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ORIGINAL RESEARCH

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Direct oral anticoagulants (DOAC) versus vitamin K antagonist in left ventricular thrombus: An updated meta-analysis

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Abstract

Background and Aims: Current clinical guidelines for treating left ventricular thrombus (LVT) are limited by inadequate evidence to inform the comparative efficacy of oral anticoagulants. In this meta-analysis, we aimed to compare the efficacy and safety of direct oral anticoagulants (DOAC) to vitamin K antagonists (VKA) in patients with LVT.

Methods: Four standard databases were searched for relevant literature comparing the efficacy and safety between DOAC and VKA for LVT treatment, published before August 19, 2023. Both the randomized controlled trials and observational studies were included in the analysis. The outcomes of interest were the resolution of LVT, all-cause mortality, stroke, systemic embolism, and bleeding. Data from the selected studies were extracted and analyzed using RevMan 5.4 using odds ratio.

Results: Among 3959 studies from the database search and bibliography review, 33 were included in the analysis. LVT resolution was observed in 72.59% in the DOAC group versus 67.49% in the VKA group (odds ratio [OR]: 1.28, confidence interval [CI]: 1.07–1.53). Mortality was lower in the DOAC group (11.71% vs. 18.56%) (OR: 0.60, CI: 0.36–1.00; borderline statistical significance). Likewise, bleeding events (9.60% vs. 13.19%) (OR: 0.65, CI: 0.52–0.81) and stroke (7.54% vs. 11.04%) (OR: 0.71, CI: 0.53–0.96) were also significantly lower in the DOAC group.

Conclusion: DOAC use for LVT showed better thrombus resolution and reduced risk of bleeding and stroke compared to VKA. Likewise, DOAC use was associated with lower mortality with borderline statistical significance.

KEYWORDS

direct oral anticoagulant, left ventricle thrombus, vitamin K antagonist

1 | INTRODUCTION

Left ventricular thrombus (LVT) formation is a clinically significant occurrence in patients with acute myocardial infarction involving the left ventricular (LV) apex.[1] It is also relatively common in patients with cardiomyopathy and reduced LV ejection fraction, owing to Virchow's triad.[2] Vitamin K antagonists (VKA) have been the standard of care for treating and preventing LVT in these high-risk individuals.[3] However, with the growing evidence for the efficacy and safety of direct oral anticoagulants (DOAC), these newer agents are increasingly considered for use among this subset of patients.[4–25]

Data for the efficacy of DOACs in this population have come from smaller studies with controversial results, and there is still conflicting data to prove the superiority of DOAC over VKA in LVT management. An earlier meta-analysis of 14 studies showed no significant difference in LVT resolution among DOAC versus VKA groups. Still, it did show a reduced risk of stroke and bleeding with DOAC compared to VKA.[26] However, the most recent American Heart Association (AHA) scientific statement on LVT management does not provide definitive recommendations on which agent is the preferred first-line therapy for LVT.[3] Given the lack of clear evidence or guidelines supporting one treatment modality, we aimed to evaluate and synthesize the available data to add to the existing pool of knowledge.

2 | METHODS

We used the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines.[27] The study protocol was duly registered in the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42022375148).[28] Participant Intervention Comparator and Outcome framework was employed to formulate the review questions.

2.1 | Criteria for considering studies for this review

2.1.1 | Types of studies

Randomized controlled trials (RCT) and observational studies comparing the efficacy and safety of VKA versus DOAC in patients with LVT were included in the review. Studies without the comparison between the two treatment arms were excluded. Viewpoints, case reports, case series, conference proceedings, editorials, and comments were excluded. Only the full-text articles have been included in the review and the meta-analysis.

2.1.2 | Type of participants

Patients aged >18 years with LVT treated with DOAC were considered participants in the study arm. Similarly, those with LVT being treated with VKA comprised the control arm.

2.1.3 | Outcomes

The impact of factors affecting clinical outcomes, including age and comorbidities, were extracted in the study and the control arms. The outcome of interest included LVT resolution, mortality, bleeding events, stroke, and systemic embolism.

2.2 | Search methods for identification of studies

We performed an extensive literature search in PubMed, PubMed Central, Scopus, and Embase. We have included relevant studies that compared the efficacy and safety of DOAC versus VKA published till August 2023. Bibliography lists from previously published meta-analyses were also reviewed to look for any possibly relevant studies that might have been overlooked during the search and extraction processes.

2.2.1 | Electronic searches

The detailed search strategy has been attached in Supporting Information: 1.

2.3 | Data analysis

2.3.1 | Selection, data extraction, and management of studies

Covidence systematic review software was used to screen studies in the title/abstract and full-text review phase.[29] The title/abstract and full-text review were performed independently by two reviewers (B.D. and S.D.), and any conflicts were resolved by the third reviewer (D.B.S.). Relevant data from each included study were extracted independently into Microsoft Excel Spreadsheet by two reviewers (S.D. and B.D.) and cross-checked by a third reviewer (D.B.S.). The disagreements on the extracted data were resolved by the consensus of the three independent reviewers. The corresponding author was contacted in the paper with incomplete data reporting to clear the doubt and get the relevant information.

2.3.2 | Assessment of risk of bias in included studies

The assessment of the quality of the included studies was independently performed by two reviewers (B.D. and S.D.). Joanna Briggs Institute's (JBI) critical appraisal tool was used to assess the quality of the included observational studies.[30] The risk of bias assessment tool (RoB 2) was used to assess the risk of bias in the clinical trials.[31] A table summarizing the risk of bias is presented in (Supporting Information: Tables 1 and 2).

TABLE 1 Baseline characteristics of the included studies, participants, and important comorbidities.

