DOI: 10.4149/BLL_2023_131

Bratisl Med J 2023; 124 (11)
848 – 855

META-ANALYSIS

Anticoagulation therapy in hospitalized patients with COVID-19: a meta-analysis of randomized clinical trials

Bruno de Matos AQUINO[1], Gabriel Tonini PALUDETO[1], Alcindo CERCI NETO[1,2], Paulo Roberto BIGNARDI[1]

School of Medicine, Pontifical Catholic University of Paraná, Londrina, Paraná, Brazil. **pbignardi@gmail.com**

ABSTRACT
Thromboembolic events are common in hospitalized patients with COVID-19, suggesting that SARS-CoV-2 infection may be related to a prothrombotic state. Several clinical trials evaluating different anticoagulation strategies were developed. Thus, we proposed conducting a meta-analysis of randomized clinical trials that evaluated the efficacy and safety of therapeutic anticoagulation with heparins in hospitalized patients with COVID-19. We searched PubMed, Cochrane, and Epistemonikos for studies published until December 22, 2022. Nine studies compared prophylactic/intermediate anticoagulation versus therapeutic anticoagulation with heparins were included. Four efficacy and one safety endpoints were analyzed: all-cause mortality, thromboembolic events, pulmonary embolism, need of intensive care unit or non-invasive ventilation, and major bleeding. Compared with prophylactic/intermediate anticoagulation, therapeutic anticoagulation with heparins was not associated with a reduction in all-cause mortality and need of intensive care unit or non-invasive ventilation in hospitalized patients with COVID-19, but showed a reduction in the number of thromboembolic events (RR 0.54, 95% CI 0.41–0.71, I^2 = 0 %) and pulmonary embolisms (RR 0.37, 95% CI 0.24–0.57, I^2 = 0 %), besides an increase in major bleeding (RR 1.67, 95% CI 1.05–2.64, I^2 = 0 %). This meta-analysis did not show a reduction in all-cause mortality in hospitalized patients with COVID-19 who received anticoagulation with heparin at a therapeutic dose compared to those who received a prophylactic/intermediate dose, as well as no significant differences were found in the need of intensive care unit admission or use of non-invasive ventilation. There was, however, a reduction in thromboembolic events, pulmonary embolism, and increased bleeding *(Tab. 1, Fig. 5, Ref. 31)*. Text in PDF *www.elis.sk*
KEY WORDS: COVID-19, anticoagulation, heparins, meta-analysis.

Introduction

Thromboembolic events are common in hospitalized patients with COVID-19. These complications can occur in both small and large venous and arterial circulation vessels, suggesting that SARS-CoV-2 infection may be related to a prothrombotic state (1). The pathophysiological mechanisms predisposing to this condition are complex, involving interactions between endothelial lesions, excessive inflammation, and hypercoagulability (2). Since the immune and hemostatic systems are closely related, even immune-mediated thrombus formation can occur, a condition called immunothrombosis, which mainly affects the microvasculature (3).

To reduce these events, a series of clinical trials evaluating different anticoagulation strategies were developed (4–13). These studies generally compared anticoagulation with heparins at prophylactic, intermediate and therapeutic doses. Prophylactic anticoagulation consists of pharmacological therapies adopted to prevent venous thromboembolism in patients at high risk. In contrast, therapeutic anticoagulation is used to treat patients with ongoing venous thromboembolism, which involves anticoagulants in higher doses (14, 15). Intermediate anticoagulation, in turn, is a middle ground between these two strategies.

Throughout the pandemic, much has been discussed regarding the best anticoagulation approach for patients hospitalized with COVID-19. Several studies showed divergent results, raising some doubts about the efficacy and safety profile of therapeutic anticoagulation compared to prophylactic or intermediate anticoagulation and whether this would change according to the severity of the disease.

Thus, we proposed carrying out a systematic review and meta-analysis of randomized clinical trials (RCTs) that evaluated the efficacy and safety of therapeutic anticoagulation with heparins. To obtain more accurate results and greater applicability in clinical practice, we stratified the patients into moderate and severe COVID-19.

Methods

This systematic review and meta-analysis were performed following the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) (16). This study has not been registered.

[1]School of Medicine, Pontifical Catholic University of Paraná, Londrina, Paraná, Brazil, [2]Section of Pulmonology, Department of Medicine, Health Science Centre, State University of Londrina, Londrina, Paraná, Brazil

Address for correspondence: Paulo Roberto BIGNARDI, Prof, School of Medicine, Pontifical Catholic University of Paraná, 485 Jockey Club ave – Vila Hípica, Zip code 86072-360 - Londrina, Paraná, Brazil. Phone: +55043 33726042/+55 043 991860539

