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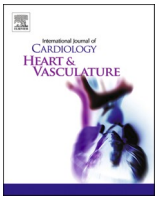

Left ventricular thrombus recurrence after anticoagulation discontinuation

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ABSTRACT

Background: Evidence regarding the duration of anticoagulation (AC) therapy for left ventricular thrombus (LVT) is lacking. This study aims to evaluate the rate and risk factors for LVT recurrence in patients with Anterior ST-Segment elevation Myocardial Infarction (STEMI) complicated by LVT.

Methods: This was a retrospective analysis of patients with Anterior STEMI complicated by LVT and reduced ejection fraction (<35 %) from 2010 to 2020. Patients with atrial fibrillation and hypercoagulable state were excluded. Recurrence of LVT was defined as a new LVT on transthoracic echocardiography (TTE) after interval resolution and AC discontinuation. Demographics, comorbidities, guideline directed medical therapy, TTE, and angiographic characteristics were assessed and compared in patients with and without LVT recurrence.

Results: 87 patients met the inclusion criteria. Nine (10.3 %) had LVT recurrence of which three (33.3 %) had cardioembolic events. More patients with recurrence had ventricular aneurysm/scarring (33 % vs 10.3 %) and multi-vessel disease (22.2 % vs 9 %).

Conclusion: This study reveals that a portion of patients with Anterior STEMI complicated by LVT are at a higher risk of recurrence after initial resolution and AC discontinuation. Larger prospective trials are needed to re-address the appropriate duration of anticoagulation.

1. Introduction

Left ventricular thrombus (LVT) is a common complication in patients with acute myocardial infarction (AMI). In the pre-reperfusion era, the incidence of LVT after AMI ranged from 20-40 % and even higher than 60 % in patients with larger infarcts [1]. Now, in the perfusion era, the incidence has dropped significantly with recent studies showing roughly 4 % of patients have this complication after receiving percutaneous coronary artery intervention (PCI) [2]. In current practice, many clinicians utilize Cardiac Magnetic Resonance Imaging (CMRI) due to its better sensitivity compared to transthoracic echocardiography (TTE). Data has shown a 6.2–8 % incidence of LVT detection in AMI cases when CMRI is utilized and it can be as high as 19.2 % in patients with STEMI and reduced left ventricular ejection fraction [3,4,5,6].

The patients who suffer from LVT have the following risk factors including anterior Myocardial Infarction (MI), left anterior descending artery infarct, left ventricular ejection fraction (LVEF) < 30 %, and delay between onset of symptoms and reperfusion. These risk factors will lead to Virchow's triad: vessel wall damage, stasis of blood flow due to lack of contractility and hypercoagulable state because of post-infarct inflammation [6]. There is insufficient evidence regarding the optimal duration of anticoagulation for patients with LVT. The American College of Cardiology (ACC) and the American Heart Association (AHA) recommend anticoagulation therapy with warfarin for at least 3 months in patients with LVT. Thereafter, a TTE is recommended to confirm resolution, after which anticoagulation can be stopped if there is no longer an LVT visualized [7–9].

In the clinical settings, a number of patients present with recurrence of LVT and/or with a complication from it including thromboembolic events. The consequence of LVT recurrence can be catastrophic and incidence of cardioembolic events such as ischemic stroke in patients

Abbreviations: AMI, Acute Myocardial Infarction; AC, Anticoagulation; CMRI, Cardiac Magnetic Resonance Imaging; CABG, Coronary Artery Bypass Graft; EF, Ejection fraction; GDMT, Guideline Directed Medical Therapy, LVEF, Left Ventricular Ejection Fraction; LVT, Left Ventricular Thrombus; MI, Myocardial Infarction, PCI, Percutaneous Coronary Artery Intervention; STEMI, ST Segment Elevation Myocardial Infarction; TTE, Transthoracic Echocardiography.

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with untreated LVT has been reported as 11 % [10]. In a study of 289 post AMI patients with LVT, it was found that 11.8 % of patients suffered an acute ischemic stroke after their AMI. In this study, despite initial resolution of thrombus, about 5.2 % had a subsequent acute ischemic stroke for which the culprit in the majority was a cardioembolic source. Additionally, LVT recurrence was thought to be an independent predictor of stroke [2].

