Direct oral anticoagulants or warfarin in patients with left ventricular thrombus after ST-elevation myocardial infarction:

A pilot trial and a prespecified meta-analysis of randomised trials

Left ventricle thrombosis

Left ventricle thrombosis (LVT) is among the major consequences of acute myocardial infarction (AMI). In the thrombolysis era, almost one-third of patients with acute anterior transmural myocardial infarction were complicated by LVT. The introduction of primary percutaneous coronary intervention (PCI) and the application of dual-antiplatelet therapy (DAPT) resulted in a drastic fall in the LVT incidence; however, still, a considerable prevalence ranging from 3% to 9 % is documented, exposing patients to cerebral and systemic embolization.

- Current international guidelines recommend **anticoagulation** for patients with definitive LVT after AMI. The 2013 American College of Cardiology Foundation/American Heart Association ST-elevation MI (STEMI) recommendations express that it is appropriate to add **vitamin K antagonist (VKA) to DAPT** in patients with STEMI and asymptomatic LVT **for 3 months,** with an international normalized ratio (INR) of **2.0 to 2.5**.
- Similarly, the 2017 STEMI recommendations of the European Society of Cardiology suggest that oral **anticoagulants be administered for up to 6 months**, guided by subsequent echocardiographic examinations and considering the bleeding risk and the requirement for concurrent antiplatelets.

- Direct oral anticoagulants (**DOACs**), they are currently recognized as the first-line treatment of AF and VTE in most clinical scenarios, distinguished by their short half-life, fast onset of action, fewer medication interactions, rare food interactions, and the lack of a need for frequent laboratory monitoring, compared with vitamin-K antagonists (VKAs).
- Although the use of DOACs has earned a **class III recommendation** for patients with **mechanical prosthetic valves**, **moderate-to-severe mitral stenosis**, and **antiphospholipid syndrome** , their application in some situations, such as acute limb ischemia and LVT, remains uncertain.

Until now, no completed randomized clinical trial has compared the efficacy and safety of DOACs versus warfarin in patients with LVT following STEMI and the existing evidence is limited to observational studies

Kajy et al. conducted a metaseries on 30 publications (41 cases) that used DOAC in patients with LVT. The majority of the patients were treated with **rivaroxaban** (51.2%), followed by **apixaban** (26.8%) and **dabigatran (**22%).

Different antithrombotic combinations were prescribed as follows: **DOACs alone** (46.3%), DOACs plus aspirin (12.2%), **DOACs plus clopidogrel** (2.4%), or **triple therapy** (39 %). **Rivaroxaban, apixaban, and dabigatran showed 81%, 100%, and 88.9% success rates for thrombus** resolution, respectively. The median duration of thrombus clearance was 40 days for rivaroxaban, 36 days for apixaban, and 24 days for dabigatran. One episode of nonfatal bleeding and 1 episode of stroke were recorded with the consumption of a DOAC 39. The most frequent underlying pathophysiology of LVT was ischemic cardiomyopathy (65.9%), followed by nonischemic cardioyopathy (22%). This study was limited by lack of a randomized design.

- Early revascularisation with primary percutaneous coronary intervention (pPCI) has reduced the incidence of left ventricular thrombus (LVT) formation. However, according to a pooled analysis of 2,072 patients with recent ST-elevation myocardial infarction (STEMI), LVT is still observed in 6% of patients; this increases up to 19% in patients with anterior STEMI and reduced left ventricular (LV) function.
- If left untreated, LVT is associated with a 4-fold increase in stroke/systemic embolisation and a 2-fold increase in long-term mortality.

- Warfarin has historically been used for treating LVT, and direct oral anticoagulants (DOACs) have recently gainedb attention, with studies in routine practice indicating their frequent use. However, there is scant evidence to support (or refute) the effectiveness of DOACs in leading to LVT resolution and their safety with respect to bleeding events.
- We compared 3-month core laboratory-confirmed imaging findings and clinical outcomes in patients with STEMI randomised to rivaroxaban or warfarin in a pilot clinical trial

Methods

- Rivaroxaban vErsus Warfarin for Antithrombotic TheRapy in Patients with Left Ventricular Thrombus After Acute ST-Elevation Myocardial Infarction (**REWARF-STEMI)** was an open-label, parallel-group, blinded-outcome pilot RCT conducted at two large tertiary cardiovascular centres in Tehran, Iran: Tehran Heart Center and Rajai Cardiovascula Institute

