Effectiveness and safety of rivaroxaban for anticoagulation therapy in COVID-19

A meta-analysis of randomized controlled trials

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ABSTRACT

الأهداف: لتقييم فعالية وسلامة مضادات تخثر الريفاروكسابان في مرضى COVID-19.

المنهجية: تم البحث في قواعد البيانات الإلكترونية PubMed و Embase ومكتبة كوكرين Cochrane Library، و ClinicalTrials.gov لتحديد جميع دراسات التجارب العشوائية ذات الصلة من 1 ديسمبر 2019 إلى 26 يوليو 2023.

النتائج: تم النظر في 6 تجارب عشوائية محكومة، شملت ما مجموعه 3323 مريضا، للتقييم. وعموماً، لم تكن معدلات الوفيات من جميع الأسباب على المدى القصير ومعدلات الاستشفاء مختلفة بشكل كبير بين الريفاروكسابان والمجموعات الشاهدة. وقد انخفضت أحداث الصرع بشكل كبير في مجموعة الوقاية ريفاروكسابان مقارنة بمجموعة التحكم الوهمية. ومع ذلك، لم يكن الانخفاض في الأحداث الخثارية مختلفة بشكل ملحوظ بين العلاج بالريفاروكسابان والهيبارين أو الهيبارين منخفض الوزن الجزيئي. قد ترتبط الوقاية من ريفاروكسابان والجرعة العلاجية بمعدل نزيف عام أعلى، ولكن معدلات النزف الرئيسية لم تختلف بشكل كبير.

الخلاصة: ريفاروكسابان قد يقلل من الأحداث الخثارية في المرضى COVID-19، ولكن لا يبدو أن لديه ميزة على الهيبارين أو LMWH، وأنه قد يزيد من خطر النزيف.

Objectives: To evaluate the effectiveness and safety of rivaroxaban anticoagulation in COVID-19 patients.

Methods: PubMed, Embase, Cochrane Library electronic databases, and ClinicalTrials.gov were searched to identify all relevant randomized controlled trial studies from December 2019 to July 2023.

Results: A total of 6 randomized controlled trials, which included a total of 3323 patients, were considered for evaluation. Overall, short-term all-cause mortality and hospitalization rates were not significantly different between the rivaroxaban and control groups. Thrombotic events were significantly reduced in the rivaroxaban prophylaxis group compared to the placebo control group. However, the reduction in thrombotic events was not significantly different between rivaroxaban therapy and heparin or low-molecular-weight heparin (LMWH). Rivaroxaban prophylaxis and the therapeutic dose may be associated with a higher rate of overall bleeding rate, but major bleeding rates did not differ substantially.

Conclusion: Rivaroxaban may reduce thrombotic events in COVID-19 patients, but it does not appear to have an advantage over heparin or LMWH, and it may increase the risk of bleeding.
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The COVID-19 pandemic resulted in an unprecedented number of illnesses and deaths.[1] More than 600 million cases were confirmed and 6 million deaths occurred worldwide.[2] Coagulopathy is a highly prevalent complication of COVID-19. Several clinical studies have shown that COVID-19 is linked to a higher risk of thrombosis.[3] Of these patients, 17% had pulmonary embolism, deep vein thrombosis (DVT), or other vascular events.[4] Autopsies of COVID-19 patients have revealed that thrombus in pulmonary vessels is a common occurrence.[5] Coagulation abnormalities are also widespread in these patients. People with

COVID-19 are at risk for thromboembolic events not only while in the hospital but also after discharge.[6]

Anticoagulants are widely used to prevent and treat thromboembolic and coagulation disorders, but the role and benefits of anticoagulants in patients with COVID-19 remain uncertain according to current clinical trials and meta-analyses.[7-9] Although prophylactic anticoagulation is recommended for hospitalized COVID-19 patients based on expert consensus and opinion, the current quality of evidence remains poor.[10,11] For anticoagulation in these patients, the recommended option is mainly low-molecular-weight heparins (LMWHs).[10,11]

Rivaroxaban is an oral inhibitor of Factor Xa approved for venous thromboembolism prophylaxis and treatment, as well as for stroke prophylaxis in non-valvular atrial fibrillation (NVAF).[12,13] There is limited high-quality literature on the use of rivaroxaban as an anticoagulant in patients with COVID-19.[10,11] Recently, there have been inconsistent conclusions on the effectiveness and safety of rivaroxaban in COVID-19 patients based on randomized controlled trials (RCTs). A meta-analysis is required to assess the safety and efficacy of rivaroxaban in clinical trials.

