# Use of anticoagulants in patients with COVID-19: a living systematic review and meta-analysis

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## ABSTRACT

**Objective:** To answer questions related to the use of anticoagulants in the treatment of COVID-19 patients. **Methods:** This was a systematic review and meta-analysis of phase 3 randomized controlled trials comparing the use of anticoagulants in non-hospitalized and hospitalized COVID-19 patients. We searched the following databases: MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov from their inception to January 22, 2022. The risk of bias was assessed by the Cochrane risk-of-bias tool, and the quality of evidence was assessed by the Grading of Recommendations Assessment, Development and Evaluation system. **Results:** A total of 401 studies were initially selected. Of those, 9 met the inclusion criteria and were therefore analyzed (a total of 6,004 patients being analyzed). In non-hospitalized COVID-19 patients, no significant difference was found between post-discharge prophylactic anticoagulation and no intervention regarding venous thromboembolism or bleeding at 30 days. In hospitalized COVID-19 patients, full anticoagulation resulted in a slight reduction in thrombotic events at 30 days (risk difference, −0.03; 95% CI, −0.06 to −0.00; p = 0.04; $I^2$ = 78%), the quality of evidence being moderate. However, no significant difference was found between full anticoagulation and no intervention regarding the risk of major bleeding, the quality of evidence being very low. No significant difference was found between intermediate- and standard-dose prophylactic anticoagulation (risk difference, −0.01; 95% CI, −0.07 to 0.06; p = 0.81; $I^2$ = 0%), the quality of evidence being very low. **Conclusions:** Therapeutic anticoagulation appears to have no effect on mortality in COVID-19 patients, resulting in a slight reduction in venous thromboembolism in hospitalized patients.

**Keywords:** Anticoagulants; COVID-19; SARS-CoV-2.

## INTRODUCTION

Almost two years after the emergence of COVID-19, efforts have been made to control the severity of disease progression and reduce the risk of death. Reports from the World Health Organization confirm that nearly 269 million confirmed cases and nearly 5.3 million deaths had been reported globally as of December 12, 2021.[1]

Viral and host cell membrane fusion in pulmonary alveolar epithelial cells allows viral replication, with local and systemic inflammatory progression. The release of systemic cytokines characteristic of the cytokine storm can increase cyclic lung damage, including diffuse alveolar damage, and cause ARDS.[2] ARDS is associated with epithelial-endothelial barrier injury that increases the influx of inflammatory cells, as demonstrated by autopsy studies of patients with severe endothelial damage and intracellular viruses, rupture of cell membranes, infiltration of airspaces, interstitial edema, and pulmonary edema.[2] Concomitantly, the activation of coagulation and consumption of clotting factors increase the risk of coagulopathy and microthrombus formation, contributing to a high incidence of thrombotic events.[3] Therefore, in patients with severe COVID-19, the risk of death is high, and viral sepsis is life-threatening because of multiorgan failure.

COVID-19 is associated with an increased risk of venous thromboembolism (VTE); this can occur in 20% of patients and mainly affects those with very severe disease.[4] Therefore, most guidelines recommend assessing the risk of VTE by using stratification and prophylaxis models.[3] However, there is uncertainty regarding how to choose the best dose of chemoprophylaxis, or even if complete anticoagulation is capable of reducing VTE or arterial thromboembolism (ATE) in comparison with a prophylactic dose.

In a Cochrane systematic review published before the publication of a randomized controlled trial (RCT),[5] descriptive information was provided on the effects of anticoagulants on COVID-19. However, other systematic reviews have not considered the subgroups of COVID-19 severity or the doses of drugs administered, and most have included retrospective observational studies.[6-8] Therefore, our main objective was to evaluate the effect of anticoagulation on COVID-19 of varying severity, as

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well as to evaluate mortality, VTE, ATE, and major bleeding associated with anticoagulation interventions.

## METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses recommendations.[9]

### *Eligibility criteria*

The study protocol followed the Patients of interest, Intervention to be studied, Comparison of interventions, and Outcome of interest (PICO) methodology. With the use of anticoagulants as the main study point, the PICO framework was as follows: patients—adult COVID-19 patients; intervention—use of anticoagulants; comparison—comparison between the standard of care (SOC) and placebo; and outcome—the 30-day all-cause mortality rate, bleeding or major bleeding, and ATE (ATE-myocardial infarction, non-hemorrhagic stroke, major adverse limb events, and cardiovascular death) or VTE at 30 days.

All phase 3 RCTs on the topic were included. No restrictions were imposed with regard to date of publication, language, or full-text availability. The study protocol was registered with the International Prospective Register of Systematic Reviews (Registration no. CRD42021289669).

Considering the living systematic review strategy, we will search for new RCTs every six months and add new information to this systematic review.

