Systematic Review

Anti-coagulation therapy on COVID-19 patients: A systematic review and meta-analysis

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ABSTRACT

A once often neglected virus from common practice has been demanding the attention of all researchers for the past decade ever since it started to infect humans from its usual wild habitats. The severe acute respiratory syndrome coronavirus 2 infection in humans is now found to have frequent manifestations of thromboembolic events as a result of a hyper-coagulable state. Anti-coagulants (ACs) have been suggested to overcome such a state, and studies have been conducted to assess its role. The objective of this meta-analysis is to determine the existence of such a role and its nature, either beneficial or not, and to assess the strength of this role if it exists. We have conducted an online search in the databases such as PubMed, Google scholar, Lancet, Elsevier, JAMA, Medline, and so on and concluded ten studies among 2562 that had results which were more precise and of better quality. The results of six studies favored the use of ACs, whereas one study showed no beneficial response and four studies discussed the effects of therapeutic versus prophylactic anti-coagulation. The result of our statistical analysis was that the odds ratio for mortality reduction of ACs in coronavirus disease 2019 (COVID-19) patients is 0.6757 (95% CI; 0.5148 to 0.961) and that for benefits of therapeutic ACs versus prophylactic ACs in COVID-19 patients is 0.809 (95% CI; 0.6137 to 1.1917). AC was associated with lower mortality and intubation among hospitalised COVID-19 patients. Compared with therapeutic AC, prophylactic AC was associated with lower mortality, although not statistically significant, and lower bleeding risks.

KEY WORDS: Artificial, hospital mortality, prophylaxis, respiration, SARS-CoV-2, therapeutic, thromboembolism

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INTRODUCTION

COVID-19, coronavirus disease 2019, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a single-stranded RNA virus first reported in Wuhan city, China, which affected every country in the world with the total number of cases being more than 235 million. The disease is transmitted by infected droplets from the affected individuals to a healthy person. It gains entry into the host through angiotensin converting enzyme 2 receptor, which is present in the nasal epithelium via S1 and S2 sub-units of spike proteins of the virus.[1-3] The viruses undergo replication, and it spreads to the upper respiratory tract through the conducting airways. In most of the patients, the disease does not progress beyond; till now, the patient may be either asymptomatic or mildly to moderately diseased.[3,4]

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In some patients, there can be lower airway involvement. The virus predominantly affects type II pneumocytes.[5] The virus exerts cytotoxicity to the pulmonary epithelium directly by its invasion and indirectly by dysregulating the immune response.[1,3,6] As the disease progresses, it damages the pulmonary endothelium, resulting in the release of massive cytokines such as IL-6, TNF-α, IL-1, IL-2, IL-7, and IL-17.[7,8] This is termed as the cytokine storm. These inflammatory cytokines lead to a hyper-coagulable state increasing the risk of micro-vascular and macro-vascular thrombosis, and the endothelial dysfunction potentiates the risk. The incidence of thromboembolic events is high among the severe COVID-19 patients; it is associated with higher rates of intensive care unit (ICU) admission, mechanical ventilation, and death.[9,10] These findings in COVID-19 played an important role for anti-coagulants (ACs) in pharmacotherapy of COVID-19, whose role is analysed in this review.

MATERIALS AND METHODS

This meta-analysis was performed according to the Preferred Reporting Items of the

Systematic review and Meta-Analysis (PRISMA) checklist. Steps were followed based on the Cochrane Handbook of Systematic Review and Meta-Analysis.

Search strategy

Two reviewers independently conducted a literature review by searching the

databases such as PubMed, Google scholar, Lancet, Elsevier, JAMA, Medline, American Medical Association, British Medical Journal, WHO, Journal of the Association of Physicians of India, AJP, PLoS, Frontier's Media, Cochrane, MDPI, NICE, medRxiv, Science Direct, PNAS, and The New

