

THE PRESENT AND FUTURE

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Left Ventricular Thrombus Following Acute Myocardial Infarction

JACC State-of-the-Art Review



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ABSTRACT

The incidence of left ventricular (LV) thrombus following acute myocardial infarction has markedly declined in recent decades caused by advancements in reperfusion and antithrombotic therapies. Despite this, embolic events remain the most feared complication of LV thrombus necessitating systemic anticoagulation. Mechanistically, LV thrombus development depends on Virchow's triad (ie, endothelial injury from myocardial infarction, blood stasis from LV dysfunction, and hypercoagulability triggered by inflammation, with each of these elements representing potential therapeutic targets). Diagnostic modalities include transthoracic echocardiography with or without ultrasound-enhancing agents and cardiac magnetic resonance. Most LV thrombi develop within the first 2 weeks post-acute myocardial infarction, and the role of surveillance imaging appears limited. Vitamin K antagonists remain the mainstay of therapy because the efficacy of direct oral anticoagulants is less well established. Only meager data support the routine use of prophylactic anticoagulation, even in high-risk patients. (J Am Coll Cardiol 2022;79:1010-1022) © 2022 Published by Elsevier on behalf of the American College of Cardiology Foundation.

Although the incidence of left ventricular (LV) thrombus after acute myocardial infarction (AMI) has substantially declined in recent decades largely caused by early primary percutaneous coronary intervention (PCI) and the adjunctive antithrombotic regimen, LV thrombus remains an important complication of AMI given the high risk for subsequent stroke and systemic embolism.¹⁻⁴ The most current American guidelines recommend vitamin K antagonists (VKAs) over direct oral anticoagulants (DOACs) for the prevention of embolic events in patients with AMI complicated by LV thrombus.^{5,6} Further complicating the matter, data from patients undergoing PCI with other indications

for oral anticoagulation, such as atrial fibrillation or mechanical heart valves, have shown an increased risk of bleeding when oral anticoagulants (OACs) are combined with dual antiplatelet therapy (DAPT).⁷ Indeed, emerging evidence favors a tailored antithrombotic regimen consisting of a single antiplatelet agent with a DOAC,⁸ but whether this can be extrapolated to patients with LV thrombus after AMI has not been studied in randomized trials. Herein we review the literature surrounding the epidemiology, pathophysiology, diagnosis, management, and surveillance of LV thrombus after AMI and provide an algorithmic approach to the diagnosis and management of this challenging clinical scenario. This review does not



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HIGHLIGHTS

- The management of patients with left ventricular mural thrombus after AMI is challenging because insufficient evidence is available from randomized trials.
- In patients with or at high risk of developing LV thrombus, serial imaging may identify features warranting more intensive or prolonged antithrombotic therapy to reduce the risk of embolism.
- Additional research is needed to determine the optimum timing of initial and surveillance imaging and evaluate alternative antithrombotic strategies for patients with LV mural thrombus after AMI.

report data on human subjects; therefore, we did not obtain ethical/Institutional Review Board approval for our submission.

EPIDEMIOLOGY

The incidence of LV thrombus after AMI has significantly declined since the introduction of reperfusion therapies. In the prethrombolytic era, the reported incidence of LV thrombus following acute anterior wall myocardial infarction (MI) was as high as 60%.⁹⁻¹² Thrombolytic therapies may reduce the occurrence of LV thrombus, but it remained highly prevalent (up to 40%), especially in patients with large infarcts.¹³⁻¹⁶ In the primary PCI era, the reported rates of LV thrombus after AMI are wide ranging, likely reflecting differences in anatomy, timing of intervention post-MI, and the type and timing of diagnostic imaging in relation to the event. In a 2016 meta-analysis of >10,000 patients with ST-segment elevation myocardial infarction (STEMI), the overall incidence of LV thrombus was 2.7% (207 of 7,471) and 9.1% (282 of 3,447) in those with anterior STEMI.¹⁷ A more recent meta-analysis of >2,000 patients with LV thrombus detected by cardiac magnetic resonance (CMR) within 1 month of STEMI described an incidence of LV thrombus up to 6.3% in patients with STEMI, 12.2% in those with anterior STEMI, and 19.2% in those with anterior STEMI and left ventricular ejection fraction (LVEF) <50%,¹⁸ suggesting that the overall incidence may be underestimated. In a broader sense, these reports have major implications on which patients would likely benefit from close follow-up for LV thrombus because the rate of left anterior descending (LAD) STEMI (ie, anterior-apical) from the contemporary SWEDEHEART (Swedish

Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies) registry was 38% (23,569 of 62,048 STEMI patients),¹⁹ and the rate of heart failure or LV dysfunction either at baseline or during hospitalization for AMI was 42% (2,347 of 5,573 AMI patients) in the VALIANT (Valsartan in Acute Myocardial Infarction) registry, of which 58.5% (n = 992) had LVEF <40%.²⁰