Methods. Two investigators (Shen, Liu) carried out a systematic search of the literature for eligible RCTs from December 2019 to July 2023. PubMed, Embase, Cochrane Library and ClinicalTrials.gov databases were searched. The search terms used were: "COVID-19" OR "Coronavirus disease 2019" OR "SARS-COV-2" AND "rivaroxaban" AND "randomized controlled trial" OR "randomized" OR "randomly" OR "controlled clinical trial" OR "trial". Subject words and free words were used for search strategies in all databases, and a manual search was carried out to ensure thoroughness. The 2 authors independently searched the databases and resolved any disagreements with a third author. This meta-analysis followed the PRISMA 2020 statement and its protocol.

The studies that were taken into consideration met the following set of standards: I) they carried out a study using an RCT design; II) study participants were aged 18 and over; III) the study involved patients who had laboratory-confirmed cases of COVID-19; and IV) participants were assigned to a rivaroxaban group using rivaroxaban anticoagulation, while the control group received a placebo, enoxaparin, or unfractionated heparin as the anticoagulation regimen. Exclusion criteria were not specified. The following 3 types of literature were excluded from this study: conference abstracts, studies lacking full text or with missing data, and non-English literature. **Figure 1** presents a flow diagram that explains the process of selecting studies.

The data was extracted using a predefined form by 2 independent reviewers (Shen and Liu) with disputes resolved by a third author (Qiu). The information extracted included the first author, publication year, country, study design, rivaroxaban dosage, control intervention, outcomes, and follow-up results. The study's main objective was to assess short-term all-cause mortality, defined as death within 35 days of initiating treatment, evaluated in the pooled mortality analysis. Secondary outcomes included bleeding complications, thrombotic event rates, and hospitalization rates. The statistical data was presented in the form of mean plus standard deviation (SD).

Zeng and Shen independently assessed the methodological quality of the included trials using the Cochrane Risk of Bias tool. Any divergences were settled by a third independent author (Qiu).

Statistical analysis. Meta-analysis was carried out using Review Manager version 5.4. Relative risk (RR) with 95% confidence intervals (CIs) was used for dichotomous data, while mean difference (MD) with 95% CIs was calculated for continuous data. We considered statistical significance at a *p*-value of <0.05.

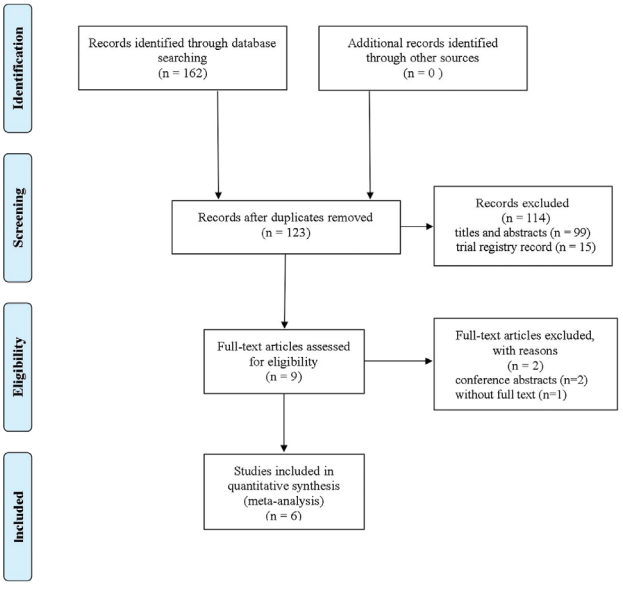

Figure 1 - The flowchart of literature inclusion.

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We calculated statistical heterogeneity using the I^2 statistic. Significant heterogeneity was present if I^2 was greater than or equal to 50%. A random-effects model was used when there was significant heterogeneity; otherwise, a fixed-effects model was used. Subgroup analysis was carried out based on the dose of rivaroxaban, including the prophylactic dose group (10 mg/day) and the therapeutic dose group (20 mg/day).

