ORIGINAL ARTICLE

A META-ANALYSIS FOR THE EFFICACY AND SAFETY OF DIRECT ORAL ANTICOAGULANTS VERSUS VITAMIN K ANTAGONISTS FOR LEFT VENTRICULAR THROMBUS

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Objectives: The objective of this updated meta-analysis is to consolidate high-quality peer-reviewed clinical evidence, including trials and observational studies, to evaluate the efficacy and safety of "direct oral anticoagulants (DOACs)" versus "vitamin K antagonists (VKAs)" for treating "left ventricular thrombus (LVT)".

Methodology: We included studies of either "observational" or "experimental" in nature reported original data for the head-to-head comparison of "DOACs" and "VKAs" for the treatment of LVT. The efficacy-related outcome of interest was "thrombus resolution" and safety-related outcomes of interest were; "mortality", "major bleeding", and "stroke". The "risk ratios (RRs)" for each outcome variable were calculated using the "Mantel-Haenszel method".

Results: The analysis included 19 studies comprised of 3,027 patients diagnosed with LVT. Among them, 881 received DOAC treatment, while 2,146 were treated with VKAs. DOACs showed comparable rates of LVT resolution (RR: 1.00 [0.93 – 1.08]), lower mortality incidence (RR: 0.65 [0.51 – 0.84]), similar stroke incidence (RR: 0.83 [0.61 – 1.14]), and similar major bleeding incidence (RR: 0.71 [0.50 – 1.00]) compared to VKAs.

Conclusion: The meta-analysis indicates that DOACs are as effective as VKAs for treating LVT, showing comparable thrombus resolution rates, lower all-cause mortality, similar stroke risks, and clinically relevant bleeding across studies. However, these conclusions are limited by the lack of evidence from large-scale randomized studies and high-quality real-life clinical data.

Keywords: meta-analysis, left ventricular thrombus, direct oral anticoagulants, vitamin K antagonists, efficacy, safety

Citation: Chand G, Hameed A, Bibi R, Balouch IJ, Haq IU, Raza MT, Raheem A. A Meta-Analysis for the Efficacy and Safety of Direct Oral Anticoagulants versus Vitamin K Antagonists for Left Ventricular Thrombus. Pak Heart J. 2023;56(03):211-218. DOI: https://doi.org/10.47144/phj.v56i3.2611

INTRODUCTION

The "left ventricular thrombus (LVT)" formation is a known complication in patients with left ventricular dysfunction, particularly after acute myocardial infarction, and it can also occur in patients with non-ischemic cardiomyopathy.[1] In the past, before reperfusion techniques were advanced, "myocardial infarctions (MIs)" were frequently complicated by the development of LV thrombi.[2] Historically, the incidence of LVT following an MI ranged from 21% to as high as 46%.[1] However, with the progress in reperfusion techniques, the prevalence of LV thrombi has significantly decreased, with rates now ranging from 1.6% to 5% in patients with "ST-segment elevation MI (STEMI)" and up to 9.1% in patients with anterior STEMI.[3] The time frame for LVT formation after acute MI varies, occurring anywhere between 1 day and up to 2 weeks.[2]

LVT poses significant challenges to patient recovery due to the risk of embolization or stroke if the thrombus gets dislodged. However, appropriate anticoagulation therapy can reduce this risk.[4] While current guidelines recommend "vitamin-K antagonists (VKAs)" like warfarin as the standard anticoagulation therapy for LVT,[5,6] VKAs have certain limitations, including the slow onset of action, a narrow therapeutic range, the need for regular monitoring of the international "normalized ratio (INR)", dietary restrictions, and potential drug interactions.[7]

As a result, off-label use of "direct oral anticoagulants (DOACs)" has become increasingly popular among patients and physicians. DOACs offer consistent anticoagulation effects without requiring continuous INR monitoring.[8,9] These agents are approved for non-valvular atrial fibrillation, venous thromboembolism, and other hypercoagulable conditions,[10] and they have

become the preferred treatment option for many eligible patients, including those with LVT. However, there is still a lack of prospective, randomized data to determine the best anticoagulation regimen specifically for LVT.[11]

