Oral anticoagulation in patients with left ventricular thrombus – a systematic review and meta-analysis

Paul M Haller[1,2], Niema Kazem[3], Stefan Agewall[4], Claudio Borghi[5], Claudio Ceconi[6], Dobromir Dobrev[7,8,9], Elisabetta Cerbai[10], Erik Lerkevang Grove[11,12], Juan Carlos Kaski[13], Basil S. Lewis[14], Alexander Niessner[3], Bianca Rocca[10,15], Giuseppe Rosano[16], Gianluigi Savarese[17], Renate Schnabel[1,2], Anne Grete Semb[18], Samuel Sossalla[19], Sven Wassmann[20], Patrick Sulzgruber[3]

1) Department of Cardiology, University Heart and Vascular Center Hamburg, Hamburg, Germany.
2) German Center for Cardiovascular Research (DZHK), Partner Site Hamburg/Kiel/Lübeck, Hamburg, Germany.
3) Division of Cardiology, Department of Internal Medicine II, Medical University of Vienna, Vienna, Austria
4) Division of Clinical Science, Danderyd hospital, Karolinska Institute Stockholm, Sweden
5) Department of Medical and Surgical Sciences, University of Bologna, IRCCS Azienda Ospedaliero-Universitaria di Bologna Bologna, Italy
6) Cardiovascular Institute, Azienda Ospedaliera Universitaria S. Anna, Ferrara, Italy
7) Institute of Pharmacology, West German Heart and Vascular Center, University Duisburg-Essen, Essen, Germany
8) Montréal Heart Institute, Université de Montréal, Montréal, Québec, Canada
9) Department of Integrative Physiology, Baylor College of Medicine, Houston, TX, USA.
10) Department of Preclinical and Clinical Pharmacology, University of Florence, Florence, Italy
11) Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark
12) Department of Clinical Medicine, Faculty of Health, Aarhus University, Aarhus, Denmark
13) Molecular and Clinical Sciences Research Institute, St George's, University of London, London, UK
14) Lady Davis Carmel Medical Center and Technion-Israel Institute of Technology, Haifa, Israel
15) Department of Safety and Bioethics, Section of Pharmacology, Catholic University School of Medicine, Rome, Italy
16) St George's Hospital Medical School, London, United Kingdom AND IRCCS San Raffaele Roma, Rome, Italy

17) Division of Cardiology, Department of Medicine, Karolinska Institutet; and Heart and Vascular and Neurology Theme, Karolinska University Hospital, Stockholm, Sweden
18) Division of Research and Innovation, REMEDY, Centre for Treatment of Rheumatic and Musculoskeletal Diseases, Diakonhjemmet hospital, Oslo, Norway
19) Department of Medicine I, Cardiology, Universitätsklinikum Gießen und Marburg GmbH, Standort Gießen, Gießen, Germany AND Abteilung für Kardiologie, Kerckhoff-Klinik gGmbH, Bad Nauheim, Germany
20) Cardiology Pasing, Munich, and Faculty of Medicine, University of the Saarland, Homburg/Saar, Germany

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Address for correspondence:
Paul M. Haller, MD, PhD
University Heart and Vascular Center Hamburg
Medical University Center Hamburg-Eppendorf
Department of Cardiology
Building O50, Empore
Martinistrasse 52
20246 Hamburg, Germany
Phone: +49 40 7410 58206
p.haller@uke.de

AND

Patrick Sulzgruber, MD, PhD, MBA
Department of Internal Medicine II, Division of Cardiology
Medical University of Vienna
Währinger Gürtel 18-20
1090 Vienna, Austria
Phone: +43 1 40400 19640
patrick.sulzgruber@meduniwien.ac.at

Abstract

Aims: Direct oral anticoagulants (DOACs) are increasingly used off-label to treat patients with left ventricular thrombus (LVT). We analyzed available meta-data comparing DOACs and vitamin K antagonists (VKAs) for efficacy and safety.

Methods: We conducted a systematic search and meta-analysis of observational and randomized data comparing DOACs versus VKAs in patients with LVT. Endpoints of interest were stroke or systemic embolism, thrombus resolution, all-cause death, and a composite bleeding endpoint. Estimates were pooled using a random-effect model meta-analysis, and their robustness was investigated using sensitivity and influential analyses.

Results: We identified 22 articles (18 observational studies, 4 small randomized clinical trials) reporting on a total of 3,587 patients (2,489 VKA vs. 1,098 DOAC therapy). The pooled estimates for stroke or systemic embolism (OR 0.81; 95% CI [0.57, 1.15]) and thrombus resolution (OR 1.12; 95% CI [0.86; 1.46]) were comparable, and there was low heterogeneity overall across the included studies. DOAC use was associated with lower odds of all-cause death (OR 0.65; 95%CI [0.46; 0.92]) and a composite bleeding endpoint (OR 0.67; 95%CI [0.47; 0.97]). A risk of bias was evident particularly for observational reports, with some publication bias suggested in funnel plots.

