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Comparison of safety and efficacy between therapeutic or intermediate versus prophylactic anticoagulation for thrombosis in COVID-19 patients: a systematic review and meta-analysis

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Background: Patients with coronavirus disease 2019 (COVID-19) infections often have macrovascular or microvascular thrombosis and inflammation, which are known to be associated with a poor prognosis. Heparin has been hypothesized that administration of heparin with treatment dose rather than prophylactic dose for prevention of deep vein thrombosis in COVID-19 patients.

Methods: Studies comparing therapeutic or intermediate anticoagulation with prophylactic anticoagulation in COVID-19 patients were eligible. Mortality, thromboembolic events, and bleeding were the primary outcomes. PubMed, Embase, the Cochrane Library, and KMbase were searched up to July 2021. A meta-analysis was performed using random-effect model. Subgroup analysis was conducted according to disease severity.

Results: Six randomized controlled trials (RCTs) with 4,678 patients and four cohort studies with 1,080 patients were included in this review. In the RCTs, the therapeutic or intermediate anticoagulation was associated with significant reductions in the occurrence of thromboembolic events (5 studies, n=4,664; relative risk [RR], 0.72; P=0.01), and a significant increase in bleeding events (5 studies, n=4,667; RR, 1.88; P=0.004). In the moderate patients, therapeutic or intermediate anticoagulation was more beneficial than prophylactic anticoagulation in terms of thromboembolic events, but showed significantly higher bleeding events. In the severe patients, the incidence of thromboembolic and bleeding events in the therapeutic or intermediate.

Conclusions: The study findings suggest that prophylactic anticoagulant treatment should be used in patients with moderate and severe COVID-19 infection groups. Further studies are needed to determine more individualized anticoagulation guidance for all COVID-19 patients.

Key Words: anticoagulants; COVID-19; thromboembolism; thrombosis

Original Article

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INTRODUCTION

Patients hospitalized for coronavirus disease 2019 (COVID-19) often have macrovascular and microvascular thrombosis and inflammation. In such cases, the prognosis is poor [1,2].

Several mechanisms have been identified for the increased thrombotic risk, and many patients hospitalized for COVID-19 further develop a cytokine storm, which leads to hyperinflammation, endothelial injury, platelet activation, and coagulopathy [3]. In addition, unlike most critically ill patients, venous thromboembolism often occurs in COVID-19 patients despite the use of thromboprophylaxis [4]. Thus, in severe cases of COVID-19 infection, systemic inflammation and coagulopathy occur with test findings similar to those of disseminated intravascular coagulation [5,6]. The anticoagulants used in most studies included unfractionated heparin, low-molecular-weight heparin, and direct oral anticoagulant. In this study, a therapeutic dose refers to a dose administered to patients with deep vein thrombosis (DVT), a prophylactic dose refers to a dose used as prophylactic therapy in patients without DVT, and an intermediate dose is between the amount of therapeutic and the prophylactic dose. Heparin has antithrombotic, anti-inflammatory, and antiviral properties [7-9]. Therefore, it has been hypothesized that administration of heparin with treatment dose would be more beneficial rather than prophylactic dose for DVT prevention in COVID-19 patients. This meta-analysis reviewed the anticoagulant effects and safety of heparin according to the doses given using current data on thrombotic risk, bleeding and mortality of COVID-19 patients admitted to general wards and intensive care units (ICUs).

KEY MESSAGES

- The mortality rate of patients with moderate coronavirus disease 2019 (COVID-19) receiving therapeutic and prophylactic anticoagulants was similar.
- Patients receiving therapeutic doses showed benefits in preventing thromboembolism but more occurrence of bleeding compared to the prophylactic group.
- In patients with severe COVID-19, there were no differences in mortality, thromboembolism, or bleeding between the therapeutic group and prophylactic group.

MATERIALS AND METHODS

This systematic review and meta-analysis were performed according to the recommendations outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [10] (Supplementary Table 1). This study was registered in the Prospective Register of Systematic Reviews (registration no. CRD42022347827).

Eligibility Criteria

The inclusion criteria were as follows: (1) studies targeting patients with confirmed COVID-19; (2) studies comparing therapeutic doses including intermediate doses of an anticoagulant to prophylactic anticoagulant administration; (3) studies reporting mortality, thromboembolic events, and bleeding, etc.; (4) studies published after 2020; (5) randomized controlled trials (RCTs) or observational studies with a comparison group; and (6) written in English or Korean languages. The exclusion criteria were as follows: (1) studies that did not target patients with confirmed COVID-19; (2) studies on animal models; and (3) duplicated studies.

Information Sources and Search Strategy

We developed search strategies with the help of a librarian and clinical experts and searched Ovid Medline, Ovid Embase, the Cochrane Central Register of Controlled Trials, and KMbase as a Korean domestic database in July 2021. Search terms related to COVID-19 were used, including "coronavirus," "novel coronavirus," "novel coronavirus 2019," "2019 nCoV," "COVID-19," "Wuhan coronavirus," "Wuhan pneumonia," "SARS-CoV-2," "thromboembolism," "anticoagulation," and "heparin." The search strategy is presented in Supplementary Table 2.

