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ORIGINAL RESEARCH

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

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ABSTRACT

BACKGROUND: The role of direct oral anticoagulants (DOACs) in the treatment of left ventricular thrombus (LVT) after ST-elevation myocardial infarction (STEMI) remains uncertain.

AIMS: We aimed to compare the effect of rivaroxaban versus warfarin in patients with STEMI complicated by LVT.

METHODS: Adult patients with STEMI and two-dimensional transthoracic echocardiography showing LVT were assigned to rivaroxaban (15 mg once daily) or warfarin (international normalised ratio goal of 2.0-2.5) in an open-label, randomised clinical trial (RCT). A prospective pooled analysis was planned comparing DOAC- versus warfarin-based anticoagulation for the same indication. The main outcome of the RCT was complete LVT resolution at 3 months, determined by a blinded imaging core laboratory. Complete LVT resolution and bleeding were investigated in the pooled analysis.

RESULTS: A total of 50 patients (median age: 55 years, 18% females) were enrolled from June 2020 to November 2022. Three-month complete LVT resolution occurred in 19/25 (76.0%) patients assigned to rivaroxaban and 13/24 (54.2%) assigned to warfarin (relative risk [RR] 1.40, 95% confidence interval [CI]: 0.91-2.15; p=0.12) with no thrombotic or major bleeding events. Pooled analysis showed numerically better complete LVT resolution with DOACs (rivaroxaban and apixaban; 93/115 [80.8%] vs 79/112 [70.5%], RR 1.14, 95% CI: 0.98-1.32; p=0.08) and less major bleeding (2/116 [1.7%] and 9/112 [8.0%], risk difference –0.06, 95% CI: –0.12 to 0.00; p=0.05) than with warfarin.

CONCLUSIONS: Although the findings are limited by a small sample size, the results suggest that DOACs are safe with at least similar outcomes concerning LVT resolution and major bleeding compared with warfarin. (ClinicalTrials.gov: NCT05705089)

KEYWORDS: adjunctive pharmacotherapy; clinical trials; STEMI

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Early revascularisation with primary percutaneous coronary intervention (pPCI) has reduced the incidence of left ventricular thrombus (LVT) formation[1]. 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[1,2]. If left untreated, LVT is associated with a 4-fold increase in stroke/systemic embolisation and a 2-fold increase in long-term mortality[3].

Warfarin has historically been used for treating LVT, and direct oral anticoagulants (DOACs) have recently gained 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[4,5]. Recently, a few, small randomised clinical trials (RCTs) showed promising early results for DOACs compared with warfarin in patients with LVT, but there is a need for more evidence[6].

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. Recognising that the RCT was planned with a relatively small number of enrollees, *a priori*, a meta-analysis was planned and registered (PROSPERO: CRD42023455855) to evaluate existing RCTs that compared DOACs versus warfarin in patients with STEMI complicated by LVT.

Editorial, see page 20

Impact on daily practice

The results of the current pilot trial and preplanned meta-analysis of available randomised clinical trials (RCTs) showed direct oral anticoagulants are at least as effective and safe compared to warfarin in patients with ST-elevation myocardial infarction complicated with left ventricular thrombus. This message should be interpreted cautiously as the sample size of currently published RCTs is limited. Large RCTs are required for a definitive recommendation.

Methods

TRIAL OVERSIGHT AND DESIGN

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 Rajaie Cardiovascular Institute. The study protocol **(Supplementary Appendix)** was approved by the ethics committees of both centres (Ethics code: IR.TUMS.THC.REC.1399.004). All patients provided written informed consent. A clinical events committee (CEC) blinded to assigned treatments adjudicated all the clinical outcomes **(Supplementary Appendix)**. An independent data and safety monitoring committee monitored the trial results **(Supplementary Appendix)**.

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[7] 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][4,8]), active bleeding, cardiogenic shock, estimated glomerular filtration rate (eGFR) <30 ml/min or those already receiving anticoagulation for other indications were excluded from the study. A full description of eligibility criteria is listed in the study protocol **(Supplementary Appendix)**.

RANDOMISATION AND TREATMENT STRATEGY

Randomisation was performed via a permuted block method with a block size of 4, using a web-based application with a 1:1 allocation ratio. 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[9].

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 non-contrast 2D TTE, mainly due to the unavailability of echocardiographic contrast agents in Iran. Although the sensitivity of contrast echocardiography is higher than non-contrast echocardiography (61% vs 33%) in diagnosing

Abbreviations

2D TTE	two-dimensional transthoracic echocardiography	**LVT**	left ventricular thrombus
DOAC	direct oral anticoagulant	**RCT**	randomised clinical trial
INR	international normalised ratio	**STEMI**	ST-elevation myocardial infarction

LVT, the specificity of non-contrast echocardiography is high (94%)[10]. Cardiac magnetic resonance was not selected because of limited resources.

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.

The same assigned expert cardiologist obtained the follow-up images for each patient who completed 3-month follow-up. All follow-up images were stored, deidentified, and sent for evaluation by the trial imaging core laboratory, consisting of two independent echocardiologists who remained blinded to the assigned treatments. All conventional measurements were carried out following the latest recommendations by the American Society of Echocardiography and the European Association of Cardiovascular Imaging[11]. Intra- and interobserver variability were tested by assessment of a series of deidentified cases for a second evaluation by the same operator and evaluation by a second operator of the core laboratory, respectively. A third operator resolved any discrepancies. Echocardiograms were acquired in the standard parasternal short- and long-axis views and apical 2-, 3- and 4-chamber view imaging planes **(Supplementary Appendix)**.

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 Society on Thrombosis and Haemostasis (ISTH) definition at 3 months from enrolment. Clinically relevant non-major bleeding (CRNMB) events based on the ISTH definition were also ascertained **(Supplementary Appendix)**. All outcomes were adjudicated by a CEC blinded to assigned treatments.

SYSTEMATIC LITERATURE REVIEW AND META-ANALYSIS

A systematic review and meta-analysis were planned, and the protocol was registered in PROSPERO (CRD42023455855) before the results of the current RCT were known. It was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline[12]. A systematic syntax search was devised using the relevant keywords to search the literature in MEDLINE (via PubMed) and the Cochrane Library up to 9 November 2023 **(Supplementary Appendix, Supplementary Table 1)**. The records were deemed eligible if they had an RCT design including adult patients (aged ≥18 years) with MI being treated in two distinct arms of antithrombotic regimens with DOACs versus warfarin and if they reported LVT resolution during follow-up at 3 months or a time interval close to that. The main outcomes for the prospective meta-analysis mirrored those of the currently reported trial. The risk of bias was assessed using the Cochrane Risk of Bias tool version 2 (RoB 2) **(Supplementary Appendix)**[13].

STATISTICAL ANALYSIS

Categorical variables are expressed as frequency counts with percentages. Continuous variables are described as the mean and standard error of the mean if normal distribution was confirmed, and if the variables were not normally distributed, data are described as median (interquartile range [IQR]). Due to the exploratory nature of the pilot RCT, no formal sample size calculation was carried out. 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).

For the meta-analysis, complete LVT resolution was the main efficacy outcome, and major bleeding was the safety outcome, comparing the pooled effectiveness of DOACs versus warfarin. The meta-analysis used the common-effect Mantel-Haenszel method, and the overall effect was reported with RR as the effect measure, except for outcomes with zero events in some trials, in which case risk difference was used as the effect measure. Further information on the methodology and statistical considerations for the meta-analysis are summarised in the **Supplementary Appendix**. Statistical analyses were performed using R version 4.2.1 (R Foundation for Statistical Computing).

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 rivaroxaban- and warfarin-based antithrombotic regimens, respectively **(Figure 1, Supplementary Appendix)**.

The two study groups were balanced regarding baseline clinical, procedural, and imaging characteristics **(Table 1)**. The majority of patients (45/50 [90%]) had anterior STEMI **(Supplementary Table 2)**. Forty-nine (98%) patients underwent pPCI, and one patient in the rivaroxaban group proceeded to emergent balloon angioplasty, followed by urgent coronary bypass graft surgery due to significant thrombotic involvement of the left main coronary artery in the diagnostic coronary angiography. All patients in both groups were compliant with and adherent to the assigned treatments. One patient in the rivaroxaban group had sudden death while sleeping 31 days post-randomisation. Consequently, 49 out of 50 (98%) patients completed the 3-month follow-up required for the primary outcome

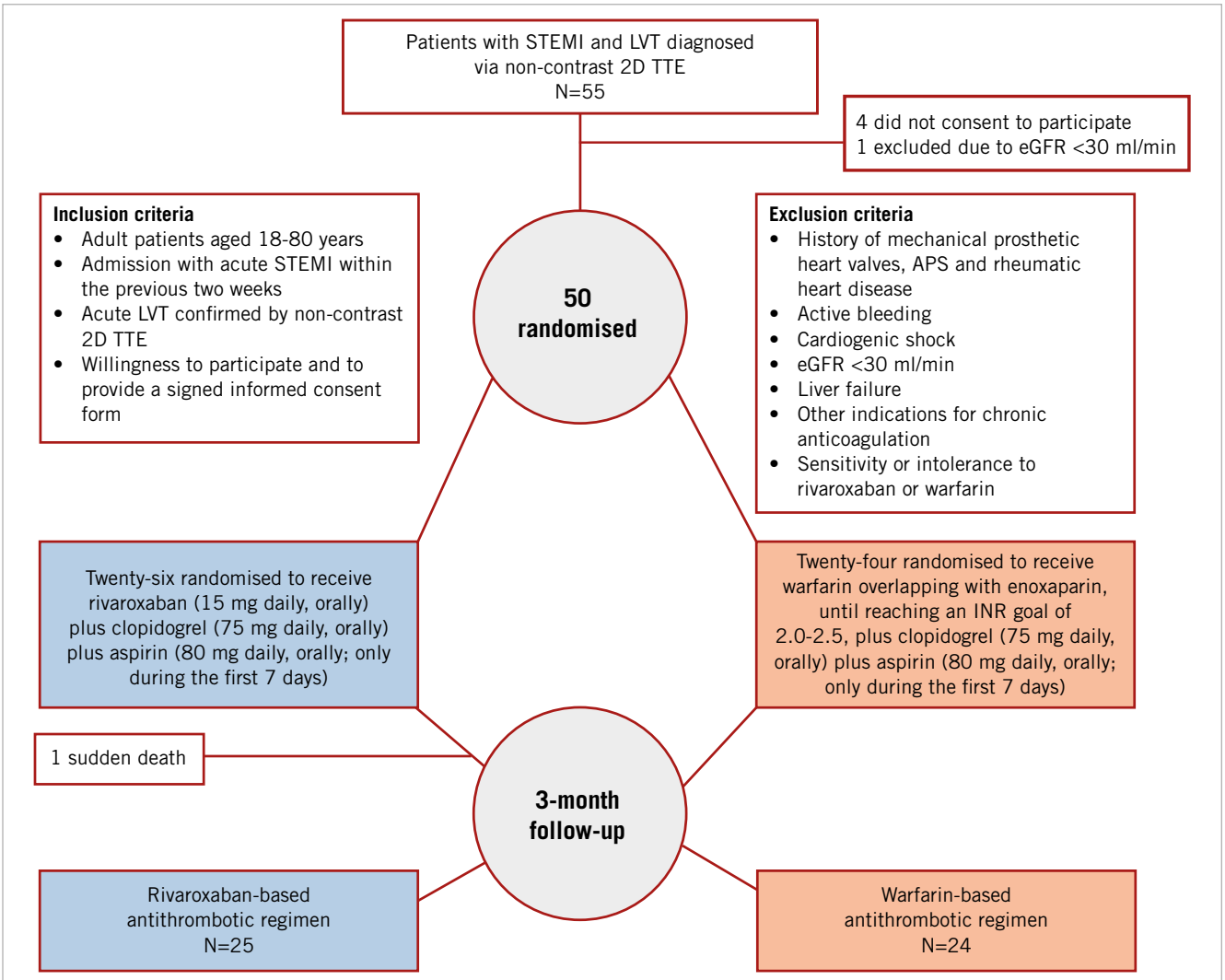


Figure 1. *Trial flow diagram. 2D: two-dimensional; APS: antiphospholipid syndrome; eGFR: estimated glomerular filtration rate; INR: international normalised ratio; LVT: left ventricular thrombus; STEMI: ST-elevation myocardial infarction; TTE: transthoracic echocardiography*

assessment. In patients treated with warfarin, the median TTR was 63% (IQR 61-66%) according to the Rosendaal method.

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 (RR 1.40, 95% CI: 0.91-2.15; p=0.12) **(Table 2)**.