Results. After carrying out a thorough literature search, 2 authors (Shen and Zeng) retrieved 162 articles that were potentially eligible for inclusion. These articles were sourced from PubMed (n=22), Embase (n=102), Cochrane Library (n=36), and ClinicalTrials.gov (n=2). After removing duplicates by one author (Qiu), 39 articles were excluded. An additional 99 articles were excluded by 2 authors (Qiu and Liu) based on their titles and abstracts. One author (Zeng) read through 24 articles and excluded 2 of them as they were conference abstracts, 15 as they were trial registry records, and one as it did not have the full text. Finally, we included 6 RCTs in the meta-analysis.[14-19]

Table 1 presents the clinical characteristics of 3323 patients from studies carried out in Brazil, Germany, and the United States.[1-3] Out of these studies, one was carried out in a single center, while the remaining 5 were multicenter studies. The intervention group received oral rivaroxaban as an anticoagulation regimen, while the control group received a placebo, enoxaparin, or unfractionated heparin.

Table 1 - The summary characteristics of the included studies.

Study	Country	Study design	Disease severity	Interventions and dosage	Controls	Primary outcome	Follow up
Lopes et al[14]	Brazil	Multicentre open-label RCT	COVID-19 patients hospitalized with symptoms for up to 14 days	Rivaroxaban 20mg OD for 30 days or a reduced dose of 15 mg/day with a creatinine clearance of 30-49 mL/min or enoxaparin or intravenous UFH for patients with an unstable condition, followed by rivaroxaban for 30 days (n=311)	Enoxaparin or unfractionated heparin (n=304) CrCl ≥30: enoxaparin 40 mg SC every 24 hours or UFH 5000 units SC every 8-12 hours if BMI is <40; enoxaparin 60 mg SC every 24 hours or 40 mg SC every 12 hours or UFH 7500 units SC every 8-12 hours if BMI is ≥40; CrCl <30: UFH 5000 units SC every 8-12 hours if BMI <40; UFH 7500 units SC every 8-12 hours if BMI is ≥40.	Time to death, length of hospital stay and number of days on oxygen support	30 days
Ananworanich et al[15]	USA	Single center RCT	Patients with mild COVID-19 and high risk for severe COVID-19	Rivaroxaban 10mg OD for 21days (n=84)	Multivitamin one tablet OD for 21 days (n=82)	Serious AEs, hypersensitivity, major bleeding events, the frequency of AEs	35 days
Ramacciott et al[16]	USA	Multicentre open-label RCT	patients at discharge who were hospitalized with COVID-19 for a minimum of 3 days	Rivaroxaban 10mg OD (n=159)	Placebo (n=159)	Venous thromboembolism with symptomatic or fatal, asymptomatic symptomatic arterial thromboembolism, and cardiovascular death	35days
Avezum et al[19]	Brazil	Multicentre open-label RCT	Patients with mild or moderate COVID-19, within ≤7 days from symptom onset	Rivaroxaban 10 mg OD for 14 days (n=327)	Routine care (n=330)	Thromboembolic events rate of ventilation and hospitalization, mortality	30 days
Piazza et al[18]	USA	Multicentre double-blind RCT	Patients with COVID-19, at least one thrombosis risk factor	Rivaroxaban 10 mg OD for 35 days (n=599)	Placebo (n=598)	Thromboembolic events, all-cause hospitalization, all-cause mortality up to day 35	35 days
Rauch-Kröhnert et al[17]	Germany	Multicentre open-label RCT	Ambulatory or hospitalized adults with moderate to severe COVID-19	Rivaroxaban 20mg OD for at least 7 days and followed with 10 mg OD for 28 days (n=43)	heparin for at least 7 days followed by no thromboprophylaxis (n=45)	The D-dimer level, the WHO 7-category ordinal scale at 7 days	35 days

RCT: randomized controlled trial, COVID: coronavirus disease, OD: once daily, UFH: unfractionated heparin, CrCl: creatinine clearance, SC: subcutaneous, BMI: body mass index, AEs: adverse events, WHO: World Health Organization

The study evaluated the quality of 6 trials. Five studies had a high risk of bias due to inadequate allocation concealment or participant blinding. In 2 of the studies, the blinding of the outcome was also at high risk of bias (Figure 2).

