

Systematic review of efficacy of direct oral anticoagulants and vitamin K antagonists in left ventricular thrombus

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Abstract

Aims Left ventricular thrombus (LVT) increases the risk of thrombotic events and mortality. Vitamin K antagonists (VKAs) used to treat LVT have several known risks, as a result of which direct oral anticoagulant (DOAC) use has recently increased. We aimed to evaluate the safety and efficacy of DOACs and VKAs in treating LVT.

Methods and results We searched PubMed, Embase, Cochrane Library trials, and Web of Science databases for studies published before 19 April 2022, involving DOAC versus VKA treatment for patients with LVT. This meta-analysis comprised 21 studies (total patients, $n = 3172$; DOAC group, $n = 888$; VKA group, $n = 2284$). A statistically significant reduction in bleeding events was observed in patients on DOACs vs. those on VKAs (risk ratio (RR) = 0.73, $P = 0.004$). Patients on DOACs residing in North American and European regions and those with ischaemic heart disease (IHD) had a significantly lower risk of bleeding events than patients residing in other regions or those with a different LVT aetiology, respectively (RR = 0.78, $P = 0.04$; RR = 0.38, $P = 0.02$; and RR = 0.63, $P = 0.009$). A statistically significant reduction in stroke in patients on DOACs versus VKAs (RR = 0.72, $P = 0.03$) was observed, and patients on DOACs residing in North America and those with IHD had a significantly lower risk of stroke (RR = 0.73, $P = 0.04$, and RR = 0.61, $P = 0.03$, respectively). Compared with VKAs, DOACs are statistically associated with an increase in LVT resolution at 1 month (RR = 1.96, $P = 0.008$). No statistical between-group difference in all-cause mortality (RR = 0.72, $P = 0.05$), systemic embolism (RR = 0.87, $P = 0.74$), stroke or systemic embolism (RR = 0.90, $P = 0.50$), and LVT resolution at the end of follow-up (RR = 1.06, $P = 0.13$) was observed.

Conclusions Compared with VKAs, DOACs significantly reduce the risk of bleeding events and stroke in LVT patients, but mortality was similar in both groups. The advantages are apparent not only in patients belonging to the predominantly white residential areas such as North American and European regions but also in patients with LVT due to IHD. DOACs show promising effects in treating LVT compared with VKAs.

Keywords Direct oral anticoagulants; Left ventricular thrombus; Vitamin K antagonist; Systematic review

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Introduction

Left ventricular thrombus (LVT) is a common and serious complication following acute myocardial infarction (AMI) and in those with severe left ventricular systolic dysfunction.^{1–3} If left untreated, LVT has been reported to markedly increase composite stroke or systemic embolism

(SSE) rates.⁴ Current consensus guidelines recommend the use of vitamin K antagonists (VKAs) such as warfarin for 3 to 6 months in patients with LVT following AMI.^{4–6} However, warfarin's disadvantages, including its slow onset of action, the frequent need to monitor the international normalized ratio (INR), the constant adjustment of the dose to achieve the therapeutic window, and noted drug-to-drug or

drug-to-food interactions, may influence patient adherence and contribute to the increasing global use of direct oral anticoagulants (DOACs).^{7–10}

DOACs may be an optimal alternative to VKAs as they have a fast onset of action, a stable drug concentration, no requirement to determine the INR, fewer interactions, and a lower rate of bleeding events.⁹ As first-line drugs, DOACs are currently used to prevent thrombus formation in patients with non-valvular atrial fibrillation (AF) and deep vein thrombosis.^{11,12} However, DOACs are used off-label as anticoagulant treatment in patients with LVT. To date, several case studies, observational studies, and randomized control trials (RCTs) have suggested analogous or contradictory safety and efficacy when comparing DOACs with VKAs to treat LVT.^{13–34} A few meta-analyses have drawn varied conclusions in terms of efficacy and safety between DOACs and VKAs,^{35,36} predominantly suggesting that DOACs use may be promising when treating patients with LVT. However, no RCTs were included in the meta-analysis of Xuan *et al.*,³⁵ resulting in a lack of clinical evidence. Almost 50% of the studies included in the study by Michael *et al.* involved abstracts without complete experimental data,³⁶ which may influence the generalizability of their results. Moreover, more studies comparing DOACs and VKAs in the treatment of LVT have been published recently.^{15,22,24,26,27,30–34} We aimed to undertake a systematic review and meta-analysis to evaluate the safety and efficacy of DOACs versus VKAs in the management of LVT in terms of clinical outcomes for all-cause mortality, bleeding events, stroke, systemic embolism (SE), SSE, and LVT size reduction or resolution particularly focusing on subgroup analyses by region and aetiology.

Methods

Search strategy and data sources

Two investigators (L. H. and Y. T.) systematically searched PubMed, Embase, Cochrane Library trials, and Web of Science core collection databases for related studies published before 19 April 2022. The PubMed search items were: (Factor Xa inhibitor OR direct thrombin inhibitor OR oral anticoagula* OR antithrombin OR NOAC OR DOAC OR dabigatran OR Pradaxa OR Rendix OR ximelagatran OR Exanta OR melagatran OR rivaroxaban OR edoxaban OR apixaban OR betrixaban OR darexaban OR Xarelto OR eliquis OR lixiana) AND ((left ventric* OR LV) AND (thromb* OR clot) OR LVT). The PubMed search strategy is shown in the Supporting Information, *Table S1*. We also searched ClinicalTrials.gov for unfinished studies as well as related study references to avoid omitting any relevant studies.

Inclusion and exclusion criteria

The inclusion criteria were studies (i) involving patients with a confirmed diagnosis of LVT; (ii) that compared DOACs with VKAs; (iii) in which efficacy and safety outcomes were available; and (iv) that were RCTs or observational studies.

The exclusion criteria were (i) studies not published in English and (ii) publications such as case studies, posters, abstracts, systematic reviews, or meta-analyses.

Data extraction and quality assessment

Two authors (L. H. and Y. T.) independently extracted the following information from the included studies: baseline study data (study title, first author, year of publication, publication type, and patient region), patient demographic data (median age, sex, region, and related primary disease), study design, method of diagnosis, sample size, interventions, follow-up durations, and study outcomes. Any disagreements between L. H. and Y. T. concerning the included studies were resolved through discussions, and a third author (Y. L. P.) was consulted to help resolve any disagreements.