Selection Process

Four authors (HJL, HJJ, JK, and JP) screened the retrieved citations by title and abstract in Covidence (https://www.covidence.org/) according to the inclusion/exclusion criteria. Full texts were assessed for final decisions regarding inclusion or exclusion. If an agreement was not reached between the authors, an agreement was reached through discussion with another author (MC).

Data Items and Extraction

The following data were extracted using a pre-defined data abstraction form: author, publication year, study design, study country, study setting, the severity of COVID-19, number in each arm, anticoagulation regimen, and outcomes of interest. Three authors (HJL, HJJ, and JP) performed data extraction and another two authors (WIC and JK) checked the data independently.

Study Outcomes

The primary outcomes were mortality, thromboembolic events, and adverse events such as bleeding. The secondary

outcomes were the need for mechanical ventilation (MV), duration of MV, hospital discharge, and length of stay (LOS) in the hospital or ICU.

Study Risk of Bias Assessment

To evaluate the risk of bias in the eligible studies, Cochrane's Risk of Bias (RoB) 1.0 [11] tool was used for RCTs, and the Risk of Bias Assessment tool for Non-randomized Studies (RoBANS) 2.0 [12], which is an update of RoBANS 1.0 [13], was used for non-randomized studies. Quality assessments of the studies were conducted by two independent authors (WIC and JJ) and disagreements were resolved by a third author (MC).

Effect Measures and Synthesis Methods

To evaluate outcomes, we used relative risks (RRs) with a 95% confidence intervals (CIs) for discrete variables and mean differences (MDs) with 95% CIs for continuous variables. Forest plots were used for the graphical display of pooled estimates with 95% CIs. To deal with heterogeneity across the included studies, random-effects models were used. We considered I^2 statistics above 75% to indicate significant heterogeneity. We performed subgroup analysis based on patient severity and therapeutic or intermediate anticoagulation. To synthesize the data, we used RevMan Manager 5.4 4 (RevMan, The Cochrane Collaboration) as a meta-analysis statistical program.

Certainty Assessment

We evaluated the level of evidence of the primary outcomes using the Grading of Recommendations Assessment Development and Evaluation (GRADE) methodology [14]. Two authors (WIC and JJ) assessed the certainty of evidence as high, moderate, low, or very low, and discrepancies were resolved through discussions with a third author (MC).

RESULTS

Study Selection

A total of 11,079 records were identified using the literature search strategy. After excluding duplicates, the titles and abstracts of 9,659 records were screened. Of the 9,659 records, 292 reports were retrieved. After examining the full texts, we included six RCTs and four cohort studies in our review (Figure 1). The list of excluded studies and reasons for exclusion are presented in Supplementary Table 3.

Study Characteristics

The characteristics of the included studies are summarized in Table 1 [15-24]. Six RCTs, which included six reports [15-20] with 4,678 patients (sample size range, 173–2,231), and four retrospective cohort studies [21-24] with 1,080 patients (sample size range, 40–709) were eligible for our review. Three studies were conducted in Europe [21,22,24], three in multiple countries [15,19,23], two in Iran [16,20], one in Brazil [17], and one in the United States [18]. Six studies [15,17,19,21,23,24] compared therapeutic-dose anticoagulation with prophylactic-dose anticoagulation, three studies [16,18,20] intermediate-dose anticoagulation with prophylactic-dose anticoagulation, and one study [22] therapeutic and intermediate-dose anticoagulation with prophylactic-dose anticoagulation. Two studies [15,17] included patients with moderate COVID-19 infections and the other studies included patients with severe COVID-19 infections.

Risk of Bias in the Studies

All RCTs showed a low risk of bias in all dimensions of RoB 1.0. Although all of the cohort studies were assessed as having a high risk of bias in the RoBANS 2.0 dimension of target group selection and one study as an unclear risk of bias in the dimension of possible target group comparisons, the other dimensions in the cohort studies were assessed as having a low risk of bias (Supplementary Figure 1).

Primary Outcomes

Mortality

Six RCT studies reported mortality. The 28-day, 30-day, and in-hospital mortality (5 studies, n=4,673, RR=1.03; 95% CI, 0.91–1.16; I^2=11%, P=0.63) [15,17-20] and 90-day mortality (1 study, n=562, RR=1.07; 95% CI, 0.89 –1.29) [16] were similar between the therapeutic or intermediate group and prophylactic group (Figure 2). Consistent results were obtained for subgroup analysis by severity (patients with moderate and severe COVID-19 infections) and subgroup analysis in the severe COVID-19 patient group comparing intermediate to prophylactic anticoagulation (Supplementary Figures 2 and 3). Three cohort studies reported mortality. Two synthesized studies [21,22] showed benefits in mortality in the therapeutic or intermediate group compared to prophylactic group (n=331, RR=0.63; 95% CI, 0.39–1.00; I^2=20%, P=0.05) (Figure 3) and one study [23] reported that therapeutic anticoagulation were associated with significant reductions in ICU mortality compared to prophylactic anticoagulation (log odds=0.64; 95% CI,

