Parenteral and Oral Anticoagulant Treatment for Hospitalized and Post-Discharge COVID-19 Patients: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: *The use of anticoagulants has been endorsed by different hematological societies as coagulation abnormalities are key features of COVID-19 patients. This systematic review and meta-analysis aims to provide the most recent update on available evidence on the clinical benefits and risk of oral and parenteral anticoagulants, as well agents with anticoagulant properties, in hospitalized and post-discharge COVID-19 patients.* ***Methods:*** *This systematic review synthesizes data on the outcome of anticoagulation in hospitalized and post-discharge COVID-19 patients. Dichotomous variables from individual studies were pooled by risk ratio (RR) and their 95% confidence interval (95% CI) using the random-effects model. Meta-analyses were performed when feasible.* ***Results:*** *We included 32 studies from 2.815 unique citations, including 7 randomized clinical trials. A total of 33.494 patients were included. Outcomes measured include mortality and survival rates, the requirement for ICU care and mechanical ventilation. A pooled meta-analysis favors anticoagulant compared to no anticoagulant with reduced mortality in hospitalized patients (RR 0,55; 95%CI 0,43-0,66; p<0,001). Higher dose of anticoagulant also showed treatment benefit compared to standard prophylactic dose in selected populations (RR 0,68; 95%CI 0,40-0,96; p<0,001). Regular, pre-hospital anticoagulation prior to hospitalization yielded mixed result. There are currently no data on the benefit of anticoagulation on post-discharge COVID-19 patients.* ***Conclusion:*** *Determination of the presence of thrombosis in COVID-19 is important, as therapeutic dosage of anticoagulants, rather than prophylatic dose, would be indicated in such clinical situation. Anticoagulants were found to decrease the mortality of hospitalized COVID-19. The results from this study are important in the tailored treatment of COVID-19 patients. Further studies on the need for oral anticoagulation for outpatients or post-discharge is warranted. This study has been registered in PROSPERO database (CRD42020201418).*

Keywords**:** *COVID-19, anticoagulant, VTE, thromboprophylaxis.*

INTRODUCTION

The coronavirus disease 2019 (COVID-19) outbreak in December 2019 developed into a pandemic of severe pneumonia, frequently with multiorgan involvement. Coagulation abnormalities in the direction of hypercoagulable state are present in a number of COVID-19 patients.[1] Additionally, acute illness and a hyperinflammatory state may predispose to thrombotic events in these patients.[2,3] The risk for venous thromboembolism (VTE) in COVID-19 patients is markedly increased, especially in intensive care unit (ICU) patients, with case series reporting a prevalence of between 20 to 43 percent among ICU patients, often despite prophylactic-dose anticoagulation.[4-8]

Data suggests that the COVID-19 associated coagulopathy is a combination of mild DIC with pulmonary thrombotic microangiopathy.[9] The pathogenesis of these abnormalities in patients with COVID-19 are still incompletely understood. The use of anticoagulants has been endorsed by different thrombosis and hematological societies based these observed findings. The guidance by the International Society of Thrombosis and Hemostasis (ISTH) states that a universal strategy of routine thromboprophylaxis with standard-dose UFH or LMWH in hospitalized non-ICU should be used after careful assessment of bleeding risk, with LMWH as the preferred agent in COVID-19 patients.[10-12] Furthermore, the American Society of Hematology (ASH) recommends the use of prophylactic dose when compared to high-intensity prophylaxis in the critically ill or acutely ill patients.[13] In the outpatient COVID-19 population, the ISTH guideline stated that it is reasonable to consider extended-duration thromboprophylaxis with LMWH or a DOAC for at least 2 weeks and up to 6 weeks post-hospital discharge in selected COVID-19 patients who are at low risk for bleeding and with key VTE risk factors.[10, 14] However, this recommendation was not specifically based on studies in COVID-19 patients.

Regardless of the recommendations above, evidence on the benefit and risk of both prophylactic or higher dose of anticoagulants in COVID-19 patients are lacking. Recently, agents with anticoagulation effects are also being studied as potential treatments for COVID-19 which could add to the repertoire of drugs used in the treatment of COVID-19.[15,16] This study aims to investigate the outcomes of parenteral and oral anticoagulants in the standard care of COVID-19 hospitalized inpatients and post-discharge outpatients. The population of interest are COVID-19 inpatients and post-discharge outpatients who tested positive with SARS-CoV-2 PCR. The interventions studied are parenteral anticoagulants, including the novel alternative anticoagulants and oral anticoagulants, with standard treatment as comparison. The main outcome includes mortality and survival rates, the requirement for ICU care and mechanical ventilation.

METHODS

This systematic review was conducted based on the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Statement.[17] The protocol of this systematic review has been registered in The International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42020201418).

Eligibility Criteria

The inclusion criteria are human study, full-text, English, randomized control trial, and observational studies that investigate the use of anticoagulants in patients infected with 2019-novel coronavirus (COVID-19). Exclusion criteria include infection of unspecific coronaviruses or other respiratory viruses and studies on pediatric patients.

Search Strategy

A systematic review was performed on the literatures gathered between 22 September 2021 and 11 March 2022 using several databases: Cochrane, EBSCO, Pubmed, and EMBASE with keywords: ((Anticoagulant) AND ("COVID-19" OR "SARS-CoV-2" OR "2019 novel coronavirus infection" OR "2019-nCoV" OR "coronavirus disease 2019" OR "coronavirus disease-19") AND ("admission" OR "hospital stay" OR "mortality" OR "morbidity" OR "outcome" OR "death" OR "survival"). The reporting of this study is based on the Preferred Reporting

Items for Systematic Review and Meta-Analysis (PRISMA) Statement.[17]

Data Extraction

Data from included studies was extracted in standardized form, including characteristics of study design, setting, population description. Study citations included the name of the first author, year of publication, and title of the study. Therapies received, comorbidities, venous and arterial thrombosis, clinical severity, bleeding events and mortality are extracted from the included studies. Measures of associations extracted included odd's ratio (OR), hazard's ratio (HR) and relative risk (RR).

Quality and Risk of Bias Assessments

Two independent reviewers conducted the quality assessment of the studies on its validity, importance, applicability, and level of evidence (RNT and ENT). The quality of observational studies and risk of bias in the randomized clinical trials was assessed using the Newcastle Ottawa Quality Assessment Scale (NOS)[18] and Cochrane risk-of-bias tool for randomized trials (ROB2),[19] respectively. Any difference in assessments between reviewers were discussed until it reached a conclusion.

Statistical Analyses

Data for meta-analyses was synthesized based on minimum of three different high-quality studies with consistent findings. The obtained data was analyzed by taking into account the method of variable analysis used, study size, odds/hazard ratio, and confidence interval. Heterogeneity was evaluated using the I^2 statistic to assess the degree of inter-study variation. I^2 values of 0–24.9%, 25–49.9%, 50–74.9%, and 75–100% were considered as having no, mild, moderate, and significant thresholds for statistical heterogeneity, respectively.[20] A random-effects model was used. We intended to assess publication bias using funnel plot techniques, Begg's rank test and Egger's regression test, when the number of studies analyzed reached a minimum of 10.[21] Statistical analyses were made using Meta-Essentials (version 1.4, Rotterdam, The Netherlands).[22]

RESULTS

Study Selection

Literature searching was done from the study databases ProQuest, Pubmed, Medline and Cochrane. Out of 2.815 unique articles identified, we included a total of 32 studies. Of these studies, 7 were randomized clinical trials, 22 were observational studies and 3 were case series. Literature searching according to keywords listed in **Table 1** detailed the 32 studies eligible for review. The study flow is presented according to the PRISMA statement (**Figure 1**).