Short-term all-cause mortality. All studies included in the analysis reported short-term all-cause mortality data of patients diagnosed with COVID-19. The rivaroxaban group had a mortality rate 2.96% (49/1657 patients) and the control group had amortality rate of 2.64% (44/1666 patients). The results of the study indicate that neither prophylactic (RR=0.60, 95% CI: [0.30-1.22], p=0.16, I^2=0%) nor therapeutic doses (RR=1.52, 95% CI: [0.93-2.48], p=0.10, I^2=0%) of rivaroxaban significantly reduced short-term all-cause mortality, as shown in Figure 3.

Major bleeding rate. The criteria for major bleeding follows the clinical definition of the International Society on Thrombosis and Haemostasis.[20] This refers to severe bleeding that can be fatal, bleeding in critical areas or organs such as the brain, spine, eyes, abdomen, joints, or heart, or bleeding that causes a significant drop in hemoglobin levels or requires a transfusion of 2 or more units of blood. The studies focused on the occurrence rate of significant bleeding. The prophylactic dose group had 2/1304 (0.15%) patients and the control group had 0/1317 (0%) patients. The therapeutic dose group had 11/353 (3.12%) patients and the control group had 4/349 (1.11%) patients. The results of the study indicate that neither prophylactic (fixed-effects model, RR=3.01, 95% CI: [0.31-28.89], p=0.34, I^2=0%) nor therapeutic doses (fixed-effects model, RR=2.53, 95% CI: [2.86-7.43], p=0.09, I^2=0%) of rivaroxaban significantly increased the major bleeding rate (Figure 4).

Overall bleeding rate. All studies included in the analysis reported bleeding complications associated with rivaroxaban. The results showed a significant increase in overall bleeding rate for both prophylactic (2.84% vs. 0.84%, RR=3.28, 95% CI: [1.7-6.33], p=0.0004, I^2=0%) and therapeutic doses (11.3% vs. 3.72%, RR=3.06, 95% CI: [1.66-5.63], p=0.0003, I^2=67%) of rivaroxaban anticoagulation (Figure 5).

Thrombotic events. Thrombotic events were investigated in all included studies. These events include symptomatic venous thromboembolism, myocardial infarction, ischemic stroke, pulmonary embolism, acute limb ischemia, and systemic arterial embolism outside of the central nervous system. The study findings indicate that rivaroxaban at a preventative dosage is more effective than the placebo group in reducing thrombotic events (0.31% vs. 1.37%, RR=0.27, 95% CI: [0.08-0.95], p=0.04, I^2=17%) in 4 RCTs. Two RCTs showed no significant difference between patients treated with therapeutic doses and the control group treated with heparin or LMWH (6.80% vs. 11.2%, RR=0.38, 95% CI: [0.06-2.31], p=0.29, I^2=69%; Figure 6).