STUDY POPULATION

Adult patients aged between **18 and 80 years** old presenting with LVT, confirmed by non-contrast two-dimensional transthoracic echocardiography (2D TTE), **within 2 weeks of confirmed STEMI** were eligible for the study. Patients with contraindications to DOACs (such as a mechanical prosthetic heart valve implantation, rheumatic heart disease, or antiphospholipid syndrome [APS], active bleeding, cardiogenic shock, estimated glomerular filtration rate (eGFR) <30 ml/min or those already receiving anticoagulationnfor other indications **were excluded from the study.**

RANDOMISATION AND TREATMENT STRATEGY

- Patients were randomised to receive either **rivaroxaban**- or **warfarin**-based antithrombotic regimens.
- Those assigned to rivaroxaban received rivaroxaban (15 mg once daily, orally) plus clopidogrel (75 mg daily, orally) and aspirin (80 mg once daily, orally).
- In the warfarin-based antithrombotic therapy group, patients received warfarin (overlapping with enoxaparin until reaching an international normalised ratio [INR] goal of 2.0-2.5) plus clopidogrel (75 mg once daily, orally) and aspirin (80 mg once daily, orally).
- In both groups, aspirin was discontinued within the first 7 days of the STEMI diagnosis.
- Time in the therapeutic range (TTR) was calculated based on the Rosendaal method.

CLINICAL FOLLOW-UP

Following randomisation, patients were visited weekly during the first month and **monthly** thereafter, until the end of the 3-month follow-up. At each visit, patients' new complaints and anticoagulation status were recorded. INR monitoring was planned during each visit for patients allocated to warfarin. For patients with non-therapeutic INR levels, shorter monitoring intervals were scheduled until reaching a therapeutic INR.

ECHOCARDIOGRAPHIC ASSESSMENT

- The diagnosis and follow-up of LVT were based on **noncontrast 2D TTE,** mainly due to the unavailability of echocardiographic contrast agents in Iran.
- Although **the sensitivity of contrast echocardiography is higher than noncontrast echocardiography** (61% vs 33%) in diagnosing LVT, **the specificity of non-contrast echocardiography is high (94%)**
- Patients with STEMI routinely underwent non-contrast 2D TTE, performed by the on-call cardiologist during the first 24 hours of hospitalisation, at both enrolling centres.
- All patients with new LVT according to the on-call cardiologist were subsequently assessed by an expert cardiologist with a subspeciality in echocardiology, blinded to the assigned treatment, to confirm the diagnosis before the enrolment in the trial.

STUDY OUTCOMES

- The primary outcome was complete LVT resolution at the 3-month follow-up based on non-contrast 2D TTE, determined by the imaging core laboratory.
- Other outcomes were the proportion of patients with adjudicated stroke and systemic embolism (SSE), major adverse cardiac events (MACE; a composite of death from cardiovascular causes, myocardial infarction [MI], or SSE), and all-cause death at 3 months from enrolment.
- The main prespecified safety outcome was the proportion of patients with adjudicated major bleeding events based on the International Societyn on Thrombosis and Haemostasis (ISTH) definition at 3 months from enrolment.

STATISTICAL ANALYSIS

- A sample size of 25 in each arm was planned. The primary outcome, complete LVT resolution at the 3-month follow-up, was analysed in patients with valid values, i.e., those who were alive and agreed to participate in the 3-month follow-up visit. Other outcomes were analysed in all randomly assigned patients.
- The effect of the intervention on the outcomes was reported with relative risk (RR) and risk difference as the measures of effect, with their respective 95% confidence intervals (CIs).

Results

- From June 2020 to November 2022, **55 patients** with STEMI and LVT were screened for eligibility.
- **Four** patients did not consent, and **one** was excluded because of an eGFR below 30 ml/min;
- Thus**, 50 patients** (median age [IQR]: 55 [50- 61] years; **9 females** [18%]) were included in the study, of whom **26 and 24 patients** were randomly assigned to the r**ivaroxaban- and warfarin-based** antithrombotic regimens, respectively

