ORIGINAL ARTICLE

Direct oral anticoagulants versus vitamin K antagonists for patients with left ventricular thrombus: a systematic review and meta-analysis

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KEY WORDS

direct oral anticoagulants, left ventricular thrombus, vitamin K antagonists

EDITORIAL

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ABSTRACT

INTRODUCTION Although vitamin K antagonists (VKAs) are recommended as first-line anticoagulants for patients with left ventricular thrombus (LVT), accumulating evidence suggests direct oral anticoagulants (DOACs) could be a safe alternative. Efficacy and safety of DOACs should be assessed to justify their usage in this population.

OBJECTIVES The aim of the study was to compare the efficacy and safety of DOACs and VKAs for the treatment of LVT.

PATIENTS AND METHODS We performed a meta-analysis of observational studies to compare DOACs with VKAs in the treatment of patients with LVT. The PubMed and EMBASE databases were searched for articles published until November 12, 2020. Pooled effects were estimated using the Mantel–Haenszel method and presented as risk ratios (RR) using fixed-effect model. Reporting followed the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guideline.

RESULTS A total of 2467 patients with LVT from 13 studies were included. Compared with VKAs, DOACs showed similar efficacy in prevention of stroke or systemic embolism (risk ratio [RR], 0.96; 95% CI, 0.8–1.16; $P = 0.68$) and thrombus resolution (RR, 0.88; 95% CI, 0.72–1.09; $P = 0.26$), but significantly lower risk of stroke (RR, 0.68; 95% CI, 0.47–1; $P = 0.048$). With regard to safety outcomes, DOAC users had similar risk of any bleedings (RR, 0.94; 95% CI, 0.67–1.31; $P = 0.7$), but a lower risk of clinically relevant bleedings (RR, 0.35; 95% CI, 0.13–0.92; $P = 0.03$) compared with VKA users.

CONCLUSIONS Compared with VKAs, DOACs had a similar efficacy and safety profile in patients with LVT, but could reduce the risk of strokes and clinically relevant bleedings.

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Received: January 14, 2021.
Revision accepted: April 1, 2021.
Published online: April 7, 2021.
Pol Arch Intern Med. 2021; 131 (5): 429-438
doi:10.20452/pamw.15923

INTRODUCTION Left ventricular thrombus (LVT) is a rare complication associated with acute myocardial infarction (MI), heart failure, and various cardiomyopathies.[1,2] Owing to the increased risk of embolic events, oral anticoagulation therapy is required to prevent stroke or systemic embolism (SSE). Current guidelines, which are based on limited evidence from observational studies, recommend vitamin K antagonists (VKAs) in patients with LVT.[1-4] However, the off-label use of direct oral anticoagulants (DOACs) for the management of LVT is gaining interest because they provide consistent anticoagulant effect and do not require continuous monitoring of international normalized ratio (INR).[1,5-9] Numerous trials and analyses have already shown that DOACs exhibit similar efficacy in SSE prevention and lower bleeding risk compared with VKAs in other clinical conditions (eg, atrial fibrillation and heart failure).[10-12] Additionally, there are reports on successful cases that achieved complete resolution of LVT and favorable long-term outcomes on DOACs.[13,14] However, affirmative evidence for the use of DOACs in patients with LVT is still lacking. Therefore, this study aimed to summarize the evidence from the latest clinical studies,

WHAT'S NEW?

In patients with left ventricular thrombus, direct oral anticoagulants showed similar efficacy for the prevention of strokes or systemic embolism, thrombus resolution, and the risk of any bleedings as compared with vitamin K antagonists. Patients with left ventricular thrombus receiving direct oral anticoagulants had lower risk of strokes and clinically relevant bleedings as compared with those on vitamin K antagonists. Direct oral anticoagulants are safe and effective alternatives of vitamin K antagonists and could be considered as primary oral anticoagulants in this patient population.

while comparing the efficacy and safety of DOACs and VKAs in patients with LVT, in order to offer novel insights for clinical practice and randomized clinical trials (RCTs) on anticoagulation therapy for LVT in the future.

PATIENTS AND METHODS **Strategies for literature search** We performed a comprehensive literature search in the Pubmed and EMBASE databases using the following search terms: *ventricular thrombi* or *ventricular thrombus*, and *direct oral anticoagulants* or *novel oral anticoagulants* or *dabigatran* or *rivaroxaban* or *apixaban* or *edoxaban* and *vitamin K antagonists* or *warfarin* or *dicoumarol* or *phenindione* or *phenprocoumon* or *acenocoumarol* or *ethyl biscoumacetate* or *fluindione* or *clorindione* or *diphenadione* or *tioclomarol*. The literature search and data extraction were conducted independently by 2 researchers (RC and JZ). The final search was performed on November 12, 2020.

Study selection Eligible studies were selected based on the following inclusion criteria: 1) trials in which the diagnosis of LVT was based on appropriate cardiac imaging techniques (eg, transthoracic / transesophageal echocardiography, cardiovascular magnetic resonance imaging); 2) RCTs or observational studies; and 3) trials comparing outcomes of patients using DOACs or VKAs. We included studies published as full-length articles and as abstracts. Studies regarding LVT secondary to the implantation of a ventricular assist device, case reports, case series, unpublished studies, and studies not published in English were excluded from the current review. In case of missing data, the authors of the original work were contacted. Studies in which data on the specific outcome were unclear, not provided, or could not be acquired after contacting the original authors were excluded from the pooled analysis for that outcome.