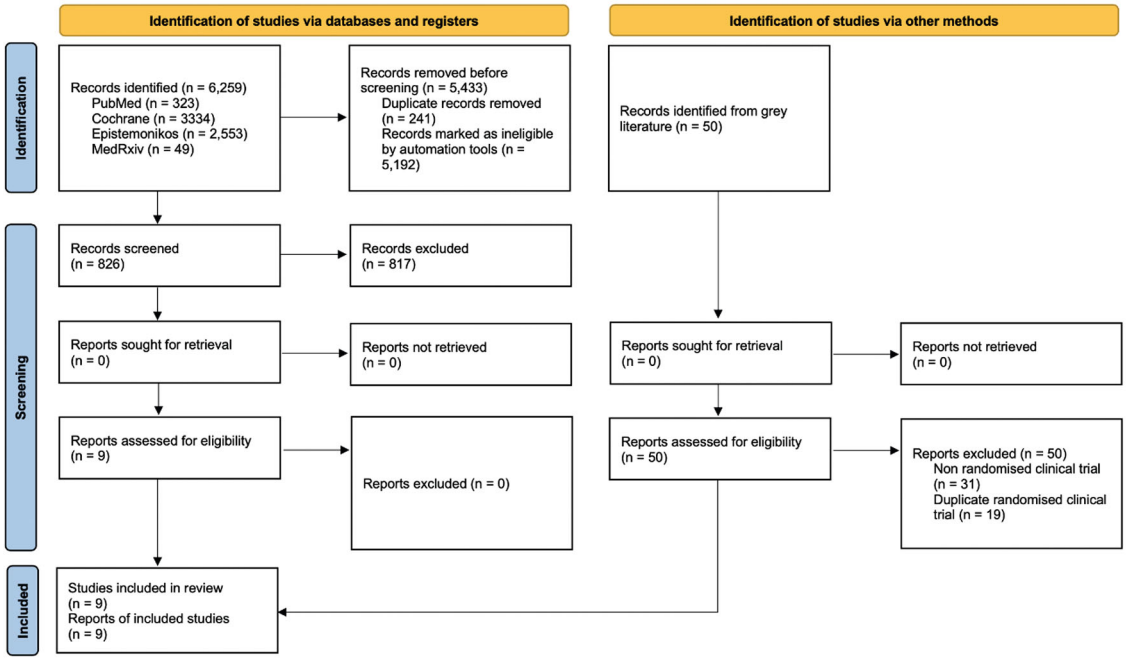

Fig. 1. Flow chart of study selection.

Search strategy

Two authors identified RCTs through a comprehensive and systematic search of the following databases: PubMed, Cochrane, and Epistemonikos. Disagreements were solved through discussion among all authors. The non-peer-reviewed sources and grey literature were used to access studies that met the inclusion and exclusion criteria but were not indexed in these databases. There were no restrictions on the language of the studies, and December 22, 2022, was determined as the deadline for including studies in the search results. Detailed search strategies for databases, non-peer-reviewed sources, and grey literature are provided in the Supplementary Appendix.

PICOT

The central question of the research was established following the anagram PICOT (population, intervention, control, outcomes, and time). RCTs that met the following inclusion criteria were considered eligible: (P) adult hospitalized patients with laboratory-confirmed SARS-CoV-2 infection; (I) administration of therapeutic anticoagulation with heparins; (C) administration of prophylactic and/or intermediate anticoagulation with heparins; (O) all-cause mortality, thromboembolic events, deep vein thrombosis, pulmonary embolism, need of intensive care unit or non-invasive ventilation, and major bleeding; (T) follow-up of approximately 30 days, with slightly shorter or longer intervals being allowed. Randomized clinical trials using new oral anticoagulants (NOACs) were considered ineligible.

The patients were divided into two groups: moderate and severe COVID-19. Any patient hospitalized with COVID-19 was considered to have a moderate form of the disease, as long as oxygen therapy was not required or only using oxygen by mask

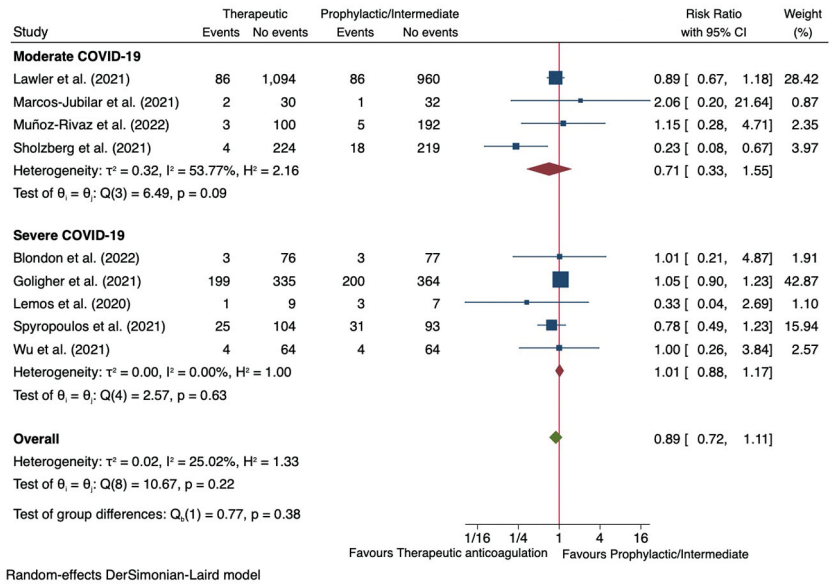

Fig. 2. Forest plot of the effect of therapeutic anticoagulation on all-cause mortality.

