

Effectiveness and Safety of Non-Vitamin K Antagonist Oral Anticoagulants Compared to Vitamin K Antagonists for the Treatment of Ventricular Thrombus: A Systematic Review and Meta-analysis of Observational Studies

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Research

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Abstract

Background To compare the effectiveness and safety of non-vitamin K antagonist oral anticoagulants (NOACs) and vitamin K antagonists (VKAs) on the rate of thrombus resolution and clinical outcomes.

Method MEDLINE, PUBMED, EMBASE, Cochrane Library, Web of Science, China National Knowledge Infrastructure Database and Wanfang Database, were searched up to August 16, 2020. Observational studies of patients with ventricular thrombus which compared the effect of two agents on the primary outcome were included. The primary outcome was rate of thrombus resolution, and the secondary outcomes were systemic embolism, bleeding and all-cause death. Odds ratio (OR) and 95% confidential intervals (CI) were utilized for the pooled results.

Result Eight studies with 905 participants were finally included. Among these cases, 66.6% of patients received VKAs and 33.4% of patients received NOACs. Rivaroxaban (71.9%) was the most commonly used NOACs. There were no significant differences between NOACs and VKAs groups in thrombus resolution (OR 1.18, 95% CI 0.73-1.91), systemic embolism (OR 0.83, 95% CI 0.34-2.05), bleeding (OR 0.65, 95% CI 0.35-1.19) and all-cause death (OR 0.95, 95% CI 0.53-1.71). In studies with rivaroxaban predominantly or only rivaroxaban in the NOACs groups, NOACs group showed high thrombus resolution rate (OR 2.31, 95% CI 1.31-4.07) and lower systemic embolism rate (OR 0.32, 95% CI 0.11-0.96) than VKAs group, but no differences in bleeding.

Conclusion Our findings showed that NOACs had a comparative complete resolution of thrombus compared with VKAs, as well as systemic embolism, bleeding events and all-cause death. In subgroups with rivaroxaban predominantly or only rivaroxaban in the NOACs group, NOACs showed better efficacy and safety profiles than VKAs, indicating that rivaroxaban might have favorable effectiveness over VKAs, though the sample size of NOACs in ventricular thrombus is small and the studies are most non-randomized. Further randomized controlled trials are urgently required to assess the effectiveness and safety of NOACs in patients with ventricular thrombus.

1 Background

Ventricular thrombus mainly refers to thrombus occurring in the right and left ventricles, with the left ventricle being more universal than the right ventricle. With the development of imaging techniques such as ultrasound, the detection rate of ventricular thrombus is increasing. Of the 137 cases of ventricular thrombus reported by Lee et al, 47.7% (n = 69) were situated in the left ventricle and 3.1% (n = 4) in the right ventricle^[1]. The mechanism of ventricular thrombus is mainly due to endocardial damage caused by cardiac diastolic dysfunction, or ischemic and hypoxic ventricular wall motion disorders leading to stagnation of blood flow in the cardiac cavity, which makes the blood flow in a hypercoagulable state and easily leads to thrombosis^[2]. With the advance of cardiac intervention and anticoagulation therapy, the incidence of ventricular thrombus in acute myocardial infarction (AMI) has been reduced from 20%-60% before thrombolysis to 2%-5%^[3,4]. However, due to the large number of patients with coronary heart disease in China, the number of people affected cannot be ignored. In addition, ventricular wall thrombosis can also cause multiple organ damage, including cardiac injury, such as pulmonary embolism^[5], stroke, AMI, and embolism of vital organs, etc. Its high all-cause death and disability rates bring a heavy disease burden and economic burden to society and families^[6,7].

To date, the epidemiological data of the antithrombotic treatment time course, clinical outcome and prognosis of patients with ventricular thrombus and its influencing factors are still blank. Since left ventricular thrombus can be a complication of myocardial infarction and cause stroke, based on myocardial infarction or stroke guidelines, warfarin is typically used clinically for anticoagulation. In the 2013 ACCF/AHA and 2015 China Acute ST Elevation Myocardial Infarction (STEMI) guidelines, it is reasonable to use warfarin anticoagulant therapy for STEMI patients with asymptomatic left ventricular thrombus (Class IIa, Level C evidence)^[8,9]. However, this recommendation is supported by expert consensus and there is a lack of evidence-based medical evidence. Due to the limitations of warfarin, patients' compliance with treatment is poor, which makes it difficult to guarantee the effectiveness and safety of treatment. In recent years, Non-vitamin K antagonist oral anticoagulants (NOACs) have been introduced, including dabigatran etexilate, rivaroxaban, apixaban, and edoxaban, which have been widely used in China. Rivaroxaban, apixaban and edoxaban are direct Xa factor inhibitors, which can inhibit tissue factor-mediated inhibition of thrombus generation, to achieve anticoagulant effect at the beginning of the common pathway of endogenous and exogenous coagulation. Dabigatran etexilate is rapidly absorbed after oral administration and is converted to dabigatran in plasma and liver by esterase-catalyzed hydrolysis. Dabigatran is a potent, competitive, reversible direct thrombus inhibitor that binds to the fibrin-specific binding site of thrombus, preventing the cleavage of fibrinogen to fibrin, thereby blocking the final steps of the coagulation waterfall network and thrombus formation. Since the introduction of NOACs into the clinic, impressive results have been made in the anticoagulation treatment of non-valvular atrial fibrillation and venous thrombotic diseases^[10,11]. The X-TRA and CLOT-AF study published in 2016 found that in patients with left atrial/left atrial appendage thrombosis, after 6 weeks of treatment with rivaroxaban, the regression rate of thrombus was 41.5%, and the regression or reduction rate was 60.4%. The incidence of stroke and hemorrhage was 0%^[12]. NOACs have many features such as a clear, rapid onset of action, a stable, predictable anticoagulant effect, a clear dose effect relationship without being metabolized by CYP450 enzymes, therapeutic window without restrictions, no routine anticoagulation monitoring, good security, and fewer agents occurring interactions etc, which indicates a better effectiveness and safety than warfarin. Therefore, NOACs may replace vitamin K antagonists (VKAs) in the treatment of ventricular thrombus^[13]. Recommended in the 2014 American AHA/ASA Stroke and transient ischemic attack (TIA) Prevention Guidelines, for patients with acute myocardial infarction combined with ischemic stroke or TIA, if left ventricular thrombus or abnormal anterior and apical ventricular wall movement combined with left ventricular ejection fraction < 40%, VKAs treatment cannot be tolerated due to non-hemorrhagic adverse events, therefore treatment with low molecular weight heparin, dabigatran, rivaroxaban or apixaban for 3 months can be regarded as VKAs replacement therapy to prevent recurrence Stroke or TIA (Class II b, Level C evidence)^[14]. The 2017 ESC STEMI guidelines also recommended that for STEMI patients with left ventricular thrombus, it suggested to maintain anticoagulation therapy for up to 6 months under the guidance of repeated imaging (Class II a, level C evidence, with the advent of NOACs, so it is not limited to warfarin)^[15]. So far, the application of NOACs in patients with ventricular thrombus has not been reliably evaluated. Only a few foreign case series studies or case reports have confirmed that NOACs are effective for ventricular thrombus. Therefore, it is controversial that whether NOACs or VKAs is

better in the treatment of ventricular thrombus. We aimed to compare the effectiveness and safety between NOACs and warfarin, to provide more evidence for clinicians conducting anticoagulation therapy for individual patients, especially those who are not suitable for warfarin anticoagulation.

2 Methods

2.1 Search strategy

This systematic review and meta-analysis was conducted under the guidelines of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement^[16] and it was registered on PROSPERO as CRD42019122791. Available from: <https://www.crd.york.ac.uk/prospero/#recordDetails>. Five international databases, Cochrane Library, MEDLINE (Ovid), PUBMED, EMBASE, and Web of Science, and two Chinese databases including China National Knowledge Infrastructure (CNKI) Database and Wanfang Database were searched to identify the studies up to August 16, 2020 by two reviewers (L.H and Q.Y.). The reference list of researches and systematic reviews was reviewed and retrieved for more trials. Potential gray literature was searched in OpenGrey.eu. The search terms were used as followed: "ventricular thrombus" or "intraventricular thrombus", "direct/new/novel oral anticoagulants" or "non-vitamin K antagonists oral anticoagulants, "warfarin", "vitamin K antagonists" and combination of these terms as keywords (The detailed search strategy is showed in Supplementary material).

2.2 Study eligibility

Eligible studies met all of the following criteria: (1) there were no restrictions on study design and language. (2) Studies were conducted among adults with ventricular thrombus in various diseases, regardless of nationality, sex, race, occupation or education. (3) The study for the treatment of ventricular thrombus should include the anticoagulation therapy with at least one agent including NOACs and VKAs. NOACs can be blood clotting factor Xa inhibitor (rivaroxaban, apixaban, edoxaban, dabigatran, or any other new oral anticoagulants. VKAs included warfarin, coumadin, phenprocoumon, acenocumarol, fludione, phenindione and anisindione. In addition, considered there did be few full-text studies (less than 5 articles) aiming to explore the two agents after searching all the databases, abstracts which met our criteria with important outcomes could be put into our analysis after we tried contacting the authors or searching more possibility if they published the full-text studies online via other methods. (4) The primary outcome was the rate of thrombus resolution. The secondary outcomes included thromboembolism events, bleeding and all-cause death. Any thromboembolism complications were defined as the composite of ischemic stroke or transient ischemic attack, acute coronary emboli (including myocardial infarction), or acute peripheral artery emboli (limb, renal, or digestive arteries). Bleeding event was defined as International Society on Thrombosis and Haemostasis (ISTH) bleeding or clinically relevant non-bleeding events^[17]. (5) The observational phase should last until the time that patients who were administered with NOACs or VKAs had achieved thrombus resolution. The following up period after the phase ended should continue for at least 3months.

Studies that met the following criteria were excluded: (1) If studies were duplicated publications, case reports, case series, or reviews; (2) If the data was incomplete or not serious, especially the important outcome events were missing or not available; (2) If the period of treatment or follow-up was too short to track the primary and secondary outcomes; (3) If there were some agents which may be interactive with NOACs or VKAs, and whether included such studies depended on the result after several conductors made discussion.