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines and the Cochrane Handbook for Systematic Reviews.³⁷ The Cochrane Collaboration's tool was used to assess bias in RCTs, and the Newcastle-Ottawa Scale (NOS) was used to assess the quality of the observational studies.^{38,39}

Data analysis

We used RevMan software version 5.4 and Stata/MP 16.0 to combine and analyse outcomes from the included studies.^{14–34} Risk ratios (RRs) with 95% confidence intervals (CIs) were used to evaluate differences between patients in the DOACs and VKAs groups. We used a random-effects model to pool all of the outcomes. A *Q* test was utilized to assess heterogeneity between studies, and an $I^2 > 50\%$ was deemed to indicate significant heterogeneity.⁴⁰ We set a *P*-value < 0.05 as statistically significant. Contour-enhanced funnel plot symmetry, trim and fill analysis (metatrim), and Egger's tests were used to evaluate the publication bias of the included studies in the meta-analysis.⁴¹ Sensitivity analyses were undertaken to estimate the influence of a single study on the whole assessment. We also performed subgroup analyses according to the region (North America, Europe, East Asia, and Middle East regions and Africa) or aetiology (ischaemic heart disease IHD, proportion $> 50\%$). IHD is defined by the incidence of coronary artery disease (CAD), myocardial ischaemia, and myocardial infarction (MI), including its complications.⁴²

Results

Literature search

In total, 2632 studies were identified in four databases, involving 555 studies from PubMed, 1231 from Embase, 156 from the Cochrane Library trials, 688 from Web of Science core collection, and 2 from reference lists and ClinicalTrials.gov. We first removed all duplicates. We reviewed the titles and abstracts and then excluded reviews, letters, case reports or case series, comments, animal studies, trials with no LVT treatment, studies with designs that did not compare between DOAC and VKA treatments, and study protocols with no experimental data. We identified 39 studies for further filtering by browsing the full text. Finally, 21 studies meeting the inclusion criteria were included in this meta-analysis. The literature search and selection process, conducted in accordance with PRISMA guideline standards,³⁷ is shown in Figure 1.

Characteristics and quality of included studies

Baseline characteristics are shown in Table 1. The 21 included studies, comprising 3 RCTs^{14,16,32} and 18 cohort studies^{15,17–31,33,34} had been published between 2019 and 2022. Studies were mainly conducted in North America, Europe, Africa, and Asia. In total, 3172 patients (DOAC group: 888 patients and VKA group: 2284 patients) were included in the meta-analysis. Rivaroxaban and apixaban were preferred among the DOACs used (rivaroxaban, apixaban, edoxaban, or dabigatran), and warfarin was preferred among the VKAs used (warfarin, acenocoumarol, or fluindione). The mean patient age ranged from 50 to 66 years, and 76.9% of the patients were males. Ischaemic cardiomyopathy (ICM) and AMI were found to be the major aetiologies of LVT.^{14,16–18,21,23,25,28–30,33,34} Most studies had used transthoracic echocardiography (TTE) to diagnose LVT, while some studies had used cardiac magnetic resonance imaging (CMRI) or others as auxiliary diagnostic methods.^{17,23–27} Follow-up duration ranged between 3 and 44 months. Thirteen studies

Figure 1 A flowchart indicating the literature search and study selection process. DOACs, direct oral anticoagulants; LVT, left ventricular thrombus; VKAs, vitamin K antagonists.

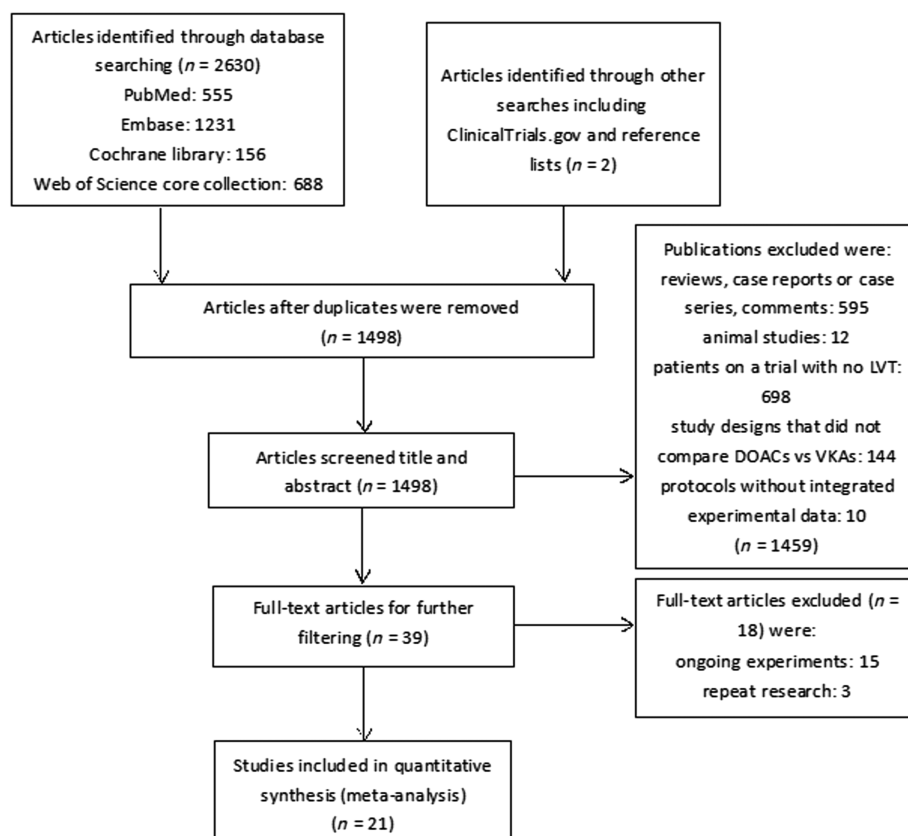


Table 1 Summary of basic characteristics and risk of bias assessment concerning the included cohort studies