Table 1. Search Queries of This Systematic Review.

Database	Keywords	Hits
ProQuest	((anticoagulant* or anticoagulation*) AND ("COVID-19" OR "SARS-CoV-2" OR "2019 novel coronavirus infection" OR "2019-nCoV" OR "coronavirus disease 2019" OR "coronavirus disease-19")) AND (hospitali?ation OR admission OR hospital stay OR mortality OR morbidity OR outcome OR death OR survival)	103
Pubmed	(anticoagulant* or anticoagulation*) AND ("COVID-19" OR "SARS-CoV-2" OR "2019 novel coronavirus infection" OR "2019-nCoV" OR "coronavirus disease 2019" OR "coronavirus disease-19") AND (hospitali?ation OR admission OR hospital stay OR mortality OR morbidity OR outcome OR death OR survival)	37
Medline	(anticoagulant* or anticoagulation*) AND ("COVID-19" OR "SARS-CoV-2" OR "2019 novel coronavirus infection" OR "2019-nCoV" OR "coronavirus disease 2019" OR "coronavirus disease-19") AND (hospitali?ation OR admission OR hospital stay OR mortality OR morbidity OR outcome OR death OR survival)	20
Cochrane	(anticoagulant* or anticoagulation*) AND (covid-19 OR coronavirus OR sars-cov-2) AND (hospitali?ation OR admission OR hospital stay OR mortality OR morbidity OR outcome or death or survival)	2
Handsearching	Anticoagulant and COVID-19	

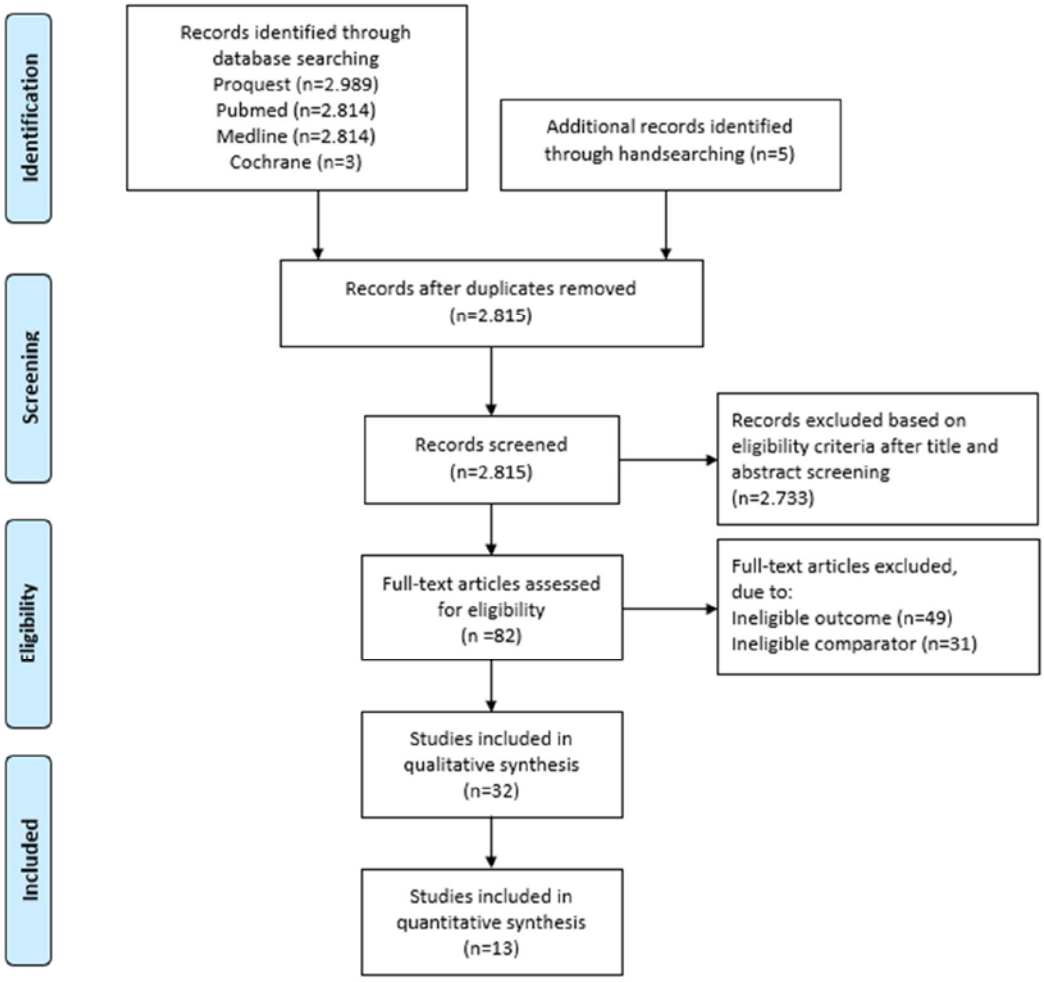

Figure 1. PRISMA flowchart of study selection.

Study Characteristics

This systematic review and meta-analysis include a total of 33,494 hospitalized COVID-19 patients from a total of 32 studies. Summary of the baseline study characteristics and results are listed in **Table 2**. We classified the studies into 3 groups, namely studies on in-hospital anticoagulant use (n=23), studies on pre-hospital anticoagulant use (n=6), and case series on the use of drugs with anticoagulant effects (n=3). Seven studies were conducted in the ICU setting, with one clinical trial involving patients categorized as requiring ICU care.[23] All observational studies used retrospective cohort design to assess the relationship between the use of anticoagulants and mortality or thromboembolism. During the course of the COVID-19 pandemic, the use of prophylactic anticoagulant was recommended by various hematological societies as standard care for hospitalized COVID-19 patients.[10,11,13] Therefore, the more recent studies compared the efficacies between standard prophylactic dose of anticoagulant vs. higher doses. Quantitative analyses were performed for 7 studies comparing anticoagulant vs. no anticoagulant use and for 6 studies comparing higher dose of anticoagulant vs. standard prophylactic dose.

Quality of Eligible Studies and Risk of Bias

The quality of each observational study was assessed using The Newcastle Ottawa Scale and all but one study was considered high quality (**Table 3**). All randomized clinical trials had low risk of bias except for one study with some concern of bias (**Figure 2**). There were inadequate numbers of included trials to properly assess a funnel plot or perform more advanced regression-based assessments

Table 2. Summary of Baseline Characteristics and Outcomes of the Included Studies.