This manuscript is a review article and does not involve a research protocol requiring approval of a relevant institutional review board or ethics committee.

Data extraction and quality assessment The following data were extracted from the studies that were included: surname of the first author, geographic location, study design, mean / median age or range of age, proportion of male sex, number of DOAC and VKA users, number of outcomes, follow-up duration, primary causes of LVT, and concomitant antiplatelet medications. Outcomes of interest included SSE, stroke, failure of thrombus resolution, any bleeding event, and clinically relevant bleeding event (ie, life-threatening bleeding and bleeding requiring hospitalization or medical interventions). The quality of the included studies was assessed by 2 independent authors (RC and LS) using the Newcastle–Ottawa Scale. If there were any discrepancies regarding data extraction and quality evaluation, a third author (JZ) was consulted to reach a consensus. Reporting was done in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.

Statistical analysis RevMan 5.3 (The Cochrane Collaboration, Oxford, England) and Stata 15.0 (StataCorp, College Station, Texas, United States) were used to perform this study. Pooled effects were estimated using the Mantel–Haenszel method and presented as risk ratios (RR) with 95% CIs. Heterogeneity across studies was assessed using the I^2 statistics and the χ^2-based Cochran Q test. An I^2 greater than 50% or P value of less than 0.1 for the Cochran Q test showed significant heterogeneity. A fixed-effect model was applied if no significant heterogeneity was observed; otherwise, a random-effects model was used. Funnel plots were used to detect potential publication bias. Begg rank correlation and Egger linear regression tests were performed when an outcome analysis included 10 or more studies. The trim-and-fill method was used to impute the missing studies and correct publication bias, with the *metatrim* command in Stata.[15] The random-effects meta-regression analyses were performed to determine whether age had an impact on various outcomes using the *metareg* command in Stata, with the between-study variance (tau squared) estimated by the residual maximum likelihood. A P value of less than 0.05 was considered statistically significant.

RESULTS **Characteristics and quality assessment of the included studies** The initial literature search identified 216 relevant records after removing duplicates (FIGURE 1). After screening the titles and abstracts, 126 articles were excluded because of irrelevance. Out of 90 eligible articles, 77 studies were further eliminated due to publication type or study design. Finally, 13 articles were included in the synthetic analysis, 2 of which were prospective studies.[5-9,16-23] Essential characteristics of included studies are summarized in TABLE 1.

The average Newcastle–Ottawa Scale score was 6.2 (Supplementary material, *Table S1*), which showed that the included studies were of moderate quality. A total of 2467 patients with LVT were included. The mean age ranged from 51.5 to 63.5 years, and the proportion of male patients was over 70%. The most common cause of LVT was ischemic heart disease. The follow-up duration