Author	Year	Country	Type of study	*N*	Treatment status	Number of participants	Age (years)	Sex (female)	Important comorbidities in percentage				
									CAD/IHD	HTN	CHF	CKD	Type 2 DM
Cochran et al.[8]	2021	USA	Observational study	73	Warfarin	59/73	62.0 (34.0–84.0)	14/59	61	Not available (NA)	81	37	39
					DOAC	14/73	51.5 (39.0–73.0)	3/14	53	NA	73	33	47
Alcalai et al.[24]	2021	Israel	RCT	35	Warfarin	17/35	58.8 (10.2)	2/17	17.64	41.17	NA	5.88	29.41
					DOAC	18/35	55.5 (12.9)	5/18	22.22	38.88	NA	16.66	44.44
Bass et al.[25]	2021	USA	Observational study	949	Warfarin	769/949	61.6 (15.3)	224/769	57.6	NA	74.5	34.9	NA
					DOAC	180/949	63.4 (16.70	55/180	42.8	NA	68.3	29.4	NA
Daher et al.[14]	2020	France	Observational study	59	Warfarin	42/59	61 (13)	7/42	74	40.5	NA	NA	21.4
					DOAC	17/59	57 (14)	3/17	88	59	NA	NA	12
Iqbal et al.[7]	2020	UK	Observational study	84	Warfarin	62/84	62 (14)	7/62	NA	29	94	NA	19/62
					DOAC	22/84	62 (13)	2/22	NA	41	95	NA	19/22
Herald et al.[5]	2022	USA	Observational study	433	Warfarin	299/433	65 (55.73)	57/299	35.8	72.6	88.3	38.8	41.5
					DOAC	134/433	66 (57.75)	18/134	35.1	67.2	88.1	32.1	33.6
Guddeti et al.[23]	2020	USA	Observational study	99	Warfarin	80/99	61.3 (12.2)	25/80	66.3	76.3	96.3	NA	43
					DOAC	19/99	60.7 (13.1)	4/19	57.9	79	100	NA	15.3
Jones et al.[21]	2020	UK	Observational study	111	Warfarin	60/111	66.8 1 (14.3)	9/60	NA	36.4	NA	8.3	16.7
					DOAC	41/111	58.73 (14.2)	7/41	NA	60.5	NA	12.1	18.4
Mihm et al.[20]	2021	USA	Observational study	108	Warfarin	75/108	60.3 (13.9)	21/75	NA	74.7	NA	14.7	26.7
					DOAC	33/108	63.3 (14.4)	10/33	NA	72.7	NA	21.2	24.2
Robinson et al.[9]	2020	USA	Observational study	357	Warfarin	236/357	58.2 (15.1)	66/236	NA	75	NA	NA	39
					DOAC	121/357	58.1 (14.9)	27/121	NA	71.7	NA	NA	29.8
Willeford et al.[6]	2020	USA	Observational study	151	Warfarin	129/151	56 (49-65.5)	25/129	NA	41.9	85.3	NA	NA
					DOAC	22/151	54 (48-64)	5/22	NA	36.4	86.4	NA	NA
Zhang et al.[17]	2021	China	Observational study	64	Warfarin	31/64	61.3 (009)	8/31	NA	35.5	NA	NA	5/31
					DOAC	33/64	60.3 (14.7)	9/33	NA	69.7	NA	NA	10/33
Albabtain et al.[18]	2021	Saudi-Arabia	Observational study	63	Warfarin	35/63	59 (15.62)	1/35	NA	54.3	NA	NA	16/35

(Continues)

TABLE 1 (Continued)

Author	Year	Country	Type of study	*N*	Treatment status	Number of participants	Age (years)	Sex (female)	Important comorbidities in percentage				
									CAD/IHD	HTN	CHF	CKD	Type 2 DM
					DOAC	28/63	58.25 (17.73)	4/28	NA	46.4	NA	NA	12/28
Varwani et al.[16]	2021	Kenya	Observational study	92	Warfarin	34/92	NA	NA	NA	NA	NA	NA	NA
					DOAC	58/92	NA	NA	NA	NA	NA	NA	NA
Xu et al.[10]	2021	China	Observational study	87	Warfarin	62/87	61.9 (12.2)	15/62	NA	43.5	NA	NA	19.4
					DOAC	25/87	59.4 (11.5)	6/25	NA	40	NA	NA	24
Yang et al.[15]	2022	China	Observational study	276	Warfarin	199/276	49.3 (15.1)	39/199	50.8	30.7	57.3	5.5	NA
					DOAC	77/276	45.3 (17.2)	12/77	39	29.9	55.8	1.3	NA
Isa et al.[19]	2021	Malasiya	RCT	27	Warfarin	13/27	55 (11.42)	1/13	NA	69.2	NA	35.7	69.2
					DOAC	14/27	55.36 (11.04)	1/14	NA	67.1	NA	53.8	50
Ali et al.[22]	2020	USA	Observational study	92	Warfarin	60/92	58 (16.3)	11/60	NA	NA	75	NA	30
					DOAC	32/92	59.2 (11.9)	6/32	NA	NA	78.1	NA	37.5
Abdelnabi et al.[13]	2021	Egypt and Bulgaria	RCT	79	Warfarin	40/79	NA	NA	NA	NA	NA	NA	NA
					DOAC	39/79	NA	NA	NA	NA	NA	NA	NA
Liang et al.[11]	2022	China	Observational study	128	Warfarin	72/128	55.1 (11.2)	10/72	NA	58.3	NA	18.1	37.5
					DOAC	56/128	55 (11.6)	5/56	NA	32.1	NA	14.3	32.1
Iskaros et al.[4]	2021	USA	Observational study	77	Warfarin	45/77	63 (55.73)	4/45	73.3	62.2	51.1	6.7	26.7
					DOAC	32/77	62 (55.74)	4/32	68.8	71.9	65.6	18.8	34.4
Ratnayake et al.[34]	2020	New Zealand	Retrospective observational cohort study	44	Warfarin	42/44	NA	NA	NA	NA	NA	NA	NA
					DOAC	2/44	NA	NA	NA	NA	NA	NA	NA
Hofer et al.[35]	2021	Austria	Prospective observational cohort study	43	Warfarin	33/43	NA	NA	NA	NA	NA	NA	NA
					DOAC	10/43	NA	NA	NA	NA	NA	NA	NA
Rahunathan et al.[36]	2022	UK	Retrospective observational study	18	Warfarin	4/18	63.5 (5.4)	1/4	NA	0	NA	NA	25
					DOAC	14/18	58.5 (12.6)	2/14	NA	28.5	NA	NA	21.4
Abdi et al.[37]	2022	Somalia	Retrospective cross-sectional study	40	Warfarin	19/39	NA	NA	NA	NA	NA	NA	NA
					DOAC	18/39	NA	NA	NA	NA	NA	NA	NA

TABLE 1 (Continued)

Author	Year	Country	Type of study	*N*	Treatment status	Number of participants	Age (years)	Sex (female)	Important comorbidities in percentage				
									CAD/IHD	HTN	CHF	CKD	Type 2 DM
Yang et al.[38]	2023	China	Retrospective observational cohort study	196	Warfarin	135/196	50 (37.0–59.0)	27/135	66/135	39/135	81/135	8/135	8/135
					DOAC	61/196	41 (27.0–56.0)	18/61	21/61	17/61	37/61	1/61	7/61
Zhang et al.[39]	2023	China	Retrospective observational cohort study	144	Warfarin	65/144	NA	NA	NA	NA	NA	NA	NA
					DOAC	79/144	NA	NA	NA	NA	NA	NA	NA
Huang et al.[40]	2023	China	Historical cohort study	122	Warfarin	65/122	38.8 (12.99)	12/65	NA	15/65	NA	NA	8/65
					DOAC	47/122	48.83 (13.29)	9/47	NA	10/47	NA	NA	4/57
Kim et al.[41]	2023	South Korea	Retrospective cohort study	205	Warfarin	182/205	NA	NA	NA	NA	NA	NA	NA
					DOAC	23/205	NA	NA	NA	NA	NA	NA	NA
Saeed et al.[42]	2023	Pakistan	Prospective cohort study	196	Warfarin	98/196	56.29 (11.04)	22/98	NA	66/98	11/98	NA	63/98
					DOAC	98/196	56.29 (11.04)	17/98	NA	68/98	13/98	NA	65/98
Zhang et al.[43]	2022	China	Retrospective observational study	187	Warfarin	78/187	63.0 (54.5–71.0)	12/78	61/78	33/78	39/78	NA	21/78
					DOAC	109/187	64.5 (54.2–70.8)	24/109	97/109	45/109	59/109	NA	57/109
Youssef et al.[44]	2023	Switzerland	Open label randomized controlled trial	100	Warfarin	25/50	53 (7.9)	NA	NA	10/25	NA	NA	11/25
					DOAC	25/50	52 (8.2)	NA	NA	11/25	NA	NA	12/25
Seiler et al.[45]	2023	Switzerland	Retrospective registry-based cohort study	101	Warfarin	53/101	62.2 (14.2)	12/53	NA	31/53	10/51	15/53	11/53
					DOAC	48/101	64.3 (12/1)	6/48	NA	24/48	6/48	8/48	8/48