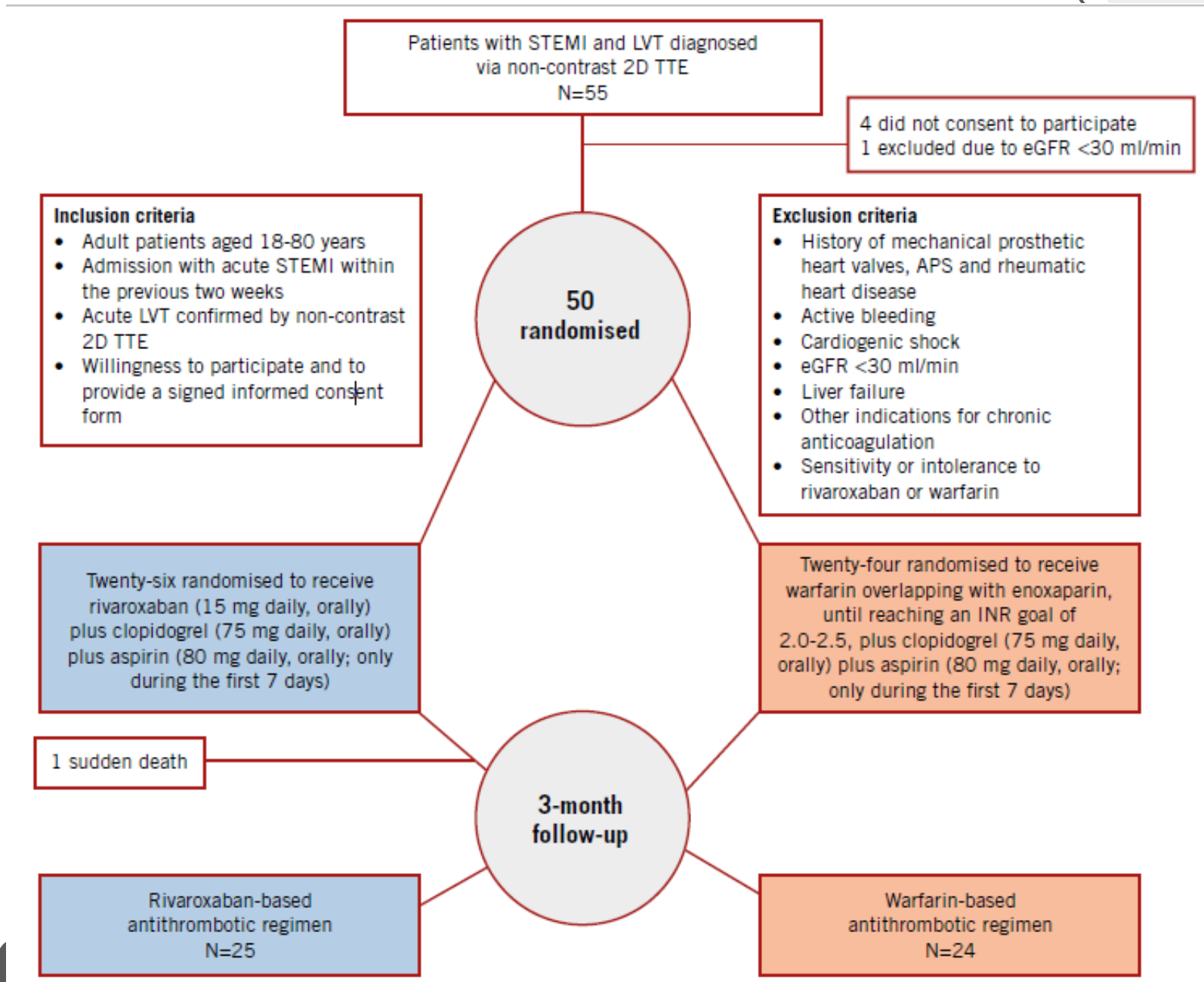

Patients with STEMI and LVT diagnosed via non-contrast 2D TTE
N=55
4 did not consent to participate
1 excluded due to eGFR <30 ml/min
Inclusion criteria
Adult patients aged 18-80 years
Admission with acute STEMI within the previous two weeks
Acute LVT confirmed by non-contrast 2D TTE
Willingness to participate and to provide a signed informed consent form
50 randomised
Exclusion criteria
History of mechanical prosthetic heart valves, APS and rheumatic heart disease
Active bleeding
Cardiogenic shock
eGFR <30 ml/min
Liver failure
Other indications for chronic anticoagulation
Sensitivity or intolerance to rivaroxaban or warfarin
Twenty-six randomised to receive rivaroxaban (15 mg daily, orally) plus clopidogrel (75 mg daily, orally) plus aspirin (80 mg daily, orally; only during the first 7 days)
Twenty-four randomised to receive warfarin overlapping with enoxaparin, until reaching an INR goal of 2.0-2.5, plus clopidogrel (75 mg daily, orally) plus aspirin (80 mg daily, orally; only during the first 7 days)
1 sudden death
3-month follow-up
Rivaroxaban-based antithrombotic regimen
N=25
Warfarin-based antithrombotic regimen
N=24

