successive imaging investigations. However, the recurrence of LVT after 6 months of anticoagulation can be as high as 18.5%, and in this case VKA should be resumed [20]. The main disadvantage of VKA is the narrow therapeutic window and drug–food or drug–drug interactions that require systematically monitoring, constant dose adjustments which decrease the overall patient adherence. As a result, multiple studies have reported that patients treated with VKA are within therapeutic range only 60% of the time [21,22].

**5. Direct oral anticoagulant therapy for LVT**

The use of DOACs has become common medical practice for the prevention of thromboembolic events given the lower bleeding rates, fewer drug and diet interactions, rapid onset of action, and

Table 1 - Guidelines for management of left ventricular thrombosis

| LVT | Recommendation | |
|---|---|---|
| *STEMI Guidelines* | | |
| **ACC/AHA-2013[13]** | | |
| **Patient with STEMI and**<br>• **asymptomatic LVT**<br>• **at high risk of developing LVT** | DAPT+VKA with INR target 2–2.5 | |
| **ESC 2012** | | |
| **LVT** | VKA for a minimum of 3 months | |
| **ESC 2017[15]** | | |
| **LVT** | Anticoagulation should be administered for up to 6 months guided by repeated imaging | |
| *Stroke Guidelines* | | |
| **AHA/ASA 2014[16]** | | |
| **Patient with ischemic stroke or TIA:**<br>• **in setting of acute MI complicated by LVT**<br>○ **VKA therapy intolerance**<br>• **in setting of acute MI at high risk of LVT** | • VKA for 3 months (INR target 2–3)<br>○ LMWH or DOAC (rivaroxaban, apixaban or dabigatran) for 3 months<br>• Consider VKA therapy (INR target 2–3) | |
| **AHA/ASA 2021[17]** | | |
| **Patient with stroke or TIA:**<br>• **LVT**<br>• **new LVT (< 3 months)**<br>• **in setting of acute MI at high risk of LVT** | • warfarin for at least 3 months<br>• the safety of anticoagulation with DOAC is uncertain<br>• empirical anticoagulation for 3 months | |
| *CHEST guidelines* | | |
| **ACCP 2012[18]** | | |
| **Patient with anterior MI + LVT/ high risk for LVT**<br>• **with no stent**<br>• **PCI with BMS**<br>• **PCI with DES** | • VKA + low dose of aspirin for 3 months<br>• triple therapy (VKA + aspirin + clopidogrel) for 1 month, then VKA + one antiplatelet for the next 2 months<br>• triple therapy (VKA + aspirin + clopidogrel) for 3-6 months | Then discontinue warfarin and continue DAPT for up to 12 months as per ACS recommendation |
| **Patient with LV systolic dysfunction + LVT without CAD** | VKA for 3 months with INR target 2–3 | |

*Abbreviations: LVT, left ventricular thrombosis; STEMI-ST, elevation acute myocardial infarction; ACC/AHA, American College of Cardiology/ American Heart Association; ESC, European Society of Cardiology; DAPT, dual antiplatelet therapy; VKA, vitamin K antagonist; INR, international normalized ratio; AHA/ASA, American Heart Association/American Stroke Association; TIA, transient ischemic attack; LMWH, low-molecular-weight heparin; MI, myocardial infarction; DOAC, direct oral anticoagulant; PCI, percutaneous coronary intervention; BMS, bare metal stent; DES, drug-eluting stent; ACS, acute coronary syndrome; CAD, coronary artery disease; LV, left ventricle.*

elimination of the need for constant monitoring of coagulation efficiency. Similarly, DOACs have been proven to have favourable risk–benefit balance in their safety and efficacy profile in the treatment of venous thromboembolism [23]. Furthermore, recent studies have analysed the benefits of DOACs in categories of patients that are not covered by current guidelines, such as, inherited thrombophilias, antiphospholipid syndrome, and heparin-induced thrombocytopenia [24–26].

Regarding anticoagulation of LV thrombi, current guidelines recommend the usage of VKAs for thrombus resolution, thus reducing the risk of stroke and systemic embolism [14,15]. Given the great performance of DOACs in atrial fibrillation, there is considerable interest in evaluating their possible use in the management of LV thrombi.

The first results regarding the efficacy of DOACs compared to VKAs for this category of patients came from case reports, some case series, and small, retrospective single-centre studies. These studies showed similar effects between DOACs and VKAs in the prevention of stroke and systemic embolism and a comparable number and gravity of bleeding events [27–32]. Furthermore, a case series of 10 patients receiving factor Xa inhibitors (rivaroxaban or apixaban) resulted in complete thrombus resolution in 8 patients, with only one bleeding event [32]. One study suggested that a conversion to VKA with a higher INR goal (3–4) was efficient in patients with DOAC and persistent LVT thrombus, in order to achieve its resolution [31]. However, all these studies included only a small number of patients monitored over a short period of time.