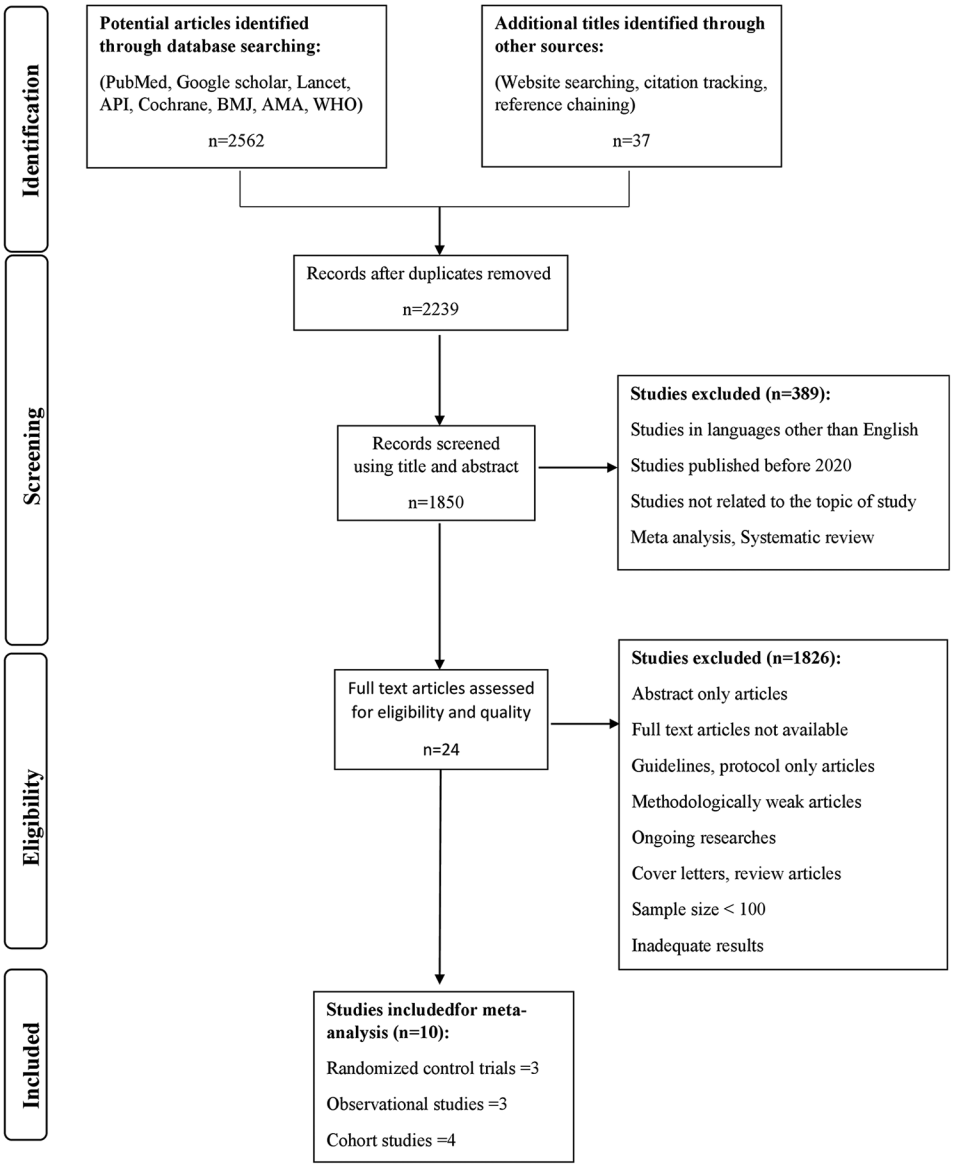

Figure 1: PRISMA flow chart showing study selection

England Journal of Medicine. The following search terms were used: 'Anticoagulants', 'Drug trials', 'Pharmacotherapy', and 'randomized control trials'. They had also included mining references from good quality articles, website searching, and citation tracking, as shown in Figure 1.

Selection criteria

After obtaining the search results, the studies were included if they were conducted between April 2020 and July 2021, if the sample size was more than 100, if there was proper explanation and reporting of methodologies, if randomisation could be performed, and if reliable results could be expressed.

Studies excluded include *in vitro* studies, articles published before 2020, articles without full-text availability, and articles published in languages other than English.

Data extraction

Data were extracted independently from the eligible studies. Authors also researched similar systematic reviews to ensure reliability of the extracted data. Authors eliminated "Selection bias" by taking results after adjustments and propensity score matching from odds ratio estimation with 95% confidence intervals (CIs) using the generic inverse variance method (ransom-effects model). The authors did not impute missing data for any of the outcomes. The corresponding authors of reviewed articles were contacted for missing outcome data and for clarification on study methods, where possible.

Statistical analysis

The pooled odds ratio with 95% CIs of the individual studies with respect to the use of ACs was determined and analysed to be 0.6757 (0.5148 to 0.961). The results of the different studies, with 95% CI, are shown in a forest plot. Thus, use of ACs in COVID-19 patients significantly reduces the mortality.

The pooled odds ratio with 95% CIs of the individual studies that assessed the therapeutic versus prophylactic usage of ACs was also determined and analysed to be 0.809 (0.6137 to 1.1917). The results of these particular studies, with 95% CI, are shown in the next forest plot. There is no significant difference in mortality reduction between therapeutic anti-coagulation and prophylactic anti-coagulation among COVID-19 patients.

RESULTS

Study selection

A total of 2599 articles were identified via database searches, website searching, and reference chaining. After eliminating duplicate studies (360), articles that were inappropriate to the study topic (389), and articles that did not fit the eligibility criteria (1826), 24 articles were eligible. After quality assessment, ten articles were taken for the meta-analysis, of which four were cohort studies, three were randomised control trials, and three were observational studies.

Study characteristics

Factors that were considered for choosing the study: date of publication, study design, sample size, country where the study was conducted, number of patients in the intervention group, ACs, combination of drugs if given, co-morbidities, number of deaths, number of ICU admissions, need for invasive mechanical ventilation, duration of hospitalisation, number of patients in the control group who received standard care of treatment/ placebo, and whether the AC was prophylactic or therapeutic in the course of the disease.

Synthesis of results

In our meta-analysis, the following parameters were evaluated:

a) Time taken for clinical improvement
b) Need for mechanical ventilation
c) Duration of hospitalisation
d) Mortality
e) Form of AC administered.