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 treated conservatively in the outpatient setting. No major bleeding occurred in any of the patients during the study follow-up time **(Table 2)**.

META-ANALYSIS

The screening process, data extraction, synthesis, and systematic review of the included RCTs are described in detail in the **Supplementary Appendix** and in **Supplementary Figure 1**. Based on the eligibility criteria, four prior RCTs, along with the current study, were included in the meta-analysis[14-17], 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[14-17] **(Figure 2)**.

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 (RR 1.14, 95% CI: 0.98-1.32; p=0.08) **(Figure 3A, Supplementary Figure 2A)**.

Major bleeding occurred in 2/116 (1.7%) and 9/112 (8%) patients in the DOAC- and warfarin-based regimens, respectively (risk difference –0.06, 95% CI: –0.12 to 0.00; p=0.05) **(Central illustration, Figure 3B, Supplementary Figure 2B)**.

One study (Isa et al)[17] had an overall "low risk", and the other studies[14-16] (including REWARF-STEMI) had "some concerns" in terms of risk of bias **(Supplementary Appendix, Supplementary Figure 3)**. No evidence of publication bias was identified **(Supplementary Figure 4A-4B)**.

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

	Rivaroxaban (N=26)	Warfarin (N=24)
Age, years	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 (%).

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

Discussion

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 between DOAC- and 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 **(Central illustration)**. Although none of the individual trials nor the pooled analysis were formally planned for non-inferiority testing[18], the lower bound of the 95% CI for reduced efficacy (for LVT resolution) of DOACs, compared with warfarin, is far smaller than the margin of reduced efficacy for RCTs of stroke prevention in atrial fibrillation (AF; a margin of relative excess risk of 1.38-1.46 in prior

Study (year)	Type of OAC (D)	Type of OAC (W)	Study population	Imaging modality for diagnosis and F/U of LVT	Study outcomes: 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	✓	✓	✓	✓	✓	✓

Figure 2. *Summary of the baseline characteristics and reported outcomes in randomised clinical trials included in the pooled analysis. Note: In all studies, apixaban 5 mg was administered (except for Abdelnabi et al[16] and REWARF-STEMI administering rivaroxaban 20 mg and 15 mg, respectively), and warfarin was adjusted to achieve an INR of 2-3. *MACE: a composite of death from cardiovascular causes, MI, or stroke. †Three trials (Alcalai et al[15], Abdelnabi et al[16], and REWARF-STEMI) and one trial (Youssef et al[14]) defined bleeding based on ISTH and BARC definitions, respectively, and one trial (Isa et al[17]) did not use a specific definition. ‡In the RCT by Alcalai et al[15], at 3 months, 17 and 15 patients were followed up in the DOAC and warfarin groups, respectively; in REWARF-STEMI, at 3 months, 25 and 24 patients were followed up in the DOAC and warfarin groups, respectively. 2D: two-dimensional; BARC: Bleeding Academic Research Consortium; CRNMB: clinically relevant non-major bleeding; D: direct; F/U: follow-up; INR: international normalised ratio; ISTH: International Society on Thrombosis and Haemostasis; LV: left ventricular; LVT: left ventricular thrombus; MACE: major adverse cardiac events; MI: myocardial infarction; NA: not available; OAC: oral anticoagulant; TTE: transthoracic echocardiography; W: warfarin*

trials)[19] or acute treatment of venous thromboembolism (a margin of relative excess risk of 1.50-2.75)[20]. Similarly, for bleeding, pooled results were favourable for DOACs, with 95% CIs indicating that bleeding events with DOACs were at least not higher than with warfarin (upper bound of the 95% CI for risk difference: 0.00). 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.

For STEMI patients with LVT, the ideal primary efficacy outcome is SSE events[1]. To date, as shown by our systematic search, no RCTs have been powered to compare different antithrombotic strategies for hard endpoints. In fact, embolic events, particularly systemic embolism other than stroke, were not even consistently reported in the available trials[14-17]. However, 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[6]. It is conceivable that if participants had major embolic events, the trialists would have reported such outcome data. Our pooled analysis showed complete LVT resolution in the majority of DOAC-treated patients

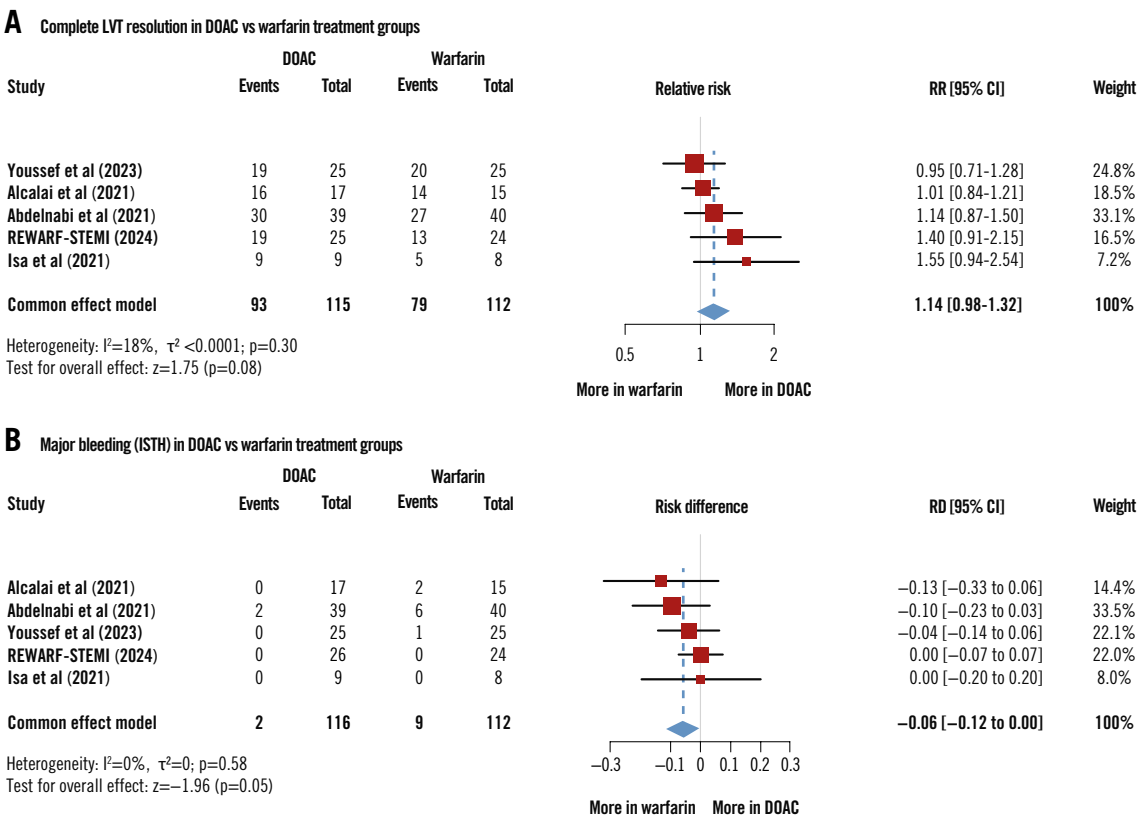


Figure 3. *Pooled analysis of complete left ventricular thrombus resolution and major bleeding. A) Complete LVT resolution in DOAC versus warfarin treatment groups. B) Major bleeding in DOAC and warfarin treatment groups. Note: The study by Isa et al[17] was conducted on patients with LVT, out of whom only patients with post-AMI LVT were included in the meta-analysis, as confirmed by the corresponding author. Similarly, the study by Abdelnabi et al[16] did not differentiate between post-AMI LVT and LVT due to other causes. However, they did not respond to our multiple inquiries. AMI: acute myocardial infarction; CI: confidence interval; DOAC: direct oral anticoagulant; ISTH: International Society on Thrombosis and Haemostasis; LVT: left ventricular thrombus; RD: risk difference; RR: relative risk*

(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[6,21]. However, prior experience related to the reduced efficacy of DOACs in conditions such as thrombotic APS[8] or AF in patients with rheumatic heart disease[22] raised uncertainty about those recommendations[4]. Findings from the current RCT and the pooled analysis of RCTs presented in this manuscript are in agreement with statements by professional societies such as the American Heart Association[6], suggesting that DOACs can be a viable option for the treatment of LVT. In a recently published meta-analysis on 22 studies comparing DOACs versus warfarin in patients with LV thrombosis, the use of DOACs was not associated with a significant increase in stroke or systemic embolism (odds ratio [OR] 0.81, 95% CI: 0.57-1.15) compared with warfarin[23]. The odds of thrombus resolution were not significantly different between the groups (OR 1.12, 95% CI: 0.86-1.46). The authors reported lower odds of all-cause mortality (OR 0.65, 95% CI: 0.46-0.92) and a composite bleeding endpoint (OR 0.67, 95% CI: 0.47-0.97) with the use of DOACs compared to warfarin. Of note, 18 of the 22 included studies were retrospective, patients with different aetiologies (ischaemic vs non-ischaemic) of LV thrombosis were all eligible for the final analysis, major bleeding was not separately reported, and REWARF-STEMI was not included in that meta-analysis[23].

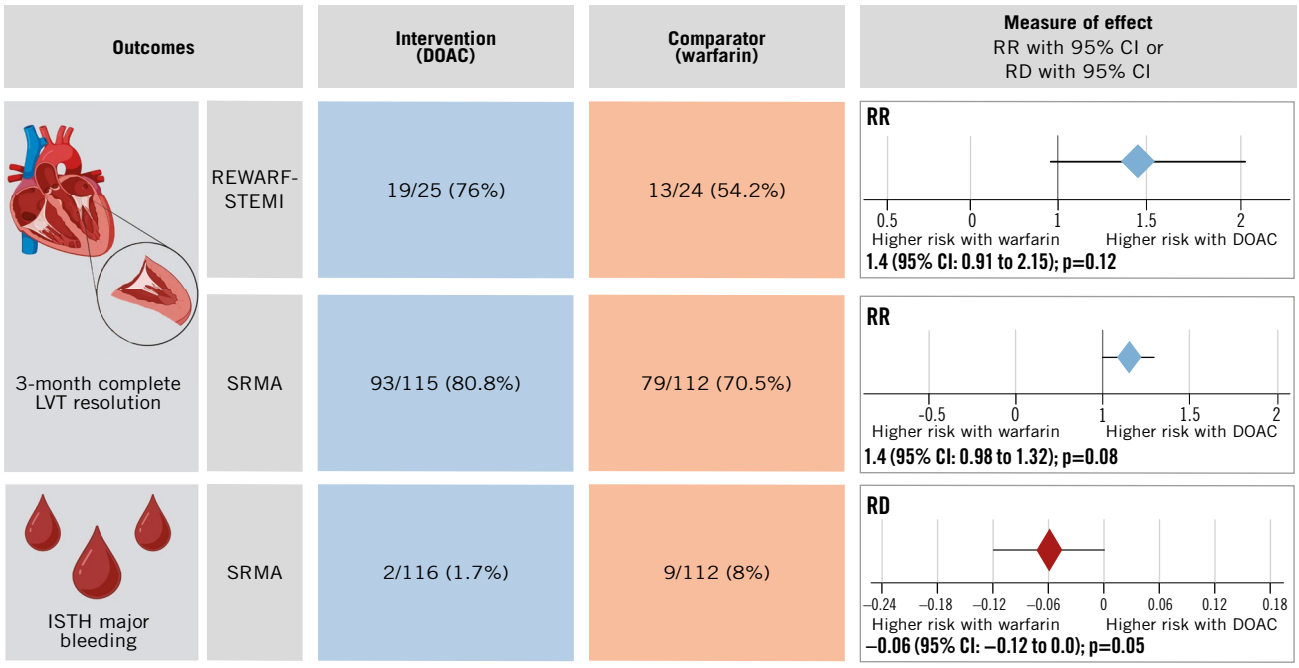
It should, however, be considered that the sample sizes for the existing individual RCTs are small, ranging from 27-79 patients, making it unfeasible to assess hard clinical endpoints with sufficient power **(Figure 2)**. In the existing RCTs, apixaban (5 mg twice daily) and rivaroxaban (15 to 20 mg 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. Findings from some additional ongoing trials[24] (ClinicalTrials.gov: NCT03764241, NCT04970576, NCT05892042, NCT05973188, NCT05794399, NCT03415386, as summarised in the **Supplementary Appendix** and **Supplementary Table 3**) have the potential to improve the confidence in alternative strategies to warfarin for LVT.