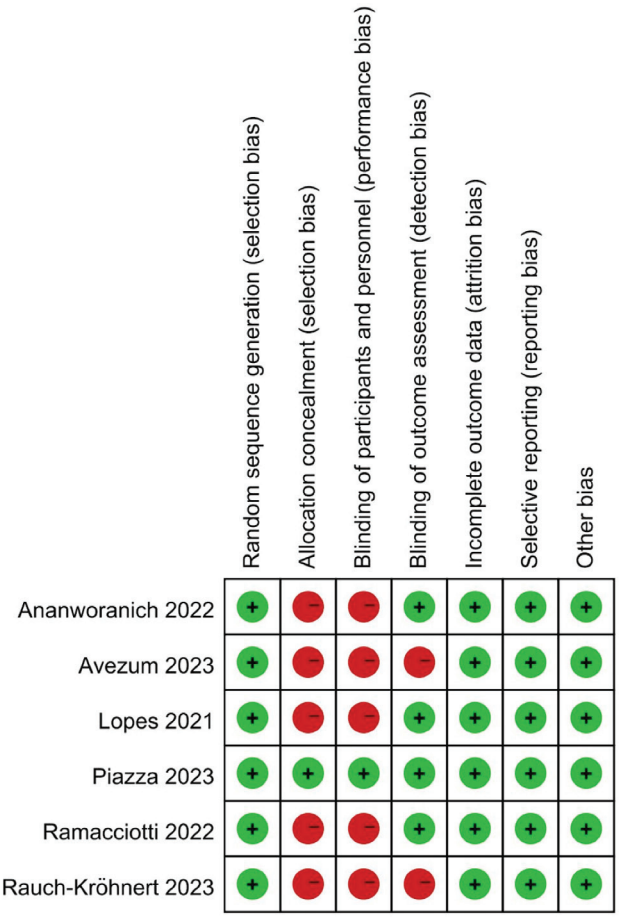

Figure 2 - Risk of bias summary of included studies.[14-19]

Hospitalization. Only 3 studies investigated hospitalization rates in outpatients. No significant differences were found between the rivaroxaban group and the control group (fixed-effects model, RR=1.08, 95% CI: [0.76-1.54], p=0.66, I^2=0%; Figure 7).

Discussion. Our meta-analysis revealed that oral prophylactic rivaroxaban anticoagulation can reduce thrombotic events in COVID-19 patients compared to the placebo. However, no significant difference was found in the administration of oral therapeutic doses of rivaroxaban compared to LMWH and heparin groups. It is worth noting that while both prophylactic and therapeutic doses of rivaroxaban did not increase the frequency of major bleeding, they may be linked to a rise in the overall incidence of bleeding.

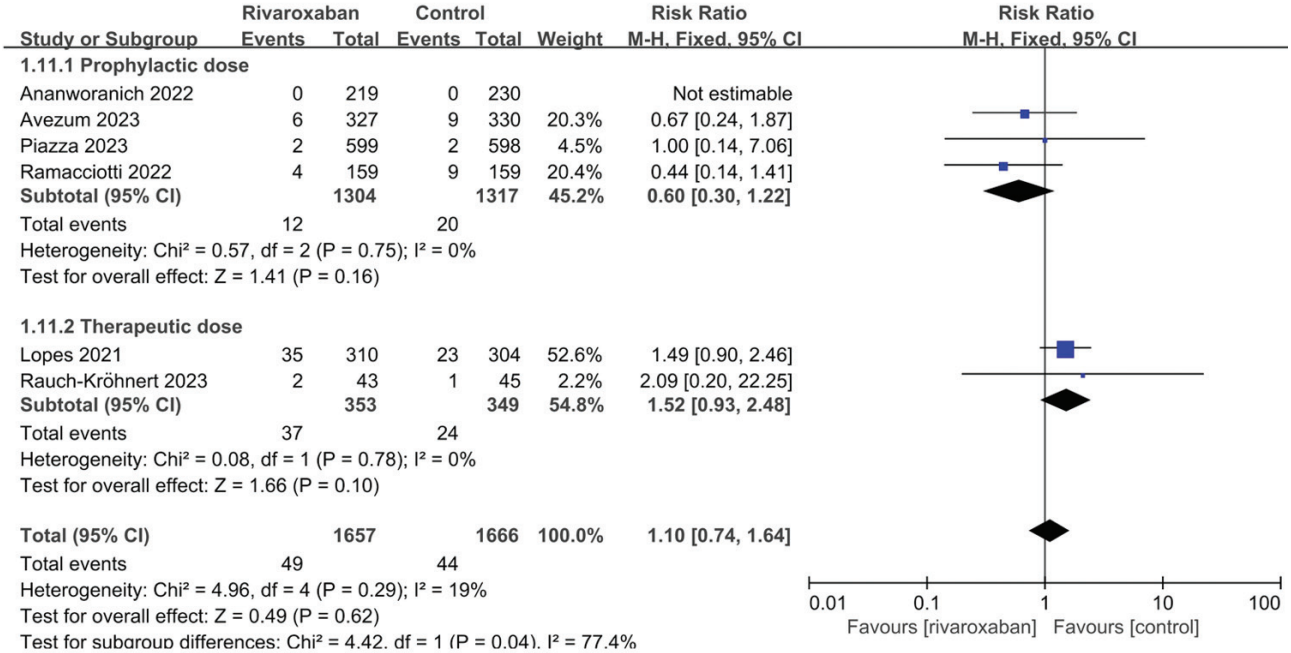

Figure 3 - Forest plot of the effects of rivaroxaban on short-term all-cause mortality.