TABLE 2 Narrative summary of the included studies for qualitative and quantitative analysis.

Article	Treatment status	Clinical stroke/ TIA	Systemic embolism	Thrombus resolution	All-cause mortality	Bleeding total	Stroke and embolism	Imaging modality for the diagnosis and follow-up of LVT	Duration of follow-up
Cochran et al.[8]	Warfarin	9/59	NA	45/59	2/59	8/59	NA	Trans-thoracic echo (TTE) with contrast	12 months
	DOAC	0/14	NA	12/14	1/14	2/14	NA		
Alcalai et al.[24]	Warfarin	1/15	NA	14/15	0/15	2/15	NA	Standard TTE	3 months
	DOAC	0/17	NA	16/17	1/17	0/17	NA		
Bass et al.[25]	Warfarin	90/769	NA	NA	NA	84/769	254/769	Not available (NA)	3 months
	DOAC	14/180	NA	NA	NA	14/180	55/180		
Daher et al.[14]	Warfarin	NA	4/42	30/42	NA	NA	NA	Standard TTE	3 months
	DOAC	NA	2/17	12/17	NA	NA	NA		
Iqbal et al.[7]	Warfarin	1/62	1/62	42/55	6/62	6/62	NA	For initial diagnosis—TTE, cardiac MRI (CMR), trans-esophageal echo (TEE) (for follow-up imaging—contrast TTE and CMR	Mean = 3 years, SD = 1.2 years
	DOAC	0/22	0/22	13/20	3/22	0/22	NA		
Herald et al.[5]	Warfarin	73/299	7/299	NA	138/299	113/299	84/1299	Standard TTE	3.4 years
	DOAC	26/134	3/134	NA	32/134	37/134	29/134		
Guddeti et al.[23]	Warfarin	2/80	NA	65/80	NA	4/80	NA	Standard TTE	1 year
	DOAC	0/19	NA	15/19	NA	1/19	NA		
Jones et al.[21]	Warfarin	3/60	NA	38/60	NA	22/60	NA	Standard TTE and CMR	2.2 years
	DOAC	1/41	NA	33/41	NA	6/41	NA		
Mihm et al.[20]	Warfarin	4/75	0/75	26/75	6/75	2/75	NA	Standard TTE and CMR	6 months
	DOAC	2/33	2/33	14/33	4/33	5/33	NA		
Robinson et al.[9]	Warfarin	NA	NA	131/236	32/236	19/236	14/236	Standard TTE, contrast TTE	351 days
	DOAC	NA	NA	56/121	14/121	8/121	17/121		
Willeford et al.[6]	Warfarin	7/129	1/129	63/129	NA	5/129	NA	Standard TTE	1 year
	DOAC	0/22	0/22	13/22	NA	1/22	NA		
Zhang et al. 2021[17]	Warfarin	NA	4/31	23/31	4/31	3/31	NA	Standard TTE	2 years
	DOAC	NA	1/33	26/33	1/33	2/33	NA		
Albabtain et al.[18]	Warfarin	1/35	0/35	24/35	3/35	1/35	NA	Standard TTE	3 years
	DOAC	1/28	1/28	20/28	2/28	2/28	NA		
Varwani et al.[16]	Warfarin	1/34	NA	16/25	NA	2/34	NA	Standard TTE	1 year
	DOAC	1/58	NA	36/36	NA	3/58	NA		
Xu et al.[10]	Warfarin	3/62	1/62	46/62	3/62	2/62	4/62	Standard TTE	Mean = 2.37 years, SD = (2.1)
	DOAC	1/25	0/25	19/25	2/25	1/25	1/25		
Yang et al.[15]	Warfarin	NA	1/199	71/92	5/199	012/199	NA	Standard TTE, contrast TTE, TEE, computed tomography (CT), CMR	1 year
	DOAC	NA	0/77	46/53	0/77	1/77	NA		

TABLE 2 (Continued)

Article	Treatment status	Clinical stroke/ TIA	Systemic embolism	Thrombus resolution	All-cause mortality	Bleeding total	Stroke and embolism	Imaging modality for the diagnosis and follow-up of LVT	Duration of follow-up
Isa et al.[19]	Warfarin	NA	NA	6/13	4/13	1/13	0/13	Standard TTE, cardiac catheterization, CT angiography, CMR	3 months
	DOAC	NA	NA	5/14	2/14	0/14	1/14		
Ali et al.[22]	Warfarin	9/60	5/60	37/60	NA	NA	NA	Standard TTE	1 year
	DOAC	2/32	0/32	18/32	NA	NA	NA		
Abdelnabi et al.[13]	Warfarin	4/40	2/40	32/40	NA	6/40 (Major Bleeding)	6/40	Standard TTE	6 months
	DOAC	0/39	0/39	34/39(In 6 months)	NA	002/39	0/39		
Liang et al.[11]	Warfarin	2/72	0/72	69/72	0/72	5/72	NA	Standard TTE	1 year
	DOAC	1/56	0/56	55/56	0/56	1/56	NA		
Iskaros et al.[4]	Warfarin	2/45	NA	34/45	NA	11/45	NA	Standard TTE, TEE, CMR	3 months
	DOAC	2/32	NA	27/32	NA	5/32	NA		
Ratnayake et al.[34]	Warfarin	NA	NA	34/42	NA	NA	NA	Standard TTE	6 months
	DOAC	NA	NA	1/2	NA	NA	NA		
Hofer et al.[35]	Warfarin	NA	NA	20/33	NA	NA	NA	Contrast TTE, CMR	Median:108 weeks, IQR: (68–173)
	DOAC	NA	NA	7/10	NA	NA	NA		
Rahunathan et al.[36]	Warfarin	0/4	0/4	1/4	NA	0/4	NA	Systemic echocardiography, CMR	Mean = 140 days. SD = 61 days
	DOAC	0/14	0/14	6/14	NA	0/14	NA		
Abdi et al.[37]	Warfarin	2/19	NA	NA	NA	NA	NA	2D TTE	NA
	DOAC	6/18	NA	NA	NA	NA	NA		
Yang et al.[38]	Warfarin	NA	1/135	57/135	3/135	9/135	NA	TTE, CT, CMR	3 months
	DOAC	NA	0/61	40/61	0/61	1/61	NA		
Zhang et al 2023.[39]	Warfarin	NA	9/65	38/65	23/65	6/65	NA	TTE	NA
	DOAC	NA	10/79	49/79	27/79	8/79	NA		
Huang et al.[40]	Warfarin	NA	NA	45/47	NA	NA	2/47	TTE, CMR (contrast)	6 months
	DOAC	NA	NA	56/65	NA	NA	3/65		
Kim et al.[41]	Warfarin	NA	NA	152/182	NA	NA	NA	TTE	NA
	DOAC	NA	NA	21/23	NA	NA	NA		
Saeed et al.[42]	Warfarin	NA	NA	76/98	NA	23/98	NA	TTE	5 months
	DOAC	NA	NA	73/98	NA	18/98	NA		
Zhang et al. 2022	Warfarin	NA	10/78	46/78	27/78	5/78	NA	TTE	Median = 17 months
	DOAC	NA	5/109	77/109	31/109	8/109	NA		
Youssef et al.[44]	Warfarin	NA	NA	23/25	NA	NA	NA	TTE	6 months
	DOAC	NA	NA	24/25	NA	NA	NA		
Seiler et al.[45]	VKA	4/48	3/48	36/48	6/48	9/48	NA	TTE	Median = 26.6 (11.8–41.2)
	DOAC	4/53	3/53	41/53	4/53	5/53	NA		