Author (year)	Region	Design	Sample size		Mean age (years)	Male (%)	Follow up (months)	Aetiology of LVT	Diagnose method	Target INR	TTR (%)	Drug combination	Outcome	Risk of bias assessment of cohort studies	
			VKAs (n)	DOACs (n)										Selection	Comparability Outcome
Abdelnabi (2021)	Egypt and Bulgaria	RCT	Warfarin (40)	Rivaroxaban 20 mg QD (39)	50	57	6	ICM (78.5%) Idiopathic (20.3%) Peripartum (1.2%)	TTE	NC	NC	Antiplatelet (53.1%)	Bleeding events Stroke, SE, SSE LVT	-	
Albahrain (2021)	Saudi Arabia	Retrospective	Warfarin (35)	Rivaroxaban 15/20 mg QD (28)	59	92	14	MI HF CM	TTE	2–3	82.3	Aspirin (61.9%) Clopidogrel (53.97%)	resolution Bleeding events Stroke, SE, SSE Mortality LVT	***	***
Alcalai (2021)	Israel	RCT	Warfarin (17)	Apixabann 5 mg BID (18)	57	80	3	AMI (100%)	TTE	2–3 bridged with LMWH	60	According to physician	Bleeding events SSE Mortality LVT	-	
Ali (2020)	USA	Retrospective	Warfarin (60)	Rivaroxaban (18) Apixaban (13) Dabigatran (1)	59	79	12	ICM (58%) Non-ICM (23%) AMI (15%) Takotsubu CM (3%)	TTE CC CTA MRI	NC	NC	Aspirin (65.45%) Clopidogrel (14.55%) Ticagrelor (0.91%) Prasugrel (1.82%) Antiplatelet (54%)	resolution Stroke, SE, SSE LVT resolution	***	**
Bass (2021)	USA	Retrospective	Warfarin (769)	Apixaban (79) Rivaroxaban (77) Dabigatran (29)	62	71	3	MI (54.8%)	NC	NC	NC	Antiplatelet (54%)	Bleeding events Stroke, SSE	***	*
Cochran (2021)	USA	Retrospective	Warfarin (59)	DOACs (14)	60	77	12	AMI (48%)	TTE	NC	NC	NC	Bleeding events Stroke, SSE Mortality LVT	***	**
Daher (2020)	France	Retrospective	Warfarin (14) Fluindione (16) Acenocoumarol (12)	Rivaroxaban (4) Apixaban (12) Dabigatran (1)	62	84	3	ICM (86.5%) DCM (13.5%)	TTE	2–3	NC	Aspirin (64.4%) P2Y12 inhibitor (47.5%)	resolution SSE LVT resolution	***	*

(Continues)

Table 1 (continued)

Author (year)	Region	Design	Sample size		Mean age (years)	Male (%)	Follow up (months)	Aetiology of LVT	Diagnose method	Target INR	TTR (%)	Drug combination	Outcome	Risk of bias assessment of cohort studies	
			VKAs (n)	DOACs (n)										Selection	Comparability Outcome
Guddeti (2020)	USA	Retrospective	Warfarin (80)	Apixaban (15) Dabigatran (2) Rivaroxaban (2)	61	71	12	AMI (20.2%) ICM (58.6%)	TTE	NC	NC	P2Y12 inhibitor (15.2%) Triple therapy (13.1%)	Bleeding events Stroke, SSE LVT resolution	***	***
Herald (2022)	USA	Retrospective	Warfarin (299)	Dabigatran (108) Rivaroxaban (6) Apixaban (20)	66	83	41	NC	TTE	NC	NC	NC	Bleeding events Stroke, SE, SSE Mortality	****	***
Iqbal (2020)	UK	Retrospective	Warfarin (62)	Rivaroxaban (20 mg QD) (13) Apixaban 5 mg BID (8) Dabigatran 150 mg BID (1)	62	75	36	ICM (87%) MI (35%) DCM (5%) HCM (4%)	TTE TOE Contrast-TTE CMR	2-3 bridged with LMWH	NC	Aspirin (57.1%) Clopidogrel (39.3%) Ticagrelor (7.1%) DAPT (38%)	Bleeding events Stroke, SE, SSE Mortality LVT resolution	***	**
Iskaros (2021)	USA	Retrospective	Warfarin (45)	Apixaban (24) Rivaroxaban (7) Dabigatran (1)	62	90	3	NC	TTE TEE CT CMR	>2 bridged with LMWH	NC	Antiplatelet (66%)	Bleeding events Stroke, SE, SSE LVT resolution	****	**
Jones (2021)	UK	Prospective	Warfarin (60)	Rivaroxaban (24) Apixaban (15) Edoxaban (2)	60	85	18	AMI (100%)	TTE CMR	2-3	NC	Triple therapy (69.3%)	Bleeding events Stroke, SSE LVT resolution	****	***
McCarthy (2019)	USA	Retrospective	Warfarin (94)	Apixaban (3) Rivaroxaban (1)	NC	NC	44	HF (68.5%) AMI (25.9%) NC	TTE Contrast-TTE TTE CMR	NC	NC	NC	LVT resolution	***	***
Mihm (2021)	USA	Retrospective	Warfarin (75)	Apixaban (23) Rivaroxaban (10)	61	77	6	NC	TTE CMR	NC	NC	NC	Bleeding events Stroke, SE, SSE Mortality LVT resolution	***	***
Ratnayake (2020)	New Zealand	Retrospective	Warfarin (42)	Dabigatran (2)	55	37	6	AMI (100%)	TTE	2-3 bridged with LMWH	NC	Aspirin (85%) Clopidogrel (42%)	LVT resolution	***	***

(Continues)

Table 1 (continued)

