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Prophylactic warfarin post anterior ST-elevation myocardial infarction: A systematic review and meta-analysis☆,☆☆

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ABSTRACT

Objectives: To determine the role of warfarin (WF) prophylaxis in the prevention of left ventricular thrombus (LVT) formation and subsequent embolic complications following an anterior ST elevation myocardial infarction (STEMI) complicated by reduced left ventricular ejection fraction (LVEF) and wall motion abnormalities.
Background: The role of oral anticoagulation prophylaxis, in addition to dual antiplatelet therapy (DAPT), in the current era of percutaneous coronary intervention has not been well studied, despite being a class IIb recommendation in the AHA/ACC STEMI guidelines.
Methods: The Cochrane search strategy was used to search PubMed, Embase and the Cochrane library for relevant results. Four studies, two retrospective, one prospective registry, and a randomized feasibility control trial met criteria for inclusion. Data was pooled using a random effects model and reported as odds ratios (OR) with their 95% confidence intervals (CI). Primary outcomes of interest were rate of stroke, major bleeding and mortality.
Results: Pooled analysis included 526 patients in the No WF group and 347 patients in the WF group. No statistical difference in rate of stroke (OR: 2.72 [95% CI: 0.47–15.88; $p = 0.21$]) or mortality (OR: 1.50 [95% CI 0.29–7.71; $p = 0.63$]) was observed. Major bleeding was significantly higher in the WF group (OR: 2.56 [95% CI: 1.34–4.89; $p = 0.004$]).
Conclusions: The routine use of DAPT and WF for prophylaxis against LVT formation following an anterior STEMI with associated decrease in LVEF and wall motion abnormalities, appears to result in no mortality benefit or reduction in stroke rates, but may increase the frequency of major bleeding.

1. Introduction

The development of a left ventricular thrombus (LVT) is a well described complication of anterior ST-elevation myocardial infarctions (STEMI) associated with significant wall motion abnormality and reduced ejection fraction [1]. In the current era of primary percutaneous coronary intervention (PCI), the incidence of LVT in anterior STEMI has significantly declined, from 40% before the era of reperfusion therapy, to as low as 4% [2,3]. A recent retrospective analysis confirmed that a reduced left ventricular ejection fraction (LVEF), and anterior STEMI are both risk factors for development of an LVT [2]. Development of an LVT is also associated with approximately a 5-fold increase (odds ratio (OR) 5.45) in the risk of systemic embolization, which includes stroke [4,5]. Nonetheless, these data cannot apply to our current practice as they were based on figures obtained prior to the current era of primary PCI and the routine use of dual-antiplatelet therapy (DAPT).

The American Heart Association currently gives a class IIa recommendation for the treatment of an LVT complicating a STEMI with a vitamin K antagonist (VKA) [6]. Prophylaxis with a VKA, such as warfarin (WF) is also recommended for patients with anterior apical akinesis or dyskinesis following a STEMI (class IIb) [6]. Both of these recommendations are based on limited evidence.

Recent studies have attempted to address the role of WF prophylaxis in addition to the current standard of care, DAPT, to prevent LVT formation in anterior STEMI associated with reduced LVEF and wall motion abnormalities [7–10]. These studies are limited in size, with the larger two studies being retrospective in nature, and the only randomized trial being a 20-patient randomized feasibility trial. Therefore the aim of this meta-analysis was to combine these results to compare the use of WF and no WF for prevention of LVT in the era of PCI and concurrent DAPT.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.
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2. Methods

A literature search was performed with the use of the PubMed database, EMBASE and Cochrane Library. Results were individually reviewed by two independent reviewers (N.M. and J.M.) for relevance. Discrepancies between datasets were resolved by consensus. Exclusion criteria for studies were: 1) studies reporting only in abstract format or conference presentation or without access to full data or manuscript; 2) non-English articles; 3) studies reporting no direct comparison of WF versus No WF; 4) studies with no possibility of separating individual outcomes; and 5) studies that did not use DAPT.

Relevant data was extracted and entered in Review Manager software ([Revman] version 5.3 (Nordic Cochrane Centre, Copenhagen, Denmark)). Key words used were: "warfarin," "anterior wall myocardial infarction," "anterior STEMI," "anterior ST elevation myocardial infarction," "anterior ST segment elevation myocardial infarction," "anterior ST elevation MI," "anterior myocardial infarction," "ST segment elevation myocardial infarction," and "anterior."