Authors, location and date	Study design	Setting	Age	Sample size, M/F	Groups	Findings	Adverse events
Studies on in-hospital anticoagulant (AC) use							
Tang et. al.,[24] China, January-February 2020	Observational	Hospitalized patients	65,1±12	449, 268/181	Heparin at least 7 days (n=99) vs. no heparin or heparin less than 7 days (n=350). 99 patients (22%) received heparin for at least 7 days, in which 94 received LMWH (40-60 mg enoxaparin/d) and five received unfractionated heparin (10 000-15 000 U/d)	Heparin treatment was associated with lower 28-day mortality in patients with SIC score ≥ 4 (40.0% vs 64.2%, P =0.029), but not in those with SIC score < 4 (29.0% vs 22.6%, P =0.419). When D-dimer level was above 3.0 μg/mL (six-fold of upper limit of normal), there was significantly lower mortality in heparin users than nonusers (32.8% vs. 52.4%, P = 0.017).	Not stated.
Yin. et. al.,[25] China, January-February 2020	Observational	Hospitalized patients	65,1±12 in COVID group, 58,4±18 in non-COVID group	553, 340/213	Heparin at least 7 days (n=99 in COVID group, n=22 in non-COVID group) vs. no heparin or heparin less than 7 days (n=350 in COVID group, n=82 in non-COVID group). Ninety-nine (22.0%) patients of COVID group received heparin treatment for at 3least 7 days, in which 94 received LMWH (40–60 mg enoxaparin/day) and 5 received UFH (10,000–15,000 U/day); 22 (21.2%) patients of non-COVID group received heparin treatment, in which 20 received LMWH (40–60 mg enoxaparin/day) and 2 received UFH (10,000–15,000 U/ day).	When D-dimer level was above 3.0 μg/mL (six-fold of upper limit of normal), there was significantly lower mortality in heparin users than nonusers in COVID group (32.8% vs. 52.4%, P = 0.017). This difference between the heparin users and non-users was not found in the non-COVID group.	Not stated.
Paranjpe et. al.,[35] USA, March-May 2020	Observational	Hospitalized patients	Not stated.	2773, Not stated	Treatment-dose systemic AC (oral, subcutaneous or intravenous; n=786) vs. no AC (n=1.987)	In-hospital mortality for patients treated with AC was 22.5% with a median survival of 21 days, compared to 22.8% and median survival of 14 days in patients who did not receive AC. In patients who required mechanical ventilation in-hospital mortality was 29.1% with a median survival of 21 days for those treated with anticoagulants vs. 62.7% with a median survival of 9 days in patients who did not receive anticoagulants. In a multivariate proportional hazards model, longer duration of AC treatment was associated with a reduced risk of mortality (adjusted HR of 0.86 per day, 95% confidence interval 0.82-0.89, p<0.001).	63% of the hospitalized patients with COVID-19 that were given systemic AC were found to have major bleeding.

Atallah et. al.,[36] Abu Dhabi, 2020	Observational	ICU	49 (40-61)	188, 154/34	Thrombotic events (n=21) vs. non-thrombotic events (n=188). Anticoagulation strategy in thrombotic events vs. non-thrombotic events were therapeutic AC with heparin or oral anticoagulant (19% vs. 12%), high-intensity prophylactic dose (29% vs. 41%), standard prophylactic dose of enoxaparin 40 mg daily (52% vs. 43%) or none (0 vs. 4%).	Overall thrombotic events were 12,2%. High-intensity thromboprophylaxis regimen, but not therapeutic dose, was associated with a lower-risk of thrombotic events compared with the regular prophylactic regimen (OR = 0.20; 95% confidence interval 0,008-1,86; p=0,01).	Thirty-one patients (16.5%) experienced haemorrhagic events during their ICU stay; 13 were classified as major bleeding. Out of the 24 patients who received therapeutic AC, five (21%) had major haemorrhagic events compared with 8 out of 164 patients (5%) who did not receive therapeutic AC (p = 0.014). Among the 75 patients who received high-intensity prophylactic regimen, only 2 (2.7%) experienced major bleeding.
Ayerbe et. al.,[40] Spain 2020	Observational	Hospitalized patients	67.57 (15.52)	2.075	Heparin (n=1734) vs. no heparin (n=285)	Heparin was associated with lower mortality when the model was adjusted for age and gender, with OR (95% CI) 0.55 (0.37–0.82), p=0.003. This association remains significant when saturation of oxygen <90%, and temperature >37°C were added to the model with OR 0.54 (0.36–0.82) p = 0.003, and when all the other drugs were included as covariates (OR 0.42, 0.26–0.66; p < 0.001).	Not stated.
Mouhat et. al.,[37] France, March-April 2020	Observational	ICU (n=48) and conventional ward (n=94)	65.57±13	349, 67.3% male	141 (87.0%, 95% CI 80.8–91.8%) out of 162 patients received AC initiated at admission, including 85.1% (95% CI 78.1–90.5%) with LMWH, 7.8% (95% CI 4.0–13.5%) with UFH and 7.1% (95% CI 3.5–12.7%) with oral AC.	D-dimer level and the lack of any anticoagulant therapy were significantly associated with the occurrence of CTPA-confirmed PE (OR 4.0 (95% CI 2.4–6.7) per additional quartile of D-dimer and OR of 4.5 (95% CI 1.1–7.4), respectively.	Not stated.
Boari et. al.,[43] Italy, February-April 2020	Observational	Hospitalized patients	71.0 ± 13.8	258, 173/	29 patients received ACs. In the beginning, prophylactic dose of 4000 Units sc once daily; then, higher doses were progressively used: 4000 Units twice daily, 6000 Units sc once daily or 100 Units/kg twice daily (anticoagulation dose), shifting after few days, when indicated, to one of the new oral AC (apixaban or edoxaban).	Enoxaparin at low, prophylactic dose (4000 Units sc once daily) was not associated with any effect on survival. On the other hand, higher doses (4000 Units twice daily, 6000 Units sc once daily or 100 Units/kg twice daily (anticoagulant dose), when considered together, significantly improved survival.	Not stated.