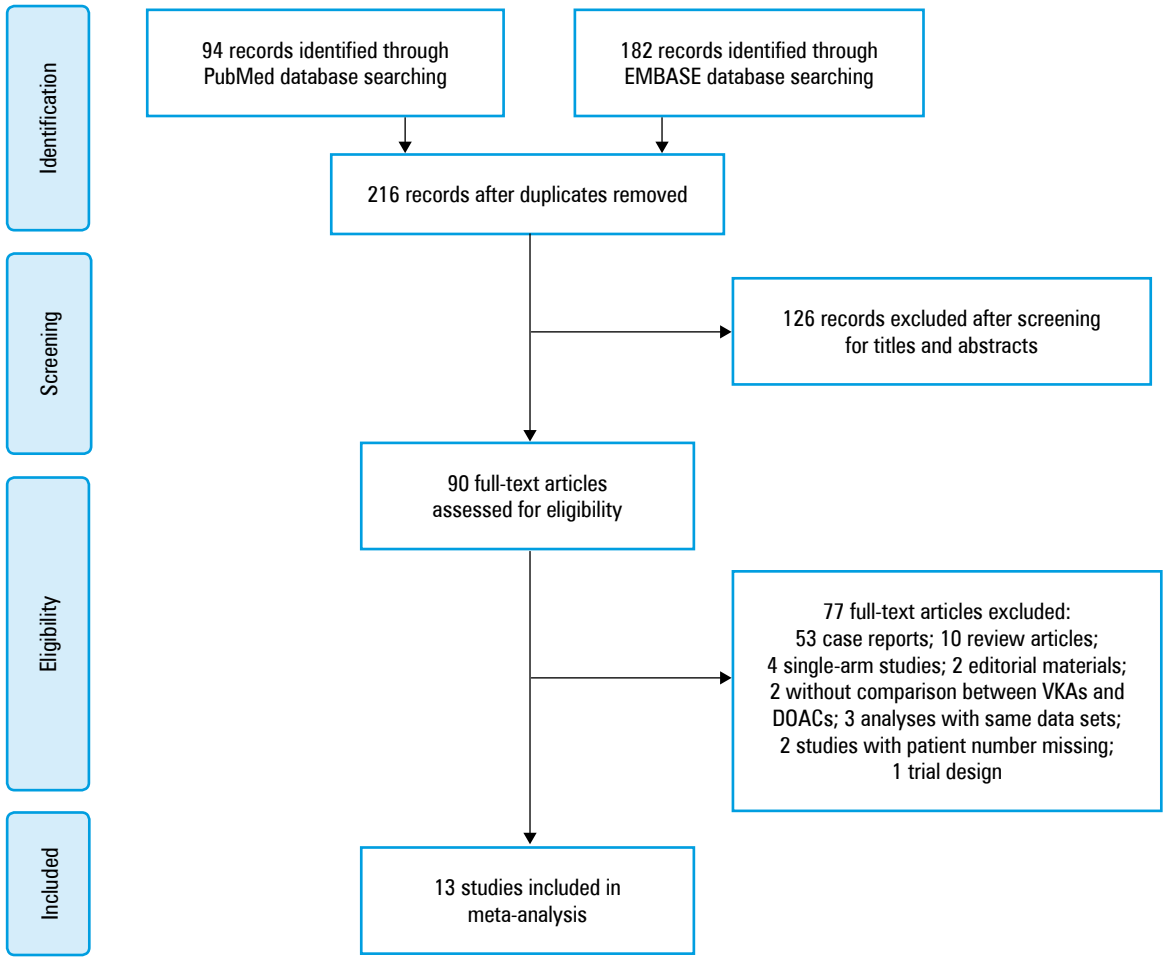

FIGURE 1 PRISMA flow diagram of study selection
Abbreviations: DOAC, direct oral anticoagulant; VKA, vitamin K antagonist

ranged from 3 months to 3 years. Among DOAC users, apixaban (50%) was the most frequently prescribed, followed by rivaroxaban (40.8%), dabigatran (8.8%), and edoxaban (0.4%). Warfarin (98.5%) was predominantly prescribed to VKA users. A concomitant antiplatelet medication was prescribed in over half of patients, although dual antiplatelet therapy was less frequently used.

Clinical outcomes **Stroke and embolic events** Ten studies reported occurrence of SSE.[5-9,19-23] The risk of SSE did not differ between users of DOACs and VKAs (RR, 0.96; 95% CI, 0.8–1.16; $P = 0.68$; $I^2 = 0\%$; FIGURE 2). Potential publication bias was detected in the funnel plot (Supplementary material, *Figure S1*) and by the Egger test ($P = 0.029$), but not by the Begg test ($P = 0.42$). After using the trim-and-fill method, the pooled effect remained the same (RR, 0.96; 95% CI, 0.8–1.16, $P = 0.68$), as no additional studies were imputed (Supplementary material, *Figure S2*). Notably, Robinson et al[8] reported treatment switches between DOACs and warfarin in 15.2% of patients (Supplementary material, *Table S2*). The exclusion of this study led to similar results: DOACs showed equivalent efficacy in SSE prevention as VKAs (RR, 0.95; 95% CI, 0.78–1.15; $P = 0.59$; $I^2 = 0$). Meta-regression against age did not show an impact on the efficacy of DOACs and VKAs (RR, 1.06; 95% CI, 0.96–1.17; $P = 0.23$, Supplementary material, *Figure S3*). Subgroup analysis by follow-up duration ($P = 0.07$ for interaction), sample size ($P = 0.09$ for interaction), concomitant antiplatelet medication ($P = 0.48$ for interaction), primary causes of LVT ($P = 0.09$ for interaction), and major types of used DOACs ($P = 0.63$ for interaction) showed consistently similar effects of DOACs and VKAs (TABLE 2).

Eight studies reported on the outcome of stroke.[5,7,9,19-23] Patients on DOACs showed a lower risk of stroke compared with those on VKAs (RR, 0.68; 95% CI, 0.47–1; $P = 0.048$; $I^2 = 0\%$, FIGURE 3). Funnel plots showed no evidence of publication bias (Supplementary material, *Figure S1*). Meta-regression did not show an impact of age (RR, 1.01; 95% CI, 0.82–1.24; $P = 0.9$; Supplementary material, *Figure S3*). Subgroup analysis (TABLE 2) showed consistent results in terms of follow-up duration ($P = 0.79$ for interaction), sample size ($P = 0.49$), concomitant use of antiplatelet agents ($P = 0.88$ for interaction), primary etiologies of LVT ($P = 0.76$ for interaction), and types of DOACs ($P = 0.91$ for interaction).

TABLE 1 Essential characteristics of included studies (continued on the next page)

