Prophylactic Anticoagulation to Prevent Left Ventricular Thrombus Following Acute Myocardial Infarction: A Systematic Review and Meta-Analysis

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Clinical practice guidelines from the American Heart Association recommend consideration of prophylactic anticoagulation to prevent left ventricular thrombus (LVT) formation in patients with anterior ST-elevation myocardial infarction. These guidelines were given a low certainty of evidence (class IIb, level C), relying primarily on case studies and expert consensus to inform practice. Our objective was to compare the safety and efficacy of prophylactic anticoagulation, in addition to dual antiplatelet therapy, in the current era of timely primary percutaneous coronary intervention. Electronic databases, including EMBASE, MEDLINE, and Cochrane Library, were systematically searched from January 2012 through June 2022. A total of 7,378 publications were screened, and 5 publications were eventually included in this review: 1 randomized control trial and 4 retrospective studies involving 1,461 patients. Data were pooled using a fixed-effects model and reported as odds ratios (ORs) with 95% confidence intervals (CIs). The primary outcome of interest was the rate of LVT formation, and the secondary outcomes were the rate of major bleeding and systemic embolism. Pooled analysis showed a significantly lower rate of LVT formation (OR 0.28, 95% CI 0.11 to 0.73, p <0.01) and significantly higher rates of bleeding (OR 2.85, 95% CI 1.13 to 7.24, p = 0.03) in the triple therapy group compared with dual antiplatelet therapy. No significant difference was observed in the rate of systemic embolism between the groups (OR 0.37, 95% CI 0.12 to 1.13, p = 0.08). In this meta-analysis, there is no conclusive evidence to either support or oppose the use of triple therapy for LVT prevention in patients with anterior ST-elevation myocardial infarction treated with primary percutaneous coronary intervention. Appropriately powered randomized controlled trials are warranted to further evaluate the benefits of LVT prevention against the risks of major bleeding in this population. **(Am J Cardiol 2024;217:10−17)**

Keywords: meta-analysis, dual antiplatelet therapy, STEMI, anticoagulants, PCI, triple therapy, left ventricular thrombus

Left ventricular thrombus (LVT) formation is a well-known complication of anterior ST-elevation myocardial infarction (STEMI), with the risk being the highest in the first 3 months after an index event.[1−3] After the emergence of timely primary percutaneous coronary intervention (pPCI), the incidence of LVT has significantly decreased to an estimated 12% of anterior STEMIs, with rates ranging from 4% to 26%.[4,5] Most patients have the culprit vessel localized to the left anterior descending artery, and nearly all patients with LVT have apical akinesia or dyskinesia demonstrated on echocardiogram.[1,2] LVT formation significantly increases the risk of systemic embolization (odds ratio [OR] 5.45) and is associated with reduced left ventricular ejection fraction (LVEF). In patients presenting with LVT, the risk of an embolic event is approximately 13%.[6,7]

The 2013 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) STEMI guidelines recommend that LVT prophylaxis be considered in patients with STEMI and anterior apical akinesia or dyskinesia, with a preference for warfarin.[8] However, this recommendation was given a low certainty of evidence (level C, class IIb), relying primarily on case studies and expert consensus. Studies of patients perceived to be at high risk of LVT remain sparse, and there is minimal high-quality evidence to inform practice.[9]

In 2017, Bastiany et al[10] conducted a systematic review of the literature up to April 2016, identifying 14 studies that examined LVT prevention in the context of anterior STEMI. Their review concluded with no definitive evidence favoring the use of prophylactic anticoagulation for LVT prevention in this patient population. Notably, only 2 of these 14 studies focused on patients who underwent exclusively pPCI, with the remainder using thrombolysis or a mixed-revascularization technique. This reflects a gap in

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contemporary research, considering that pPCI has become the standard of care supported by the widespread availability of dedicated pPCI catheterization laboratories. To address this gap, we carried out an updated meta-analysis specifically targeting patients with anterior STEMI treated with pPCI. Our meta-analysis investigates the safety and efficacy of prophylactic anticoagulation, in addition to dual antiplatelet therapy (DAPT), in patients with anterior STEMI after pPCI.