Limitations

This study has several limitations. First, the sample size and the pilot nature of the original trial rendered the

EuroIntervention — Central **Illustration**

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



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No ISTH major bleeding event was registered in REWARF-STEMI. CI: confidence interval; DOAC: direct oral anticoagulant; ISTH: International Society on Thrombosis and Haemostasis; LVT: left ventricular thrombus; RCT: randomised clinical trial; RD: risk difference; REWARF-STEMI: Rivaroxaban vErsus Warfarin for Antithrombotic TheRapy in Patients with LeFt Ventricular Thrombus After Acute ST-Elevation Myocardial Infarction; RR: relative risk; SRMA: systematic review and meta-analysis; STEMI: ST-elevation myocardial infarction

trial underpowered for its results. The pooled analysis of findings from REWARF-STEMI and previous pilot RCTs was prespecified and had consistent results. Second, 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[25-28]. Third, contrast echocardiography was not performed in the trial, in large part due to resource limitations. However, prior RCTs on this subject[14-17] also used non-contrast 2D TTE which had high specificity (98%)[29] and reasonable positive predictive value (72%) **(Supplementary Appendix, Supplementary Figure 5)**, and this has been endorsed by the American Heart Association statement[6] as one of the acceptable modalities for the diagnosis of LVT. Given the randomised design, any limited sensitivity would have affected the results similarly in both groups. Lack of clinical (stroke) events further reduces the possibility of missing major clinically relevant residual LVT. Of note, the majority of included patients had anterior STEMI, in whom non-contrast 2D TTE has higher sensitivity[2]. Finally, only two centres participated in patient recruitment for REWARF-STEMI, which limits the generalisability of the findings. However, the results are consistent with other independent trials reported in the pooled analysis.

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.

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Conflict of interest statement

G. Piazza has received research grants (paid to his institution) from BMS/Pfizer, Janssen, Alexion, Bayer, Amgen, Boston Scientific, Esperion, and the NIH (1R01HL164717-01); and has received consulting fees for advisory roles from Boston Scientific, Amgen, PERC, NAMSA, BMS, Janssen, Penumbra, and Thrombolex. H.M. Krumholz received expenses and/or personal fees from UnitedHealth, Element Science, Aetna, Reality Labs, Tesseract/4Catalyst, the Siegfried and Jensen Law Firm, Arnold and Porter Law Firm, Martin/Baughman Law Firm, and F-Prime; he is a co-founder of Refactor Health and Hugo Health; and has contracts through Yale New Haven Hospital from the Centers for Medicare & Medicaid Services and through Yale University from Johnson & Johnson. G.Y.H. Lip is a consultant and speaker for BMS/Pfizer, Boehringer Ingelheim, Daiichi Sankyo, and Anthos, although no fees are received personally; and he is a National Institute for Health and Care Research (NIHR) senior investigator and co-principal investigator of the AFFIRMO project on multimorbidity in AF, which has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement no. 899871, outside the submitted work. B. Bikdeli is supported by a Career Development Award from the American Heart Association and VIVA Physicians (#938814); was supported by the Scott Schoen and Nancy Adams IGNITE Award; is supported by the Mary Ann Tynan Research Scientist award from the Mary Horrigan Connors Center for Women's Health and Gender Biology at Brigham and Women's Hospital, and the Heart and Vascular Center Junior Faculty Award from Brigham and Women's Hospital; reports that he was a consulting expert, on behalf of the plaintiff, for litigation related to two specific brand models of IVC filters but was not involved in the litigation in 2022-2024 nor did he receive any compensation in 2022-2024; he reports that he is a member of the Medical Advisory Board for the North American Thrombosis Forum; and serves on the Data Safety and Monitory Board of the NAIL-IT trial funded by the National Heart, Lung, and Blood Institute, and Translational Sciences. The other authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Appendices:

- CEC members.
- Data and safety monitoring board.
- Steering committee members.
- Systematic review and meta-analysis.
- Trial protocol.
- CONSORT checklist.

Supplementary Figure 1. PRISMA flow diagram of the systematic search.

Supplementary Figure 2A. Forest plot representing the pooled analysis of complete left ventricular thrombus resolution in direct oral anticoagulants versus warfarin treatment groups, using risk difference as the effect measure.

Supplementary Figure 2B. Forest plot representing the pooled analysis of major bleeding in direct oral anticoagulants versus warfarin treatment groups using relative risk as the effect measure.

Supplementary Figure 3. Quality assessment of the randomised controlled trials using the Cochrane Risk of Bias (RoB 2) tool.

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

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Supplementary Figure 5. Forest plot of the pooled analysis on the positive predictive value for the LV thrombus diagnosis using non-contrast transthoracic echocardiography versus cardiac magnetic resonance imaging.

Supplementary Table 1. Systematic syntax search for databases with results up to 9 November 2023.

Supplementary Table 2. Territory of infarction in the study population.

Supplementary Table 3. Ongoing trials on testing different DOAC-based antithrombotic regimens in patients with left ventricular thrombosis.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-24-00527

Supplementary Data

Direct Oral Anticoagulants or Warfarin in Patients with Left Ventricular Thrombus After ST-Elevation Myocardial Infarction: A Pilot Trial and A Pre-specified Meta-Analysis of Randomized Trials

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Clinical Event Committee (CEC)

Based on the reported events, the CEC members held online meetings. The data were deidentified, and the treatment arms remained blinded when the data was provided to the CEC. Case vignettes were being presented real-time by a trained physician. Deidentified imaging tests, laboratory values, and surgical/interventional procedural reports were presented as proof of related events. The CEC members discussed each case and adjudicated the reported outcomes. An official report regarding the serious adverse events assessed during each meeting was made at the end of each CEC meeting.

CEC members

Behnood Bikdeli, MD, MS

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Data and Safety Monitoring Board (DSMB)

Safety supervision was under the auspices of the DSMB, composed of individuals with the appropriate expertise and free from conflict of interest, and no steering committee members or the study's authors. DSMB meetings were held based on the occurrence of adverse events.

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Systematic review and meta-analysis

Methods

Systematic literature search

The study protocol was registered in PROSPERO (CRD42023455855). A systematic search was performed through MEDLINE (via PubMed) and Cochrane Library from the inception through November 9, 2023. We also ran a hand search and reviewed the references of all the included studies. The keywords used were 'Left ventricle,' 'Thrombus,' 'Clot, blood,' 'myocardial infarction,' 'warfarin,' 'Vitamin K/ antagonists & inhibitors,' 'Rivaroxaban,' 'Direct-Acting Oral Anticoagulant,' DOAC,' 'NOAC,' 'Factor Xa inhibitors,' 'Dabigatran,' 'Apixaban,' and 'Edoxaban,.' No restriction was imposed on the study design and language. The systematic search syntax is represented in Table S1.

Eligibility Criteria and Outcomes of Interest

The studies were included if: a) Had a randomized controlled trial (RCT) design, b) included adult patients (aged ≥18 years), c) reported individuals who were diagnosed with LVT following acute myocardial infarction (AMI) d) had an intervention arm receiving a DOAC-based antithrombotic regimen, including rivaroxaban, apixaban, edoxaban, and dabigatran, d) had a comparison arm receiving warfarin. The studies were excluded if: a) had a design other than RCT (i.e., observational studies, comments, abstracts, editorials, conference papers, expert opinions, and reviews), b) reported LVT in contexts other than AMI, c) had no follow-up data on the outcomes of interest.

The main efficacy outcome of interest was complete LVT resolution within 3 months from enrollment. The main safety outcome of interest was major bleeding within 3 months from enrollment.

Selection Process

The records obtained from the database search were first transferred to EndNote software, version X9 (Clarivate Plc). After the removal of duplicates, two independent researchers (A.R. and Y.P.) screened all the records in a stepwise process. Firstly, all records were screened by the title and abstracts. Secondly, the full texts of the remaining records were further evaluated. The records that did not meet the eligibility criteria were excluded. Conflicts were resolved by the consensus of the authors.

Quality Assessment

The methodological quality of included RCTs was assessed using the Cochrane risk of bias 2 (RoB 2) tool. Two investigators (Y.P. and A.R.) independently assessed the risk of bias and the quality of the included studies. In case of discrepancy, the consensus was achieved by discussion with a third author (P.S.).

Data Extraction, Synthesis, and statistical analysis

The data of interest were extracted as follows: (1) study-related variables (first author's name, publication year, sample size); (2) antithrombotic therapy variables, including DOAC types and dosage (3) demographic variables, including age and sex (4) outcome-related variables, including number of patients with complete LVT resolution, imaging method used for LVT resolution, time to follow-up imaging. Two independent researchers (A.R. and Y.P.) extracted the data and completed the predesigned forms. Discrepancies were discussed with two additional authors (P.S. and B.B.). The predefined outcomes in patients with LVT undergoing treatment with DOACs and warfarin were compared, and the pooled effect size (risk difference and relative risk and 95% confidence interval) of the comparison was calculated using the Mantel-Haenszel method by the "metabin" function. Statistical heterogeneity was assessed by Cochran's Q test and Higgin's I^2 test. In case of a high degree of heterogeneity (I^2>50%), a random-effects model was applied to pool the estimates; otherwise, a common-effects model

was implemented. All the analyses were conducted using R package 'meta' 5.2-0, R version 4.2.1 (R Foundation for Statistical Computing).

Results

Study selection

Of the 1295 records identified initially during the systematic search, 184 were duplicates. The remaining 1111 were screened based on the titles and abstracts, out of which 1065 were irrelevant. Full texts of the 46 remaining records were evaluated based on the pre-established eligibility criteria, of which 42 records were excluded: 4 review studies, 33 observational studies, and 9 studies with treatment arms not meeting the inclusion criteria. Ultimately, 4 RCTs were included in the systematic review and meta-analysis. The PRISMA flow diagram in Figure S1 summarizes the selection process.

Quality assessment

Regarding risk of bias assessment, based on the Cochrane ROB-2 tool, one study was "low-risk," and REWARF-STEMI and three others had "some concerns" majorily due to the open-label design (Figure S3). The study by Abdelnabi et al. had "some concerns" regarding 2 criteria: “Bias due to deviations from the intended intervention” and “Bias due to outcome measurements” (Figure S3).

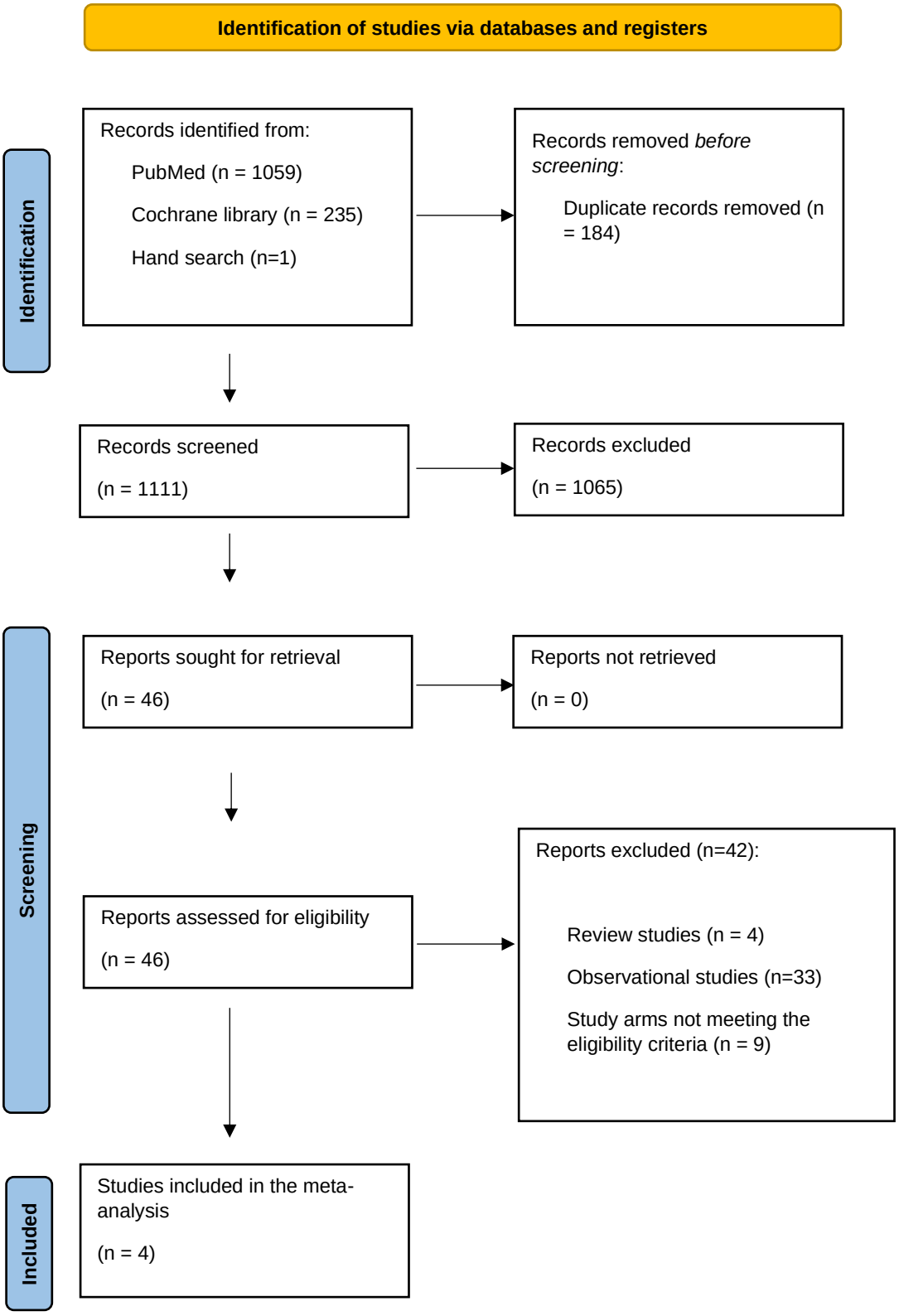
Study characteristics

Four RCTs were included in the present study. Each study compared DOAC- versus warfarin-based antithrombotic regimens on LVT. Two studies have limited their studied population to post-acute MI patients. The study by Isa et al. had a mixed population, and the required data for patients with post-MI LVT were provided through an email inquiry from the authors. The etiology of LVT in the RCT by Abdelnabi et al. was not defined, and the authors did not