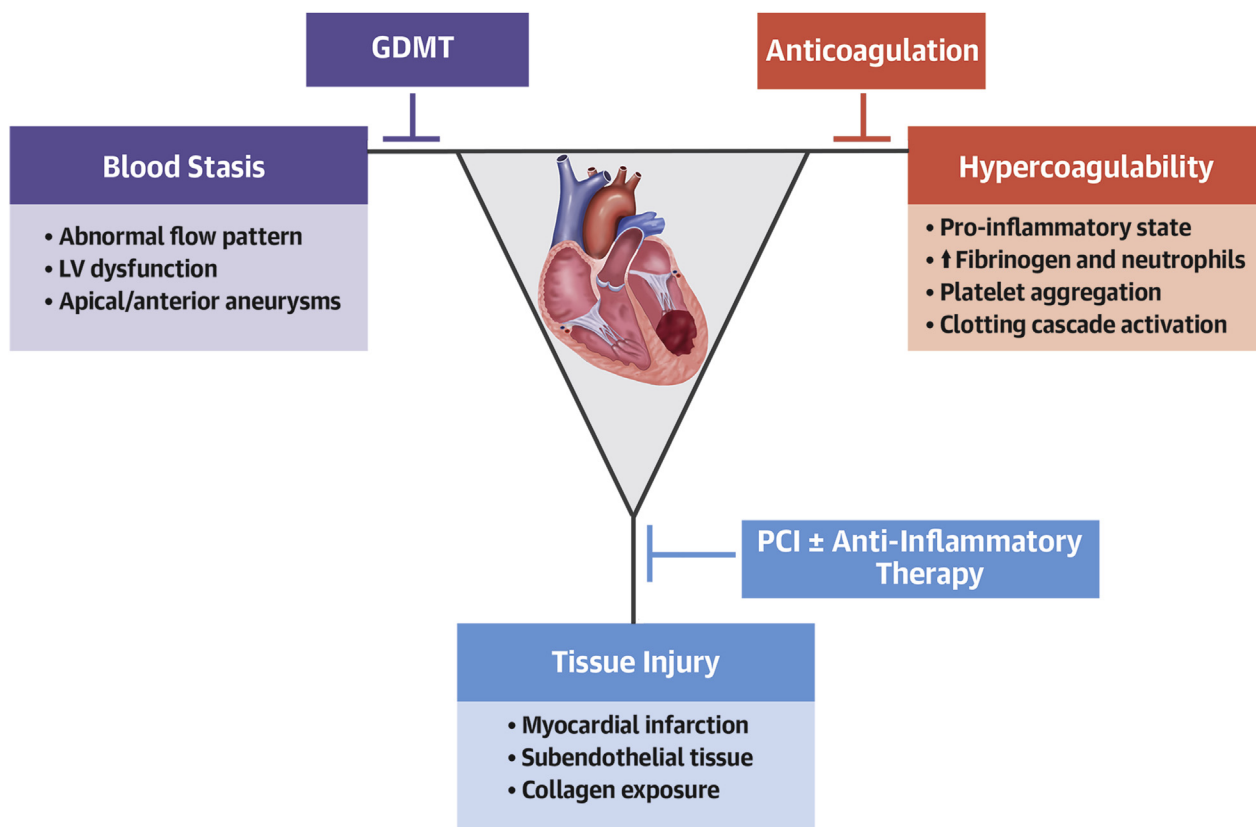
These findings may be explained by the imaging modality used to detect LV thrombus because multiple studies have demonstrated the superiority of CMR imaging over transthoracic echocardiography (TTE) in detecting smaller, laminar LV mural thrombus.^{18,21-23} As reported in a recent meta-analysis of 2,072 patients with STEMI, among the 431 with both CMR and TTE data, the sensitivity of TTE was 29% (95% CI: 17%-45%) with a specificity of 98% (95% CI: 96%-99%) compared with CMR; however, none of the studies in this meta-analysis included ultrasound-enhancing agents or newer 3-dimensional volumetric methods when TTE was used to detect LV thrombus.¹⁸ Consequently, these data suggest not only that the incidence of LV thrombus after MI has been underestimated but also that it was likely underestimated in the pre-PCI era as well.

Thromboembolic events caused by LV thrombi can be devastating. The risk of embolism in patients with documented LV thrombus appears most closely related to 2 imaging characteristics: thrombus mobility and protrusion.²⁴⁻²⁶ One study of 92 patients with LV thrombus after MI found a 16% incidence of systemic embolism over a median follow-up of 5.4 years, driven largely by an incidence of 19% in patients on warfarin with a time in the therapeutic range <50% compared with 3% in those with more consistently therapeutic anticoagulation.²⁷ McCarthy et al²⁸ found incidence rates of all-cause death of 13% and embolic events of 1.9% over a 1-year follow-up in patients with LV thrombus; however, 25.9% of the patients had LV thrombus precipitated by AMI compared with 68.5% occurring in the setting of chronic heart failure. The incidence of embolic events in patients presenting with AMI was not specified. A more recent investigation of >90,000 consecutive TTEs performed at a single center from 2011 to 2018 found an overall incidence of LV thrombus of 0.18% (n = 159; 74 associated with acute MI) during a median follow-up of 632 days.²⁹ Patients with LV thrombus were subsequently treated with VKAs

ABBREVIATIONS AND ACRONYMS

- ACS** = acute coronary syndrome
AHA = American Heart Association
AMI = acute myocardial infarction
CMR = cardiac magnetic resonance
CT = computed tomography
DAPT = dual antiplatelet therapy
DOAC = direct oral anticoagulant
LAD = left anterior descending
LGE = late gadolinium enhancement
LV = left ventricular
LVEF = left ventricular ejection fraction
MI = myocardial infarction
OAC = oral anticoagulant
PCI = percutaneous coronary intervention
STEMI = ST-segment elevation myocardial infarction
TEE = transesophageal echocardiography
TTE = transthoracic echocardiography
VKA = vitamin K antagonists

CENTRAL ILLUSTRATION Virchow's Triad: Pathophysiological Basis and Treatment Targets



