EVIDENCE SUMMARY

Should anticoagulation be used in treating patients diagnosed with COVID-19?

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RECOMMENDATIONS

We recommend the use of prophylactic over therapeutic dose anticoagulation among hospitalized patients with moderate, severe or critical COVID-19 disease unless there are any contraindications. *(Low certainty of evidence; Strong recommendation)*

We recommend the use of standard dose prophylactic anticoagulation over intermediate dose prophylactic anticoagulation among hospitalized patients with COVID-19 disease unless there are any contraindications. *(Moderate certainty of evidence; Strong recommendation)*

Consensus Issues

A strong recommendation in favor of prophylactic dose anticoagulation was unanimously given despite the low certainty of evidence to give emphasis on preventing harm, as the risk of bleeding was significantly higher with therapeutic dose anticoagulation. It was further emphasized that the duration of anticoagulation, which was not directly addressed in the studies included in this review, should be individualized based on the patient's thromboembolic and bleeding risks.

PREVIOUS RECOMMENDATION

We suggest the use of prophylactic anticoagulation in patients admitted with COVID-19 infection, unless with contraindications. *(Very low quality of evidence; Conditional recommendation)*

We suggest the use of prophylactic dose anticoagulation over therapeutic anticoagulation in critically ill patients with COVID-19 infection. *(Low quality of evidence; Conditional recommendation)*

Previous Consensus Issues
The common dosing for prophylactic anticoagulation are: (1) enoxaparin – 40 mg; (2) heparin – 5000 units based on the studies that specified the dose. The frequency depends on the creatinine clearance of the patients. Relative contraindications to be considered prior to giving anticoagulation include active and clinically significant bleeding, severe bleeding diathesis, severe thrombocytopenia, major trauma, previous intracranial hemorrhage, recent invasive procedure and major trauma. The recommendations for critically ill patients may change once the results of big trials come out.

What's new in this version?

- A total of eight RCTs, seven of which are new, were reviewed to update the current recommendation on anticoagulation in COVID-19. The previous recommendation evaluated evidence from eight observational studies and one RCT.
- Similar recommendations are placed forward but are now based on moderate certainty of evidence. Subgroup analysis of moderate and critically ill patients was also done.

Key Findings

Eight randomized controlled trials (RCTs) were included in this review to compare therapeutic versus prophylactic anticoagulation and to compare intermediate dose versus standard dose prophylactic anticoagulation in COVID-19 patients. Quality of evidence ranged from very low to moderate due to issues regarding risk of bias, and imprecision due to underpowered population, and wide confidence intervals.

Comparing therapeutic and prophylactic anticoagulation (AC), there was no significant difference over-all in terms of mortality and organ support-free days among critically ill and stable patients. There was a significantly lower over-all incidence of venous thromboembolism (VTE) for therapeutic anticoagulation but there was significantly higher risk for major and minor bleeding for therapeutic anticoagulation considering all population. However, no significant difference was seen in the incidence of VTE among critically ill patients. There was no significant difference in major bleeding among subgroups of critically ill and stable patients but the trend pointed to a higher incidence among those undergoing therapeutic anticoagulation. For minor bleeding, there was a significantly higher observed incidence among critically ill patients.

For the comparison of intermediate versus standard prophylactic anticoagulation dose among severely ill patients, there was no statistically significant difference in terms of mortality and

incidence of venous thromboembolism. There was also no significant difference in terms of major and minor bleeding, but the trend showed higher incidence for intermediate prophylactic dose anticoagulation.

Introduction

Microthrombi formation is a possible key mediator of organ dysfunction among COVID-19 patients. A relatively high prevalence rate of venous thromboembolic events (VTE) at 31%, including pulmonary embolism (PE), deep vein thrombosis (DVT), cerebrovascular accident (CVA) and myocardial infarction (MI), has been reported in a meta-analysis among ICU-admitted patients diagnosed with COVID-19.[1] Anticoagulants are the first line of therapy [2] in cases among the general population hence its possible role in decreasing COVID-19 morbidity and mortality is being investigated.