Authors (year)	Region	Study design	Sample size	Age, y	Male sex, n (%)	Follow-up period	Primary causes of LVT, n (%)	DOAC vs VKA users, n (%)	Types of DOACs, n (%)	Types of VKAs, n (%)	Antiplatelet treatment, n (%)	NOS score
Ali et al (2020)[23]	United States	Retrospective	92	Mean (SD), 59 (14)	75 (80.6)	1 y	Ischemic cardiomyopathy,[a] 58%; nonischemic cardiomyopathy, 23%; acute myocardial infarction, 15%; takotsubo cardiomyopathy, 3%	32 (34.8) vs 60 (65.2)	Rivaroxaban, 18 (56.2); apixaban, 13 (40.6); dabigatran, 1 (3.1)	Warfarin, 60 (100)	Aspirin, 60 (65.5); P2Y12i, 16 (17.4)	7
Alizadeh et al (2019)[16]	United Kingdom	Prospective	98	NA	NA	Median, 1.8 y	Acute myocardial infarction, 98 (100)	38 (38.8) vs 60 (61.2)	Rivaroxaban, 22 (57.9); apixaban, 14 (36.8); edoxaban, 2 (5.3)	Warfarin, 60 (100)	NA	4
Bass et al (2019)[20]	United States	Retrospective	949	63.5	670 (70.6)	≥90 d	Comorbidities: atrial fibrillation, 463 (48.8); thromboembolic stroke, 189 (19.9); myocardial infarction, 520 (54.8); chronic kidney disease, 321 (33.8); heart failure, 696 (73.3)	180 (19) vs 769 (81)	Rivaroxaban, 77 (41.6); apixaban, 79 (42.7); dabigatran, 29 (15.7)	Warfarin, 769 (100)	Antiplatelet agents, 512 (54)	5
Cochran et al (2020)[21]	United States	Retrospective	73	Median (IQR); VKA users, 62 (34–84); DOAC users, 51.5 (39–73)	56 (76.7)	12 mo	Comorbidities: coronary artery disease, 44 (60.3); congestive heart failure, 58 (79.5); arrhythmia, 13 (17.8); chronic kidney disease, 27 (37); type 2 diabetes, 30 (41.1)	14 (19.2) vs 59 (80.8)	NA	Warfarin, 59 (100)	NA	8
Daher et al (2020)[6]	France	Retrospective	59	Mean (SD), 62 (14)	49 (83.1)	3 mo	Ischemic cardiomyopathy, 51 (86.4)	17 (28.8) vs 42 (71.2)	Rivaroxaban, 4 (23.5); apixaban, 12 (70.6); dabigatran, 1 (5.9)	Warfarin, 14 (33.3); acenocoumarol, 12 (28.6); fluindione, 16 (38.1)	Aspirin, 38 (64.4); P2Y12i, 28 (47.5)	5
Durrer-Ariyakuddy et al (2019)[17]	Switzerland	Retrospective	53	63	39 (61.9)	Median (IQR), 20 (6–35) mo	Recent myocardial infarction, 25 (47.2); ischemic heart disease, 7 (13.2); nonischemic cardiomyopathy, 21 (39.6)	20 (37.7) vs 33 (62.3)	NA	NA	SAPT, 28 (52.8); DAPT, 9 (17)	5
Guddeti et al (2020)[5]	United States	Retrospective	99	Mean (SD), 61 (12.3)	70 (70.7)	Mean (SD), 10.4 (3.4) mo	Ischemic cardiomyopathy, 58 (58.6); others, 41 (41.4)	19 (19.2) vs 80 (80.8)	Rivaroxaban, 2 (10.5); apixaban, 15 (78.9); dabigatran, 2 (10.5)	Warfarin, 80 (100)	Aspirin, 65 (65.7); P2Y12i, 15 (15.2)	5
Iqbal et al (2020)[9]	United Kingdom	Retrospective	84	Mean (SD), 62 (14)	75 (89.3)	Mean (SD), 3 (1.4) y	Ischemic heart diseases, 73 (86.9); dilated cardiomyopathy, 4 (4.8); acute myocarditis, 3 (3.6); myocarditis, 2 (2.4); unknown, 2 (2.4)	22 (26.2) vs 62 (73.8)	Rivaroxaban, 13 (59.1); apixaban, 8 (36.4); dabigatran, 1 (4.5)	Warfarin, 62 (100)	Aspirin, 48 (57.1); P2Y12i, 39 (46.4); SAPT, 55 (65.5); DAPT, 32 (38.1)	5
Jones et al (2020)[7]	United Kingdom	Prospective	101	Mean (SD), 59.6 (14.1)	84 (83.2)	Median, 2.2 y	Acute myocardial infarction, 101 (100)	41 (40.6) vs 60 (59.4)	Rivaroxaban, 24 (58.5); apixaban, 15 (36.6); edoxaban, 2 (4.9)	Warfarin, 60 (100)	SAPT, 23 (22.8); DAPT, 70 (69.3)	8
Lim et al (2019)[18]	Malaysia	Retrospective	23	Mean (SD), 55 (9.6)	17 (73.9)	≥3 mo	Ischemic heart diseases, 20 (87); thyroid cardiomyopathy, 2 (8.7); spontaneous coronary dissection, 1 (4.3)	5 (21.7) vs 18 (78.3)	Rivaroxaban, 2 (40); dabigatran, 3 (60)	Warfarin, 18 (100)	NA	5

TABLE 1 Essential characteristics of included studies (continued from the previous page)

Authors (year)	Region	Study design	Sample size	Age, y	Male sex, n (%)	Follow-up period	Primary causes of LVT, n (%)	DOAC vs VKA users, n (%)	Types of DOACs, n (%)	Types of VKAs, n (%)	Antiplatelet treatment, n (%)	NOS score
Robinson et al (2020)[8]	United States	Retrospective	421	Mean (SD), 57.8 (14.7)	308 (73.2)	Median (IQR), 351 (51–866) d	Ischemic heart diseases,[a] 59.9%; nonischemic cardiomyopathies, 25.3%; unknown, 7.8%; others, 7.1%;	135 (32.1) vs 286 (67.9)	Rivaroxaban,[b] 24.9%; apixaban, 76.2%; dabigatran, 4.9%	Warfarin, 300 (100)	Aspirin, 191 (45.4); P2Y12i, 88 (20.9); SAPT, 215 (51.1); DAPT, 64 (15.2)	7
Willeford et al (2020)[22]	United States	Retrospective	151	Median (IQR), 56 (49–65)	121 (80.1)	Median (IQR), 254 (98–343) d	Comorbidities: atrial fibrillation, 27 (17.9); heart failure, 129 (85.4); stroke/TIA, 13 (8.6); myocardial infarction, 39 (25.8); peripheral artery disease, 13 (8.6); coronary artery disease, 83 (55); chronic kidney disease, 21 (13.9)	22 (14.6) vs 129 (85.4)	Rivaroxaban, 18 (81.8); apixaban, 4 (18.2)	Warfarin, 129 (100)	Aspirin, 75 (49.7); P2Y12i, 39 (25.8); SAPT, 56 (37.1); DAPT, 29 (19.2)	9
Yunis et al (2020)[19]	United States	Retrospective	264	NA	NA	2 y	NA	64 (24.2) vs 200 (75.8)	NA	Warfarin, 200 (100)	NA	7

a Etiologies for left ventricular thrombus were only presented in percentages, as original authors only report concrete numbers for each etiology for the whole cohort, including those not receiving anticoagulants or excluded from the original study.

b Authors report treatments switches between anticoagulants, and concrete numbers of patients using various types of DOACs are not reported and could not be calculated.