2.3 Data collection and analysis

We searched the above databases for related literature, imported articles into the database created by Endnote (Endnote X9.3.1; Thomson Reuters, San Francisco, CA), and filtered for duplicates. Two reviewers independently screened the titles and abstracts. If appropriate, full texts of the records were reviewed to identify all potentially eligible studies. Cross-referencing was also applied to check for the possibly missed studies, and an additional reviewer resolved the discrepancies. The screening flow chart of this study was presented in Fig. 1.

After screening the eligible studies, a data collection form was set up to extract the participant and study characteristics, which included: (1) General information: first author, title, journal, type of publication, year of publication, country, source of funding. (2) Methods: design, sample size, inclusion criteria and exclusion criteria were studied. (3) Subjects: baseline information (age, sex), medical history (hypertension, diabetes mellitus (DM), smoking history, atrial fibrillation (AF), history of thromboembolism, ischemic cardiomyopathy, dyslipidemia), cardiac imaging data (left ventricular ejection fraction, LVEF), antiplatelet therapy. (4) Therapy: type and dosage of medications, course of treatment. (5) Results: primary and secondary outcomes, adverse effects and follow-up.

2.4 Assessment of quality in the included studies

Two reviewers extracted the data independently and compared the results to ensure coherence. The Newcastle-Ottawa Scale (NOS) was operated by two reviewers to independently evaluate the quality for each included study^[18]. It evaluated cohort studies for three blocks, including selection, comparability, and outcome evaluation, with a score of 9 out of 10 stars. A study can be awarded a maximum of one star for each numbered item within the selection and outcome categories. A maximum of two stars can be given for comparability. Article quality was evaluated as follows: low quality (0–3); moderate quality (4–6); high quality (7–9). Any disagreement was addressed with by discussion or by involving another review author.

2.5 Statistics analysis

The continuous data was expressed as mean and standard deviation (SD), and the dichotomous outcomes were calculated by the OR with 95% CIs. A random-effects model was used for meta-analysis considering the possible heterogeneity existing in the eligible studies. Heterogeneity was assessed by visual inspection of the forest plots and detected by standard Chi-squared test and I^2 statistic. $I^2 < 50\%$ was considered that the studies included were homogeneous, while $I^2 > 50\%$ was taken as evidence of representing substantial heterogeneity. To explore the possible sources of heterogeneity, planned subgroup analyses were conducted according to the interested baseline characteristics. Sensitivity analysis were performed to examine the stability of the

pooled results. Publication bias was visually evaluated using funnel plot and statistically accessed by Egger's regression test. Furthermore, when Egger's regression tests or funnel plots indicated publication bias, we utilized the trim-and-fill method to identify whether funnel plot asymmetry should be corrected. All comparisons were considered as two-sided, and the $p < 0.05$ was considered as statistical significance. All the analyses were scheduled for completion with Stata Version 15.0.

3 Results

3.1 Literature search

The process of the literature search was represented in Fig. 1. A total of 905 citations were yielded by searching Cochrane Library, MEDLINE, PUBMED, EMBASE, and Web of Science, CNKI and Wanfang Database, of which 787 records remained after 118 duplicates had been removed. After reviewing titles and abstracts, 17 citations were remained for the full text screening and 771 records were deleted owing to irrelevance to our study. 9 articles were deleted for the following reasons: full texts were not available ($n = 8$), uncomplete data ($n = 1$). Finally, a total of 8 eligible studies were identified for meta-analysis^[19–26].

3.2 Study and Patient characteristics

Eight studies containing 905 participants were included in our study, among which three in China^[24–26], two in UK^[20,22], two in USA^[21,23], one in France^[19]. All five foreign studies were conducted in 2020, and the rest four Chinese studies were published in recent five years. Observational durations ranged from 3 to 36 months, and four studies lasted for 12 months or even longer^[20–23] (Table S1).

Among these cases, 66.6% of patients ($n = 603$) received VKAs and 33.4% of patients ($n = 302$) received NOACs. At a median follow-up period of 10.1 (IQR 3.7–21) months, 65.8% ($n = 397$) of patients in the VKAs group and 69.9% ($n = 211$) in the NOACs group had complete thrombus resolution. Rivaroxaban (71.9%, $n = 217$) was the most commonly used NOACs, followed by apixaban (24.5%, $n = 74$), edoxaban (3.3%, $n = 10$), and dabigatran (0.3%, $n = 1$). In total, 64 (7.1%) embolic events (NOACs vs VKAs: 23 (7.5%) vs 41 (6.8%)), 57 (6.3%) bleeding events (NOACs vs VKAs: 14 (4.6%) vs 41 (7.1%)), and 55 (6.1%) all-cause death (NOACs vs VKAs: 17 (5.6%) vs 38 (6.3%)) had occurred in the included studies with the FDA-approved doses. (Details of each study were showed in Table 2). Most of the studies had a higher proportion of men than women, where there were 77.8% ($n = 235$) men in NOACs group and 77.8% ($n = 469$) in VKAs group as well. Among the total of 905 patients, the mean age of participants varied from 51 to 61 years, with a median age of 60.8 years old in the 8 studies. The medical history varied among studies but was similar in the NOACs and VKAs groups in each study (Table 1). Seven studies reported baseline LVEF which ranged from 25–38%, indicating a poor systolic cardiac function. Seven studies reported AF, comprising 122 patients of whom 37.7% were received NOACs. Six studies included the history of thromboembolism, with a median rate of 56.6% (interquartile range, IQR 32.2–71.3) in NOACs group and 47.5% (IQR 31.9–69.8) in VKAs group. Hypertension, DM, ischemic cardiomyopathy and antiplatelet therapy were reported in all of studies. Only four studies reported dyslipidemia. Details of the included studies were listed in Supplementary material.

3.3 Quality assessment

The quality assessment stated that the quality of five studies was at high levels while the rest was at moderate levels, and the average score was 7.25 (Table S2). All studies had an adequacy of follow-up by description of missing visits. Owing to the retrospective studies, all of them had record linkages. Five studies did not adequately consider the comparability of the exposed and unexposed groups in their design and statistical analysis, and in particular, the studies did not account for or control for any confounders other than the most significant ones. And the follow-up period was not enough for outcomes to occur in three studies, such as Daher 2020^[19] and LI Xiu-fen 2015^[26] only had a 3-month observational time, which was not possible to track the hard endpoint such as death.

3.4 Outcomes of Meta-analysis

A total of ten observational eligible studies reported thrombus resolution, systemic embolism, bleeding and all-cause death. Eight studies with total patients of 905 (mean \pm SD: 113.13 \pm 103.34; Table S1) included comparisons between NOACs and VKAs groups, and two studies with total patients of 50 (mean \pm SD: 25.00 \pm 14.14; Table S1) only had NOACs group. There were only seven studies with comparisons between NOACs and VKAs reported the bleeding events, one of which reported zero bleeding event.

3.4.1 Thrombus resolution

As shown in Fig. 2 and Table 2, there was no significant difference in thrombus resolution rate between NOACs and VKAs groups (OR 1.18, 95% CI 0.73–1.91) with moderate heterogeneity ($I^2 = 43.3\%$). In two studies of NOACs without the comparisons with VKAs, the thrombus resolution rate was 83% (29/35) and 100% (15/15) respectively.

3.4.2 Systemic embolism

As shown in Fig. 3 and Table 2, no significant difference in systemic embolism rate between NOACs and VKAs groups (OR 0.83, 95% CI 0.34–2.05) were observed and moderate heterogeneity ($I^2 = 39.9\%$) was observed. In two studies of with only NOACs group, the systemic embolism rate was 2.8% (1/35) and 0% (0/15) respectively.

3.4.3 Bleeding

As shown in Fig. 4 and Table 2, there no significant difference in bleeding rate between NOACs and VKAs groups (OR 0.65, 95% CI 0.35–1.19) with moderate heterogeneity ($I^2 = 0\%$). In two studies of NOACs without the comparisons with VKA, the bleeding rate was 11.4% (4/35) and 6.7% (1/15) respectively.

3.4.5 All-cause death

As shown in Fig. 5 and Table 2, there were no significant difference in all-cause death between NOACs and VKAs groups (OR 0.95, 95% CI 0.53–1.71) with moderate heterogeneity ($I^2 = 0\%$). In two studies of NOACs without the comparisons with VKAs, the all-cause mortality was 8.6% (3/35) and 0% (0/15) respectively.

3.5 Subgroup analysis

Table 2 shows the subgroup analyses that were stratified by baseline characteristics on the thrombus resolution, systemic embolism, bleeding and all-cause death. The planned baseline characteristics for stratified analyses included rivaroxaban predominantly (yes or not), baseline LVEF, baseline antiplatelet therapy, baseline prevalence of AF, DM and ischemic cardiomyopathy. In studies with rivaroxaban predominantly or only rivaroxaban in the NOACs group, NOACs group showed high thrombus resolution rate (OR 2.31, 95% CI 1.31–4.07) and lower systemic embolism rate (OR 0.32, 95% CI 0.11–0.96) than VKA group, but no difference in bleeding. The heterogeneity was nearly zero in the subgroups stratified by types of NOACs (rivaroxaban predominantly or not), which suggested the types of NOACs might be one of the possible sources of heterogeneity for the analysis of thrombus resolution and systemic embolism. The pooled results of thrombus resolution, systemic embolism and bleeding in subgroups stratified by additional factors were insignificant between NOACs and VKAs groups. As shown in Table 2, baseline LVEF, baseline prevalence of AF, DM and ischemic cardiomyopathy might be also possible sources of heterogeneity for the analysis of thrombus resolution and systemic embolism.

3.6 Sensitivity analyses

Sensitivity analyses were conducted on the thrombus resolution, systemic embolism and bleeding, which omitted each study one by one to examine the impacts of any individual study on the final results (Figure S1-S3). The omission of any individual study did not significantly change the overall results of thrombus resolution, systemic embolism and bleeding.

3.7 Publication bias

No visible publication bias was found in the current study, which was visually exhibited through the trimmed funnel plot (Figure S4). Statistical evaluations via Egger's test showed no significant publication bias ($P = 0.336$).