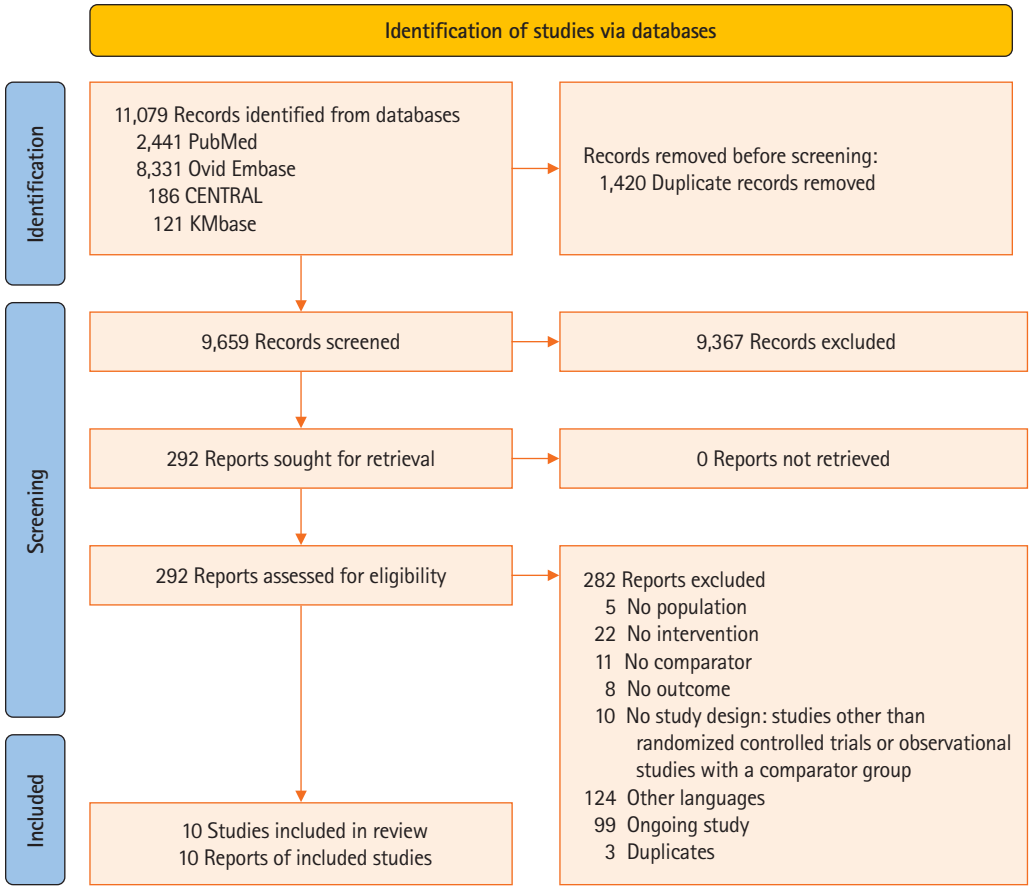


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart.

0.18–1.1; P=0.0069).

Thromboembolic events

Five RCTs [15-19] reported the occurrence of thromboembolic events. Therapeutic or intermediate anticoagulation compared to prophylactic anticoagulation reduced the occurrence of thromboembolic events (n=4,664, RR=0.72; 95% CI, 0.56–0.93; I^2=0%, P=0.01). Subgroup analysis showed that the therapeutic anticoagulation did not reduce thromboembolic events in the severe COVID-19 patient group, but did reduce thromboembolic events in the moderate COVID-19 patient group (Figure 4). In four cohort studies [21-24], the preventive effects on thromboembolic events were similar between the therapeutic or intermediate group and prophylactic groups (n=1,043, RR=0.67; 95% CI, 0.34–1.32; I^2=78%, P=0.25) (Figure 5).

Bleeding

Five RCTs [15-19] reported major bleeding. The risk of major bleeding was significantly higher in the therapeutic or intermediate group compared to the prophylactic group (n=4,667, RR=1.88; 95% CI, 1.23–2.87; I^2=0%, P=0.004). The risk of bleeding in the therapeutic group was higher in the subgroup of patients with moderate COVID-19 (n=2,841, RR=2.25; 95% CI, 1.19–4.27; I^2=0%, P=0.01), but was similar in patients with severe COVID-19 (Figure 6). Three cohort studies [21-23] reported the risk of bleeding, which was similar between the therapeutic or intermediate group and prophylactic group (n=1,040, RR=0.69; 95% CI, 0.38–1.25; I^2=0%, P=0.22) (Figure 7).