Ionescu et. al.,[38] USA, March-April 2020	Observational	Hospitalized patients.	74 years (±15)	127, 68	Therapeutic AC (n=67) vs. not on therapeutic AC (n=60). Among those not on therapeutic AC, 47 were on prophylactic dose.	Median time to death was longer with higher doses of AC (11 days for tAC, 8 days for pAC, and 4 days for no AC, p < 0.001). In multivariate analysis, AC was associated with longer time to death, both at prophylactic (hazard ratio [HR] = 0.29; 95% confidence interval [CI]: 0.15 to 0.58; p < 0.001) and therapeutic doses (HR = 0.15; 95% CI: 0.07 to 0.32; p < 0.001) compared with no AC.	Bleeding rates were similar among tAC and remaining patients (19 vs. 18%; p =0.877).
Iionescu et. al.,[39] USA, March-May 2020	Observational	Hospitalized patients. 18.5% (n = 642) in ICU.	64.5± 17.0	3480, 51.5% female	60.9% received pAC (n = 2121), 28.7% received ≥3 days of tAC (n = 998), and 10.4% (n = 361) received no AC.	Kaplan-Meier plot demonstrated different 25-day survival probability in the tAC and pAC groups (57.5% vs 50.7%). In a multivariate proportional hazards model, AC was associated with reduced risk of death at prophylactic (hazard ratio [HR] 0.35 [95% confidence interval CI 0.22-0.54]) and therapeutic doses (HR 0.14 [95% CI 0.05-0.23]) compared to no AC.	Major bleeding occurred more frequently in tAC patients (81 [8.1%]) compared to no AC (20 [5.5%]) or pAC (46 [2.2%]) subjects.
Musoke et. al.,[26] USA, March-May 2020	Observational	Hospitalized	66.21 ± 14.21	355, 181/174	Prophylactic dose for VTE n=216, subtherapeutic dose n= 23, therapeutic dose n=101, no anticoagulant n=15. Prophylactic doses of anticoagulation were based on institutional protocols (heparin 5000 units subcutaneously 2–3 times/day or low molecular weight heparin (LMWH) 30-40 mg daily. Therapeutic anticoagulation was based on indication with VTE (80 units/kg IV bolus followed by 18 units/kg/h infusion) while for atrial fibrillation/flutter or acute coronary syndrome (12 units/kg/h infusion). For therapeutic LMWH dose was 1 mg/kg q12 hours.	After multivariable logistic regression, only age OR 1.04 95% CI (1.01 to 1.07) p = 0.008, D-dimer≥ 1500 ng/mL OR 5.89 95% CI (2.84 to 12.20) p < 0.0001 and the use of therapeutic AC were independently associated with higher inpatient mortality OR 6.16 95% CI (2.96 to 12.83) p ≤ 0.0001	Therapeutic AC had a significantly higher rate of major bleeding compared to prophylactic doses (p = 0.04).
Tomasoni et. al.,[41] Italy, March-April 2020	Observational	Hospitalized	67.4 ± 13.2	692, 481/211	In-hospital heparin treatment (n=364) vs. no heparin treatment (n=328).	Heparin was associated with lower mortality at both univariate and multivariable analysis (HR 0.57; 95% CI 0.41–0.81; P <0.001; adjusted HR 0.41; 95% CI 0.25–0.67; P <0.001)	Not stated.
Yethindra et. al.,[46] Kyrgyzstan, until May 2020.	Observational	Hospitalized	58.54	110, 68/42	UFH vs. no AC.	AC with UFH was found to be correlated with lower mortality when the analysis was adjusted for age and gender (odds ratio (OR) [95% confidence interval]: 0.68 [0.48–0.94], *P* = 0.002). This correlation was significant for body temperature >37°C and SaO_2< 90% (OR: 0.67 [0.47–0.94], *P* = 0.002) as well as for other treatments added (OR: 0.54 [0.38–0.76], *P* < 0.001).	Not stated.

Yu et. al.,[42] China, December 2019 – April 2020	Observational	Hospitalized	61.86 ± 12.43	142, 81/61	AC vs. no AC	No anticoagulant was a risk factor for DVT (OR 3.0, 95% CI 1.1-7.8, p=0.025).	Not stated.
Lopes et. al., [32] ACTION trial Brazil, June 2020 – February 2021	Open-label, multicenter, randomized controlled trial	Hospitalized	56·6 years (SD 14·3	615, 368/247	Therapeutic (n=311) vs. prophylactic (n=304) AC. Therapeutic AC was in-hospital oral rivaroxaban (20 mg or 15 mg daily) for stable patients, or initial subcutaneous enoxaparin (1 mg/kg twice per day) or intravenous unfractionated heparin (to achieve a 0·3-0·7 IU/mL anti-Xa concentration) for clinically unstable patients, followed by rivaroxaban to day 30. Prophylactic AC was standard in-hospital enoxaparin or unfractionated heparin.	The primary efficacy outcome (win ratio of time to death, duration of hospitalization, duration of supplemental O2 to day 30) was not different between groups, with 34·8% wins in the therapeutic group and 41·3% in the prophylactic group (win ratio 0·86 [95% CI 0·59-1·22], p=0·40).	Bleeding was higher in the therapeautic AC group (relative risk 3·64 [95% CI 1·61-8·27], p=0·0010).
Goligher et. al.,[28] REMAP-CAP Trial US, Canada, UK, Brazil, Mexico, Nepal, Australia, the Netherlands, and Spain April – December 2020	Open-label, randomized clinical trial	Critically ill hospitalized patients	60.4±13.1	1.098, 772/326	Therapeutic-dose AC (n=534) and usual-care thromboprophylaxis (n=564)	The percentage of patients who survived to hospital discharge was similar in the two groups (62.7% and 64.5%, respectively; adjusted OR, 0.84; 95% credible interval, 0.64 to 1.11).	Major bleeding occurred in 3.8% in the therapeutic AC group and in 2.3% of thromboprophylaxis group.
Lawler et. al.,[27] ATTACC Trial US, Canada, UK, Brazil, Mexico, Nepal, Australia, the Netherlands, and Spain; April 2020 – January 2021	Open-label, randomized clinical trial	Non-critically ill hospitalized patients	59.0±14.1	2.219, 1.310/909	Therapeutic-dose AC (n=534) and usual-care thromboprophylaxis (n=564)	Therapeutic-dose anticoagulation increased organ support-free days as compared with usual-care thromboprophylaxis (adjusted OR, 1.27; 95% credible interval, 1.03 to 1.58)	Major bleeding occurred 1.9% in the therapeutic-dose AC group and in 0.9% of the thromboprophylaxis group
Di Castelnuovo et. al., [29] CORIST study Italy, February – June 2020	Observational	Hospitalized patients	NA	2.574	LMWH or UFH (n=1.827) vs. no AC (n=747)	40% lower risk of death in patients receiving heparin (HR=0.60; 95% confidence interval: 0.49-0.74.	Not stated.

Perepu et. al.,[44] US, April 2020 – January 2021	Multi-center, open-label, randomized controlled trial	Hospitalized patients in ICU (62%) or had evidence of coagulopathy	64 (24–86)	176, 99/77	Standard prophylactic dose enoxaparin (n=88) vs. intermediate weight-adjusted dose enoxaparin (n=88). The standard dose was 40 mg SC daily if the body mass index (BMI) was <30 kg/m2 and either 30 mg SC twice daily or 40 mg SC twice daily if the BMI was ≥30. The choice of 30 mg twice daily or 40 mg twice daily was determined by the treating physician according to the local institutional standard of practice. The intermediate dose was 1 mg/kg SC daily if the BMI was <30 or 0.5 mg/kg SC twice daily if the BMI was ≥30.	All-cause mortality at 30 days was 15% for intermediate dose enoxaparin and 21% for standard prophylactic dose enoxaparin (OR 0.66; 95% confidence interval, 0.30-1.45; P = .31 by Chi-square test)	Major bleeding occurred in 2% of patients in each arm.
Sadeghipour et. al.,[45] INSPIRATION trial Iran, July 2020 – November 2020	Multicenter randomized trial	Hospitalized patients in ICU	62 (51-70.7)	600, 325/275	Intermediate-dose enoxaparin, 1 mg/kg daily (n = 276) vs standard prophylactic enoxaparin, 40 mg daily (n = 286)	The primary efficacy outcome was a composite of venous or arterial thrombosis, treatment with extracorporeal membrane oxygenation, or mortality within 30 days. The primary efficacy outcome occurred in 45.7% in the intermediate-dose group and 44.1% in the standard-dose prophylaxis group OR 1.06 [95% CI, 0.76-1.48]; P = 0.70).	Major bleeding occurred 2.5% in the intermediate-dose group and 1.4% in the standard-dose prophylaxis group OR 1.83 (1-sided 97.5% CI, 0.00-5.93)
Lemos et. al.,[30] HESACOVID trial Brazil, April – July 2020	Randomized, open-label, phase II clinical trial	Hospitalized patients requiring mechanical ventilation	58 ± 16	20, 16/4	Therapeutic enoxaparin vs. standard anticoagulant thromboprophylaxis.	Patients of the therapeutic group had a higher ratio of successful liberation from mechanical ventilation (HR: 4.0 [95% CI 1.035-15.053]), p = 0.031 and more ventilator-free days (15 days [interquartile range IQR 6-16] versus 0 days [IQR 0-11]), p = 0.028	There were no major bleeding events in both groups.
Rentsch et. al.,[31] US, March – July 2020	Observational	Hospitalized patients	69.0 (58.0-76.5)	4.297, 4.015/282	Prophylactic AC (LMWH and UFH) vs. no AC	Compared with patients who did not receive AC, those who had prophylactic AC had a 27% decreased risk for 30-day mortality (HR 0.73, 95% confidence interval 0.66 to 0.81).	Prophylactic AC compared to no AC was not associated with an increased risk of bleeding events that required transfusions (0.87, 0.71 to 1.05).