Conclusion: In this comprehensive analysis of mainly observational data, the use of DOACs was not associated with a significant difference in stroke or systemic embolism, or thrombus resolution compared to VKA therapy. The use of DOACs was associated with a lower rate of all-cause death and fewer bleeding events. Adequately sized randomized clinical trials are needed to confirm these findings, which could allow a wider adoption of DOACs in patients with LVT.

Key words: left ventricular thrombus; oral anticoagulation; DOAC; DOAC; VKA; meta-analysis

Introduction

Left ventricular thrombus (LVT) may develop due to severe deterioration of left ventricular systolic function. LVTs are typically found in areas of regional akinesia that promote stasis of blood and clot formation. Endothelial injury arising from myocardial infarction (MI) and concomitant inflammation may additionally contribute to thrombus formation [1]. Although MI and ischemic cardiomyopathy are common causes of LVT, formation of the latter has also been detected in other clinical conditions, such as in patients with severe systolic heart failure or stress cardiomyopathy [2-4].

Although advances in the management of patients with MI over the past few decades, particularly reperfusion therapy, have reduced the incidence of LVT in patients with MI [5], recent studies report a prevalence of LVT ranging from 2-15%. [6-10].

Oral anticoagulation (OAC) therapy is the cornerstone of LVT treatment [3,5]. However, its benefit is intricately intertwined with the challenge of potential bleeding complications, which are more likely in patients with LVT as they commonly present with comorbidities that further increase bleeding risk.

In recent years, direct oral anticoagulants (DOACs) have replaced vitamin K antagonists (VKAs) in many clinical indications. This shift is attributed to their favourable safety profile, similar or superior efficacy and ease of administration [11,12]. Their increasing usage has prompted discussions about their potential use in patients with LVT[13], but dedicated trials in this scenario are scarce. In view of this, we carried out a systematic review and meta-analysis comparing results in the available literature regarding DOAC versus VKA therapy in patients with LVT, and providing pooled effect estimates for efficacy and safety endpoints.

Methods

Reference search and study selection

This systematic review and meta-analysis was conducted according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (Supplementary Material, Table S1). A systematic search of PubMed, Embase, and Web of Science databases was performed up to Dec 13, 2023, with the intention to retrieve studies reporting on a comparison of DOACs and VKAs in patients with LVT. We used the following subject headings and keywords in different combinations to retrieve potential references: "ventricular thrombus", "left ventricular thrombus", “ventricle thrombus”, "therapy", “resolution”, "NOAC", “non-vitamin K antagonist”, “direct oral anticoagulation”, "DOAC", "VKA", "vitamin K antagonist", " oral anticoagulation", “heparin”, “LMWH”, “low molecular weight heparin”. No restrictions were applied with respect to study design (retrospective, prospective observational, randomized clinical trial), but only studies reporting results in the English language were included. Studies reported only in abstract form were not included. Individual references were retrieved and independently screened by two investigators (P.M.H. and N.K.) by title and abstract and, if deemed suitable, by full text. Additionally, references cited by the articles included were screened for potential identification of further studies. Disagreements were resolved by consensus.

Data extraction and endpoints

Relevant data of all studies included was extracted using a pre-specified data record form by two independent investigators (P.M.H. and N.K.) and was evaluated for potential inconsistencies. We extracted data on first author, year of publication, study design, number of participants, study drug agent, mode of LVT detection, classical cardiovascular risk

factors, history of recent MI, concomitant anti-platelet therapy, cardiac function in terms of left ventricular ejection fraction (LVEF), follow-up time, and the endpoints of interest. The latter consisted of the efficacy endpoint ischemic stroke and/or systemic embolism, with thrombus resolution, all-cause death, and bleeding events investigated as safety endpoint. Due to the high heterogeneity with respect to the bleeding endpoint definitions used in the studies included, we assessed a combined bleeding endpoint including clinically relevant and major bleeding. This gathered all bleeding events corresponding to the following definitions: International Society of Thrombosis and Haemostasis (ISTH) clinically relevant non-major and major bleeding events, respectively, thrombolysis in myocardial infarction (TIMI) minor and major bleeding events, Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) moderate & severe bleeding events, and Bleeding Academic Research Consortium (BARC) bleeding events > 2.

Meta-analysis

We compared patients treated with DOACs versus VKAs for LVT using a random effects model with inverse-variance testing and a Paule-Mandel estimator for tau^2 to derive odds ratios (OR) and corresponding 95% confidence intervals (CI). We applied Hartung-Knapp adjustment for random effects models, and the prediction interval was based on a *t*-distribution. Heterogeneity of the overall effect was assessed using I^2 statistics and tau^2 and tested for significance at a level of 0.05. Sub-analyses were performed according to study type (randomized controlled trial (RCT) vs. non-randomized studies) if at least three trials reported on the investigated outcome.