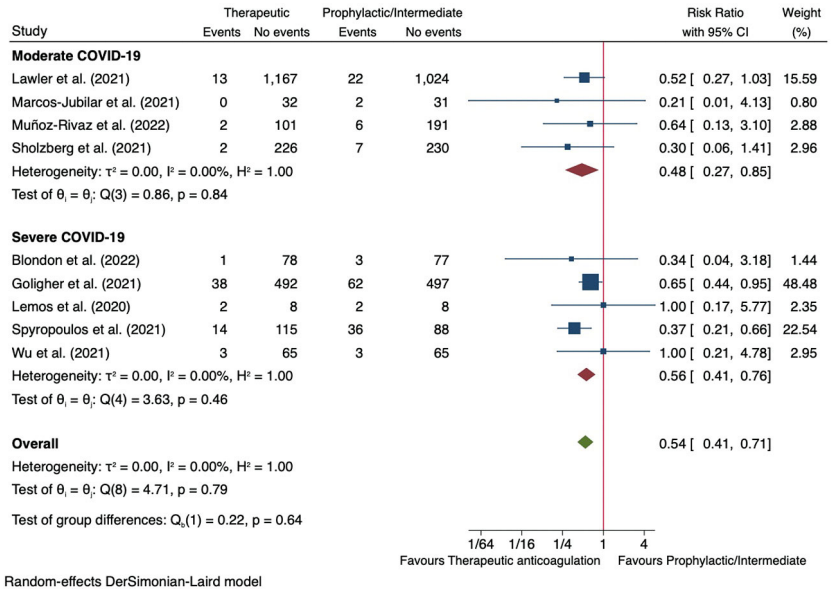

Fig. 3. Forest plot of the effect of therapeutic anticoagulation on thromboembolic events.

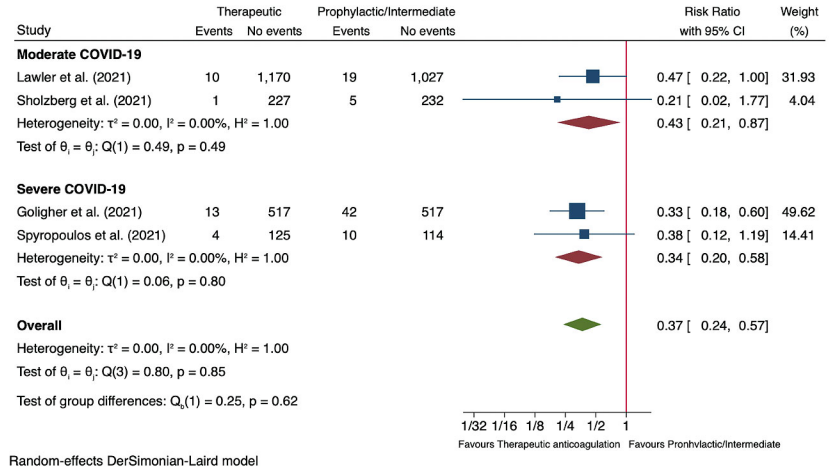

Fig. 4. Effect of therapeutic anticoagulation on pulmonary embolism.

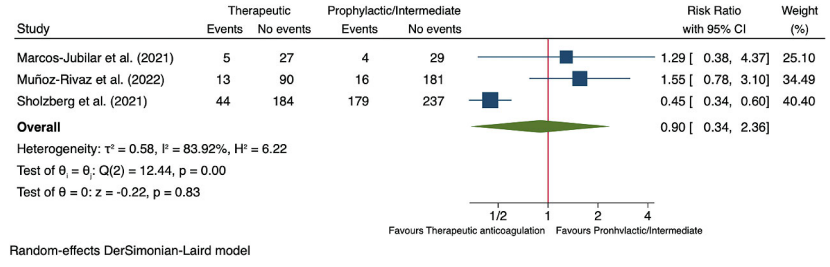

Fig. 5. Effect of therapeutic anticoagulation on the need of intensive care unit or non-invasive ventilation.

or nasal prongs was necessary. COVID-19 was considered severe when the patient also met at least one of the following criteria: (1) requiring intensive care unit admission; (2) undergoing respiratory organ support (high-flow nasal cannula, non-invasive ventilation, invasive mechanical ventilation, or extracorporeal life support); (3) undergoing cardiovascular organ support (vasopressors, inotropes, or extracorporeal life support). These definitions for moderate and severe COVID-19 agree with those established by the WHO clinical progression scale (17–19).

Data extraction

In order to extract the main data from each article, two researchers independently transcribed the main information from the randomized clinical trials using a standardized form with the following points: (1) name of the first author and year of publication; (2) region in which the study was performed (country of origin or international, in the case of multicenter studies); (3) type of study; (4) data on the clinical trial population, like details on the inclusion factors for each article; (5) the number of patients and anticoagulation regimen in the control group; (6) the number of patients and anticoagulation regimen in the intervention group; (7) the outcomes and their events; and (8) the follow-up time of each trial.

Outcomes

Four efficacy and one safety endpoints were used to evaluate the intervention with therapeutic anticoagulation: (1) all-cause mortality; (2) thromboembolic events, whether venous (upper extremity deep vein thrombosis, lower extremity deep vein thrombosis, pulmonary embolism, splanchnic vein thrombosis, and cerebral sinus thrombosis) or arterial (acute myocardial infarction, acute ischemic stroke, acute limb ischemia, peripheral arterial thromboembolism, and systemic arterial thromboembolism); (3) pulmonary embolism; (4) need of intensive care unit or non-invasive ventilation; and (5) major bleeding (those that result in death, are life-threatening, cause chronic sequelae or consume major health-care resources). Additionally, we also evaluated the composite endpoint of deaths and thromboembolic events in patients with

moderate COVID-19 with D-dimer levels less and greater than 1000 ng/ml.

Quality of the selected studies

Two independent authors assessed the quality of studies according to the Cochrane guidelines (20). Any disagreements were resolved through discussion with a third author. Five domains were assessed: (1) bias arising from the randomization process; (2) bias due to deviations from the intended interventions; (3) bias due to missing outcome data; (4) bias in the measurement of the outcome; (5) bias in the selection of the reported results.