4 Discussion

This is the first systematic review and meta-analysis quantitatively and systematically evaluate the efficacy and safety between NOACs and VKAs in the treatment of ventricular thrombus. There were no significant differences in ventricular thrombus resolution, systemic embolism, bleeding events and all-cause death between NOACs and VKAs, though the data are of low quality due to a limited sample size of our studies. What is more, our findings found that NOACs group showed more than two times higher thrombus resolution rate than VKAs group in studies with rivaroxaban predominantly or only rivaroxaban in the NOACs group. And patients who chose rivaroxaban for ventricular thrombosis had a 32% lower risk of systemic embolism than those who did not. Nevertheless, because of the very low numbers of patients with NOACs it is difficult to draw conclusions about the most favorable results with individual NOACs. But when considering the disadvantages of VKAs such as slow onset of action, susceptibility to food, drugs and genetic polymorphisms, narrow therapeutic window, frequent monitoring of the International Normalized Ratio and poor treatment compliance, NOACs may be a better choice for clinics and patients to apply in the treatment of ventricular thrombus.

Since we had only eight eligible studies which met criteria to conduct an analysis, in order to provide further evidence, we also analyzed two single-arm studies which showed that NOACs led to ventricular thrombus resolution in 83–100%. One single-center retrospective study in 2019 included 35 patients with left ventricular thrombus who received NOACs and had a follow-up transthoracic echocardiography (TTE), and 83% of patients had achieved thrombus resolution with a mean duration of 264 days, 1 (2.8%) patient had stroke or systemic embolism (SSE), 4 (11.4%) patients had bleeding events and 3 (8.6%) patient suffered from all-cause death. According to different NOACs, 16 (45.7%), 17 (48.6%) and 2 (5.7%) patients received apixaban, rivaroxaban and dabigatran had a 93.75%, 76.5%, 50% ventricular thrombus resolution separately after a follow-up TTE^[27]. Another study in 2019 which was a tertiary care center experience enrolled 15 patients with left ventricular thrombus who received dabigatran. Overall, all of patients achieved ventricular thrombus resolution after 6-months follow-up, with 1 bleeding event (6.7%) and no SSE^[28].

A meta-analysis conducted by Robinson et al in 2016 revealed that left ventricular thrombus was a universal complication after myocardial infarction^[29]. Therefore thrombosis remains one of the most frequent complications after myocardial infarction, and its all-cause death and disability rates remain high. However, 2020 Sedhom et al^[30] published a systematic review which collected studies of direct oral anticoagulants for treatment of left ventricular thrombus from January 1st, 2009 till April 25th. Among the 85 patients who were included in the case reports and case series, seventy-four patients (87%) were prescribed a NOAC and had follow-up imaging which showed complete resolution in 69 patients (93.2%). Three patients (3.5%) died during follow-up, 5 patients (5.9%) suffered from SSE and 3 patients (3.5%) had bleeding events. They concluded that the routine use for the treatment of left ventricular thrombus cannot be recommended, but this review included case reports and case series which were liable to publication bias and lacked a thorough data analysis. And our meta-analysis included observational studies aiming to provide a stronger evidence to support our result.

To represent the best evidence to explore the efficacy of NOACs for ventricular thrombus, we also analyzed 52 case reports or series describing 90 cases, which were found by searching Medline, Embase, Cochrane Library Web of Science and Pubmed databases from inception to August 2020. Among the 90 cases, rivaroxaban ($n = 46, 51.1\%$) was the most common used NOACs, and 28.9% ($n = 26$), 17.8% ($n = 16$), 2.2% ($n = 2$) patients received apixaban, dabigatran and edoxaban. At a median follow-up period of 60(28–111) days, 92.5% (74/80) patients had complete thrombus resolution. Patients who were treated with

dabigatran and edoxaban achieved 100% ventricular thrombus resolution, while those with apixaban and rivaroxaban therapy had 88.4% and 95.8% resolution dependently. There was a total of 5(5.5%) embolic events and 3(3.3%) deaths while being treated with rivaroxaban and dabigatran, and 3(3.3%) bleeding events only occurred in the rivaroxaban group. Those cases indicated that, the application of NOACs showed a great complete resolution of thrombus, with few thromboembolism or hemorrhagic events.

The strength of this meta-analysis resided in the creativity and timing. First, this article was the first international meta-analysis comparing the effectiveness and safety of NOACs and VKAs in the treatment of ventricular thrombus, and based on the results of observational studies, we added existing case series or case reports to provide further evidence for the use of NOACs in the treatment of ventricular thrombus. Second, the studies included in the article covered both domestic and international, and 62.5% (5/8) of the articles published in 2020 included the most recent observational findings. Third, we not only analyzed the effectiveness of different oral anticoagulants but also predicted the prognosis of thrombosis by stratified analysis or meta-regression, which had significant public health implications.

Our meta-analysis presents several limitations. Firstly, only observational studies were included in the current study due to the lack of relevant randomized controlled trials at present, which may have resulted in a lack of strength of evidence for the article. However, we will continue to keep track of the results of the latest clinical trials to add more robust persuasion. Secondly, the sample size of studies included were small owing to the limits of the relatively low incidence of ventricular thrombus in clinical practice. Finally, the diagnosis of ventricular thrombus were inconsistent given no authoritative guideline providing uniform criteria. Echocardiography which may have a lower sensitivity and specificity for detection compared with other imaging modalities, such as cardiac magnetic resonance imaging (MRI)^[31]. Among our included studies, the echocardiography was utilized to detect ventricular thrombus amongst five studies, and the others applied MRI as well. It is difficult to evaluate the accuracy and precision in the diagnosis of ventricular thrombus because of the high heterogeneity of the different methods.

With the increasing use of NOACs in clinical practice, it is reasonable to believe that NOACs will gradually be favored by physicians and patients in the treatment of ventricular thrombus, achieving high rates of thrombus cure, rapid regression, few adverse events, and good patient compliance. In addition, NOACs may not only promote thrombus regression, but may also have a protective effect against some cardiac diseases. Recently, Jumeau et al found that NOACs could slow down the process of atrial dilation by preventing interstitial fibrosis, extracellular interstitial remodeling, and heart failure-associated atrial hypertrophy, and improve left ventricular remodeling while reducing left atrial size and left ventricular diameter, the latter of which could further promote thrombus regression^[32].

To date, the therapeutic effect of NOACs on ventricular thrombus has not been formally evaluated in validated randomized controlled trials, which may be linked with the small number of patient cases and difficulty in enrollment. The optimal type, dose and duration of treatment of NOACs is therefore unclear. In light of the 2016 CHEST practice guidelines for the treatment of venous thromboembolism, an updated version may expand the use of loading doses of NOACs for the treatment of intracardiac thrombosis^[11]. Four randomized trials, currently in the pilot phase, aim to evaluate the efficacy of rivaroxaban versus warfarin (EARLY-MYO-LVT trial)^[33], and dabigatran vs warfarin (NCT 03415386) for the treatment of left ventricular thrombus respectively. Another two ongoing prospective clinical trials randomly assign patients with left ventricular thrombus to treatment of either warfarin or apixaban. One study enrolls 50 patients with acute STEMI and left ventricular thrombus. The primary efficacy end-point is the existence and dimensions of left ventricular thrombus as assessed by TTE. The secondary outcomes are SSE, bleeding, or all-cause death at 3 months^[34]. The other study includes 40 patients diagnosed with left ventricular thrombus. The primary outcome is the reduction of left ventricular thrombus size at 3 months. The secondary outcomes are reduction of left ventricular thrombus size by > 50%, the occurrence of cardioembolic stroke, or life-threatening bleeding at 3 months^[35]. We hope these upcoming results will provide more reliable data and further insight into the effectiveness of the application of NOACs and safety to expand the therapeutic prospects of NOACs. Overall, the results with NOACs appear to be favorable, which is an encouraging sign for broader researches to better assess their feasibility.

5 Conclusion

To conclude, our findings showed that there were no significant differences in effectiveness and safety between NOACs and VKAs. Considering the recognized advantages of NOACs over VKAs in other aspects, patients with ventricular thrombus might obtain more benefits from the treatment of NOACs compared to VKAs. Moreover, studies with rivaroxaban predominantly or only rivaroxaban showed NOACs group had better effectiveness but comparative safety profiles compared with VKAs group, which suggested the promising values of rivaroxaban in clinical practice. However, high-quality randomized controlled trials are required to further demonstrate our findings.

6 List Of Abbreviations

NOACs: non-vitamin K antagonist oral anticoagulants

VKAs: vitamin K antagonists

OR: odds ratio

CI: confidential intervals

SD: standard deviation

AMI: acute myocardial infarction

LVEF: ventricular ejection fraction

AF: atrial fibrillation

DM: diabetes mellitus

STEMI: ST elevation myocardial infarction

TIA: transient ischemic attack

PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses

CNKI: China National Knowledge Infrastructure

ISTH: International Society on Thrombosis and Haemostasis

NOS: Newcastle-Ottawa Scale

SSE: stroke or systemic embolism

TTE: transthoracic echocardiography

MRI: magnetic resonance imaging

7 Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

YQ and LY put forward the concept of research, formulated the retrieval strategy, and YQ and HLY drafted the manuscript. LY contributed to the revision of the manuscript and provided suggestions for the research. YQ and HLY assessed the risk of deviations and complete the data synthesis. All the authors read and approved the final manuscript.