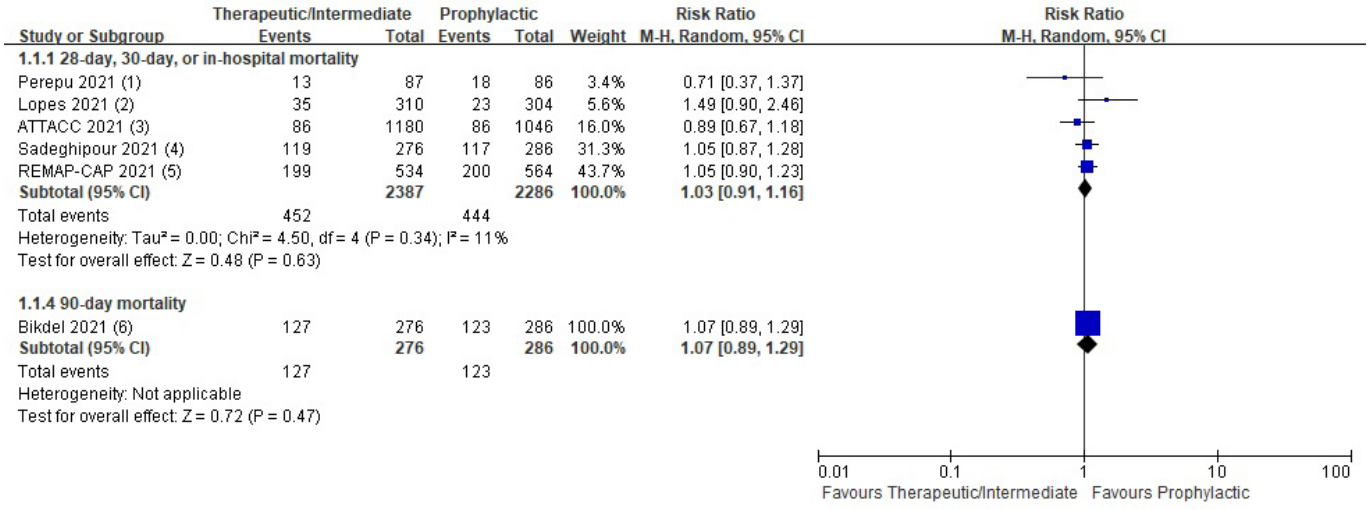
Secondary Outcomes

In the RCTs, the MV rate [17], MV duration [17], hospital discharge [15,17,19], and hospital LOS [17] were similar between the therapeutic group and prophylactic group. However, ICU LOS [20] was significantly shorter in the intermediate group compared to the prophylactic group (1 study, n=562; MD, –1 day; 95% CI, –1.98 to –0.02 day; P=0.05). In one cohort study [21], ICU LOS was similar between the therapeutic group and

Table 1. Basic characteristics of studies included in meta-analysis

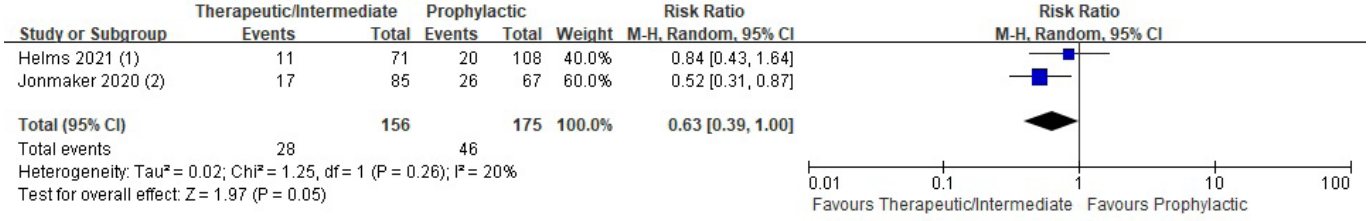
First author (study)	Year	Study design	Country	Setting	Severity	Sample size (intervention/control)	Anticoagulation	
							Intervention	Control
ATTACC investigators [15]	2021	RCT (REMAP-CAP, ACTIV-4a, ATTACC)	US, Canada, UK, Brazil, Mexico, Nepal, Australia, Netherlands, Spain	Multicenter	Moderate	1,181/1,050	Therapeutic dose - LMWH, according to patient weight	Prophylactic dose - According to local guidelines or usual practice
REMAP-CAP investigators [19]	2021	-		-	Severe	534/564	- Alternative UFH, target for aPTT 1.5–2.5 times the upper limit of normal or anti-Xa levels (0.3–0.7 IU/ml)	-
Bikdeli [16], Sadeghipour [20]	2021	RCT (INSPIRATION)	Iran	Multicenter	Severe	276/286	Intermediate dose - Enoxaparin 1 mg/kg qd sc - UFH 10,000 units bid, if severe kidney insufficiency	Prophylactic dose - Enoxaparin 40 mg qd sc - UFH 5,000 units bid, if severe kidney insufficiency
Lopes [17]	2021	RCT (ACTION)	Brazil	Multicenter	Moderate	310/304	Therapeutic dose - Rivaroxaban 15–20 mg qd po - Enoxaparin 1 mg/kg bid or UFH, target for aPTT 1.5–2.5 times the mean normal level or anti-Xa levels (0.3–0.7 IU/ml) if clinically unstable patients	Prophylactic dose - Standard venous prophylaxis with enoxaparin or unfractionated heparin
Perepu [18]	2021	RCT	US	Multicenter	Severe	87/86	Intermediate dose - Enoxaparin 1 mg/kg qd sc	Prophylactic dose - Enoxaparin 30–40 mg bid sc
Helms [21]	2021	Retrospective cohort study	France	Multicenter	Severe	71/108	Therapeutic dose - LMWH 100 IU/kg bid sc, not exceeding 10,000 IU/12 hr - UFH 500 IU/kg qd, if creatinine clearance <30 ml/min	Prophylactic dose - Enoxaparin ≤6,000 IU bid - UFH 200 IU/kg qd, if creatinine clearance <30 ml/min
Taccone [24]	2020	Retrospective cohort study	Belgium	Single center	Severe	18/22	Therapeutic dose - Enoxaparin 4,000 IU bid sc - UFH 1,500–2,200 IU/hr continuous infusion, in case of RRT and/or ECMO	Prophylactic dose - Enoxaparin 4,000 IU qd sc
Lavinio [23]	2021	Retrospective cohort study	UK, Italy, Spain, Belgium, Austria	Multicenter	Severe	274/435	Therapeutic dose - Enoxaparin 50–100 IU/kg bid	Prophylactic dose - Not reported
Jonmarker [22]	2020	Retrospective cohort study	Sweden	Single center	Severe	85/67	Therapeutic dose (n=37) - Tinzaparin ≥175 IU/kg or Dalteparin ≥200 IU/kg Intermediate dose (n=48) - Tinzaparin >4,500 IU but <175 IU/kg or Dalteparin >5,000 IU but <200 IU/kg	Prophylactic dose -Tinzaparin 2,500–4,500 IU or Dalteparin 2,500–5,000 IU