Review Methods

For this update, peer-reviewed and non-peer reviewed databases such as MEDLINE, Cochrane Library, MedRxIV, and BioRxIV databases were searched until September 10, 2021 with an updated search of ongoing RCTs done on October 10, 2021. Population included were confirmed COVID-19 patients, receiving any anticoagulation agent being used for treating VTE. Keywords used were 1) COVID-19 or SARS-CoV-2 [MeSH], and 2) anticoagulation [MeSH]. Studies with a non-randomized controlled design were excluded as well as studies using investigational or off-label anticoagulating agents. Two comparisons were made in this review: (1) prophylactic versus therapeutic dose anticoagulation and (2) intermediate versus standard dose prophylactic anticoagulation.

Results

Summary of Characteristics of included studies

A total of eight (8) RCTs were included in this review, of which one was previously included in the initial recommendation. Observational studies were excluded in this update to generate better quality evidence provided by the RCTs. Of the eight included, six studies [3-8] compared therapeutic versus prophylactic anticoagulation doses while two RCTs [9,10] investigated intermediate dose prophylactic anticoagulation versus standard dose prophylactic anticoagulation. All studies included were open-label trials, however objective findings were used as primary outcomes; specifically, mortality, incidence of venous thromboembolism (VTE) and major and minor bleeding events.

A. Therapeutic versus prophylactic anticoagulation (6 RCTs)

Six RCTs investigated therapeutic versus prophylactic anticoagulation (n=4730). Two RCTs made this comparison among unstable patients [6,7] described as those admitted at the ICU, or who required oxygen support via high flow nasal cannula or mechanical ventilation, those on pressors, inotropes, or extracorporeal membrane oxygenation, and those unable to take oral medications. Meanwhile, two other RCTs made use of hospitalized patients with stable COVID-19 disease (moderate COVID-19 patients or those not requiring ICU-level care and not on high flow oxygen support).[4,5] The last two RCTs [3,8] investigated a mixed group population and outcomes were reported for the population as a whole and not based on disease severity, though one of these did a subgroup analysis of ICU-admitted and non-ICU patients only for the safety outcome of major bleeding and not for the efficacy outcomes.[8]

The studies made use of different anticoagulation agents mostly low molecular weight heparin (LMWH) (e.g. enoxaparin [3-8], tinzaparin [4-6], dalteparin [4-6,8]) with unfractionationated heparin (UFH) as an alternative for patients with low creatinine clearance (CrCl).[3-8] One study made use of oral rivaroxaban, a factor Xa inhibitor, as an alternative to enoxaparin in the therapeutic dose intervention group.[3] Given this, analysis to identify the best anticoagulation agent could not be done.

Five studies were open-label trials by design but outcome measures were objective findings (such as mortality and deep vein thrombosis). One study was able to blind the participants and outcome assessors; however, those that were directly involved in the care of the patients were not blinded. Therapeutic anticoagulants were given for 14 days in three RCTs [4,6,7], 28 [5] and 30 [3] days in two, and until hospital discharge or if with any indication to change in the other.[8] Meanwhile, prophylactic anticoagulation treatment was dependent on the treating physician for five RCTs [3-6, 8] and until discharge or day 28, whichever was shorter, for the other RCT.[7]

Major concerns for these studies included two RCTs which had populations not reaching their target sample size [5,7], hence had underpowered results as listed in the limitations of their work, while one did not employ intention to treat analysis, making their data also not consistent (i.e. different number of participants in different outcomes).[4] In addition, one study enrolled those with clinically proven high risk for thromboembolism, which may enhance the result of the intervention.[8] Since patients were already at high risk for thromboembolism, majority of the participants were already on anticoagulating agents (LMWH and UFH) even prior to randomization (82.8% for therapeutic dose, 78.2% for prophylactic dose). No statistical adjustment was performed and no mention of the baseline dosage was made.