Table 1. Baseline clinical, imaging, and procedural characteristics in REWARF-STEMI.

Table 1. Baseline cl	Rivaroxaban (N=26)	Warfarin (N=24)
	55 (50-60)	55 (50.00-62.75)
Female sex	4 (15.3)	5 (20.8)
Body mass index, kg/m^2	26.3 (24.5-27.7)	25 (23-28)
Previous medical condition		
Diabetes mellitus	7 (26.9)	5 (20.8)
Hypertension	9 (34.6)	14 (58.3)
Current smoker	11 (42.3)	10 (41.7)
Coronary artery disease	9 (34.6)	6 (25.0)
Ischaemic stroke	3 (11.5)	1 (4.1)
Previous coronary revascularisation		
Percutaneous coronary intervention	5 (19.2)	3 (12.5)
Coronary artery bypass graft	1 (3.8)	0 (0)
Laboratory values at baseline		
Creatinine, mg/dl	1.1 (1.02-1.23)	1.1 (0.9-1.3)
Haemoglobin, mg/dl	14.8 (14.1-16.1)	14.7 (13.2-15.7)
Platelets x 10^3/µl	211.5 (193-247)	210 (187-297)
Imaging characteristics		
Left ventricular ejection fraction, %	32 (25-40)	30 (25-35)
Thrombus long-axis diameter, mm	15 (9.75-18)	18 (14-22.7)
Thrombus short-axis diameter, mm	8 (5-10)	9 (5-17)
Revascularisation strategy for acute myocardial infarction		
Primary percutaneous coronary intervention	25 (96.1)	24 (100)
Coronary artery bypass graft	1 (3.9)	0 (0)

Data are presented as median (25th-75th percentile) or n (%).

OUTCOME

- **PRIMARY OUTCOME**: Three-month complete LVT resolution occurred in 19/25 (76.0%) patients assigned to rivaroxaban versus 13/24 (54.2%) patients assigned to warfarin)
- **OTHER OUTCOMES**: There were no SSE events. Two CRNMB events occurred in the rivaroxaban group: one patient had haematuria and one had rectorrhagia, which were both treate conservatively in the outpatient setting. No major bleeding occurred in any of the patients during the study follow-up time

Table 2. Three-month study outcomes in the REWARF-STEMI trial population.

Outcome	Rivaroxaban N=26	Warfarin N=24	Relative risk (95% CI)	Risk difference (95% CI)	*p*-value
Primary outcome					
Complete LVT resolution	19/25 (76.0)*	13/24 (54.2)	1.40 (0.91-2.15)	0.22 (–0.04 to 0.48)	0.12
Other outcomes					
All-cause death	1/26 (3.8)	0	NA	0.04 (–0.03 to 0.11)†	0.30
MACE	1/26 (3.8)	0	NA	0.04 (–0.03 to 0.11)†	0.30
SSE	0	0	NA	NA	NA
Major bleeding	0	0	NA	NA	NA
CRNMB	2/26 (7.7)	0	NA	0.07 (–0.02 to 0.18)†	0.14

Data are presented as n/N (%). *Calculated based on the population who completed the 3-month follow-up (i.e., all participants except the one who died before the 3-month follow-up). †For events with zero incidence in one group, only risk difference was reported. CI: confidence interval; CRNMB: clinically relevant non-major bleeding; LVT: left ventricular thrombus; MACE: major adverse cardiac events; NA: not applicable; SSE: stroke and systemic emboli

Supplementary Table 2- Territory of infarction in the study population

Infarction territories	Number of patients (Total=50)
Anterior	45 (90)
Lateral	1 (2)
Inferior	3 (6)
Posterolateral	1 (2)
Data represented as n (%)	