RCT: randomized clinical trial; LMWH: low-molecular weight heparin; UFH: unfractionated heparin; aPTT: activated partial thromboplastin time; qd: once a day; sc: subcutaneous; bid: twice a day; po: per oral; RRT: renal replacement therapy; ECMO: extracorporeal membrane oxygenation.



Footnotes
(1) 30-day mortality; Intermediate dose vs. prophylactic dose
(2) 30-day mortality; Therapeutic dose vs. prophylactic dose
(3) 28-day mortality (ACTIV-4a, ATTACC), in-hospital mortality (REMAP-CAP); Therapeutic dose vs. prophylactic dose
(4) 30-day mortality; Intermediate dose vs. prophylactic dose
(5) 28-day mortality (ACTIV-4a, ATTACC), in-hospital mortality (REMAP-CAP); Therapeutic dose vs. prophylactic dose
(6) Intermediate dose vs. prophylactic dose

Figure 2. Mortality in randomized controlled trials. M-H: Mantel-Haenszel test; CI: confidence interval.



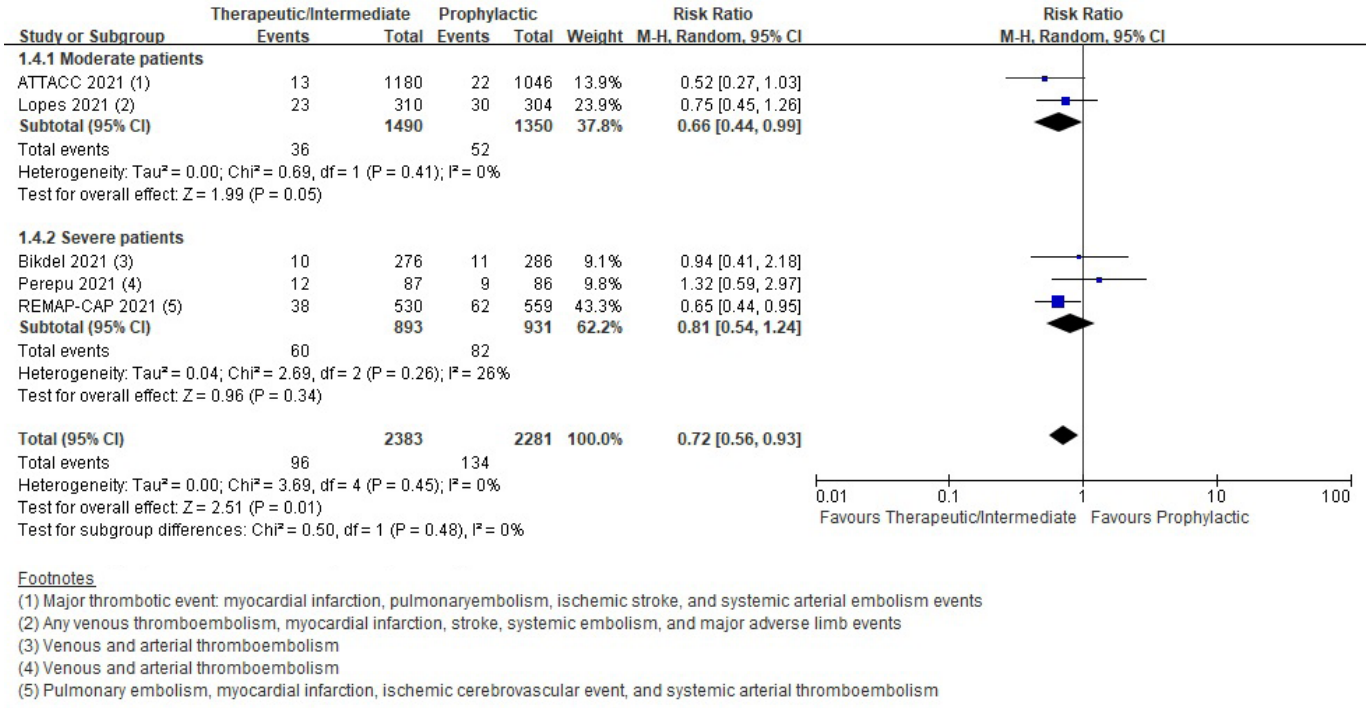
Footnotes
(1) ICU mortality; Therapeutic dose vs. prophylactic dose
(2) 28-day mortality; Therapeutic/Intermediate dose vs. prophylactic dose

Figure 3. Mortality in cohort studies. M-H: Mantel-Haenszel test; CI: confidence interval; ICU: intensive care unit.

prophylactic group (Supplementary Figures 4–8). A summary of the primary outcome findings according to GRADE guidelines is presented in Table 2.