Efficacy outcomes
Pooled results for three efficacy outcomes were obtained from the studies: mortality, incidence of VTE, and organ support-free days.

Mortality was not significantly different between the therapeutic and prophylactic groups (RR 0.90, 95% CI 0.66-1.24, very low quality). This association was maintained in the subgroups of stable (RR 0.50, 95% CI 0.13-1.88, very low quality) and unstable patients (RR 0.84, 95% CI 0.37-1.87, moderate quality). There was noted significant heterogeneity over-all and even after subgroup analysis this heterogeneity was maintained. Possible source of heterogeneity is the treatment regimen and crossover of treatment which also contributed to the risk of bias. Downgrading of quality of evidence was based on the concerns for bias as stated above, inconsistent results and wide range effect estimate (see Appendix 4).

Incidence of VTE on the other hand was noted to be significantly less in the therapeutic group (RR 0.56, 95% CI 0.41-0.77, low quality). This observation was maintained for the subgroup of stable patients (RR 0.51, 95% CI 0.29-0.90, moderate quality) but among critically ill patients, there was no significant difference between the therapeutic and prophylactic groups (RR 0.96, 95% CI 0.44-2.13, moderate quality). Although a significant difference was noted in the pooled results, the individual results of the five RCTs showed no significant difference between the therapeutic and prophylactic group. Only the study that recruited those with high risk for thromboembolic events showed a significant benefit for the therapeutic dose group.

Organ support-free days did not differ significantly between the two groups as a whole (OR 1.11, 95% CI 0.79-1.56, low quality) based on three RCTs but subgroup analysis showed that stable patients receiving therapeutic anticoagulation had significantly longer organ support-free days as compared to those receiving prophylactic anticoagulation (OR 1.29, 95% CI 1.07-1.56, low

quality). This trend was not observed among critically ill patients (OR 0.83, 95% CI 0.67-1.03, high quality) based on one RCT. High heterogeneity was observed in the overall pooled result but this was not seen in the subgroup effect estimate.

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Safety outcomes

Collectively, major bleeding was significantly higher among the therapeutic dose anticoagulation group compared to the prophylactic dose anticoagulation group (RR 1.82, 95% CI 1.18-2.82, low quality); however, subgroup analyses of the stable and unstable patients both showed no significant difference in incidence of major bleeding. It was noted though that the trend showed more events for the therapeutic group both in the stable (RR1.43, 95% CI 0.61-3.32, low quality) and unstable patients (RR 1.85, 95% CI 0.79-4.31, moderate quality). Minor bleeding events, defined as bleeding events warranting attention of a physician but not satisfying the criteria for major bleeding (BARC and ISTH criteria), was also noted to be significantly higher in the therapeutic group among the unstable patients (RR 2.74, 95% CI 1.03-7.26, moderate quality) and mixed population (RR 3.77, 95% CI 1.76-8.09, moderate quality). No data was available for stable patients.

B. Intermediate dose prophylactic anticoagulation versus standard dose prophylactic anticoagulation (2 RCTs)

Both RCTs compared the effect of intermediate (1mg/kg/day) and standard (40mg daily) prophylactic anticoagulation doses among patients with severe COVID-19 admitted at the ICU.[9,10] Both used enoxaparin, a LMWH as the primary agent of choice with dose adjustment as needed based on BMI (see Appendix 3). UFH was used in cases of severe renal injury. One study had concerns in the design since some participants (n= 37) were also allowed to participate in other COVID-19 trials [9], while the other study had low risk of bias.[10] Intervention was continued until hospital discharge or a clinically significant event warranted dose adjustment of the drug in one study, while it was continued until 30 days of follow-up in the other RCT regardless of the discharge status of the patient.