Statistical analysis

Pooled RR and 95% confidence interval (CI) were calculated. The $p \leq 0.05$ for the Q test represented a significant difference between the groups, and an $I^2 \geq 50$ % statistic revealed substantial heterogeneity. If the heterogeneity test was not statistically significant, the analyses were performed using a fixed-effects model; otherwise, a random-effects model was used. Finally, the publication bias was examined by the Egger test and funnel plot. All analyses were performed with Stata/SE v.16.1 software (StataCorpLP, USA).

Results

Characteristics of included studies

Based on the search strategies previously described, we found a total of 7,844 studies potentially relevant to the research objectives. The use of automation tools and the exclusion of duplicate studies shortened this number to 867 studies. After screening and applying the eligibility criteria, nine studies remained and were included in the meta-analysis, totaling a population of 4,562 patients (4–12). The main data from each study can be found in Table 1. Detailed studies selection is provided in Figure 1.

Effect of therapeutic anticoagulation on all-cause mortality

Nine studies were included in the analysis of all-cause mortality in hospitalized patients with COVID-19 (4–12). Compared with prophylactic/intermediate anticoagulation, therapeutic anticoagulation was not associated with all-cause mortality in hospitalized patients with COVID-19 (RR 0.89, 95% CI 0.72–1.11, $I^2 = 2$ 5%) (Fig. 2).

Nine studies were included in the subgroup analysis according to the COVID-19 stage. Therapeutic anticoagulation did not reduce all-cause mortality in patients with moderate (RR 0.71, 95% CI 0.33–1.55, $I^2 = 54$ %) or severe COVID-19 (RR 1.01, 95% CI 0.88–1.17, $I^2 = 0$ %) compared to prophylactic/intermediate anticoagulation (Fig. 2).

Effect of therapeutic anticoagulation on thromboembolic events

Nine studies were included in analysing thromboembolic events in hospitalized patients with COVID-19. Compared with prophylactic/intermediate anticoagulation, therapeutic anticoagulation was associated with a reduction in thromboembolic events in hospitalized patients with COVID-19 (RR 0.54, 95% CI 0.41–0.71, $I^2 = 0$%) (Fig. 3).

Subgroup analysis included four studies of patients with moderate COVID-19 and five trials of patients with severe COVID-19. Therapeutic anticoagulation reduced thromboembolic events in patients with moderate (RR 0.48, 95% CI 0.27-0.85, $I^2 = 0$ %) and severe COVID-19 (RR 0.56, 95% CI 0.41–0.76, $I^2 = 0$ %) compared to prophylactic/intermediate anticoagulation (Fig. 3).

Effect of therapeutic anticoagulation on pulmonary embolism

Four studies were included in analysing pulmonary embolism events in hospitalized patients with COVID-19 (4, 5, 9, 10). Compared with prophylactic/intermediate anticoagulation, therapeutic anticoagulation was associated with reduced pulmonary embolism in hospitalized patients with COVID-19 (RR 0.37, 95% CI 0.24–0.57, $I^2 = 0$ %) (Fig. 4).

Subgroup analysis revealed that treatment reduced pulmonary embolism events regardless of the stage of COVID-19 when compared with the control group: moderate COVID-19, RR 0.43, 95% CI 0.21–0.87, I^2=0 %; severe COVID = 19, RR 0.34, 95% CI 0.20–0.58, $I^2 = 0$ % (Fig. 4).

Effect of therapeutic anticoagulation on need of intensive care unit or non-invasive ventilation

The data was extracted and pooled from three studies (5–7). Compared with prophylactic/intermediate anticoagulation, therapeutic anticoagulation was not associated with a reduction in the need of intensive care unit or non-invasive ventilation in hospitalized patients with moderate COVID-19 (RR 0.90, 95% CI 0.34–2.36, $I^2 = 84$ %) (Fig. 5).

Effect of therapeutic anticoagulation on major bleeding

Five studies were included in the analysis of major bleeding in hospitalized patients with COVID-19 (4, 5, 9, 10, 11). Compared with prophylactic/intermediate anticoagulation, therapeutic anticoagulation was associated with increased major bleeding in hospitalized patients with COVID-19 (RR 1.67, 95% CI 1.05–2.64, $I^2 = 0$ %).

Subgroup analysis revealed that therapeutic anticoagulation showed no difference in major bleeding in patients with moderate (RR 1.30, 95% CI 0.34–4.98, $I^2 = 56$ %) and severe (RR 1.65, 95% CI 0.90–3.04, $I^2 = 0$ %) COVID-19 compared to prophylactic/intermediate anticoagulation.

Thromboembolic events or death by D-dimer level

The data was extracted and pooled from three studies (4, 5, 7) for analysis of thromboembolic events or death in patients with moderate COVID-19 by D-dimer level (< 1000 ng/ml and > 1000 ng/ml). No significant difference in thromboembolic events or death was found in either of the two groups.

Incidence of outcomes

In Table S1, we present the incidence of all analyzed outcomes.

Numbers needed to treat (NNT) and numbers needed to harm (NNH)

The numbers needed to treat (NNT) calculations reflect the number of treated patients needed to prevent an outcome, while

Tab. 1. Characteristics of included clinical trials.