2.3.3 | Assessment of heterogeneity

The heterogeneity in the included studies was determined using the I^2 test using the Cochrane Handbook for systematic reviews of interventions.[32] Heterogeneity above 40% was considered significant, and a random effect model was applied.

2.3.4 | Data synthesis

The extracted data was analyzed using Cochrane Review Manager (RevMan) version 5.4.[33] The Mantel Haenszel method was used for the analysis of dichotomous outcomes. The effect size was measured using odds ratio (OR) with a 95% confidence interval employing a fixed and random effect model depending on the heterogeneity of the data.

3 | RESULTS

3.1 | Narrative summary

Three thousand nine hundred and forty-six studies were imported into the covidence employing a comprehensive search strategy. Thirteen studies were added from other sources; thus, 3959 total studies were used in the initial screening. After removing 394 duplicates, 3565 studies were subjected to title and abstract screening. In the initial screening, a total of 3505 irrelevant studies were excluded. The full text of 59 studies was retrieved for further eligibility testing and comprehensively reviewed. Finally, 33 studies were included in the Qualitative synthesis (Tables 1 and 2). Relevant data from these 33 studies were used in the quantitative synthesis for meta-analysis. The majority of studies used trans-thoracic echocardiogram (TTE) with or without other imaging modalities for initial diagnosis and confirmation of thrombus resolution, with average follow-up (3 months to 3.4 years) (Table 2). The details of these processes are presented in the PRISMA flow diagram in Figure 1.

3.2 | Quantitative result

3.2.1 | LVT resolution

Twenty-nine studies have reported on LVT resolution. LVT resolution occurred in 72.59% (813/1120) in the DOAC group versus 67.49% (1318/1953) in the VKA group. The pooled data from 29 studies showed 28% higher odds of LVT resolution in the DOAC group using the fixed-effect model (OR: 1.28, 95% CI: 1.07–1.53; p: 0.006; $n = 3073$; $I^2 = 18\%$) (Figure 2).

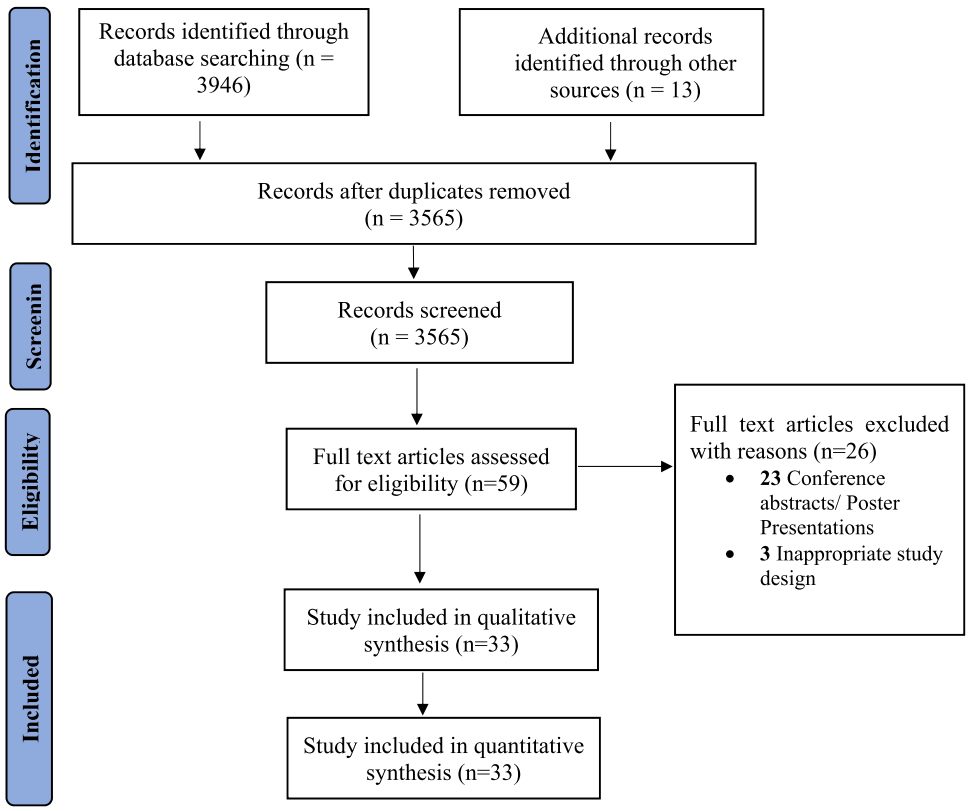
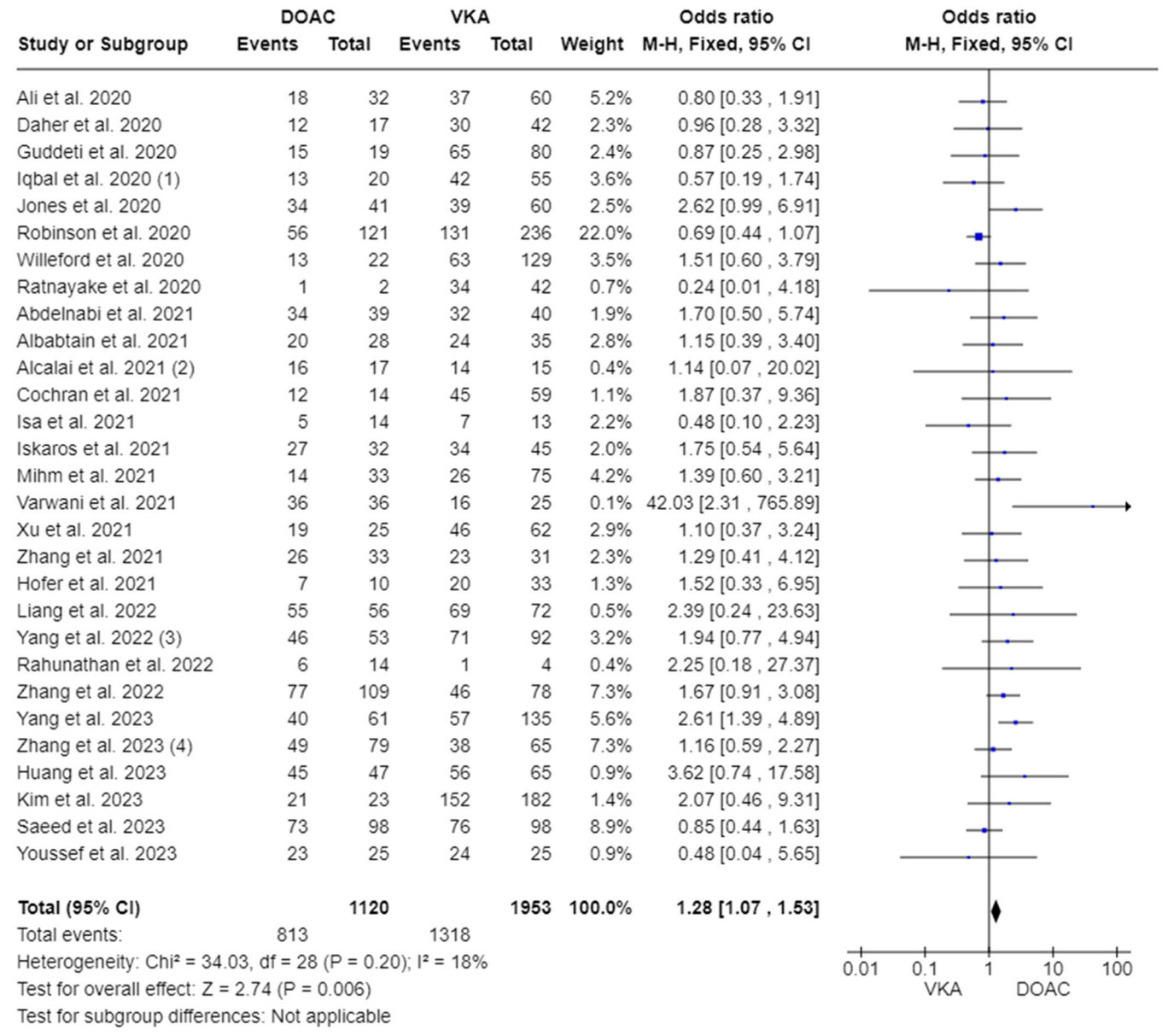


FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.



Footnotes

(1) Only those individuals with follow up data for thrombus resolution is included
(2) Only those individuals available for follow-up at 3 months are included
(3) Only individuals with follow up data available at 12 months are included in the analysis
(4) Only elderly population included for analysis

FIGURE 2 Forest plot using fixed effect model comparing thrombus resolution in LVT patients among DOAC and VKA group showing increased odds of thrombus resolution in the DOAC arm. DOAC, direct oral anticoagulants; LVT, left ventricular thrombus; VKA, vitamin K antagonists.

3.2.2 | All-cause mortality

All-cause mortality was reported as an outcome in 15 studies. The mortality events reported were 11.71% (96/820) in the DOAC group and 18.56% (262/1412) in the VKA group. The pooled analysis from the 15 studies showed 40% lower odds of mortality events in the DOAC group using the random-effect model (OR: 0.60, 95% CI: 0.36–1.00; *p*: 0.05; *n* = 2232; I^2 = 54%) (Figure 3). However, this was borderline significant.

3.2.3 | Bleeding events

Bleeding events were reported in 24 studies. Significant bleeding events occurred in 9.60% (131/1365) of the DOAC group and 13.19% (360/2770) of the VKA group. The pooled results from the 24 studies showed 35% lower odds of bleeding events in the DOAC group using the fixed effect model (OR: 0.65, 95% CI: 0.52–0.81; *p*: 0.0002; *n* = 4095; I^2 = 0) (Figure 4).