Author (year)	Region	Design	Sample size		Mean age (years)	Male (%)	Follow up (months)	Aetiology of LVT	Diagnose method	Target INR	TTR (%)	Drug combination	Outcome	Risk of bias assessment of cohort studies	
			VKAs (n)	DOACs (n)										Selection	Comparability Outcome
Robinson (2020)	USA	Retrospective	Warfarin (236)	DOACs (121)	58	74	12	ICM (59.9%)	TTE	NC	NC	Antiplatelet (68%)	Bleeding events SSE Mortality LVT	***	** ***
Varwani (2021)	Kenya	Retrospective	Warfarin (34)	Rivaroxaban (46) Dabigatran (7) Apixaban (5)	61	77	24	Post MI (28%) ICM (42%) Non-ICM (30%)	TTE	NC	13.1	NC	Bleeding events Stroke, SSE LVT	***	* ***
Willeford (2021)	USA	Retrospective	Warfarin (129)	Apixaban (4) Rivaroxaban (18)	56	80	8.5	HF (85.4%) MI (25.8%)	TTE	2-3 bridged with parenteral therapy	NC	Aspirin (49.7%) P2Y12 inhibitor (25.8%)	Bleeding events Stroke, SSE LVT	****	* **
W. Isa (2020)	Malaysia	RCT	Warfarin (13)	Apixaban 5 mg BID/ 2.5 mg BID (14)	55	93	3	NC	TTE	2-3 bridged with LMWH	NC	NC	Mortality Size reduction of LVT	-	
Xu (2021)	China	Retrospective	Warfarin (62)	Rivaroxaban (16) Dabigatran (9)	62	79	28	ICM (75.9%)	TTE	2-3	NC	Aspirin (43.7%)	Bleeding events Stroke, SSE Mortality LVT	***	* **
Zhang (2021)	China	Retrospective	Warfarin (31)	Rivaroxaban (33)	60	59	25	AMI (100%)	TTE	2-2.5	NC	Triple therapy (100%)	resolution Bleeding events SE, SSE Mortality LVT	***	* **

AMI, acute myocardial infarction; BID, twice daily dosing; CC, cardiac catheterization; CM, cardiomyopathy; CMRI, cardiovascular magnetic resonance imaging; CTA, computed tomography angiography; DOAC, direct oral anticoagulant; HF, heart failure; ICM, ischaemic cardiomyopathy; INR, international normalized ratio; LVT, left ventricular thrombus; MI, myocardial infarction; MRI, magnetic resonance imaging; NC, not clear; OD, once-daily dosing; RCT, randomized controlled trial; SE, systemic embolism; SSE, stroke or SE; TTE, transthoracic echocardiogram; TTR, time in therapeutic range for the warfarin; TOE, trans-oesophageal echocardiography; VKA, vitamin K antagonist.

The risk of bias assessment for the cohort studies was performed using the Newcastle-Ottawa Scale indicating points for cohort studies. A study could be awarded a maximum of 4 stars (*) for selection, 2 stars (**) for comparability, and 3 stars (***) for the outcome.

described a combination treatment using antiplatelet drugs.^{14,15,17,18,20,21,23,25,28,31–34} We assessed the quality of RCTs according to the Cochrane risk of bias tool,³⁸ as shown in the Supporting Information, *Figure S1*. We used the NOS to assess the quality of cohort studies,³⁹ as shown in *Table 1*.

Outcomes

Main safety outcomes

Ten studies mentioned all-cause mortality as an important safety endpoint of LVT treatment.^{15,16,19,22,23,27,29,32–34} Among these studies, 14.0% of patients on DOACs and 22.3% of patients on VKAs had died, but no statistical difference was observed between the two groups (RR = 0.72, 95% CI = 0.52–1.00, $P = 0.05$, $I^2 = 11\%$; *Figure 2A*). Bleeding events, as the main safety endpoint of LVT treatment, were reported in 16 studies.^{14–16,18,19,21–25,27,29–31,33,34} In those studies, 10.9% of patients treated with DOACs and 14.3% of patients treated with VKAs were reported to have had bleeding events with a significant difference between the two groups (RR = 0.73, 95% CI = 0.58–0.90, $P = 0.004$, $I^2 = 0\%$; *Figure 2B,C*). Based on the principle of geographical proximity, we divided the included studies into four subgroups: North America, Europe, East Asia, and Middle East regions and Africa. After stratification according to patient region, further analysis indicated that the rate of bleeding events in patients receiving DOACs was markedly inferior to that in those being treated with VKAs among patients residing in North America, mainly including the United States of America (USA) (RR = 0.78, 95% CI = 0.61–0.99, $P = 0.04$, $I^2 = 0\%$; *Figure 2B*) and in European countries mainly including the United Kingdom (UK) (RR = 0.38, 95% CI = 0.17–0.83, $P = 0.02$, $I^2 = 0\%$; *Figure 2B*). We also analysed subgroups in terms of the incidence of bleeding events, stratified according to the aetiology of LVT, and observed that the incidence of bleeding events in the DOACs group was significantly lower than that in the VKA group among patients with IHDs (RR = 0.63, 95% CI = 0.44–0.89, $P = 0.009$, $I^2 = 0\%$; *Figure 2C*).

Main efficacy outcomes

The occurrence of stroke, an important efficiency outcome of LVT treatment, was reported in 14 studies.^{14,15,17–19,21–25,27,30,31,33} Stroke occurrence was 7.4% in patients on DOACs versus 11.6% in patients on VKAs. A statistically significant reduction in the incidence of stroke was found when comparing patients on DOACs with those on VKAs (RR = 0.72, 95% CI = 0.54–0.96; $P = 0.03$; $I^2 = 0\%$; *Figure 3A,B*). We similarly divided the included studies into four regional subgroups: North America, Europe, East Asia, and Middle East regions and Africa. The subgroup analysis indicated that the

risk of stroke in patients being treated with DOACs was markedly inferior to those receiving VKAs among patients residing in North America, primarily including the USA (RR = 0.73, 95% CI = 0.54–0.99, $P = 0.04$, $I^2 = 0\%$; *Figure 3A*). We also analysed subgroups in terms of the incidence of stroke, stratified according to the aetiology of LVT, and observed that the incidence of stroke in the DOACs group was significantly lower than that in the VKAs group among patients with IHD (RR = 0.61, 95% CI = 0.39–0.96, $P = 0.03$, $I^2 = 0\%$; *Figure 3B*).

Ten studies^{14,15,17,22–24,27,31,33,34} reported SE data, in which SE occurred in 1.4% of patients on DOACs and 2.4% of patients on VKAs; however, this between-group difference was not statistically significant (RR = 0.87, 95% CI = 0.37–2.02, $P = 0.74$, $I^2 = 0\%$; *Figure 3C*). Eighteen studies^{14–25,27,29–31,33,34} reported SSE outcomes, in which SSE occurred in 13.5% of patients on DOACs compared with 19.6% of patients on VKAs; however, SSE occurrences did not differ significantly between the two groups (RR = 0.90, 95% CI = 0.65–1.23, $P = 0.50$, $I^2 = 23\%$; *Figure 3D*).