Abbreviations: DAPT, dual antiplatelet therapy; IQR, interquartile range; LVT, left ventricular thrombus; NA, not available; NOS, Newcastle–Ottawa Scale; P2Y12i, P2Y12 inhibitors; SAPT, single antiplatelet therapy; TIA, transient ischemic attack; others, see FIGURE 1

Thrombus resolution Eleven studies investigated the outcome of failure in thrombus resolution,[5-7,9,16-19,21-23] and the resolution rate was similar between the 2 groups (RR, 0.88; 95% CI, 0.72–1.09; $P = 0.26$, FIGURE 4); analysis showed low statistical heterogeneity ($I^2 = 26\%$; $P = 0.2$) and no significant publication bias based on the results of the funnel plot (Supplementary material, *Figure S1*) and statistical tests (Begg test, $P = 0.48$; Egger test, $P = 0.19$). Age did not have substantial impact on thrombus resolution according to the results of meta-regression (RR, 1.08; 95% CI, 0.95–1.22; $P = 0.22$, Supplementary material, *Figure S3*). The efficacy of thrombus resolution was consistent regardless of variations in follow-up duration ($P = 0.94$ for interaction), sample size ($P = 0.26$ for interaction), antiplatelet medication ($P = 0.43$ for interaction), and types of DOACs ($P = 0.67$ for interaction) in the subgroup analysis (TABLE 2). However, interactions were observed for primary causes of LVT (MI, RR, 0.57; 95% CI, 0.38–0.84; $P = 0.005$; $I^2 = 0\%$; mixed etiologies, RR, 1.09; 95% CI, 0.85–1.41; $P = 0.47$; $I^2 = 0\%$; $P = 0.006$ for interaction)

Bleeding events Nine studies reported on bleeding events.[5,7,9,16,19-23] The risk of any bleeding event was similar for DOAC and VKA users (RR, 0.94; 95% CI, 0.67–1.31; $P = 0.7$; $I^2 = 24\%$; FIGURE 5), without publication bias, as shown in the funnel plot (Supplementary material, *Figure S1*). Meta-regression showed that age did not affect the safety of DOACs or VKAs (RR, 1.03; 95% CI, 0.81–1.31; $P = 0.76$; Supplementary material, *Figure S3*). Subgroup analysis (TABLE 2) showed that bleeding risk was similar, regardless of variations in sample size ($P = 0.21$ for interaction), etiologies ($P = 0.14$ for interaction), and types of DOACs ($P = 0.91$ for interaction). However, significant interactions were observed in terms of follow-up duration ($P = 0.02$ for interaction) and antiplatelet medications ($P = 0.006$ for interaction).

In 6 studies reporting on clinically relevant bleeding events,[5,7,9,16,22,23] favorable outcomes were seen in DOAC users (RR, 0.35; 95% CI, 0.13–0.92; $P = 0.03$; $I^2 = 0\%$; FIGURE 6), and no significant publication bias was detected using the funnel plot (Supplementary material, *Figure S1*). Age did not affect the difference in risk of clinically relevant bleeding events between DOAC and VKA users (RR, 0.83; 95% CI, 0.41–1.69; $P = 0.52$; Supplementary material, *Figure S3*). Subgroup analysis showed no interactions with follow-up duration ($P = 0.09$ for interaction), sample size ($P = 0.83$ for interaction), antiplatelet medication ($P = 0.2$ for interaction), etiologies ($P = 0.23$ for interaction), and types of DOACs ($P = 0.28$ for interaction) for the risk of clinically relevant bleeding events in DOAC or VKA users (TABLE 2).

DISCUSSION

The major findings of this systematic review and meta-analysis were as follows: 1) only observational studies were conducted regarding anticoagulation treatment for LVT, and