### *Information sources and search strategy*

Two of the authors developed search strategies that were revised and approved by the research team; selected information sources; and systematically searched the following databases: MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov. Search strategies included the following: ("COVID-19" OR "COVID" OR "coronavirus" OR "SARS-CoV-2") AND ("anticoagulant" OR "anticoagulation" OR "agents anticoagulant") AND ("indirect thrombin inhibitors" OR "enoxaparin" OR "fondaparinux" OR "heparin" OR "warfarin") AND (therapy/narrow[filter] OR prognosis/narrow [filter] OR comparative study OR comparative studies); and (COVID-19 OR COVID OR CORONAVIRUS OR SARS-CoV-2) AND (anticoagulant).

### *Study selection*

Two researchers independently selected and extracted data from the included studies. First, articles were selected by title and abstract. Then, the selected articles were read in their entirety to decide whether they should be included or excluded, with disagreements being resolved by consensus or following a discussion with a third researcher.

### *Data collection and investigated outcomes*

Data regarding authorship, year of publication, patient description, interventions (anticoagulant use and SOC), absolute numbers of outcomes, and follow-up duration were independently extracted from the studies by two researchers, and the extracted values were compared.

### *Risk of bias and quality of evidence*

The risk of bias for RCTs and other important data were assessed with the Cochrane risk-of-bias tool for randomized trials (RoB 2),[10,11] being expressed as very serious, serious, or non-serious. The risk of bias was assessed by two independent reviewers, disagreements being resolved through discussion with a third reviewer. The quality of evidence was extrapolated from the risk of bias and was described by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) terminology[12] as very low, low, or high; for meta-analyses, the GRADEpro Guideline Development Tool[13] describes the quality of evidence as very low, low, moderate, or high.

### *Synthesis of results and analysis*

Categorical outcomes were expressed by group (anticoagulant use or SOC), number of events, and calculated risk (in %) for each group (by dividing the number of events by the total number of patients in each group). If the risk difference (RD) between the groups was significant, a 95% CI was expressed on the basis of the number needed to treat (NNT) or the number needed to harm. We analyzed separate RCTs assessing outpatients and hospitalized patients or full anticoagulation and intermediate prophylactic doses. We also analyzed the subgroups of patients with moderate COVID-19 (non-ICU patients) and severe COVID-19 (ICU patients).

We used fixed- or random-effects meta-analysis to evaluate the effect of anticoagulant use vs. SOC on the outcomes when these data were available in at least two RCTs. The effects were reported as RDs and corresponding 95% CIs; a 95% CI including 0 in its range indicated that there was no difference in the outcome effect between the anticoagulant and SOC arms. RDs show the absolute effect size in the meta-analysis when compared with the relative risk or odds ratio, and this technique can be used when the binary outcome is zero in both study arms. Heterogeneity of effects across studies was quantified with the $I^2$ statistic, an $I^2 > 50\%$ indicating high heterogeneity. For the meta-analysis, we used the Review Manager software, version 5.4 (RevMan 5; Cochrane Collaboration, Oxford, United Kingdom).

## RESULTS

A total of 401 studies were retrieved from the selected databases. After eliminating duplicates and including studies that met the eligibility criteria, we selected 11 studies for full-text assessment. Of those, 2 were excluded (Figure 1). Therefore, 9 RCTs were included in the present systematic review and meta-analysis.[14-22] The study characteristics, risk of bias, and quality of evidence are presented in Tables 1 and 2, as well as in Tables S1-S3).

The study population included 6,004 patients with mild to severe COVID-19. Of those, 3,037 received anticoagulants and 2,967 received SOC or placebo. When the study population was stratified by COVID-19 hospitalization, post-discharge COVID-19 patients were represented in 1 RCT including 160 patients in the placebo group and 160 patients in the prophylactic group.[22] We included 8 RCTs of hospitalized patients with moderate to severe disease, stratified by type of anticoagulation: full anticoagulation vs. SOC and intermediate prophylactic dose vs. SOC.[14-21]

With regard to the risk of bias of RCTs,[14-22] 4 had randomization and blinded allocation with risk of bias.[15,17,20,22] Furthermore, only 1 RCT was double-blinded,[21] whereas the others (i.e., 8) were single-blinded, allowing the assessment of outcomes without being blinded .[14-20,22] Five RCTs used composite outcomes.[16-19,22] One study did not report baseline characteristics, thus precluding demonstration of similarity across groups for comparison.[21] One study did not describe the sample size calculation,[15] and one did not use intention-to-treat analysis[21]; all of these were considered a risk of bias (Table 2). Therefore, the global risk of bias was considered to be moderate.