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Not applicable

8 References

1. Lee JM, Park JJ, Jung HW, et al. Left ventricular thrombus and subsequent thromboembolism, comparison of anticoagulation, surgical removal, and antiplatelet agents.[J]. *J Atheroscler Thromb*, 2013, 20:73–93
2. Delewi R, Zijlstra F, Piek JJ. Left ventricular thrombus formation after acute myocardial infarction.[J]. *Heart*, 2012, 98(23):1743-1749.
3. Gianstefani S, Douiri A, Delithanasis I, et al. Incidence and predictors of early left ventricular thrombus after ST-elevation myocardial infarction in the contemporary era of primary percutaneous coronary intervention.[J]. *Am J Cardiol*, 2014, 113(7):1111-6.
4. Turpie AG, Robinson JG, Doyle DJ, et al. Comparison of high-dose with low-dose subcutaneous heparin to prevent left ventricular mural thrombosis in patients with acute transmural anterior myocardial infarction. [J]. *N Engl J Med*, 1989, 320(6):352-7.
5. Caldeira, D., Joaquim J. Costa J Fau - Ferreira, Gregory Y. H. Ferreira Jj Fau - Lip, et al. Non-vitamin K antagonist oral anticoagulants in the cardioversion of patients with atrial fibrillation: systematic review and meta-analysis[J], 2015, (1861-0692 (Electronic)).
6. Abdelnaby M, Almaghaby A, Abdelkarim O, Saleh Y, Hammad B, Badran H. The role of rivaroxaban in left ventricular thrombi[J]. *Anatol J Cardiol*, 2019, 21(1):47-50.

7. Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC), Steg PG, James SK, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation[J]. *Eur Heart J*, 2012, 33(20):2569-2619.
8. O'Gara, Patrick T., Frederick G. Kushner, Deborah D. Ascheim, et al. 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction[J]. *A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines*, 2013, 61(4):e78-e140.
9. 中华医学会心血管病学分会, 中华预防医学会. ST段抬高型急性心肌梗死(2019). *中华心血管病杂志*. 2019:766-783.
10. Connolly SJ, Ezekowitz MD, Yusuf S, et al Dabigatran versus warfarin in patients with atrial fibrillation.[J]. *The New England journal of medicine*, 2009, 361(12):1139-51.
11. Kearon C, Akl EA, Ornelas J, et al Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report.[J]. *Chest*, 2016, 149(2): 315-52.
12. Lip GY, Hammerstingl C, Marin F. Left atrial thrombus resolution in atrial fibrillation or flutter: Results of a prospective study with rivaroxaban (X-TRA) and a retrospective observational registry providing baseline data (CLOT-AF)[J]. *Am Heart J*, 2016, 178:126-34.
13. Orenes-Pinero E, Esteve-Pastor MA, Valdes M, Lip GYH, Marin F. Efficacy of non-vitamin-K antagonist oral anticoagulants for intracardiac thrombi resolution in nonvalvular atrial fibrillation.[J]. *Drug Discov Today*, 2017, 22:1565–1571.
14. Kemcn WN, Ovbiagele B, Black HR. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack—A guideline for healthcare professionals from the American Heart Association—American Stroke Association[J]. *Stroke*, 2014, 45(7):216–236.
15. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC)[J]. *Eur Heart J*, 2018, 39(2):119-77.
16. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement[J]. *Ann Intern Med*, 2009, 151(4):264-269, w264.
17. Schulman, S., C. Kearon. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients[J]. *J Thromb Haemost*, 2005, 3(4):692-4.
18. Wells G, Shea B, O'Connell D, et al. Newcastle-Ottawa Quality Assessment Scale –Cohort Studies[EB/OL]. 2012-06-15.
19. Daher, J., A. Da Costa, C. Hilaire, et al. Management of Left Ventricular Thrombi with Direct Oral Anticoagulants: Retrospective Comparative Study with Vitamin K Antagonists[J]. *Clin Drug Investig*, 2020, 40(4):343-353.
20. Iqbal, H., S. Straw, T. P. Craven, et al. Direct oral anticoagulants compared to vitamin K antagonist for the management of left ventricular thrombus[J]. *ESC Heart Fail*, 2020.
21. Robinson, A. A., C. R. Trankle, G. Eubanks, et al. Off-label Use of Direct Oral Anticoagulants Compared With Warfarin for Left Ventricular Thrombi[J]. *JAMA Cardiol*, 2020, 5(6):685-92.
22. Jones, D. A., P. Wright, M. A. Alizadeh, et al. The Use of Novel Oral Anti-Coagulant's (NOAC) compared to Vitamin K Antagonists (Warfarin) in patients with Left Ventricular thrombus after Acute Myocardial Infarction (AMI)[J]. *Eur Heart J Cardiovasc Pharmacother*, 2020.
23. Guddeti, R. R., M. Anwar, R. W. Walters, et al. Treatment of Left Ventricular Thrombus With Direct Oral Anticoagulants: A Retrospective Observational Study[J]. *Am J Med*, 2020.
24. 李, 李, 李, et al. *中华心血管病杂志*[J]. *中华心血管病杂志*(2019), 2019, 3(002):69-73.
25. 李, 李, 李, 李. *中华心血管病杂志*[J]. *中华心血管病杂志*, 2018:1184-1188.
26. 李, 李, 李-李. *中华心血管病杂志*[J]. *中华心血管病杂志*, 2015, 000(006):559-561.
27. Fleddermann, A. M., C. H. Hayes, A. Magalski, et al. Efficacy of Direct Acting Oral Anticoagulants in Treatment of Left Ventricular Thrombus[J]. *Am J Cardiol*, 2019, 124(3):367-372.
28. Verma, B., A. Singh, M. Kumar. Use of dabigatran for treatment of left ventricular thrombus: A tertiary care center experience[J]. *J Family Med Prim Care*, 2019, 8(8):2656-2660.
29. Robinson AA, Jain A, Gentry M, et al. . Left ventricular thrombi after STEMI in the primary PCI era: a systematic review and meta-analysis[J]. *Int J Cardiol*, 2016, 221:554-559.
30. Sedhom, R., P. Abdelmaseeh, M. Megaly, et al. Use of Direct Oral Anticoagulants in the Treatment of Left Ventricular Thrombi: A Systematic Review[J]. *Am J Med*, 2020.
31. McCarthy CP, Vaduganathan M, McCarthy KJ, Januzzi JL, Bhatt DL, McEvoy JW. . Left ventricular thrombus after acute myocardial infarction: screening, prevention, and treatment.[J]. *JAMA Cardiol*, 2018, 3:642.
32. Jumeau, C., A. Rupin, P. Chieng-Yane, et al. Direct Thrombin Inhibitors Prevent Left Atrial Remodeling Associated With Heart Failure in Rats[J]. *JACC Basic Transl Sci*, 2016, 1(5):328-339.
33. He J, Ge H, Dong JX, et al. Rationale and design of a prospective multi-center randomized trial of EARLY treatment by rivaroxaban versus warfarin in ST-segment elevation Myocardial infarction with Left Ventricular Thrombus (EARLY-MYO-LVT trial). [J]. *Ann Transl Med*, 2020, 8(6):392.
34. R., Alcalai. Apixaban Versus Warfarin in Patients With Left Ventricular Thrombus. [J]. Published 2018. Accessed May 5, 2020., NCT03232398.
35. Apixaban Versus Warfarin in Patients With Left Ventricular Thrombus. [J]. NCT02982590., Published 2016. Accessed May 5, 2020.

Tables

Table 1
Baseline characteristics of studies included

Study	Country	Follow-up, mon	Comparison	Sample size	Male n (%)	Age, years*	LVEF, %*	Medical history			
								Atrial fibrillation, n (%)	thromboembolism s, n (%)	Hypertension, n (%)	Diabetes, n (%)
Daher et al, 2020	France	3	NOACs	17	14(82.4)	57(14)	41(8)	-	-	10(59)	2(12)
			VKA	42	35(83)	61(13)	36(12)	-	-	17(40.5)	9(21)
Iqbal et al, 2020	UK	36	NOACs	22	16(73)	62(13)	31(13)	3(14)	2(9)	9(41)	19
			VKA	62	57(92)	62(14)	35(13)	3(5)	11(17.7)	18(29)	19
Robinson et al, 2020	USA	12	NOACs	121	94(77.7)	58.1(14.9)	27.7(13.8)	30(24.8)	79(65.3)	86(71.1)	36
			VKA	236	170(72)	58.2(15.1)	28.2(12.4)	45(19.1)	123(52.1)	177(75)	92
Jones et al, 2020	UK	24	NOACs	41	33(80.4)	58.7(14.2)	33.5(10)	0	21(55.3)	23(60.5)	7(17)
			VKA	60	51(85)	60.8(14.3)	35.4(9)	0	22(36.7)	22(36.4)	10
Raviteja et al, 2020	USA	12	NOACs	19	15(79)	60.7(13.1)	25(30)	4(21.1)	11(57.9)	15(79)	3(16)
			VKA	80	55(68.8)	61.3(12.2)	25(27.5)	18(22.5)	49(61.2)	61(76.3)	34
Yan et al, 2019	China	6	NOACs	11	9(81.8)	64.2(12.2)	38.6(4.27)	0	-	6(42.9)	4(36)
			VKA	37	34(91.9)	59.0(12.2)	39.6(5)	0	-	22(59.5)	12
Chao et al, 2018	China	8.3	NOACs	56	45(80.3)	61.2(10.3)	46.8(9.2)	4(7.1)	50(89.3)	37(66.1)	31
			VKA	70	55(78.6)	60.4(9.1)	35.3(7.1)	6(8.6)	67(95.7)	45(64.3)	40
Li et al, 2015	China	3	NOACs	15	11(73.3)	51.6(13.3)	-	5(33)	6(40)	3(20)	2(13)
			VKA	16	12(75)	52.4(12.7)	-	4(25)	7(43)	5(31)	4(25)

*Values are mean ± SD.

Abbreviations: NOACs: non-vitamin K antagonist oral anticoagulants; VKAs: vitamin K antagonists; LVEF: left ventricular ejection fraction.