Data was pooled using a random effects model, and reported as OR with their 95% confidence intervals (CI). Heterogeneity was based on the I^2 statistic test with I^2 value of <25% considered low heterogeneity, 25% to 50% moderate, and a value of >50% substantial heterogeneity. Funnel plots were constructed and inspected visually for evidence of publication bias. The weight of each trial on the overall results of 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.

Primary outcome measures of interest in all four studies included stroke, death and major bleeding. Definitions of major bleeding varied but were grouped under the outcome of major bleeding episodes for analysis. Two of the four studies did not categorize stroke into hemorrhagic versus ischemic and therefore these outcomes were grouped for analysis. All outcome measures in the studies were obtained between three and six-months post-discharge from the primary hospital admission.

3. Results

One hundred and forty-five results were reviewed, with four studies included in the final analysis (Fig. 1). Two studies were retrospective, one was a prospective registry and one was a randomized control feasibility trial. All were unicentric studies (Table 1). One of the four studies did not have atrial fibrillation or other indications for WF as an exclusion criteria (Table 1).

Pooled analysis resulted in a total of 873 patients, with 347 in the WF group and 526 in the No WF group being analyzed. Baseline characteristics of the pooled population are shown in Table 2. Average age of the two groups was similar and relatively young (WF: 60.9 years old vs. No WF 61.8 years old). Male sex predominated in both groups (WF: 77% vs. No WF: 72%). Baseline co-morbidities including hypertension, diabetes, smoking history, dyslipidemia, previous myocardial infarction and stroke were all similar between the two groups. 97% of patients in both groups received DAPT therapy. 93% of patients in the WF group and 94% of patients in the No WF group underwent PCI. High rates of optimal medical therapy were achieved in both groups, with only beta-blockers (83%) in the WF group not having a rate over 90%. Total duration of triple therapy with WF was between 3 and 6 months.

All four studies performed pre-discharge echocardiograms, and three performed follow-up examinations (Table 3). LVEF in the WF group was slightly lower with an average of 36% compared to 40% in the No WF group. Follow-up echocardiographic studies revealed average LVEFs of 41% in the WF group and 46% in the No WF group.

A complete data set of baseline characteristics (Table 2), including cardiovascular medications and follow-up echocardiograms (Table 3), was available in 67% (584/873) of the pooled patient population. Given the limited population size, patients with incomplete data sets were included in the analysis.

No statistical difference between the two groups was found relating to the rate of stroke (OR: 2.72 [95% CI: 0.47–15.88; $p = 0.27$]) or mortality (OR: 1.50 [95% CI 0.29–7.71; $p = 0.63$]) (Fig. 2A & B). Heterogeneity

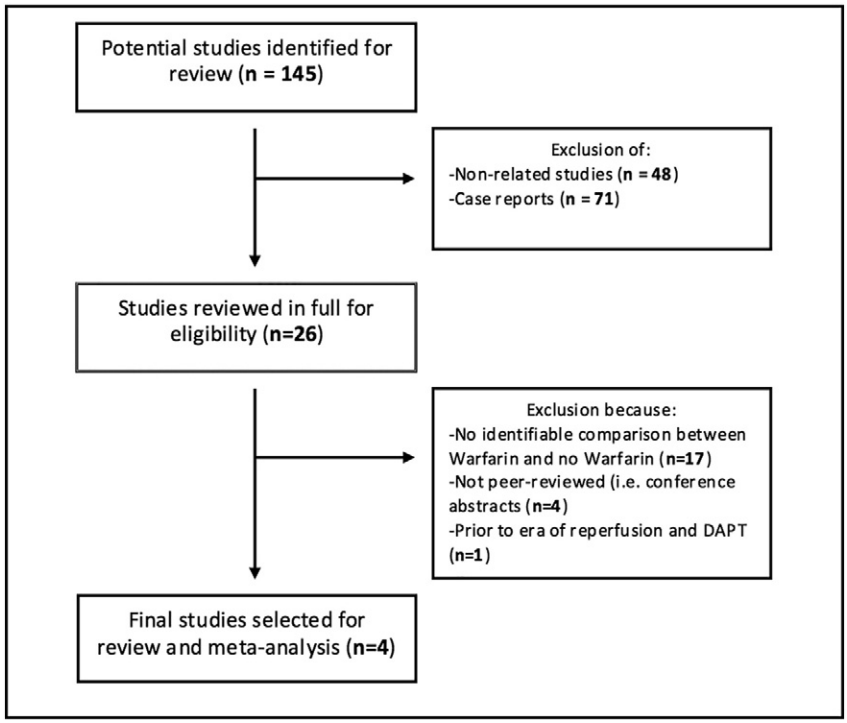

Fig. 1. Flowchart depicting study selection for meta-analysis.