### *Non-hospitalized COVID-19 patients*

One RCT[22] was included in the analysis of non-hospitalized patients with COVID-19. The study in

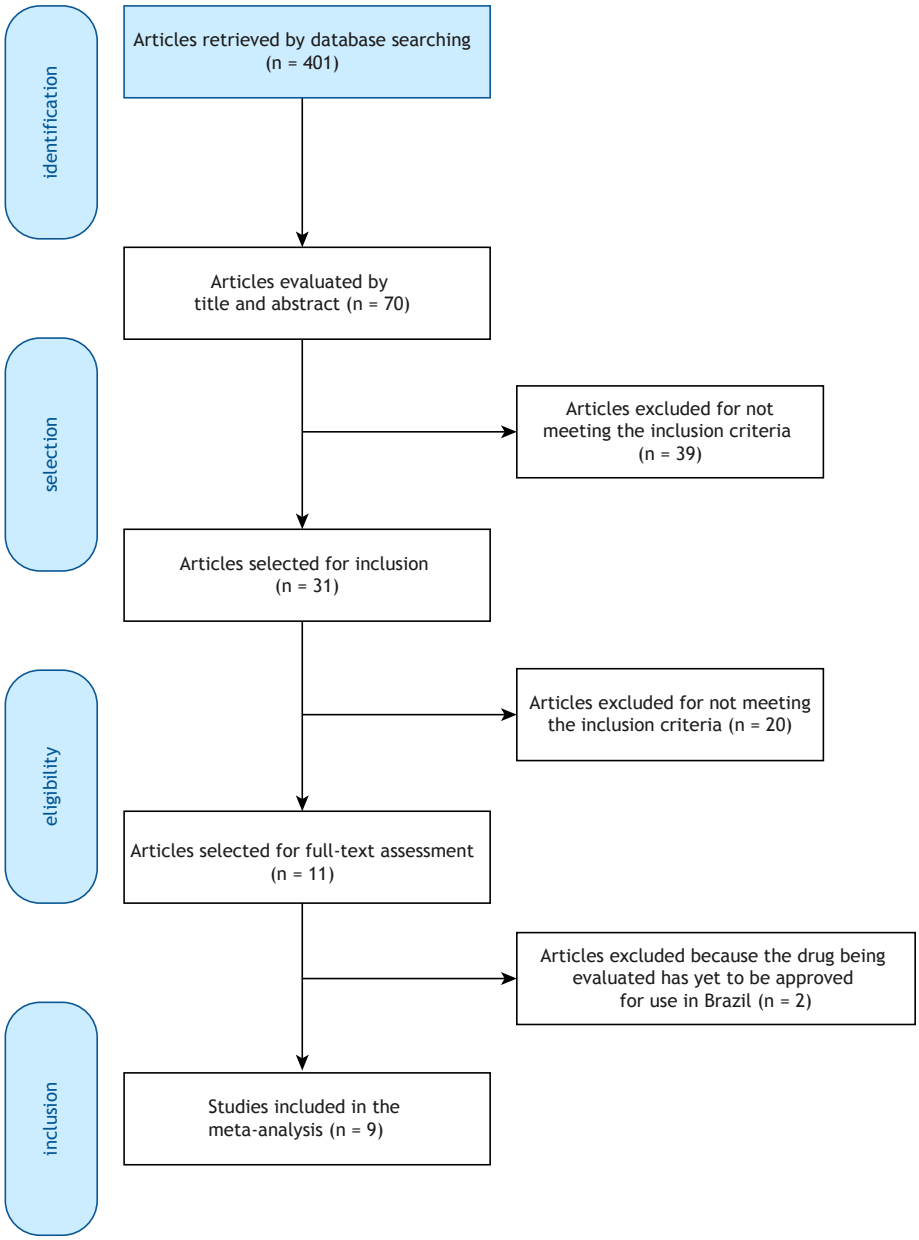



**Figure 1.** Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of the process of including studies in our systematic review and meta-analysis.