Hsu et. al.,[33] US, February – April 2020	Observational	Hospitalized patients	60 [49–73]	468, 257/211	Standard VTE prophylaxis vs. high-intensity prophylaxis vs. therapeutic AC vs. no AC. Standard VTE prophylaxis was defined as LMWH 40 mg once daily, unfractionated heparin subcutaneous (HSQ) 5000 units three times daily, or apixaban 2.5 mg twice daily. High-intensity prophylaxis was defined as LMWH 40 mg twice daily or HSQ 7500 units three times daily. Therapeutic AC was defined as intravenous heparin, LMWH 1 mg/kg twice daily, dose-adjusted warfarin with a target international normalized ratio (INR) of 2.0 to 3.0, apixaban 5 mg twice daily, or rivaroxaban 20 mg daily.	30-day mortality was significantly lower among all patients who received high-intensity thromboprophylaxis (adjusted RR vs. standard-intensity, 0.26; 95% confidence interval [CI], 0.07–0.97, p = 0.045).	No significant increased rate of bleeding (p = 0.11) in group with AC vs. no AC.
Nadkarni et. al.,[34] US, March – April 2020	Observational	Hospitalized patients	65	4.389, 2.457/1.931	Therapeutic AC vs. prophylactic AC vs. no AC. AC used includes UFH, LMWH and oral anticoagulants.	Compared with no AC (n = 1,530; 34.9%), therapeutic AC (n = 900; 20.5%) and prophylactic AC (n = 1,959; 44.6%) were associated with lower in-hospital mortality (adjusted HR [aHR]: 0.53; 95% confidence interval [CI]: 0.45 to 0.62 and aHR: 0.50; 95% CI: 0.45 to 0.57, respectively), and intubation (aHR: 0.69; 95% CI: 0.51 to 0.94 and aHR: 0.72; 95% CI: 0.58 to 0.89, respectively).	Major bleeding occurred in 3% on therapeutic, 1.7% on prophylactic, and 1.9% on no AC.
Spyropoulos et. al.[23] HEP-COVID trial US, May 2020 – May 2021	Multicenter randomized trial	Hospitalized high-risk patients in ICU (n=83) and non-ICU	65±13,9	253, 136/117	Therapeutic AC (n=129) vs. standard prophylactic dose (n=124). In the standard-dose group, patients received prophylactic doses of heparin (enoxaparin, ≤40 mg daily) or intermediate doses of heparin (enoxaparin, 30 mg twice daily, enoxaparin, 40 mg twice daily, enoxaparin, 0.5 mg/kg twice daily,	The primary efficacy outcome was venous thromboembolism (VTE), arterial thromboembolism (ATE), or death from any cause. It was met in 52 of 124 patients (41.9%) (28.2% VTE, 3.2% ATE, 25.0% death) with standard-dose heparins vs 37 of 129 patients (28.7%) (11.7% VTE, 3.2% ATE, 19.4% death) with therapeutic-dose LMWH (relative risk [RR], 0.68; 95% CI, 0.49-0.96; P = .03), including a reduction in thromboembolism (29.0% vs 10.9%; RR, 0.37; 95% CI, 0.21-0.66; P < .001). The primary efficacy outcome was reduced in non-ICU patients (36.1% vs 16.7%; RR, 0.46; 95% CI, 0.27-0.81; P = .004) but not ICU patients (55.3% vs 51.1%; RR, 0.92; 95% CI, 0.62-1.39; P = .71).	The incidence of major bleeding was 1.6% with standard-dose vs 4.7% with therapeutic-dose heparins (RR, 2.88; 95% CI, 0.59-14.02; P = .17).

Studies on regular, pre-hospital AC use								
Rivera-Caravaca et. al.,[48] USA	Observational		Hospitalized	81.5 (IQR 75-87)	1.002, 593/409	Patient on prior (n=892) vs. without prior AC (n=110)	Patients with prior OAC had higher mortality risk compared to patients without prior OAC (HR 1.53, 95% CI 1.08-2.16). Patients with prior AC had significantly higher all-cause mortality (p<0.001) and higher combined all-cause mortality or any thromboembolic event (p<0.001). Respiratory insufficiency during hospitalization (HR 6.02, 95% CI 2.18-16.62), systemic inflammatory response syndrome (SIRS) during hospitalization (HR 2.29, 95% CI 1.34-3.91) and the Short-Form CCI (HR 1.24, 95% CI 1.03-1.49) were the main risk factors for mortality in patients with prior OAC.	Bleeding was significantly higher in the group with prior AC (p<0.001).
Rossi et. al.,[49] Italy, February-April 2020	Observational		Hospitalized	79 (range: 70–92)	70, 35/35	Patients with prior DOAC (n=26) vs. without prior DOAC (n=44)	In a multivariate analysis, age [HR 1.39 (1.24 – 1.57), p<0.0001], absence of chronic DOAC intake [HR 0.38 (0.17 – 0.58), p<0.01] and male gender [HR 1.49 (1.11 - 1.63), p<0,02] was associated with increased mortality risk.	Not stated.
Khider et. al.,[47] France, March 2020	Observational		Hospitalized	66.0 [54.3-79.8]	96, 44/52	COVID-19 positive patients (n=66) with prior AC (n=12) vs. without prior AC (n=54)	COVID-19-positive patients had significantly more CECs at admission (P = .008) than COVID-19-negative ones. COVID-19-positive patients treated with curative AC prior to admission had fewer CECs (P = .02) than those without. Patients treated with curative AC and angiotensin-converting-enzyme inhibitors or angiotensin receptor blockers had even fewer CECs (P = .007).	Not stated.
Russo et. al.,[50] Italy, February-April 2020	Observational		Hospitalized	67.7 (15.2)	192, 115/77	Patients with prior AC (n=26) vs. without prior AC (n=166)	Pre-admission AC was not associated with increased risk of ARDS at admission and in-hospital mortality in COVID-19 patients.	Not stated.
Menager et. al.,[51] France, March – June 2020	Observational		Hospitalized in geriatric acute unit	88.8 ± 4.5 years	82, 43/49	No regular use of VKA (n=73) vs. regular use of VKA (n=9)	HR for 7-day mortality in those regularly using VKA was 5.68 (95% CI: 1.17-27.53; p=0.031)	Not stated.
Tremblay et. al.[68] March – April 2020	Observational		Hospitalized	56.6 (18.2)	3.772, 1.533/2.239	Patients with prior AC (n=241) vs. without prior AC/antiplatelet (n=2.859)	No evidence for an effect of prediagnosis anticoagulation on mortality.	Major bleeding was significantly higher in group with prior AC (p=0,007).
Case series on drugs with AC effects								
Doi et. al.,[52] Japan, April 2020	Case series	ICU	68 (60–69)		11, 10/1	Nafamostat mesylate treatment in combination with favipiravir	(8 [73%]) who required MV requirement; however, the mortality rate was low (1 patient [9%])	Not stated.
Jang et. al.,[53] South-Korea, February-March 2020	Case series	Hospitalized	Over 65 years		3, 3/0	Nafamostat	administration of nafamostat was followed by improvement in clinical status, demonstrated by the decrease in CRP levels and WBC count.	Not stated