We conducted influence analysis to investigate the robustness of the observed overall effect size of the meta-analysis, and whether specific studies, or combination of studies, had a particular influence on the effect size or on the heterogeneity of the effect size. For this we applied the “InfluenceAnalysis” function of the r package “dmetar” and conducted graphic

display of heterogeneity (GOSH) plot analysis. Hereby the treatment effect and heterogeneity are plotted for all possible subsets of all studies included. Further assessment of GOSH plots was conducted using unsupervised machine learning algorithms to detect clusters of studies with substantial influence on either treatment effect and/or heterogeneity using a specific diagnostic function for GOSH plot analysis. All analyses were conducted using R version 4.3.1 (R Foundation for Statistical Computing)[14] and the "metafor" packages[15].

Risk of bias

We used the RoB 2 tool for the risk of bias assessment of RCTs as described previously [16]. All other included studies of non-randomized, observational nature were considered to have a high risk of bias. Publication bias for the individual outcomes was assessed by using funnel plots and Egger's test.

Data availability

Data of the included articles is available with the respective publications. The data extraction sheet and the code used for the analysis is available upon reasonable request to the corresponding authors.

Results

Studies included

Our search yielded 1,364 unique articles that were screened initially. Of these, 22 studies fulfilled our inclusion criteria (Supplementary Material Figure S1) that reported on a total of 3,587 patients. Of those, 2,489 patients were treated with VKAs, and 1,098 patients were treated with any DOAC for LVT. Among DOACs, most patients (>85%) received rivaroxaban and apixaban. The main study metrics are summarized in Table 1. Only four articles reported results of an RCT [17-20], whereas the other 18 articles reported results of retrospective analyses [21-38]. In most studies transthoracic echocardiography without contrast media (or without reporting on the use of contrast media) was used for the detection of LVT [17-21,25-27,33-35,37,38]. Two studies reported the use of echocardiography contrast media [24,32], and five studies reported a mix of modalities for the detection of LVT [29,30,36]. Five studies included only patients with recent MI and acute onset of LVT (VKA n=146, DOAC n=131), reflecting a small proportion of the overall study population (277/3587, 7.7%) [18-20,30,38].

A summary of baseline characteristics of the individual studies is reported in Table 1 and Supplementary Material Table S2. The mean age in both treatment groups ranged from ~50 to 65 years, and 2,672/3,587 patients were male (74.5%; range in each study 57-100%). Fifteen studies reported on the mean left ventricular ejection fraction at baseline, ranging from 23% to 39% in each study. Seventeen studies reported on the additional use of antiplatelet agents; as reported by each study 1,342 VKA-treated (57.9%) and 573 DOAC-treated (57.5%) patients took at least one additional antiplatelet agent at baseline, with the proportion ranging between trials from 9% to 100%.

Stroke and systemic embolism

Twenty-one studies reported on the occurrence of ischemic stroke or additionally on systemic emboli (Figure 1A), with 437 (17.7%) events in VKA-treated patients, and 128 (11.9%) in DOAC-treated patients. The pooled odds ratio comparing VKA and DOAC use was 0.81 (95% CI [0.57, 1.15]). Heterogeneity as measured by I^2 (20.8% [0.0%; 53.4%]) or tau^2 (0.086) was low (p for heterogeneity 0.19). In the subset of RCTs, the pooled OR was 0.34 (95%CI [0.003; 40.5], Supplemental Figure S2) with low heterogeneity (I^2 30.6%, tau^2 0.09).

Thrombus resolution

Eighteen trials reported on thrombus resolution, including 674 patients treated with any DOAC and 1,110 patients treated with a VKA (Figure 1B). The follow-up duration and the number of reassessments during that period to detect potential thrombus resolution varied considerably, ranging between 3 and 12 months. Across the different studies, the number of patients with follow-up data on imaging was lower as compared to the number of patients with reported clinical follow-up. Of the subset of patients with reported imaging follow-up, 794/1,110 VKA-treated patients (71.5%), and 509/674 DOAC-treated patients (75.5%) had confirmed thrombus resolution. The pooled OR comparing DOAC and VKA use was 1.12 (95% CI [0.86; 1.46]), with low heterogeneity (I^2 9.2% [0.0, 45.2%], tau^2 0.02, p for heterogeneity 0.35). In the subset of three RCTs reporting on thrombus resolution, the follow-up duration varied between 3 months and approximately 3 years (Table 1). In this subset, 73/81 (90.1%) patients in the DOAC group and 70/70 (87.5%) patients in the VKA group had full resolution during follow-up. The pooled OR in this subset was 1.29 (95%CI [0.30; 5.51], Supplemental Figure S3) with low heterogeneity (I^2 0.0%, tau^2 0.025).

All-cause death

Thirteen studies reported on all-cause death, including 676 patients treated with a DOAC and 1,219 patients treated with a VKA (Figure 2A). Of these, 236/1,219 (19.4%) and 101/676 (14.9%) died. The pooled OR comparing DOAC and VKA use was 0.65 (95%CI [0.46; 0.92]), with low heterogeneity (I^2 15.4% [0, 54.4], tau^2 0.026, p for heterogeneity 0.29). Two RCTs reported on all-cause death, with 3/32 (9.4%) deaths in the DOAC group and 4/30 (13.3%) deaths in the VKA group.