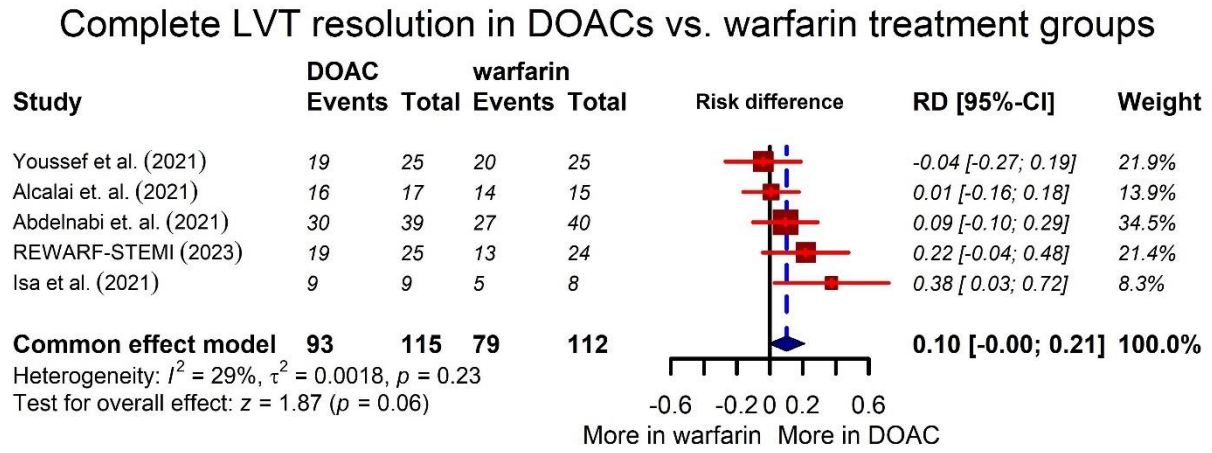
respond to multiple inquiries. For the purpose of this analysis, the events were considered as post-MI.

Three studies used apixaban 5 mg twice daily, and one used rivaroxaban 20 mg once daily as DOAC. LVT was diagnosed based on non-contrast 2D TTE in all 4 RCTs, and none of the four trials applied a core laboratory for the assessment of the imaging outcome. Two RCTs reported major bleeding according to ISTH criteria (Trial protocol, Appendix C), one according to BARC classification, and the last one, described the bleeding event, whereas no criteria were utilized. For the latter 2 studies, we redefined bleeding events, i.e., bleeding events were considered as major bleeding if the description of the event met the ISTH criteria (Trial protocol, Appendix C) for major bleeding. The main efficacy (3-month complete LVT resolution) and the main safety (3-month major bleeding) outcome of this pooled analysis were captured from all included RCTs. The 3-month outcomes of complete LVT resolution and major bleeding were reported in all 4 RCTs, except for the 3-month major bleeding in the study by Abdelnabi et al., in which they have not distinguished whether their report of major bleeding corresponds to 1-, 3-, or 6-month follow-ups.

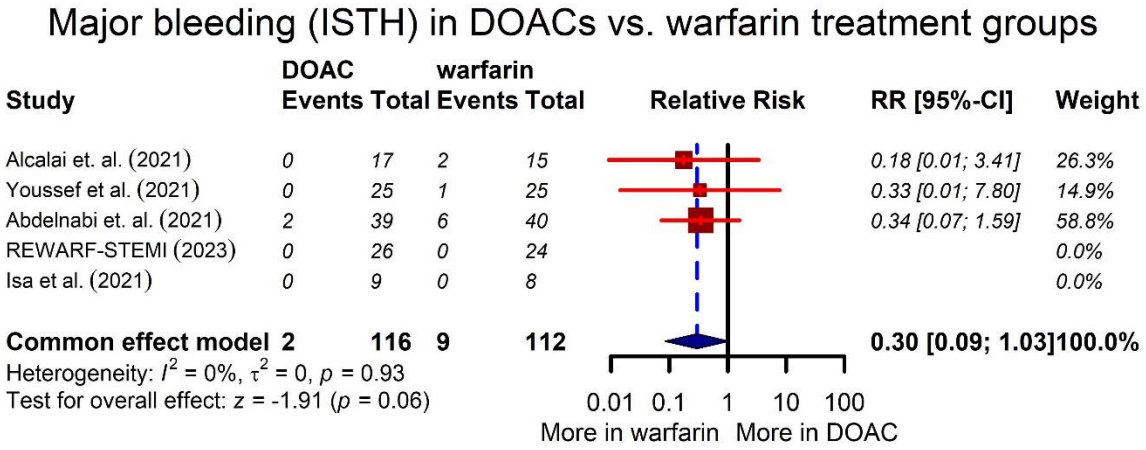
Supplementary Figure 1- PRISMA flow diagram of the systematic search



Supplementary Figure 2A- Forest plot representing the pooled analysis of complete left ventricular thrombus resolution in direct oral anticoagulants versus warfarin treatment groups, using risk difference as the effect measure.

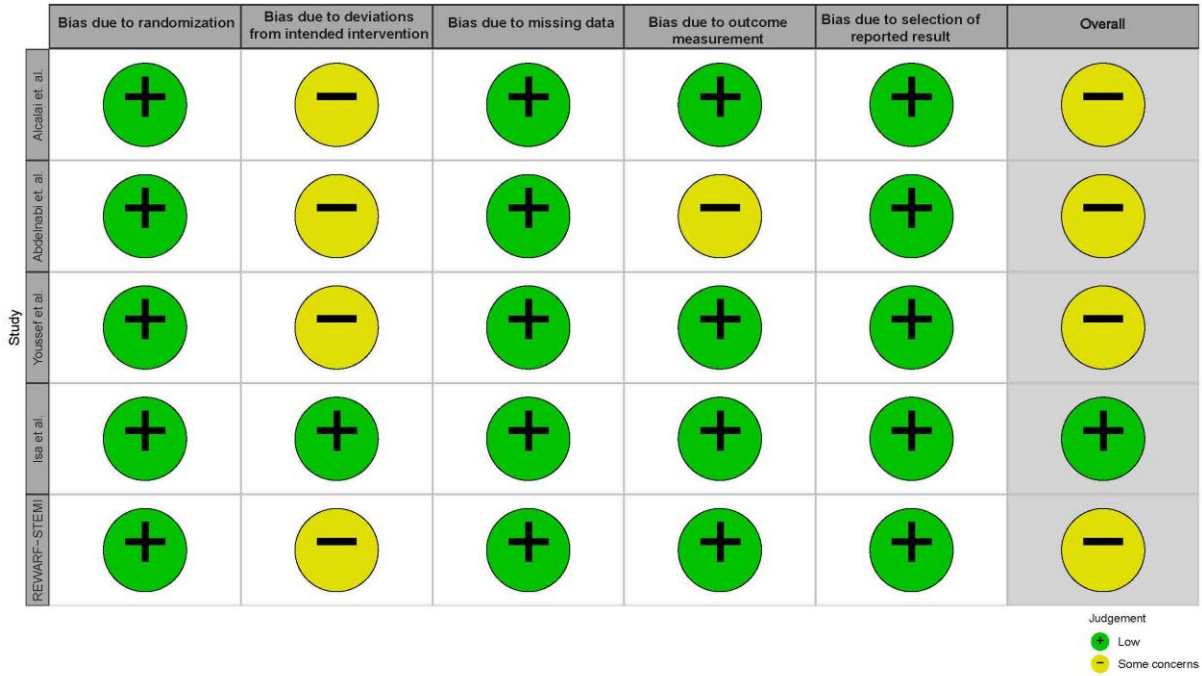


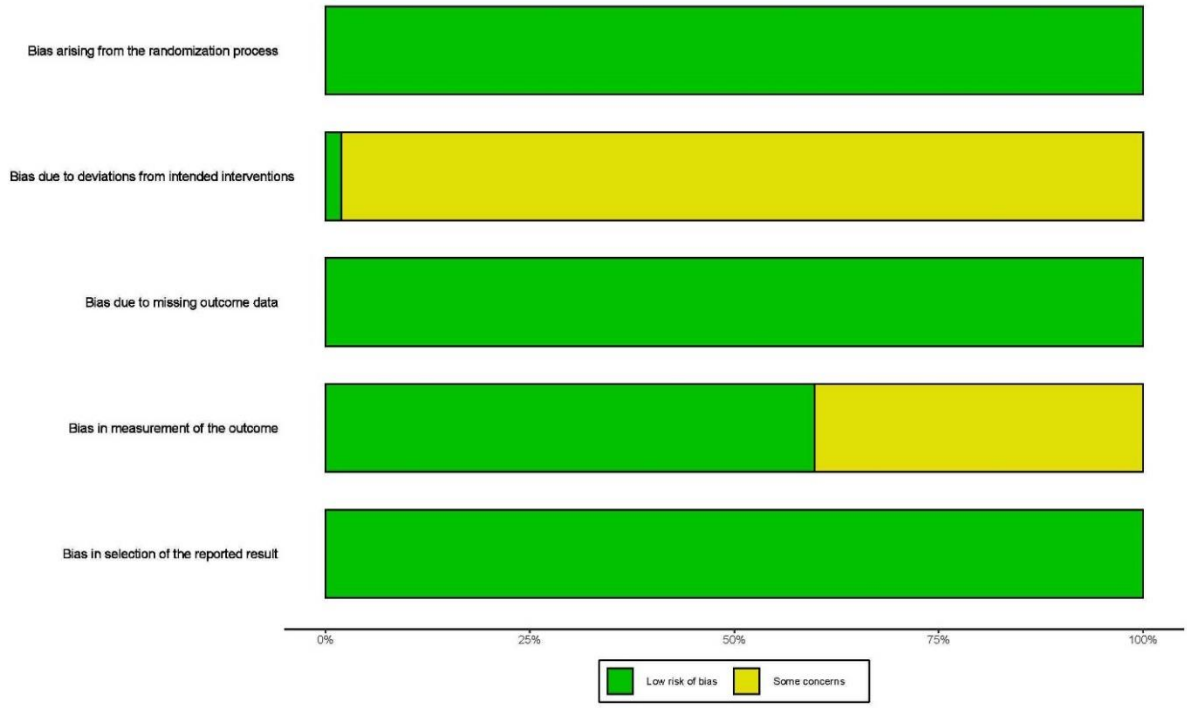
Supplementary Figure 2B- Forest plot representing the pooled analysis of major bleeding in direct oral anticoagulants versus warfarin treatment groups using relative risk as the effect measure.