Rambaldi et. al.,[54] Italy, March 2020	Case series	ICU	56.5 (47–63)	6, 5/1	Narsoplimab	Following treatment, all patients improved clinically. Four patients (67 %) reduced ventilatory support from CPAP to non-rebreather or Venturi oxygen mask after a median of 3 narsoplimab doses (range 2–3). In three of these patients, oxygen support was weaned and then discontinued, and discharge followed a median of 6 (range 5–8) total narsoplimab doses. No bleeding event.

Table 3. Quality Assessment of the Included Studies Using Newcastle Ottawa Scale.

Studies	Selection				Comparability	Outcome			Total score
	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Outcome of Interest Was Not Present at Start of Study	Comparability on the basis of the design or analysis	Assessment of outcome	Follow up long enough for outcomes to occur	Adequacy of follow up cohorts	
Tang et. al.,[24]	*	*	*	*	*	*	*	*	8
Yin. et. al.,[25]	*	*	*	*	*	*	*	*	8
Paranjpe et. al.,[35]	*	-	*	*	**	*	*	*	8
Atallah et. al.,[36]	*	*	*	*	*	*	*	*	8
Ayerbe et. al.,[40]	*	*	*	*	**	*	*	*	9
Mouhat et. al.,[37]	*	-	*	*	*	*	*	*	7
Boari et. al.,[43]	*	-	*	*	*	*	*	*	7
Ionescu et. al.,[38]	*	-	*	*	*	*	*	*	7
Iionescu et. al.,[39]	*	*	*	*	**	*	*	*	9
Musoke et. al.,[26]	*	-	*	*	**	*	*	*	8
Tomasoni et. al.,[41]	*	*	*	*	**	*	*	*	9
Yethindra et. al.,[46]	*	-	-	*	*	*	*	*	6
Yu et. al.,[42]	-	-	*	*	*	*	*	*	6
Di Castelnuovo et. al.[29]	*	*	*	*	**	*	*	*	9
Rentsch et. al.,[31]	*	*	*	*	*	*	*	*	8
Hsu et. al.,[33]	*	*	-	*	**	*	*	*	8
Nadkarni et. al.,[34]	*	*	*	*	**	*	*	*	9
Rivera-Caravaca et. al.,[48]	*	*	*	*	**	*	*	*	9
Rossi et. al.,[49]	*	-	*	*	**	*	*	*	8
Khider et. al.,[47]	*	-	*	*	*	*	*	*	7
Russo et. al.,[50]	*	-	*	*	*	*	*	*	7
Menager et. al.,[51]	*	*	*	*	*	*	*	*	8
Tremblay et. al.[68]	*	-	*	*	**	*	*	*	8

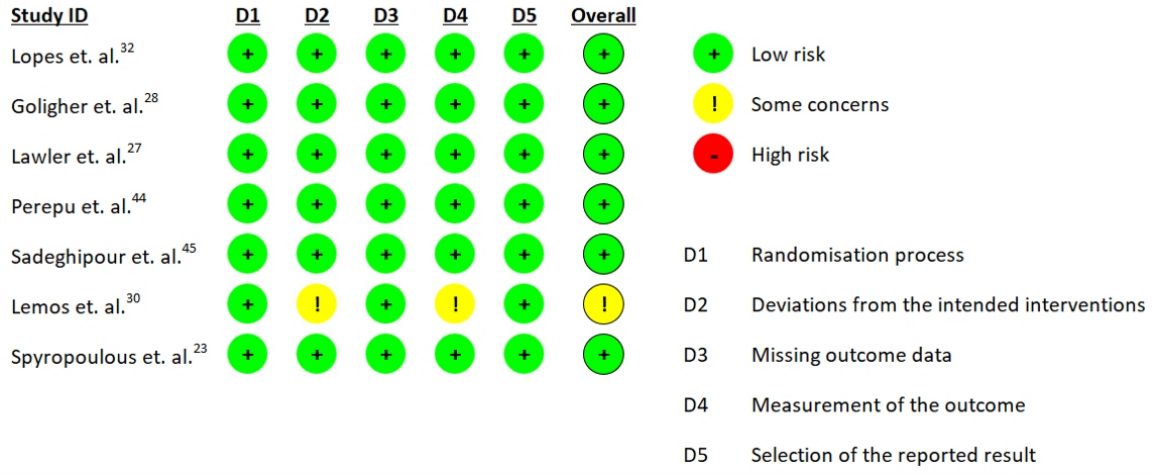

Figure 2. Risk of bias in the randomized clinical trials.

Meta-analysis of In-hospital Anticoagulants and Outcome of COVID-19 Patients

Diverse ACs were used in 23 studies on in-hospital anticoagulation. There were eight studies using UFH and LMWH;[24-34] eight using oral anticoagulants, UFH and LMWH;[35-39] three without specifying the type of AC used;[40-42] four with LMWH only[23, 43-45] and one with UFH only.[46] Eleven studies compare anticoagulant vs. no anticoagulant,[24, 25, 29, 31, 34, 35, 37, 40-42, 46] while the remaining studies involve comparisons between standard prophylactic dose vs higher doses of anticoagulant.[26-28, 32, 36, 38, 39, 43] The combined effect of anticoagulation on decreased mortality in 18.437 hospitalized patients is shown in **Figure 3** (RR 0.55; 95%CI 0.43-0.66; p<0.001).