Evaluation for failure rate of short-term anticoagulation therapy (i.e. development of further cardioembolic events) will help clinicians identify if a larger prospective trial needs to be done to re-address the duration of anticoagulation in patients with higher risk of recurrent LVT. Furthermore, investigation of patients failing short-term therapy would also help clinicians understand the risk factors contributing to recurrence of LVT and further risk stratify patients who are at higher risk. We propose to do a retrospective analysis of all patients admitted to our tertiary care center with acute anterior ST segment elevation myocardial infarction (STEMI), resulting a new LVEF<35 % complicated by LVT. We aim to study the rate and risk factors associated with the recurrence of LVT along with cardioembolic events among this cohort.

2. Study design/method

2.1. Study population and setting

This is a retrospective cohort analysis of all patients aged 18 years or older who were admitted to Geisinger Medical Center (located in Central Pennsylvania) with acute STEMI and found to have a newly reduced LVEF (<35 %) complicated by LVT throughout 2010–2020. A manual chart review was utilized to ensure that all patients included in the study had LVT following AMI and placed on warfarin as the AC of choice. Initially, all patients were initiated on dual antiplatelet therapy in addition to warfarin. However, after one week, one of the antiplatelet agents was discontinued. Further inclusion criteria ensured that all patients had resolution of LVT on subsequent echocardiograms and were eventually taken off anticoagulation accordingly. Recurrence of LVT was defined as a new LVT on transthoracic echocardiography (TTE) after interval resolution and AC discontinuation.

We excluded patients with atrial fibrillation, previous history of LVT prior to STEMI, non-ischemic cardiomyopathy, reduced LVEF of less than 35 % prior to STEMI, contraindication to anticoagulation, pre-existing ventricular aneurysm, congenital heart disease, and patients with hypercoagulable state (such as malignancy and congenital clotting factor deficiency, etc).

2.2. Outcomes

The patients were grouped into LVT with no recurrence versus LVT with recurrence after AC discontinuation. Data including demographics, comorbidities, medication lists, echocardiogram features, coronary angiogram details, and follow up imaging to assess for resolution of LVT was collected. The rate of LVT recurrence and cardioembolic events was compared among these groups.

2.3. Statistics

The frequency and percentage were used to describe categorical data and the median and IQR for continuous data. A Chi-square, Fisher's exact test, where appropriate was used to assess statistically significant associations between categorical variables. To examine statistically significant differences in continuous variables between groups, the Wilcoxon (Mann-Whitney) test was conducted. All analyses were conducted in SAS Enterprise Guide v8 with a p-value < 0.05 defined as significant. Due to the limited sample size, we were unable to calculate a statistically significant and meaningful odds ratio. This protocol was approved by the Institutional Review Board on Human Research (IRB No. 2022–0945).

3. Results

3.1. Study population

In this retrospective study, we found 198 patients in our tertiary care center who had AMI complicated by LVT and reduced EF. After conducting a manual chart review, 87 patients were identified who met the inclusion criteria. These patients had a confirmed LVT and received AC treatment for at least 3 months along with antiplatelet agents. A higher percentage were male (71.8 %) and smokers (66.7 %). The median BMI was 28.7 kg/m^2. Of the 87 patients, nine (10.3 %) had a recurrence. Among the nine patients who had LVT recurrence, 3 (33 %) had cardioembolic events as compared to 3 patients (3.8 %) in the non-recurrence group, which was statistically significant with $p < 0.01$. Length of AC duration was fairly similar between two groups, 144 days vs 167 days, Table 1.

3.2. Descriptive data

Utilization of guideline-directed medical therapy (GDMT) did not show a significant difference in the rate of LVT recurrence. Table 2 demonstrates the comparison of GDMT classes, including ACE inhibitors, Spironolactone, and Beta Blocker initiation following AMI upon discharge. However, it's important to note that this analysis only shows the initial prescription and does not evaluate up-titration or compliance due to the retrospective nature of the study.

Each patient underwent additional investigation of their culprit vessel for the AMI and the treatment modality to determine if recurrence was more prevalent. Table 3 shows that multi-vessel disease had a higher recurrence incidence (22.2 % vs. 9.0 %) compared to single-vessel coronary artery disease (CAD). Furthermore, a slightly smaller proportion of patients without recurrence did not undergo CABG (97.4 % vs. 100 %) and underwent PCI compared to patients with recurrence.