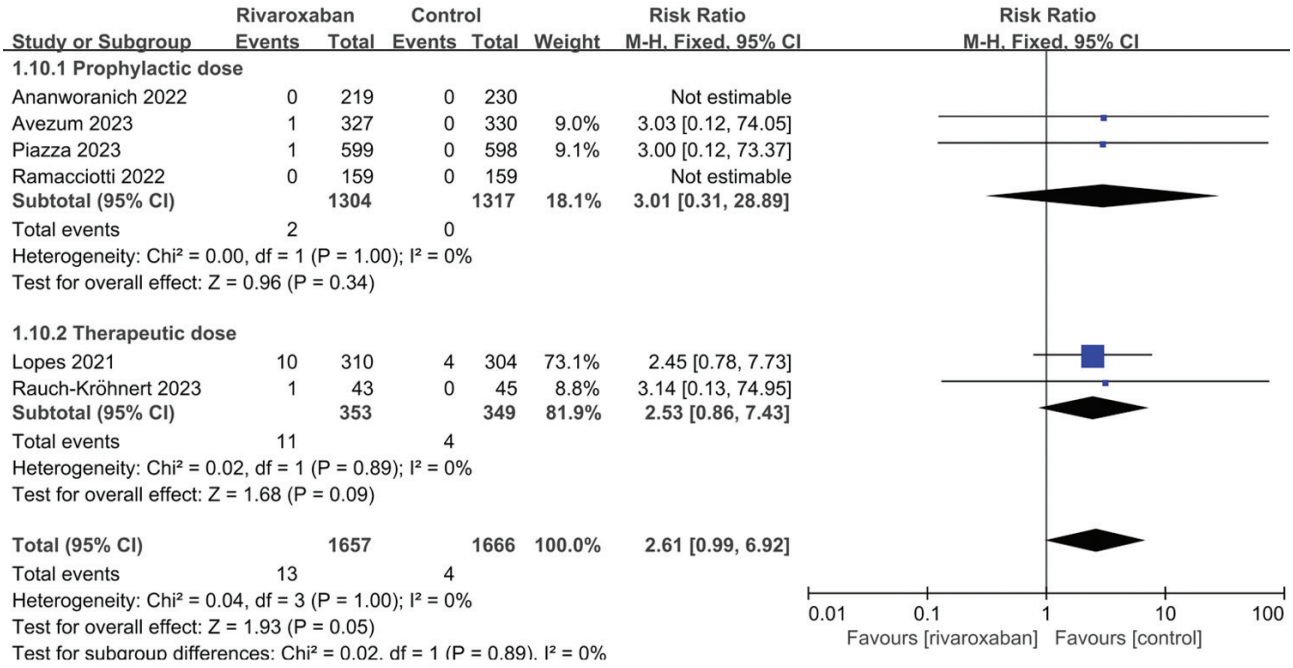

Figure 4 - Forest plot of the effects of rivaroxaban on the major bleeding rate.

One published meta-analysis assessed the clinical efficacy of rivaroxaban for prophylactic anticoagulation in COVID-19 by pooling data from 2 RCTs.[21] The study found no reduction in mortality, myocardial infarction, ischemic strokes, acute limb ischemia, or hospitalizations.[21] The pooled analysis revealed that rivaroxaban could reduce arterial and venous thrombotic events without any critical site or fatal