In 3,210 patients from 6 studies we found that higher dose of anticoagulant, which ranged from high intensity prophylactic dose to therapeutic dose, showed treatment benefit when compared to the standard prophylactic dose (RR 0.69; 95%CI 0.31-1.07; **Figure 4**). The studies include the following populations: patients with D-dimer above the upper limit of normal,[32] the critically ill patients,[28, 45] ICU patients and/or patients who had laboratory evidence of coagulopathy,[44] unselected hospitalized patients,[33] and hospitalized adult patients with D-dimer levels more than 4 times the upper limit of normal or sepsis-induced coagulopathy score of 4 or greater.[23] Two studies out of the 6 studies showed clear survival benefit of higher dose of anticoagulant.[23, 33]

Regular, Pre-hospital Anticoagulation and Outcome of COVID-19 Patients

Five studies involving 1,442 subjects investigated the impact of regular, pre-hospital oral anticoagulation on mortality and other parameters with mixed, conflicting results.[47-51] Two studies involve patients with the use of both direct acting oral anticoagulant (DOAC) and vitamin K antagonist (VKA),[48,50] one with DOAC only,[49] one with VKA only,[51] and two without specifications on the type of anticoagulant used.[47] These studies generally consisted of older adults above 60 years old, and one study specifically was aimed to investigate the geriatric population in the acute care unit.[51]

Alternative Agents with Anticoagulant Properties

With regards to the use of alternative agents with anticoagulant properties, three case series reported the use of nafamostat mesylate and narsoplimab. Despite having low sample size, being used in conjunction with other drugs and lacking control groups, the patients showed improved outcome in all studies without any reported bleeding event.[52-54]

DISCUSSION

This systematic review and meta-analyses, which consists of 32 studies including 7 recently published randomized clinical trials, and a total

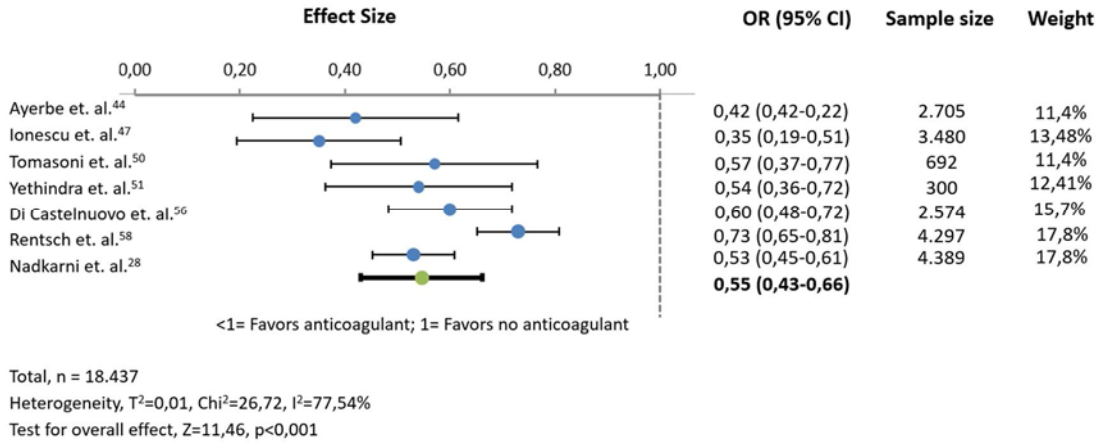

Figure 3. Forest plot for odds ratio for mortality in patients receiving anticoagulants.

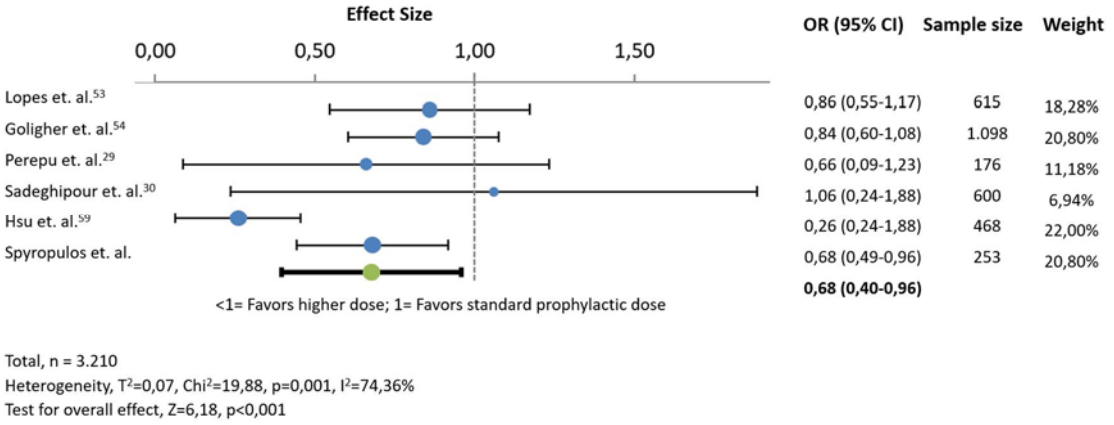

Figure 4. Forest plot for odds ratio for mortality in patients receiving anticoagulants with dose higher than standard prophylaxis.

of 33,494 patients show that anticoagulants reduce mortality and improve survival in COVID-19 patients when compared to no anticoagulation. The survival benefit was also found when comparing high-intensity and therapeutic dose anticoagulant with standard prophylactic dose. There are inconclusive, conflicting evidence on the effect of regular, pre-hospital anticoagulation on mortality as shown by this systematic review. These findings support the current recommendations of anticoagulant use in COVID-19 patients endorsed by ISTH and ASH.[10, 12-14] The use of standard prophylactic dose was endorsed in the critically ill and acutely ill population due to the lack of additional treatment benefit and the higher bleeding risk of higher-dose anticoagulation. However, in selected populations such as shown by the HEP-COVID trial, the use of therapeutic-dose LMWH reduced major thromboembolism and death compared with standard prophylactic heparin among inpatients with COVID-19 with very elevated D-dimer levels.[23] Indeed, understanding the risks and benefits of increased dose of anticoagulation in critically ill COVID-19 patients is especially challenging, with some conflicting evidence reported from different trials.[23, 27, 32, 44]

Critically ill patients are at increased risk of VTE due to the presence of patient factors such as age, pregnancy, obesity, immobilization, past history of VTE, cancer, sepsis, respiratory or heart failure, stroke, trauma or recent surgery) as well as ICU risk factors (sedation, vasopressors or central venous catheters).[55] Beyond ICU factors, increased VTE risk in COVID-19 patients may occur as a result of not