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Table 1
Study characteristics.

Study	Study design	Publication year	Years of operation	Unicentric vs. multicentric	Inclusion	Exclusion
Le May et al.	Retrospective cohort	2015	2004–2010	Unicentre	(1) Anterior STEMI (2) Primary PCI (3) Akinesis or dyskinesis on Transthoracic ECHO	(i) Clinical: (1) On warfarin at admission (2) Atrial fibrillation (3) Mechanical heart valve (4) CABG same admission (5) Bleeding before ECHO (6) Stroke before ECHO (7) History of intracranial hemorrhage (8) Death within 72 h or in setting of shock/encephalopathy (ii) ECHO: (1) LV thrombus (2) Absence of akinesis or dyskinesis (3) ECHO done >7 days after admission (4) ECHO not performed or suboptimal
Buss et al.	Prospective registry	2013	2001–2010	Unicentre	(1) Anterior STEMI (2) Post MI LVEF < 40%	(1) Death during index hospitalization (2) Urgent CABG performed (3) Known LV thrombus
Oyetayo et al.	Retrospective cohort	2015	2003–2012	Unicentre	(1) Anterior wall MI (2) Primary PCI [included rescue PCI] (3) DAPT (4) Extensive wall motion abnormalities [hypokinetic or akinetic] on ECHO (5) LVEF < 35%	(1) Death prior to discharge (2) Oral anticoagulation required for another indication (3) No follow-up within 16 weeks of discharge (4) LV thrombus identified on pre-discharge ECHO
Schwalm et al.	Randomized feasibility trial	2010	2006–2008	Unicentre	(1) Anterior STEMI (2) LVEF < 40% (3) No LV thrombus prior to randomization (4) Able/willing to give informed consent	(1) <18 y.o. or >85 y.o. (2) Alternate indication for oral anticoagulation (3) Relative or absolute contraindication for OAC: (i) History of intracranial hemorrhage (ii) G.I. bleed within 6 months (iii) Hb < 90 (iv) Platelets < 100 (vi) Ischemic stroke < 30 days (vii) Intracranial tumor or aneurysm (viii) Significant pericardial effusion (ix) Severe chronic kidney disease [Cr > 250 μmol/L]

was moderate for the outcome of stroke ($I^2 = 36\%$) and high for the outcome of mortality ($I^2 = 82\%$). Major bleeding was significantly higher in the WF group (OR: 2.56 [95% CI: 1.34–4.89; $p = 0.004$]) with minimal heterogeneity ($I^2 = 4\%$) observed between the groups (Fig. 2C).

4. Discussion

Our study found that the addition of WF to DAPT appears to result in no statistically significant difference in rates of stroke or death. It did

Table 2
Patient characteristics.

Study	Subjects		Mean age (years)		Male (%)		Hypertension (%)		Diabetes (%)		Smoking history (%)	
	WF	No WF	WF	No WF	WF	No WF	WF	No WF	WF	No WF	WF	No WF
Le May et al.	131	329	62	61	73	75	41	39	17	13	39	42
Buss et al.	162	107	60	67	NR	NR	NR	NR	25	28	47	49
Oyetayo et al.	44	80	58	64	93	60	61	59	25	25	48	46
Schwalm et al.	10	10	54	66	60	70	60	30	10	30	90	60
Average**			61	62	77	72	47	43	21	18	45	44

Study	Dyslipidemia (%)		Previous MI (%)		Previous stroke (%)		Previous angioplasty (%)		ASA (%)		DAPT (%)	
	WF	No WF	WF	No WF	WF	No WF	WF	No WF	WF	No WF	WF	No WF
Le May et al.	33	36	8	10	6	4	8	6	100	99	99	97
Buss et al.	NR	NR	NR	NR	9	9	NR	NR	100	95	94	93
Oyetayo et al.	50	43	9	15	0	3	11	15	100	100	100	100
Schwalm et al.	40	40	20	0	NR	NR	10	0	100	100	100	100
Average**	37	38	9	11	7	5	9	8	100	98	97	97

Study	ACE inhibitor (%)		ARB (%)		Beta-blocker (%)		Statin (%)		PCI performed (%)	
	WF	No WF	WF	No WF	WF	No WF	WF	No WF	WF	No WF
Le May et al.	90	86	3	5	79	90	96	98	100	95
Buss et al.	NR	NR	NR	NR	NR	NR	NR	NR	90	90
Oyetayo et al.	95	91	0	0	93	99	98	99	86	93
Schwalm et al.	90	90	NR	NR	90	90	90	90	100	90
Average**	91	87	2	4	83	91	96	98	93	94

** Weight averages.

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Table 3
Echocardiographic characteristics.