Methods

Electronic databases, including EMBASE, MEDLINE, and the Cochrane Library, were systematically searched from January 2012 through June 2022, according to the principles of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guideline.[11] The search strategy included the following terms: "STEMI," "myocardial infarction," "LVT," "left ventricular thrombus," "PCI," "percutaneous coronary intervention," "dual antiplatelet therapy," and "triple antithrombotic therapy." The literature search was conducted in July 2022 and a detailed search strategy is presented in Supplementary Material 1.

Two independent reviewers (ES and DK) performed literature screening and data extraction. Any inconsistencies were reviewed and resolved by a third researcher (BA). To be considered for inclusion, studies needed to meet the following criteria: (1) population of adult (≥18 years old) human patients diagnosed with STEMI; (2) pPCI used as the lone revascularization technique; (3) LVT data reported for patients treated with prophylactic anticoagulation in addition to DAPT versus DAPT alone; (4) and primary study design published in English.

Pertinent data from the included studies were entered into a predefined electronic data extraction form, which encompassed study characteristics, patient demographics, and outcome data. The accuracy of the data entry was verified by comparing the information presented in the meta-analysis with that in the data extraction form. Any inconsistencies were resolved through consensus among all authors.

Studies where patients received G2b3a inhibitors after STEMI were excluded. Studies in which patients received therapeutic anticoagulation for an indication other than LVT prophylaxis were also excluded. Studies of patients not treated solely with pPCI (i.e., patients who received thrombolysis) were excluded. Conference abstracts, editorials, review articles, and nonprimary studies were excluded. The references of all retained articles were reviewed for additional sources not identified by the initial database search. All authors verified the pertinence and completeness of the articles included in this review.

The risk of study bias was assessed using the "Risk of Bias" (RoB 2) tool for randomized trials and the "Risk of Bias in Non-randomized Studies of Interventions" (ROBINS-I) tool, developed according to the guidelines of the Cochrane Collaboration.[12,13] Two authors (ES and DK) independently assessed the risk of bias, and any conflict on the attribution of the risk of bias was resolved by a third author (BA).

The RoB 2 tool assessed bias associated with the randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of the reported results. Overall risk of bias was attributed and classified as "low risk," "high risk," or "some concerns."

The ROBINS-I tool addressed 7 domains, including confounding, selection of participants, classification of interventions, deviations from intended intervention(s), missing data, measurement of outcomes, and reported results. Each category was rated as "low," "moderate," "serious," or "critical" risk. We derived the overall risk of bias judgment from the highest classified domain. The risk of bias assessments from RoB 2 and ROBINS-I are available in Supplementary Material 2.

The primary study outcome was the occurrence of LVT, and the secondary outcomes were the occurrence of major bleeding and systemic embolism. For each outcome, ORs and 95% confidence intervals (95% CIs) between DAPT and triple therapy (TT) were calculated. All outcome measures in the studies were obtained between 30 days and 6 months after discharge from the primary hospital admission. The data were pooled in a fixed-effects meta-analysis using the method provided by Bakbergenuly et al[14] in 2020. The weight of each trial on the overall results of the meta-analysis outcome was calculated as a percentage of the number of patients in that given trial over the total number included in each outcome analysis. Heterogeneity among studies was assessed using the I^2 statistic, with values considered low, moderate, or considerable for I^2 <25%, 25% to 50%, and >50%, respectively. Publication bias was assessed through inspection of funnel plots (Supplementary Material 3). All p values <0.05 were considered significant, and all statistical analysis was performed using R software version 4.3.2.

Results

The literature search returned 9,105 articles, of which 1,727 were removed as duplicate studies. A total of 7,378 study abstracts were independently reviewed by 2 authors, with 56 articles (0.76%) advancing to full-text review. Five studies (0.07%) were ultimately included in this systematic review, with 1 study being a randomized control trial (RCT)[15] and 4 being retrospective cohort studies.[16–19] A PRISMA diagram demonstrating the literature search and study selection is displayed in Figure 1.

The included studies had sample sizes of 124, 172, 279, 426, and 460 patients at follow-up. They had a median (interquartile range) of 279 patients (148 to 443), totaling 1,461 patients. The studies encompassed patients treated with both DAPT (n = 915, 62.6%) and TT (n = 546, 37.4%). Infarct territory involved anterior STEMI in all study patients. Prophylactic anticoagulation included the use of oral warfarin, low-dose rivaroxaban, and subcutaneous enoxaparin. Study follow-up periods ranged from 30 to 180 days, and a summary of the included articles is outlined in Table 1.