Table 2
Outcomes of studies included

Study	Comparison	Sample size	Thrombus resolution, n (%)	Systemic embolism, n (%)	Bleeding, n (%)	All-cause death, n (%)
Daher et al, 2020	NOACs	17	12(70.6)	2(11.8)	-	0
	VKA	42	30(71.5)	4(9.5)	-	0
Iqbal et al, 2020	NOACs	22	13(65)	0	0	3(14)
	VKA	62	42(76)	2(3.2)	3(5)	6(10)
Robinson et al, 2020	NOACs	121	56(46.3)	17(14)	8(6.6)	15(12.4)
	VKA	236	131(55.5)	14(5.9)	19(8.05)	33(14.0)
Jones et al, 2020	NOACs	41	39(95)	1(2.4)	0	0
	VKA	60	51(85)	3(5)	4(6.7)	0
Raviteja et al, 2020	NOACs	19	15(80)	0	1(5.3)	0
	VKA	80	65(81)	2(2.5)	4(5)	0
Yan et al, 2019	NOACs	11	7(63.6)	0	0	0
	VKA	37	19(51.3)	3(8.1)	2(5.4)	1(2.7)
Chao et al, 2018	NOACs	56	29(51.7)	2(3.6)	5(8.9)	0
	VKA	70	22(31.4)	12(17.1)	11(15.7)	0
Li et al, 2015	NOACs	15	13(87)	1(6.7)	0	0
	VKA	16	12(75)	1(6.3)	0	0

Abbreviations: NOACs: non-vitamin K antagonist oral anticoagulants; VKAs: vitamin K antagonists; LVEF: left ventricular ejection fraction.

Table 3
Subgroup analyses on the effectiveness and safety of NOACs versus VKAs

Subgroup	Thrombus resolution			Systemic embolism			Bleeding		
	K	Pooled OR (95% CI)	Heterogeneity	K	Pooled OR (95% CI)	Heterogeneity	K	Pooled OR (95% CI)	Heterogeneity
Rivaxaban predominantly									
Yes*	4	0.72(0.50,1.03)	0.0%	4	2.08(1.08,4.01)	0.0%	3	0.46(0.17,1.25)	0.0%
No	4	2.31(1.31,4.07)	0.0%	4	0.32(0.11,0.96)	0.0%	3	0.79(0.37,1.72)	0.0%
Baseline LVEF									
>=30%	5	1.51(0.85,2.68)	24.8%	5	0.43(0.17,1.11)	0.0%	5	0.45(0.18, 1.17)	0.0%
< 30%	2	0.70(0.46,1.06)	0.0%	2	2.43(1.18, 5.01)	0.0%	2	0.84(0.38, 1.86)	0.0%
Baseline prevalence of AF									
>=15%	3	0.74(0.49,1.10)	0.0%		0.29(0.10,0.87)	0.0%	3	0.45(0.18,1.17)	0.0%
< 15%	4	1.65(0.83,3.27)	42.3%	3	2.31(1.15,4.67)	0.0%	4	0.84(0.38,1.86)	0.0%
Prevalence of pre-thrombilism									
>=50%	4	1.33(0.58,3.02)	71.8%	4	0.71(0.14,3.55)	72.2%	4	0.67(0.35, 1.25)	0.0%
< 50%	2	0.92(0.35,2.45)	11.1%	2	0.78(0.10,6.33)	0.0%	2	0.38(0.002,7.61)	0.0%
Baseline DM									
>=30%	5	0.94(0.56,1.57)	19.5%	5	1.91(1.02,3.58)	0.0%	3	0.74(0.34,1.61)	0.0%
< 30%	3	1.44(0.65,3.19)	46.9%	3	0.25(0.07,0.88)	0.0%	3	0.52(0.19,1.39)	0.0%
Baseline antiplatelet therapy									
>=60%	5	1.38(0.68,2.77)	63.8%	5	0.77(0.22,2.69)	64.4%	4	0.64(0.331,2.22)	0.0%
< 30%	3	0.88(0.43,1.81)	0.0%	3	0.79(0.14,4.45)	0.0%	2	0.73(0.12,4.42)	0.0%
Baseline prevalence ischemic cardiomyopathy									
>=80%	4	1.36(0.73,2.52)	29.5%	4	0.42(0.15,1.19)	0.0%	3	0.52(0.19,1.39)	0.0%
< 80%	4	1.06(0.51,2.17)	38.9%	4	2.02(1.03,3.96)	0.0%	3	0.74(0.34,1.61)	0.0%
* Studies in which the NOACs groups use only Rivaxaban or participants administrated with Rivaxaban accounted for more than 75%.									
Abbreviations: K: Number of studies. OR: odds ratio; CI: Confidence interval. NOACs: non-vitamin K antagonist oral anticoagulants; VKAs: vitamin K antagonists. LVEF: ventricular ejection fraction; AF: Atrial fibrillation; DM: Diabetes mellitus.									