These early enquiries were followed by larger single and multicenter retrospective cohort studies, with a longer follow-up period, but with contradictory results. Two recent studies, each evaluating a number of approximately 100 patients with LVT, showed no statistical difference between the rates of stroke, systemic embolism, thrombus resolution, bleeding, rehospitalization, and all-cause mortality [30,33]. However, a larger study conducted on over 500 patients reported some negative results of the DOAC treatment in LVT, with an increased risk of embolism after a median of 351 days of follow-up. Out of the entire study group, 43.9% of patients received DOAC (76.2% apixaban, 24.9% rivaroxaban, and 4.9% dabigatran). However, the study did not evaluate the number of haemorrhagic events, which theoretically should be lower in the DOAC patients [34].

Recently, a prospective randomized, multicentre open-label clinical trial compared the efficacy of apixaban versus warfarin in patients with LVT. The trial enrolled 35 patients, with post-MI LVT diagnosed through 2D TTE. Out of these, 17 patients were randomized to warfarin and 18 patients to apixaban. The primary endpoint of this study was thrombus resolution at 3 months, while the secondary endpoints were major bleeding, stroke or systemic embolism; rehospitalization; and all-cause mortality. The primary endpoint was achieved in 93.3% of the patients in the warfarin group and in 94% of the patients in the apixaban group ($p = 0.026$ for non-inferiority). In the warfarin group, two major bleedings and one stroke were recorded, while in the DOAC group there was one death [35].

Another recent multicenter open-label randomized, controlled trial (RCT) has randomized 79 patients with LVT 1:1 on either rivaroxaban or warfarin. The primary outcome was thrombus resolution at 1, 3, and 6 months; and the secondary outcomes were major bleeding, stroke, or systemic embolism. The study showed a statistically significant difference ($p = 0.03$) in the resolution of LVT at 1 month, in favour of DOAC. Furthermore, the number of stroke and ischemic events was higher in the warfarin group ($p = 0.04$). There was no difference regarding the main safety outcome, which was defined as the occurrence of major bleedings [36].

A recent meta-analysis has evaluated 16 cohort studies and the 2 RCTs mentioned above, covering 2666 patients with LVT taking oral anticoagulation (674 patients on DOAC and 1992 patients with VKA). The results of these analyses showed a significant statistical difference in the reduction of strokes favouring DOACs (OR 0.63, 95% CI 0.42–0.96; $p = 0.03$), with no differences regarding other endpoints such as bleeding (OR 0.72, 95% CI 0.50–1.02; $p = 0.07$), systemic embolies (OR 0.77, 95% CI 0.41–1.44; $p = 0.41$), thrombus resolution (OR 1.29, 95% CI 0.83–1.99; $p = 0.26$) and mortality (OR 1.01, 95% CI 0.64–1.57; $p = 0.98$). Probably the most important limitation of this study is the fact that most patient data was pooled from retrospective studies in which information on important variables (dose of DOAC, time in therapeutic INR and concurrent DAPT) were unavailable. Secondly, the mean age of the pooled population was 49–63 years, so these results might not be extrapolated to elderly patients who have a higher risk of bleeding and thromboembolic events [37].

Most patients develop LVT in the first 10–14 days after an AMI. Therefore, these patients usually require SAPT or even DAPT in the first year after AMI and the addition of an oral anticoagulant results in an important risk of bleeding. Current guidelines recommend reduction of the DOAC dose for the prevention of stroke, when combined with antiplatelet medication [38,39]. However, most of the studies evaluating DOACs for LVT used a standard dose or were inconsistent in reporting the DOAC dose. In this context, it will be important to evaluate the efficacy of lower DOAC dose in the prevention of thromboembolism, thrombus resolution, and also their safety profiles regarding major bleedings.

According to the aforementioned studies, oral anticoagulation with DOAC should be administered similarly to current guidelines and for time ranges between 3 and 6 months with periodic echocardiographic re-evaluation of the thrombus. Nevertheless, a certain category of patients can present a persistent thrombus on serial imaging analyses despite long-term DOAC or even VKA therapy. For these patients, there is no current consensus on how long anticoagulant treatment should be continued; however, studies showed that the highest risk for embolic events occurs 3 to 4 months after MI [40]. One suggested therapeutic strategy was increasing the treatment with VKA with a higher INR goal (3–4) in patients with persistent LVT thrombus, in order to achieve its resolution [28]. Unfractionated or low-molecular-weight heparin can be used as alternative therapeutic approaches, but there are no current studies regarding their efficiency [40]. Left ventricular thrombectomy is not a common procedure and therefore is not mentioned in international guidelines. Although surgical removal of LVT might decrease the incidence of thromboembolism than anticoagulant treatment more efficiently, it is also associated with an increase of mortality and morbidity which outweighs its benefits [3]. It can be an option, however, for patients that undergo other cardiac surgeries or in case of recurrent thromboembolic events.

## Conclusions

LVT remains one of the most important complications of STEMI, as it is associated with increased mortality and increased risk of stroke and systemic embolism. The main therapeutic option for LVT management remains anticoagulants, but it can be associated with an important level of bleeding risk. VKA is recommended by most guidelines as the best anticoagulant option, but its multiple interactions are associated with lower therapeutic range and patient adherence. Recent studies that evaluate DOACs as an alternative for VKA show promising results, with reduced embolic rates and bleeding events and with faster thrombus resolution. However, larger randomized, control trials are required to confirm these benefits.

## Conflicts of interest

none declared.

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