DOACs may be a promising alternative to VKAs, offering advantages such as a rapid onset of action, stable drug concentration, fewer interactions, and a lower rate of bleeding events.[12] Despite this potential, DOACs as an anticoagulant treatment for patients with LVT remain off-label. Existing evidence on the safety and efficacy of DOACs compared to VKAs for LVT treatment comes from various case studies, retrospective observational studies, and a few small-scale "randomized control trials (RCTs)".[12] However, these studies have produced conflicting or similar results, and several meta-analyses have been conducted. The main limitation of these meta-analyses is the inclusion of conference abstracts and studies with low methodological quality. Therefore, this updated meta-analysis aims to consolidate high-quality peer-reviewed clinical evidence, including trials and observational studies, to evaluate the efficacy and safety of DOACs versus VKAs for treating LVT.

METHODOLOGY

The "Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)" guidelines are adopted for the reporting of this meta-analysis.[13]

Literature sources: We have assigned two independent investigators to carry out a literature search through electronic databases, libraries, and search engines that included "PubMed/MEDLINE", "EMBASE", "Web of Science", "Cochrane Library", and "Google Scholar". Additionally, current and past issues of major cardiology journals have also been reviewed to identify any relevant literature.

Search strategy: Both of the investigators agreed to a pre specified search string that consisted of a combination of mesh terms and logical operators, which included "left ventricular", "LV", "thrombus", "clot", "thrombi", "LVT", "vitamin K antagonists", "VAK", "warfarin", "novel oral anticoagulants", "non-vitamin K antagonist anticoagulants", "NOACs", "direct oral anticoagulants", "DOACs", "rivaroxaban", "apixaban", "dabigatran", or "edoxaban". The literature search frame was limited from January 2020 to May 2023. Additionally, the reference list of already published systematic reviews and meta-analyses were also screened for the relevant literature.

Study selection criteria: The primary inclusion criteria was any study of either "observational" or "experimental" in nature reported original data for the head-to-head comparison of "DOACs" and "VKAs" for the treatment of LVT. However, this meta-analysis did not include conference abstracts, case reports, single-arm case series, and studies that failed to meet the minimum methodological quality. Additionally, studies published in a language other than English or in a non-peer-reviewed journal were excluded from the analysis.

The outcome of interest: The efficacy-related outcome of interest was "thrombus resolution" and safety-related outcomes of interest were; "mortality", "major bleeding", and "stroke".

Assessment of quality: The methodological quality of the studies was assessed by two independent reviewers using standard quality assessment criteria. The RCTs were assessed for methodological quality with the help of Jadad scoring, and studies with a score of ≥3 over the range of 0 to 5 were considered good quality.[14] The Newcastle-Ottawa scale (NOS) was used for the methodological quality assessment of observational studies, and studies with a score of ≥6 over the range of 0 to 9 were considered good quality.[15]

Statistical Analysis: The Mantel-Haenszel method was used to compute the "relative risk (RR)" and "corresponding 95% confidence interval (CI)" to compare "DOACs" versus "VKAs" for the rate/risk of "LVT resolution", "mortality", "major bleeding", and "stroke". Cochran's Q statistic and Higgins' and Thompson's I^2 statistics were calculated to assess the heterogeneity among the studies. The fixed effect or random effect model was applied based on the heterogeneity assessment. The open-source software R (version 4.3.1) was used to conduct this meta-analysis with the help of packages "metasens" and "meta".

RESULTS

Literature screening: The initial search on electronic databases, using a predefined search string, yielded a total of 2,616 results. To eliminate duplicates, 1,104 redundant records were removed, leaving 1,512 unique articles. Among these, 1,469 articles were excluded as they consisted of case reports, case series, reviews, meta-analyses, or single-armed studies, leaving 43 articles for further screening. After a thorough assessment, 19 studies were deemed eligible for inclusion in this meta-analysis (as shown in Figure 1).