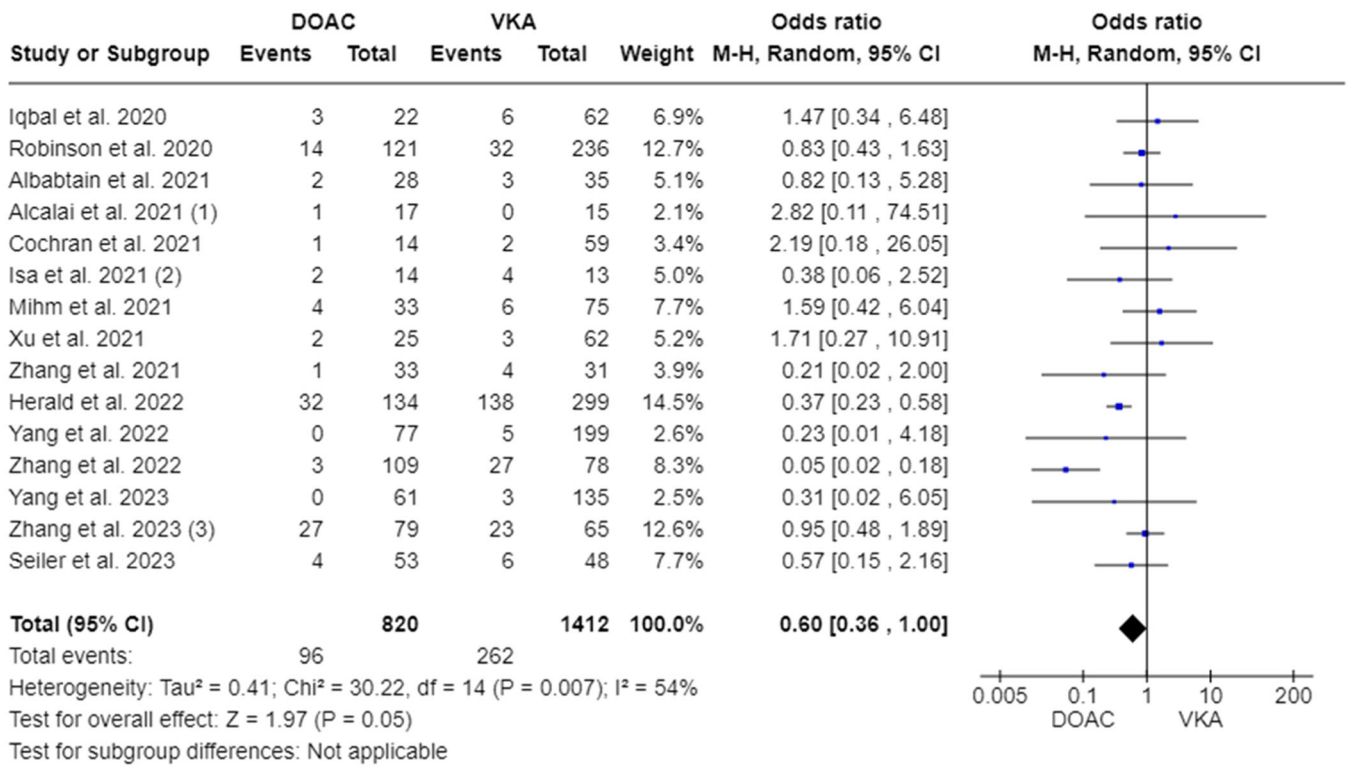


FIGURE 3 Forest plot using random effect model comparing mortality during the study period in LVT patients among DOAC and VKA groups depicting better mortality outcomes in patients treated with DOAC compared to VKA. DOAC, direct oral anticoagulants; LVT, left ventricular thrombus; VKA, vitamin K antagonists.

3.2.4 | Stroke

The occurrence of stroke events was reported in 19 studies. It occurred in 7.54% (63/835) of the DOAC group and 11.04% (222/2010) of the VKA group. The pooled data from the 19 studies showed 29% lower odds of stroke events in the DOAC group using the fixed effect model (OR: 0.71, 95% CI: 0.53–0.96; p: 0.03; $n = 2845$; $I^2 = 0$) (Figure 5).

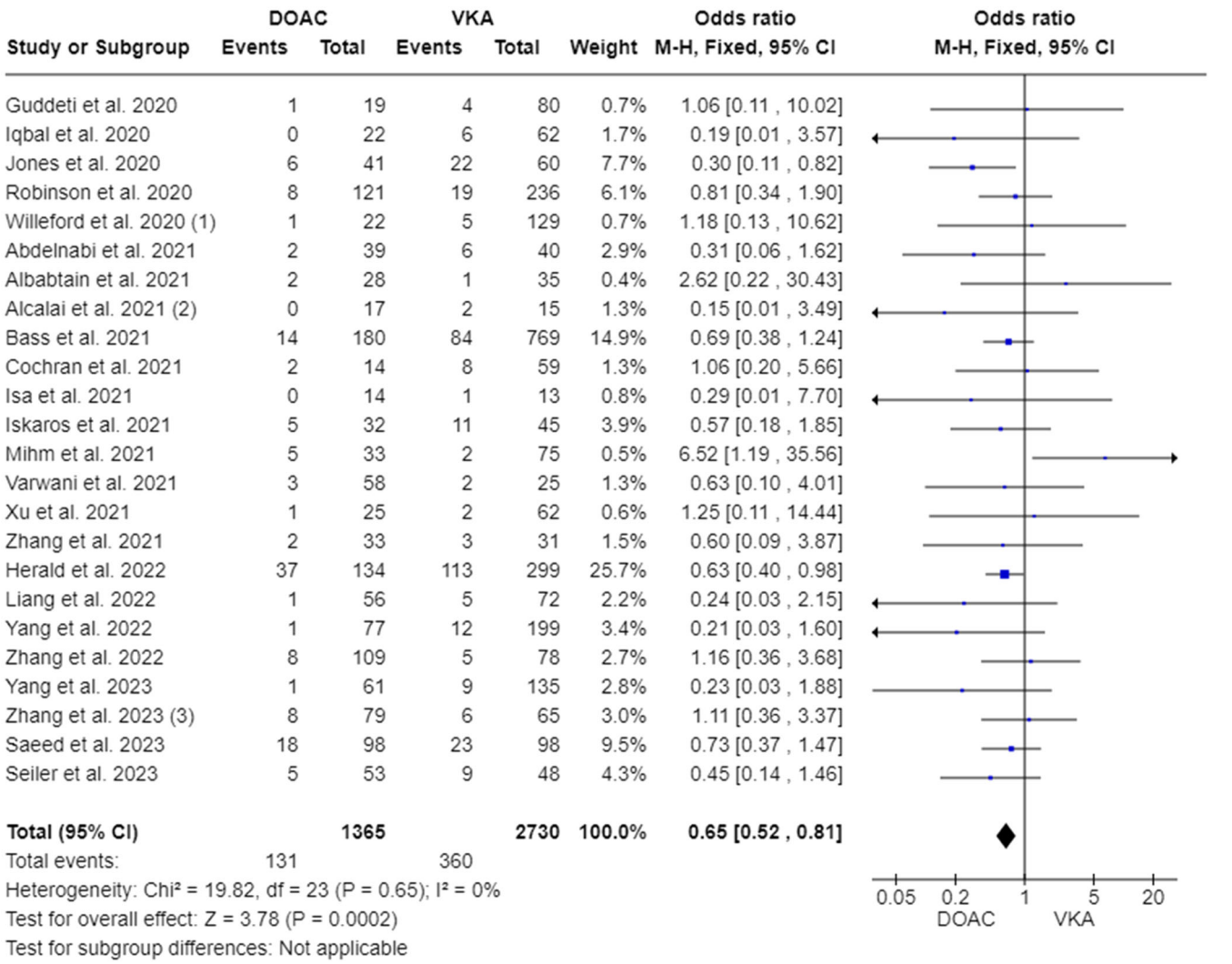
3.2.5 | Stroke and embolism

The combined stroke and embolism events were reported in 21 studies. Both events occurred in 11.12% (117/1052) of the DOAC group and 16.34% (422/2583) of the VKA group. The pooled result from 21 studies showed lower odds of stroke and embolism events in the DOAC group (OR: 0.83, 95% CI: 0.65–1.04; p: 0.10; $n = 3635$; $I^2 = 6\%$) (Figure 6). However, it was not statistically significant.

3.2.6 | Subgroup and sensitivity analysis

The subgroup analysis was conducted considering the study design. The included studies were categorized into RCTs and non-RCTs (observational studies). There were only four RCTs, whereas the rest were observational studies. The subgroup analysis including data from RCTs only showed no significant difference for LVT resolution (OR: 0.96, CI: 0.42–2.19), bleeding (OR: 0.26, CI: 0.07–1.00), and stroke (OR: 0.15, CI: 0.02–1.28) (Supporting Information: S1, Figures 1–10). However, analysis among non-RCT, the analysis results were consistent with the original results except for the stroke events (OR: 0.75, CI: 0.55–1.01) (Supporting Information: S1, Figure 1–10). The comparatively fewer RCTs can be attributed to this difference.

The sensitivity analysis was conducted with the exclusion of the individual studies (Supporting Information: S1, Tables 3–7). There was no significant change in the obtained results in every outcome.