Author	Region	Type	Population	Control group		Intervention group		Main outcomes and results	Longest follow-up
				n	Drugs	n	Drugs		
Lawler et al (2021)	International	Open-label, multicenter, multiplatform RCT.	Hospitalised patients with moderate COVID-19 (not requiring intensive care unit admission)	1050	Prophylactic or intermediate anticoagulation (according to local site protocols)	1181	Therapeutic anticoagulation (according to local site protocols)	All-cause mortality: 86/1046 or 8.2% (PA) vs 86/1180 or 7.3% (TA) Thrombotic events: 22/1046 or 2.1% (PA) vs 13/1180 or 1.1% (TA) Major bleeding: 9/1047 or 0.9% (PA) vs 22/1180 or 1.9% (TA)	21 days
Sholzberg et al (2021)	International	Open-label, multicenter, RCT.	Hospitalised patients with moderate COVID-19 (requiring conventional hospital ward admission)	237	Prophylactic anticoagulation (first line: heparins)	228	Therapeutic anticoagulation (first line: heparins)	All-cause mortality: 18/237 or 7.6% (PA) vs 4/228 or 1.8% (TA) Thrombotic events: 7/237 or 2.6% (PA) vs 2/228 or 0.9% (TA) Major bleeding: 4/237 or 1.7% (PA) vs 2/228 or 0.9% (TA)	28 days
Marcos-Jubilar et al (2021)	Spain	Open-label, multicenter, RCT.	Hospitalised patients with moderate COVID-19 (non severe pneumonia with baseline D-dimer > 500 ng/mL)	33	Prophylactic anticoagulation (first line: bemiparin, 3500 IU SC daily)	32	Therapeutic Anticoagulation (first line: bemiparin, 115 IU/kg SC daily)	All-cause mortality: 1/33 or 3.0% (PA) vs 2/32 or 6.3% (TA) Thrombotic events: 2/33 or 6.1% (PA) vs 0/32 or 0.0% (TA) Major bleeding: 0/33 or 0.0% (PA) vs 0/32 or 0.0% (TA)	30 days
Muñoz-Rivaz et al (2022)	Spain	Open-label, multicenter, RCT.	Hospitalised patients with moderate COVID-19 (requiring conventional hospital ward admission)	106 91	Prophylactic anticoagulation (first line: tinzaparin, 4500 IU SC daily) Intermediate anticoagulation (first line: tinzaparin 100 IU/kg SC daily)	103	Therapeutic anticoagulation (first line: tinzaparin 175 IU/kg SC daily)	All-cause mortality: 2/106 or 1.9% (PA) vs 3/91 or 3.3% (IA) vs 3/103 or 1.9% (TA) Thrombotic events: 4/106 or 3.8% (PA) vs 2/91 or 2.2% (IA) vs 2/103 or 1.9% (TA) Major bleeding: 0/106 or 0.0% (PA) vs 0/91 or 0.0% (IA) vs 0/103 or 0.0% (TA)	30 days
Lemos et al (2020)	Brazil	Open-label, single center RCT.	Hospitalised patients with severe COVID-19 (undergoing mechanical ventilation; and D-dimer levels greater than 1000 µg/L)	10	Prophylactic anticoagulation (first line: enoxaparin, 40 mg SC daily)	10	Therapeutic anticoagulation (first line: enoxaparin, 1 mg/kg SC twice daily)	All-cause mortality: 3/10 or 30.0% (PA) vs 1/10 or 10.0% (TA) Thrombotic events: 2/10 or 20.0% (PA) vs 2/10 or 20.0% (TA) Major bleeding: 0/10 or 0.0% (PA) vs 0/10 or 0.0% (TA)	28 days
Goligher et al (2021)	International	Open-label, multicenter, multiplatform RCT.	Hospitalised patients with severe COVID-19 (requiring intensive care unit admission; and undergoing respiratory or cardiovascular organ support)	567	Prophylactic or intermediate anticoagulation (according to local site protocols)	536	Therapeutic anticoagulation (according to local site protocols)	Death in hospital: 200/564 or 35.5% (PA or IA) vs 199/534 or 37.3% (TA) Thrombotic events: 62/559 or 11.1% (PA or IA) vs 38/530 or 7.2% (TA) Major bleeding: 13/562 or 2.3% (PA or IA) vs 20/529 or 3.8% (TA)	28 days

Tab. 1.