Data of 21,294 patients collected from ten studies conducted in the US, Spain, Iran, Brazil, and China are shown in Table 1.

Out of the seven studies selected, the results of six studies favored the use of

ACs, whereas one study showed no beneficial response. The result of our statistical analysis was that the odds ratio for mortality reduction of ACs in COVID-19 patients is

0. 6757 (95% CI; 0.5148 to 0.961), as shown in Figure 2.

Out of the ten studies selected, four discussed the effects of therapeutic versus prophylactic anti-coagulation. The

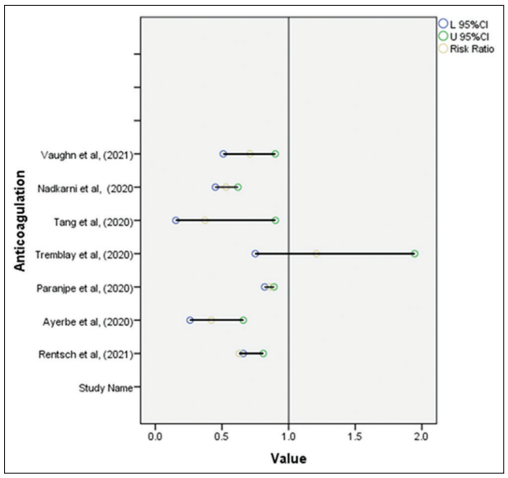

Figure 2: Odds ratio of mortality reduction by ACs as per the data of analysed studies

Table 1: Summary of studies analysed in the meta-analysis

Study ID	Country	Study design	Sample size	Experimental group	Comparative group	Results	Description
Christopher Rentsch *et al*.[11] (2021)	United States	Cohort	4297	Patients with prophylactic anti-coagulation (2156)	Patients with no anti-coagulation (2141)	HR=0.73 and 0.69 for 30 days mortality and in-patient mortality of patients receiving prophylactic AC compared to those on no AC, respectively.	Patients who received the prophylactic anti-coagulation showed 27% decreased risk in 30 days mortality rate.
INSPIRATION Investigators *et al*. [12](2021)	Iran	RCT	600	Patients with intermediate dosages of prophylactic anti-coagulation (299)	Patients with standard dosages of prophylactic anti-coagulation (299)	OR=1.06 for efficacy outcome with intermediate dosing when compared to standard doses.	The efficacy outcome of standard versus intermediate dosage of prophylactic anti-coagulation is not much significant.
Luis Ayerbe *et al*. [13](2020)	Spain	RCT	2075	Patients who received heparin (1734)	Patients who did not receive heparin (285)	OR=0.42 for mortality in patients treated with heparin compared to those on no heparin.	Patients treated with heparin are associated with lower mortality.
Ishan Paranjpe *et al*.[14] (2020)	New York	Observational study	2773	Mechanically ventilated patients who received anti-coagulation (786)	Mechanically ventilated patients who did not receive anti-coagulation (1987)	aHR=0.86 for risk of mortality of patients who received AC when compared with patients who do not.	The median survival days of those treated with AC is twice the median survival days of patients not treated with AC.
Douglas Tremblay *et al*. [15](2020)	New York	Cohort study	3772	Patients who received AC (241)	Patients who received no AC or anti-platelet therapy (2859)	HR=1.208, 0.905, and 1.027 for all-cause mortality, mechanical ventilation, and hospital admission in the AC versus no-AC/anti-platelet groups, respectively.	There was no statistically significant difference in survival (p=0.367) or time to mechanical ventilation in those receiving anti-coagulation.
Ning Tang *et al*.[16] (2020)	China	Observational study	449	Patients who received heparin (99)	Patients who received no heparin (350)	OR=0.372 for 28-day mortality in patients with SIC score>4 who received heparin when compared with patients with no heparin.	Heparin treatment in COVID-19 shows lower mortality when there is sepsis-induced coagulopathy.
Girish N Nadkarni *et al*.[17] (2020)	New York	Observational study	4389	Patients who received prophylactic AC and Therapeutic AC (2859)	Patients who received no anti-coagulation treatment (1530)	aHR=0.53 for mortality in patients on therapeutic and prophylactic AC when compared to those not on AC.	Anti-coagulation is associated with lower mortality and intubation among hospitalised COVID-19 patients.
Valerie M. Vaughn *et al*.[18] (2021)	Michigan	Cohort study	1351	Patients who received prophylactic AC (970)	Patients who received no anti-coagulation treatment (162)	aHR=0.71 for mortality in patients on prophylactic AC when compared to those not on AC.	60 days mortality was significantly lowered among patients who were administered prophylactic dose AC.
Renato D Lopes *et al*.[19] (2021)	Brazil	RCT	615	Patients who received therapeutic AC (311)	Patients who received prophylactic AC (304)	Win ratio=0.86 for primary efficacy outcomes of therapeutic AC to prophylactic AC.	Therapeutic anti-coagulation did not improve clinical outcomes and also has increased bleeding when compared to prophylactic anti-coagulation.
Bo Yu *et al*. [20] (2021)	USA	Retrospective cohort	973	Patients who received empirical therapeutic AC (209)	Patients who received prophylactic AC (764)	HR=0.476 for mechanically ventilated patients receiving therapeutic anti-coagulation compared to those not on anti-coagulants.	Therapeutic AC is found to lower mortality in mechanically ventilated patients.