Footnotes

(1) The data on the bleeding event is derived from the safety end point (summing up the blood transfusions and hemorrhagic stroke eve
(2) Data of only the major bleeding events available
(3) Only elderly population included for analysis

FIGURE 4 Forest plot using fixed effect model comparing significant bleeding during the study period in LVT patients among DOAC and VKA group. DOAC is deemed to be superior in terms of the occurrence of significant bleeding events. DOAC, direct oral anticoagulants; LVT, left ventricular thrombus; VKA, vitamin K antagonists.

3.2.7 | Publication bias

Publication bias assessed by visual Funnel plots. Funnel plots showed the symmetrical distribution of studies (Supporting Information: S1, Figures 11 and 12) in all outcomes assessed except for all-cause outcomes, suggesting minimal/acceptable publication bias of included studies.

4 | DISCUSSION

In this meta-analysis, we aimed to compare the effectiveness and safety profile of DOAC and VKA in treating LV thrombus. Our study included all full-text articles with complete data, making the evidence more credible and increasing the reproducibility of the analysis. We performed an updated meta-analysis by including recently published

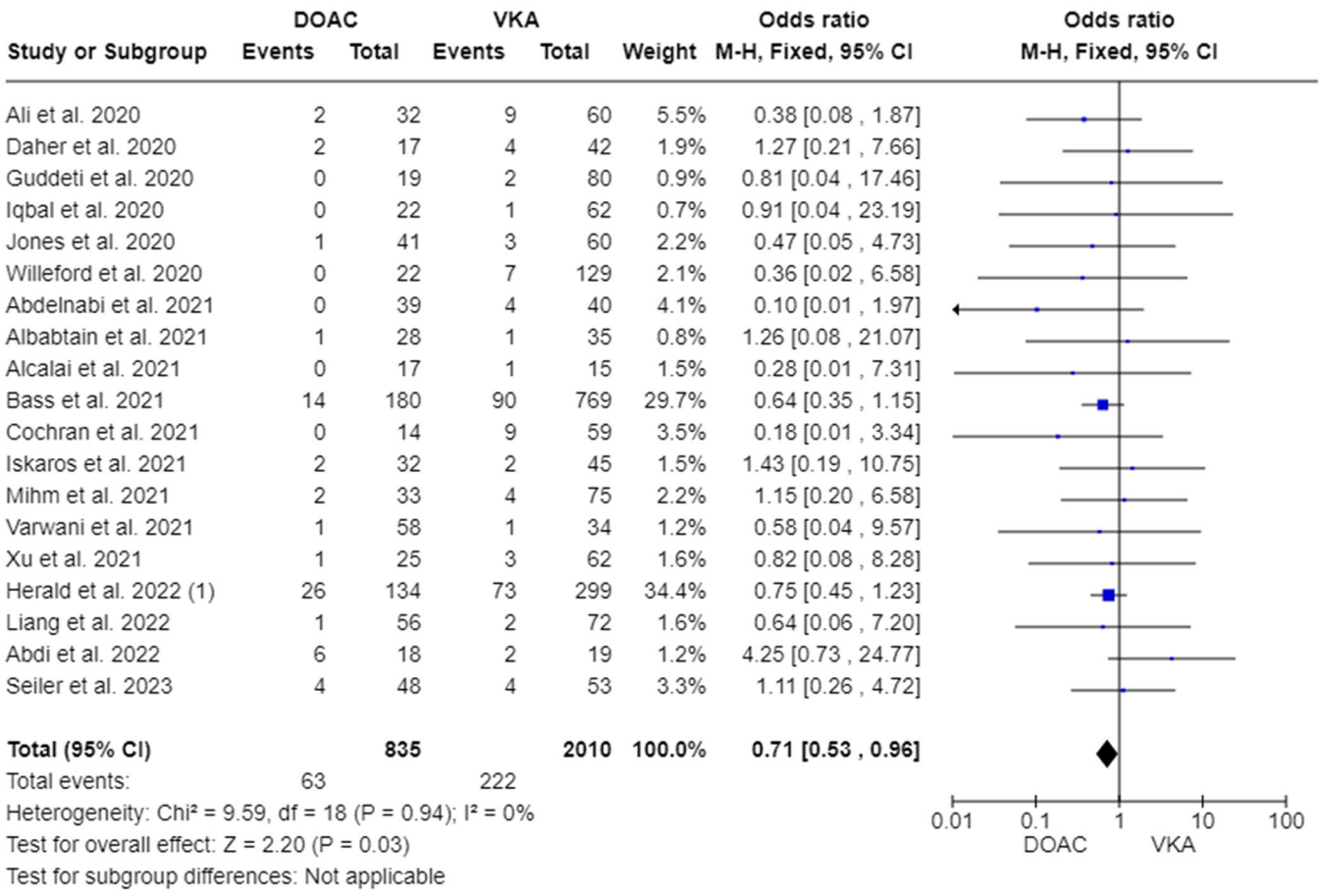


FIGURE 5 Forest plot using fixed effect model comparing stroke during the study period in LVT patients among DOAC and VKA groups. DOAC outweighed VKA in terms of the lower odds of occurrence of stroke events. DOAC, direct oral anticoagulants; LVT, left ventricular thrombus; VKA, vitamin K antagonists.

studies. We found that DOAC use showed lower rates of mortality when compared to VKA use. No individual studies included in our quantitative assessment showed a clear significant benefit of either agent, possibly due to small sizes.[5,7–11,15,17–20,24]

Likewise, we found significant LVT resolution in the DOAC group from our study. This finding showed the superiority of DOAC over VKA; however, earlier meta-analyses, including the latest scientific statement from the AHA, reported a trend favoring thrombus resolution with DOAC compared to VKA, though statistically insignificant (OR: 1.21, 95% CI: 0.89–1.64; $n = 2108$; $I^2 = 39\%$).[3] Based on the pooled analysis of 24 studies, the DOAC group experienced a significantly lower rate of bleeding events than the VKA group. A similar finding was reported in prior published studies.[46–49]

Based on the pooled analysis from 19 studies, we found that the observed stroke rates were significantly lower in the DOAC group, with a similar trend in composite events of stroke and systemic embolism between the DOAC and VKA arms. Our findings corroborated with the results from recently conducted similar studies comparing DOAC to VKA for the treatment of LVT.[46,47,50] DOACs are attractive in clinical practice because their use does not require monitoring of PT/INR levels as it is necessary with VKA. They have lower drug-food interactions, and the fixed dose is easier for the patients. These desirable features of DOAC improve patients' compliance in comparison with VKA. On the other hand, there is limited data about the usage of DOAC in patients with advanced CKD and oncological patients.

Our meta-analysis is the most robust and up-to-date study, including all relevant studies. Given the robustness and largest size including 33 studies, our analysis showed significant differences between VKA and DOACs, which was not observed with prior small-scale meta-analyses by Huang et al., Condello et al., Chen et al., Kido et al., Li et al., Camilli et al., and scientific documents.[3,46–51] Based on our findings, it is advisable to use the DOAC over VKA to manage LVT, given the better efficacy (thrombus resolution) and safety (lower mortality, bleeding, and stroke rates) profile of DOACs.