Major or clinically relevant non-major bleeding

Seventeen studies reported on bleeding events, including 874 patients treated with a DOAC and 2,108 patients treated with a VKA. Definitions of bleeding across the individual studies varied considerably. We pooled data reflecting a combined bleeding endpoint of major or clinically relevant non-major bleeding. Overall, a bleeding event was reported for 193/2,108 VKA-treated patients (9.2%) and 58/841 DOAC-treated patients (6.6%; Figure 2B). The pooled OR comparing DOAC and VKA use was 0.67 (95%CI [0.47; 0.97]), with low heterogeneity (I^2 0.0% [0, 51.1], tau^2 0.0, p for heterogeneity 0.47). In the subset of three RCTs, there were 2/96 (2.1%) bleeding events reported in the DOAC group and 8/95 (8.4%) events in the VKA group. Since one of the three studies reported no event in either, we derived no pooled OR.

Influence analysis

We conducted several sensitivity and influence analyses to test whether a specific study, or a subset of studies, had substantial influence on the pooled effect estimate or on the heterogeneity observed in the pooled analyses. Detailed results are provided in the Supplemental Material (Figures S4). Overall, we observed substantial influence of specific studies on the investigated outcomes, and we provided sensitivity analyses omitting those studies or clusters of studies. A summary of the pooled treatment estimates of the main analyses and the sensitivity analyses is provided in Table 2.

Risk of bias assessment

Publication bias was assessed by visual inspection of funnel plots, which are provided for all four outcomes in Supplemental Material, Figure 5A-D. The funnel plot for the outcome of stroke or systemic embolism showed a leftward shift of reported studies, reflecting a potential publication bias favouring studies reporting on a benefit of DOAC therapy on this endpoint. A similar trend is seen for the analysis of major or clinically relevant non-major bleeding events. For both other endpoints, the funnel plots appear more balanced. Eggers' test for all four outcomes did not indicate the presence of funnel plot asymmetry (Supplemental Material, Figure S5A-D).

A summary of the risk of bias assessment for the RCTs is provided in Supplemental Material (Figure S6), which shows overall a moderate concern of bias. For all other studies included, as they were of observational nature with retrospective collection of data in almost all cases, we deemed these data to be at potentially high risk of bias.

Discussion

In recent years, DOACs have become widely adopted in clinical practice as a preferred treatment over VKAs in various clinical scenarios where oral anticoagulation is indicated. Their increased use relates to a favourable safety profile in terms of bleeding complications, particularly a lower risk of intracranial haemorrhage compared to VKA, while demonstrating similar efficacy in preventing thromboembolic events. The convenience of fixed-dose regimens without routine monitoring requirements improves patients' quality of life, and treatment's adherence and persistence, thus reducing the burden on the healthcare system[39]. With this development, the off-label use of DOACs for indications of oral anticoagulation beyond those investigated in dedicated RCTs has increased. However, despite their favourable risk/benefit ratio in the context of approved indications, such as atrial fibrillation[11], DOACs have yielded unfavourable results in other clinical settings[40], generally warranting caution upon expanding the indications for their application without solid scientific evidence derived from adequately powered RCTs. For example, in with mechanical heart valves [41], rheumatic heart disease-associated atrial fibrillation [42], or patients with left ventricular assist devices [43] DOACs have not been proven to be effective and safe.

The use of DOACs for management of LVT serves as a prominent example of the use of these agents in conditions that have not been systematically assessed by dedicated large clinical trials, and therefore lack of approval for this specific condition. Due to their global and widespread availability, the long-lasting experience in terms of safety and efficacy, and potential cost-related advantages, VKAs are established as the default choice for oral anticoagulation in many scenarios and countries. Although VKAs have not been formally tested in patients with LVT, their predominance has naturally given them a role as inherent benchmark against which newer compounds are evaluated. The aim of this meta-analysis was to provide a comprehensive summary of the available literature on this topic, incorporating data from observational and randomized clinical trials, and to compare DOACs versus VKAs for clinically important events and thrombus resolution in patients with LVT.

Although some meta-analyses have been previously conducted on this comparison[3,44-46], we also aimed at investigating the robustness of the available literature in more detail. Unfortunately, only four small RCTs were identified, focusing on two different agents (apixaban and rivaroxaban), while the majority of available data stems from observational, primarily retrospective studies. Therefore, data are insufficient to draw firm conclusions regarding the superiority and routine use of DOACs over VKAs in patients with LVT. In our analysis of the endpoints of stroke or systemic embolism, use of DOACs was not associated with an increased event-rate compared to VKA treatment. However, sensitivity analyses revealed variability in pooled effect estimates partly due to heterogeneity between individual studies, highlighting potential biases and uncertainties (Table 2). Despite no overt funnel plot asymmetry, publication bias favouring studies reporting on an association with reduced event rates in DOAC-treated patients over VKAs was also observed to some degree. As such, these summary estimates may not be particularly robust. Additional uncertainty exists due to the non-randomized nature of most studies included. Yet, the only RCTs available to date lack sufficient power to study stroke or systemic embolism, as also indicated by the reported variation in treatment effect (OR varying from 0.07 to 3.0), resulting in remarkably wide confidence intervals of the pooled OR (Figure S2) and hereby leaving large room for uncertainty.