Author	Region	Type	Population	Control group		Intervention group		Main outcomes and results	Longest follow-up
				n	Drugs	n	Drugs		
Spyropoulos et al (2021)	United States	Pseudo-blinded, multicenter RCT.	Hospitalised patients with severe COVID-19 (undergoing respiratory organ support, and D-dimer levels more than 4 times the upper limit of normal or sepsis-induced coagulopathy score of 4 or greater)	38	Prophylactic or intermediate anticoagulation (according to local site protocols)	45	Therapeutic anticoagulation (first line: enoxaparin, 1 mg/kg SC twice daily)	All-cause mortality: 31/124 or 25.0% (PA or IA) vs 25/129 or 19.4% (TA) Thrombotic events: 36/124 or 29.0% (PA or IA) vs 14/129 or 10.9% (TA) Major bleeding: 2/124 or 1.6% (PA or IA) vs 6/129 or 4.7% (TA)	30 days
Blondon et al (2022)	Switzerland	Open-label, multicenter, RCT.	Hospitalised patients with severe COVID-19 (requiring intermediate care unit admission; or requiring intensive care unit admission; or D-dimer level >1000 ng/ml)	80	Prophylactic or intermediate anticoagulation (first line: enoxaparin, 40 mg SC daily; or enoxaparin, 40 mg SC twice daily)	79	Therapeutic anticoagulation (first line: enoxaparin, 1 mg/kg SC twice daily)	All-cause mortality: 3/80 or 3.8% (PA or IA) vs 3/79 or 3.8% (TA) Thrombotic events: 3/80 or 3.8% (PA or IA) vs 1/79 or 1.3% (TA) Major bleeding: 2/80 or 2.5% (PA or IA) vs 1/77 or 1.3% (TA)	30 days
Wu et al (2021)	Italy	Open label, single center RCT.	Hospitalised patients with severe COVID-19 (requiring intermediate care unit admission; and respiratory failure with Pa02/ Fi02 < 250 and/or D-dimer levels above 2000 ng/ml)	68	Prophylactic anticoagulation (first line: enoxaparin)	68	Therapeutic anticoagulation (first line: enoxaparin)	All-cause mortality: 4/68 or 5.9% (PA) vs 4/68 or 5.9% (TA) Thrombotic events: 3/68 or 4.4% (PA) vs % 1/68 or 1.5% (TA) Major bleeding: 0/68 or 0.0% (PA) vs 0/68 or 0.0% (TA)	30 days

RCT – randomised clinical trial, PA – prophylactic anticoagulation, IA – Intermediate anticoagulation, TA – therapeutic anticoagulation, SC – subcutaneous

the numbers needed to harm (NNH) calculations reflect the number of treated patients needed to cause an outcome. In table S2 we present the NNT and NNH of all analyzed outcomes. Both NNT and NNH values are presented, considering intervention with therapeutic anticoagulation.

Analysing the NNT of thromboembolic events and the NNH of major bleeding, we found that for hospitalized patients with COVID-19 on therapeutic anticoagulation, one major bleeding is caused for every 3.4 thromboembolic event prevented. This ratio is 1.9 and 4.6 for patients with moderate and severe COVID-19, respectively.

Quality assessment of selected studies and risk of bias

Among the 9 studies selected for the meta-analyses, four trials were considered to have a high risk of bias, one as some concerns, and four as a low risk of bias. Eight trials were randomized, open-label, controlled studies, and one randomized, pseudo-blinded controlled trial. The quality assessments of the studies included in the meta-analysis are shown in Figure S3. The estimated bias coefficient results ranged from 0.235 to 1.078, giving a $p > 0.05$ for all analyses. Therefore, the tests provide weak evidence for the presence of publication bias. A funnel plot was performed for the 3 outcomes but failed to detect possible small study effects.

Discussion

This meta-analysis found no difference in all-cause mortality between prophylactic/ intermediate and therapeutic anticoagulation use in hospitalized patients with moderate and severe COVID-19. However, there was a reduction in thromboembolic events and increased major bleeding among patients who used the therapeutic dose. The reduction in thromboembolic events occurred in hospitalized patients and subgroups of moderate or severe COVID-19. The increase in major bleeding was observed in hospitalized patients but not in the subgroups, that could explain the low number of events in these samples. These results are in alignment with those found by other meta-analyses (21, 22).

There are a few possible approaches to explaining the lack of efficacy of therapeutic anticoagulation in reducing all-cause mortality. The first is the simplest: there are no benefits in using a higher dose of heparins in the anticoagulation of patients with COVID-19. This may occur because the thrombo-inflammatory state is already well-established in certain patients. Even if heparins have some anti-inflammatory effect, they may not be enough to change the natural course of the disease in the same way that corticosteroids do (23). Furthermore, the benefits of reducing thromboembolic events may be nullified by the increase in major bleeding, leaving all-cause mortality unchanged.

A second approach is based on the premise that therapeutic anticoagulation can reduce mortality. However, it would be necessary to better stratify patients according to D-dimer and determine an anticoagulation strategy by the length of hospital stay (24, 25). D-dimer is a marker of endogenous fibrinolysis widely used as an initial test to screen for venous thromboembolism in patients with signs and symptoms suggestive of the disease since it has a high negative predictive value. In the context of COVID-19, it has also been adopted as a marker associated with a worse disease prognosis (26, 27).

For this reason, we decided to perform a subgroup analysis (with the cutoff present in the studies < 1,000 ng/ml and > 1,000 ng/ml – equivalent to 2x ULN). Although the analysis revealed a tendency to reduce death and thromboembolic events in the > 1,000 ng/ml group, the analysis showed no difference between the two treatments.

This finding may have been caused by the low number of events and/or by the cutoff adopted in the selected studies. Because although all studies in this meta-analysis included patients with D-dimer above the upper limit of the normal range (ULN), they may not have been high enough to justify and benefit from therapeutic anticoagulation in the mortality endpoint. This hypothesis is supported by data from a retrospective cohort, in which prophylactic anticoagulation was compared with anticoagulation based on D-dimer levels; that is, the higher the baseline D-dimer presented by the patient, the higher the dose of heparin administered (24).

Tassiopoulos et al observed a reduction in mortality when patients hospitalized with COVID-19 received prophylactic (if D-dimer < 4 times the ULN), intermediate (if D-dimer between 4-11 times the ULN) or therapeutic (if D-dimer ≥ 12 times the ULN) according to D-dimer rather than marker-independent prophylactic anticoagulation. It is important to note that patients who received therapeutic doses had a much higher D-dimer than patients in the clinical trials included in this meta-analysis, in which eight studies had patients with a mean D-dimer between 2-8 times the ULN and only one (10) with mean D-dimer ≥ 12 times the ULN.