Eighteen studies^{14–17,19–21,23–31,33,34} reported LVT resolution, one study³² reported LVT size reduction, and three studies^{14,17,34} reported thrombus resolution rates at 1 month. LVT resolution was reported for 65.8% of patients on DOACs and for 63.2% of patients on VKAs. LVT size reduction was reported in 65.1% of patients on DOACs and in 61.5% of patients on VKAs, and LVT resolution at 1 month occurred in 46.2% of patients on DOACs and in 22.1% of patients on VKAs. No statistical differences were found between the two groups in terms of LVT resolution (RR = 1.06, 95% CI = 0.98–1.13, $P = 0.13$, $I^2 = 0\%$; *Figure 3E*) or LVT size reduction ($P = 0.82$). However, a statistically significant increase in LVT resolution at 1 month follow-up was found for patients on DOACs when compared with those on VKAs (RR = 1.96, 95% CI = 1.19–3.22, $P = 0.008$, $I^2 = 31\%$; *Figure 3F*).

Publication bias and sensitivity analysis

Contour-enhanced funnel plots for outcomes were drawn, and no asymmetry was detected when they were assessed using Egger's regression (bleeding events: $P = 0.64$; stroke: $P = 0.52$; SE: $P = 0.95$; SSE: $P = 0.08$; LVT resolution: $P = 0.75$; *Figure 4*). We conducted sensitivity analyses for the main endpoints to assess the robustness of the results by sequentially eliminating one study. Remarkable differences were noted when we tested the mortality data after excluding studies by Cochran *et al.*, Iqbal *et al.*, Mihm *et al.*, and Xu *et al.*^{19,23,27,33} Subsequently, we found significant differences when the stroke data was tested after excluding studies by Bass *et al.* and also when we tested the LVT resolution data after excluding studies by Robinson *et al.*^{18,29} No remarkable differences were found when we tested the data of bleeding events, SE, and SSE.

Figure 2 A Forest plot of mortality and bleeding events. (A) Mortality; (B) bleeding event subgroups stratified according to region; (C) bleeding event subgroups stratified according to LVT aetiology. CI, confidence interval; df, degrees of freedom; DOACs, direct oral anticoagulants; M-H, Mantel-Haenszel; LVT, left ventricular thrombus; VKAs, vitamin K antagonists.

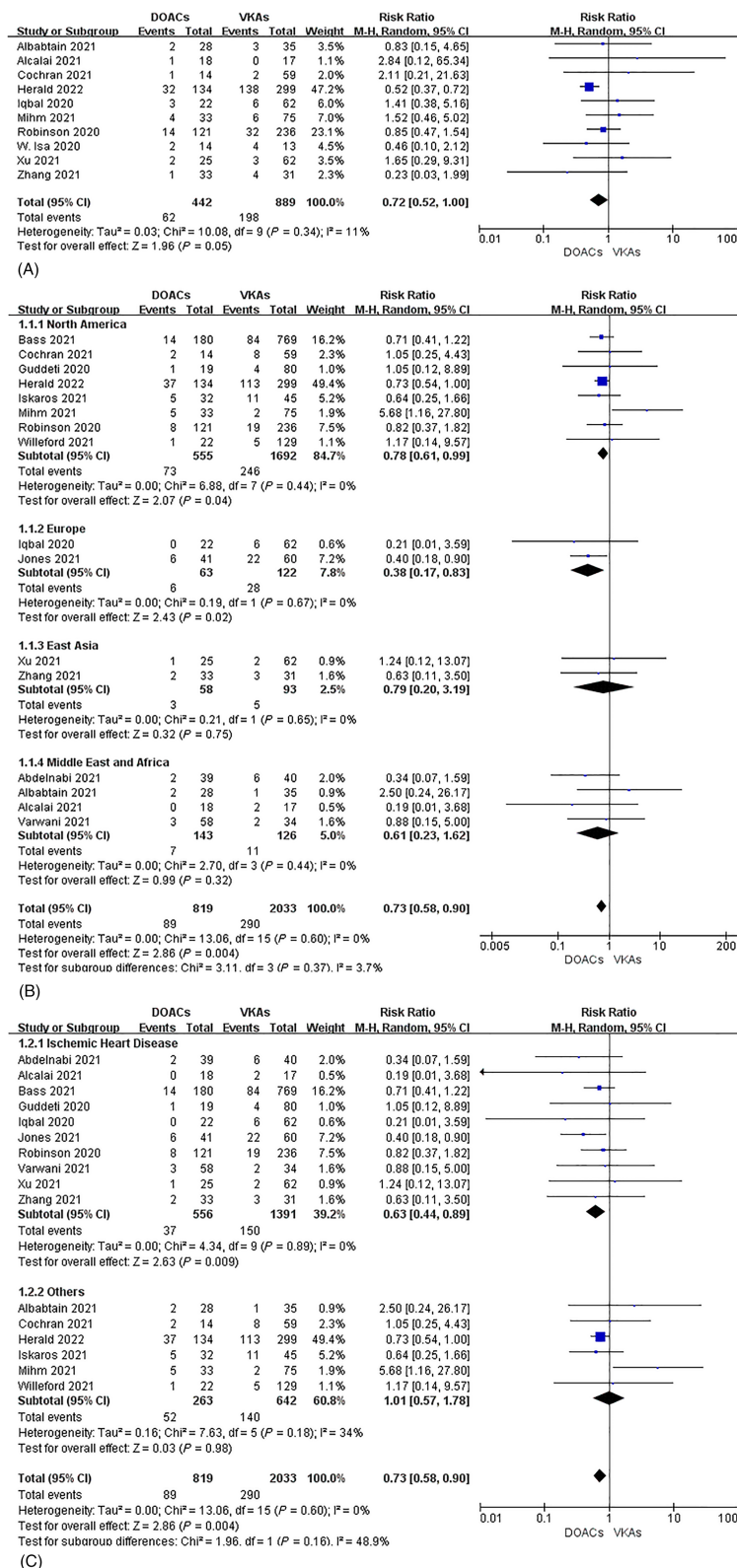
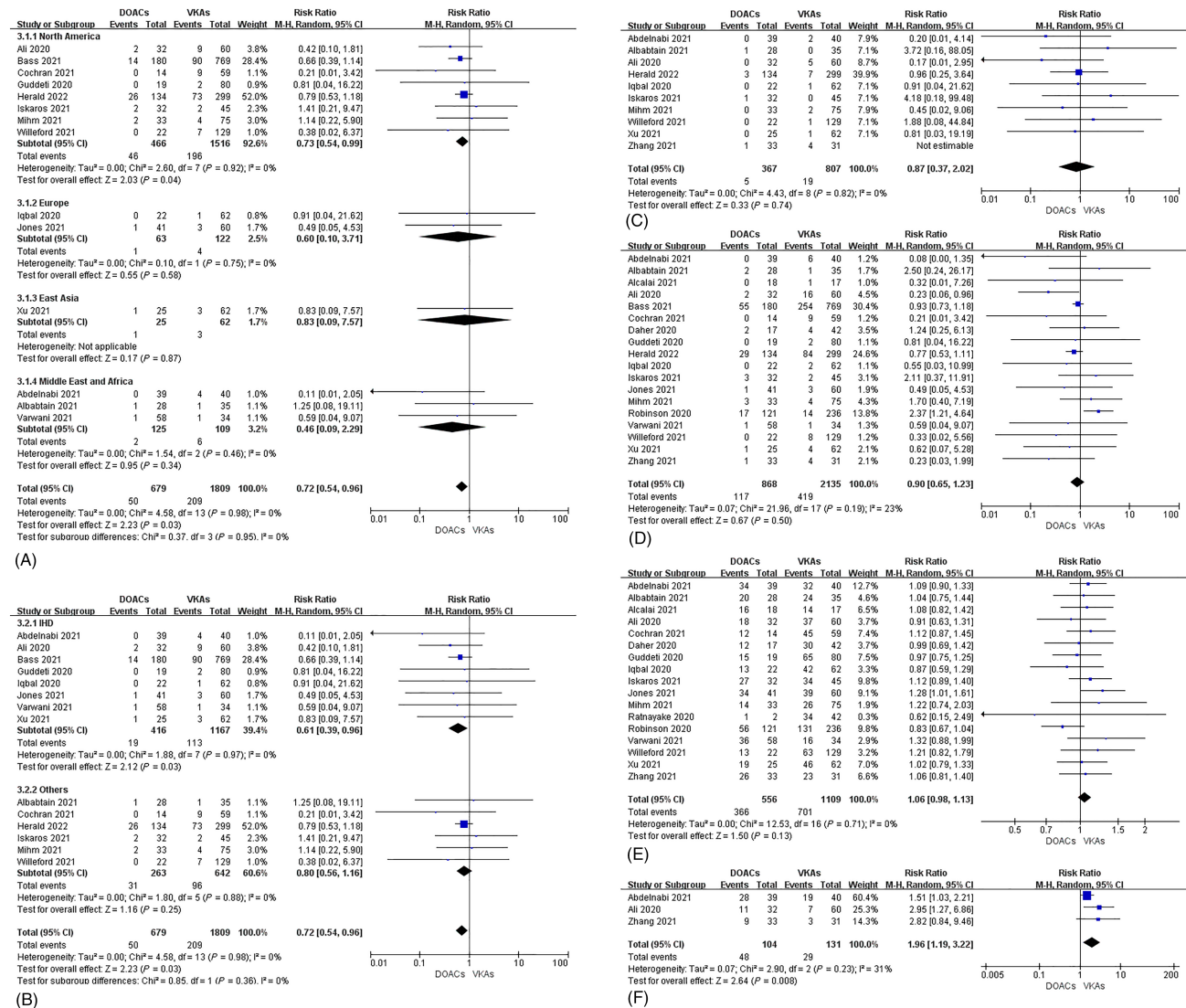