Patient demographics are detailed in Table 2, comparing the characteristics of patients treated with DAPT and TT in each study. Overall, baseline demographic characteristics, including age and gender distribution, were well-balanced among the treatment groups in each study. The average age ranged from 58 to 65 years. Male gender predominated in both groups. Across all 5 studies, baseline co-morbidities

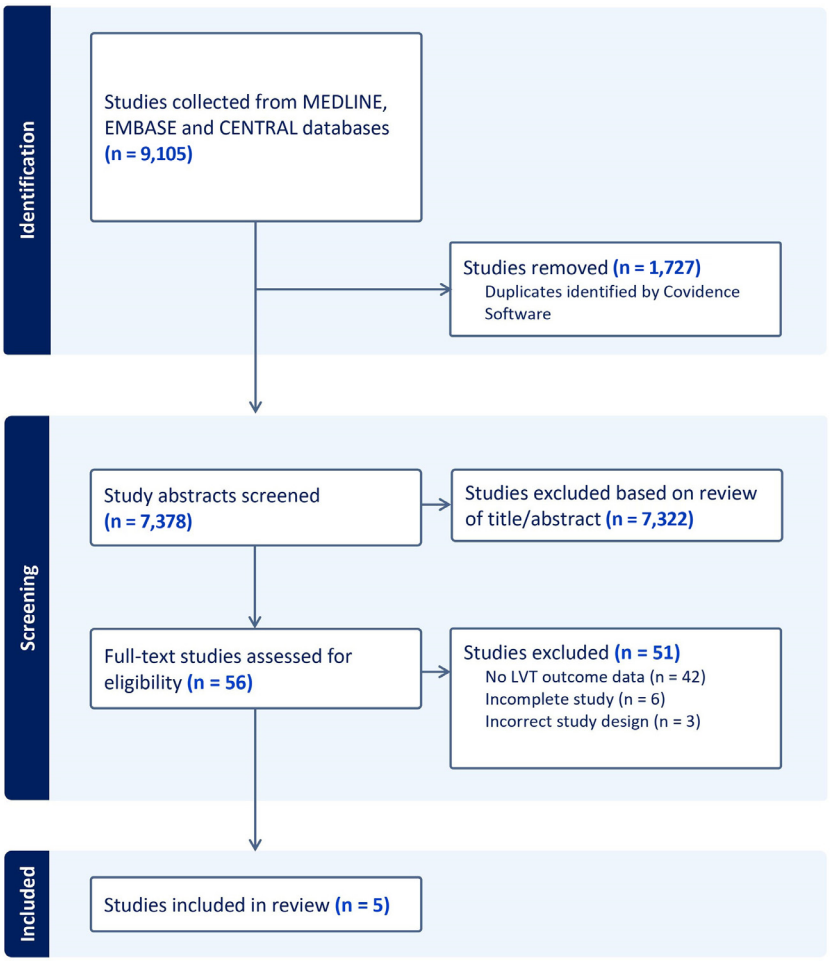

Figure 1. PRISMA diagram of the search strategy.

such as hypertension, diabetes, smoking history, and dyslipidemia were similar between the 2 groups. Each of the 5 studies performed predischarge echocardiograms to measure LVEF and follow-up echocardiograms were used to assess LVT formation.