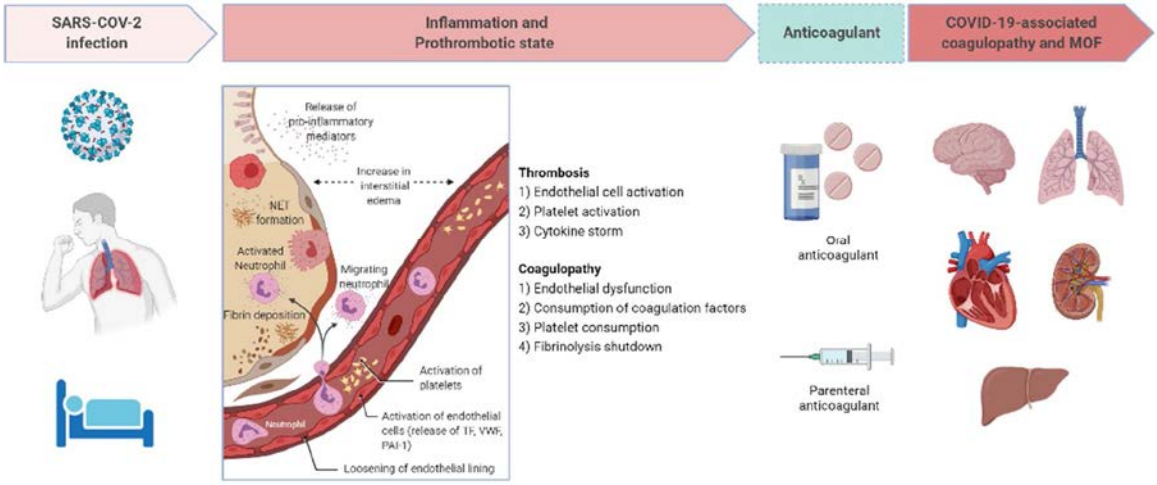

Figure 5. The potential pathophysiology of COVID-19-associated coagulopathy and the role of anticoagulants. The potential pathophysiological process underlying COVID-19-associated coagulopathy are the followings: infection, thromboinflammation, and coagulopathy with bleeding tendencies and multiple organ failure (MOF). Firstly, the SARS-CoV-2 is entering the respiratory tract through the angiotensin-converting enzyme 2 (ACE-2) in the epithelial cells in the trachea or lung tissues. Secondly, the viral proliferation and dissemination within the lung tissue lead to in situ endothelial cell, platelet and immune system activation. Activation of endothelium, neutrophils and platelets further induces neutrophil extracellular trap (NET) formation, contributing to the microthrombus with fibrin. This process is characterized by upregulation of inflammmatory mediators such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), C-reactive protein (CRP), interferon (IFN), as well as molecules playing a role in thrombosis such as von-Willebrand factors (VWF), tissue factor (TF) and plasminogen activator inhibitor-1 (PAI-1). Oral and parenteral may play a role in preventing the development of prothrombotic state and its further consequences of coagulopathy and MOF. Thirdly, coagulopathy together with inflammation drive the progress of multiple organ failure (MOF), including in the major organs of brain, heart, lung, liver, and kidney.

only acute infection *per se*, but also the presence of respiratory failure and reduced mobility due to the need of oxygen supplementation and the isolation imposed by hospital restrictions.[56] However, given the diversity of the critically ill COVID-19 patients, the current body of evidence does not support routine empirical use of high-intensity or therapeutic dose anticoagulation in unselected patients with COVID-19 admitted to the ICU.

Infection with SARS-CoV-2 has been associated with a pattern of coagulopathy that is commonly characterized by elevations in plasma levels of fibrinogen (as an acute phase response) and D-dimer, and unlike the appearance of classic DIC in bacterial sepsis or trauma, prolongation of APTT and PT is minimal, with only modest thrombocytopenia.[57, 58] Occasionally, patients with severe COVID-19 and multiorgan failure may progress to overt DIC, reflected by more severe thrombocytopenia, prolonged PT and APTT, marked elevation of D-dimer and decreased fibrinogen. Taken together, data suggest that the COVID-19 associated coagulopathy is a combination of mild DIC with pulmonary thrombotic microangiopathy.[9] Coronavirus infections are also associated with an excessive activation of the fibrinolytic system tissue-type plasminogen activator (t-PA) compared to those with no infection. It is thought that inflammation-induced endothelial cell injury could result in the release of plasminogen activators, which could explain the high concentrations of D-dimer and fibrin degradation products in patients with severe COVID-19.[9, 59] Thrombotic microangiopathy is typically caused by pathological state of platelet-endothelial interaction due to ultra-large von Willebrand factor multimers that are cleaved by ADAMTS13.[60] In a hyperinflammatory state, secondary deficiency of ADAMTS13 due increased consumption have been reported.[61] There is currently no data on platelet-endothelial interaction and ADAMTS13 levels in patients COVID-19. Patients with VTE have been shown to have increased risk of in-hospital mortality.[62] A summary of the pathophysiology and potential role of anticoagulants is presented in **Figure 5**.

The proposed mechanism of the benefit of anticoagulation in COVID-19 patients is by

suppressing the pro-thrombotic coagulopathy and thereby preventing thrombosis in both the micro- and macro-vaculatures.[63] Considerations for the use of heparin in the setting of COVID-19 also include acknowledgement of its anti-inflammatory and anti-viral potential. Heparan sulfate may bind to SARS-CoV-2 spike protein and block viral attachment and entry and may attenuate inflammatory response by neutralization of proinflammatory proteins such as histone and HMGB1.[64] Selection of COVID-19 patients who are suitable for escalated dose of anticoagulant treatment using Padua or Geneva scores which predict the risk for VTE and pulmonary embolism, respectively, are reasonable but still lack validation as they may perform differently in patients with COVID-19 pneumonia.[65, 66]

Findings in this systematic review demonstrate the benefit of anticoagulation in hospitalized COVID-19 patients, especially in the setting of increased VTE in patients with severe disease. The ASH recommendation states that all unless patients are deemed to be at increased bleeding risk, patients with COVID-19 should receive thromboprophylaxis with LMWH or fondaparinux.[67] Furthermore, the Italian Society on Thrombosis and Haemostasis (SISET) suggested the administration of thromboprophylaxis at home for 7–14 days after hospital discharge or during the pre-hospital phase, especially in subjects with pre-existing or persisting VTE risk factors. Surprisingly, to date we found no published studies reporting the use of anticoagulants in COVID-19 patients post-discharge.

Newer drugs that have anticoagulant effects are currently under investigation. Nafamostat, a serine proteinase inhibitor, has been used in Japan to treat disseminated intravascular coagulation (DIC) and pancreatitis. Although nafamostat originally an antithrombin drug, it has a characteristically strong antiplasmin action and has recently been shown to block viral entry by inhibiting membrane fusion between SARS-CoV-2 and human cells.[15] Narsoplimab, a lectin inhibitor, down-modulates SARS-CoV-2-induced activation of the lectin pathway and endothelial cell damage and is thought to reduce the thrombotic risk of COVID-19 patients.[54]

The limitation of this study is the large heterogeneity observed. This may be due to the diverse populations, comparison groups, and types as well as doses of anticoagulant use. Although the use of prophylactic anticoagulant is a widespread practice, our study shows that therapeutic or high intensity anticoagulant should be used judiciously and only in selected population such as those with higher risk of thromboembolic events. We recommend that future clinical trials not only address the use of anticoagulant in COVID-19 patients but also their doses and indications, pre-existing comorbidities, risk of bleeding and the degree of severity, as well as regular, pre-hospital use of anticoagulation.

CONCLUSION

The administration of anticoagulant results in improved survival of hospitalized COVID-19 patients. Determination of thrombosis in COVID-19 is essential, as this would indicate therapeutic dose of anticoagulation. Selecting between standard vs. higher dose prophylaxis in nonthrombotic patients warrant judicious considerations of the risk benefit ratio and individual patient profile. The results from this study are important in the tailored treatment of COVID-19 patients, especially those at risk for increased complications, and in addressing the gap in knowledge from currently available evidence. Areas of uncertainties in the literature include the indications or risk stratifications and targeted populations for prophylactic or high-intensity prophylactic dose in COVID-19 patient, the need for supratherapeutic dose in selected patient population; and the need for oral anticoagulants for patients not admitted or after discharge from hospital. The use of anticoagulants is currently recommended by international hematological and thrombosis societies in selected COVID-19 population. However, precise parameters are still needed to identify those that may benefit the most from anticoagulants during admission and post-discharge.

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