With respect to thrombus resolution, in our meta-analysis DOACs were not associated with a lower efficacy over VKAs. However, the follow-up period, the number of and interval of repeated imaging assessments, and the imaging modalities applied varied considerably, which introduced major limitations. Only two RCTs, with a total of 111 patients, reported data on thrombus resolution, which does not provide a sufficient basis to draw definitive conclusions.

The optimal treatment duration for oral anticoagulation (irrespective of VKA or DOAC) for patients with LVT remains unclear to date. In this regard, we observed considerable heterogeneity within all included studies, reflecting different clinical practice patterns and the

lack of standardization. Thus, for the conduction of a pooled analysis, this adds further complexity which cannot be addressed to its full extent, leaving uncertainties with respect to the efficacy data. While there may be intuitive differences regarding the risk of embolism derived from LVT depending on, e.g., endothelialisation, size, or protrusion, it remains unclear whether patients with successful resolution of LVT need further treatment or how long patients without completely resolved LVT should be treated.

Differences in imaging modalities also contributed to the overall heterogeneity. The detection of LVT is clinically challenging, and the reported prevalence of LVT varies greatly according to the effort made to detect LVT [5,9,10,47]. Therefore, despite the promising result of our analysis on all investigated outcomes, the great heterogeneity of study designs with mostly retrospective data collection, different approaches for LVT detection, and varying imaging follow-up durations and intervals, warrant a cautious interpretation of the results.

DOAC treatment is considered to have a more favourable safety profile than therapy with VKAs in the approved clinical indications [11,39]. This notion stems from large-scale RCTs comparing the two treatment strategies in different indications. For example, in patients with atrial fibrillation treated with DOACs, the safety profile with respect to bleeding endpoints favours DOAC therapy, a finding particularly pronounced regarding intracranial haemorrhage and fatal bleeding events. In line with this, a lower rate of all-cause death has been observed in patients treated with DOACs [11]. In the present analysis, we observed differences in all-cause death and bleeding events between the treatment strategies, which is generally consistent with previous data [11]. However, potential publication bias and selection bias inherently associated with observational data still might have influenced our estimates derived from the present meta-analysis. For instance, this might be reflected in the very low OR for all-cause death associated with DOACs (Figure 2) seen in our analysis. While our pooled OR suggests a 35% relative reduction, this estimate appears to overstate the treatment effect reported for other indications [11]. As previously reported, the benefits seen in, e.g., patients with atrial fibrillation [11] do not necessarily apply to other clinical settings,

wherefore we emphasizing the need for careful interpretation of our study on the one hand and the need for dedicated clinical trials on the other [40,43].

Our conclusions differ from previous analyses in this field. Some authors endorsed DOACs over VKA in patients with LVT as fully supported by their findings [44], or use language implying the observed associations as definitive treatment-caused effects [46]. However, we urge for a cautious interpretation of results for the reasons discussed above.

In our view, the current body of literature supports the design of and underscores the need for a dedicated RCT. Since our and other's findings require further validation, the direct implementation to clinical practice is too preliminary at this stage, and based only on observational data and small-scale, underpowered and heterogeneous RCTs.

Conclusion

The data available on the use of DOACs in patients with LVT derives largely from observational studies, and thus firm conclusions regarding their routine use for this indication cannot be drawn. Although the results of the present meta-analysis suggest a potential role of DOAC therapy in LVT patients, dedicated RCTs are required to prove and validate their potential benefits in routine clinical practice.

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Table 1: Summary of characteristics of studies included