Our study also carries certain limitations. Firstly, this is a secondary analysis of published data, so it comes with inherent bias and limitations from the primary studies and methodology-associated limitations due to study design. Also, all outcomes of interest were

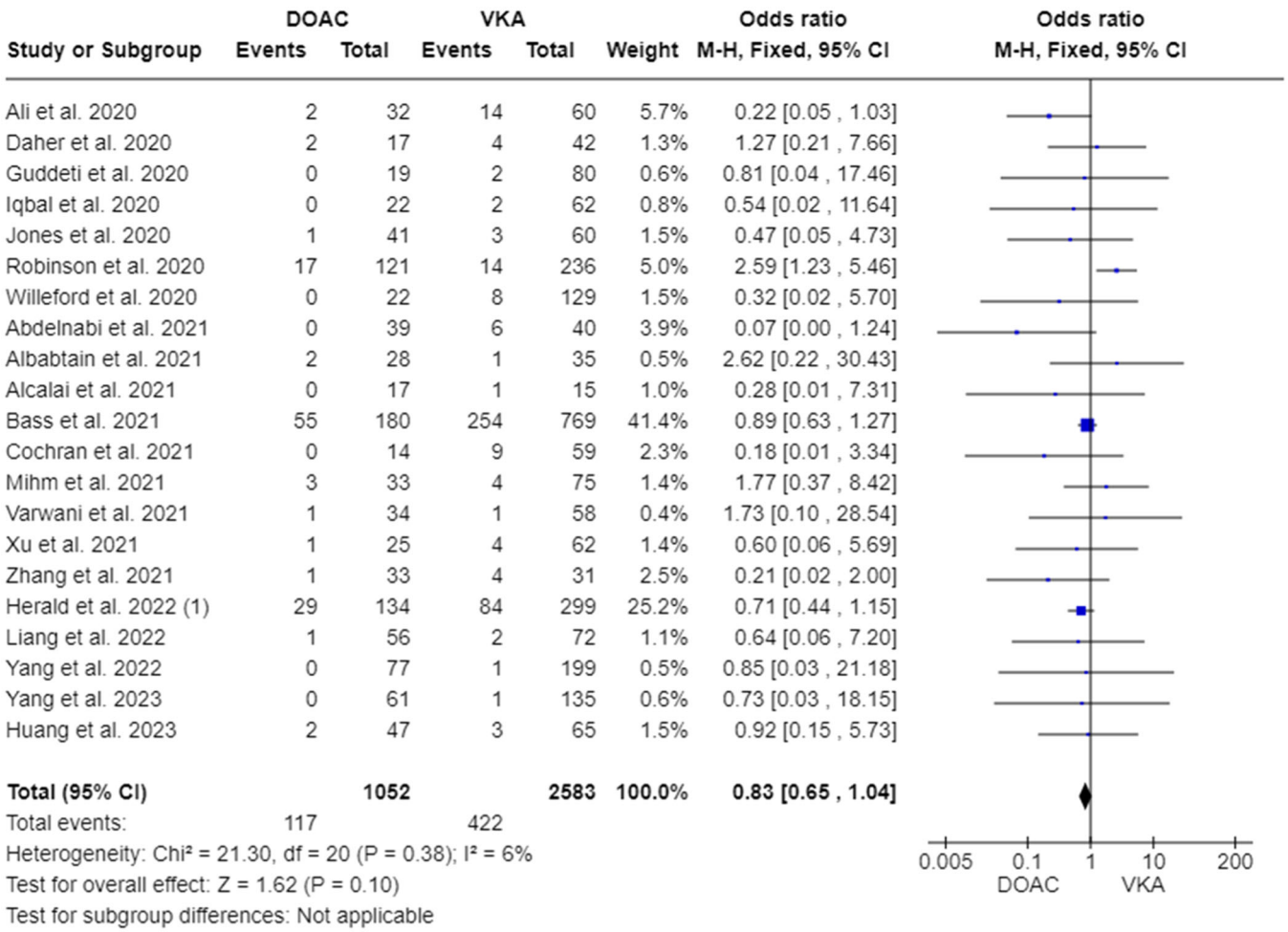


FIGURE 6 Forest plot using fixed effect model comparing stroke and embolism during the study period in LVT patients among DOAC and VKA group. However, a statistically insignificant adverse event profile was observed with the DOAC arm. DOAC, direct oral anticoagulants; LVT, left ventricular thrombus; VKA, vitamin K antagonists.

not reported in all the included studies. The average follow-up duration varied from 3 months to 3.5 years among the different studies. So, the long duration of the follow-up may have added to the observed effects, as the late safety outcomes may not be directly attributed to the treatment (anticoagulation) or the disease process (LVT). In addition, the drug, dosing of the anticoagulation regime, duration of therapy, and the type of cardiomyopathy in the study population varied in the included studies. Finally, there is a certain degree of variation in the patient population with imposed biological heterogeneity of the studied groups.

5 | CONCLUSION

Based on our results, we found DOAC use for patients with LVT to be associated with better LVT resolution and lower bleeding and stroke rates than VKA use. The mortality events were lower in the DOAC group; however, it was borderline statistical significance. Our study, being the largest with the most comprehensive evaluation of the data from the pooled analysis of 33 published studies, supports the benefit of DOAC compared to the VKA for managing LVT. The current guidelines do not recommend one over another; therefore, using either agent must be cautiously addressed by a patient-physician-informed decision. In the future, data from large randomized controlled trials are needed to confirm the superiority of DOAC over VKA in LVT treatment.

AUTHOR CONTRIBUTIONS

Dhan B. Shrestha: Conceptualization; data curation; formal analysis; methodology; project administration; resources; software; supervision; validation; writing—original draft; writing—review & editing. **Sagun Dawadi**: Data curation; methodology; project administration; resources; software; writing—original draft; writing—review & editing. **Bishal Dhakal**: Data curation; methodology; project administration;

resources; software; writing—original draft; writing—review & editing. **Jurgen Shtembari**: Conceptualization; project administration; resources; validation; writing—review & editing. **Toralben Patel**: Project administration; resources; supervision; validation; writing—review & editing. **Rafae Shaikh**: Methodology; project administration; resources; visualization; writing—review & editing. **George M. Bodziock**: Investigation; project administration; validation; writing—review & editing. **Ghanshyam Shantha**: Methodology; project administration; supervision; validation; writing—review & editing. **Cory R. Trankle**: Investigation; methodology; project administration; supervision; validation; writing—review & editing. **Nimesh K. Patel**: Conceptualization; investigation; methodology; project administration; supervision; validation; writing—review & editing. All authors have read and approved the final version of the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article [and/or] its supplementary materials. The corresponding author had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

TRANSPARENCY STATEMENT

The lead author Sagun Dawadi affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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SUPPORTING INFORMATION

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

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