Figures

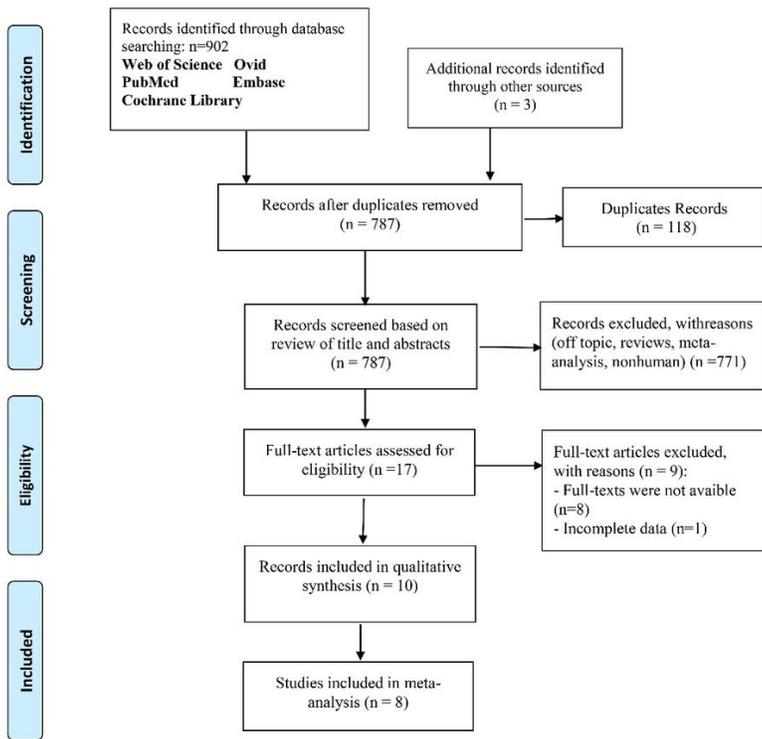


Figure 1

Flow chart of literature search strategies

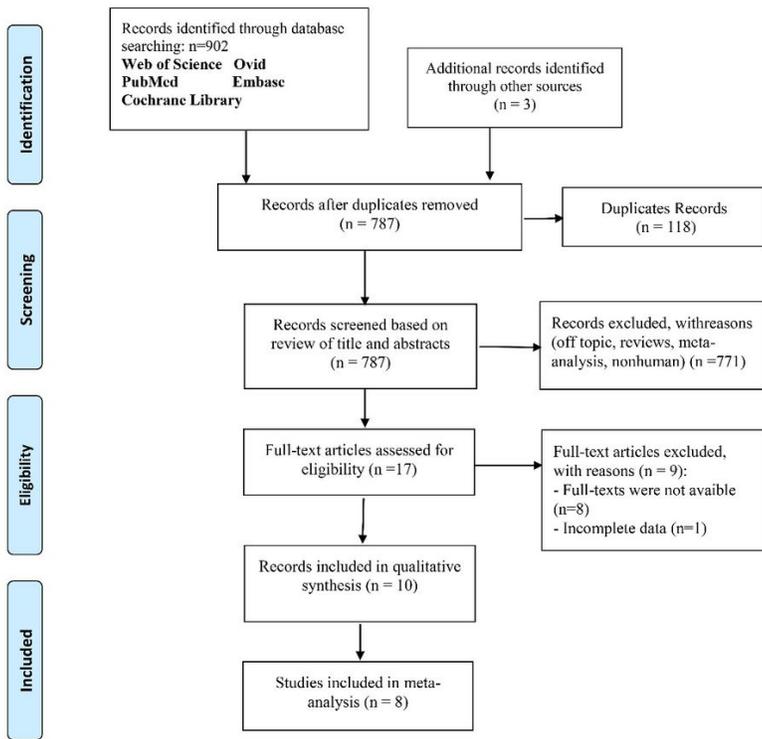


Figure 1

Flow chart of literature search strategies

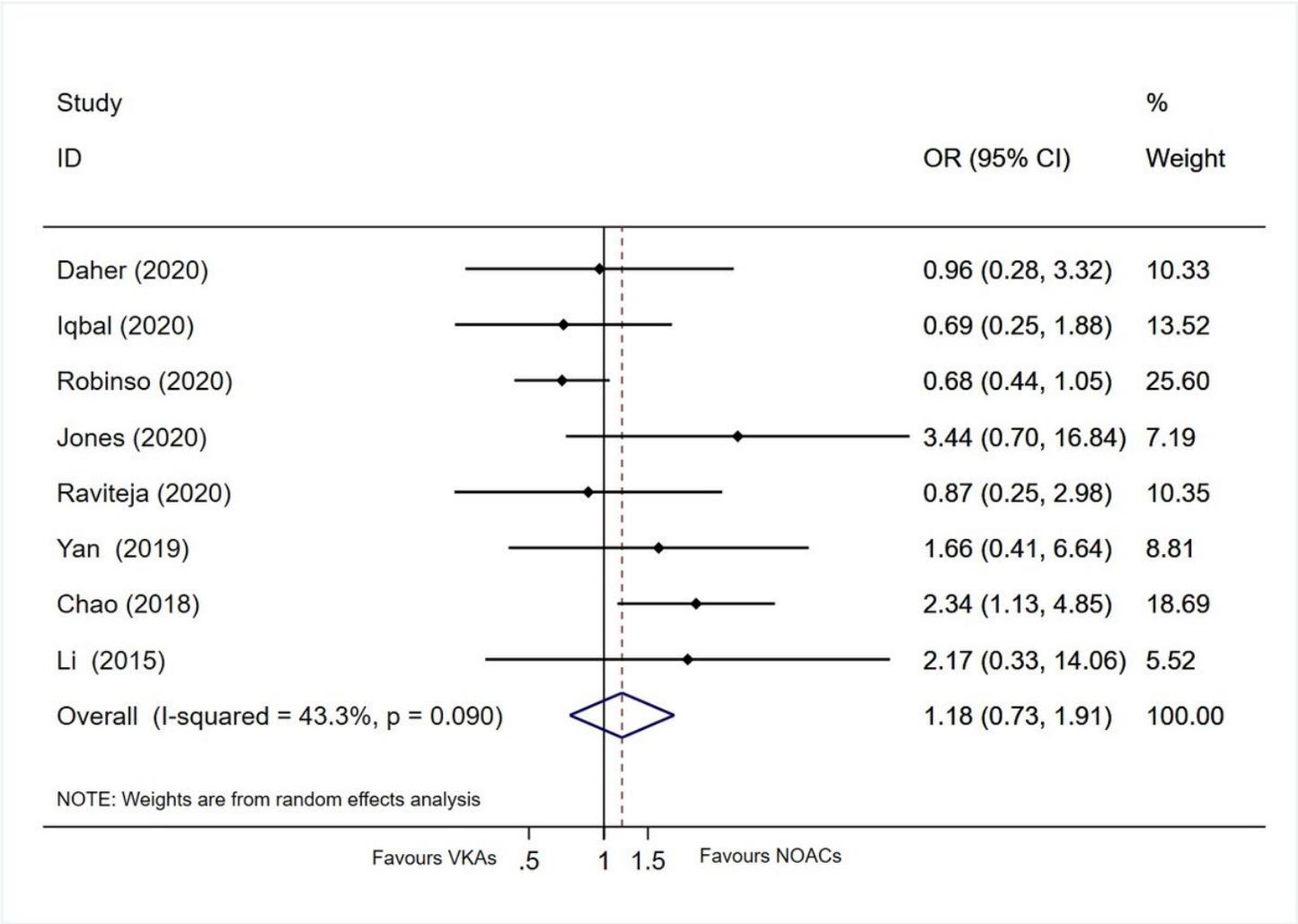


Figure 2
 Forest plot of thrombus resolution between NOACs versus VKAs Abbreviation: OR: odds ratio; CI: Confidence interval; NOACs: non-vitamin K antagonist oral anticoagulants; VKAs: vitamin K antagonists.

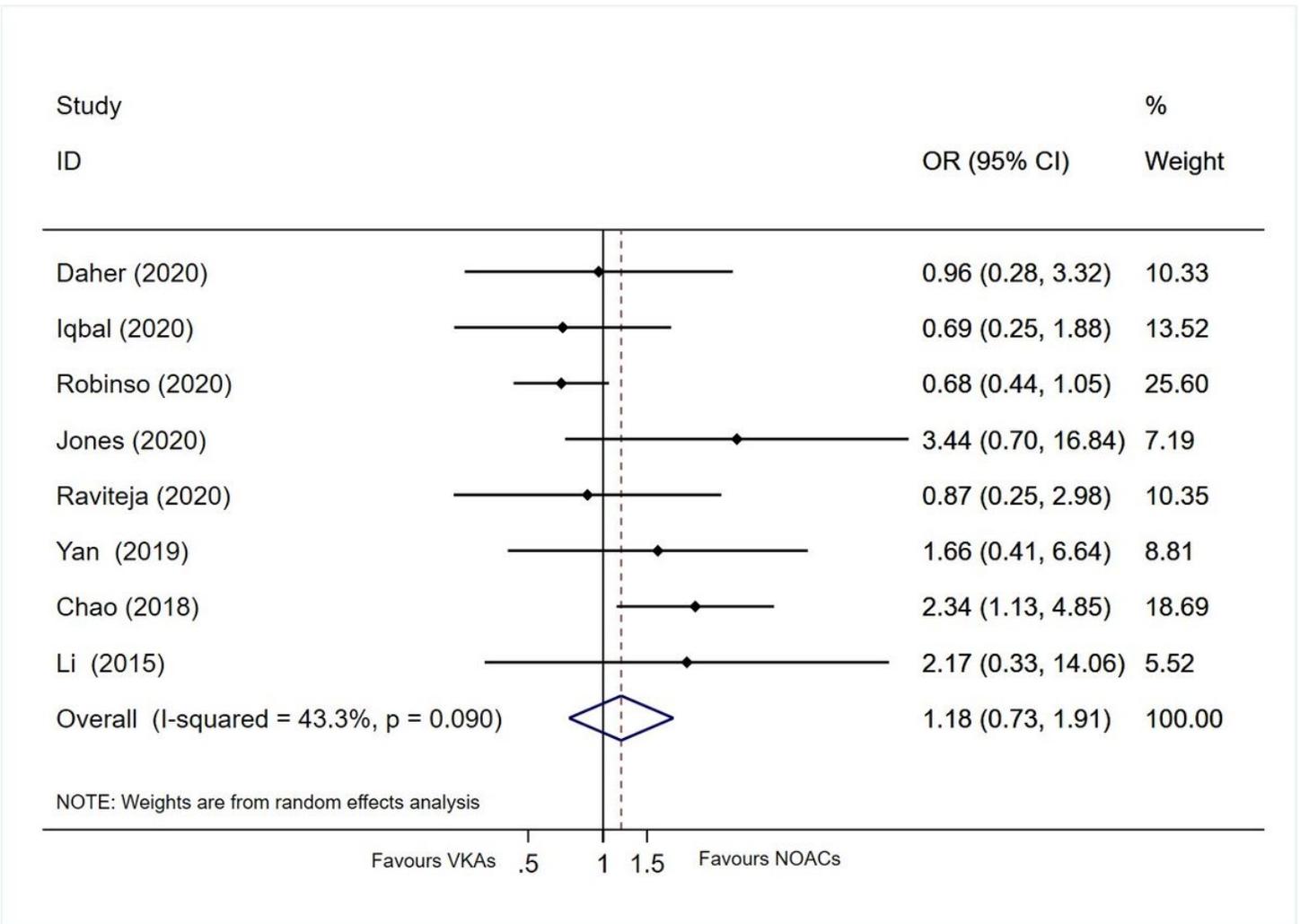


Figure 2

Forest plot of thrombus resolution between NOACs versus VKAs Abbreviation: OR: odds ratio; CI: Confidence interval; NOACs: non-vitamin K antagonist oral anticoagulants; VKAs: vitamin K antagonists.

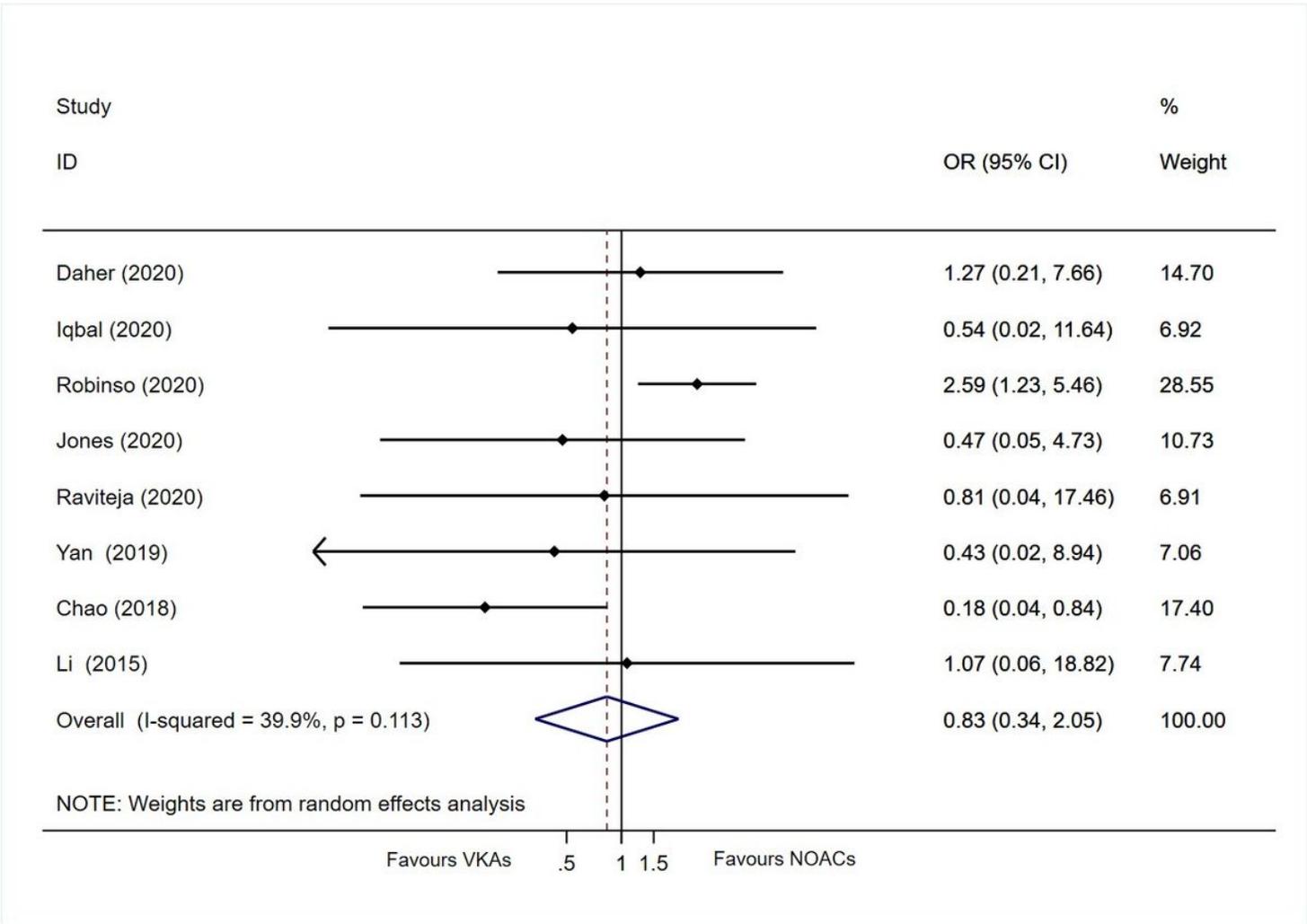


Figure 3
 Forest plot of systemic embolism between NOACs versus VKAs Abbreviation: OR: odds ratio; CI: Confidence interval; NOACs: non-vitamin K antagonist oral anticoagulants; VKAs: vitamin K antagonists.