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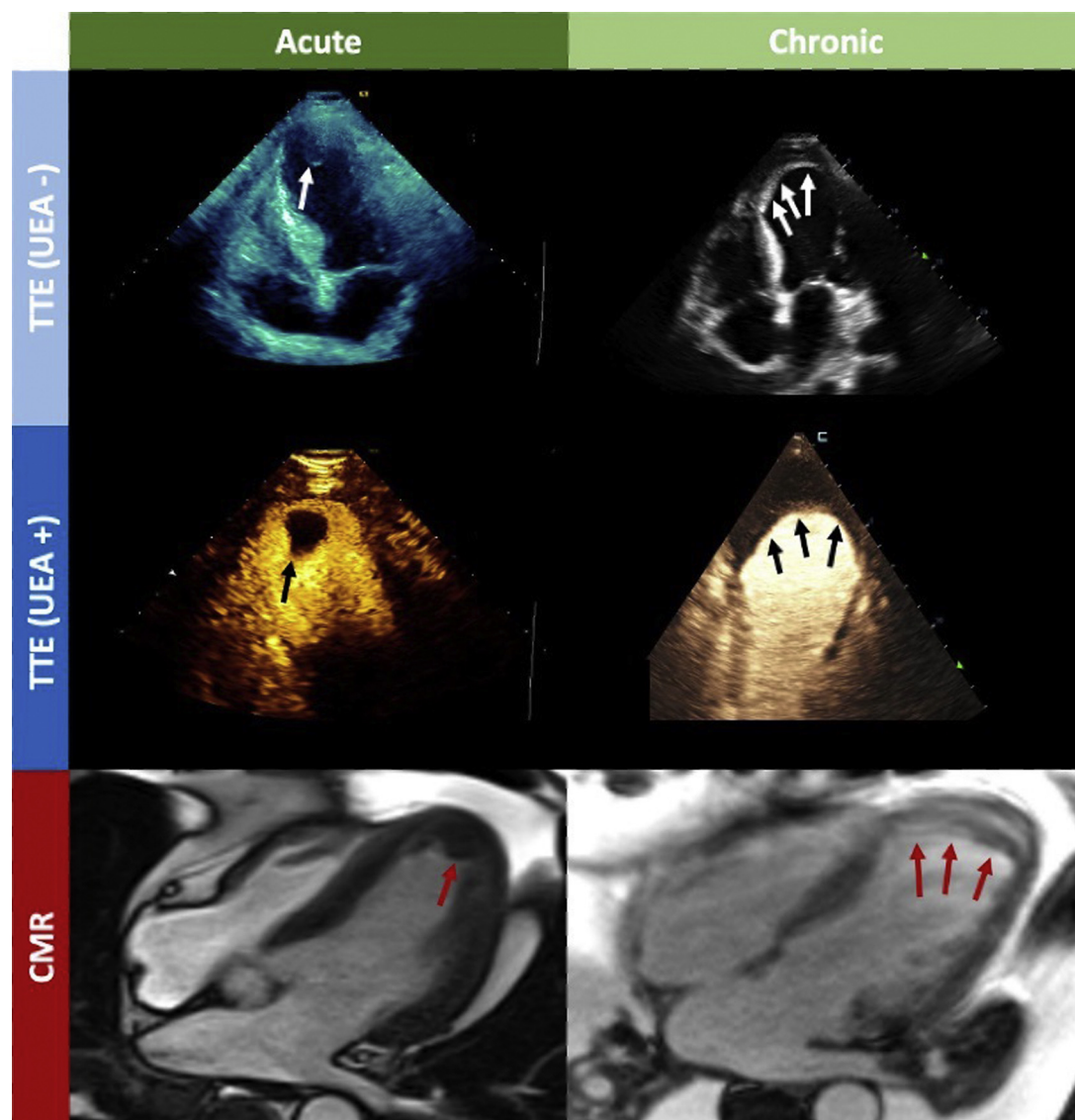
Left ventricular (LV) thrombus development following acute myocardial infarction is driven by the elements of Virchow's triad: endothelial injury, blood stasis, and hypercoagulability. Each of these components further serves as a therapeutic target in the treatment and prevention of left ventricular thrombus following acute myocardial infarction. GDMT = guideline-directed medical therapy; PCI = percutaneous coronary intervention.

(48.4%), parenteral heparins (27.7%), and DOACs (22.6%). In patients with treated LV thrombus, all-cause death occurred in 18.9%, major adverse cardiovascular events in 37.1%, embolic complications in 22.2%, and major bleeding in 13.2%.²⁹ Although there was a significant reduction in mortality in patients with LV thrombus regression (15.2% vs 25.0%; HR: 0.48; 95% CI: 0.23-0.98; $P = 0.039$) compared with persistent thrombus at a median of 338 days after baseline TTE, there was no significant difference in embolic complications between these groups (22.2% vs 22.0%).²⁹ These findings implicate persistent thrombus as a marker of persistent LV dysfunction, which was associated with more major adverse cardiovascular events, and not necessarily as the cause of death.

PATHOPHYSIOLOGY, ANATOMY, AND NATURAL HISTORY

Virchow's triad, the cornerstone of LV thrombus formation following AMI, includes endothelial injury, blood stasis, and hypercoagulability (Central Illustration). Mechanically, infarct expansion with regional thinning and dilation of the damaged endothelium in the infarct zone begins almost immediately, increases wall stress, and may lead to ventricular aneurysm formation.³⁰ Blood stasis is primarily driven by LV dysfunction with a reduced ejection fraction and/or large apical or anterior LV akinesis or dyskinesis (ie, aneurysm) and reduced contractile function facilitating stasis caused by an abnormal vortex. Indeed, the presence of LV

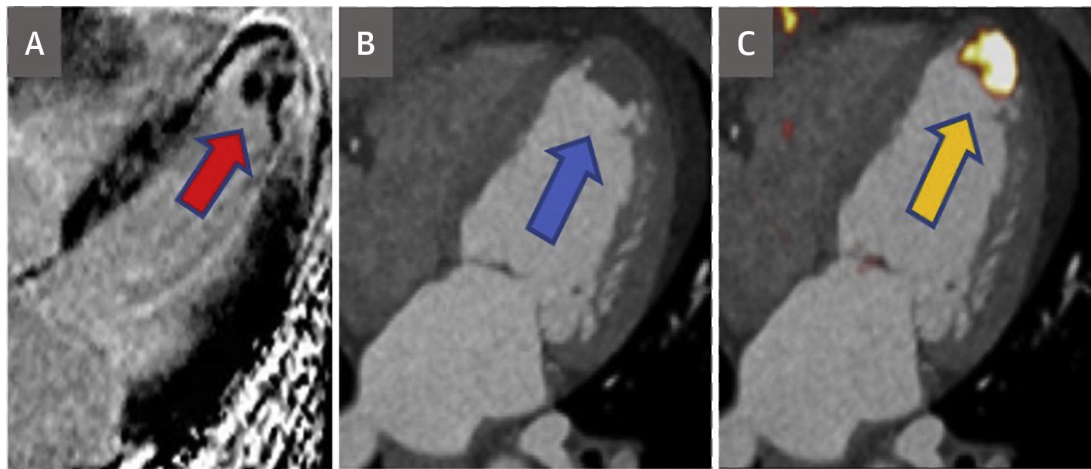
FIGURE 1 Visual Representation of Acute and Chronic Left Ventricular Thrombi



Acute and chronic left ventricular thrombi as seen by transthoracic echocardiography (TTE) with and without an ultrasound-enhancing agent (UEA) and cardiac magnetic resonance (CMR). **Single arrows (white, black, and red)** depict acute thrombus formation characterized as a protruding apical mass. **Triple arrows (white, black, and red)** show chronic thrombus formation characterized as a smooth, laminar apical mass. **Black and white arrows** show thrombus detected by TTE with and without the use of a UEA, respectively. **Red arrows** show thrombus detected by CMR.