Study	Pre-discharge ECHO		Post-discharge ECHO					
	LVEF (%)		Follow-up (%)		LVEF (%)		LV thrombus	
	WF	No WF	WF	No WF	WF	No WF	WF	No WF
Le May et al.	39	45	54	36	42	48	0	0
Buss et al.	34	34	NR	NR	NR	NR	NR	NR
Oyetayo et al.	30	31	98	81	40	40	3	2
Schwalm et al.	38	38	100	100	42	50	1	0
Average[b]	36	40	66	46	41	46	4[a]	2[a]

NR = not reported.
WF = warfarin.
[a] Absolute total (not average).
[b] Weighted averages.

however, result in an increased rate of major bleeding in patients taking WF in addition to DAPT for LVT prophylaxis. 97% of the patients analyzed in both groups were on DAPT and 93% or greater underwent PCI, therefore reflecting the current medical practice and likely answer our intended research question. It also highlights the lack of evidence on this specific topic, as only four relevant articles were found, with no large published randomized control trials.

The use of DAPT following an ACS and/or stent placement as part of a PCI reperfusion strategy has led to significant decreases in morbidity and mortality [11,12]. The addition of WF to DAPT for any indication is referred to as "triple therapy" (TT). TT has been shown to have significantly higher rates of bleeding (reported up to 2–5 times higher) compared to various combinations of anti-platelets and/or WF [13–17]. Furthermore, most of this data is centered around patients anticoagulated for indications other than LV thrombus prophylaxis and hence outcome data in our study population remain limited. The efficacy from a risk–benefit perspective of TT has recently been drawn into question with results from the WOEST and ISAR-TRIPLE trials. WF with either ASA or clopidogrel was shown to be as effective as TT in preventing thrombotic complications, and in the case of the WOEST trial significantly decreased bleeding complications in patients on WF for various indications including LVT [13,18]. Our result of significantly increased rates of major bleeding with TT (OR = 2.56) was therefore not unexpected given this current evidence base.

In our study, TT was found to have no statistical effect on rates of stroke or mortality. Of note, a trend towards higher rates of both was observed. Large confidence intervals and overall small population limit interpretation of these trends, however, given WF's presumptive role of LVT prophylaxis and subsequent embolization prevention, this is an area that will require close attention in future studies.

Neither Oyetayo et al. nor Buss et al. provided a breakdown of hemorrhagic vs. ischemic strokes [7,9]. Le May et al. (2015) interestingly found higher rates of both ischemic and hemorrhagic stroke in the WF group. Also of note were the exceedingly low rates of overall stroke in