HR - Hazard Ratio

result of our statistical analysis was that the odds ratio for benefits of therapeutic ACs versus prophylactic ACs in COVID-19 patients is 0.809 (95% CI; 0.6137 to 1.1917). Thus, there is no significant difference in mortality reduction between therapeutic anti-coagulation and prophylactic anti-coagulation among COVID-19 patients shown in Figure 3.

Quality assessment

For quality assessment, the authors used The Newcastle Ottawa Scale for non-randomized controlled trials [Table 2] and the Cochrane risk of bias Assessment Tool Version 2 for randomised control trials [Figure 4]. Each study was reviewed by at least two reviewers; the studies were ranked as " low risk", " unclear", or "high risk" of bias with

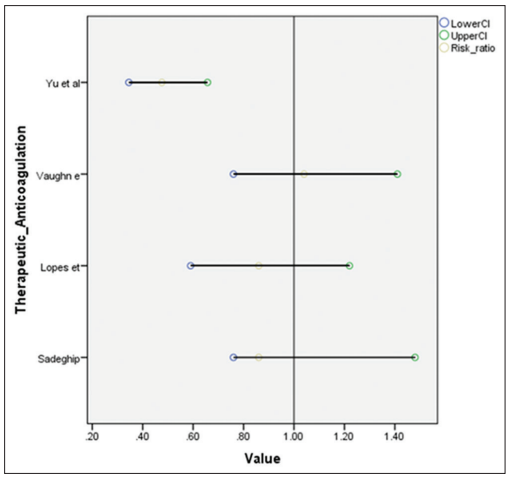

Figure 3: Odds ratio of the effect of therapeutic anti-coagulation versus prophylactic anti-coagulation as per the data of analysed studies

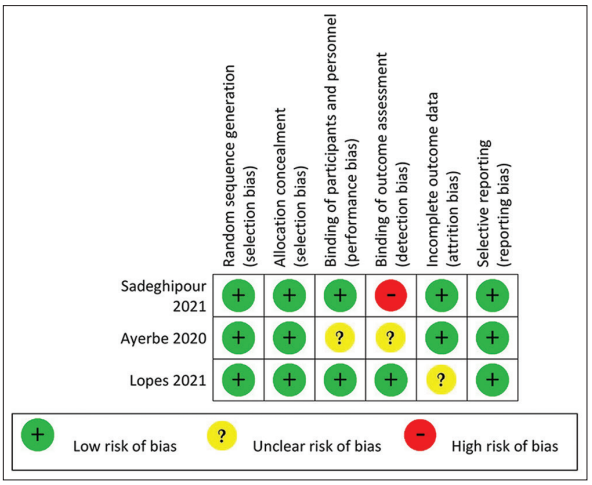

Figure 4: Cochrane risk of bias assessment for analyzed randomized control trial studies

Table 2: New Castle Ottawa scale for analyzed non-randomised controlled trial studies

Study ID	Selection			Comparability* (★★)	Outcome		Total (7 ★)
	Representativeness of exposed cohort (★)	Selection of non-exposed cohort (★)	Ascertainment of exposure (★)		Assessment of outcome (★)	Adequacy of follow up (★)	
Rentsch 2021[11]	-	★	★	★	★	★	★★★★★★ (6)
Paranjpe 2020[14]	★	★	-	★	★	★	★★★★★ (5)
Tremblay 2020[15]	★	★	★	★	★	-	★★★★★ (5)
Tang 2020[16]	-	★	★	★	★	★	★★★★★ (5)
Nadkarni 2020[17]	-	★	★	★★	★	-	★★★★★ (5)
Vaughn 2021[18]	★	★	★	★	★	★	★★★★★★ (6)
Bo Yu 2021[20]	★	★	★	★	★	-	★★★★★★ (6)

regard to selection bias, performance bias, detection bias, attrition bias, and reporting bias, and the overall outcome was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE). Disagreements aroused were resolved through a panel among the authors.

DISCUSSION

SARS-CoV-2 primarily affects the lungs, which cause a ground glass appearance on the high-resolution computed tomography (CT) scan of the thorax, but in the elderly or patients with co-morbidities, the incidence of systemic complications is high. The systemic complications are associated with dysregulated immune response causing the hyper-inflammatory response, endothelial dysfunction, and hyper-coagulability.[9,10,21] Various thromboembolic events such as pulmonary embolism, stroke, and myocardial infarction have been reported in COVID-19 patients. To prevent such manifestations arising from the hyper-coagulable state, ACs have been sought out. This article used a systematic review methodology to investigate the usage of ACs in the treatment of COVID-19 patients and to compare the prophylactic and therapeutic administration following the common notion of the inclusion in protocols.