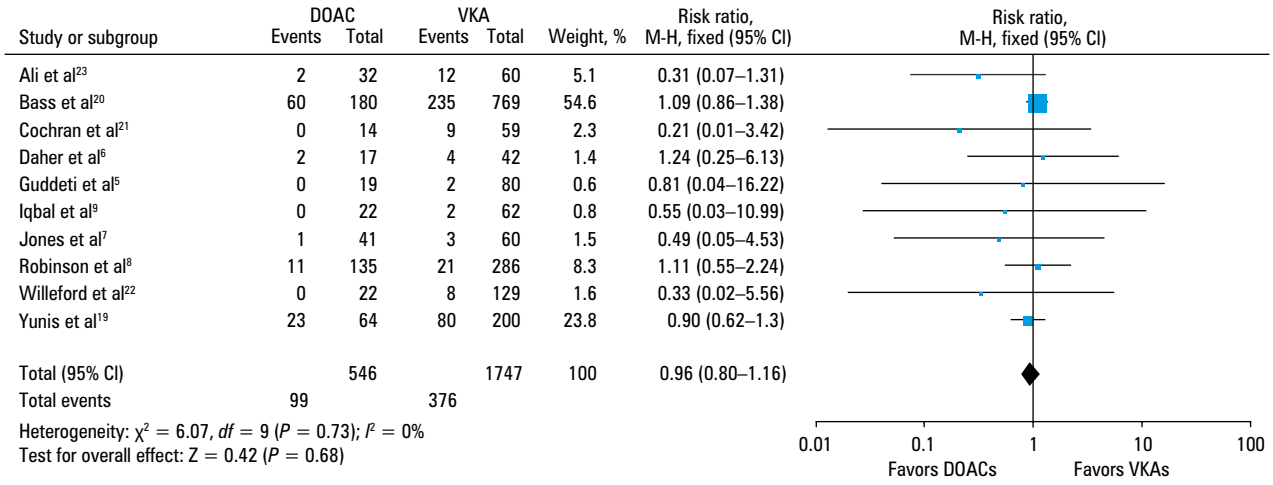

FIGURE 2 Forest plot for the comparative risk of stroke or systemic embolism with direct oral anticoagulants (DOACs) versus vitamin K antagonists (VKAs)

most of them were retrospective; 2) DOAC users showed similar risk of SSE, failure of LVT resolution, but lower risk of stroke compared with that of VKA users; and 3) DOAC users showed a similar risk of any bleeding event but lower risk of clinically relevant bleeding event as compared with that of VKA users.

Efficacy of direct oral anticoagulants and vitamin K anticoagulants According to the current guidelines, warfarin is still recommended as the first-line treatment for LVT, although there is no evidence from RCTs.[1,3,4] However, DOACs are gaining interest in the context of LVT treatment as they help achieve consistent anticoagulant effects while reducing bleeding risk.[1,24] A growing number of cases and clinical studies also show satisfactory outcomes in patients with LVT using DOACs.[5-7,9] Although the current analysis showed no difference between DOACs and VKAs in terms of efficacy in SSE prevention, as has been reported in recently published meta-analyses,[21,25] it is definitely of great clinical importance because it showed a 32% risk reduction of stroke in DOAC users. The subgroup analysis also showed a marked homogenous reduction in the risk of stroke across various confounders. A recently published pooled analysis by Zhou et al[25] showed no difference in the occurrence of stroke (odds ratio, 0.79; 95% CI, 0.5–1.23) among DOAC and VKA users; however, we included 3 newly published studies[21-23] which increased the sample size and provided greater power to test the difference between the 2 medications. Although the interpretation of these findings could be challenging, one of the main reasons could be the fluctuation in INR. Ali et al[23] reported that 71% of patients with stroke receiving warfarin had suboptimal control of INR. In a study by Jones et al,[7] nearly half of warfarin users could not sustain INR within the recommended range for over 65% of the time during anticoagulation treatment, of whom 75% were below the target value, and all thromboembolic events occurred in patients with suboptimally controlled INR. Therefore, physicians should consider initiating treatment with DOACs to provide long-term and consistent anticoagulation for patients with LVT, especially when there are difficulties in monitoring or maintaining INR within the recommended range. Additionally, it should be noted that there are discrepancies among included studies regarding the effects of DOACs. Robinson et al[8] reported a substantial increase in the risk of SSE in DOAC users (hazard ratio, 2.67; 95% CI, 1.31–5.57), which is in contrast with the results of numerous other studies that were included. However, up to 15% of patients included in their analysis switched anticoagulants during the follow-up, making it difficult to estimate the true risk difference between DOACs and warfarin. In 2 recent studies on the same topic, the impact owing to this issue is less discussed.[21,25] In this analysis, wherein we considered an intention-to-treat approach, the inclusion and exclusion of this study did not substantially alter the pooled effect and heterogeneity to the pooled effect, which affirmed the neutral results of the pooled analysis. To summarize, DOACs did not increase the risk of SSE in patients with LVT and they effectively reduced the risk of stroke as compared with VKAs, possibly because of its more consistent anticoagulant effects.

Moreover, we showed that the thrombus resolution rate was similar for DOAC and VKA users, which is consistent with the results of previous studies.[21,25] Notably, patients with MI receiving DOACs showed significantly higher rates of thrombus resolution compared with those using VKAs. These discrepancies could be due to the increased thrombotic burden after MI. In a recent meta-analysis by Low et al,[26] only triple therapy (dual antiplatelet therapy plus oral anticoagulant) was associated with a higher resolution rate of LVT after MI, while the anticoagulation alone was less effective, suggesting a need for more intensive antithrombotic treatment in patients with MI complicated by LVT. In patients with MI, LVT is dynamically formed

TABLE 2 Subgroup analysis of various outcomes for users of direct oral anticoagulants and vitamin K antagonists