dysfunction and/or large apical or anterior LV akinesis or dyskinesis has been strongly associated with LV thrombus formation in the first 7 days after AMI,^{17,18} evidence that stasis caused by MI is an important component of thrombus formation.^{22,31} Additionally, abnormal flow patterns resulting from regional LV dysfunction are closely associated with thrombus formation compared with normal flow patterns.³²

Local tissue injury in combination with the low shear rate in the infarct zone activates the coagulation system, leading to the accumulation of fibrin via cross-linking (common pathway), platelets (intrinsic pathway), and erythrocytes, which collectively form the fresh thrombus.³³ This fundamental understanding of tissue injury, stasis, and fibrin cross-linking during thrombus formation is the rationale for the

FIGURE 2 Imaging Assessments of LV Thrombus Following Acute Anterior Myocardial Infarction

(A) Late gadolinium enhancement cardiovascular magnetic resonance image demonstrating an apical left ventricular (LV) thrombus (**red arrow, black filling defect**) overlying a transmural apical myocardial infarction with microvascular obstruction; (B) contrast CT coronary angiogram demonstrating a small thrombus at the apex (**blue arrow**); which (C) demonstrates avid uptake (**yellow arrow**) of the positron emission tomographic radiotracer ^{18}F -GP1, which targets activated platelet glycoprotein IIb/IIIa receptors.

use of anticoagulants rather than antiplatelet drugs in patients with LV thrombus.³⁴

Endothelial injury in the setting of AMI triggers an inflammatory and prothrombotic state (ie, hypercoagulability) by exposing subendothelial tissue and collagen to the circulating blood.³³ Larger infarcts, evidenced by higher levels of cardiac enzymes, have also been associated with increased rates of LV thrombus formation compared with patients with smaller infarcts.³⁵ Baseline C-reactive protein, fibrinogen, and the neutrophil-lymphocyte ratio are independent predictors of early LV thrombus formation after AMI.³⁶ In this context, the propagation and growth of small thrombi into larger thrombi protruding into the ventricular cavity and exposed to circulating blood flow may lead to embolism.³³ The hypercoagulable state following AMI appears to persist for up to 6 months or longer.³⁷ Fresh thrombus may contribute to a persistent inflammatory reaction in the underlying myocardium and is itself thrombogenic,^{30,33} whereas chronic thrombus is less prone to embolism once it becomes more firmly anchored to the endocardium, more laminar and less protruding, and isolated from the dynamic forces of circulating blood.^{33,34} The recovery of ventricular function after treatment increases blood flow and lessens stasis, whereas the resolution of myocardial inflammation slows thrombus expansion. Treatment with intravenous heparin appears to reduce mural rather than protruding thrombus.³⁸ In 1 study of 261 patients with

AMI in the prereperfusion era, 46 (17.6%) developed LV thrombus, and 43 were followed for a mean of 15 months with serial TTE.³⁹ Embolism occurred in 7 patients, none of whom had received anticoagulation, and all occurred within 4 months of the incident MI.³⁹ Indeed, it is likely that thrombus will resolve in >50% of patients by 6 months after the index MI.^{30,40} For those without thrombus resolution beyond this period, fibrosed, endothelialized mural LV thrombus may play a salutary role by limiting infarct expansion, reducing wall stress, limiting aneurysm development, and restoring partial thickness to the myocardium, improving global myocardial performance.³⁰ Thus, physical characteristics of the thrombus (ie, its size, shape, mural [sessile] or protruding morphology, mobility, and age relative to the acute event) may influence its consequences.

DIAGNOSIS

CMR IMAGING. CMR remains the optimum imaging modality for the diagnosis and assessment of LV thrombus, with a sensitivity of 82%-88% and specificity approaching 100% compared with surgical and/or pathological confirmation.⁴¹ When imaging LV thrombus with CMR, cine CMR is more commonplace, but late gadolinium enhancement (LGE) CMR, which uses an inversion recovery pulse sequence with “long T1” imaging (T1 = 600 milliseconds) after cine CMR, has been shown to improve

thrombus detection; however, its widespread use is limited by significant cost and limited clinical applicability, particularly in those with end-stage renal disease.²² Because of their avascular composition, LV thrombi do not demonstrate gadolinium uptake and therefore appear black during CMR imaging and can be readily differentiated from the surrounding infarcted myocardium and blood pool after contrast administration (**Figures 1 and 2A**).²² Beyond its diagnostic capabilities, CMR has also demonstrated value in identifying structural risk factors for LV thrombus formation, particularly myocardial scar burden or infarct size.⁴² In 1 study, despite nearly identical LVEFs, LV thrombus detected by delayed enhancement CMR (LGE CMR) was >5-fold more prevalent in patients with ischemic than nonischemic cardiomyopathy, and infarct size (ie, the proportion of scarred myocardium) was independently associated with thrombus formation (OR: 1.02; 95% CI: 1.002–1.04 per % LV transmural infarction; $P = 0.03$).⁴² Furthermore, the increased prevalence observed in patients with ischemic heart disease was mirrored by a >3-fold increase in scar burden compared with patients with nonischemic cardiomyopathy.⁴² Widespread use of CMR has been limited by cost and availability. To that end, data suggest that LV thrombus detected by CMR but missed by TTE is associated with clinical outcomes similar to those in patients with thrombus evident on TTE. In a large cohort of patients with LV thrombus detected by LGE CMR, the annualized incidence of embolism was 3.7% despite the use of contemporary anticoagulant treatment in 89% of patients. This compared with a 0.8% annual incidence of embolism in matched patients without LV thrombus. Among patients with LV thrombus detected by LGE CMR ($N = 157$), the rate of embolism was independent of whether the LV thrombus was identified echocardiographically.⁴³ In this study, 110 patients had TTE performed within 10 days of the CMR, of whom 64% (70 of 110) had TTE with contrast. Although CMR may detect small mural thrombi more frequently than other imaging modalities, the clinical impact of smaller, laminar thrombi may be less severe.