A pooled analysis of the 5 studies revealed an overall LVT event rate of 1.6% in the TT group (n = 486) and 5.1% in the DAPT group (n = 705), detected by echocardiography. The overall rate of LVT was 4.7% in Zhang et al[15] (TT = 0.7%, DAPT = 8.6%), 4.0% in Oyetayo et al[18] (TT = 6.8%, DAPT = 2.5%), 5.9% in Chen et al[16] (TT = 2.4%, DAPT = 8.1%), and 0.6% in Bastiany et al[17] (TT = 0%, DAPT = 0.9%). At clinical follow-up, Le May et al[19] performed transthoracic echocardiograms on 71 patients treated with TT and 119 patients treated with DAPT to assess LVT formation. However, as no LVT was observed in either group, data from Le May was excluded from our forest plot for LVT formation. Of the 4 remaining studies, Chen et al[16] (OR 0.28, 95% CI 0.09 to 0.82) and Zhang et al[15] (OR 0.08, 95% CI 0.01 to 0.60) showed a significant difference in LVT formation between the treatment groups. In contrast, results from Bastiany et al[17] (OR 0.56, 95% CI 0.02 to 13.84) and Oyetayo et al[18] (OR 2.85, 95% CI 0.46 to 17.77) did not demonstrate statistical significance for LVT formation. The pooled analysis of these 4 studies indicated a significant reduction in LVT formation in patients treated with TT compared with those receiving DAPT (OR 0.28, 95% CI 0.11 to 0.73, p <0.01) (Figure 2). Statistical heterogeneity was considerable, with $I^2 = 59\%$.

Regarding major bleeding events, the overall rate of major bleeding was 3.85% in the TT group (n = 546) and 1.42% in the DAPT group (n = 915). Four of the 5 studies reported an OR >1, and 1 study showed a statistically significant increase in major bleeding risk with TT treatment. The pooled analysis of these 5 studies revealed a statistically significant increase in major bleeding events in the TT group compared with the DAPT group (OR 2.85, 95% CI 1.13 to 7.24, p = 0.03) (Figure 3). Statistical heterogeneity was low, with $I^2 = 21\%$.

Of the 3 studies that reported outcome data on systemic embolism, the overall rate was 1.14% in the TT group (n = 351) and 3.14% in the DAPT group (n = 478). All 3 studies reported lower rates of embolism in TT compared with DAPT (Oyetayo = 0.0% vs 2.5%; Zhang = 0.7% vs 2.86%; and Chen = 1.8% vs 3.5%). Regarding the severity of systemic embolic events, most events in the pooled DAPT group were severe (9 of 15, or 60%), whereas in the TT group, half were severe (2 of 4, or 50%). Of the 15 embolic events reported in the DAPT group, 9 were ischemic strokes, 2 were peripheral embolisms, and 4 were

Table 1
Characteristics of included studies, all of which use pPCI as the lone method of revascularization

Reference	Country	Study Design	Sample Size (DAPT)	Sample Size (TT)	Infarct Territory Criteria	LV Dysfunction Criteria	Anticoagulation	Antiplatelet Therapy	Follow-Up
Oyetayo et al,[18] 2015	USA	Retrospective	80	44	Anterior	LVEF ≤ 35%	Warfarin (3 months)	Clopidogrel, Prasugrel, or Ticagrelor DAPT	49 days
Le May et al,[19] 2015	Canada	Retrospective	329	131	Anterior	≥ 1 dysfunctional apical segment	Warfarin (6 months)	Clopidogrel DAPT	180 days
Bastiany et al,[17] 2018	Canada	Retrospective	108	64	Anterior	≥ 1 dysfunctional apical segment	VKA (4 months)	Ticagrelor DAPT	120 days
Chen et al,[16] 2020	China	Retrospective	258	168	Anterior	LVEF ≤ 40%	Enoxaparin SC (7 days)	Clopidogrel DAPT	30 days
Zhang et al,[15] 2022	China	RCT	140	139	Anterior	None	Rivaroxaban (2.5mg BID x 30 days)	Clopidogrel or Ticagrelor DAPT	30 days

DAPT = dual antiplatelet therapy; LV = left ventricular; LVEF = left ventricular ejection fraction; RCT = randomized control trial; TT = triple therapy; VKA = vitamin K antagonist.