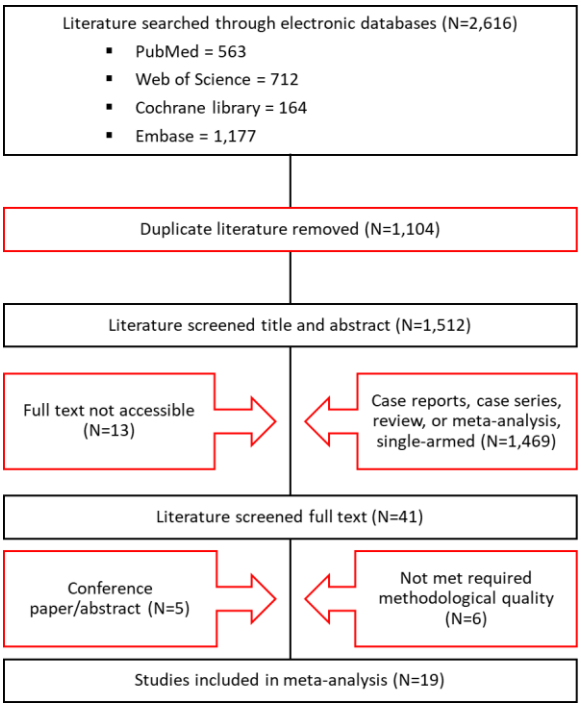

Figure 1: Study selection flow chart

Study characteristics: Out of the 19 selected studies, three were randomized clinical trials, while the remaining 16 were observational studies.[3,16-33] The combined dataset from these studies involved a total of 3,027 patients diagnosed with LVT. Of these patients, 881 were treated with DOACs, and the remaining 2,146 received VKAs. The follow-up duration across the studies ranged from 3 to 40 months, providing valuable insights into the long-term effects of the treatments. The quantitative synthesis of clinical characteristics for the included studies is summarized in Table 1.

Thrombus resolution: The resolution of LVT was reported by 17 studies at varying duration ranging from 3 to 36 months. The crude cumulative LVT resolution rate was 65.3% with DOACs and 63.3% with VAKs. A similar proportion of LVT resolution was reported for DOACs as compared to VAKs with a pooled OR of 1.00 [95% CI: 0.93 – 1.08], and there was no heterogeneity with I^2=0%; p=0.69, Figure 2.

Mortality: The mortality was reported in 11 studies. The crude death rate was 14.1% in the DOACs group and 22.7% in the VAKs group. There was a lower incidence of mortality with DOACs as compared to VAKs with a pooled RR of 0.65 [95% CI: 0.51 – 0.84], and there was no heterogeneity among the studies with I^2=10%; p=0.35, Figure 3A.

Stroke: The incidence of stroke was reported by 18 studies. The crude incidence rate of stroke was 7.5% vs. 8.7% for DOACs vs. VAKs groups. There was a similar incidence of stroke with DOACs as compared to VAKs with a pooled RR of 0.83 [95% CI: 0.61 – 1.14], and there was no heterogeneity among the studies with I^2=4%; p=0.41, Figure 3B.

Major bleeding: The incidence of major bleeding was reported by 16 studies. The crude incidence rate of major bleeding was 6.4% vs. 6.4% for DOACs vs. VAKs groups. There was a similar incidence of major bleeding with DOACs compared to VAKs with a pooled RR of 0.71 [95% CI: 0.50 – 1.00] and no heterogeneity among the studies with I^2=0%; p=0.59, Figure 3C.