Trial	Type of study	Drugs used	Imaging	DOAC, N	VKA, N	Exclusively MI patients	Age (mean±SD)		Male Sex N (%)		Follow-up duration
							DOAC	VKA	DOAC	VKA	
Abdelnabi et al 2021 [17]	RCT	Rivaroxaban	TTE no information on contrast	39	40	No	n.s.*	n.s.*	n.s.*	n.s.*	6 months
Alcalai et al 2022[18].	RCT	Apixaban	TTE no information on contrast	18	17	Yes	55.5±12.9	58.8±10.2	13 (72.2)	15 (88.2)	3 months
Isa et al 2020 [19]	RCT	Apixaban	TTE no information on contrast	14	13	Yes	55.36±11.0	55.0±11.4	13 (92.9)	12 (92.3)	3 months
Youssef et al 2023[20]	RCT	Apixaban	TTE, without contrast	25	25	Yes	52.0±8.2	53.0±7.9	n.s.	n.s.	6 months
Albabtain et al 2021 [21]	Observational	Rivaroxaban	TTE no contrast	28	35	No	58.3±17.7	59±15.6	24 (85.7)	34 (97.1)	VKA: 14 (IQR: 3-41); DOAC: 9.5 (IQR: 6, 32.5)
Ali et al 2020 [22]	Observational	Apixaban, Rivaroxaban, Dabigatran,	TTE no information on contrast, cMR, cardiac CT	32	60	No	59.2±11.9	58.0±16.3	26 (81.3)	49 (81.7)	12 months
Bass et al 2021 J [23]	Observational	Apixaban, Rivaroxaban, Dabigatran	no information (ICD 9 or ICD 10 code)	180	769	No	63.4±16.7	61.6±15.3	125 (69.4)	545 (70.9)	3 months
Cochran et al 2021 [24]	Observational	Apixaban, Rivaroxaban, Dabigatran, Edoxaban	TTE contrast	14	59	No	Median: 51.5 (IQR: 39.0-73.0)	Median: 62 (IQR 34.0-84.0)	11 (78.6)	45 (76.3)	12 months
Daher et al 2020 [25]	Observational	Apixaban, Rivaroxaban, Dabigatran	TTE no information on contrast	17	42	No	57.0±14.0	61.0±13.0	14(82.4)	35 (83.3)	3
Gudetti et al 2019 [26]	Observational	Apixaban, Rivaroxaban, Dabigatran	TTE no information on contrast	19	80	No	60.7±13.1	61.3±12.2	15 (79.0)	55 (68.8)	mean: 12 months; 10.4±3.4
Herald et al 2022 [27]	Observational	Apixaban, Rivaroxaban,	TTE no information	134	299	No	66 (IQR 57-75)	65 (IQR 55-73)	116 (86.6)	242 (80.9)	40.8(IQR 22.8-70.8)

		Dabigatran	on contrast								
Huang et al 2023[28]	Observational	Rivaroxaban, Dabigatran	TTE, no routine contrast, cMR	47	65	No	43.8±13.3	38.9±13.0	38 (81.9)	53 (81.5)	6 months
Iqbal et al 2020 [29]	Observational	Apixaban, Rivaroxaban, Dabigatran	TTE contrast, TTE no contrast, TEE, cMR	22	62	No	62.0±13.0	62.0±14.0	20 (90.9)	55 (88.7)	36±16.8 months
Jones et al 2021 [30]	Observational	Apixaban, Rivaroxaban, Edoxaban	TTE no information on contrast, cMR	41	60	Yes	58.7±14.2	60.8±14.3	33 (80.5)	51 (85.0)	26.4 months
Mihm et al 2021[31]	Observational	Apixaban, Rivaroxaban	n/r	33	75	No	63.3±14.4	60.3±13.9	23 (69.7)	54 (72.0)	6 months
Robinson et al 2020 [32]	Observational	Apixaban, Rivaroxaban, Dapigatran	TTE contrast	121	236	No	58.1±14.9	58.2±15.1	94 (77.7)	170 (72.0)	Approx. 12 months
Seiler et al. 2023 [33]	Observational	Apixaban, Rivaroxaban	TTE, no information on contrast	48	53	No	64.3±12.1	62.2±14.2	42 (87.5%)	41 (77.4%)	26.6 (11.8; 41.2) months
Willeford et al 2022 [34]	Observational	Apixaban, Rivaroxaban	no information (ICD 10 code)	22	129	No	54 (IQR: 48-64)	56 (IQR: 49-65.5)	17 (77.3%)	104 (80.6%)	254 days (IQR: 98-343)
Xu et al 2021 [35]	Observational	Rivaroxaban, Dabigatran	TTE no information on contrast	25	62	No	59.4±11.5	61.9±12.2	19 (76.0)	47 (75.8)	28.44±25.2 months
Yang et al 2022 [36]	Observational	Apixaban, Rivaroxaban, Dabigatran	TTE contrast, TTE no contrast, TEE, cMR, cardiac CT	77	199	No	45.3±17.2	49.3±15.1	55 (71.4)	160 (80.4)	468 days
Zhang et al 2022 [37]	Observational	Rivaroxaban	TTE no information on contrast	109	78	No	Median: 64.5 (54.2-70.8)	Median: 63 (IQR: 54.5-71.0)	85 (78.0)	66 (84.6)	17 (IQR: 6.0-24.0) months

Zhang et al 2021 [38]	Observational	Rivaroxaban	TTE no information on contrast	33	31	Yes	60.3±14.7	61.3±9	33 (100.0)	23 (74.2)	8.5 (IQR: 5.0-17.0) months

*Only pooled data have been reported without treatment stratification (age 49.6±12.5, male sex 45 (57%). **Abbreviations:** cMR, cardiac magnetic resonance imaging; CT, computed tomography; ICD, implanted cardioverter defibrillator; DOAC non-vitamin K oral anticoagulant; RCT, random controlled trial; TTE transthoracic echocardiography; VKA, vitamin K antagonist