Table 2
Baseline patient characteristics of included studies

Reference	Age (DAPT)	Age (TT)	Males % (DAPT)	Males % (TT)	HTN % (DAPT)	HTN % (TT)	Diabetes % (DAPT)	Diabetes % (TT)	Dyslipidemia % (DAPT)	Dyslipidemia % (TT)	Smoking % (DAPT)	Smoking % (TT)	LVEF (DAPT)	LVEF (TT)
Oyetayo et al,[18] 2015	64	58	60	71	59	61	25	25	43	50	46	48	31	30
Le May et al,[19] 2015	60.6 ± 14.2	61.5 ± 14.1	75.4	73.3	40.1	42.5	13.2	17	37.7	34.4	42.3	39.2	44.7 ± 8.2	39.0 ± 8.5
Bastiany et al,[17] 2018	62.2 ± 10.9	64.6 ± 13.6	73	71	38	54	9	25	40	45	NR	NR	37 ± 9	39 ± 9
Chen et al,[16] 2020	62 (52−72)	61 (51−71)	82.5	79.8	55.8	62.5	16.3	28.6	52.4	33.3	58.9	59.5	25 (19−28)	25 (20−32)
Zhang et al,[15] 2022	59.0 (52.0−66.0)	56.0 (49.0−64.0)	77.1	82.7	39.3	32.4	22.1	15.8	48.6	47.5	46.4	56.1	53.0 (44.0−60.0)	55.0 (46.8−60.0)

Values are reported as median, median (interquartile range) or mean ± standard deviation.
DAPT = dual antiplatelet therapy; HTN = hypertension; LVEF = left ventricular ejection fraction; NR = not recorded; TT = triple therapy.

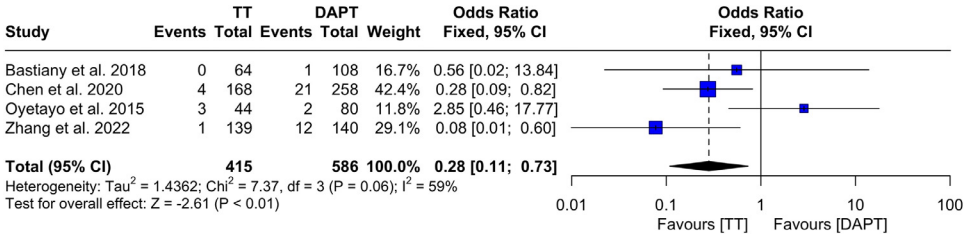

Figure 2. Forest plot demonstrating fixed-effects meta-analysis of left ventricular thrombus formation in patients treated with TT versus DAPT.

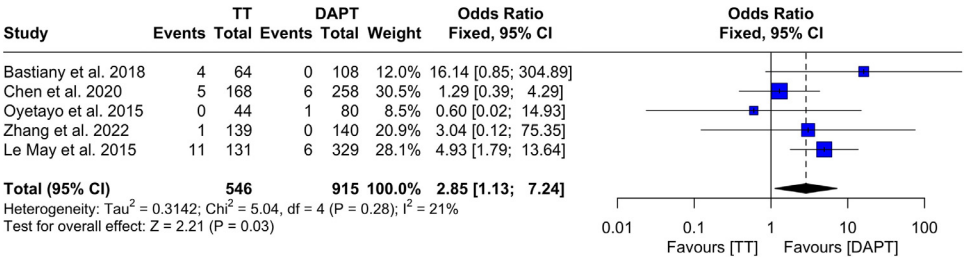

Figure 3. Forest plot demonstrating fixed-effects meta-analysis of major bleeding events in patients treated with TT versus DAPT.

unspecified. In the TT group, there were 4 embolic events: 2 ischemic strokes, 1 peripheral embolism, and 1 unspecified. The rate of ischemic stroke was 1.88% in the DAPT group (9 of 478) and 0.57% in the TT group (2 of 351). Although the studies all demonstrated OR <1, none showed a statistically significant difference in systemic embolism between treatment with DAPT and TT. The pooled analysis of these studies revealed a notable reduction in embolic events with the use of TT, although no statistically significant difference was observed (OR 0.37, 95% CI 0.12 to 1.13, p = 0.08) (Figure 4). Statistical heterogeneity was low, with $I^2 = 0\%$.

Finally, the risk of bias in the only randomized study was rated as low using the RoB 2 assessment tool, and the overall risk of bias in the observational studies was rated as moderate using the ROBINS-I assessment tool (Supplementary Material 2). After assessing the risk of publication bias through funnel plot inspection, the results were symmetric and did not indicate significant publication bias (Supplementary Material 3).