TTE. Considering its widespread availability and affordability relative to CMR and its utility in assessing ventricular function and structural abnormalities, TTE is the most commonly used imaging modality to diagnose LV thrombus after AMI.^{2,18} An LV thrombus typically appears as an echo-dense mass distinct from the surrounding endocardium and adjacent to an akinetic or hypokinetic LV segment or aneurysm most commonly observed at the LV apex because this is the

region of slowest flow and greatest stasis after large anteroapical MI in the territory supplied by the LAD.^{9,22} LV thrombi can be classified as protuberant and/or mobile when acute or mural and/or sessile and flat in the chronic period (**Figure 1**) post-MI. TTE has high diagnostic accuracy for LV thrombus after acute MI with specificity in the range of 95% to 98% offset by relatively low sensitivity (21%–35%), suggesting that many LV thrombi will be missed by TTE.^{21–23,41} This low sensitivity may be related to inadequate visualization of the LV apex, small thrombus size, and poor acoustic windows. The addition of an intravenous ultrasound-enhancing (contrast) agent improves both the specificity (99%) and sensitivity (64%) of TTE, particularly in patients with anterior MI, by enhancing the endocardial border definition.²²

The severity of wall motion abnormalities as assessed by TTE has been proposed as a screening test before CMR imaging. Using the apical wall motion score, Weinsaft et al²² showed that higher scores (≥ 7 with contrast and ≥ 5 without contrast) had a sensitivity of approximately 100% and a negative predictive value of 100% for detecting LV thrombi. These findings suggest that TTE with a high apical wall motion score (poorer apical function) appropriately identifies patients who would benefit from further imaging with CMR while avoiding unnecessary additional testing. Transesophageal echocardiography (TEE) has limited added utility to TTE in diagnosing LV thrombus because the LV apex, particularly in patients with a dilated left ventricle and apical dyskinesia, is typically foreshortened and may be poorly visualized from either the transesophageal or transgastric views.

COMPUTED TOMOGRAPHY. Computed tomography (CT) has not been validated as a diagnostic imaging modality for LV thrombus; however, in 1 study, the use of CT for detecting left atrial appendage thrombus has been shown to have a sensitivity and specificity of 100% and 92%, respectively, with a negative predictive value of 100% and a positive predictive value of 23% compared with TEE offering promise for its potential role in detecting LV thrombus.⁴⁴ Additionally, a meta-analysis of 2,955 patients corroborated these findings with a sensitivity of 96% and a specificity of 92% for detecting left atrial or left atrial appendage thrombi with CT compared with TEE; these values increased to 100% and 99%, respectively, when delayed imaging was performed during CT.⁴⁵ Contrast-enhanced coronary CT angiography has great potential for widespread adoption in the detection of LV thrombus given its very high spatial (<1 mm) resolution, excellent depiction of cardiac morphology, rapidity of use, and low cost.⁴⁶ Moreover, the use of spectral CT with dual-substance

separation technology including blood vs iodine-based technology has been proposed as a technique for identifying LV thrombus but warrants further investigation (**Figure 2B**).⁴⁷

MOLECULAR IMAGING. Emerging positron emission tomography techniques targeting active thrombus formation hold promise to improve our understanding of LV thrombus development and its cerebrovascular complications. Early data indicate that the radiotracer ¹⁸F-GP1, which binds to activated platelet glycoprotein IIb/IIIa receptors, demonstrates a high signal in both regions of LV thrombus following MI (**Figure 2C**) and areas of cerebral and coronary thromboembolism.^{48,49} Longitudinal studies are investigating the activity of this tracer in both the hearts and brains of patients following anterior MI and how this is affected by anticoagulant therapy ([NCT04829825](#)).

TIMING. The timing of imaging relative to the incident MI appears to have diagnostic relevance. In a series of 92 consecutive patients with acute anterior MI treated with antithrombotic therapy consisting of aspirin, heparin (5,000 IU twice daily subcutaneously during immobilization), and thrombolytics, LV thrombus was identified by TTE in 30 patients (27% within the first 24 hours, 57% between 48 and 72 hours, 75% at 1 week, and 96% at 2 weeks post-MI).¹² In another series of 198 consecutive patients with acute MI, thrombus was identified before discharge (10.6 ± 4.1 days post-MI) in 38 (31%) of the 124 patients with anterior MI and none of the 74 patients with inferior MI.⁴⁰ An ancillary report of the HEART (Healing and Early Afterload Reducing Therapy) study that aimed to assess the prevalence of LV thrombus by TTE following AMI (97% receiving reperfusion therapy) showed a prevalence of 0.6% at day 1, 3.7% at day 14, and 2.5% at day 90.⁵⁰ Contemporary studies have corroborated these findings. One report demonstrated that the highest rate of LV thrombus (approximately 40%) was in those with TTE performed between 8 and 15 days after MI.⁵¹ Another recent analysis showed the highest rate of LV thrombus (25%) in those with CMR performed between 9 and 12 days after the incident MI and <5% and 10% between days 0 to 2 and 3 to 5, respectively.⁵² These data suggest that most LV thrombi can be diagnosed within 2 weeks of AMI, and high-risk patients without LV thrombus on early imaging (eg, within 48 hours of incident MI) should be reimaged 2 weeks after the acute event. These findings also raise the possibility that underestimation of LV thrombi post-MI in the current era may be related to earlier hospital discharge and lack of surveillance imaging in the outpatient setting; in fact, in 1 single-

center, tertiary care registry of all-comers with LV thrombus, 35% of patients with LV thrombus treated with anticoagulation did not undergo repeat imaging within 1 year of follow-up, calling into question how many patients without LV thrombus but with high-risk features for LV thrombus undergo surveillance imaging.²⁸ Moreover, these studies failed to distinguish between smaller, endothelialized thrombi that eluded detection by standard TTE and protruding thrombi that have greater embolic potential.