META-ANALYSIS

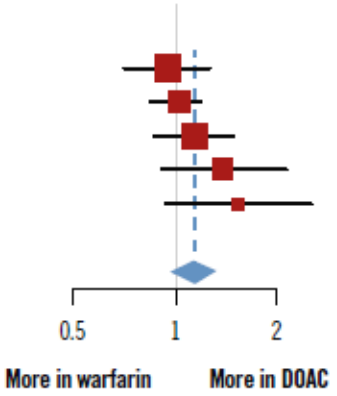
- Based on the eligibility criteria, four prior RCTs, along with the current study, were included in the meta-analysis14-17, including a total of 228 patients with post-MI LVT. Of these, 116 patients were assigned to DOACs (51 patients to apixaban and 65 to rivaroxaban, respectively), and 112 patients were assigned to warfarin.
- Complete LVT resolution occurred in 93/115 (80.8%) patients in the DOAC-based regimen and 79/112 (70.5%) in the warfarin-based regimen.
- Major bleeding occurred in 2/116 (1.7%) and 9/112 (8%) patients in the DOAC- and warfarin-based regimens, respectively.

Study (year)	Type of OAC		Study population		Imaging modality for diagnosis and F/U of LVT	Study outcomes					
	D	W	♂	♀		Complete LVT resolution	Stroke and systemic emboli	MACE*	All-cause death	Major bleeding†	CRNMB†
Alcalai et al[15] (2021)	18	17‡	Acute MI 28	7	Non-contrast 2D TTE	✓	✓	✗	✓	✓	✗
Abdelnabi et al[16] (2021)	39	40	Not specified 45	34	Non-contrast 2D TTE	✓	✓	✗	✗	✓	✗
Youssef et al[14] (2023)	25	25	Recent anterior MI NA		Non-contrast 2D TTE	✓	✓	✓	✓	✓	✓
Isa et al[17] (2021)	14	13	Not specified 25	2	Non-contrast 2D TTE	✗	✓	✗	✓	✓	✗
REWARF-STEMI (2024)	26	24‡	Not specified 41	9	Non-contrast 2D TTE	✓	✓	✓	✓	✓	✓

A Complete LVT resolution in DOAC vs warfarin treatment groups

Study	DOAC Events	DOAC Total	Warfarin Events	Warfarin Total	RR [95% CI]	Weight
Youssef et al (2023)	19	25	20	25	0.95 [0.71-1.28]	24.8%
Alcalai et al (2021)	16	17	14	15	1.01 [0.84-1.21]	18.5%
Abdelnabi et al (2021)	30	39	27	40	1.14 [0.87-1.50]	33.1%
REWARF-STEMI (2024)	19	25	13	24	1.40 [0.91-2.15]	16.5%
Isa et al (2021)	9	9	5	8	1.55 [0.94-2.54]	7.2%
Common effect model	**93**	**115**	**79**	**112**	**1.14 [0.98-1.32]**	**100%**

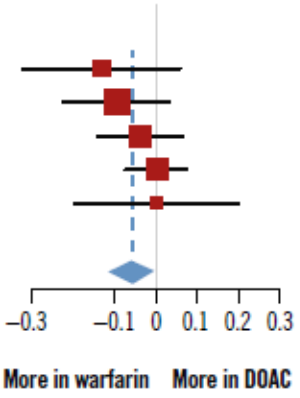
Heterogeneity: I^2=18%, τ^2 <0.0001; p=0.30
Test for overall effect: z=1.75 (p=0.08)



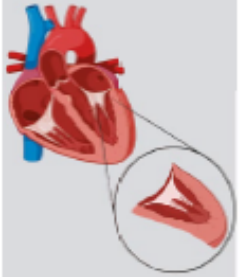
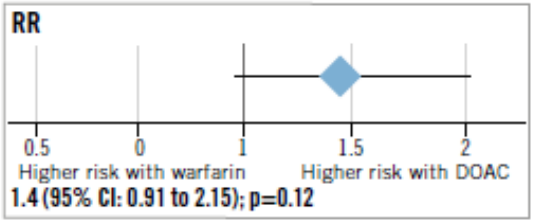
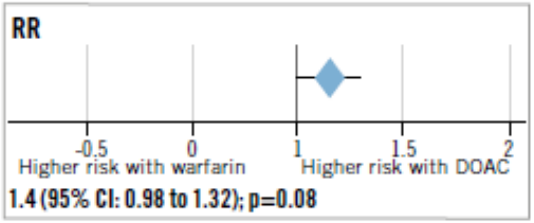
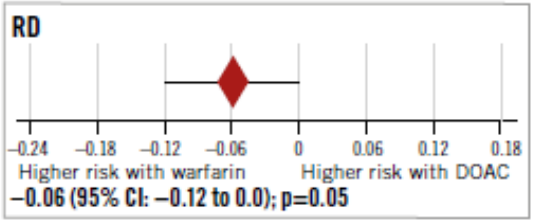
B Major bleeding (ISTH) in DOAC vs warfarin treatment groups