**Table 1.** Description of the studies included in the meta-analysis.

| Study | Design | Population | Intervention | Comparator | Outcome | Duration |
|---|---|---|---|---|---|---|
| Perepu et al.[20]) | Open-label RCT | Adults hospitalized with COVID-19 | N = 88 Intermediate dose of enoxaparin (of 1 mg/kg/day for a BMI of < 30 kg/m$^2$ or of 0.5 mg/kg 12/12 h for a BMI > 30 kg/m$^2$) | N = 88 Prophylactic enoxaparin 40 mg/day (for a BMI of < 30 kg/m$^2$) or 30-40 mg 12/12 h (for a BMI > 30 kg/m$^2$) | Mortality at 30 days<br>Venous/arterial thromboembolism<br>Bleeding | 30 days |
| INSPIRATION Investigators et al.[21] | RCT with blinded outcome assessment | Adult ICU COVID-19 patients within 7 days of hospitalization | N = 280 Enoxaparin 1 mg/kg/day (120 kg) Changed to unfractionated heparin if kidney function < 30 ml/min | N = 286 Enoxaparin 40 mg/kg/day | Venous/arterial thromboembolism<br>Need for ECMO<br>No. of days free of mechanical ventilation<br>ICU discharge<br>Bleeding | 30 days |
| REMAP-CAP Investigators et al.[16] | Open-label RCT | Adult ICU COVID-19 patients requiring respiratory or cardiac support | N = 534 Anticoagulation with unfractionated or low-molecular-weight heparin | N = 564 Low-dose thromboprophylaxis or enhanced intermediate-dose thromboprophylaxis | Venous/arterial thromboembolism<br>No. of organ support-free days<br>Bleeding<br>Survival to hospital discharge | 21 days |
| ATTACC Investigators et al.[18] | Open-label RCT | Adult ward patients with COVID-19 not requiring respiratory or cardiac support | N = 1,190 Anticoagulation with unfractionated or low-molecular-weight heparin | N = 1,054 Low-dose thromboprophylaxis or enhanced intermediate-dose thromboprophylaxis | Venous/arterial thromboembolism<br>No. of organ support-free days<br>Bleeding<br>Survival to hospital discharge | 21 days |
| Sholzberg et al.[17] | Open-label RCT | Adults hospitalized with COVID-19, a D-dimer above the upper limit of normal, and an $SpO_2$ of < 93% on room air | N = 228 Anticoagulation with unfractionated or low-molecular-weight heparin | N = 237 Low-dose thromboprophylaxis with unfractionated or low-molecular-weight heparin | Mortality<br>Mechanical ventilation or death<br>No. of days free of mechanical ventilation<br>ICU admission or death<br>Venous/arterial thromboembolism<br>No. of organ support-free days<br>Bleeding | 28 days |

Continue...▶

**Table 1.** Description of the studies included in the meta-analysis. (Continued...)

| Study | Design | Population | Intervention | Comparator | Outcome | Duration |
|---|---|---|---|---|---|---|
| Lopes et al.[14] | Open-label RCT | Adults hospitalized with COVID-19 within 14 days of the onset of symptoms, a D-dimer above the upper limit of normal, and an $SpO_2$ of < 93% on room air | N = 310 Rivaroxaban 20 mg/day for stable patients or enoxaparin 1 mg/kg 12/12 h for unstable patients | N = 304 Low-dose thromboprophylaxis with unfractionated or low-molecular-weight heparin | Mortality<br>Hospital length of stay<br>Duration of oxygen use<br>Venous/arterial thromboembolism<br>Bleeding | 30 days |
| Oliynyk et al.[15] | Open-label RCT | Adults hospitalized with COVID-19, a D-dimer > 3 mg/L, and a $PaO_2$ of < 60 mmHg on room air | N = 84 Anticoagulation with unfractionated or low-molecular-weight heparin | N = 42 Low-molecular-weight heparin | Mortality<br>Mechanical ventilation or death | 28 days |
| Spyropoulos et al.[19] | Open-label RCT | Adults hospitalized with COVID-19 and a D-dimer > 4 times the upper limit of normal, requiring supplemental oxygen | N = 130 Anticoagulation with enoxaparin 1 mg/kg 12/12 h or 0.5 mg/kg 12/12 h if CrCl = 15-39 mL/min/1.73 $m^2$ | N = 127 Enoxaparin 30-40 mg/kg once or twice daily or unfractionated heparin 22,500 IU | Venous/arterial thromboembolism<br>Mortality<br>Bleeding<br>Endotracheal intubation<br>Rehospitalization | 30 days |
| Ramacciotti et al.[22] | Open-label RCT | Discharged COVID-19 patients with an IMPROVE VTE risk score ≥ 4 or = 2-3 and a D-dimer > 1,000 ng/ml during hospitalization | N = 160 Rivaroxaban 10 mg/day for 35 days | N = 160 Standard of care | Mortality related to venous/arterial thromboembolism<br>Bleeding | 30 days |