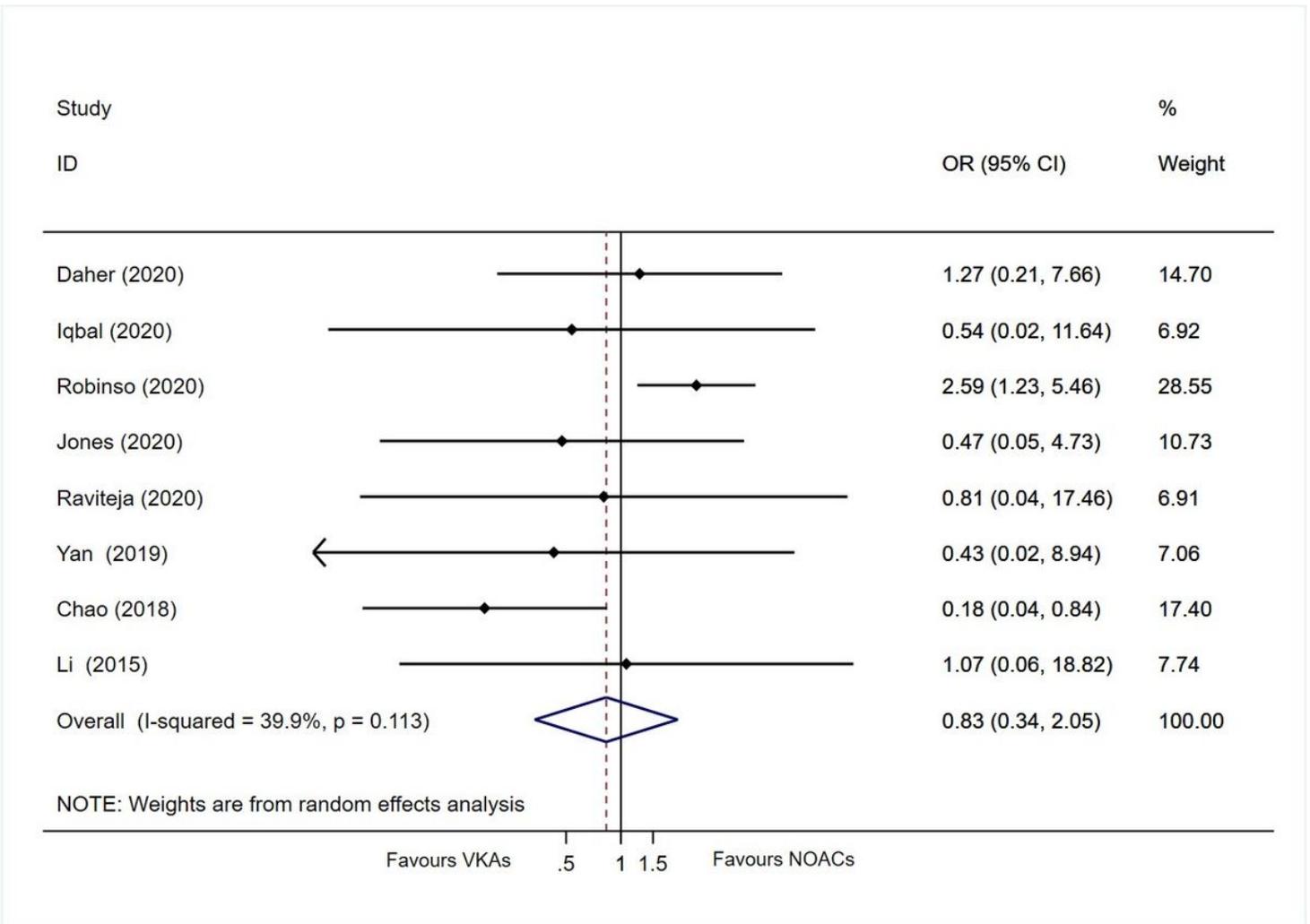


Figure 3
 Forest plot of systemic embolism between NOACs versus VKAs Abbreviation: OR: odds ratio; CI: Confidence interval; NOACs: non-vitamin K antagonist oral anticoagulants; VKAs: vitamin K antagonists.

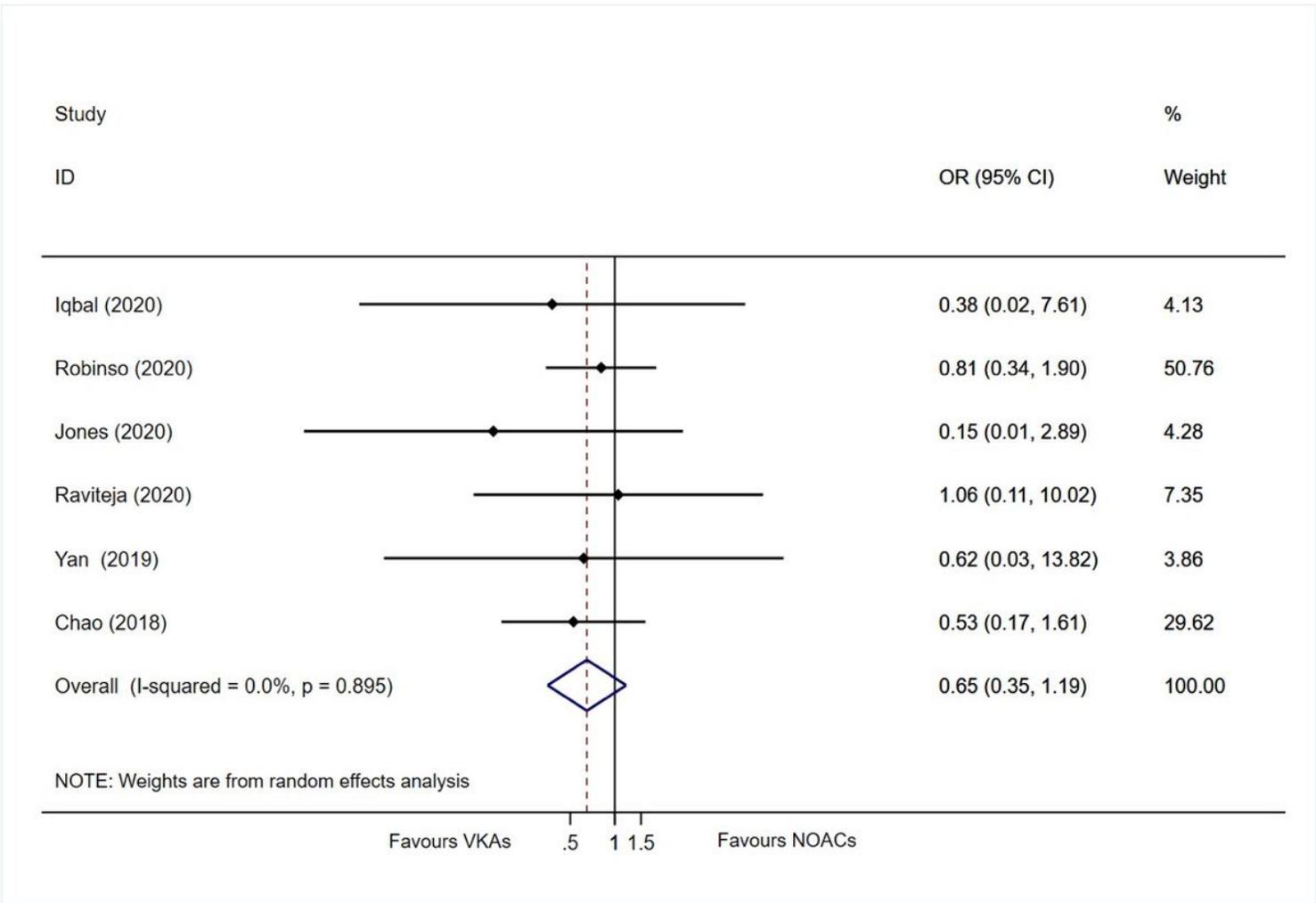


Figure 4

Forest plot of major bleeding between NOACs versus VKAs Abbreviation: OR: odds ratio; CI: Confidence interval; NOACs: non-vitamin K antagonist oral anticoagulants; VKAs: vitamin K antagonists.