Study	DOAC Events	DOAC Total	Warfarin Events	Warfarin Total	RD [95% CI]	Weight
Alcalai et al (2021)	0	17	2	15	−0.13 [−0.33 to 0.06]	14.4%
Abdelnabi et al (2021)	2	39	6	40	−0.10 [−0.23 to 0.03]	33.5%
Youssef et al (2023)	0	25	1	25	−0.04 [−0.14 to 0.06]	22.1%
REWARF-STEMI (2024)	0	26	0	24	0.00 [−0.07 to 0.07]	22.0%
Isa et al (2021)	0	9	0	8	0.00 [−0.20 to 0.20]	8.0%
Common effect model	**2**	**116**	**9**	**112**	**−0.06 [−0.12 to 0.00]**	**100%**

Heterogeneity: I^2=0%, τ^2=0; p=0.58
Test for overall effect: z=−1.96 (p=0.05)



Summary of REWARF-STEMI trial results and published RCTs on the role of DOAC versus warfarin in patients with echocardiographically diagnosed LVT after STEMI.

Outcomes		Intervention (DOAC)	Comparator (warfarin)	Measure of effect RR with 95% CI or RD with 95% CI
 3-month complete LVT resolution	REWARF-STEMI	19/25 (76%)	13/24 (54.2%)	
	SRMA	93/115 (80.8%)	79/112 (70.5%)	
 ISTH major bleeding	SRMA	2/116 (1.7%)	9/112 (8%)	

- In this RCT of 50 patients with STEMI complicated by LVT, three-quarters and nearly a half of the patients treated with rivaroxaban- and warfarin-based antithrombotic regimens, respectively, had complete LVT resolution.
- No major thromboembolic, ischaemic, or bleeding events were observed in either group.
- More importantly, in the pooled analysis of available RCTs, including the present study, there were no significant differences betwee DOACand warfarin-based regimens in terms of complete LVT resolution or major bleeding events, with the 95% CI estimates suggesting that it would be very unlikely that DOACs fared worse than warfarin for either effectiveness or safety.

- In summary, the current best evidence, albeit still limited by the relatively small sample size, is suggestive that DOACs are at least as effective and as safe as warfarin for the treatment of LVT.
- The 3-month complete LVT resolution is often regarded as a measure to stop anticoagulation due to the negligible risk of future embolic events after LVT resolution.
- Our pooled analysis showed complete LVT resolution in the majority of DOAC-treated patients (80.8%), which is statistically not different from patients treated with warfarin (70.5%).

- Some professional societies have already considered DOACs as a potential alternative to warfarin for the treatment of LVT.However, prior experience related to the reduced efficacy of DOACs in conditions such as thrombotic APS or AF in patients with rheumatic heart disease raised uncertainty about those recommendations.
- Findings from the current RCT and the pooled analysis of RCTs presented in this manuscript are in agreement with statements by professionalsocieties such as the American Heart Association, suggesting that **DOACs can be a viable option for the treatment of LVT.**
- In the existing RCTs, apixaban (5 mg twice daily) and rivaroxaban (15 to 20 mg once daily) were the DOACs administered. Different dual antiplatelet therapy regimens and durations are assigned for different studies, and thus, the safety of dual versus triple therapy is still inconclusive in the LVT population.