TTE data following AMI for all patients was analyzed to compare regional versus diffuse akinesis of the segments as well as the characteristics and features of the thrombus. This investigation illustrated that a higher proportion of patients with diffuse akinesis (10.3 % vs. 0 %) had lower incidence of recurrence. Thrombus characteristics, including whether it was a mobile thrombus at initial detection or if it was a laminated thrombus, were compared, however due to insufficient

Table 1
Demographic and co-morbidities for patient with and without LVT recurrence.

	Total **n = 87**	Recurrence **n = 9**	No recurrence **n = 78**	p-value
BMI in kg/m^2, median (IQR)	28.7 (25.1, 32.4)	28.2 (22.7, 30.9)	28.9 (25.5, 32.4)	0.59
Age in years, mean (SD)	59.5 (12.4)	58.3 (18.4)	59.6 (11.7)	0.84
Gender, n (%)				NS
Female	24 (28.2 %)	2 (22.2 %)	22 (28.9 %)	
Male	61 (71.8 %)	7 (77.8 %)	54 (71.1 %)	
Smoker, n (%)				0.47
Yes	58 (66.7 %)	5 (55.6 %)	53 (67.9 %)	
No	29 (33.3 %)	4 (44.4 %)	25 (32.1 %)	
DLD, n (%)				NS
Yes	50 (59.5 %)	5 (55.6 %)	45 (60.0 %)	
No	34 (40.5 %)	4 (44.4 %)	30 (40.0 %)	
HTN, n (%)				0.71
Yes	57 (67.9 %)	7 (77.8 %)	50 (66.7 %)	
No	27 (32.1 %)	2 (22.2 %)	25 (33.3 %)	
Length of AC in days, median (IQR)	167.0 (100.0, 241.0)	144.0 (107.5, 184.0)	167.0 (95.0, 256.0)	0.66
Cardioembolic event, n (%)				0.01
Yes	6 (6.9 %)	3 (33.3 %)	3 (3.8 %)	
No	81 (93.1 %)	6 (66.7 %)	75 (96.2 %)	

Table 2
Goal directed medical therapy analysis between patients with and without LVT recurrence.

	Total n = 87	Recurrence n = 9	No recurrence n = 78	p-value
ACE inhibitor/ARBs, n (%)				0.48
Yes	56 (64.4 %)	7 (77.8 %)	49 (62.8 %)	
No	31 (35.6 %)	2 (22.2 %)	29 (37.2 %)	
Spironolactone, n (%)				NS
Yes	10 (11.5 %)	1 (11.1 %)	9 (11.5 %)	
No	77 (88.5 %)	8 (88.9 %)	69 (88.5 %)	
Beta Blocker, n (%)				NS
Yes	68 (78.2 %)	7 (77.8 %)	61 (78.2 %)	
No	19 (21.8 %)	2 (22.2 %)	17 (21.8 %)	
Greater than 2 GDMT drugs				0.73
Yes	49 (56.3 %)	6 (66.7 %)	43 (55.1 %)	
No	38 (43.7 %)	3 (33.3 %)	35 (44.9 %)	

Table 3
Angiography findings and treatment modalities among patients with and without LVT recurrence.

	Total n = 87	Recurrence n = 9	No recurrence n = 78	p-value
Multivessel disease, n (%)				0.23
Yes	9 (10.3 %)	2 (22.2 %)	7 (9.0 %)	
No	78 (89.7 %)	7 (77.8 %)	71 (91.0 %)	
Single vessel CAD, n (%)				0.23
Yes	78 (89.7 %)	7 (77.8 %)	71 (91.0 %)	
No	9 (10.3 %)	2 (22.2 %)	7 (9.0 %)	
CABG, n (%)				NS
Yes	2 (2.3 %)	0 (0 %)	2 (2.6 %)	
No	85 (97.7 %)	9 (100.0 %)	76 (97.4 %)	
PCI, n (%)				NS
Yes	84 (96.5 %)	9 (100.0 %)	75 (97.4 %)	
No	2 (3.5 %)	0 (0 %)	2 (2.6 %)	

number of data points, it was not possible to establish any associations to the risk of recurrence. Ejection fraction recovery was evaluated at the time of AC discontinuation, and it demonstrated that a greater number of patients with no recurrence had recovered ejection fractions (9 % vs. 0 %) but this finding was not statistically significant. Additionally, a higher percentage of patients who experienced recurrence was found to have ventricular aneurysm scarring (33 % vs. 10.3 %), as illustrated in Table 4.