In addition to the D-dimer anticoagulation strategy, another aspect that may be important for reducing mortality is the time to start therapeutic anticoagulation (25). Tacquard et al pointed out that most thromboembolic events occur seven days after hospitalisation, while most haemorrhages occur eleven days after hospitalisation – considering a 35-day follow-up. Thus, in patients with a very high D-dimer, it may be interesting to adopt therapeutic anticoagulation at first and then gradually de-escalate the doses until prophylactic anticoagulation is achieved.

Taken together, these measures may result in an even lower NNT for thromboembolic events and an even higher NNH for major bleeding than those exposed in this meta-analysis, which was 33 and 111 for hospitalized COVID-19 patients, respectively. These data show that, on average, one major bleeding is caused for every three thromboembolic events prevented using therapeutic anticoagulation. Thus, even without a reduction in mortality, therapeutic doses can potentially promote some clinical benefit, which must be analyzed individually according to each patient's risks for thrombosis and haemorrhage.

A final point that deserves attention is heparin resistance, which can be understood as a failure to achieve a desired level of anticoagulation even with an adequate drug dose (28). This phenomenon has been observed in patients with critical COVID-19 and, despite not being well understood, it is known that it is more relevant in the case of unfractionated heparin than low molecular weight heparins – both used in clinical trials (28–30). In these cases, monitoring the anticoagulant effect of heparin does not fractionate essential, as high doses may not play the expected therapeutic role and even cause more bleeding (31).

This study has several strengths. To our knowledge, this is the meta-analysis that assessed therapeutic anticoagulation in COVID-19 patients with the largest number of patients involved. This study informs physicians regarding the efficacy and safety of therapeutic anticoagulation doses for COVID-19. Some limitations of our study were the small number of randomized trials, trials without D-dimer cutoff stratification, studies performed without blinding, and substantial heterogeneity. Differences in population characteristics and sample sizes may have contributed to heterogeneity.

Conclusion

This meta-analysis did not show a reduction in all-cause mortality when using therapeutic versus prophylactic/intermediate doses. However, it showed a reduction in the number of thromboembolic events and increased major bleeding. More randomized controlled trials that separate COVID-19 patients in terms of disease severity and risk of thromboembolic events by D-dimer levels are needed to investigate the role of anticoagulant therapy in the mortality of COVID-19 patients.

References

1. Bikdeli B, Madhavan M V., Jimenez D et al. COVID-19 and Thrombotic or Thromboembolic Disease. Implications for Prevention, Antithrombotic Therapy, and Follow-Up. JACC State-of-the-Art Review. J Am Coll Cardiol 2020; 75: 2950–2973. DOI: 10.1016/j.jacc.2020.04.031.

2. Thilagar B, Beidoun M, Rhoades R et al. COVID-19 and throm bo sis. searching for evidence. Amer i can Soc Hematol Published Online First. 2021.http //ashpublications.org/hematology/article-pdf/2021/1/621/1869451/621thilagar.pdf.

3. Loo J, Spittle DA, Newnham M. COVID-19, immunothrombosis and venous thromboembolism. Biological mechanisms. Thorax 2021; 76. 412–420. DOI: 10.1136/thoraxjnl-2020-216243.

4. PR L, EC G, JS B et al. Therapeutic Anticoagulation with Heparin in Noncritically Ill Patients with Covid-19. N Engl J Med 2021; 385. 790–802. DOI: 10.1056/nejmoa2105911.

5. Sholzberg M, Tang GH, Rahhal H et al. Effectiveness of therapeutic heparin versus prophylactic heparin on death, mechanical ventilation, or intensive care unit admission in moderately ill patients with covid-19 admitted to hospital. RAPID randomised clinical trial. BMJ 2021; 375. DOI: 10.1136/bmj.n2400.

6. Marcos-Jubilar M, Carmona-Torre F, Vidal R et al. Therapeutic versus Prophylactic Bemiparin in Hospitalized Patients with Nonsevere COVID-19 Pneumonia (BEMICOP Study). An Open-Label, Multicenter, Randomized, Controlled Trial. Thromb Haemost 2022; 122: 295–299. DOI: 10.1055/a-1667–7534.

7. Muñoz-Rivas N, Aibar J, Gabara-Xancó C et al. Optimal thromboprophylaxis strategies in non-critically ill patients with COVID-19 pneumonia. The PROTHROMCOVID Randomized Controlled Trial. medRxiv 2022; 2022.05.03.22274594. DOI: 10.1101/2022.05.03.22274594.

8. Lemos ACB, do Espírito Santo DA, Salvetti MC et al. Therapeutic versus prophylactic anticoagulation for severe COVID-19. A randomized phase II clinical trial (HESACOVID). Thromb Res 2020; 196: 359–366. DOI: 10.1016/j.thromres.2020.09.026.

9. EC G, CA B, BJ M et al. Therapeutic Anticoagulation with Heparin in Critically Ill Patients with Covid-19. N Engl J Med 2021; 385: 777–789. DOI: 10.1056/NEJMOA2103417.

10. Spyropoulos AC, Goldin M, Giannis D et al. Efficacy and Safety of Therapeutic-Dose Heparin vs Standard Prophylactic or Intermediate-Dose Heparins for Thromboprophylaxis in High-risk Hospitalized Patients with COVID-19. The HEP-COVID Randomized Clinical Trial. JAMA Intern Med 2021; 181: 1612–620. DOI: 10.1001/jamainternmed.2021.6203.