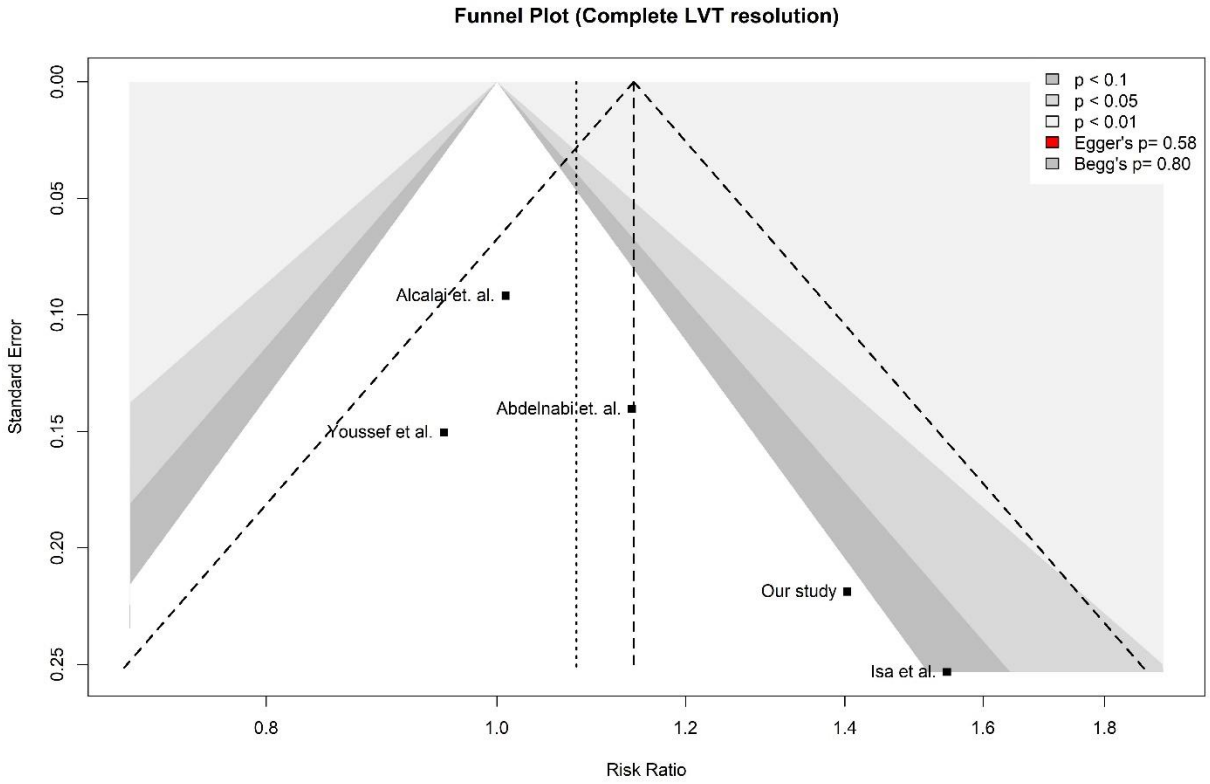
Note that due to zero events, two trials did not contribute to this analysis.

Supplementary Figure 3- Quality assessment of the Randomized Controlled Trials using the Cochrane Risk of Bias (RoB2) tool.

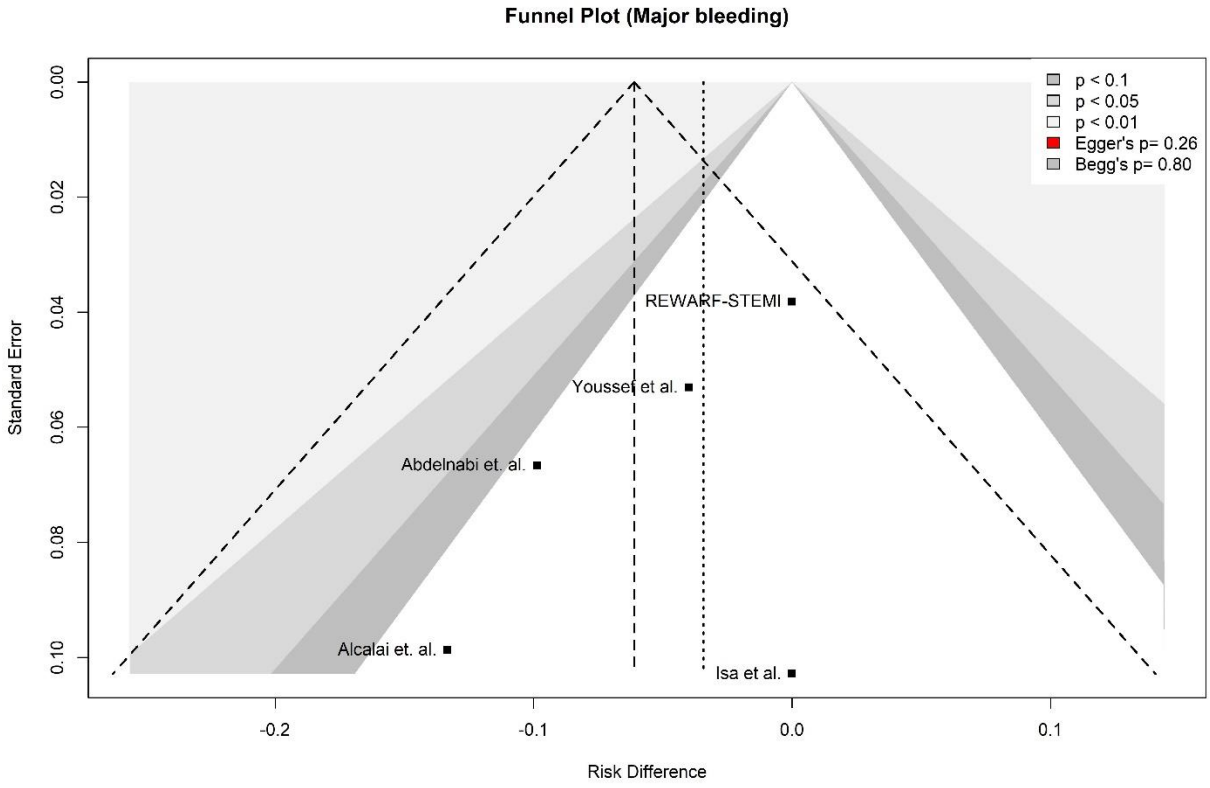




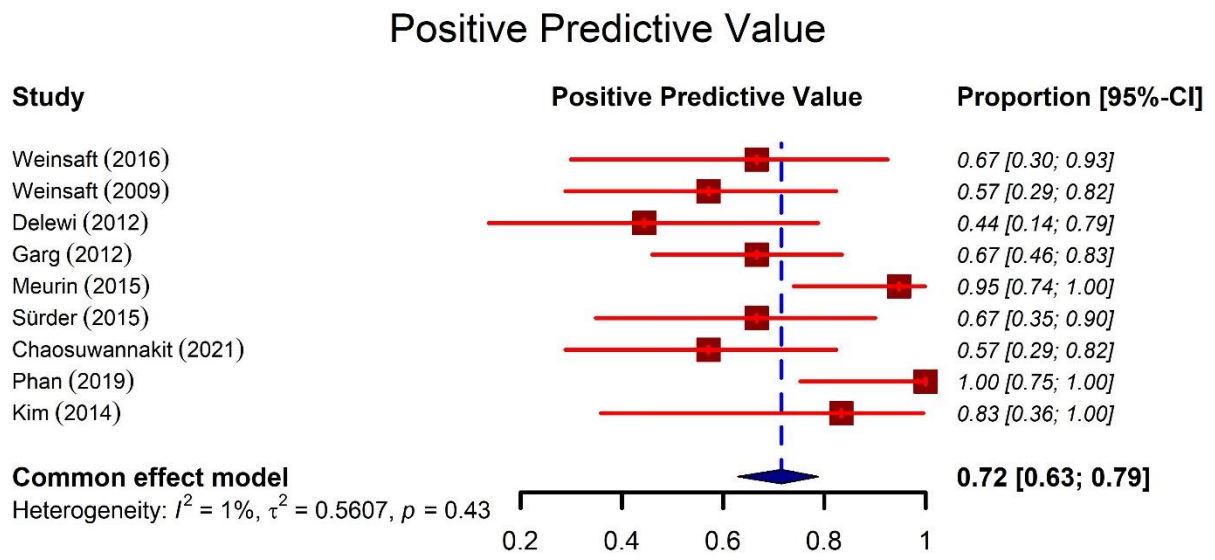
Supplementary Figure 4A- Funnel plot representing publication bias for studies with complete left ventricular thrombus resolution as an outcome.



Supplementary Figure 4B- Funnel plot representing publication bias for studies with major bleeding as an outcome.



Supplementary Figure 5- Forest plot of the pooled analysis on the positive predictive value for the LV thrombus diagnosis using non-contrast transthoracic echocardiography vs. cardiac magnetic resonance imaging.



Note: The included studies are derived from the meta-analysis article by Phuah et al.[8]. The positive predictive values were calculated using the numbers provided in the supplemental file of the article by Phuah et al..[8] Due to the high heterogeneity of the pooled analysis, we further performed a leave-one-out analysis. Subsequently, the study by Weinsaft et al. (2011) was excluded from our pooled analysis, resulting in a final I^2 index of 1%.

Supplementary Table 1- Systematic syntax search for databases with results up to 9 November 2023.

MEDLINE (via Pubmed)		
No.	Syntax	No. of results
1.	(“Left”[All Fields] AND "Heart Ventricles"[Mesh]) OR “Left ventric*”[All Fields]	250,054
2.	"Thrombosis"[Mesh] OR "Thromb*"[All Fields] OR "Blood clot*"[All Fields]	650,698
3.	"Left Ventricular Thromb*"[All Fields] OR "LVT"[All Fields] OR "LV thromb*"[All Fields]	1,763
4.	"Warfarin"[Mesh] OR “warfarin”[All Fields] OR “VKA*”[All Fields] OR “Vitamin K antagonist*”[All Fields] OR “Vitamin K inhibitor*”[All Fields]	40,813
5.	"Factor Xa Inhibitors"[Mesh] OR "Factor Xa Inhibitor*"[All Fields] OR “Rivaroxaban”[All Fields] OR “Edoxaban”[All Fields] OR “Apixaban”[All Fields] OR “Dabigatran”[All Fields] OR “DOAC”[All Fields] OR “NOAC”[All Fields] OR “Direct-Acting Oral Anticoagulant*”[All Fields] OR “Factor Xa inhibitor*”[All Fields] OR “Oral Anticoagul*”[All Fields]	37,344
6.	((#1 AND #2) OR #3) AND (#4 OR #5)	1059

Cochrane Library		
No.	Syntax	No. of results
1.	(Left AND [mh "Heart Ventricles"]) OR ("Left" NEXT ventric*)	24,649
2.	[mh Thrombosis] OR Thromb* OR ("Blood" NEXT clot*)	71,080
3.	("Left Ventricular" NEXT Thromb*) OR LVT OR ("LV" NEXT thromb*)	158
4.	[mh Warfarin] OR warfarin OR VKA* OR ("Vitamin K" NEXT antagonist*) OR ("Vitamin K" NEXT inhibitor*)	6482
5.	[mh "Factor Xa Inhibitors"] OR ("Factor Xa" NEXT Inhibitor*) OR Rivaroxaban OR Edoxaban OR Apixaban OR Dabigatran OR DOAC OR NOAC OR ("Direct-Acting Oral" NEXT Anticoagulant*) OR ("Factor Xa" NEXT inhibitor*) OR ("Oral" NEXT Anticoagul*)	7043
6.	((#1 AND #2) OR #3) AND (#4 OR #5)	235

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 (%)	

Supplementary Table 3. Ongoing trials on testing different DOAC-based antithrombotic regimens in patients with left ventricular thrombosis.