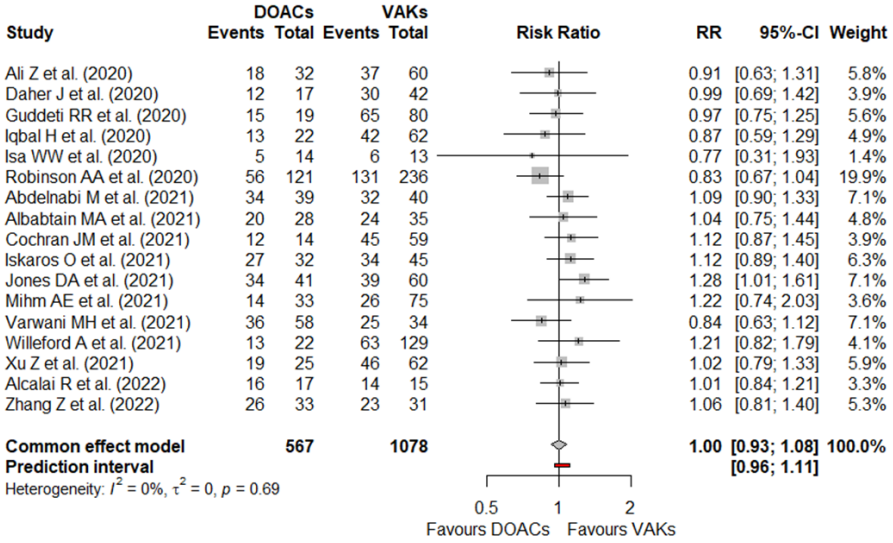

Figure 2: Forest plot for major adverse cardiovascular events

DOACs="Direct Oral Anticoagulants", VAKs="vitamin K antagonists", RR="risk ratio", CI="confidence interval"