Efficacy outcomes

Pooled results from the two RCTs (n= 646) show no significant difference in terms of all-cause mortality (RR 1.0, 95% CI 0.78-1.28) and incidence of VTE (RR 1.03, 95% CI 0.52-2.02) between intermediate and standard dose anticoagulation.[9,10] Results are based on low quality of evidence due to some issues for risk of bias (participation in other clinical trials, significant difference in coadministration of azithromycin between treatment groups in one study) and wide confidence interval among all outcomes.

Safety outcomes

In terms of safety, there was no significant difference for major (RR 1.54, 95% CI 0.55-4.31) and minor (RR 1.62, 95% CI 0.67-3.91) bleeding events but there was a trend towards higher incidence among those receiving the intermediate anticoagulation dose (low quality of evidence). The INSPIRATION trial also reported similar ventilator-free days (p=0.50), ICU-length of stay (p=0.14), and number of patients discharged from ICU (OR 1.01, 95% CI 0.72-14.2) between the intermediate and standard dose group.

Evidence to Decision

Different societies have advocated the use of prophylactic anticoagulation for those with increased risk of VTE from COVID-19 (see below). This recommendation also came from results of studies which were presented in this review. There is no study available directly discussing the cost of anticoagulation therapy in COVID-19 however one study has demonstrated that in non-COVID-related critically-ill patients anticoagulation-associated major bleeding led to higher in-hospital mortality (adjusted OR 1.49, 95% CI 1.16-1.9), prolonged hospital stay (median of 11 days vs 6 days, p=0.02), and had higher expenses among those that survived. [11] This supports using the lowest acceptable dose that minimizes the risk of bleeding.

Recommendations from Other Groups

Listed below are recommendations for the use anticoagulation in COVID-19 from different notable societies/institutions.

Association/Institution (date last updated)	Recommendation
Australian Living CPG [12] (9/6/21)	Hospitalized patients with COVID-19 - VTE prophylaxis recommended (conditional recommendation) for moderate, severe and critical disease including pregnant and post-partum patients unless there is absolute contraindication (e.g. major risk for bleeding) - No additional indication for therapeutic anticoagulation dose based on current data and therefore should not be routinely offered - For pregnant and postpartum patients with moderate disease, should be continued for at least 14 days post discharge or until COVID-19 related morbidity has resolved. If with severe or critical disease, continued for at least 4 weeks post discharge or until morbidity has resolved
American Society of Hematology [13] (7/15/2021)	All hospitalized patients with COVID-19 - Prophylactic anticoagulation recommended unless risk of bleeding outweighs risk - LMWH recommended over UFH; if with contraindications to heparins, fondaparinux is recommended - Standard dose prophylaxis suggested over intermediate or therapeutic dose - Giving of anticoagulation after discharge suggested not to be given in the absence of any indication
National Institute of Health (NIH) [14] (2/11/2021)	Non-hospitalized patients with COVID-19 - Anticoagulation should not be initiated unless there are other indications or patient is participating in a clinical trial Hospitalized patients with COVID-19 - All non-pregnant adults recommended to receive prophylactic anticoagulation. There is insufficient evidence to support the use of higher than standard dose of AC outside of clinical trials - Pregnant patients with severe COVID-19 also recommended to receive prophylactic anticoagulation unless there is a contraindication - VTE prophylaxis after discharge is not recommended

World Health Organization (WHO) [15] (1/25/21)	Hospitalized patients with COVID-19 (conditional recommendation) - Standard dose prophylactic anticoagulation rather than higher prophylactic dose or therapeutic dose unless there is a warranted indication

Research Gaps

There is a uniform consensus among different organizations about the recommendation of using prophylactic dose anticoagulation among hospitalized COVID-19 patients. Current evidence however has yet to address which anticoagulating agent can best prevent VTEs while minimizing the risk of bleeding. There are currently 19 listed active ongoing studies, some of which are investigating not only LMWH but also other anticoagulating agents, among which are oral anticoagulants that are seen to cost less than injectable agents (Appendix 6). Another recommendation from some societies that still need further evidence is the duration of anticoagulation treatment after discharge from the hospital. Data on the incidence of DVTs post-recovery among previously hospitalized COVID-19 patients is still coming into light as part of the post-COVID symptoms .