Figure 3 A Forest plot for stroke, SE, SSE, LVT resolution at the end of follow-up, and LVT resolution at 1 month follow-up. (A) Stroke subgroups stratified according to regions; (B) stroke subgroups stratified according to LVT aetiology; (C) SE; (D) SSE; (E) LVT resolution at the end of follow-up; (F) LVT resolution at 1 month follow-up. CI, confidence interval; df, degrees of freedom; DOACs, direct oral anticoagulants; M-H, Mantel-Haenszel; LVT, left ventricular thrombus; SE, systemic embolism; SSE, composite stroke or systemic embolism; VKAs, vitamin K antagonists.

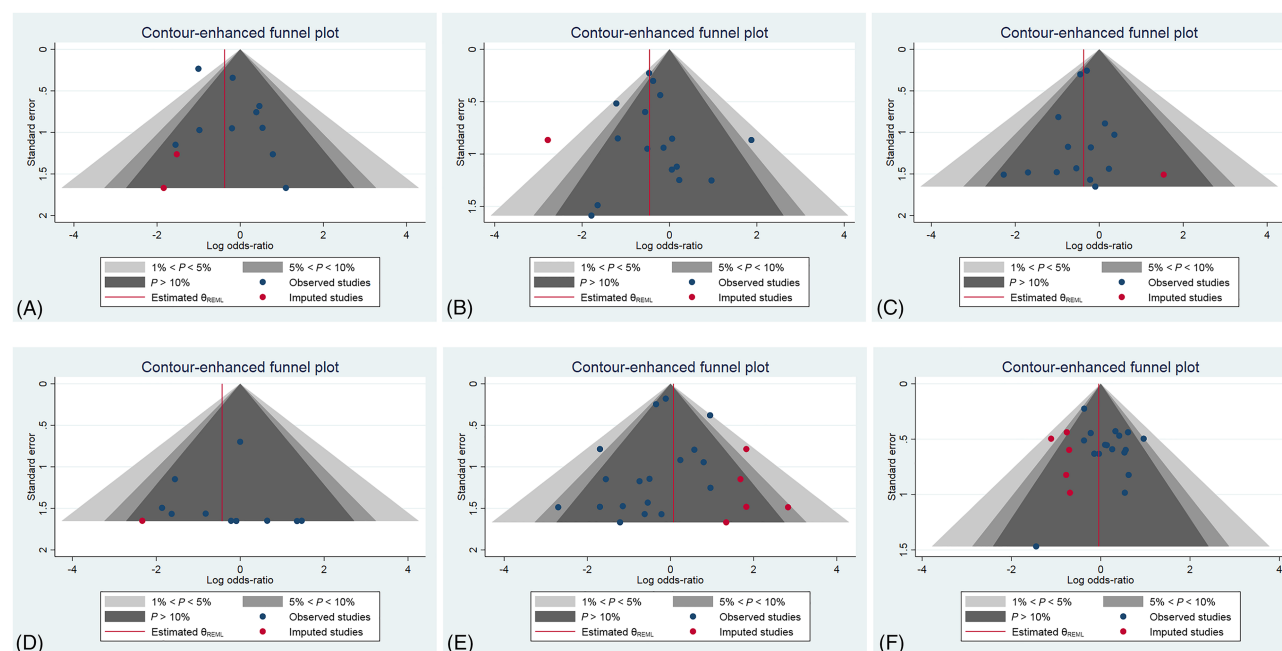


Discussion

LVT formation has been reported to complicate 1.6–39% of AMIs during the acute phase and remains common in patients with severely impaired left ventricular systolic function.^{1,2} With the timely treatment of emergency percutaneous coronary intervention (PCI) and the improvement of perioperative management, the incidence of left ventricular thrombosis after MI decreased substantially.¹ However, the overall incidence of LVT in anterior ST-segment elevation myocardial infarction (STEMI) patients is 12.2%, while the incidence of LVT in anterior STEMI patients with left ventricular

ejection fraction (LVEF) < 50% is as high as 19.2%.⁴³ LVT is associated with serious embolic complications as thrombi may flow downstream into the arterial system, resulting in devastating stroke events, SE, and SSE.⁴ Furthermore, it is also associated with detrimental cardiac events and increased mortality, which may be attributed to delayed reperfusion, severe myocardial damage, and lower LVEF.^{44,45} Mechanisms of LVT development after AMI mainly include endothelial injury in the area of MI, blood stasis caused by decreased ventricular contractility, and hypercoagulability triggered by inflammation. Therefore, anticoagulation represents an important therapeutic target.⁴⁶ However, anticoagulation

Figure 4 Publication bias analysis of DOACs versus VKAs for bleeding events, stroke, SSE, and resolution of LVT endpoints using contour-enhanced funnel plots. (A) mortality; (B) bleeding events; (C) stroke; (D) SE; (E) SSE; (F) LVT resolution. DOACs, direct oral anticoagulants; LVT, left ventricular thrombus; SSE, composite stroke or systemic embolism; VKAs, vitamin K antagonists.



treatment concurrently carries a potential risk of bleeding; therefore, it is essential that patient management can balance the risks and benefits of such treatment.

VKAs have a good anticoagulant effect with widely inhibiting the activation of coagulation factors (II, VII, IX, X) and proteins (C, S). Warfarin is the most commonly used and recommended VKA in the treatment of LVT; however, its use requires frequent monitoring and dosage adjustment. Moreover, its slow action and interaction with drugs and food may reduce patient adherence,^{7–9} influence the therapeutic effect, and decrease patient quality of life. DOACs are highly selective direct inhibitors of coagulation factor Xa or thrombin and do not require patient monitoring. Considering the major advantages of DOACs compared with VKAs, in terms of the clinical benefits observed in patients with AF and venous thromboembolism, such as lower rates of intracranial haemorrhage and bleeding events, stable drug concentration, and ease of administration,^{11,12} there has recently been considerable interest in the use of DOACs to treat LVT. However, their use in LVT treatment has still not been recommended in guidelines owing to a lack of evidence.

In this evidence-synthesis study, we evaluated the safety and efficacy of DOACs for patients with LVT. Our analysis included 3172 patients in 21 studies and showed that DOACs might be a better treatment option than warfarin for LVT treatment, especially in patients residing in North American and European regions or those with a diagnosis of IHD.

Our findings suggest that all-cause mortality rates were similar among differing oral anticoagulants. Owing to the small sample sizes in most of the included studies and the differing follow-up durations, evidence concerning mortality rates may have been affected. When we conducted sensitivity analyses for mortality data, we noted remarkable differences after excluding studies by Cochran *et al.*, Iqbal *et al.*, Mehmet *et al.*, and Xu *et al.*^{19,23,27,33} These four studies are limited due to small sample size. In contrast, among the studies mentioning mortality, the study by Herald *et al.*²² had a large sample size (DOACs: 134 vs. VKAs: 299) and a relatively long follow-up time (median of 3.4 years). It concluded that the mortality in the DOACs group was significantly lower than that in the VKAs group ($P = 0.008$).

Significant inferior rates in terms of the occurrence of bleeding events in the DOACs group versus VKAs group were identified in our study. The bleeding occurrence was lower for patients residing in North American and European regions, and patients with IHD treated with DOACs than patients residing in other regions or those with a different LVT aetiology, respectively. Our findings concerning bleeding events were influenced by several factors that may have affected our conclusions. First, several studies have shown a similar risk reduction across ethnic groups in terms of major bleeding events involving patients on DOACs compared with those on VKAs.^{47,48} In the North American subgroup, the average white population accounts for a relatively high proportion

according to the studies by Ali *et al.*, Bass *et al.*, Herald *et al.*, Mihn *et al.*, and Robinson *et al.* (68.5%, 74.3%, 45.0%, 75.9%, and 53.8%, respectively).^{17,18,22,27,29} Tedla *et al.*⁴⁹ recently conducted a study in America and reported that DOACs significantly reduced the incidence of bleeding only in white patients compared with VKAs. Lähteenmäki *et al.* reported that ABCB1 variants are potential factors affecting bleeding events in apixaban users.⁵⁰ Zhao *et al.* concluded that interindividual differences in bleeding events induced by rivaroxaban might be potentially driven by genetic alterations related to abnormal metabolism and transport of rivaroxaban.⁵¹ Therefore, consideration of ethnic and genetic factors may be important when evaluating the risk of bleeding. Second, an antiplatelet therapy strategy is necessary for patients with LVT and IHD, and dual antiplatelet therapy and triple antithrombotic therapy are common, which considerably increase the risk of bleeding.²⁵ Our conclusions suggest that DOACs combined with an appropriate antiplatelet strategy can reduce the risk of bleeding in patients with LVT and IHD compared with the VKA-antiplatelets combination therapy, which was consistent with findings reported in real-world studies.^{52–54} In a recent meta-analysis, apixaban was found to have had higher effectiveness and safety for stroke prevention compared with other DOACs when used to treat AF⁵⁵; however, further studies are needed to confirm whether this advantage exists for LVT. In addition, to unify the different definitions of bleeding events in various trials, we analysed data concerning major and minor bleeding events, including intracranial haemorrhage, gastrointestinal bleeding, and epistaxis. Further studies with specific definitions of bleeding events may allow drawing more precise conclusions. Last, target INR levels and the rate of reaching the INR standard were inconsistent across the included studies, which affected our evaluation in terms of the risk of bleeding events.