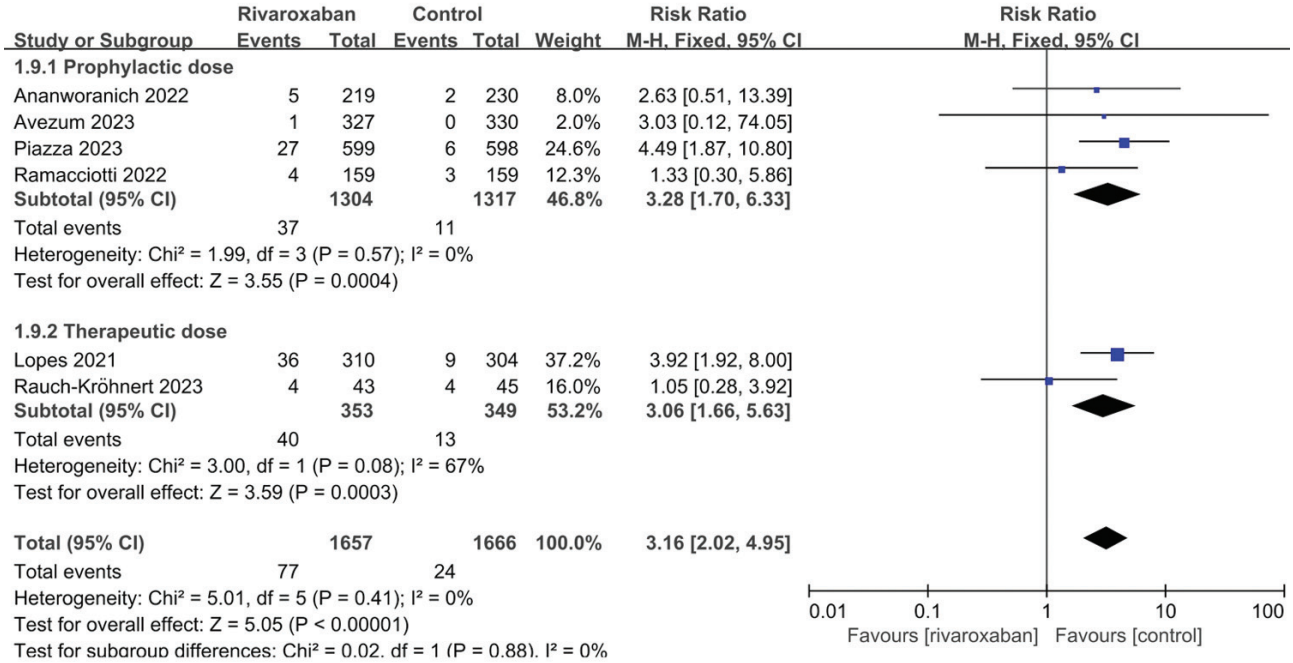

Figure 5 - Forest plot of the effects of rivaroxaban on the overall bleeding rate.