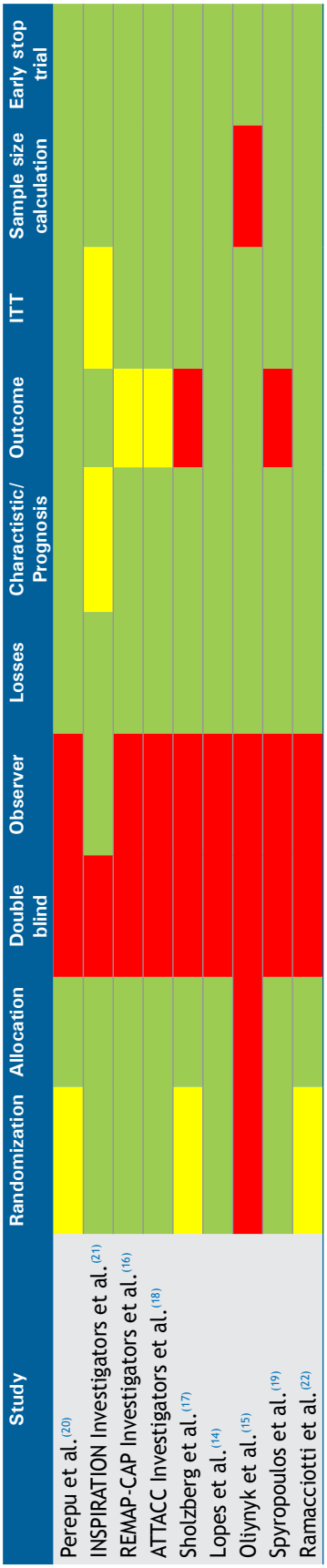
RCT: randomized controlled trial; IMPROVE: International Medical Prevention Registry on Venous Thromboembolism; VTE: venous thromboembolism; and ECMO: extracorporeal membrane oxygenation.

question randomized COVID-19 patients on the day of hospital discharge to receive rivaroxaban 10 mg (extended thromboprophylaxis) or no pharmacological intervention after 35 days. These patients presented with a high risk of VTE. To define this population, the authors used an International Medical Prevention Registry on Venous Thromboembolism VTE risk score > 4 or an International Medical Prevention Registry on Venous Thromboembolism VTE risk score of 2/3 with an elevated D-dimer (> 500 ng/mL or twice the baseline value). The primary outcome was a composite of the following: symptomatic VTE; VTE-related death; asymptomatic VTE detected by venous duplex ultrasound of the lower extremities and CT pulmonary angiography; symptomatic ATE; and cardiovascular death at day 35. The results of the study showed no significant difference in VTE between the intervention group and the SOC group (RD, −0.02; 95% CI, −0.04 to 0.01). There was also no significant difference in symptomatic pulmonary thromboembolism between the intervention group and the SOC group (RD, −0.01; 95% CI, −0.03 to 0.01). Finally, there was no significant difference in fatal pulmonary embolism between the intervention group and the SOC group (RD, −0.02; 95% CI, −0.04 to 0.01), the quality of evidence being very low (Table S1).[22]

### *Hospitalized COVID-19 patients*

Six RCTs[14-19] were included in the analysis of hospitalized COVID-19 patients, with 2,491 patients in the therapeutic dose group (full anticoagulation) and 2,422 patients in the SOC group. As can be seen in Figure 2A, there was no significant reduction in the 30-day mortality rate in patients with moderate to severe disease (RD, −0.01; 95% CI, −0.04 to 0.02; p = 0.50; $I^2$ = 59%), the quality of evidence being

**Table 2.** Risk of bias of the randomized controlled trials included in the meta-analysis.[a]




ITT: intention to treat. [a]Red, risk of bias; yellow, not clear; and green, no risk of bias.

very low (Table S2). When patients with moderate COVID-19[14,15,17,18] or severe COVID-19[16] were analyzed separately, no significant difference was found between full anticoagulation and SOC in those with moderate COVID-19 (RD, −0.02; 95% CI, −0.06 to 0.03; p = 0.41; $I^2$ = 75%; Figure 2B), the quality of evidence being very low (Table S2). Only one study assessed severe COVID-19 patients, showing no significant difference in the mortality rate between the two groups (RD, 0.01; 95% CI, −0.04 to 0.07; p = 0.66), with a very low quality of evidence (Table S2).

Thrombotic events (VTE events, ATE events, or both) were assessed in 5 studies,[14,16-19] with a total of 2,449 patients in the therapeutic dose group and 2,338 patients in the SOC group. As can be seen in Figure 2C, there was a significant reduction (of 3%) in thrombotic events at 30 days in the therapeutic dose group in comparison with the SOC group (RD, −0.03; 95% CI, −0.06 to −0.00; p = 0.04; $I^2$ = 78%), the NNT being = 33. The quality of evidence was moderate (Table S2). This result was persistently significant when the severity of COVID-19 was evaluated. For patients with moderate COVID-19,[17,18] 2 studies demonstrated a reduction of 1% in RD (95% CI, −0.02 to −0.00; Figure 2D), the NNT being = 100 and the quality of evidence being low (Table S2). For severe COVID-19 patients,[16] 1 study demonstrated a significant reduction (of 4%) in VTE after 30 days (95% CI, −0.04 to −0.01; p = 0.02), the NNT being = 25 and the quality of evidence being low (Table S2).