4. Discussion

LVT is seen as a complication in individuals who have suffered from AMI. Current society guidelines recommend at least 3 months of anticoagulation therapy to manage patients with LVT. Following this treatment, a repeat TTE is recommended to confirm resolution of the thrombus. If no LVT is detected on repeat TTE, discontinuation of anticoagulation can be considered by the clinician. Investigating the efficacy of short-term anticoagulation therapy in preventing cardioembolic events, such as those associated with LVT recurrence, is crucial for preventing potential catastrophic outcomes. In the literature, there are reports indicating a strong association between LVT and ischemic strokes in patients with normal sinus rhythm. It's interesting to note that over half of systemic embolic events occur beyond 6 months post-AMI in these patients, suggesting that extended anticoagulation may be indicated in select cases [11]. These patients could potentially benefit from extended anticoagulation, although existing literature lacks robust data regarding the optimal duration of anticoagulant therapy or individuals at higher risk [12].

This study illustrates the significance of AC duration assessment by revealing that a significant proportion of patients (10.3 %) experienced LVT recurrence despite initial resolution following discontinuation of anticoagulation therapy. Moreover, the increased incidence of cardioembolic events observed among the recurrence group is further concerning about the cessation of AC in such patients, further supporting the need for investigation in a larger patient cohort.

Current guidelines recognize the possibility of LVT recurrence and discuss how patients with persistently impaired left ventricular function may face an increased risk [13]. However, the decision to continue anticoagulation in such patients ultimately rests with clinicians, who must carefully weigh the potential benefits against the bleeding risks associated with AC. In a *meta*-analysis of 1461 patients, although no robust evidence was found in support or opposition of AC to reduce LVT formation in anterior STEMI patients with prophylactic AC therapy, it did identify a lower rate of LVT formation and increased incidence of bleeding [14]. This underscores the importance of individualized assessment when determining the continuation of AC.

In our study, we specifically included individuals with reduced ejection fraction as part of our criteria, given their elevated risk and susceptibility for LVT recurrence after discontinuing anticoagulation [15]. Our investigation revealed that a small but notable percentage (9 %) of patients in the non-recurrence group had ejection fraction recovery, compared to none in the recurrence group. This further supports that patients who have recovery of the ejection fraction may have lower chance of recurrence. Moreover, this cohort revealed that patients with diffuse akinesis experienced a lower recurrence rate (10.33 % vs. 0 %). While previous studies have linked low ejection fraction and significant

Table 4
Transthoracic echocardiography findings and features following AMI.

	Total n = 87	Recurrence n = 9	No recurrence n = 78
Diffuse akinesis, n (%)			
Yes	8 (9.2 %)	0 (0 %)	8 (10.3 %)
No	70 (80.5 %)	7 (77.8 %)	63 (80.8 %)
Missing	9 (10.3 %)	2 (22.2 %)	7 (9.0 %
LAD Territory WMA, n (%)			
Yes	70 (80.5 %)	7 (77.8 %)	63 (80.8 %)
No	8 (9.2 %)	0 (0 %)	8 (10.3 %)
Missing	9 (10.3 %)	2 (22.2 %)	7 (9.0 %)
Ejection Fraction Recovered, n (%)			
Yes	7 (8.0 %)	0 (0 %)	7 (9.0 %)
No	80 (92.0 %)	9 (100 %)	71 (91.0 %)
Laminated thrombus, n (%)			
Yes	2	–-	2 (100.0 %)
Missing	85	9	76
Thrombus mobility, n (%)			
Yes	3 (3.5 %)	0 (0 %)	3 (3.9 %)
No	30 (34.5 %)	2 (22.2 %)	28 (35.9 %)
Missing	54 (62.1 %)	7 (77.8 %)	47 (60.3 %)
Ventricular aneurysm/scarring, n (%)			
Yes	11 (12.6 %)	3 (33.3 %)	8 (10.3 %)
No	66 (75.9 %)	3 (33.3 %)	63 (80.8 %)
Missing	10 (11.5 %)	3 (33.3 %)	7 (9.0 %)

wall motion abnormalities to LVT formation, our study did not observe this association for unclear reasons [16,17]. However, in a larger sample size, this incidence may become more apparent.