Discussion

To the best of our understanding, this study is the most contemporary meta-analysis of LVT prevention in patients treated with pPCI and DAPT for acute STEMI. Our pooled statistical analysis indicated a significant reduction in LVT for patients treated with TT compared with those receiving DAPT (OR 0.28, 95% CI 0.11 to 0.73, p <0.01), but it also demonstrated an increase in major bleeding events (OR 2.85, 95% CI 1.13 to 7.24, p = 0.03). There was no statistically significant difference in the occurrence of systemic embolism (OR 0.37, 95% CI 0.12 to 1.13, p = 0.08). Our results suggest that there is no conclusive evidence to either support or oppose the use of TT for the prevention of LVT in patients with anterior STEMI treated with pPCI, and the benefits of LVT prevention should be weighed against the risks of bleeding in the context of each individual patient.

In the prePCI era, studies indicated that the risk of major bleeding was 2 to 5 times higher with TT compared with DAPT in patients who underwent coronary stenting.[20–22] Subsequent findings in the pPCI era have echoed these results. A notable example is the 2013 WOEST (What is the Optimal antiplatElet therapy in patients with oral anticoagulation and coronary StenTing) trial, an open-label, multicenter RCT conducted by Dewilde et al[9] in 15 centers across Belgium and the Netherlands. This trial revealed that, within 1 year of pPCI, 19.4% of patients on DAPT and 44.4% on TT experienced bleeding episodes (hazard ratio 0.36, 95% CI 0.26 to 0.50, p <0.0001).[9] The HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) trial further

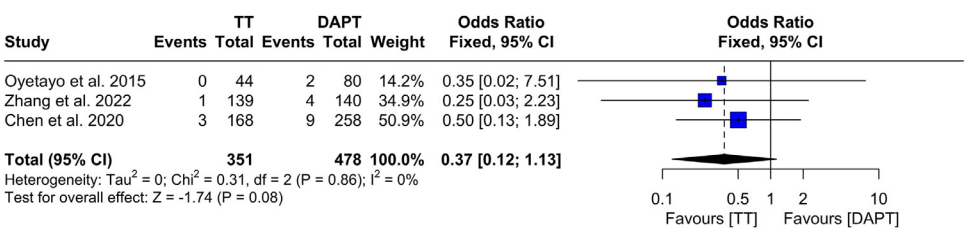

Figure 4. Forest plot demonstrating fixed-effects meta-analysis of systemic embolism in patients treated with TT versus DAPT.

substantiated these findings, showing that patients with STEMI treated with TT had similar ischemic outcomes but a significantly higher incidence of major bleeding compared with DAPT (17.1% vs 6.5%, p <0.0001).[23] Furthermore, the focus of WOEST, HORIZONS-AMI, and similar studies has largely been on patients anticoagulated for reasons other than LVT prophylaxis after STEMI, limiting the applicability of these findings to our study population.

Much of the research in this domain, including the study by Le May et al,[19] has centered on the long-term use of warfarin (>6 months). This approach is at odds with current guidelines, which suggest a maximum duration of 3 months for triple antithrombotic therapy, coinciding with the most common period for LVT development (usually within 30 days).[8] Such a mismatch in treatment duration may explain the statistically significant increase in bleeding rates reported by Le May et al[19] at 180-day follow-up—a finding that was not replicated in the other studies included in our analysis. Despite these uncertainties, our observation of a notable increase in major bleeding with TT (OR 2.85) is consistent with the existing literature.

Regarding LVT prophylaxis, our study contributes to the existing body of evidence, which suggests that TT may reduce LVT incidence in high-risk patients with STEMI. For example, it aligns with the 2013 ACCF/AHA STEMI guidelines, which recommend that prophylactic anticoagulation be considered in patients with STEMI and anterior apical akinesia or dyskinesia to prevent LVT formation. However, our analysis underscores a significant gap in current research, with few screened studies (5 of 7,378, 0.07%) comprehensively addressing this clinical question. It highlights the paucity of data in this area and a need for more appropriately powered clinical trials to fill the existing data void. This shortcoming is reflected in the low certainty of evidence (level C, class IIb) assigned to the AHA/ACCF STEMI guidelines on LVT prophylaxis.