Limitations

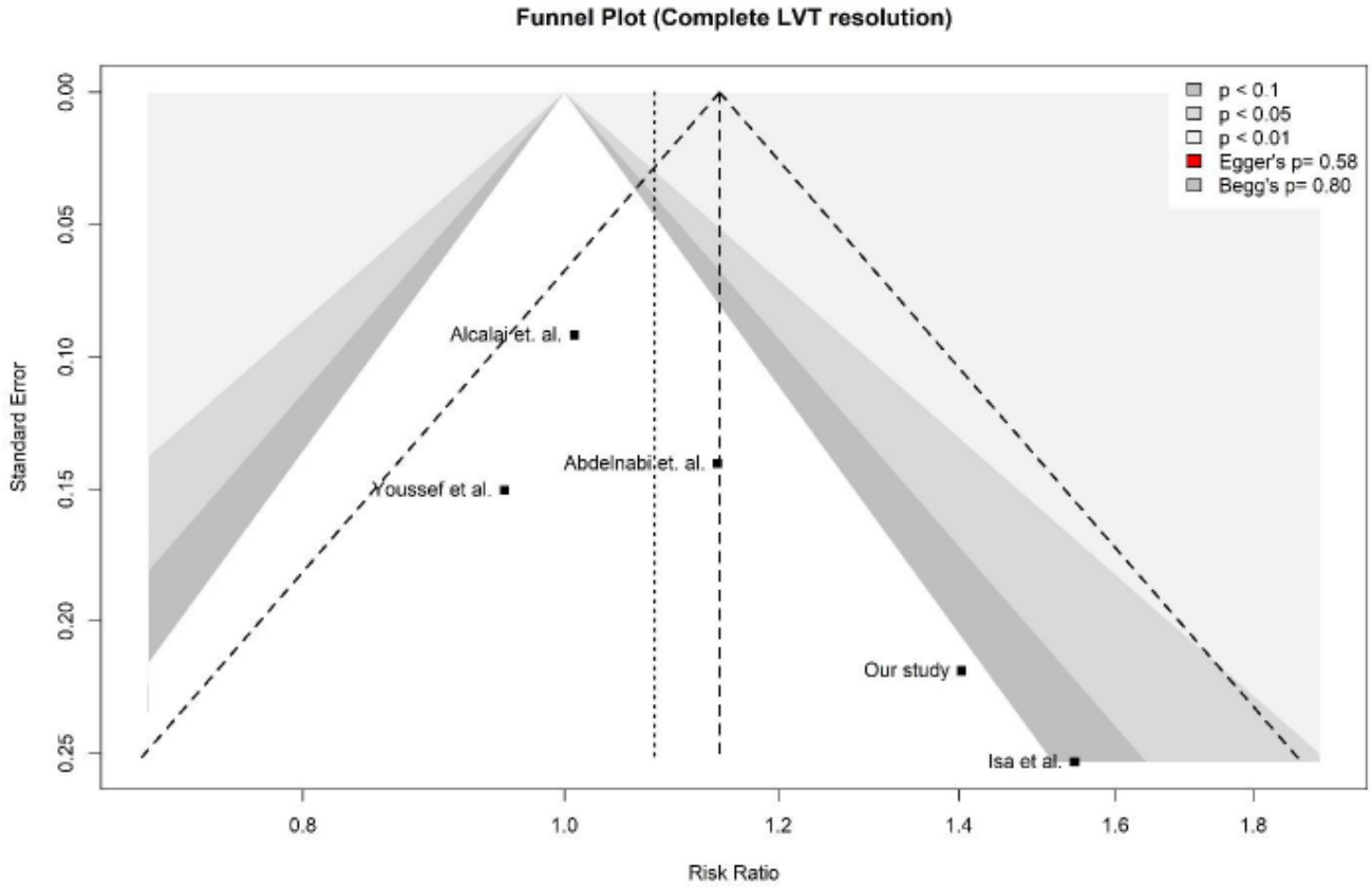
1. The sample size and the pilot nature of the original trial rendered the trial underpowered for its results
2. The trial included few female individuals. However, this is largely reflective of the disease epidemiology, which is consistent with the disproportionately higher relative frequency of LVT post-STEMI in male individuals compared to females
3. Contrast echocardiography was not performed in the trial, in large part due to resource limitations.

Conclusions

Findings from the REWARF-STEMI pilot trial of patients with STEMI complicated by LVT, paired with the preplanned meta-analysis of RCTs presented herein, suggest that **DOACs are at least as effective and safe as warfarin** with respect to LVT resolution and the risk of major bleeding.

Therefore, despite the limitations of the existing evidence, **DOACs appear to be a reasonable option for the management of patients with LVT after STEMI.**

Supplementary Figure 4A- Funnel plot representing publication bias for studies with complete left ventricular thrombus resolution as an outcome.




Thank You