Effect on in-hospital mortality

Ayerbe *et al.*,[13] Paranjpe *et al.*,[14] and Nadkarni *et al.*[15] conclusively conclude that the administration of ACs lowers in-hospital mortality except for Tremblay *et al.*,[15] who state that ACs have no beneficial effect as they studied only the early stages of the disease retrospectively, and they have also been recommended for more prospective studies in that direction.

Ayerbe *et al.*[13] states that 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 remained significant when saturation of

oxygen <90% and a temperature >37°C were added to the model with OR 0.54 (0.36–0.82), $P = 0.003$, and also when all the other drugs were included as covariates OR 0.42 (0.26–0.66), $P < 0.001$. Paranjpe *et al.*[14] state that a longer duration of AC treatment was associated with a reduced risk of mortality (aHR of 0.86 per day; 95% CI: 0.82 to 0.89; $P < 0.001$). Nadkarni *et al.*[17] state that on comparison 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 (aHR: 0.53; 95% CI: 0.45 to 0.62 and aHR: 0.50; 95% CI: 0.45 to 0.57, respectively). Finally, Tremblay *et al.* concluded that the HR for all-cause mortality in the AC versus no-AC/anti-platelet groups is 1.208 (95% CI, 0.750–1.946) and that heparin was not found to be beneficial in reducing the in-hospital mortality.[15]

Prophylactic versus therapeutic usage

Nadkarni *et al.*,[17] Lopes *et al.*,[19] and Yu *et al.*[20] conclusively narrow down that the administration of prophylactic anti-coagulation being beneficial than therapeutic anti-coagulation is statistically insignificant. The in-hospital mortality, risk of mechanical ventilation, and incidence of thromboembolism in prophylactic anti-coagulation versus therapeutic anti-coagulation had no statistical difference in their results. Yu *et al.*[20] added that the intubated patients under therapeutic anti-coagulation had an improved survival rate, but it cannot be attributed as there were too many independent factors deciding the mortality of the patients.

Nadkarni *et al.*[17] found that both therapeutic AC (aHR: 0.53; 95% CI: 0.45 to 0.62; $P < 0.001$) and prophylactic AC (aHR: 0.50; 95% CI: 0.45 to 0.57; $P < 0.001$) were associated with a reduction in the hazard of in-hospital mortality when compared with no AC group. In the study by Lopes *et al.*,[19] the total percentages of wins in the therapeutic and prophylactic treatment groups had no differences in time to death, duration of hospitalisation, or duration of supplemental oxygen between the groups. According to Yu *et al.*,[20] no statistical difference between the two groups was found when assessing for rates of invasive mechanical ventilation (73.7% versus 65.6%, $P = 0.133$) and mortality (60.2% versus 60.9%, $P = 0.885$). Patients receiving therapeutic AC had a longer median stay in the hospital (9 days vs. 7 days, $P < 0.001$) and an increased risk of major bleeding in therapeutic AC (13.8% vs. 3.9%, $P < 0.001$). However, among patients requiring invasive mechanical ventilation, those receiving empiric therapeutic AC showed lower mortality when compared to those receiving prophylactic AC only (75.5% vs. 83.7%, $P < 0.001$). After adjusting for baseline characteristics on admission for intubated patients, therapeutic AC remained an independent predictor of improved survival (aHR: 0.476, 95% CI: 0.345–0.657, $P < 0.001$). However, empiric therapeutic AC had no significant correlation to mortality ($P = 0.063$) when evaluating the entire cohort. Besides, advanced age, critical COVID-19 infection, and sepsis on admission appeared to be independent predictors of all-cause mortality regardless of invasive mechanical ventilation. Also, there was no significant difference in the median survival between the two AC cohorts ($P = 0.056$).[20]

Requirement of mechanical ventilation

The study by Tremblay *et al.*[15] indicates the use of ACs more than no administration of ACs to have a lesser need for mechanical intubation in COVID-19 patients, but Nadkarni *et al.*[17] have shown that their retrospective study had no statistically significant difference in risk of intubation, which is in concordance with the results of Yu *et al.*[20]

Tremblay *et al.*[15] concluded that the HR for mechanical ventilation in the AC versus no-AC/anti-platelet groups was 0.905 (95% CI, 0.571 to 1.435). The results of Nadkarni *et al.*[17] point out that 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 intubation (aHR: 0.69; 95% CI: 0.51 to 0.94 and aHR: 0.72; 95% CI: 0.58 to 0.89, respectively). According to Yu *et al.*,[20] After PSM stratification, no statistical difference between the two groups of prophylactic and therapeutic anti-coagulation was found when assessing for rates of invasive mechanical ventilation (73.7% versus 65.6%, $P = 0.133$)

Therapeutic effect on severity of infection

Through Tang *et al.*[16] and Nadkarni *et al.*,[17] we conclude initiation of ACs regardless of them having therapeutic or prophylactic benefits only to patients in severe hyper-coagulable states assessed by the SIC Score.

Tang *et al.*[16] state that ACs were found to be beneficial only when the SIC score is more than 4. If the SIC score is less than 4, ACs were not associated with a reduction in mortality. It is also noted that in patients with higher D-dimer levels, AC therapy was found to show greater benefits. Nadkarni *et al.*[17] add that when initiated ≤48 h from admission, there was no statistically significant difference between therapeutic (n = 766) and prophylactic ACs (n = 1,860) (aHR: 0.86; 95% CI: 0.73 to 1.02; $P = 0.08$).