Study Title	Target Population with LVT	Estimated Sample Size	DOAC tested against VKA[1,2,3]		Imaging method	Primary outcome	Secondary outcomes	Status
			Intervention	Comparison				
EARLYmyo-LVT (NCT03764241)	STEMI	280	3-month DAPT+ rivaroxaban 15 mg once daily	3-month DAPT+ warfarin	CMR	-Efficacy: 3-month LVT resolution -Safety: 3-month major bleeding	-Composite of major adverse events[4] -Non-major bleeding events -SSE -Time to LVT resolution	Recruiting
Rivaroxaban in Left Ventricular Thrombus (NCT04970576)	ACS	320	3-month rivaroxaban 20 mg once daily	3-month warfarin	TTE	3-month complete LVT resolution	-SSE -Major bleeding	Recruiting
ACTonLVT (NCT05892042)	STEMI	320	Rivaroxaban 15 mg once daily	DAPT	TTE or CMR	12-month composite of SSE	-Composite major adverse events[5] - LVT resolution - Total LVT present time[6] - Percentage of participants with clinically significant bleeding -Percentage of participants with major bleeding -Percentage of participants with minor bleeding - Cardiovascular mortality	Recruiting
WRAP (NCT05973188)	not defined	141	Rivaroxaban 20 mg once daily or Apixaban 5mg twice daily [7]	Warfarin	TTE	6-month complete LVT resolution	-Time to LVT resolution (in months) -Minor bleeding events -SSE	Recruiting
WaRMIN (NCT05794399)	STEMI	196	Rivaroxaban 20 mg once daily	Warfarin	CMR	3-month	-Major bleeding -SSE	Recruiting

Study Title	Target Population with LVT	Estimated Sample Size	DOAC tested against VKA[1,2,3]		Imaging method	Primary outcome	Secondary outcomes	Status
			Intervention	Comparison				
						LVT resolution		
OATH-AMI (NCT03415386)	STEMI	120	1-month DAPT + dabigatran110 mg twice daily	1-month DAPT + Warfarin	TTE	1-, 3-, and 6-month complete LVT resolution	-Major bleeding -Minor bleeding	Unknown

ACS, acute coronary syndrome; BARC, Bleeding Academic Research Consortium; CMR, cardiac magnetic resonance imaging; DAPT, dual antiplatelet therapy; LVT, left ventricular thrombus; SSE, stroke/systemic embolism; STEMI, ST-elevation myocardial infarction; TTE, transthoracic echocardiography.

[1] DAPT will be prescribed according to available guidelines in all trials focusing on the ACS population.

[2] An INR range of 2-3 has been set in all the ongoing studies, except for the EARLYmyo-LVT study, defined as 2-2.5, and OATH-AMI, defined as 1.8-2.2.

[3] The duration of antithrombotic regimens was only defined in EARLYmyo-LVT and Rivaroxaban in the Left Ventricular Thrombus trials.

[4] The incidence of composite adverse events, including all-cause death, recurrent myocardial infarction, ischemic stroke, and other events of systemic embolism.

[5] Composite major adverse events are defined as the incidence of composite adverse events, including all-cause mortality, recurrent myocardial infarction, ischemic stroke, and other systemic embolism

[6] Total LVT present time will be assessed by TTE or CMR every month in the first 3 months and every 3 months thereafter to determine the presence of LVT.

[7] Apixaban will be adjusted to 2.5 mg twice daily if having two or more of the following: patients with age ≥80years and/or creatinine≥1.5 and/or body weight ≤60kg

Trial Protocol

Rivaroxaban vErsus Warfarin for Antithrombotic TheRapy in Patients with LeFt Ventricular Thrombus After Acute ST-Elevation Myocardial Infarction (REWARF-STEMI): A Pilot Randomized Clinical Trial

Principal Investigators

Yaser Jenab, MD; Parham Sadeghipour, MD

Protocol version: 1.0, 06.20.2020

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Background

Left ventricle thrombosis (LVT) is among the major consequences of acute myocardial infarction (AMI) [30]. 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 [31,32]. A recent cohort study on 157 patients with LVT with mixed etiologies matched with 400 non-LVT individuals showed a 3.7% annual rate for a composite of stroke, transient ischemic attack (TIA), and extracranial systemic arterial embolism, which was four times the rate in the matched non-LVT group [33].

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 [34]. 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 [35]. Both documents state the absence of prospective randomized clinical trial (RCT) data in this field [34,35].

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) [36]. 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 [37,38], 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 cardiomyopathy (22%). This study was limited by lack of a randomized design.

In a multicenter, retrospective study, Robinson et al. evaluated 514 patients with LVT. The median duration of follow-up was 351 (interquartile range [IQR], 51-866) days. Contrary to the Kajy et al. study, in the multivariable analysis, DOACs versus warfarin anticoagulation (HR, 2.64; 95 % CI, 1.28-5.43; P-value =0.01) and previous stroke and systemic embolism (SSE) (HR, 2.07; 95 % CI, 1.17-3.66; P =.01) remained significantly associated with current

SSE. Even after adjustment for other variables, treatment with a DOAC was associated with a greater incidence of SSE events than warfarin anticoagulation. The most common etiologies of LVT in this study were ischemic cardiomyopathy in 59.9% of the cases, followed by nonischemic cardiomyopathy in 25.3% of the population [40].

The studies cited above have several limitations, such as observational design with the possibility of residual and unmeasured confounding, varying thrombus resolution definition, heterogenous DOAC dose regimens, limited sample sizes, retrospective design, uncontrolled heterogeneous population and lack of imaging core laboratory and thus underscores the need for RCTs to determine the most effective and safest treatment strategy for patients with LVT.

In the present open label pilot RCT, we will compare 3-month thrombus resolution evaluated by core laboratory based non-contrast 2D transthoracic echocardiography (TTE) between patients with acute STEMI within the past two weeks complicated by LVT who are randomized to warfarin versus antithrombotic regimen in patients.

Objectives

Primary objective

- To compare the proportion of patients with complete LVT resolution between rivaroxaban and warfarin-based antithrombotic regimens based on non-contrast 2D TTE as performed by imaging core laboratory in patients with LVT following acute STEMI at 3 months from enrollment

Other objectives

- To compare the proportion of the patients with adjudicated SSE between rivaroxaban and warfarin-based antithrombotic regimens in patients with LVT following acute STEMI at 3 months from enrollment (Appendix A)
- To compare the proportion of the patients with adjudicated major adverse cardiac events (MACE) (a composite of death from cardiovascular causes, myocardial infarction, or stroke) between rivaroxaban and warfarin-based antithrombotic regimens in patients with LVT following acute STEMI at 3 months from enrollment
- To compare the proportion of the patients with adjudicated all-cause death between rivaroxaban and warfarin-based antithrombotic regimens in patients with LVT following acute STEMI at 3 months from enrollment (Appendix B)
- To compare adjudicated major bleeding events according to the International Society on Thrombosis and Hemostasis (ISTH) definition between rivaroxaban and warfarin-based antithrombotic regimens in patients with LVT following acute STEMI at 3 months from enrollment (Appendix C)
- To compare adjudicated clinically relevant non-major bleeding (CRNMB) events according to the ISTH definition between rivaroxaban and warfarin-based antithrombotic regimens in patients with LVT following acute STEMI at 3 months from enrollment (Appendix C)

Design

Pilot, open-label, parallel-group RCT with a 1:1 allocation ratio, concealed allocation sequences, and blinded outcome assessments

Setting

Two large cardiovascular tertiary centers in Tehran, Iran:

- Rajaie Cardiovascular Medical and Research Center, Tehran, Iran
- Tehran Heart Center, Tehran, Iran

Participants

Patients with confirmed acute STEMI complicated by LVT as assessed by non-contrast 2D TTE [41]. (Appendix D)

Eligibility criteria

Inclusion criteria

1. Adult patients aged 18-80 years
2. Admission with acute STEMI within the past two weeks (Appendix D)
3. Acute LVT confirmed by non-contrast TTE
4. Willingness to participate and to provide a signed informed consent form

Exclusion criteria

1. Mechanical prosthetic heart valve, rheumatic heart disease, and confirmed case of antiphospholipid syndrome
2. Active bleeding

3. Cardiogenic shock[1] defined as persistent hypotension (systolic blood pressure <90 mm Hg, or requirement of vasopressor to maintain systolic pressure >90 mm Hg) and clinical signs of hypoperfusion (cold, sweated extremities, oliguria, mental confusion, dizziness, narrow pulse pressure)
4. Acute kidney injury or chronic kidney disease with a glomerular filtration rate <30 ml/min (calculated based on the Cockcroft-Gault formula)
5. Liver failure (Child-Pugh class C)
6. Other indications for chronic anticoagulation (e.g., AF, VTE, etc.)
7. Sensitivity or intolerance to rivaroxaban/warfarin

[1] ESC AHF 2016 guideline definition

Randomization

Randomization will be performed via a permutated block method with a block size of 4, using a web-based application with a 1:1 design. The unit of randomization will be designated by individual participants. The participants will be randomly allocated into the two arms of the study without stratification.

Intervention and Comparator

A. Intervention

All patients assigned to the rivaroxaban-based antithrombotic regimen will receive rivaroxaban (15 mg once daily, orally) plus clopidogrel (75 mg daily, orally) plus aspirin (80 mg once daily, orally). Aspirin will be discontinued within seven days of its initiation. The antithrombotic regimen (i.e., rivaroxaban plus clopidogrel) will be planned to be continued for 3 months after randomization.

B. Comparator

All patients assigned to the warfarin-based antithrombotic regimen will receive warfarin (overlapping with enoxaparin until reaching an INR goal of 2-2.5) plus clopidogrel (75 mg once daily, orally) plus aspirin (80 mg once daily, orally). Aspirin will be discontinued within seven days of its initiation. The antithrombotic regimen (i.e., warfarin plus clopidogrel) will be planned to be continued for 3 months after randomization.

Outcomes

Primary outcome

- Complete LVT resolution according to non-contrast 2D TTE performed by the imaging core laboratory, blinded to the allocation assignment at 3 months from enrollment

Other outcomes

- The proportion of patients with adjudicated SSE at 3 months from enrollment (Appendix A)
- The proportion of patients with adjudicated MACE at 3 months from enrollment
- The proportion of patients with adjudicated all-cause death at 3 months from enrollment (Appendix B)

Main safety outcomes

- The proportion of patients with adjudicated major bleeding events based on ISTH definition at 3 months from enrollment (Appendix C)

Additional safety outcome

- The proportion of patients with adjudicated CRNMBs based on ISTH definition at months from enrollment (Appendix C)

Imaging Core Laboratory

In the present study, the diagnosis of LVT will be based on non-contrast 2D-TTE, mainly due to the non-availability of echocardiographic contrast agents in Iran. Although contrast echocardiography's sensitivity is higher than non-contrast echocardiography (61% versus 33%)

in diagnosing LVT, the specificity of non-contrast echocardiography (99% versus 94%) is acceptable [42]. Cardiac magnetic resonance was not selected due to limited resources.

In both centers, patients with a confirmed diagnosis of acute STEMI routinely undergo non-contrast TTE by the on-call cardiologist. Acute LVT should be confirmed by the assigned expert cardiologist with a subspecialty in echocardiology (1 in each center), blinded to the research group assignment. All images will be deidentified and restored by the core laboratory to evaluate thrombosis resolution in follow-up sessions. Follow-up non-contrast TTE will be performed at 3 months with the same echocardiography machine model. The core laboratory will consist of two cardiologists with a subspecialty in echocardiology. All conventional measures will be carried out in accordance with the latest recommendations [43].

Echocardiograms will be acquired via non-contrast 2D-TTE in the standard parasternal view in short and long-axis and apical 2, 3, and 4-chamber view imaging planes. LVT resolution, the primary outcome of the study, is defined as the complete absence of LVT in a non-contrast 2D TTE assessment Thrombus will be diagnosed based on the established anatomic criteria. LVT typically appears as a mass within the LV cavity with borders distinct from the ventricular endocardium, distinguishable from trabeculations, papillary muscles, chordae, and technical artifacts [44].

All deidentified cases will be recirculated for a second evaluation by the same and a second operator of the core laboratory. Potential discrepancies will be resolved by a third operator.