Major bleeding within 30 days was described in 5 studies, with a total sample of 4,787 patients.[14,16-19] As can be seen in Figure 2E, there was no significant difference in major bleeding between full coagulation and SOC (RD, 0.02; 95% CI, −0.00 to 0.04; p = 0.13; $I^2$ = 71%), the quality of evidence being very low. When moderate COVID-19 patients were analyzed,[15,18-20] no significant difference was found between the two groups (RD, 0.01; 95% CI, −0.02 to 0.04; p = 0.40; $I^2$ = 72%), the quality of evidence being very low (Table S2). For patients with severe COVID-19, 2 RCTs showed no significant differences in major bleeding between the two groups (RD, 0.04; 95% CI, −0.03 to 0.11; p = 0.11; $I^2$ = 61%; Figure 2G),[16,19] the quality of evidence being very low (Table S2).

### *Intermediate prophylactic dose vs. prophylactic dose (SOC)*

A total of 771 patients from 2 RCTs[21,22] were analyzed for an intermediate prophylactic dose in comparison with SOC. Both studies assessed interventions in patients with severe COVID-19. As can be seen in Figure 3A, no significant difference was found between the two groups regarding the 30-day mortality rate (RD, −0.01; 95% CI, −0.07 to 0.06; p = 0.81; $I^2$ = 0%), the quality of evidence being very low (Table S3).

As can be seen in Figure 3B, there was no significant difference between the two groups regarding VTE events (RD, −0.00; 95% CI, −0.03 to 0.03; p = 0.99; $I^2$ = 0%), the quality of evidence being low (Table S3). As