Table 2: Summary of pooled effect estimates and heterogeneity in the main analysis and sensitivity analyses stratified by endpoint

Model	Pooled OR [95% CI]	I^2 % [95% CI]	Excluded studies
Stroke and systemic emboli			
Main Model	0.81 [0.57, 1.15]	21 [0, 53]	
Model 1	0.75 [0.60, 0.95]	0 [0, 48]	Robinson et al [32]
Model 2	0.77 [0.61, 0.96]	0 [0, 49]	Abdelnabi et al [17], Robinson et al [32]
Model 3	0.72 [0.47, 1.08]	0 [0, 52]	Abdelnabi et al [17], Ali et al [22], Bass et al [23], Herald et al [27], Robinson et al [32]
Thrombus resolution			
Main Model	1.2 [0.86, 1.54]	18 [0, 55]	
Model 1	1.3 [1.05, 1.71]	0 [0, 55]	Robinson et al [32]
Model 2	1.1 [0.9, 1.46]	0 [0, 58]	Jones et al [30], Robinson et al [32], Zhang et al [37]
Death			
Main Model	0.65 [0.46, 0.92]	15 [0, 54]	
Model 1	0.84 [062, 1.14]	0 [0,58]	Herald et al [27]
Major or clinically relevant non-major bleeding			
Main Model	0.67 [0.47, 0.97]	0 [0, 51]	
Model 1	0.61 [0.46, 0.81]	0 [0, 52]	Herald et al [27]
Model 2	0.59 [0.46, 0.81]	0 [0, 52]	Herald et al [27], Mihm et al [31]

We conducted sensitivity analyses by removing studies or set of studies found to have considerable high influence on the pooled effect estimate and/or heterogeneity as described in the methods section and in Supplemental Material (Figure S3A-D). Studies, or set of studies, are excluded and the effect estimates, and heterogeneity are provided for these sensitivity models. Studies excluded for a respective model are shown in the right column.

Figure 1: Pooled estimates for stroke or systemic emboli and thrombus resolution of DOACs versus VKA in patients with left ventricular thrombus