Study Flow Diagram

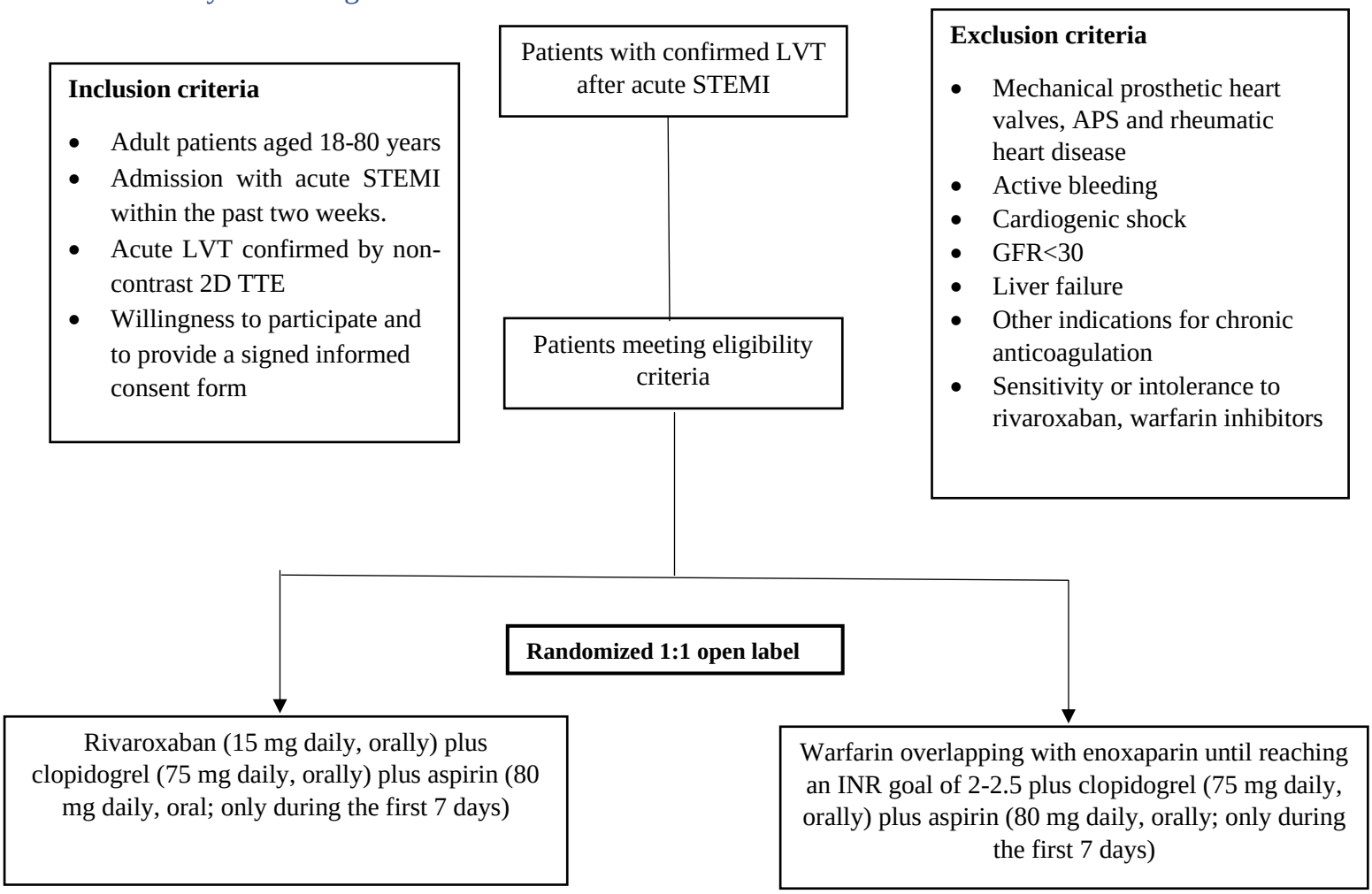

Figure 1. Study flow diagram

APS, antiphospholipid syndrome; GFR, Glomerular filtration rate; INR, International normalized ratio; LVT, Left ventricular thrombosis; STEMI, ST-segment-elevation myocardial infarction; TTE, Transthoracic echocardiography

Study Baseline Variables and Outcomes

Variables	Units	Definitions
Baseline		
Age	Years	Years passed from the person's date of birth
Sex	Male/Female	As reported in the medical records
Weight	Kg	As measured when hospitalized
Height	cm	As measured when hospitalized
Body mass index	kg/m^2	As measured when hospitalized
Systolic and diastolic blood pressure	mmHg	Pressure of the fluid within blood vessels during screening
Heart rate	beats per minute	Number of heartbeats within a minute on screening
Respiratory rate	breaths per minute	Number of breaths per minute during screening
Past medical history		
Diabetes mellitus	Yes/No	History of diabetes mellitus based on medical records and patient interview
Hypertension	Yes/No	History of *hypertension* based on medical records and patient interview
Dyslipidemia	Yes/No	History of dyslipidemia based on medical records and patient interview
Chronic kidney disease	Yes/No	History of chronic kidney disease based on medical records and patient interview
Congestive heart failure	Yes/No	History of congestive heart failure based on medical records and patient interview
Cigarette smoking	No/Current/Former	History of cigarette smoking based on medical records and patient interview
Coronary artery disease	Yes/No	History of established coronary artery disease by noninvasive and invasive diagnostic tests or history of coronary artery revascularization
Myocardial infarction	Yes/No	History of myocardial infarction based on medical records
Percutaneous coronary intervention	Yes/No	History of percutaneous coronary intervention based on medical records
Coronary artery bypass graft surgery	Yes/No	History of coronary artery bypass graft surgery based on medical records
Venous thromboembolism	Yes (if yes, determine: pulmonary embolism or deep vein thrombosis or both) /No	History of venous thromboembolism based on medical records
Atrial fibrillation	Yes/No	History of atrial fibrillation based on medical records
Stroke	Yes (if yes, determine: ischemic, hemorrhagic, or transient ischemic attack or both) /No	History of stroke based on medical records
Carotid revascularization	Yes/No	History of carotid revascularization based on medical records
Systemic embolization	Yes/No	History of systemic embolization based on medical records
Recent Drug History		

Angiotensin-converting enzyme inhibitors	Yes/No	According to medication history
Angiotensin receptor blockers	Yes/No	According to medication history
Angiotensin receptor/neprilysin inhibitor	Yes/No	According to medication history
β-blockers	Yes/No	According to medication history
Mineralocorticoid receptor antagonists	Yes/No	According to medication history
Diuretics	Yes/No	According to medication history
Nitrates	Yes/No	According to medication history
Oral agents for diabetes mellitus	Yes/No	According to medication history
Injectable insulin	Yes/No	According to medication history
Aspirin	Yes/No	According to medication history
P2Y12 inhibitors	Yes/No	According to medication history
Statins	Yes/No	According to medication history
Nonsteroidal anti-inflammatory drugs	Yes/No	According to medication history
Corticosteroid	Yes/No	According to medication history
Baseline laboratory tests (measured on randomization)		
Hemoglobin	g/dL	Blood level of hemoglobin, assessed by a uniform assay in both study sites
Platelets	$\times 10^3$/mL	Blood platelet count, assessed by a uniform assay in both study sites
White blood cells	cells/mm3	White blood cell count, assessed by a uniform assay in both study sites
Lymphocyte count	cells/mm3	Blood lymphocyte count, assessed by a uniform assay in both study sites
Fasting blood glucose	mmol/L	Blood level of fasting blood glucose, assessed by a uniform assay in both study sites
Blood urea nitrogen	mg/dL	level of blood urea nitrogen, assessed by a uniform assay in both study sites
Creatinine	mg/dL	Blood level of creatinine, assessed by a uniform assay in both study sites
Alanine transaminase	IU/L	Blood level of alanine transaminase, assessed by a uniform assay in both study sites
Aspartate transaminase	IU/L	Blood level of aspartate transaminase, assessed by a uniform assay in both study sites
Low-density lipoprotein	mmol/L	Blood level of low-density lipoprotein
High-density lipoprotein	mmol/L	Blood level of high-density lipoprotein
Total cholesterol	mmol/L	Blood level of total cholesterol
Triglyceride	mmol/L	Blood level of triglyceride
Prothrombin time (PT)	Seconds	Prothrombin time

International normalized ratio (INR)	-	INR = Patient PT ÷ Control PT
Estimated glomerular filtration rate	mL/min	*Estimated glomerular filtration rate according to the Cockcroft-Gault equation: 1.23 × (140 – age)/serum creatinine) × weight (× 0.85 for women)
Baseline echocardiography data		
Left ventricle thrombus size	cm^2	Largest area of the left ventricular thrombus as assessed by transthoracic echocardiography.
Left ventricle thrombus motion [45]	Fixed/ mobile	Thrombus may be fixed along the left ventricular wall or present an independent motion to a variable extent. Motion may involve either the whole thrombus or, more frequently, a part of the thrombus. Motion is independent of the underlying myocardium, and that characteristic differentiates a true thrombus from an artifact.
Left ventricular ejection fraction	%	The left ventricle ejection fraction is estimated by the eyeball assessment method.
Outcome assessment		
Left ventricular thrombus resolution	Yes/No	Complete absence of left ventricular thrombosis based on transthoracic echocardiography. Left ventricular thrombosis is characterized as an echo-dense mass within the left ventricular cavity next to an area with wall motion abnormalities with borders separate from the left ventricular wall and distinguished from artifacts and intrinsic structures, such as papillary muscles.
Ischemic stroke [46]	Yes/No	Acute episodes of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury resulting from hemorrhage or infarction
Transient ischemic attack [46]	Yes/No	Transient ischemic attack is a transient episode of focal neurological dysfunction caused by brain, spinal cord, or retinal ischemia without acute infarction.
Systemic embolic events	Yes/No	Any acute non-cerebral embolic events with a cardiac origin
All-cause death (a composite of the following causes:) [46] A. Cardiovascular B. Non-cardiovascular	Yes/No	A. Death resulting from an acute myocardial infarction, sudden cardiac death, death due to heart failure, death due to pulmonary thromboembolism, death due to stroke, death due to cardiovascular procedures, death due to cardiovascular hemorrhage, and death due to other cardiovascular causes B. A non-cardiovascular death is defined as a death with a specific etiology that

C. Undetermined Cause		is not thought to be cardiovascular in nature. C. An undetermined cause of death refers to a death not attributable to one of the above categories of cardiovascular death or a non-cardiovascular cause. The inability to classify the cause of death may be due to a lack of availability of sufficient information (e.g., the only available information is "patient died") or when there is not sufficient supporting information or detail to assign the cause of death between competing potential causes.
Major adverse cardiac events	Yes/No	Composite of cardiovascular death, myocardial infarction, and stroke
Bleeding events [47] Major bleeding Clinically relevant non-major bleeding	Yes/No	According to the International Society on Thrombosis and Hemostasis definition

Statistical Considerations and Sample Size Calculation

The primary endpoint of interest will be the 3-month non-contrast 2D TTE-based complete LVT resolution proportion in both arms of the study. Regarding the exploratory nature of this pilot study, no formal sample size calculation was carried out. A sample size of 25 in each arm is planned.

Data normality will be first assessed using the Shapiro-Wilk and one-sample Kolmogorov-Smirnov tests. Hence, normally-distributed data will be analyzed using parametric tests and otherwise with non-parametric tests. Categorical variables will be demonstrated as frequencies (%) and will be compared between the two arms using the Chi-squared test or Fisher's exact test. Continuous variables will be reported as the mean (standard error of mean [SEM] and 95% confidence interval [CI]) or median (interquartile range [IQR]) and will be compared using the independent t-test or ANOVA (or their nonparametric counterparts, the Mann-Whitney U test, and Kruskal-Wallis tests, respectively). The statistical significance will be considered a P-value <0.05.

The effect size for the primary outcome (i.e., complete LVT resolution) and other outcomes comprised SSE, all-cause death, MACE, major bleeding, and CRNMB will be calculated as relative risk (RR) and 95% CI. For outcomes with zero event in either arm, RR will be substituted by risk difference and 95% CI.

Ethical Considerations

The Rajaie Cardiovascular, Medical, and Research Center (RCMRC) Ethic Committee approved the study protocol and the patient's informed consent. The RCMRC ethical approval is considered valid by the other participating hospital (i.e., Tehran Heart Center) alongside the RCMRC (IR.TUMS.THC.REC.1399.004). Written informed consent for study participation will be obtained from the patients or their next of kin. During the study and afterward, the

patients will be provided with thorough free-of-cost medical care in case of any complication arising from the trial.

Registration

The trial will be registered at the Iranian Registry of Clinical Trials (www.irct.ir) as mandated for all randomized trials in Iran. Moreover, the trial will also be registered at clinicaltrials.gov.

Serious Adverse Events

All patients will be carefully followed for any major adverse events immediately after enrollment and will remain under their physician's care until the withdrawal of consent, death, or the conclusion of the trial. Any adverse event observed by the study physician or reported by patients will be meticulously documented, and patients will be closely monitored until the condition resolves or stabilizes. Serious adverse events include bleeding (based on the ISTH definition), cerebrovascular accidents, systemic embolization, and acute coronary events.

Clinical Event Committee (CEC)

The members of the CEC are listed in Appendix E. Based on reported events, CEC members will have online meetings, with the meetings considered valid with the participation of all the three the members. The data will be deidentified, and the treatment arms will remain blinded when the data are provided to the CEC. Deidentified imaging tests, laboratory values, and surgical/interventional procedural reports will be presented as proof of related events. The CEC will adjudicate the reported outcomes. The adjudicated data will be registered in an electronic database by a research nurse separate from the recruiting centers. An official report regarding the assessed serious adverse events during each meeting will be made at the end of each CEC meeting.

Data and Safety Monitoring Board (DSMB)

Safety supervision will be under the auspices of the DSMB, composed of individuals with the appropriate expertise and free from conflict of interest (Appendix F), and no steering committee members (Appendix G) or the study's authors. DSMB meetings will be held based on the occurrence of adverse events. Considering the pilot nature of the study, no pre-specified criteria were decided by the Steering Committee to terminate the clinical trial for efficacy. However, a stopping rule for harm (non-ICH major bleeding events and ICH) was defined. Since this was a pilot trial, no specific stopping rule boundaries were defined and the decision was left to the discretion of the DSMB.