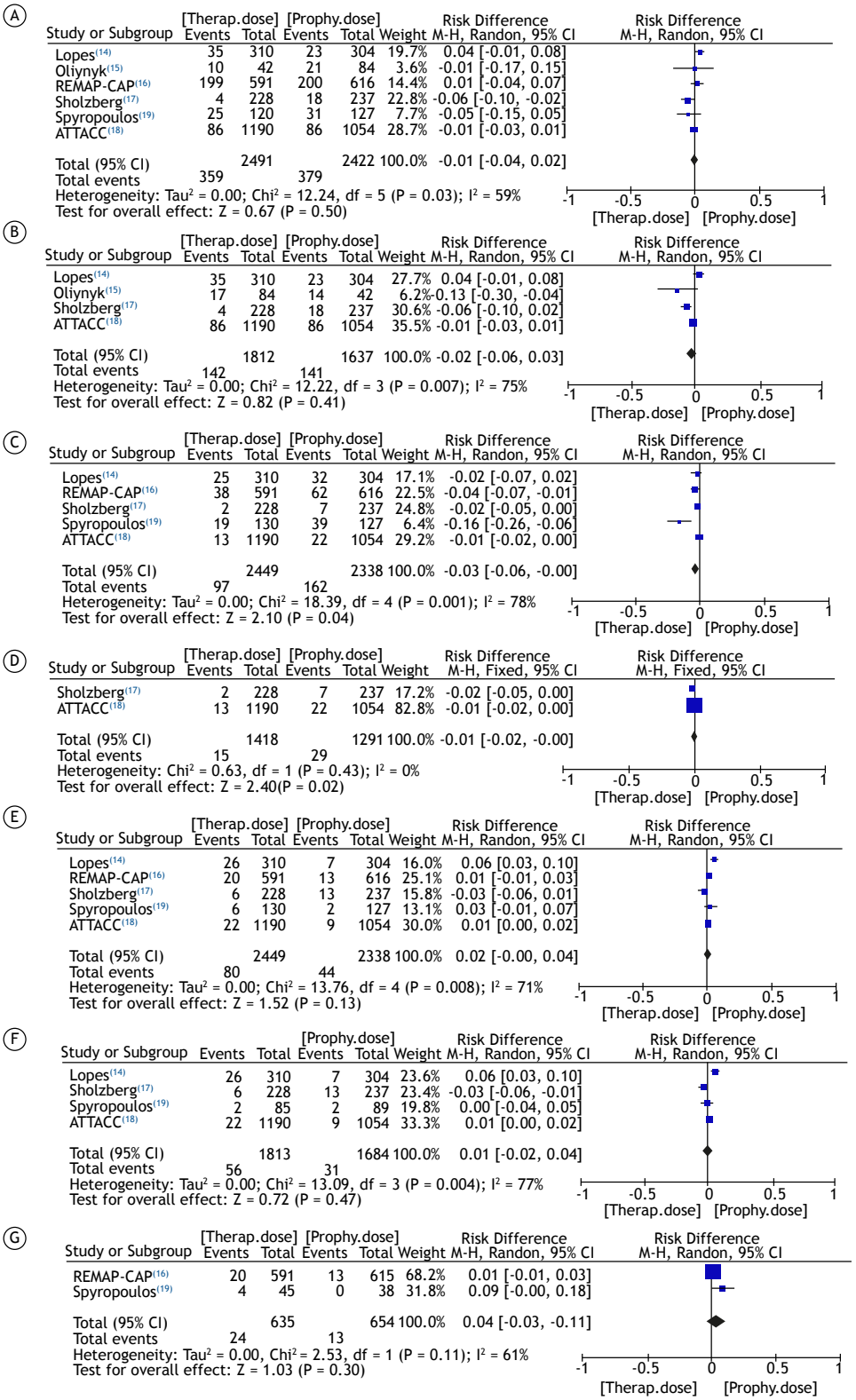



**Figure 2.** Forest plot of comparison: 1 Therapeutic anticoagulation vs. standard of care - randomized controlled trials, outcome: A: mortality at 30 days in all hospitalized COVID-19 patients, B: mortality at 30 days in patients with moderate COVID-19, C: venous thromboembolism at 30 days in all hospitalized COVID-19 patients, D: venous thromboembolism at 30 days in patients with moderate COVID-19, E: major bleeding at 30 days in all hospitalized COVID-19 patients, F: major bleeding at 30 days in patients with moderate COVID-19, G: major bleeding at 30 days in patients with severe COVID-19. M-H: Mantel-Haenszel (method); and df: degrees of freedom.

can be seen in Figure 3C, the risk of ATE events was similar between the two groups (RD, 0.01; 95% CI, −0.04 to 0.05; p = 0.77; $I^2$ = 62%), the quality of evidence being very low (Table S3). As can be seen in Figure 3D, there was no significant difference between the two groups regarding major bleeding (RD, 0.01; 95% CI, −0.01 to 0.03; p = 0.44; $I^2$ = 0%), the quality of evidence being very low (Table S3).

## DISCUSSION

The present systematic review and meta-analysis showed no effect of therapeutic anticoagulation on reducing mortality or increasing major bleeding events in patients with moderate to severe COVID-19. We observed a slight reduction in VTE events in hospitalized patients with moderate to severe COVID-19 at 30 days when therapeutic anticoagulation was used. The use of an intermediate prophylactic dose or post-discharge prophylactic intervention was not associated with reduced mortality, reduced VTE, reduced ATE, or increased bleeding.

With regard to the mortality outcome in hospitalized COVID-19 patients, our results are similar to those of other systematic reviews.[5,8] Therapeutic anticoagulation in these patients may not be directly associated with mortality, but it may be related to a reduction in VTE. VTE can be life-threatening in hospitalized patients and, if not recognized, can increase the risk of mortality. We observed a consistent effect of therapeutic anticoagulation on the reduction of VTE, even when moderate patients (ward patients) or severe patients (ICU patients) were analyzed as a subgroup. Moreover, therapeutic anticoagulation in this population did not increase major bleeding during treatment as a primary safety outcome. This finding is consistent with those of previous systematic reviews showing a reduction in VTE events in hospitalized patients.[23-25] However, the authors of the aforementioned reviews pooled all RCTs with different doses of anticoagulation as the intervention group. In our results, we were able to emphasize the reduction in VTE when therapeutic anticoagulation was used as an intervention. On the other hand, the reduction in VTE was small, a large NNT being required in order to reduce VTE by one. In addition, the quality of evidence was low, increasing the uncertainty. Further RCTs are needed in order to increase the certainty of the results.

The effect of intermediate anticoagulation was not related to the reduction in VTE in comparison with SOC. This finding is consistent with the literature.[24-26]