Drug dosage

It is noted that only Lopes *et al.*[19] and Rentsch *et al.*[11] had studied the different available drugs where therapeutic anti-coagulation 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 to 0·7 IU/mL anti-Xa concentration) for clinically unstable patients, followed by rivaroxaban to day 30, and prophylactic anti-coagulation was standard in-hospital enoxaparin or unfractionated heparin in the study by Lopes *et al.*,[19] whereas Rentsch *et al.*[11] had studied warfarin, IV heparin,

low-molecular weight heparin such as enoxaparin, fondaparinux, dalteparin, and direct oral ACs such as apixaban, rivaroxaban, and dabigatran. INSPIRATION Investigators *et al.*[12] had concluded that there was no significant difference in the administration of standard versus intermediate doses of ACs.

The studies were conducted in different regions with heterogeneous populations, and the majority of participants were elderly as a result of their vulnerability to SARS-CoV-2. There were only three studies, namely, Sadeghipour *et al.*,[12] Ayerbe *et al.*,[13] and Lopes *et al.*,[19] that were conducted on homogeneous populations and with very limited participants; also, they described the randomisation and concealment methods. This may lead to the polarisation of results, thus jeopardising the generalisability of findings to all ages and populations. Application of our inclusion and exclusion criteria to the search results identified ten papers for this review, a surprisingly small number given the widespread inclusion of ACs in various protocols around the world. Despite this, maneuvering the search strategy and fortification of the search results with hand searching and searching of reference lists of included papers allow confidence in the conclusion that all relevant research was included in this meta-analysis and that conclusions arising from this review can be based on the synthesis of all available evidence.

Table 3: Risk analysis of thromboembolic episodes in COVID-19 patients

Study Name	Risk of VTE	Risk of PE	Risk of DVT
Gratz *et al.*, 2021[23]	18% CI: 13-24%	8% CI: 4-11%	14% CI: 9-20%
Tan *et al.*, 2021[24]	14.7% CI: 12.1 to 17.6%	7.8% CI: 6.2 to 9.4%	11.2% CI: 8.4 to 14.3%
Hasan *et al.*, 2020[25]	31% CI: 20-43%	-	-
Minno *et al.*, 2020[26]	31.3% CI: 24.3 to 39.2%	18.9% CI: 14.4 to 24.3%	19.8% CI: 10.5 to 34%
Porfidia *et al.*, 2020[27]	26% CI: 6-66%	12% CI: 2-46%	14% CI: 1-75%
Mohamed *et al.*, 2021[28]	31% CI: 24-39%	14% CI: 9-20%	23% CI: 14-32%
Wu *et al.*, 2021[29]	28.4% CI: 20.0 to 36.8%	16.4% CI: 10.1 to 22.7%	25.6% CI: 17.8 to 33.4%
Pooled Risk	25.77% CI: 17.05 to 37.94%	11.01% CI: 6.52 to 19.05%	15.37% CI: 8.67 to 29.81%

CI - Confidence Interval. VTE - Venous Thromboembolism. PE - Pulmonary Embolism. DVT- Deep Venous Thrombosis

Adverse events

Many studies on anti-coagulation therapy on COVID-19 patients have observed both major and minor bleeding tendencies as the most common side effects. Thrombocytopenia has also been encountered to a mild to moderate degree. The major bleeding can be life-threatening like retroperitoneal hemorrhage, intra-cranial hemorrhage, and gastro-intestinal hemorrhage. The bleeding manifestations because of AC therapy warrant emergency care, or it may put the patient's life at risk.[22] ACs are a double-edged sword while treating COVID-19. The risks and benefits must be well analysed before administering the anti-coagulation therapy in COVID-19 patients.

Risk benefit analysis of anti-coagulation therapy on varying dosages

The risk of venous thromboembolism, pulmonary embolism, and deep vein thrombosis is increased in COVID-19 patients because of hyper-inflammatory response and endothelial dysfunction. Pooled data of the meta-analysis revealed that the rate of VTE, PE, and DVT is 25.77%, 11.01%, and 15.37%, respectively [Table 3]. The high risk of thromboembolism warrants the use of ACs in COVID-19 patients. Many researchers assessed the effectiveness between therapeutic and prophylactic dosages of ACs. The effectiveness was assessed by many determinants such as mortality reduction, in-hospital mortality, 60-day mortality, duration of hospital stay, and risk of intubation or mechanical ventilation. The experimental group who are subjected to AC therapy with either a therapeutic dosage or prophylactic dosage show mortality reduction compared to the control group, who do not take ACs. Various researchers such as INSPIRATION Investigators *et al.*,[12] Nadkarni *et al.*,[17] Vaughn *et al.*,[18] Lopes *et al.*,[19] Yu *et al.*,[20] and

Table 4: Risk and benefit analysis of therapeutic vs prophylactic anti-coagulation