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Appendix 1. Evidence to Decision

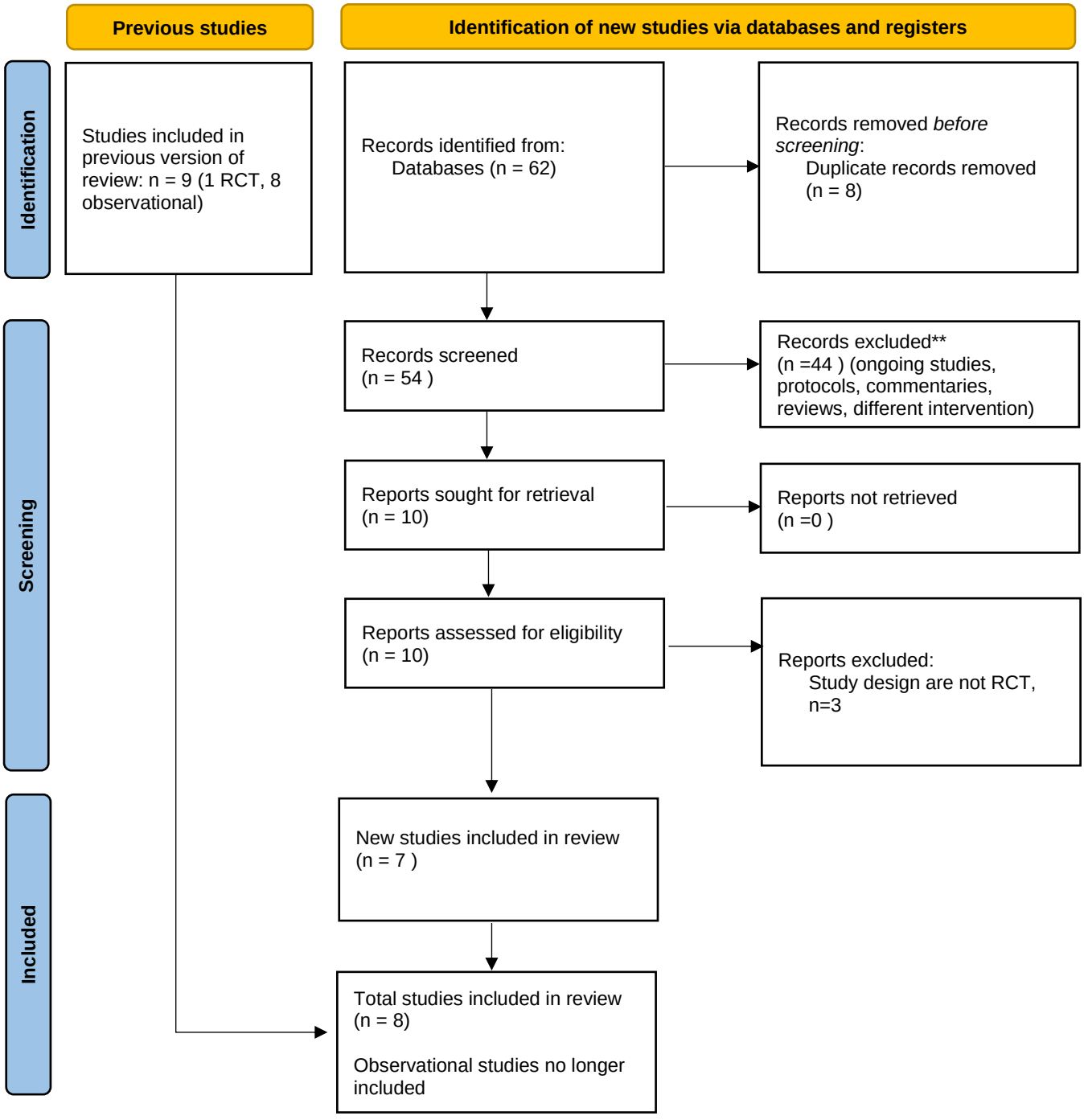
Table 1. Summary of initial judgements prior to the panel discussion: anticoagulation (N=10)