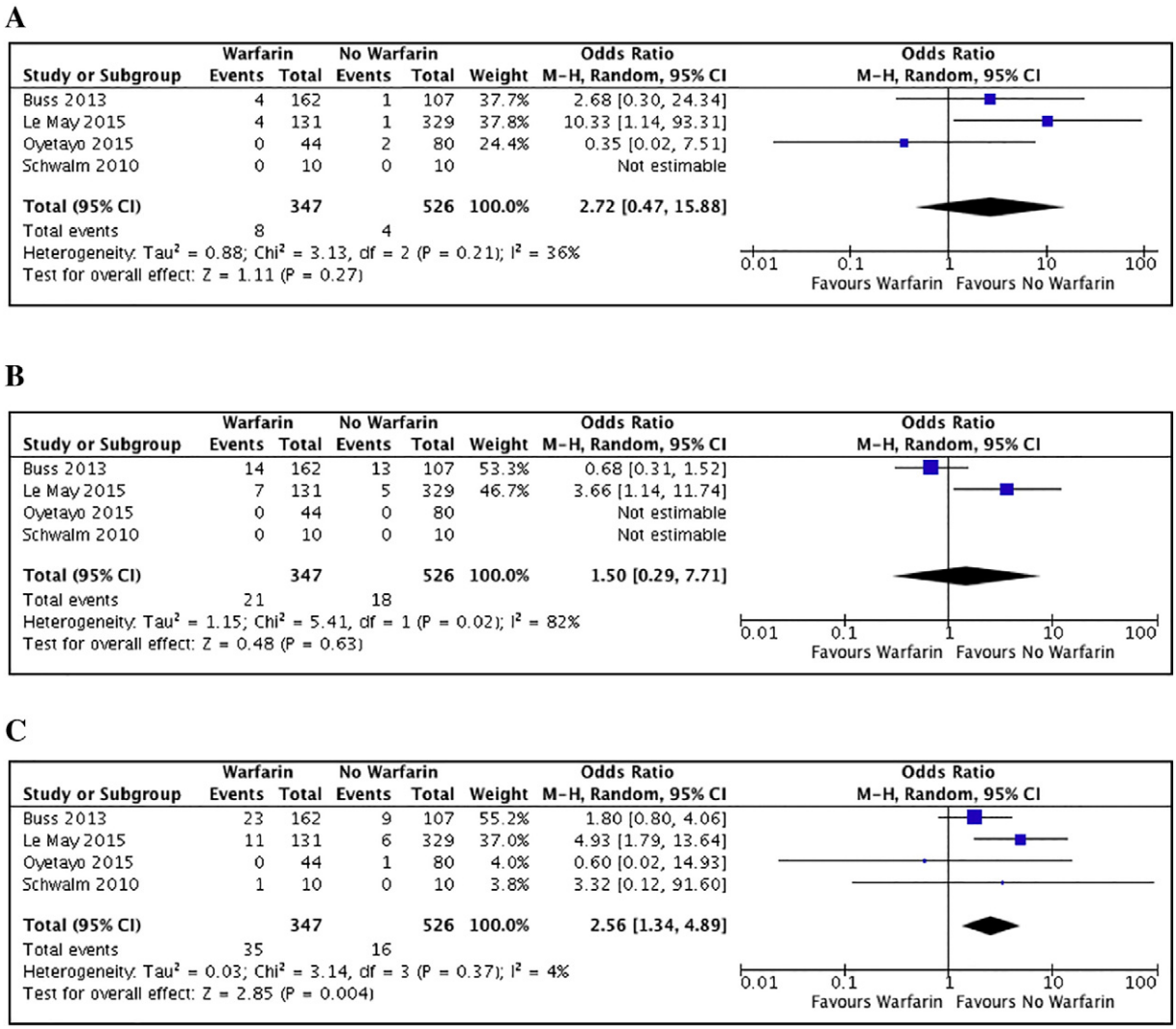

Fig. 2. Forest plots for stroke (A), death (B) and major bleeding (C) outcomes across all studies.

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both groups (WF: 2% vs. No WF: 0.8%). The rate of stroke being 0.8% in the No WF group is substantially lower than rates of 10%–15% reported in patients with a known LVT not treated with anticoagulation prior to routine DAPT usage [4,5]. This contradictory finding may reflect strokes being rare events in the current era of PCI and DAPT in association with a relatively small sample size. It may also reflect a high bleeding risk associated with TT resulting in an increase in hemorrhagic strokes. This may balance or exceed the apparent minimal protective benefit against ischemic strokes that TT conveys over DAPT. Alternatively, the fact that atrial fibrillation was not an exclusion criteria for one trial (Buss et al.) could represent a potential confounder [7]. The elevated stroke risk may reflect unreported patients with atrial fibrillation representing a higher risk population.

The trend towards increased mortality in the WF group appears to be due to higher rates of major bleeding, including hemorrhagic stroke. Additionally, patients in the WF group tended to have marginally worse LVEF (WF: 36% vs. No WF: 40%) and were less likely to receive beta-blockers as a result (WF: 83% vs. No WF: 91%). This may reflect larger infarcts, and in turn a worse prognosis. Follow-up Transthoracic Echocardiography (TTE) was not performed in one study as well, representing a possible confounder for this conclusion. The fact, the majority of the data is retrospective, and along with the small population and large confidence intervals, may reflect unforeseen variables accounting for this trend and should be interpreted with caution.