We found a statistically significant decrease in stroke in patients using DOACs (7.4% of patients) compared with those using VKAs (11.6% of patients), which differed from findings reported in another meta-analysis analysing DOACs versus VKAs in patients with AF, in which no difference was reported in terms of the occurrence of ischaemic stroke.⁵⁵ After subgroup analysis by region and aetiology, we found that the occurrence of stroke was lower for patients residing in North America and patients with IHD who had been treated using DOACs than patients residing in other regions or those with a different LVT aetiology, respectively. This variation may further confirm the findings by Tedla *et al.*⁴⁹ that DOACs significantly reduced the incidence of stroke compared with VKAs, especially in white patients. Subsequently, it may suggest that DOACs with proper antiplatelet therapy can decrease the occurrence of stroke in patients with LVT and IHD. The significant difference found in this regard may also be attributable to the low or uncertain rate of reaching the INR standard on VKAs, as mentioned by Ali *et al.* and Jones

et al.^{17,25} When conducting sensitivity analyses for stroke, we found significant differences after excluding the study conducted by Bass *et al.*¹⁸ This study had the largest sample size and its findings on the outcome of stroke were consistent with most other studies^{14,17,19,21–23,25,30,31,33}; the incidence of stroke in the DOACs group was lower than that in the VKAs group. Therefore, there is a need for more studies with a large sample size to make further robust conclusions.

No significant difference was detected in terms of the incidence of SE between patients taking DOACs (1.4% of patients) and those taking VKAs (2.4% of patients). Our outcome was possibly affected by several factors, such as the small sample sizes and very low morbidity rates for SE following treatment. After synthesizing all the included studies that mentioned SSE, no difference was found between patients in either group, whereas in Ali *et al.*'s¹⁷ cohort study and Abdelnabi *et al.*'s¹⁴ RCT, the incidence of SSE was significantly reduced in DOACs groups compared with VKAs groups ($P = 0.0001$ and $P = 0.01$, respectively); however, given the small sample sizes in these studies, further large-scale RCTs are needed to validate these findings.

Although no distinction in LVT resolution was found between the two groups on completion of the follow-up period, a statistically significant increase in LVT resolution at 1 month was found in patients on DOACs versus VKAs (46.2% vs. 22.1%). Two studies conducted by Albabtain *et al.*¹⁵ and Iskaros *et al.*²⁴ mentioned a shorter time of thrombus resolution in the DOACs group compared with that in the warfarin group ($P = 0.019$ and $P = 0.003$, respectively). Isa *et al.*³² conducted an RCT and found an increased size reduction in LVT in patients in the DOAC group than those in the VKAs group without a statistical difference ($P = 0.816$). McCarthy *et al.*²⁶ found that thrombus resolution occurred in 100% who received DOACs compared with 75% who received warfarin. DOACs directly act on factor Xa or thrombin, and their rapid action allows for faster thrombus resolution. Even after warfarin began to manifest its action, DOACs were found to be at least as effective as warfarin in the entire follow-up period. However, the difference in size reduction or LVT resolution between the two groups was influenced by the therapeutic target of INR (TTR), diagnosis method, and the follow-up duration. The sub-optimal TTR may affect the resolution rate of LVT on VKAs, as mentioned in studies conducted by Alcalai *et al.*, Ratnayake *et al.*, Zhang *et al.*^{16,28,34} One previous study recommended performing LVT imaging using delayed enhancement CMRI and transesophageal echocardiography, with follow-up time points in the range of 3–12 months.³⁶ The diagnostic methods and follow-up duration of the included studies were not entirely consistent, which may have influenced our findings. Despite this consideration, we suggest adding a 1 month time-point to the follow-up, which may reduce the treatment duration for some patients.

All the aforementioned outcomes suggest equal or better safety and efficacy of DOACs versus VKAs in LVT treatment.

Although DOACs are not currently recommended as a first-line treatment for LVT, our meta-analysis adds strength and power to current recommendations and provides support for potentially expanding the use of DOACs in LVT. The current evidence suggests that DOACs achieve the same or better clinical outcomes than VKAs in LVT treatment; however, further prospective large-scale RCTs are required to obtain more robust clinical evidence.

Study limitations

This meta-analysis had several limitations. First, the included studies did not use a uniform DOACs regimen, and different DOACs may have different efficacy and safety levels. Second, our meta-analysis included only 3 RCTs and 18 observational cohort studies, mainly including studies with small sample sizes. Hence, more high-quality, large-scale, randomized clinical trials are required to validate our findings. Third, the following factors critical for the assessment of outcomes remain to be elucidated: the LVT diagnostic method, which may be better confirmed using delayed enhancement CMRI or transesophageal echocardiography; dual antiplatelet therapy strategies, which directly affect bleeding and stroke outcomes; the TTR, which directly influences the effects of VKAs; the follow-up duration, which is important when determining mortality and LVT resolution rates; and DOAC types and dosages, which may affect individual efficacy. Finally, we defined the IHD group as the number of IHD patients was higher than 50% in the study population, possibly representing a confounding factor; we used regional classification as an indirect racial classification, because only few studies mentioned the race of the patients.

Conclusions

Mortality of patients with LVT was similar for DOACs and VKAs, but, compared with VKAs, DOACs significantly reduce the risk of bleeding events and stroke in LVT patients. The advantages are apparent not only in predominantly white residential areas such as North America and European regions but also in patients with LVT owing to IHD. Moreover, compared with VKAs, DOACs are statistically associated with

an increase in LVT resolution at 1 month. This meta-analysis showed that DOACs are likely to be promising candidates for LVT treatment compared with the recommended VKAs.

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Conflict of Interest

The authors declare there are no competing interests.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Randomized controlled trials risk of bias assessment

The Cochrane risk of bias tool was used to assess the risk of bias in the randomized controlled trials.

*the study met the domain criterion; ?it was unclear whether the domain criterion had been met; –the study did not meet the domain criterion

Table S1. Search strategy for PubMed

Abbreviations: NOAC, novel oral anticoagulants; DOAC, direct oral anticoagulants; LVT, left ventricular thrombus

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