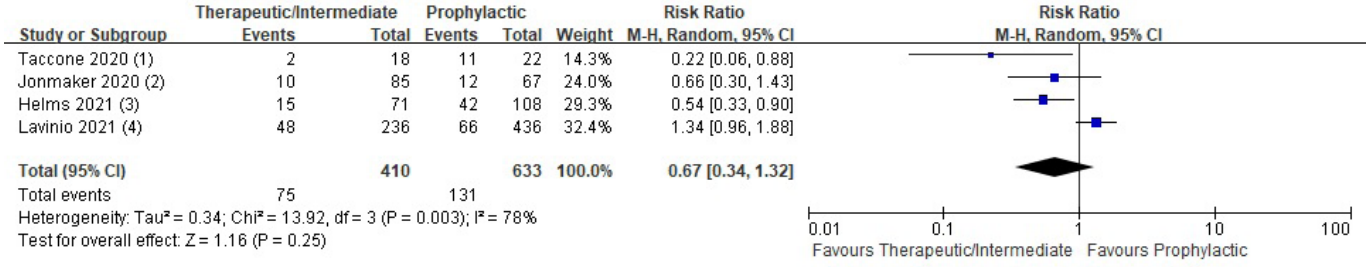
DISCUSSION

COVID-19 pneumonia is associated with a hypercoagulable condition caused by endothelial disturbance and an intense prothrombotic inflammatory response [25], which results in pulmonary microvascular thrombosis linked to poor outcomes [26,27]. In a situation where the importance of anticoagulation is emerging, this meta-analysis of previous RCT studies found no significant difference in mortality [15,17] between the group using an anticoagulant as a therapeutic dose and a group using an anticoagulant as a prophylactic dose in moderate-severity patients admitted due to COVID-19. Although the incidence of thrombosis was significantly lower in the anticoagulant-treated group, the frequency of major bleeding in the above two studies was significantly higher in the therapeutic group than in the prophylactic group. Sixteen fewer patients in the prophylactic group (1,350 patients) developed thrombosis than in the treated group (1,490 patients). In the treated group (1,490 patients), the frequency of thrombosis was less than in the prophylactic dose group (1,350 patients), but there were 19 more patients with major bleeding events in the treated group. Since anticoagulant treatment can be accompanied by bleed-



Footnotes
(1) Major thrombotic event: myocardial infarction, pulmonaryembolism, ischemic stroke, and systemic arterial embolism events
(2) Any venous thromboembolism, myocardial infarction, stroke, systemic embolism, and major adverse limb events
(3) Venous and arterial thromboembolism
(4) Venous and arterial thromboembolism
(5) Pulmonary embolism, myocardial infarction, ischemic cerebrovascular event, and systemic arterial thromboembolism

Figure 4. Thromboembolic events in randomized controlled trials. M-H: Mantel-Haenszel test; CI: confidence interval.



Footnotes
(1) Pulmonary embolism
(2) Thromboembolic events
(3) Thromboembolic complications
(4) Thromboembolic complications

Figure 5. Thromboembolic events in cohort studies. M-H: Mantel-Haenszel test; CI: confidence interval.

ing, both the frequency of thrombosis and bleeding must be considered when evaluating the clinical benefits. Therefore, it seems that there was no clinical benefit of therapeutic dose of anticoagulation to hospitalized patients with moderate-severe COVID-19. In addition, no significant difference in the progression of organ failure was observed according to the dosage of anticoagulants.

There was no significant difference in mortality in the RCT studies in this analysis between patients with COVID-19 given an anticoagulant as a therapeutic or intermediate dose and those given a prophylactic dose of anticoagulant. In two previous RCTs [18,19], the incidence of thrombosis in the therapeutic group (50 out of 617 patients) and the prophylactic group (71 out of 645 patients) was lower in the therapeutic group, whereas major bleeding was more common in the therapeutic group by seven patients. In the meta-analysis, no significant difference was observed between the two groups in thrombus formation and bleeding. In critically ill COVID-19 patients, therapeutic anticoagulant administration did not appear to have significant benefits.