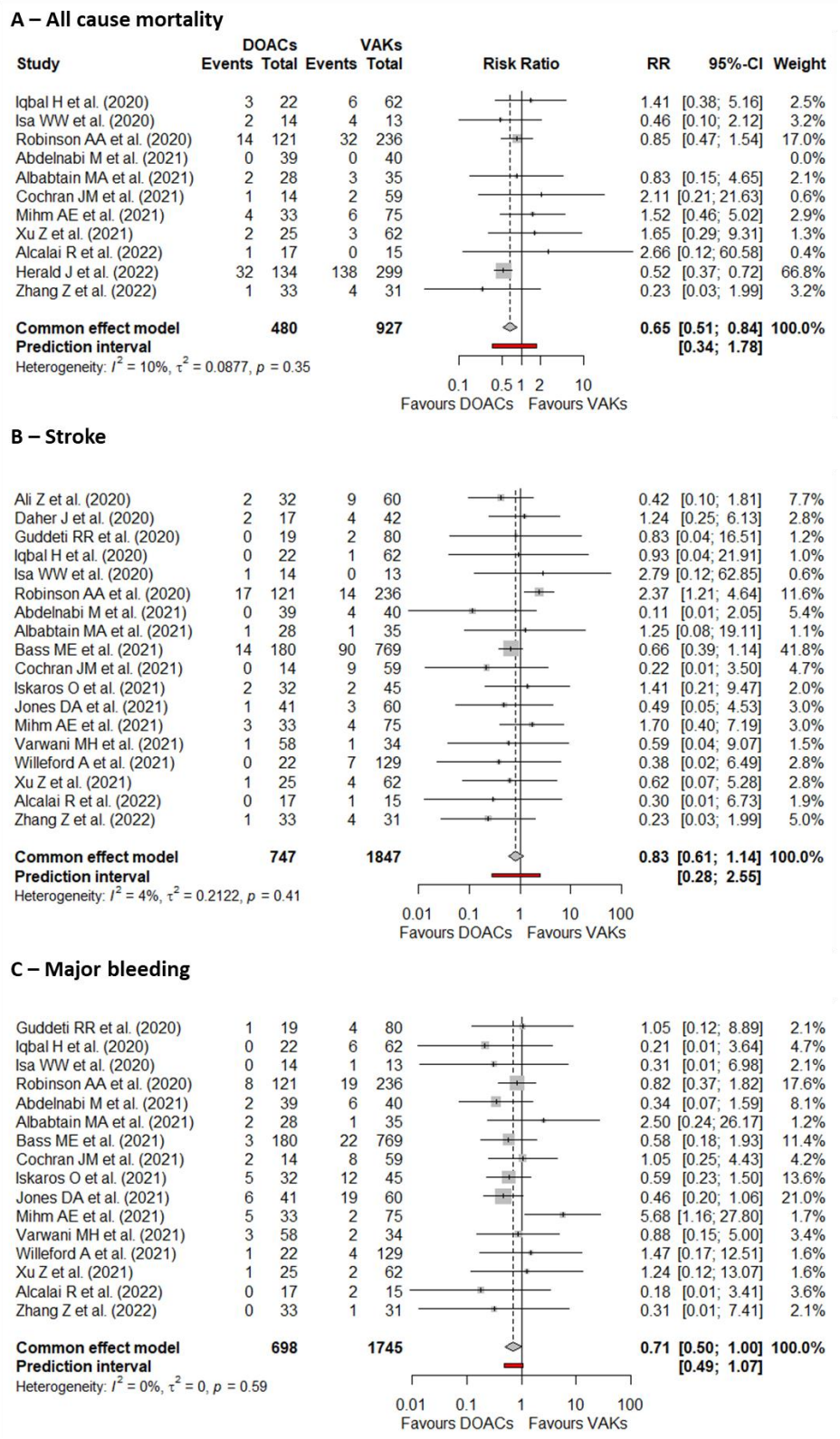

Figure 3: Forest plot for all-cause mortality (A), myocardial infarction (B), target vessel/lesion revascularization (C), and stent thrombosis (D)

DOACs="Direct Oral Anticoagulants", VAKs="vitamin K antagonists", RR="risk ratio", CI="confidence interval"

Table 1: Distribution of patients' medical history and clinical characteristics among included trial

Reference Number	Study	Study Design	Quality	Follow-up (months)	Total Patients		Male		Age (mean years)		Hypertension		Diabetes	
					DOACs	VKAs	DOACs	VKAs	DOACs	VKAs	DOACs	VKAs	DOACs	VKAs
16	Ali Z et al. (2020)	OBS	6	12	32	60	26	49	59	58	-	-	12	18
3	Daher J et al. (2020)	OBS	6	3	17	42	14	35	57	61	10	17	2	9
17	Guddeti RR et al. (2020)	OBS	6	12	19	80	15	55	61	61	15	61	3	34
18	Iqbal H et al. (2020)	OBS	8	36	22	62	20	55	62	62	9	18	19	19
29	Isa WW et al. (2020)	RCT	4*	3	14	13	-	-	-	-	-	-	-	-
20	Robinson AA et al. (2020)	OBS	9	12	121	236	94	170	58	58	86	177	36	92
21	Abdelnabi M et al. (2021)	RCT	4*	6	39	40	-	-	-	-	-	-	-	-
22	Albabtain MA et al. (2021)	OBS	7	12	28	35	24	34	58	59	13	19	12	16
23	Bass ME et al. (2021)	OBS	8	3	180	769	125	545	63	62	-	-	-	-
24	Cochran JM et al. (2021)	OBS	6	12	14	59	11	45	52	62	-	-	7	23
25	Iskaros O et al. (2021)	OBS	7	3	32	45	29	41	62	62	-	-	-	-
26	Jones DA et al. (2021)	OBS	9	26	41	60	33	51	59	61	23	22	7	10
27	Mihm AE et al. (2021)	OBS	8	6	33	75	23	54	63	60	24	56	8	20
28	Varwani MH et al. (2021)	OBS	6	12	58	34	-	-	-	-	-	-	-	-
29	Willeford A et al. (2021)	OBS	8	8	22	129	17	104	54	56	8	54	4	37
30	Xu Z et al. (2021)	OBS	7	27	25	62	19	47	59	62	10	27	6	12
31	Alcalai R et al. (2022)	RCT	4*	3	17	15	-	-	-	-	-	-	-	-
32	Herald J et al. (2022)	OBS	8	40	134	299	-	-	66	66	-	-	-	-
33	Zhang Z et al. (2022)	OBS	8	24	33	31	24	23	60	61	23	11	10	5

OBS=observational, DOACs="Direct Oral Anticoagulants", VAKs="vitamin K antagonists", RCT="randomized controlled trial"
**Study methodological quality assessed using Jadad scoring*

DISCUSSION

This systematic review aimed to assess if DOACs can be a viable alternative to VAKs in the treatment of LVT. Our analysis findings show potential evidence to support the use of DOACs over VAKs with respect to the outcomes of LVT resolution, stroke, or major bleeding. In addition, there is evidence that DOACs result in a lower incidence of mortality in this population.