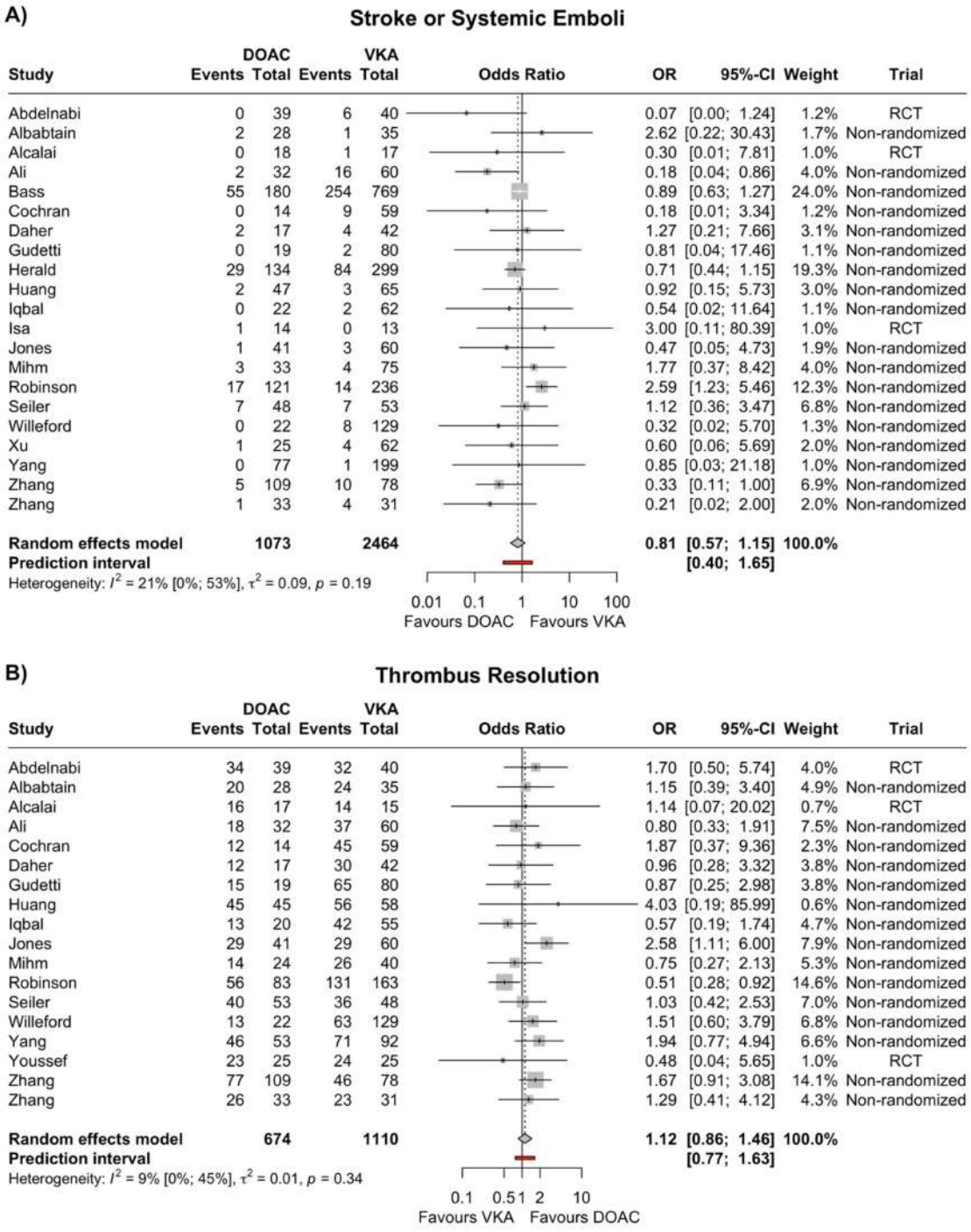
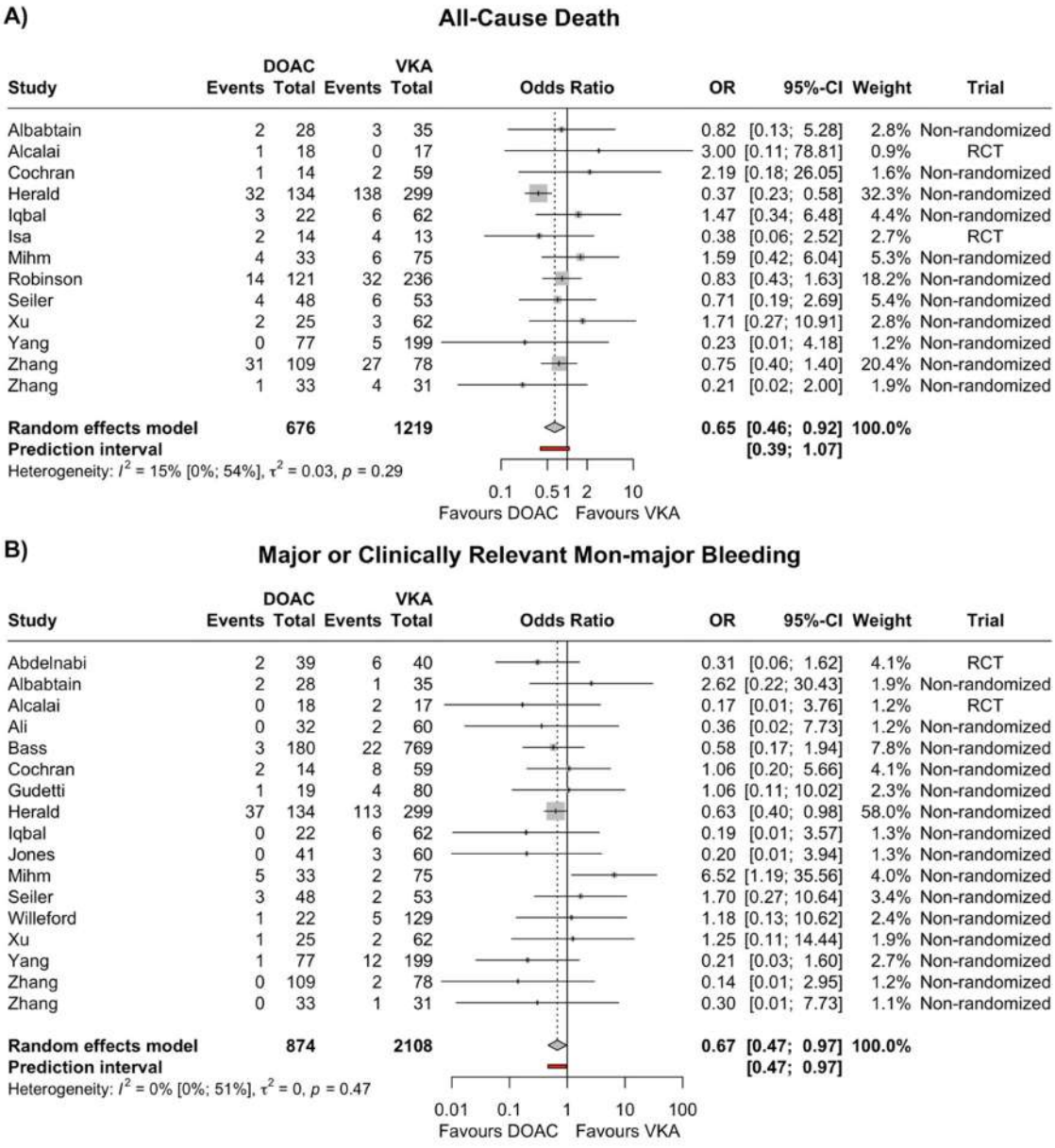


Figure 2: Pooled estimates for all-cause death and the composite bleeding endpoint of DOACs versus VKA in patients with left ventricular thrombus



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