TREATMENT AND PREVENTION OF EMBOLIC EVENTS

PROPHYLAXIS. The 2013 American College of Cardiology Foundation/American Heart Association (AHA) STEMI guidelines provide a soft, Class 2b, Level of Evidence: C recommendation for prophylactic anticoagulant therapy, stating that a VKA may be considered for patients with STEMI and anterior apical akinesis or dyskinesis.⁵ They advise targeting therapy to a lower international normalized ratio (INR: 2.0-2.5) in patients with STEMI concurrently receiving DAPT.⁵ The 2014 AHA/American Stroke Association stroke guidelines provide a similar recommendation (Class 2b, Level of Evidence: C) for treatment with VKA therapy (target INR: 2.5; range: 2.0-3.0) for 3 months in patients with ischemic stroke or transient ischemic attack in the setting of acute anterior STEMI without demonstrable LV mural thrombus in whom anterior apical akinesis or dyskinesis is identified by imaging.⁶ The American College of Chest Physicians guidelines recommend VKA therapy in addition to DAPT (Grade 2C) for 3-6 months among patients with anterior MI at high risk for LV thrombus (ie, LVEF <40% and anterior-apical wall motion abnormality).⁵³ These recommendations were based mainly on meta-analyses.^{54,55} The 2017 European Society of Cardiology STEMI guidelines do not provide a recommendation for prophylactic VKA therapy in patients post-STEMI.⁵⁶

A meta-analysis from 1993 of 4 studies enrolling 307 patients with anterior MI from the prereperfusion era showed a 68% relative risk reduction (OR: 0.32; 95% CI: 0.20-0.52) in mural thrombus formation with anticoagulation.⁵⁴ Similarly, a later meta-analysis from 2006 comprising 25,307 patients with acute coronary syndrome (ACS) found a statistically significant reduction in the incidence of nonfatal thromboembolic strokes in patients treated with aspirin plus warfarin compared with those given aspirin alone (OR: 0.81; 95% CI: 0.67-0.97).⁵⁵ This difference was accentuated when limited to studies in which the target INR was 2 to 3 (OR: 0.43; 95% CI: 0.27-0.70) but

TABLE 1 Descriptive Characteristics of Studies Comparing Vitamin K Antagonists With Direct Oral Anticoagulants in Patients With Left Ventricular Thrombus

First Author (Ref. #)	Year	Sample Size	Study Design	Inclusion	Exclusion	Treatment Assignment	Follow-Up	LVT Resolution	Embolic Events	Bleeding
Abdelnabi et al ⁷⁴	2021	79	Unblinded RCT	Adults with newly diagnosed LVT by TTE	CrCl <50 mL/min, AF, DVT/PE, other indication for OAC	Warfarin: 40 (50.6) Rivaroxaban: 39 (49.4)	6 mo	Warfarin: 32 (80) Rivaroxaban: 34 (87.2)	Warfarin: 6 (15) Rivaroxaban: 0 (0)	Warfarin: 6 (15) Rivaroxaban: 2 (5.1)
Lattuca et al ²⁹	2020	159	Retrospective observational	All patients with reported LVT	RV and/or atrial thrombus	VKA: 77 (48.4) DOAC: 36 (22.6) LMWH: 37 (23.3) UFH: 7 (4.4) APT: 2 (1.2)	632 d (IQR: 187–1,126 d)	121 (76.1)	35 (22.2)	BARC ≥2: 27 (17) BARC ≥3: 21 (13.2)
Daher et al ⁶²	2020	59	Retrospective observational	All patients with TTE-confirmed LVT	N/A	VKA: 42 (71.2) DOAC: 17 (28.8)	N/A	VKA: 30 (71.4) DOAC: 12 (70.6)	VKA: 4 (9.5) DOAC: 2 (11.8)	N/A
Guddeti et al ⁶³	2020	99	Retrospective observational	All patients with diagnosed LVT	N/A	VKA: 80 (81) DOAC: 19 (19)	1 y	VKA: 65 (81) DOAC: 15 (80)	VKA: 2 (2) DOAC: 0 (0)	VKA: 4 (5) DOAC: 1 (5.3) (<i>P</i> = 0.96)
Iqbal et al ⁶⁴	2020	84	Retrospective observational	All patients with LVT, treated with DOAC or VKA	N/A	VKA: 62 (73.8) DOAC: 22 (26.2)	3 ± 1.4 y	VKA: 42 (76) DOAC: 13 (65)	VKA: 4 (4) DOAC: 0 (0)	VKA: 6 (10) DOAC: 0 (0) <i>P</i> = 0.13
Jones et al ⁶⁵	2020	101	Retrospective observational	LVT post AMI	Patients without AMI or recent MI	VKA: 60 (59.4) DOAC: 41 (40.6)	1 y	VKA: 39 (64.4) DOAC: 34 (82) <i>P</i> = 0.0018	VKA: 3 (5) DOAC: 1 (2.4) <i>P</i> = 0.388	BARC 2 VKA: 4 (6.7) DOAC: 0 (0) <i>P</i> = 0.03
Robinson et al ⁶⁶	2020	514	Retrospective observational	All patients with TTE-diagnosed LVT	N/A	VKA: 300 (58.4) DOAC: 185 (36)	351 d (IQR 51–866 d)	VKA: 131 (43.7) DOAC: 56 (30.3)	VKA: 14 (4.7) DOAC: 17 (9.2)	VKA: 19 (6.3) DOAC: 8 (4.3)
Bass et al ⁶⁷	2021	949	Retrospective observational	ICD-9/10 criteria for LVT	N/A	VKA: 769 (81) DOAC: 180 (19)	90 d	N/A	VKA: 254 (33) DOAC: 55 (30.6) <i>P</i> = 0.53	VKA: 80 (10.9) DOAC: 14 (7.8) <i>P</i> = 0.40
Ali et al ⁶⁸	2020	110	Retrospective observational	All patients with confirmed LV thrombus	N/A	VKA: 60 (63) DOAC: 32 (33) LMWH: 4 (3)	1 y	VKA: 37 (61.7) DOAC: 18 (56.3)	VKA: 16 (26.6) DOAC: 2 (6)	N/A

Values are n (%) unless otherwise indicated.
AF = atrial fibrillation; AMI = acute myocardial infarction; BARC = Bleeding Academic Research Consortium; CrCl = creatinine clearance; DOAC = direct oral anticoagulant; DVT = deep vein thrombosis; ICD-9/10 = International Classification of Diseases-9th Revision/10th Revision; IQR = interquartile range; LMWH = low-molecular-weight heparin; LVT = left ventricular thrombus; PE = pulmonary embolism; RCT = randomized controlled trial; RV = right ventricular; TTE = transthoracic echocardiography; UFH = unfractionated heparin; VKA = vitamin K antagonist.

offset by an increased risk of major bleeding. However, none of the trials examined in this meta-analysis included patients treated with primary PCI and/or DAPT. The FRAMI (Fragmin in Acute Myocardial Infarction) study randomized 776 patients with acute MI and found a statistically significant reduction in the risk of LV thrombus formation with dalteparin compared with placebo (14.2% vs 21.9%; OR: 0.63; 95% CI: 0.43–0.92) at the expense of major bleeding.⁵⁷ This study only included patients with AMI who had received thrombolytic therapy and aspirin, and the results are likely not generalizable to the modern PCI era.