11. Blondon M, Cereghetti S, Pugin J et al. Therapeutic anticoagulation to prevent thrombosis, coagulopathy, and mortality in severe COVID-19. The Swiss COVID-HEP randomized clinical trial. Res Pract Thromb Haemost 2022; 6. DOI: 10.1002/rth2.12712.

12. Wu M, Arquati M, Russo U et al. Efficacy and safety of enoxaparin at prophylactic or therapeutic dose in 136 hospitalized COVID-19 patients. preliminary results from a randomized controlled trial. In. 122° Congresso Nazionale della Società Italiana di Medicina Interna. 2021.

13. Oliynyk O, Barg W, Slifirczyk A et al. Comparison of the effect of unfractionated heparin and enoxaparin sodium at different doses on the course of covid-19-associated coagulopathy. Life 2021; 11. DOI: 10.3390/life11101032.

14. Schünemann HJ, Cushman M, Burnett AE et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism. Prophylaxis for hospitalized and nonhospitalized medical patients. Blood Adv 2018; 2: 3198–3225. DOI: 10.1182/bloodadvances.2018022954.

15. Ortel TL, Neumann I, Ageno W et al. American society of hematology 2020 guidelines for management of venous thromboembolism. Treatment of deep vein thrombosis and pulmonary embolism. Blood Adv 2020; 4: 4693–4738. DOI: 10.1182/bloodadvances.2020001830.

16. Page MJ, McKenzie JE, Bossuyt PM et al. The PRISMA 2020 statement. An updated guideline for reporting systematic reviews. BMJ. 2021; 372. DOI: 10.1136/bmj.n71.

17. WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection. A minimal common outcome measure set for COVID-19 clinical research. Lancet Infect Dis 2020; 20 (8): e192-e197. DOI: 10.1016/S1473-3099(20)30483-7.

18. Gandhi RT, Lynch JB, del Rio C. Mild or Moderate Covid-19. N Engl J Med 2020; 383: 1757–1766. DOI: 10.1056/nejmcp2009249.

19. Berlin DA, Gulick RM, Martinez FJ. Severe Covid-19. N Engl J Med 2020; 383: 2451–2460. DOI: 10.1056/nejmcp2009575.

20. Higgins JP, Savović J, Page MJ et al. Chapter 8. Assessing risk of bias in a randomized trial | Cochrane Training. Cochrane. 2019.https. // training.cochrane.org/handbook/current/chapter-08 (accessed 9 Jun 2020).

21. Zhang S, Li Y, Liu G et al. Intermediate-to-therapeutic versus prophylactic anticoagulation for coagulopathy in hospitalized COVID-19 patients. a systemic review and meta-analysis. Thromb J 2021; 19. DOI: 10.1186/s12959-021-00343-1.

22. Kow CS, Ramachandram DS, Hasan SS. The effect of higher-intensity dosing of anticoagulation on the clinical outcomes in hospitalized patients with COVID-19. A meta-analysis of randomized controlled trials. J Infect Chemother 2022; 28: 257–265. DOI: 10.1016/j.jiac.2021.11.008.

23. Sterne JAC, Murthy S, Diaz J V. et al. Association between Administration of Systemic Corticosteroids and Mortality among Critically Ill Patients with COVID-19. A Meta-analysis. JAMA - J Am Med Assoc 2020; 324: 1330–1341. DOI: 10.1001/jama.2020.17023.

24. Tassiopoulos AK, Mofakham S, Rubano JA et al. D-Dimer-Driven Anticoagulation Reduces Mortality in Intubated COVID-19 Patients. A Cohort Study With a Propensity-Matched Analysis. Front Med 2021; 8. DOI: 10.3389/fmed.2021.631335.

25. Tacquard C, Mansour A, Godon A et al. Anticoagulation in COVID-19. not strong for too long? Anaesth. Crit. Care Pain Med. 2021; 40. 100857. DOI: 10.1016/j.accpm.2021.100857.

26. Pulivarthi S, Gurram MK. Effectiveness of D-dimer as a screening test for venous thromboembolism. An update. N Am J Med Sci 2014; 6: 491–499. DOI: 10.4103/1947-2714.143278.

27. Tang N, Li D, Wang X et al. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost 2020; 18: 844–847. DOI: 10.1111/jth.14768.

28. White D, MacDonald S, Bull T et al. Heparin resistance in COVID-19 patients in the intensive care unit. J Thromb Thrombolysis 2020; 50: 287–291. DOI: 10.1007/s11239-020-02145-0.

29. Beun R, Kusadasi N, Sikma M et al. Thromboembolic events and apparent heparin resistance in patients infected with SARS-CoV-2. Int J Lab Hematol 2020; 42: 19–20. DOI: 10.1111/ijlh.13230.

30. Streng AS, Delnoij TSR, Mulder MMG et al. Monitoring of Unfractionated Heparin in Severe COVID-19. An Observational Study of Patients on CRRT and ECMO. TH Open 2020; 4: e365–375. DOI: 10.1055/s-0040-1719083.

31. Levy JH, Connors JM. Heparin Resistance – Clinical Perspectives and Management Strategies. N Engl J Med 2021; 385: 826–832. DOI: 10.1056/nejmra2104091.

Received April 26, 2023.
Accepted May 31, 2023.