FACTORS	JUDGEMENT					RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (10)				• Relatively high prevalence rate of venous thromboembolic events (VTE) at 31% including pulmonary embolism (PE), deep vein thrombosis (DVT), cerebrovascular accident (CVA) and myocardial infarction (MI) has been reported in a meta-analysis among ICU-admitted patients diagnosed with COVID-19
Benefits	Large (2)	Moderate (5)	Small (3)	Uncertain		• <u>Therapeutic vs prophylactic AC:</u> No difference for mortality over-all and in subgroups analyze Favors therapeutic dose in terms of decreasing incidence of VTE overall and in stable and mixed population. No difference in unstable subgroup No difference over-all and in unstable group for organ support free days, with more organ0support free days in stable group • <u>Intermediate dose vs standard dose AC:</u> No benefit over the other for mortality and VTE

Harm	Large (3)	Small (7)	Uncertain	No response			• <u>Therapeutic vs prophylactic AC:</u> Major bleeding increased in therapeutic group overall, not significant but trend towards more incidence in the same group (stable and critical) Minor bleeding more in therapeutic • <u>Intermediate dose vs standard dose AC:</u> No benefit over the other for major and minor bleeding
Certainty of Evidence	High	Moderate (7)	Low (3)	Very low			• Very low to moderate
Balance of effects	Favors drug (6)	Does not favor drug (4)	Uncertain				• There is increased risk of possible harm (major and minor bleeding) for therapeutic anticoagulation dosing, and less incidence of VTE for the critically ill receiving this regimen, prophylactic anticoagulation dose is recommended. • Standard dose is shown to provide similar safety and harm outcomes as the intermediate dose.
Values	Important uncertainty or variability (2)	Possibly important uncertainty or variability (3)	Possibly NO important uncertainty or variability (4)	No important uncertainty or variability (1)			
Resources Required	Uncertain (7)	Large cost (1)	Moderate Cost (2)	Negligible cost	Moderate savings	Large savings	

Certainty of evidence of required resources	No included studies (9)	Very low	Low	Moderate	High		
Cost effectiveness	No included studies (8)	Favors the comparison (1)	Does not favor either the intervention or the comparison	Favors the intervention (1)			
Equity	Uncertain (7)	Reduced (1)	Probably no impact (1)	Increased (1)			
Acceptability	Uncertain (4)	No	Yes (6)				
Feasibility	Uncertain (3)	No	Yes (7)				

Appendix 2. Search Yield and Results



Appendix 3. Study Characteristics of Included Studies (n)

Study ID	Study Design	Setting	Total population	Population	Intervention	Comparator	Outcomes
Perepu	multi-center, open-label RCT	three centers in the US	176	hospitalized adults with documented SEVERE COVID-19 (admitted to ICU and/or have laboratory evidence of coagulopathy) *exclusion: with indication for full dose AC, major bleeding, severe thrombocytopenia, current pregnancy, hx of acute venous/arterial thromobisis past 3 months, acute or chronic renal insufficiency (CrCl < 30)	intermediate dose enoxaparin 1mg/kg SC daily, fpr BMI < 30 0.5mg/kg SC twice dail for BMI > 30	standard prophylactic dose enoxaparin 40mg SC daily for BMI < 30 30 or 40mg SC BID for BMI > 30	all cause mortality at 30 days arterial/venous thromboembolism major bleeding minor bleeding
Sadeghipour (INSPIRATION)	open label RCT	10 academic centers in Iran	562	adult COVID-19 patients admitted to the ICU *exclusion: life expectancy < 24hrs, established indication for	intermediate dose enoxaparin <u>if CrCl >30</u> 1mg/kg SC daily if wt <120kg or BMI<35	standard prophylactic AC <u>if CrCl >30</u> 40mg SC daily if wt <120kg or BMI<35	COMPOSITE of mortality within 30 days, venous/arterial thrombosis and treatment with ECMO major bleeding severe thrombocytopenia