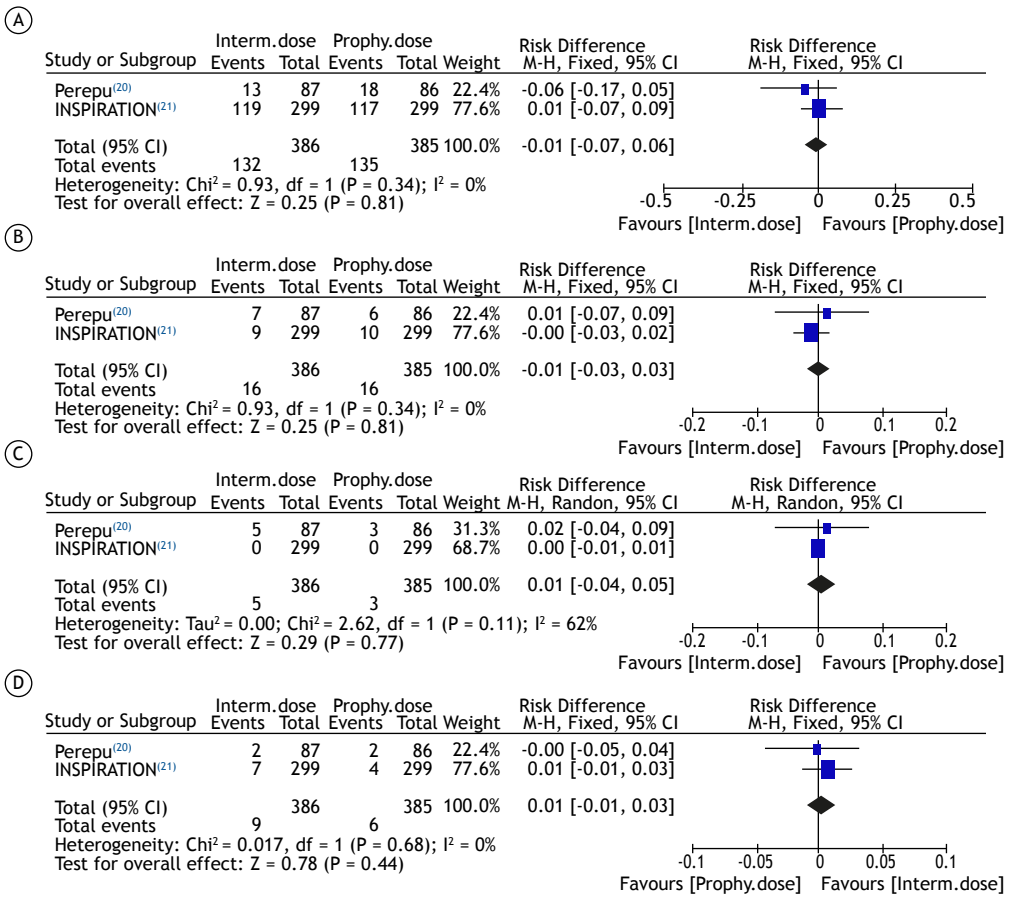



**Figure 3.** Forest plot of comparison: 1 Intermediate prophylactic anticoagulation vs. standard of care/placebo - randomized controlled trials, outcome: A: mortality at 30 days, B: venous thromboembolism at 30 days, C: major bleeding at 30 days. M-H: Mantel-Haenszel (method); and df: degrees of freedom.

Most clinical COVID-19 guidelines recommend the use of prophylactic anticoagulation therapy during hospitalization. However, only 2 RCTs analyzed the effectiveness of this intervention. This important clinical recommendation needs to be evaluated on the basis of the clinical practice for patients whose characteristics are similar to those of patients included in the RCTs. We need to consider whether therapeutic intervention is recommended for all COVID-19 patients, even when they do not have elevated levels of systemic inflammatory markers. Some RCT protocols considered the need for an elevated level of systemic inflammation in the inclusion criteria. It is important to mention the NNT that is required in order to reduce the occurrence of VTE events by one. We identified a minimum of 100 patients who received therapeutic anticoagulation therapy to reduce VTE. Ongoing trials can determine whether therapeutic-dose anticoagulation provides an incremental effectiveness benefit in specific outcomes. Therefore, we need to evaluate the best balance to switch from prophylactic to therapeutic anticoagulation and attempt a VTE diagnosis.

In non-hospitalized COVID-19 patients, we observed no reduction in mortality, VTE, or ATE following the use of a prophylactic dose after hospital discharge. However, we need to consider the clinical condition of the patients when they are discharged. Most critically ill patients need to be rehabilitated for long periods of immobility, and we need to consider the risk of VTE events after hospital discharge. Unfortunately, only one of the RCTs included in the present study addressed this issue, and we do not have a robust answer to this question. Moreover, symptomatic COVID-19 outpatients need to be assessed in RCTs to evaluate the beneficial use of anticoagulants. To answer this question, RCTs are currently ongoing worldwide.

The present systematic review and meta-analysis has strengths and limitations. Because only phase 3 RCTs were included in the present study, we were able to demonstrate the real influence that the intervention used had on the selected outcomes. The certainty of the present results is dependent on novel RCTs and future analyses of larger populations. Other limitations include the characteristics of the study population, the outcomes evaluated at different time points, and the differences in interventions across studies, suggesting heterogeneity across studies. Moreover, one of the studies included in the present systematic review and meta-analysis included outpatients and had a small sample size, thus limiting the certainty of our results. Therefore, we cannot affirm whether the results presented herein will change in the future.

In conclusion, it appears that therapeutic anticoagulation does not reduce mortality in COVID-19 patients. In hospitalized patients, therapeutic anticoagulation appears to result in a slight reduction in VTE without an increased risk of major bleeding.

## AUTHOR CONTRIBUTIONS

SET, HAB, IF, and WMB: study concept and design. WMB, SET, DRB, and IF: data collection, statistical analysis, and interpretation of data. WMB, DRB, and SET: drafting of the manuscript. SET, HAB, AN, AS, and WMB: critical revision of the manuscript for important intellectual content and approval of the final version.

## CONFLICT OF INTEREST

None declared.

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