No randomized controlled trial has evaluated the role of adjunctive OAC therapy for the prevention of LV thrombus in the modern PCI era. Earlier studies examining adjunctive OAC therapy after ACS yielded conflicting results. In the RE-DEEM (RandomizEd Dabigatran Etxilate Dose Finding Study in Patients With Acute Coronary Syndromes Post Index Event With Additional Risk Factors for Cardiovascular Complications Also Receiving Aspirin and Clopidogrel:

Multi-centre, Prospective, Placebo Controlled, Cohort Dose Escalation) trial, 1,861 patients (99.2% on DAPT) 7 days post-ACS were randomized to 4 doses of dabigatran or placebo.⁵⁸ There was a dose-dependent increase in the risk of major or clinically relevant nonmajor bleeding during the 6-month treatment period. Similarly, in patients with ACS and at least 2 additional ischemic risk factors in the APPRAISE-2 (Apixaban for Prevention of Acute Ischemic Events 2) trial (N = 7,392), apixaban (5 mg twice daily) on top of DAPT increased the risk of thrombolysis in MI major bleeding from 0.5% to 1.3% (*P* = 0.001) without reducing major adverse cardiovascular events.⁵⁹ The difference in ischemic strokes was not statistically significant (*P* = 0.14).⁵⁹ In the ATLAS ACS 2-TIMI 51 (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects With Acute Coronary Syndrome 2-Thrombolysis In Myocardial Infarction 51) trial (N = 15,526), combining low-dose rivaroxaban (2.5 mg twice daily or 5 mg twice daily) with DAPT after ACS reduced the composite of cardiovascular death, MI, or stroke from 10.7% to 8.9%

FIGURE 3 Proposed Diagnostic and Management Approach to LV Thrombus Following AMI

```
graph TD
    Start([TTE with contrast within 24 h of AMI]) --> NoThrombus1[No LV thrombus]
    Start --> Thrombus1[LV thrombus]
    
    NoThrombus1 --> HighRisk[Apical akinesis/dyskinesis  
OR  
High apical wall motion score  
OR  
Unable to visualize LV apex]
    HighRisk -- "+" --> TTE72[TTE with contrast within 72 h of MI]
    HighRisk -- "-" --> DAPT[DAPT x12 months]
    
    TTE72 --> RepeatTTE2w[Repeat TTE with contrast after 2 weeks]
    RepeatTTE2w -- "?" --> CMR[CMR or CT]
    CMR -- "+" --> Thrombus2[LV thrombus]
    CMR -- "-" --> DAPT
    
    Thrombus1 --> Anticoag[VKAs/DOAC* + P2Y12 inhibitor]
    Anticoag --> RepeatTTE3m[Repeat TTE with contrast after 3 months]
    RepeatTTE3m --> NoThrombus2[No LV thrombus]
    RepeatTTE3m -- "+" --> Thrombus2
    
    NoThrombus2 --> StopOAC{{Stop OAC}}
    DAPT --> StopOAC
    Thrombus2 --> StopOAC
```

Here we propose an algorithmic approach to the diagnosis and management of left ventricular (LV) thrombus following acute myocardial infarction (AMI) that begins with transthoracic echocardiography (TTE) with contrast within 24 hours of index myocardial infarction (MI). In patients without evidence of LV thrombus and no high-risk features, we do not recommend anticoagulation. In those with thrombus, we recommend anticoagulation, preferably with a vitamin K antagonist (VKA), and a P2Y₁₂ receptor inhibitor for 3 months with surveillance imaging at that time. In patients without LV thrombus on the initial TTE but with high-risk features, we recommend repeat TTE with contrast at 72 hours and cardiac magnetic resonance (CMR) or computed tomography (CT) in those with equivocal findings. *Direct oral anticoagulant (DOAC) if VKA contraindicated. DAPT = dual antiplatelet therapy; OAC = oral anticoagulant.

TREATMENT. Observational studies comparing the efficacy of VKAs vs DOACs for the treatment of LV thrombus have yielded conflicting results (**Table 1**).^{29,62-68} One small, retrospective study of 52 cases of confirmed LV thrombus treated with DOACs found thrombus resolution in 83% of cases after a mean of 264 days.⁶⁹ In a study of 514 patients with TTE-

identified LV thrombi from 3 tertiary medical centers, anticoagulation with DOACs was associated with a higher risk of stroke or systemic embolism compared with VKAs (HR: 2.64; 95% CI: 1.28-5.43; $P = 0.01$).⁶⁶ In 1 single-center registry of 128 all-comer patients with LV thrombus (25.9% presenting with acute MI), 87% were treated with a VKA, 9.2% with low-molecular-weight heparin, 2.8% with apixaban, and 0.9% with rivaroxaban.²⁸ On the other hand, in another single-center study of 159 patients with LV thrombus, 48.4% were treated with VKAs, 27.7% with parenteral heparins, and 22.6% with DOACs.²⁹ In reality, and despite the limited data, the clinical use of DOACs for the treatment of LV thrombus is likely more common than expected given their overall ease of use compared with VKAs (ie, absence of blood testing and INR monitoring). Randomized trials of PCI in patients with atrial fibrillation without proven left atrial appendage thrombus demonstrated better safety with DOACs (rather than VKAs) combined with single antiplatelet therapy (without aspirin, rather than DAPT),⁸ but whether the advantage of this strategy extends to patients with LV thrombus following MI is unknown, particularly because the atrial fibrillation trials were not powered to assess antithrombotic efficacy.⁷⁰⁻⁷³