				therapeutic AC, weigh less than 40kg, pregnancy, history of heparin induced thrombocytopenia, platelet less than 50, and overt bleeding	0.6mg/kg SC twice daily if wt?120kg or BMI .35 If CrCl 15-30 Enoxaparin 0.5mg/kg SC daily (at least 40mg) If CrCl<15 UFH 10,000U SC twice daily n= 276	40mg SC twice daily if wt?120kg or BMI .35 If CrCl 15-30 Enoxaparin 30mg SC daily If CrCl<15 UFH 5,000 U SC twice daily	
Lopes (ACTION)	multi-center, open-label RCT	31 hospitals in Brazil	615	hospitalised symptomatic COVID-19 patients (>18 years old) with elevated D-dimer concentration up to 14 days before randomisation *exclusion: indication for therapeutic AC, contraindications to rivaroxaban or heparin and high risk for bleeding	therapeutic AC oral rivaroxaban 15-20mg daily for stable patients OR initial SC enoxaparin (1mg/kg BID)/ IV unfractionated heparin (to achieve 0.3-0.7 IU/mL anti-Xa concentration) for clinically unstable patients followed by oral rivaroxaban to day 30 n=311	prophylactic AC standard in-hospital enoxaparin, UFH, or fondaparinux for CrCl>30 if BMI < 40: enoxaparin 40mg SC daily, fondaparinux 2.5mg SC daily, UFH 5000U SC q8-12hrs if BMI >40 enoxaparin 60mg SC daily or 40mg SC BID, fondaparinux not recommended,	hierarchical composite of the ff: time to death duration of hospitalisation duration of supplemental O2 to day 30 major bleeding clinically significant non-major bleeding through D30

						UFH7500 U SC q8-12h if CrCl< 30 if BMI < 40: UFH 5000 SC U q8-12 If BMI >40 UFH 7500 U SC every8-12hours *may receive therapeutic dose if with clinical indication at the discretion of treating physician n=304	
Goligher (REMAP-CAP, ACTIV-4a, ATTACC)	open label, adaptive, multiplatform RCT	121 sites in 9 countries	1098	critically-ill patients with severe COVID-19 *exclusion- if admitted in ICU for 48hours or longer prior to randomisation OR admiited in hospital for 72 hours or longer, imminent risk of death, no commitment to organ support, high risk for bleeding, reeceiving dual antiplatelet	therapeutic AC Enoxaparin 1mg/kg SC daily (CrCl >/30), 0.6mg/kg SC BID (w>120kg or BMI >35), 0.5mg/kg SC daily (CrCl 15-130), UFH 10000 units SC BID (CrCl </15) n= 534	prophylactic AC Enoxaparin 40mg SC daily (CrCl >/30), 40mg SC BID (weight >120, BMI > 35), 30mg SC daily (CrCl 15-30), UFH 5000 units SC twice daily (CrCl </15ml/min) n=564	organ support-free days up to 21 days (combined in-hospital death and number of days free of cardiovascular/respiratory organ support)