DOACs represent a more recent class of anticoagulants, with the first agent approved by the "Food and Drug Administration (FDA)" in 2010. These drugs are indicated for treating conditions like venous thromboembolism and non-valvular atrial fibrillation. Factor Xa inhibitors, including rivaroxaban, edoxaban, and apixaban, work by competitively inhibiting factor Xa in the coagulation cascade's common pathway, effectively preventing thrombin formation.[1] On the other hand, dabigatran, a direct thrombin inhibitor, reversibly inhibits both free and fibrin-bound thrombin, inhibiting thrombin-mediated platelet aggregation.[34]

In recent years, DOACs (off-label) have gained popularity for LVT treatment among physicians and patients. This popularity is attributed to their ease of administration, lesser dietary restrictions, and the advantage of not requiring regular blood draws.[8,9] The convenience and practicality of DOACs have contributed to their increasing acceptance and utilization in the management of LVT.

In recent years, DOACs have emerged as a promising alternative to VKAs in various medical conditions, including pulmonary embolism, non-valvular atrial fibrillation, and deep vein thrombosis.[10] Studies have shown that DOACs are generally safe and effective, with fewer drug interactions than VKAs.[11] However, despite these positive findings, current guidelines still recommend VKAs as the preferred treatment for patients with LVT due to a lack of sufficient evidence supporting the use of DOACs in this specific setting.[5,6]

Our analysis predominantly favored DOACs, with most studies indicating comparable or better outcomes than VKAs. Nonetheless, a few studies reported an increased risk of thromboembolic events associated with DOACs. For instance, Robinson et al.[21] found that compared to VKAs, DOAC is associated with a 2.6-fold higher risk of systemic embolism and stroke. The pooled stroke rates were 7.5% in the DOAC group and 8.7% in the VKA group. While these rates were lower than those reported by Lattuca et al.[35] (22%), they were higher than the rates from the review conducted by Daher et al.,[3] which showed embolic events of 0 to 2.6% in LVT treated with DOACs. One significant confounding factor in embolic events was atrial fibrillation (AF). However, AF was not associated with an increased risk of systemic embolism and stroke compared to patients without AF in both Robinson et al. and Lattuca et al.[21,35] In fact, the risks of stroke and systemic embolism were even lower in patients with AF, likely due to the necessity of long-term anticoagulation in AF patients. More studies are needed to evaluate the effect of DOACs on stroke and systemic embolism in patients without AF.[36]

Another critical consideration is the concurrent use of antiplatelet therapy, which is widespread in clinical practice. However, the risk of stroke and systemic embolism was significantly affected by the use of antiplatelet medications in the investigation by Robinson et al.,[21] most likely due to the fact that most of the patients in this study had underlying coronary artery disease. Further research is necessary to assess the impact of antiplatelet therapy on LVT, apart from its combination with anticoagulant medications.[36]

Regarding LVT resolution, our analysis found that the rates were similar between the DOAC and VKA groups with a pooled OR of 1.00 [95% CI: 0.93 – 1.08]. Out of the 19 studies, 17 were eligible for assessing LVT resolution. All included studies had a follow-up duration of at least three months, in line with current recommendations.[5,6] The "2013 ACCF/AHA Guideline for the Management of ST-Elevation MI" suggests anticoagulant treatment for 3 to 6 months, and this is also recommended in the European 2017 STEMI guideline.[5,6]

In this meta-analysis, the pooled rates of LVT resolution were 65.3% vs. 63.3% in the DOAC and VKA groups. The rate of resolution of LVT is consistent with the reported rate by Lattucca et al., in which a complete resolution rate of 62% was observed after a 1.7-year follow-up.[35] Similarly, Daher et al. conducted a literature review of 104 patients, comprised of small observational studies and 20 case reports, and reported 80% resolution of LVT with DOACs.[3] Furthermore, regardless of the anticoagulation treatment strategies, a 64% LVT resolution rate has been reported by Robinson et al.[21]

Notably, Jones et al.[27] reported that DOACs demonstrated quicker thrombus resolution throughout their follow-up period than the VKA group, with an odds ratio of 1.8 (95% CI: 1.2 - 2.9). These findings are encouraging and suggest that DOACs may have an advantage in promoting more rapid LVT resolution.