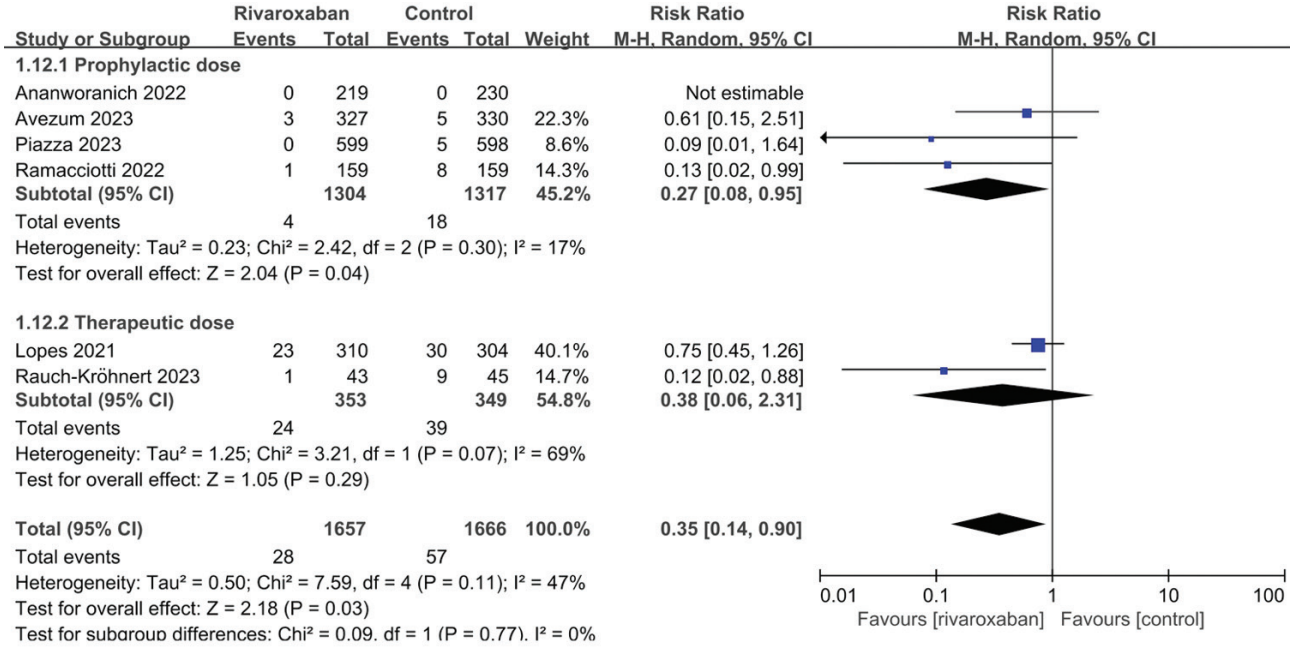

Figure 6 - Forest plot of the effects of rivaroxaban on the thrombotic events.

bleeding events. Given the limited information in the aforementioned study, our research yielded similar results by incorporating data from more published RCTs.

The prevention of thrombotic events in patients taking rivaroxaban is consistent with its effect on thrombotic prevention in patients with other diseases. Several meta-analyses have investigated the safety and efficacy of rivaroxaban thromboprophylaxis in patients who do not have COVID-19. Chen et al[22] reported that the bleeding risks associated with rivaroxaban depended on dosage. Rinaldi et al[23] found that rivaroxaban as a

Figure 7 - Forest plot of the effects of rivaroxaban on the hospitalization rates in outpatients.

thromboprophylaxis agent for orthopedic surgery had better efficacy than enoxaparin but the same safety profile. A meta-analysis showed the superiority of rivaroxaban over enoxaparin for the treatment of deep vein thrombosis in total knee replacement patients.[24] However, in our study no such advantage was found for rivaroxaban.

A spectrum of anticoagulants, including LMWH, and direct oral anticoagulants such as rivaroxaban, are used to manage COVID-19 in both prophylactic and therapeutic approaches. Most clinical guidelines and consensus recommend LMWH and unfractionated heparin as lead anticoagulants in COVID-19. Rivaroxaban is recommended in some selected populations with COVID-19 such as those with mild symptoms, with suspicion of heparin-induced thrombocytopenia, and who have been discharged. The quality of the evidence for these guidelines and consensus is low. Our work suggested that patients with COVID-19 do not benefit from oral rivaroxaban anticoagulant.

We did not find any significant differences in short-term all-cause mortality, major bleeding rate, and hospitalization rates between the rivaroxaban and control groups. In the rivaroxaban prophylaxis group, thrombotic events were significantly decreased compared with the placebo control group (RR=0.27, 95% CI: [0.08-0.95], p=0.04, I^2=17%). No notable differences were observed in the rivaroxaban therapeutic dose group compared with the heparin or LMWH group (RR=0.38, 95% CI: [0.06-2.31], p=0.29, I^2=69%). Furthermore, this requires care as rivaroxaban prophylaxis (RR=3.28, 95% CI: [1.7-6.33], p=0.0004, I^2=0%) and therapeutic dose (RR=3.06, 95% CI: [1.66-5.63], p=0.0003, I^2=67%) were related to a higher frequency of overall bleeding rate.

Study limitations. In discussing the results of this meta-analysis, it is important to consider several limitations. small number of studies in your meta-analysis First, due to limited data, more indicators evaluating other aspects between the rivaroxaban and control groups were not presented. Second, this study enrolled small number of studies, which may lead to biased results. Finally, the control groups included blank controls, placebo controls, and controls treated with enoxaparin or heparin; the different types of control groups may have led to bias.

In conclusion, this meta-analysis indicated that prophylactic or therapeutic doses of rivaroxaban could not improve clinical outcomes for patients with COVID-19. However, it may reduce the risk of thrombotic events in these patients, but it will also lead to an increased risk of overall bleeding rates. Further research is required to confirm our findings, specifically through larger sample sizes and methodologically rigorous prospective studies.

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