Considering the lack of published RCTs reporting bleeding event rates in LVT patients treated with rivaroxaban, the stopping rules for bleeding events and ICH were defined according to the meta-analysis of pivotal RCTs (including PIONEER AF-PCI, RE-DUAL PCI, AUGUSTUS, and ENTRUST-AF-PCI [48-51]) on the efficacy and safety of DOAC-based regimens versus VKA-based regimens in patients with concomitant AF having undergone PCI [52]. The major bleeding absolute risk for the DOAC and warfarin groups were 4.3% and 7%, respectively. Consequently, considering the sample size of the current trial (i.e., 50 patients), every single major bleeding event in rivaroxaban group in any timeline in the trial should be considered as a stopping rule and to be evaluated by the DSMB.

Data Collection and Management Responsibilities

Data collection will be the responsibility of the study physician at each site under the supervision of the site principal investigator, who will ensure that the reported data are accurate, comprehensive, readable, and timely. The data recorded in the electronic case report form extracted from source documents should match the data contained in the source documents.

Appendix

Appendix A [46]

Definition of Stroke and Transient Ischemic Attack

These definitions of Stroke and Transient Ischemic Attack apply to a wide range of clinical trials. They are general, overarching, and widely applicable definitions combined with a specific clinical measurement of disability. They are flexible in their application and consistent with the contemporary understanding of the pathophysiology of stroke. This approach enables clinical trials to assess the clinically relevant consequences of vascular brain injury to determine the safety or effectiveness of an intervention.

The distinction between an Ischemic Stroke and a Transient Ischemic Attack is the presence of infarction. The persistence of symptoms is an acceptable indicator of acute infarction. Thus, the duration of symptom persistence that will be used to distinguish between transient ischemia and acute infarction should be defined for any clinical trial in which it is used.

In trials involving patients with stroke, evidence of vascular central nervous system injury without recognized neurological dysfunction may be observed. Examples include microhemorrhage, asymptomatic infarction, and asymptomatic hemorrhage. When encountered, the clinical relevance of these findings may be unclear. However, if appropriate for a given clinical trial, they should be precisely defined and categorized.

Subdural hematomas are intracranial hemorrhagic events and not strokes.

Transient Ischemic Attack

Transient ischemic attack (TIA) is defined as a transient episode of focal neurological dysfunction caused by the brain, spinal cord, or retinal ischemia *without* acute infarction infarction documented computed tomography or magnetic resonance imaging.

Stroke

Stroke is defined as an acute episode of focal or global neurological dysfunction caused by the brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction documented computed tomography or magnetic resonance imaging.

Classification:

A. Ischemic Stroke

Ischemic stroke is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of central nervous system tissue.

Hemorrhage may be a consequence of ischemic stroke. In this situation, the stroke is an ischemic stroke with hemorrhagic transformation, not a hemorrhagic stroke.

B. Hemorrhagic Stroke

Hemorrhagic stroke is defined as an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage.

C. Undetermined Stroke

Undetermined stroke is defined as an acute episode of focal or global neurological dysfunction caused by the presumed brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction but with insufficient information to allow categorization as either ischemic or hemorrhagic.

Appendix B [46]

All-cause mortality is defined as a composite of cardiovascular, non-cardiovascular and undetermined cause of death.

Definition of Cardiovascular Death

Cardiovascular death includes death resulting from an acute myocardial infarction (MI), sudden cardiac death, death due to heart failure (HF), death due to stroke, death due to cardiovascular (CV) procedures, death due to CV hemorrhage, and death due to other CV causes.

1. **Death due to Acute Myocardial Infarction** refers to death by any CV mechanism (e.g., arrhythmia, sudden death, HF, stroke, pulmonary embolus, peripheral arterial disease) ≤ 30 days[2] after a MI, related to the immediate consequences of the MI, such as progressive HF or recalcitrant arrhythmia. We note that there may be assessable mechanisms of CV death during this time period, but for simplicity, if the CV death occurs ≤ 30 days of the MI, it will be considered a death due to MI.

   Acute MI should be verified to the extent possible by the diagnostic criteria outlined for acute MI (see Appendix 6) or by autopsy findings showing recent MI or recent coronary thrombosis.

   Death resulting from a procedure to treat a MI (percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG)), or to treat a complication resulting from MI, should also be considered death due to acute MI.

   Death resulting from an elective coronary procedure to treat myocardial ischemia (i.e., chronic stable angina) or death due to a MI that occurs as a direct consequence of a CV investigation/procedure/operation should be considered as a death due to a CV procedure.

2. **Sudden Cardiac Death** refers to a death that occurs unexpectedly and not within 30 days of an acute MI. Sudden cardiac death includes the following scenarios:

   a. Death witnessed and occurring without new or worsening symptoms

[2] The 30 day cut-off is arbitrary.

b. Death is witnessed within 60 minutes of the onset of new or worsening cardiac symptoms unless the symptoms suggest acute MI

c. Death witnessed and attributed to an identified arrhythmia (e.g., captured on an electrocardiographic (ECG) recording, witnessed on a monitor, or unwitnessed but found on implantable cardioverter-defibrillator review)

d. Death after unsuccessful resuscitation from cardiac arrest (e.g., implantable cardioverter defibrillator (ICD), unresponsive sudden cardiac death, pulseless electrical activity arrest)

e. Death after successful resuscitation from cardiac arrest and without identification of a specific cardiac or non-cardiac etiology

f. Unwitnessed death in a subject seen alive and clinically stable ≤ 24 hours prior to being found dead without any evidence supporting a specific non-cardiovascular cause of death (information regarding the patient's clinical status preceding death should be provided, if available)

General Considerations

- Unless additional information suggests an alternate specific cause of death (e.g., Death due to Other Cardiovascular Causes) if a patient is seen alive ≤ 24 hours of being found dead, sudden cardiac death (criterion 2f) should be recorded. For patients not observed alive within 24 hours of death, an undetermined cause of death should be recorded (e.g., a subject found dead in bed but had not been seen by the family for > 24 hours).

3. **Death due to Heart Failure** refers to a death in association with clinically worsening symptoms and/or signs of HF regardless of HF etiology (see Appendix 9). Deaths due to HF can have various etiologies, including single or recurrent MIs, ischemic or nonischemic cardiomyopathy, hypertension, or valvular disease.

4. **Death due to Stroke** refers to death after a stroke that is either a direct consequence of the stroke or a complication of the stroke. The acute stroke should be verified to the extent possible by the diagnostic criteria outlined for stroke (see Appendix 8).

5. **Death due to Cardiovascular Procedures** refers to death caused by the immediate complications of a cardiac procedure.

6. **Death due to Cardiovascular Hemorrhage** refers to death related to hemorrhage such as a non-stroke intracranial hemorrhage (e.g., subdural hematoma) (see Appendix 8), non-procedural or

non-traumatic vascular rupture (e.g., aortic aneurysm), or hemorrhage causing cardiac tamponade.

7. **Death due to Other Cardiovascular Causes** refers to a CV death not included in the above categories but with a specific, known cause (e.g., pulmonary embolism or peripheral arterial disease).

Definition of Non-Cardiovascular Death

Non-cardiovascular death is defined as any death with a specific cause that is not considered CV in nature, as listed in Appendix 3. Detailed recommendations on the classification of non-CV causes of death are beyond the scope of this document. The level of detail required and the optimum classification will depend on the nature of the study population and the anticipated number and type of non-CV deaths. Any specific anticipated safety concern should be included as a separate cause of death. The following is a suggested list of non-CV causes of death:

- Pulmonary
- Renal
- Gastrointestinal
- Hepatobiliary
- Pancreatic
- Infection (includes sepsis)
- Inflammatory (e.g., Systemic Inflammatory Response Syndrome (SIRS) / Immune (including autoimmune) (may include anaphylaxis from environmental (e.g., food allergies))
- Hemorrhage that is neither CV bleeding nor a stroke (see Appendix 3, Section 6, and Appendix 8)
- Non-CV procedure or surgery
- Trauma (includes homicide)
- Suicide
- Non-prescription drug reaction or overdose
- Prescription drug reaction or overdose (may include anaphylaxis)
- Neurological (non-CV) (excludes CV death from ischemic stroke, hemorrhagic stroke, or undetermined cause of stroke or CV hemorrhage of the central nervous system)
- Malignancy (e.g., leukemia, lymphoma, or other malignancy)
- Other non-CV, specify: _____

Definition of Undetermined Cause of Death

Undetermined Cause of Death refers to death not attributable to one of the above categories of CV death or a non-CV cause. The inability to classify the cause of death may be due to a lack of information (e.g., the only available information is "patient died") or when there is insufficient supporting information or detail to assign the cause of death. In general, most deaths should be classifiable as CV or non-CV, and the use of this category of death, therefore, should be discouraged and should apply to few patients in well-run clinical trials.

A common analytic approach for the cause of death analyses is to assume that all undetermined cases are included in the CV category (e.g., presumed CV death, specifically "death due to other CV causes"). Nevertheless, the appropriate classification and analysis of undetermined causes of death depend on the population, the intervention under investigation, the duration of follow-up, and the disease process (presuming CV death does not seem appropriate, for example, for people with late-stage cancer, advanced pulmonary disease, long-standing infections, etc.). The approach should be prespecified and described in the protocol and other trial documentation, such as the endpoint adjudication procedures and/or the statistical analysis plan.

Appendix C [47]

ISTH definition for major bleeding and definition of clinically relevant non-major bleeding

Definition of major and clinically relevant non-major bleeding in AF and non-surgical VTE studies:

1. ISTH **clinically relevant non-major bleeding** in non-surgical patients is defined as:
   any sign or symptom of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for the ISTH definition of major but does meet at least one of the following criteria:
   i. requiring medical intervention by a healthcare professional
   ii. leading to hospitalization or increased level of care
   iii. prompting a face to face (i.e., not just a telephone or electronic communication) evaluation
2. ISTH **major bleeding** in non-surgical patients is defined as having a symptomatic presentation and:
   i. Fatal bleeding, and/or
   ii. Bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome, and/or
   iii. Bleeding causing a fall in hemoglobin level of 20 $g.L^{-1}$ (1.24 $mmol.L^{-1}$) or more, or leading to transfusion of two or more units of whole blood or red cells.

Appendix D [41]

STEMI

Type 1 MI criteria
Detection of a rise and/or fall of cardiac troponin values with at least 1 value above the 99th percentile upper reference limit and with at least 1 of the following:
• Symptoms of acute myocardial ischemia
• New ischemic ECG changes
• Development of pathological Q waves
• Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology
• Identification of a coronary thrombus by angiography including intracoronary imaging or by autopsy
ST-elevation criteria
New ST-elevation at the J-point in 2 contiguous leads with the cut-point: ≥1 mm in all leads other than leads V_2–V_3 where the following cut-points apply: ≥2 mm in men ≥40 years; ≥2.5 mm in men <40 years, or ≥1.5 mm in women regardless of age.

Appendix E

CEC members

Behnood Bikdeli, MD, MS (Chair)

Azita H. Talasaz, PharmD

Melody Farrashi, MD

Appendix F

DSMB members

Saeedeh Mazloomzadeh, MD, PhD

Mostafa Mousavizadeh, MD

Appendix G

Steering committee members

Yaser Jenab, MD

Parham Sadeghipour, MD

Behnood Bikdeli, MD

Azita H. Talasaz, PharmD

Raheleh Kaviani, MD

CONSORT checklist

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4
	2b	Specific objectives or hypotheses	4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	5
	4b	Settings and locations where the data were collected	5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	7
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	8
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	6

Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	6
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	NA
	11b	If relevant, description of the similarity of interventions	NA
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	8 & 9
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	NA
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	9 & 21 (Figure 1)
	13b	For each group, losses and exclusions after randomisation, together with reasons	21 (Figure 1)
Recruitment	14a	Dates defining the periods of recruitment and follow-up	9
	14b	Why the trial ended or was stopped	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	18 (Table 1)
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	9
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	10 & 19 (Table 2)
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	19
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	10 & 23 (Figure 3)
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	NA
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	13
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	12 & 13
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	11 & 12
Other information			

Registration	23	Registration number and name of trial registry	3
Protocol	24	Where the full trial protocol can be accessed, if available	Supplement
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	15

Citation: Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMC Medicine. 2010;8:18.

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up-to-date references relevant to this checklist, see www.consort-statement.org.