To date, only 1 randomized controlled trial has compared an OAC with a DOAC (rivaroxaban 20 mg daily) vs warfarin.⁷⁴ In the No-LVT (Comparative Study of Oral Anticoagulation in Left Ventricular Thrombi) trial, 79 patients at 5 centers in Egypt and Bulgaria with LV thrombus newly detected by TTE were randomized to rivaroxaban ($n = 39$) or warfarin ($n = 40$) in unblinded fashion. Patients in the warfarin group were bridged to an INR of 2-3 with enoxaparin. Just >50% of patients were on DAPT, and the time in the therapeutic range for those in the warfarin group was 82%. Complete thrombus resolution occurred in 72%, 77%, and 87% in the rivaroxaban group and in 48%, 68%, and 80% in the warfarin group at 1, 3, and 6 months ($P = 0.084$, 0.7, and 0.7, respectively). At 1 month, LV thrombus resolution was significantly more frequent in the rivaroxaban group (OR: 2.813; $P = 0.03$). There were no strokes in the rivaroxaban group vs 4 in the warfarin group ($P = 0.08$). Major bleeding occurred in 2 patients (5%) in the rivaroxaban group compared with 6 (15%) in the warfarin group ($P = 0.11$); 75% of bleeding events occurred in patients who were concurrently receiving DAPT. The results from this small trial should be considered hypothesis generating given the small sample size and unblinded design.⁷⁴

The 2013 American College of Cardiology Foundation/AHA STEMI guidelines recommend as reasonable (Class 2a, Level of Evidence: C) 3 months of VKA therapy for patients with STEMI and asymptomatic LV

mural thrombus with a target INR of 2.0-2.5 when combining OAC with DAPT.⁵ The 2014 AHA/American Stroke Association stroke guidelines recommend 3 months of VKA (Class 1, Level of Evidence: C) in patients with ischemic stroke or TIA in the setting of acute MI complicated by LV mural thrombus with a target INR of 2.0-3.0.⁶ The 2017 European Society of Cardiology STEMI guidelines recommend that OAC be considered guided by repeated TTE after considering bleeding risk and the need for concomitant antiplatelet therapy.⁵⁵ The American College of Chest Physicians guidelines recommend VKA in addition to DAPT (Grade 2C) for 3-6 months for patients with anterior MI and definite LV thrombus.⁵³ These recommendations notwithstanding, it is unclear whether the risk of LV thrombus persists over the long-term, particularly in patients with LV aneurysm. Additionally, the value of long-term anticoagulation over no antithrombotic therapy requires further investigation.

ALGORITHMIC APPROACH TO THE DIAGNOSIS AND MANAGEMENT OF LV THROMBI FOLLOWING AMI

A proposed algorithm for the diagnosis and management of LV thrombi following AMI is shown in [Figure 3](#). All patients presenting with AMI should undergo TTE with contrast at least 24 hours after presentation. If LV thrombus is identified, a dual pathway inhibitor antithrombotic regimen consisting of a P2Y₁₂ inhibitor and VKA with heparin bridging to a target INR of 2.0-3.0 is recommended to reduce the risk of bleeding, with repeat imaging at 3 months. It is important to note that heparin bridging in this context will likely necessitate a prolonged hospital stay until the INR is therapeutic. Alternatively, based on the experience of patients with atrial fibrillation undergoing PCI, one may consider narrowing the INR target to 2.0 to 2.5 when a triple therapy regimen (ie, DAPT + VKA) is selected, although this narrow target can be difficult to achieve.^{75,76} The duration of triple therapy should be determined on a case-by-case basis depending on the patient's individual risk of ischemic and bleeding events and the recovery of LV function. If the patient cannot tolerate VKA therapy, a DOAC should be considered in its place, and, similarly, the characterization of the individual patient's risk of ischemic and bleeding events should dictate the choice of dual vs triple therapy as well as the duration of therapy. OAC can be stopped and antiplatelet therapy resumed if repeat imaging at 3 months shows no residual thrombus and LV function has improved; however, OAC should be resumed if the thrombus persists with repeat imaging again 3 months later. Once OAC has

been discontinued, repeat TTE to exclude later recurrence of LV thrombus should be performed 3 months following OAC discontinuation and otherwise as clinically indicated.

In patients with larger infarcts, anteroapical wall motion abnormalities, and reduced ejection fraction following LAD-related STEMI, an echocardiogram with contrast should be performed within 72 hours post-PCI. In the absence of LV thrombus, DAPT should be continued and TTE with contrast repeated 1 to 2 weeks post-MI to determine if thrombus has developed. In some centers, CMR may be preferred over contrast-enhanced TTE, but CMR should generally be reserved for equivocal or nondiagnostic contrast-enhanced TTE or a poorly visualized LV apex in which the detection of thrombus would influence therapy. If no thrombus is visualized, routine DAPT should be continued for 6-12 months.

Another strategy, which is potentially associated with greater bleeding risk, is off-label administration of low-dose DOAC therapy in addition to DAPT to prevent thrombus formation in high-risk patients. Following large, anterior STEMI involving a large territory of anteroapical and apical myocardium, the risk of thrombus formation is greatest within the first 2 weeks before LV function improves. The risk of bleeding could be mitigated by discontinuing DOAC therapy if LV function has improved without evidence of LV thrombus on TTE 1 month post-MI. This theoretical approach may have the most value in settings where access to routine imaging may be limited; however, it still warrants further investigation in a randomized trial to justify clinical application.

CONCLUSIONS

The diagnosis and management of LV thrombus after AMI is a clinical conundrum despite significant

progress in medical and device-based therapies. Early diagnosis of LV thrombus is critical to avoid thromboembolism, and the choice of imaging modality and timing in relation to the incident MI are important. These factors of imaging modality affect the likelihood of thrombus detection as well as clinical significance. The role of DOACs remains poorly defined, and VKA remains the mainstay of anticoagulation therapy until higher-quality evidence at least demonstrates noninferiority for the prevention of thromboembolic events. While awaiting more data, clinicians should personalize the screening, surveillance, and treatment of patients according to their relative risks of ischemic and bleeding events. Strategies that target Virchow's triad by mitigating myocardial injury and preventing LV remodeling (stasis) and inflammation are likely to form the basis of the prevention and management of LV thrombus well into the future.

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