The results of this meta-analysis suggest the addition of WF to DAPT provides no added benefit in regards to stroke and mortality and increased major bleeding rates. The potential role of non-vitamin K antagonist oral anticoagulants (NOACs); dabigatran, rivaroxaban, apixaban, and edoxaban, as part of TT for any indication has not been well studied. Given their favorable risk–benefit profile to WF, including reduction in all-cause mortality and a 48% relative risk of intra-cranial hemorrhage (ICH), NOACs have the potential to improve major bleeding outcomes [19,20]. Real-world follow-up of rivaroxaban found similar low rates of adverse outcomes, including ICH [21]. Existing evidence for NOACs as a component of TT is derived from sub-group analysis, such Dans et al. from the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial for dabigatran [22,23]. The results suggest dabigatran in combination with DAPT has a similar increase in relative risk for major bleeding compared to WF. Lower dose dabigatran 110 mg, which was found to be non-inferior to WF in RE-LY, and has a lower major hemorrhage risk, again demonstrated lower rates of major hemorrhage when combined with DAPT [22,23]. The role of lower dose NOACs, or any specific NOAC in combination with a single or dual antiplatelet agent is unknown for any indication, let alone for LVT prophylaxis following an anterior STEMI with reduced LVEF, but has the potential to reduce major bleeding. Despite this level of uncertainty recent expert consensus suggests NOACs be considered first-line therapy for patients with non-valvular atrial fibrillation receiving coronary stents and requiring DAPT therapy [24].

Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI (PIONEER AF-PCI), Evaluation of Dual Therapy with Dabigatran vs. Triple Therapy with Warfarin in Patient's with AF that Undergo a PCI with Stenting (REDUAL-PCI), A Study of Apixaban in Patients with Atrial Fibrillation, not caused by a Heart Valve Problem, Who are at Risk for Thrombosis (Blood Clots) Due to Having had a Recent Coronary Event, such as a Heart Attack or a Procedure to Open the Vessels of the Heart (AUGUSTUS), and Edoxaban Treatment Versus Vitamin K Antagonist in Patients with Atrial Fibrillation Undergoing Percutaneous Coronary Intervention (ENTRUST AF-PCI) are four large randomized multicenter trials currently completed, enrolling or planned. These studies are looking at the role of rivaroxaban, dabigatran, apixaban and edoxaban respectively, in low and regular doses and in combination with both single and dual antiplatelet agents compared to TT for patients with non-valvular atrial fibrillation following PCI with stent placement [25–28]. While these results will not answer our specific research question, extrapolating them to further indications for combination anti-platelets and oral-anticoagulants, including LVT prophylaxis following an anterior STEMI with reduced LVEF, may suffice until further research can be done on this topic.

With the ongoing development and increasing access to cardiac magnetic resonance imaging (CMRI), specifically the use of delayed enhancement (DE) with gadolinium, the sensitivity of TTE for detection of LVT has been more thoroughly scrutinized. The sensitivity for detection of a LVT by TTE has been reported to be anywhere from 33% to 95% [29,30]. Weinsaft et al. performed four imaging modalities on patients presenting with a STEMI; noncontrast TTE, contrast TTE, Cine-CMRI, and DE-CMRI, and found an 8% rate of LVT using DE-CMRI as the gold-standard, with a sensitivity of 35% for non-contrast TTE and 64% for contrast TTE [31]. 94% of the infarcts occurred in the left anterior descending artery territory, and those who developed an LVT had a significantly reduced LVEF (39%) compared to those who did not (52%) [31]. This suggests LVT complicating STEMIs may be currently underdiagnosed. Despite this likely ongoing under-diagnosis, our results again did not show an increase in embolic complications or mortality, suggesting that the addition of WF to routine DAPT from both a prophylaxis and potentially a treatment perspective of LVT may cause more harm than benefit.

4.1. Limitations

Our meta-analysis was limited by the fact no large randomized control trials exist, and the analyzed trials were largely retrospective. Additionally, given the small patient pool and wide confidence intervals, there are significant limitations in interpretation of our results. For only 67% of patients could a complete baseline characteristic dataset be obtained, leading to the potential for unappreciated variables confounding these results. The analyzed studies all used varying definitions of bleeding and major or clinically significant bleeding. This may have either over or underestimated our results. Given the fact stroke events were significantly lower than previously appreciated, the pooled patient population may have not been large enough to detect a difference in regards to mortality and stroke rates.

5. Conclusion

The routine use of TT, with warfarin, for prophylaxis against LVT formation following an anterior STEMI associated with a decreased LVEF, appears to result in significant increase in the rate of major bleeding, with no mortality benefit or stroke reduction. Careful interpretation of these observational data is essential, with additional research needed to clarify the most appropriate approach in this group of patients.

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