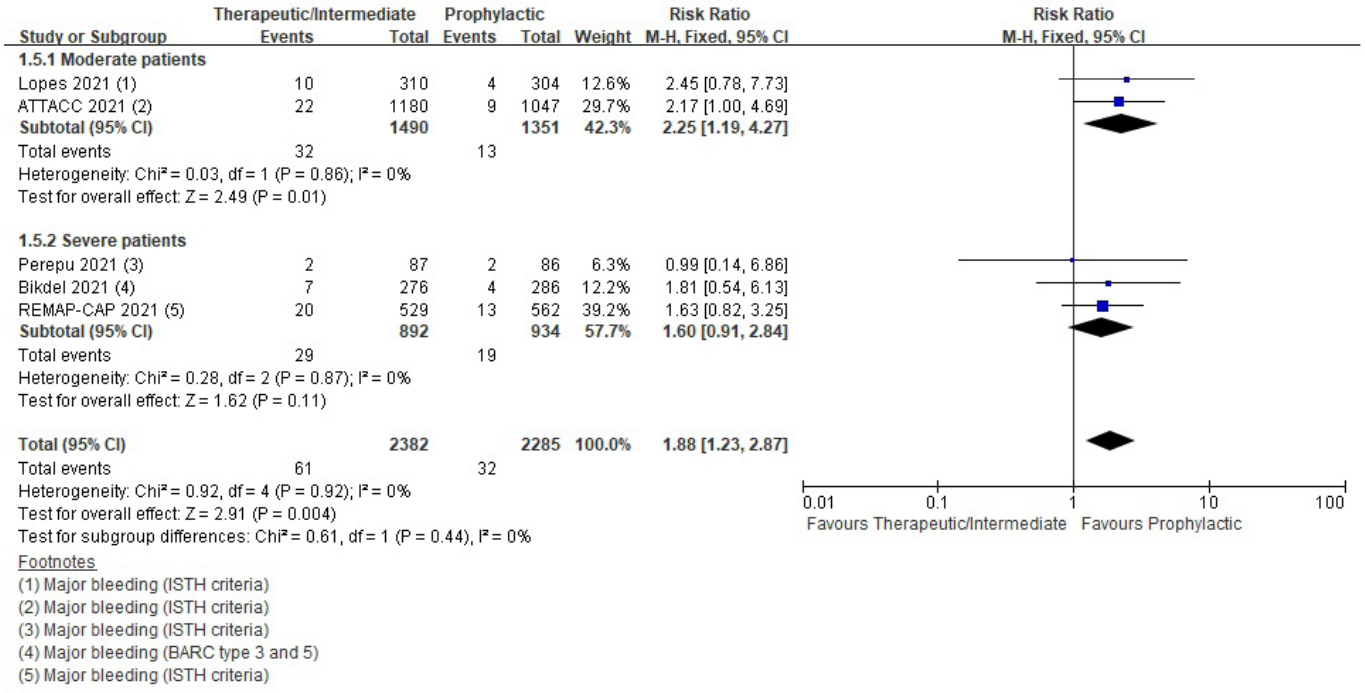


Figure 6. Bleeding in randomized controlled trials. M-H: Mantel-Haenszel test; CI: confidence interval; ISTH: International Society on Thrombosis and Haemostasis; BARC: Bleeding Academic Research Consortium.

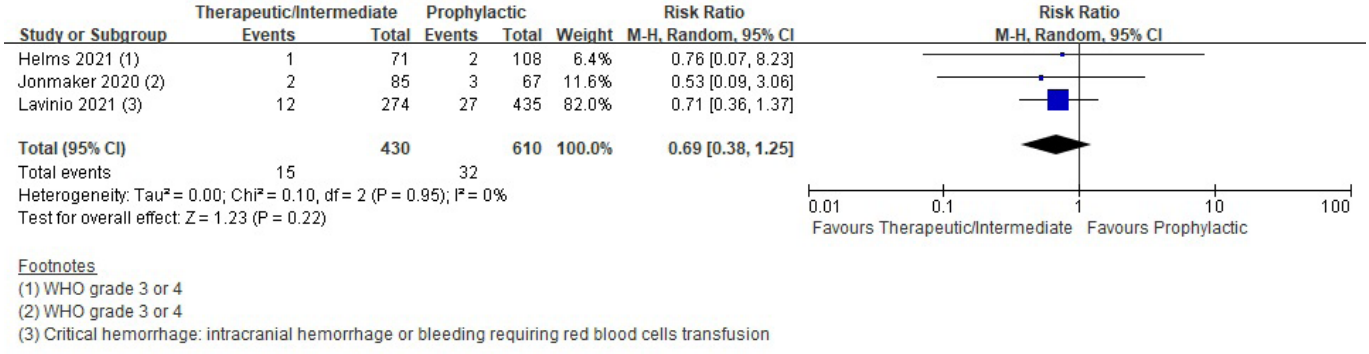


Figure 7. Bleeding in cohort studies. M-H: Mantel-Haenszel test; CI: confidence interval; WHO: World Health Organization.

Based on these results, the risk of bleeding was evaluated, and it seems possible to selectively apply a therapeutic dose of anticoagulant treatment for DVT prophylaxis to the low-risk COVID-19 patient group. Heparin, which exerts anti-inflammatory and antiviral effects, is preferred over mechanical methods worn on the lower extremities (compression stockings or intermittent air compression devices) for thrombosis prevention therapy in patients hospitalized for COVID-19. A previous study found no difference in the antithrombotic effect of administering low-dose unfractionated heparin two or three times a day [28]. Although low-molecular-weight heparin has the advantage of being administered once a day, the thrombotic prevention effect is almost the same as that of a prophylactic dose of unfractionated heparin, but the risk of bleeding is lower [29-31].