Subgroups		SSE					Stroke					Failure of thrombus resolution					Any bleedings					Clinically relevant bleedings				
		N	RR (95% CI)	I^2, %	P	P_{int}	N	RR (95% CI)	I^2, %	P	P_{int}	N	RR (95% CI)	I^2, %	P	P_{int}	N	RR (95% CI)	I^2, %	P	P_{int}	N	RR (95% CI)	I^2, %	P	P_{int}
All		10	0.96 (0.8–1.16)	0	0.68	–	8	0.68 (0.47–1)	0	0.048	–	11	0.88 (0.72–1.09)	26	0.26	–	9	0.94 (0.67–1.31)	24	0.7	–	6	0.35 (0.13–0.92)	0	0.03	–
Follow-up duration	≥1 y	5	0.73 (0.52–1.05)	0	0.09	0.07	5	0.72 (0.42–1.25)	0	0.25	0.79	7	0.88 (0.69–1.13)	54	0.32	0.94	6	0.59 (0.35–1)	16	0.05	0.02	4	0.18 (0.04–0.77)	0	0.02	0.09
	<1 y	5	1.08 (0.86–1.34)	0	0.51		3	0.65 (0.39–1.1)	0	0.92		4	0.9 (0.59–1.35)	0	0.52		3	1.39 (0.88–2.19)	0	0.16		2	1.11 (0.25–4.96)	0	0.89	
Sample size	≥100	5	1.02 (0.84–1.23)	0	0.85	0.09	4	0.72 (0.48–1.08)	0	0.11	0.49	3	0.75 (0.52–1.07)	60	0.12	0.26	4	1.04 (0.72–1.5)	61	0.83	0.21	3	0.27 (0.07–1.05)	16	0.06	0.83
	<100	5	0.46 (0.19–1.12)	0	0.09		4	0.47 (0.15–1.46)	0	0.19		8	0.97 (0.74–1.26)	0	0.81		5	0.54 (0.21–1.4)	0	0.21		3	0.48 (0.11–2.02)	0	0.31	
Concomitant antiplatelet medication	Complete[a]	2	0.51 (0.09–3.04)	0	0.46	0.48	2	0.59 (0.1–3.6)	0	0.57	0.88	2	0.76 (0.5–1.17)	76	0.22	0.43	2	0.37 (0.17–0.81)	0	0.01	0.006	2	0.14 (0.02–1)	0	0.05	0.2
	Incomplete	8	0.97 (0.81–1.17)	0	0.77		6	0.69 (0.47–1.01)	0	0.06		9	0.93 (0.73–1.19)	9	0.56		7	1.25 (0.85–1.85)	0	0.26		4	0.61 (0.19–1.97)	0	0.41	
Primary cause of LVT	MI	2	0.34 (0.1–1.25)	0	0.11	0.09	1	0.49 (0.05–4.53)	–	0.63	0.76	2	0.57 (0.38–0.84)	0	0.005	0.006	2	0.22 (0.03–1.67)	0	0.14	0.14	2	0.14 (0.02–1.03)	0	0.05	0.23
	Mixed	8	1 (0.83–1.21)	0	0.96		7	0.69 (0.47–1.01)	0	0.96		9	1.09 (0.85–1.41)	0	0.47		7	1.02 (0.72–1.44)	26	0.91		4	0.57 (0.18–1.85)	0	0.35	
Types of DOACs	Apixaban ≥50%	3	1.11 (0.59–2.08)	0	0.75	0.63	1	0.81 (0.04–16.2)	–	0.89	0.91	2	1.02 (0.51–2.04)	0	0.96	0.67	1	1.05 (0.12–8.89)	–	0.96	0.91	1	1.05 (0.12–8.89)	–	0.96	0.28
	Apixaban <50%	7	0.94 (0.78–1.15)	0	0.56		7	0.68 (0.46–1)	0	0.048		9	0.87 (0.7–1.09)	40	0.22		8	0.93 (0.66–1.31)	34	0.69		5	0.28 (0.09–0.86)	0	0.03	

a Complete medication indicates all patients of a study received at least a single antiplatelet agent along with anticoagulants; incomplete medication indicates studies with some of patients receiving no antiplatelet agents or not reporting data on antiplatelet medications.

Abbreviations: MI, myocardial infarction; P_{int}, *P* for interaction; RR, risk ratio; SSE, stroke or systemic embolism; others, see **FIGURE 1** and **TABLE 1**

within a few days after the initial cardiac damage.[27,28] Moreover, the exposure of subendothelial layer because of myocardial necrosis intensifies the prothrombotic states, which could last as long as 6 months.[1,29] Therefore, it is reasonable to start effective and regular anticoagulation therapy as soon as possible to limit thrombus formation. However, the effects of VKAs peak in 72 to 96 hours after the initial dosage, before the existing clotting factors are depleted, whereas suboptimal control of INR is frequently reported in warfarin users.[7,23] Such disadvantages could have led to a reduced efficacy for thrombus resolution in patients with MI. In this scenario, DOACs could be reasonable alternatives to VKAs to provide an effective and safe triple therapy. In a recent study by Jones et al,[7] nearly 70% of patients were on triple therapy at discharge, among whom no embolic events occurred; in addition, DOAC users have demonstrated earlier resolution of LVT, which could be beneficial as existing thrombus could directly cause SSE.[7,23] To maximize the antithrombotic effect while controlling the risk of bleeding, triple therapy including aspirin, clopidogrel, and a lower dose of DOACs (eg, dabigatran 110 mg twice daily, rivaroxaban 15 mg once daily, or apixaban 2.5 mg twice daily) has been proved feasible in several cases and endorsed by relevant consensus document for patients with MI in need of anticoagulation.[7,30-32] To sum up, DOACs and VKAs showed similar efficacy in thrombus resolution, while DOACs could be a more suitable choice for patients with MI.