A recent study by Di Odoardo et al[24] revealed that among 104 European cardiac centers surveyed, 67% of cardiologists prefer TT, whereas 25% predominantly use anticoagulation plus antiplatelet monotherapy. This survey highlights significant variability in LVT thromboprophylaxis, including its use, indications, duration, and type, across these centers.[24] Although there is data on the use of anticoagulation combined with single antiplatelet therapy in patients with acute coronary syndrome and atrial fibrillation, evidence regarding this approach in patients with acute coronary syndrome and LVT is lacking. Notably, the 2017 European Society of Cardiology STEMI guidelines do not address LVT prophylaxis in their management guidelines.[25]

Moreover, there remains an unresolved question about the ideal candidate for prophylactic anticoagulation, such as between oral warfarin and a nonvitamin-K antagonist oral anticoagulant, such as rivaroxaban. In the realm of atrial fibrillation thromboprophylaxis, rivaroxaban has been shown to be as effective as warfarin while posing a relatively lower risk of fatal bleeding.[26,27] This favorable risk-benefit profile, evidenced in various clinical studies, suggests its potential efficacy in left ventricular thromboprophylaxis.[28] Supporting this notion are the findings from Zhang et al,[15] which reported significantly lower rates of LVT and no significant increase in major bleeding risk when using low-dose rivaroxaban as the third agent in TT. Nevertheless, because this was the sole RCT exploring this therapy, there is a clear need for more evidence to solidify these findings. In addition, the study of Chen et al[16] showed efficacy in the use of subcutaneous enoxaparin as the third agent in TT, which warrants further analysis.

Some limitations of the current review must be acknowledged. Notably, this meta-analysis was confined to the prevention of LVT. Consequently, the number of studies included was small (n = 5), resulting in a limited overall sample size (n = 1,461). Furthermore, the follow-up periods in these studies varied from 30 to 180 days, contributing to clinical heterogeneity in the data. There was also variability in the types of anticoagulation used, with some studies using warfarin-based TT, whereas others used rivaroxaban-based TT or enoxaparin-based TT. In addition, 4 of the included studies were retrospective observational studies, and only 1—conducted by Zhang et al[15]—was an RCT. Given the limited number of studies, the small number of events within those studies, and the differences in study design, the results should be approached with caution.

A final limitation relates to the absence of serial echocardiographic examinations across the studies. It is conceivable that LVT could have developed and resolved during the follow-up period, which may have led to an underdetection of LVT on echocardiography. In 4 of the 5 studies, the detection of LVT was solely through transthoracic echocardiography, which is less sensitive than contrast-enhanced cardiac magnetic resonance.[29] Although Zhang et al[15] reported the highest baseline LVEF (median >50%), they demonstrated the second-highest rate of LVT in our analysis. This finding appears contradictory, as previous research has indicated that the incidence of LVT is typically lower in patients with an ejection fraction >40% (4% vs 10.5%, p <0.0001).[29–31] This might be explained by their confirmation of suspected LVT diagnoses with cardiac magnetic resonance, which was not performed in the other studies in our analysis.

In conclusion, the results of our meta-analysis demonstrate that there is no conclusive evidence to either support or oppose the use of TT for LVT prevention in patients with anterior STEMI treated with primary pPCI. Although TT may be considered in high-risk groups—such as those presenting with apical akinesia or dyskinesia on echocardiogram and LVEF ≤40%—the standard of care for this patient population remains DAPT. In addition, more appropriately powered RCTs are needed to provide more robust data in this area. Careful interpretation of the existing data is essential, with additional research required to clarify the most valuable approach in this patient population.

Declaration of competing interest

The authors have no competing interests to declare.

CRediT authorship contribution statement

Ethan Sacoransky: Writing – review & editing, Writing – original draft, Visualization, Software, Methodology, Investigation, Formal analysis, Data curation. **Danny Yu Jia Ke:** Writing – review & editing, Writing – original

draft, Resources, Project administration, Methodology, Investigation, Data curation. **Bryce Alexander:** Writing – review & editing, Validation, Supervision, Methodology, Investigation, Conceptualization. **Wael Abuzeid:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Conceptualization.

Data availability

The authors confirm that the data supporting the findings of this study are available within the article and Supplementary Material. Any other data, not reported in the manuscript, but used to support the findings of this study is available from the corresponding author, upon reasonable request.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2024.02.023.

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