Oral anticoagulants can be directly used at low doses for thrombosis prevention in patients hospitalized for internal medical conditions. A previous study reported that the bleeding frequency was higher than that of low-molecular-weight heparin administered prophylactically [32], and in patients

Table 2. Summary of findings and grading quality of the evidence

Outcome	Study design	Anticipated absolute effect (95% CI)		Relative risk (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
		Risk with thromboprophylaxis	Risk with therapeutic anticoagulation			
28-Day, 30-day, ICU, or in-hospital mortality	RCT	194 Per 1,000	200 Per 1,000 (177–225)	1.03 (0.91–1.16)	4,673 (5)	⨁⨁⨁◯ Moderate[a]
	Cohort study	263 Per 1,000	166 Per 1,000 (13–263)	0.63 (0.39–1.00)	331 (2)	⨁◯◯◯ Very low[b,c]
		Lavinio et al. [23] reported therapeutic dose of anticoagulants was associated with significant reduction in ICU mortality compared to prophylactic dose (log odds, 0.64; 95% CI, 0.18–1.1; P=0.0069).			709 (1)	
Thromboembolic event	RCT	59 Per 1,000	42 Per 1,000 (33–55)	0.72 (0.56–0.93)	4,664 (5)	⨁⨁⨁◯ Moderate[a]
	Cohort study	207 Per 1,000	139 Per 1,000 (70–273)	0.67 (0.34–1.32)	1,043 (4)	⨁◯◯◯ Very low[b,d]
Bleeding	RCT	14 Per 1,000	26 Per 1,000 (17–40)	1.88 (1.23–2.87)	4,667 (5)	⨁⨁⨁◯ Moderate[a]
	Cohort study	52 Per 1,000	40 Per 1,000 (22–72)	0.69 (0.38–1.25)	1,040 (3)	⨁◯◯◯ Very low[b,c]

CI: confidence interval; GRADE: Grading of Recommendations Assessment Development and Evaluation; ICU: intensive care unit; RCT: randomized clinical trial.
a) One study has heterogeneity regarding anticoagulants dose; b) Overall serious risk of bias across studies; c) Imprecision due to limited sample size; d) Very few events in both intervention and control group.

with high D-dimer values. Another study found that the thrombotic prevention effect was similar to that of prophylactic low-molecular-weight heparin administration without increasing the frequency of bleeding [33]. Oral Factor Xa therapy is not preferred over prophylaxis with low-molecular-weight heparin because of its high bleeding rate, but it can be considered when low-molecular-weight heparin cannot be used. Considering the risk of bleeding [34], if the risk of bleeding is judged to be low, heparin therapy may be selected.

According to the International Society on Thrombosis and Haemostasis (ISTH), low-molecular-weight heparin is recommended first after careful evaluation of the side effects related to using the drug, and it is needed to evaluate bleeding risk as a universal strategy for routine thrombosis prevention using standard-dose unfractionated heparin or low-molecular-weight heparin in COVID-19 patients admitted to general wards other than ICUs [35,36]. In a minority opinion, mid-dose low-molecular-weight heparin could also be considered [35,36].

ISTH recommends a prophylactic dose of unfractionated heparin or low-molecular-weight heparin for COVID-19 patients admitted to ICUs after the careful assessment of bleeding risk [16,18,35]. In patients at high risk for thrombosis, the use of medium-dose low-molecular-weight heparin may be considered. Therapeutic doses of heparin should not be considered for DVT prophylaxis until the results of RCTs are available. Thrombosis prevention using mechanical methods (i.e., intermittent air compression devices) in addition to drug therapy should also be considered [36].

The guidelines of the American Society of Hematology make conditional recommendations regarding the use of therapeutic or intermediate anticoagulants in patients with COVID-19 without thrombosis, but the level of evidence is low [37]. These recommendations were issued prior to the release of important RCT results and may be revised in the future. The National Institute of Health does not recommend an anticoagulant for prophylactic anticoagulation therapy in COVID-19 patients [38]. However, these guidelines were issued prior to the release of important RCT results and may be revised in the future.

This review had some limitations. First, we did not perform subgroup analysis according to known risk factors such as age, body mass index, and underlying comorbidities. Even if COVID-19 patients are hospitalized in a general ward, there would be differences in thromboembolic risks depending upon individual medical history, including bedridden or ambulatory status. Second, several retrospective cohort studies and trial-level data were included. However, most of the patients were those included in RCTs rather than cohort studies, and we showed the results of both RCTs and cohort studies. Third, the anticoagulation drug type and dosage were different

in each study. However, we did not control for confounding variables, which could affect bleeding risks. Recommendations should be changed based on new evidence. We have been updated our recommendations periodically by living guideline development scheme for including new published studies (last update was done in May 2022). And we are also monitoring other countries or institutions' recent recommendations [39].

In conclusion, there was no significant difference in mortality in the RCT studies between hospitalized patients (in the general ward or ICU) with COVID-19 given an anticoagulant as a therapeutic or intermediate dose and those given an anticoagulant as a prophylactic dose. In patients with moderate COVID-19, thromboembolic events were less common at the therapeutic or intermediate dose, but bleeding events was significantly higher. The incidence of thromboembolic and bleeding events was not statistically significant in the group of patients with severe COVID-19 in the RCTs. Therefore, prophylactic doses of anticoagulants is recommended for both groups. Future studies are needed to determine more individualized anticoagulation guidance for all COVID-19 patients.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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Conceptualization: HJL, HJJ, MC. Methodology: MC. Formal analysis: HJL, HJJ, JK. Data curation: HJL, HJJ, WC, JJ. Visualization: JP. Project administration: MC, JP. Funding acquisition: MC. Writing–original draft: HJL, HJJ. Writing–review & editing: MC, WC, JJ, JK, JP.

SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.4266/acc.2022.01424.

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