Study Name	Therapeutic anti-coagulation		Prophylactic anti-coagulation		Odds Ratio with 95% Confidence Interval
	Risk of Bleeding	Benefits	Risk of Bleeding	Benefits	
INSPIRATION Investigators *et al.*, 2021[12]	2.5%	45.7%	1.4%	44.1%	*1.06 (0.76 to 1.48) RR=1.83 (0.00 to 5.93)
Nadkarni *et al.*, 2021[17]	1.7%	54.1%	3.0%	75.1%	*0.86 (0.73 to 1.02) RR=3 (2 to 4.4)
Vaughn *et al.*, 2021[18]	-	60.3%	-	79.1%	*1.31 (0.99 to 1.73)
Lopes *et al.*, 2021[19]	8%	34.8%	2%	41.3%	*0.86 (0.59 to 1.22) RR=3.64 (1.61 to 8.27)
Yu *et al.*,2021[20]	13.8%	39.8%	3.9%	39.1%	*0.476 (0.345 to 0.657) RR=1.482 (1.110 to 1.980)
Ortega-Paz *et al.*, 2021[30]	2.4%	17.8%	1.4%	18.6%	*0.96 (0.78 to 1.18) RR=1.73 (1.15 to 2.60)
Pooled ratio	4.73%	42.08%	1.95%	49.55	*0.754 (0.699 to 1.214) RR=2.34 (1.37 to 4.98)

*Odds Ratio of mortality reduction (benefit) comparing therapeutic anti-coagulation to prophylactic anti-coagulation. RR - Risk ratio of bleeding tendencies encountered when using therapeutic anti-coagulation to prophylactic anti-coagulation

Ortega-Paz *et al*.[30] compared the benefits between the groups with therapeutic anti-coagulation and prophylactic anti-coagulation; they also observed the risk of adverse events in both the groups. Pooled data of our meta-analysis showed that the risk of bleeding in therapeutic AC and prophylactic AC was 4.73% and 1.95%, respectively, and the benefit of mortality reduction was about 42.08% and 49.55% in therapeutic AC- and prophylactic AC-taking groups, respectively [Table 4]. The pooled odds ratio of mortality reduction between the therapeutic AC group and prophylactic AC group was not statistically significant [OR = 0.754 (0.699 to 1.214)]. There was not much mortality benefit or in-hospital stay duration between either of the groups. However, the risk of bleeding is much higher in patients who received therapeutic anti-coagulation [RR = 2.34 (1.37 to 4.98)]. Therefore, in assessing the risks and benefits of therapeutic AC and prophylactic AC usage in COVID-19 patients, it is better to use prophylactic anti-coagulation therapy in COVID-19 patients despite the patients being critically ill.

Limitations

There are two limitations in this review that could be addressed in future research. First, there were only three randomised control studies. Secondly, they did not address proper drug dosages with regard to their risk of major bleeding events. The risk of such events has hindered the therapy for susceptible individuals and possibly would have led to a compromised result. If possible, future research can formulate a scoring system for safe administration with minimal risks for SARS-CoV-2-infected patients. Such research must be powered adequately and consider creating a comprehensive study design to ensure robust and conclusive results.

CONCLUSION

AC was associated with lower mortality and intubation among hospitalised COVID-19 patients. Compared with therapeutic AC, prophylactic AC was associated with lower mortality, although not statistically significant, and lower bleeding risks. Autopsies revealed frequent thromboembolic disease. These data may inform trials to determine optimal AC regimens.

While choosing ACs for protocols, we suggest that policymakers should consider the cost efficiency, quality-adjusted life expectancy, and patient acceptance when advising for a more general population.