Regarding bleeding risk, DOACs were comparable to VKAs in the treatment of LVT, with pooled bleeding events observed at 6.4% in both the DOAC and VKA groups. These results align with findings from previous studies.[3,35] Interestingly, the risks of bleeding were inversely correlated with the resolution of LVT, indicating that successful resolution may lead to a reduced risk of bleeding.[35]

Moreover, our meta-analysis revealed a significantly lower mortality rate in the DOAC group, with a pooled relative risk (RR) of 0.65 [95% CI: 0.51 – 0.84]. These findings suggest that DOACs may offer equal or potentially better safety and efficacy than VKAs in treating LVT. Although current guidelines do not recommend DOACs as a first-line treatment for LVT due to limited evidence, our meta-analysis strengthens the existing recommendations and supports considering the broader use of DOACs in this context.

This meta-analysis has several limitations that should be taken into account. Firstly, the included studies utilized different DOAC regimens, potentially leading to variations in efficacy and safety levels among the different DOACs. Secondly, our meta-analysis comprised only three randomized controlled trials (RCTs) and 14 observational studies, most of which were retrospective with small sample sizes. Consequently, further high-quality, large-scale, randomized clinical trials are necessary to corroborate and strengthen our findings.

Thirdly, critical factors require more investigation for a comprehensive assessment of outcomes. These factors include the LVT diagnostic method, where

improved confirmation methods such as delayed enhancement CMRI or transesophageal echocardiography may enhance accuracy. Additionally, the impact of dual antiplatelet therapy strategies needs to be clarified, as it directly influences bleeding and stroke outcomes. The follow-up duration is also crucial for effectively assessing mortality and LVT resolution rates. Lastly, the specific types and dosages of DOACs may have varying effects on individual patient efficacy, necessitating more in-depth research.

Despite these limitations, our meta-analysis contributes valuable insights to the current knowledge on DOACs' role in treating LVT. By highlighting these limitations, we hope to encourage further investigation and prompt the design of more robust studies to strengthen the evidence base, ultimately guiding clinicians in making well-informed decisions regarding the optimal management of patients with LVT.

CONCLUSION

The findings from this comprehensive meta-analysis indicate that DOACs are as effective as VKAs in treating patients with LVT. The analysis revealed a comparable rate of thrombus resolution between the two treatment options. Moreover, DOAC therapy was associated with a lower incidence of all-cause mortality than VKAs. Additionally, the risk of stroke and clinically relevant bleeding was found to be similar between the two groups, and the results showed a high degree of homogeneity among the available studies.

However, it is essential to acknowledge that these conclusions have certain limitations due to the absence of evidence from large-scale randomized studies and the reliance on varying quality real-life clinical data. The lack of extensive randomized trials hinders the ability to draw definitive conclusions on the superiority of one treatment over the other. Additionally, the inclusion of real-life clinical evidence introduces inherent variations in study design, patient characteristics, and treatment protocols, which could potentially impact the overall outcomes.

Therefore, while the results suggest promising outcomes for DOACs as a treatment option for LVT, it is crucial to interpret these findings with caution. Further research, especially large-scale randomized studies with robust methodologies, is warranted to validate and strengthen the current evidence. By addressing these limitations, future studies can provide more robust and reliable insights into the optimal anticoagulation therapy for patients with LVT, helping clinicians make more informed and evidence-based decisions for their patient's care.

AUTHORS' CONTRIBUTION

GC, AH, RB and AR: Concept and design, data acquisition, interpretation, drafting, final approval, and agree to be accountable for all aspects of the work. IJB, IUH, and MTR: Data acquisition, interpretation, drafting, final approval and agree to be accountable for all aspects of the work.

Conflict of interest: Authors declared no conflict of interest.

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