Furthermore, this study investigated the utilization of GDMT following AMI. Regardless of medication class or combination therapy, no significant differences were observed. This finding is limited by the study's small sample size and the retrospective nature, which prevented the investigators from assessing compliance and medication up-titration following discharge. This underscores the importance of continued attention to impaired ejection fraction as a potential risk for recurrence and the need for aggressive management of GDMT utilization, compliance, and up titration.

This study further investigated the angiographic findings with a focus on the culprit vessel and the treatment modality that was utilized. Notably, patients with multivessel disease showed a higher recurrence rate of 22.2 % compared to 9 %. This observation suggests that individuals with multivessel disease may have experienced larger infarctions, leading to greater myocardial insult and a higher incidence of recurrence. Additionally, this study investigated the method of reperfusion, comparing the results between PCI and CABG. Interestingly, both modalities showed similar recurrence rates.

TTE was used to detect LVT and eventual thrombus resolution, however echocardiograph can have certain limitations depending on the windows and operator proficiency at detecting LVT. CMRI has been shown to have a higher sensitivity for LVT detection compared to TTE [18]. While TTE is the traditional method of LVT assessment, CMRI's clarity and precision in detecting LVT is useful in challenging patients. This difference likely arises because echocardiography primarily relies on morphological identification of LVT, whereas CMRI with gadolinium contrast detects LVT based on both morphology and avascular tissue characteristics. In a study of 201 patients with STEMI, CMRI detected more LVT cases, while TTE helped stratify which patients would benefit from further CMRI evaluation [3]. Therefore, in high-risk patients, such as those with persistently reduced EF and/or LV aneurysm/scarring, clinicians may utilize CMRI to ensure complete LVT resolution if they are considering discontinuing AC. This can further help ensure that the initial LVT has completely resolved since these patients are at higher risk of having LVT for a longer period of time as seen in this study.

The study had several limitations, notably its sample size of 87, which could impact the generalizability of the findings. Other limitations within this study are the ability to assess for compliance and up titration of GDMT. It's important to acknowledge that this was a single-center retrospective study in a rural setting. For the next steps, we recommend pursuing a larger sample size in a multicenter setting to validate and confirm the above observed risk factors and the results.

5. Conclusion

This study looked at the rate and risk factors for LVT recurrence following AC discontinuation in patients with anterior STEMI with reduced EF. It revealed that a subset of patients experiences LVT recurrence following initial resolution and discontinuation of AC. Moreover, patients who experienced LVT recurrence showed a significantly elevated incidence of cardioembolic events after AC discontinuation. These findings demonstrate the need for larger prospective trials to re-evaluate the optimal duration of AC therapy in such patients. This study suggests that there is a need to further characterize patients with an increased risk of LVT recurrence, enabling clinicians to have a more effective patient center treatment strategy to prevent LVT recurrence. By addressing these opportunities for improvement, we can enhance our understanding and management of this clinically significant complication and close our knowledge gap.

CRediT authorship contribution statement

Kamran Namjouyan: Writing – review & editing, Writing – original draft, Project administration, Investigation, Funding acquisition, Data curation, Conceptualization. **Aastha Mittal:** Writing – review & editing, Writing – original draft, Project administration, Data curation. **Seth Krueger:** Writing – review & editing, Investigation, Data curation, Conceptualization. **Devon Chosky:** Writing – review & editing, Funding acquisition, Formal analysis. **Enrique Soltero:** Writing – review & editing, Supervision, Project administration, Investigation, Conceptualization. **Idorenyin Udoeyo:** Writing – review & editing, Software, Resources, Formal analysis.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author contributions: K. N., A. M. takes responsibility for the content of the manuscript, including data and analyses. I.U. is responsible for data analysis and interpretation. All authors contributed to the development of the final manuscript.

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IRB registration number

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