Safety of direct oral anticoagulants and vitamin K antagonists This analysis showed that DOACs did not reduce the risk of any bleeding events in patients with LVT, but significantly lowered the risk of clinically relevant bleeding events compared with VKAs. These findings were consistent with those of previous studies regarding patients with atrial fibrillation and heart failure.[10,11] Notably, DOACs showed homogenous reduction in clinically relevant bleeding events across various subgroups, which could be very important for patients with LVT. Although the rate of life-threatening bleeding events was quite low with various anticoagulant agents,[5-7,9] there is still an increasing need for greater reduction in major bleeding events because oral anticoagulants are frequently prescribed in combination with antiplatelet agents for LVT patients with complex etiologies, which inevitably and substantially increases bleeding risk.[1,3,4] In case of any bleeding events, despite the neutral pooled effects, DOACs still showed lower bleeding rates during long-term follow-ups and in patients taking antiplatelet medications, which could be beneficial for improving the quality of life and adherence of patients in need of long-term anticoagulation or antiplatelet treatments.[33,34] Another issue to be noticed is the impact of comorbidities. In fact, chronic kidney disease (13.9%–36.2%) and cancer (4.8%–12.9%) are quite common in patients with LVT,[7,9,20-22] which might substantially increase bleeding events during anticoagulation.[35,36] Current evidence generally suggests that the use of DOACs in patients with these comorbidities is associated with lower risk of bleeding as compared with VKAs, although its clinical benefit becomes diminished or inconclusive with the progression of underlying diseases.[36] Considering the reduced risk of clinically relevant bleedings, DOACs might be more reasonable choices as primary anticoagulants for patients with LVT complicated by relevant comorbidities increasing the risk of bleeding. Moreover, physicians need to individualize anticoagulation for such patients based on careful consideration regarding the risk of SSE, bleeding, and patient preferences. To summarize, DOACs possessed a better safety profile than VKAs because they effectively reduced clinically important bleeding events and showed a potential to reduce overall bleeding rates in patients on long-term and intense antithrombotic treatment.

Limitations The general limitations of this meta-analysis are as follow. Firstly, only observational studies were included in the current analysis. Although baseline characteristics were generally consistent among DOAC and VKA users in most of the included studies, confounding effects could be present due to no adjustment from individual data. Besides, some of the included studies were published as abstracts only and might have not undergone strict review. Secondly, the regimen and dosage of DOACs were different in each study, which might undermine its comparability with VKAs in pooled analysis. Thirdly, bleeding outcomes were not reported according to standard definitions (like the Bleeding Academic Research Consortium classification). Future well-designed RCTs could be safely initiated to assess efficacy of DOACs and VKAs in patients with LVT based on the evidence from the current analysis.[37]

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/paim.

ARTICLE INFORMATION

ACKNOWLEDGMENTS This study was supported by the Chinese Academy of Medical Sciences Innovation Fund for Medical Sciences (2016-I2M-1-009; to HY), National Natural Science Foundation of China (81970308; to HY) and the Fund of "Sanming" Project of Medicine in Shenzhen (SZSM201911017; to HJ).

We sincerely thank Dr Raviteja R. Guddeti (Creighton University School of Medicine) for helping us perform the current analysis by providing necessary outcomes data, and Dr Weida Liu (Medical Research & Biometrics Center, Fuwai Hospital) for his professional advice in statistical analysis.

CONTRIBUTION STATEMENT RC and HY contributed to the concept or design of the work. RC, JZ, CL, PZ, JL, XZ, YW, YC, LS, and HZ contributed to the acquisition, analysis, or interpretation of data. RC, JZ, and LS drafted the manuscript. RC, HZ, and HY critically revised the manuscript. All authors gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

CONFLICT OF INTEREST None declared.

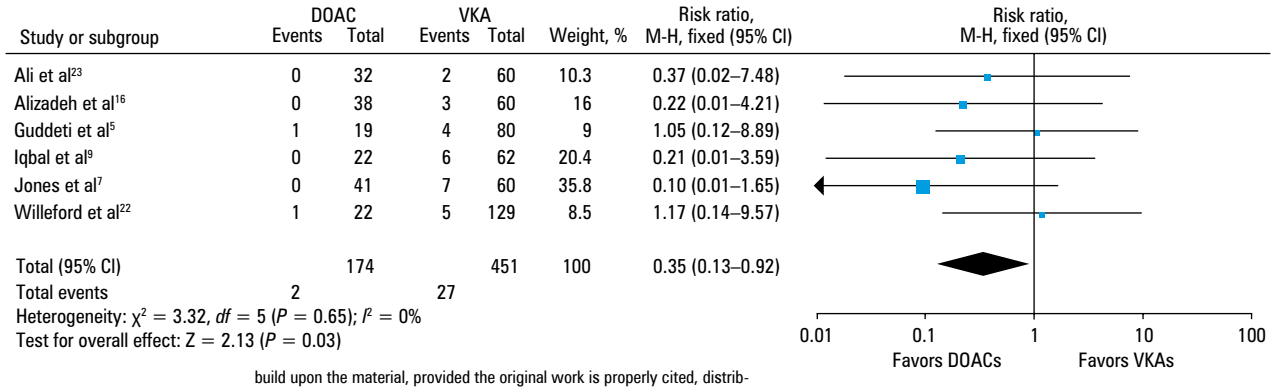

FIGURE 6 Forest plot for the comparative risk of clinically relevant bleeding events with direct oral anticoagulants (DOACs) versus vitamin K antagonists (VKAs)

HOW TO CITE Chen R, Zhou J, Liu C, et al. Direct oral anticoagulants versus vitamin K antagonists for patients with left ventricular thrombus: a systematic review and meta-analysis. Pol Arch Intern Med. 2021; 131: 429-438. doi:10.20452/pamw.15923

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