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Abbreviations: ACs - anti-coagulants; aHR- adjusted hazard ratio; CI - confidence interval.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Srikumar S, Perumal S. A systematic review of immune pathogenesis of SARS-COV-2 infection. Int J Adv Med 2021;8:978-83.
2. Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: A review. Clin Immunol 2020;215:108427.
3. Cascella M, Rajnik M, Aleem A, Dulebohn SC, Di Napoli R. Features, Evaluation and Treatment Coronavirus (COVID-19). In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2022.
4. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by novel coronavirus from Wuhan: An analysis based on decade-long structural studies of SARS. J Virol 2020;94:e00127-20. doi: 10.1128/JVI.00127-20.
5. Polidoro RB, Hagan RS, de Santis Santiago R, Schmidt NW. Overview: Systemic inflammatory response derived from lung injury caused by SARS CoV 2 infection explains severe outcomes in COVID 19. Front Immunol 2020;11:1626.
6. Teuwen LA, Geldhof V, Pasut A, Carmeliet P. COVID 19: The vasculature unleashed. Nat Rev Immunol 2020;20:389-91.
7. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, *et al*. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506.
8. Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, *et al*. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. Clin Infect Dis 2020;71:762-8.
9. Ackermann M, Verleden SE, Kuehnel M. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in COVID-19. N Engl J Med 2020;383:120–8.
10. Klok FA, Kruip M, van der Meer NJ, Arbous MS, Gommers D, Kant KM, *et al*. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res 2020;191:145–7.
11. Rentsch CT, Beckman JA, Tomlinson L, Gellad WF, Alcorn C, Kidwai-Khan F, *et al*. Early initiation of prophylactic anticoagulation for prevention of coronavirus disease 2019 mortality in patients admitted to hospital in the United States: Cohort study. BMJ 2021;372:n311. doi: 10.1136/bmj.n311.
12. INSPIRATION Investigators, Sadeghipour P, Talasaz AH, Rashidi F, Sharif-Kashani B, Beigmohammadi MT, *et al*. Effect of intermediate-dose vs standard-dose prophylactic anticoagulation on thrombotic events, extracorporeal membrane oxygenation treatment, or mortality among patients with COVID-19 admitted to the intensive care unit: The INSPIRATION randomized clinical trial. JAMA 2021;325:1620-30.
13. Ayerbe L, Risco C, Ayis S. The association between treatment with heparin and survival in patients with Covid-19. J Thromb Thrombolysis 2020;50:298-301.
14. Paranjpe I, Fuster V, Lala A, Russak AJ, Glicksberg BS, Levin MA, *et al*. Association of treatment dose anticoagulation with in-hospital survival among hospitalized patients with COVID-19. J Am Coll Cardiol 2020;76:122-4.
15. Tremblay D, van Gerwen M, Alsen M, Thibaud S, Kessler A, Venugopal S, *et al*. Impact of anticoagulation prior to COVID-19 infection: A propensity score-matched cohort study. Blood 2020;136:144-7.
16. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost 2020;18:1094-9.
17. Nadkarni GN, Lala A, Bagiella E, Chang HL, Moreno PR, Pujadas E, *et al*. Anticoagulation, bleeding, mortality, and pathology in hospitalized patients with COVID-19. J Am Coll Cardiol 2020;76:1815-26.
18. Vaughn VM, Yost M, Abshire C, Flanders SA, Paje D, Grant P, *et al*. Trends in venous thromboembolism anticoagulation in patients hospitalized with COVID-19. JAMA Netw Open 2021;4:e2111788. doi: 10.1001/jamanetworkopen. 2021.11788.

19. Lopes RD, de Barros E Silva PG, Furtado RH, Macedo AV, Bronhara B, Damiani LP, *et al*. Therapeutic versus prophylactic anticoagulation for patients admitted to hospital with COVID-19 and elevated D-dimer concentration (ACTION): An open-label, multicentre, randomised, controlled trial. Lancet 2021;397:2253-63.
20. Yu B, Gutierrez VP, Carlos A, Hoge G, Pillai A, Kelly JD, *et al*. Empiric use of anticoagulation in hospitalized patients with COVID-19: A propensity score-matched study of risks and benefits. Biomark Res 2021;9:29.
21. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost 2020;4:844-7.
22. Ohn MH, Ng JR, Ohn KM, Luen NP. Double-edged sword effect of anticoagulant in COVID-19 infection. BMJ Case Rep 2021;14:e241955. doi: 10.1136/bcr-2021-241955.
23. Gratz J, Wiegele M, Maleczek M, Herkner H, Schöchl H, Chwala E, *et al*. Risk of clinically relevant venous thromboembolism in critically ill patients with COVID-19: A systematic review and meta-analysis. Front Med (Lausanne) 2021;8:647917.
24. Tan BK, Mainbourg S, Friggeri A, Bertoletti L, Douplat M, Dargaud Y, *et al*. Arterial and venous thromboembolism in COVID-19: A study-level meta-analysis. Thorax 2021;76:970-9.
25. Hasan SS, Radford S, Kow CS, Zaidi ST. Venous thromboembolism in critically ill COVID-19 patients receiving prophylactic or therapeutic anticoagulation: A systematic review and meta-analysis. J Thromb Thrombolysis 2020;50:814-21.
26. Di Minno A, Ambrosino P, Calcaterra I, Di Minno MN. COVID-19 and venous thromboembolism: A meta-analysis of literature studies. Semin Thromb Hemost 2020;46:763-71.
27. Porfidia A, Valeriani E, Pola R, Porreca E, Rutjes AW, Di Nisio M. Venous thromboembolism in patients with COVID-19: Systematic review and meta-analysis. Thromb Res 2020;196:67-74.
28. Mohamed MF, Al-Shokri SD, Shunnar KM, Mohamed SF, Najim MS, Ibrahim SI, *et al*. Prevalence of venous thromboembolism in critically ill COVID-19 patients: Systematic review and meta-analysis. Front Cardiovasc Med 2021;7:598846.
29. Wu C, Liu Y, Cai X, Zhang W, Li Y, Fu C. Prevalence of venous thromboembolism in critically ill patients with coronavirus disease 2019: A meta-analysis. Front Med (Lausanne) 2021;8:603558.
30. Ortega-Paz L, Galli M, Capodanno D, Franchi F, Rollini F, Bikdeli B, *et al*. Safety and efficacy of different prophylactic anticoagulation dosing regimens in critically and non-critically ill patients with COVID-19: A systematic review and meta-analysis of randomized controlled trials. Eur Heart J Cardiovasc Pharmacother [Internet]. 2021; Available from: http://dx.doi.org/10.1093/ehjcvp/pvab070.