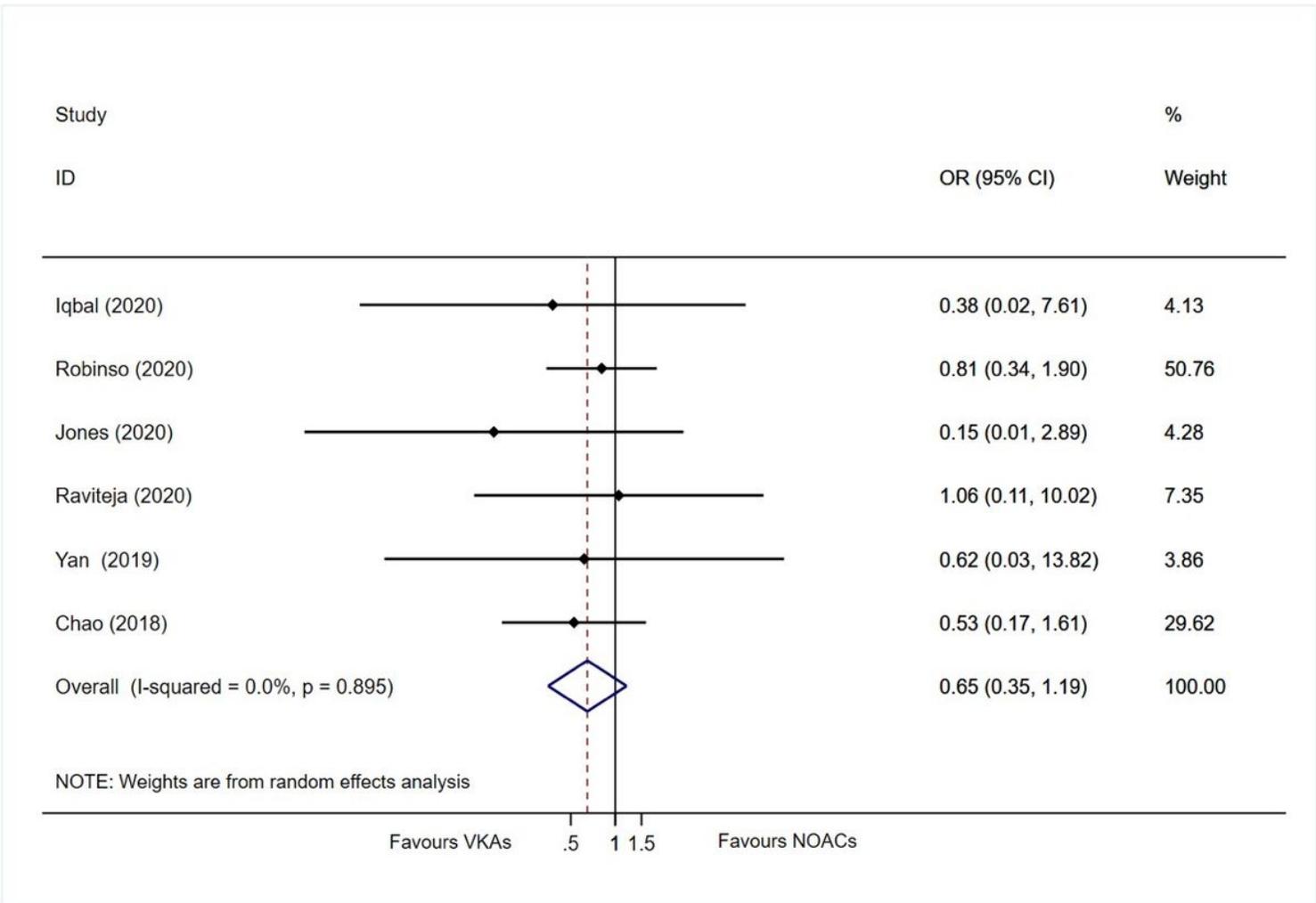


Figure 4

Forest plot of major bleeding between NOACs versus VKAs Abbreviation: OR: odds ratio; CI: Confidence interval; NOACs: non-vitamin K antagonist oral anticoagulants; VKAs: vitamin K antagonists.

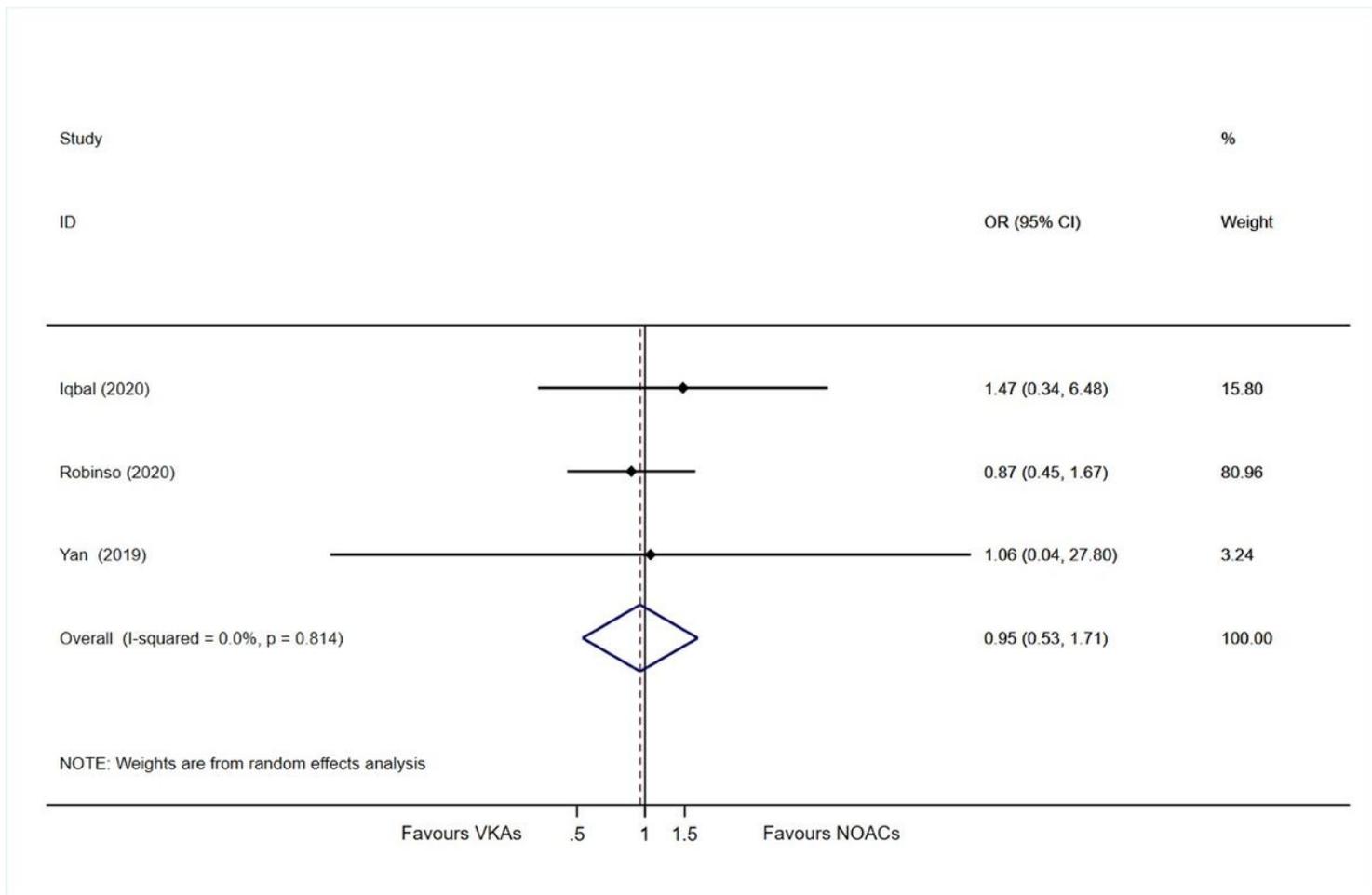


Figure 5

Forest plot of all-cause death between NOACs versus VKAs Abbreviation: OR: odds ratio; CI: Confidence interval; NOACs: non-vitamin K antagonist oral anticoagulants; VKAs: vitamin K antagonists.

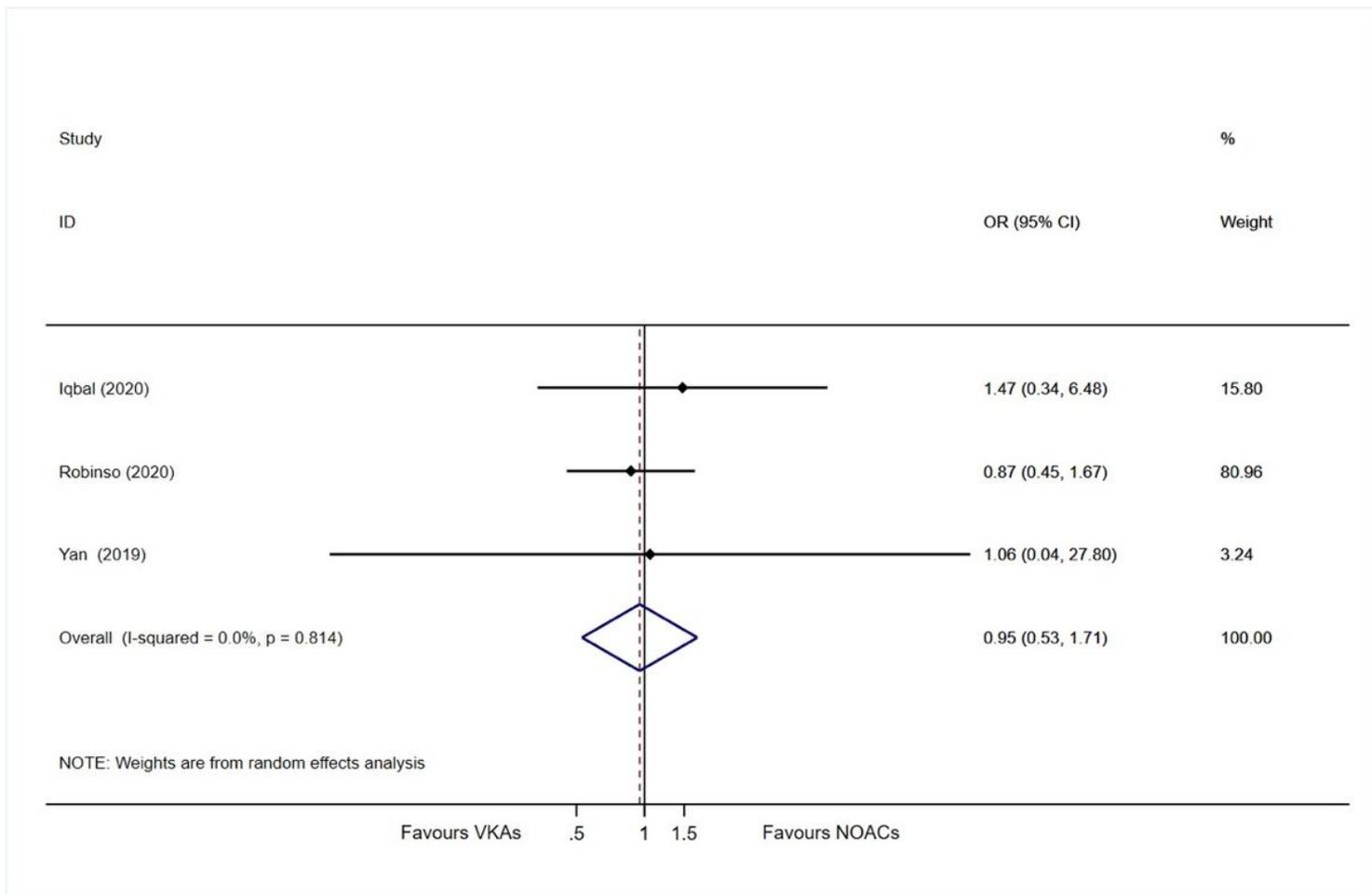


Figure 5

Forest plot of all-cause death between NOACs versus VKAs Abbreviation: OR: odds ratio; CI: Confidence interval; NOACs: non-vitamin K antagonist oral anticoagulants; VKAs: vitamin K antagonists.

Supplementary Files

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