				therapy, has a non-covid indication for AC, or history of heparin sensitivity			
Lawler (REMAP-CAP, ACTIV-4a, ATTACC)	open label, adaptive, multiplatform RCT	121 sites in 9 countries	2219	hospitalized COVID-19 patients not receiving critical care management (as above) *exclusion- if >72 hrs since admission or inhospital confirmation of COVID-19 to randomisation, or >14 days since admission, discharge expected within 72 hrs, clinical indication for therepeutic AC, high risk of bleeding, or history of heparin sensitivity	therapeutic AC LMWH or UFH based on weight and CrCl dose dependent on local hospital policy or guidelines to treat VTE n=1171	prophylactic AC (either standard dose or intermediate dose prophylaxis) LMWH or UFH based on standard thrombopohylaxis dose n=1048	organ support-free days up to 21 days (combined in-hospital death and number of days free of cardiovascular/respiratory organ support)
Sholzberg (RAPID)	multi-center, open-label RCT	28 sites in 6 countries	465	moderately ill hositalised ward COVID-19 patients with elevated D-dimer within first five days of admission	therapeutic AC CrCl >30 if BMI < 40 enoxaparin1mg/kg SC q12 or 1.5mg/kg SC q24, dalteparin 200u/kg sc q 24	Prophylactic AC CrCl >30 if BMI < 40 enoxaparin 40mg SC q24, dalteparin 5000 U q 24, Tinzaparin	composite of death, invasive and non-invasive mechanical ventilation, ICU admission major bleeding

				*exclusion- major bleeding risk, absolute indication for AC, any contraindication for use of heparin, pregnant, meet or imminent risk to develop component of primary outcome soon	or 100u/kg q12, Tinzaparin 175U/kg q24 UFH titrate to institution specific anti-Xa or aPTT values If BMI >40 Enoxaparin 1mg/kg q12, dalteparin 100u/kg q12, tinzaparin 175u/kg q24, UFH as above If CrCl< 30 Whether BMI >40 or < 40 UFH IV bolus to titrate to institution specific anti-Xa or aPTT values or LMWH as per institution-based BMI n= 228	4500U q24, Fondaparinux 2.5mg q24, UFH 5000u q8-12 If BMI >40 enoxaparin 40mg SC q12, dalteparin 5000 U q 12, Tinzaparin 9000 U q24, Fondaparinux not recommended UFH 7500u q8 If CrCl< 30 BMI <40 UFH 5000 U Q8-q12 or LMWH as per institution-based BMI BMI > 40 UFH 7500 U q8 or LMWH as per institution-based BMI n= 237	
Lemos (HESACOVID)	open-label phase 2 RCT	single center in Brazil	20	COVID-19 patients with ARDS (by Berlin definition) requiring mechanical ventilation	therapeutic AC SC enoxaparin adjusted for age and CrCl *if CrCl worsened during study,	prophylactic (according to doctor's judgment) UFH 5,000 IU TID (weight	gas exchange over time (paO2/FiO2) at baseline, d7 and d14 time until weaning off MV, ventilator-free days

				*exclusion- older than 85y/o, CrCl <10, advanced end organ diseases (liver, circulatory, renal), COPD requiring o2 at home, significant disability from stroke and other neurocognitive problems, pregnant, significant risk of bleeding, participating in other RCTs, with indication for therapeutic AC other than COVID	transitioned to UFH 24h after last dose of enoxaparin n=10	<120kg), 7500 IU TID (>120kg) OR enoxaparin 40mg OD (w<120kg), 40mg BID (w>120kg) n=10	
Spyropoulos (HEP-COVID)	Multi-center RCT	12 academic centers in US	253	Hospitalized non-pregnant adult COVID-19 patients with elevated D-dimer (>4x ULN) or sepsis induced coagulopathy score of 4 or greater AND requiring oxygen support *exclusion criteria: Indication for full dose AC or dual antiplatelet	Therapeutic AC SC enoxaparin 1 mg/kg BID or 0.5mg/kg SC BID (if CrCl 15-29) n= 129	Prophylactic AC (based on local standard) Standard dose Or intermediate dose Included UFH 22,500 BID-TID, enoxaparin 30-40mg SC OD-BID, or dalteparin 2500-5000 IU SC OD n=124	Venous or arterial thromboembolism, death, major bleeding

				therapy, bleeding within the past month, active GI or intracranial cancer, bronchiectasis or pulmonary cavitation, hepatic dysfunction with elevated baseline INR, CrCl < 15, platelet < 25000,history of heparin-induced thrombocytopenia , and hypersensitivity to study drugs			

Study ID	Directness	Validity	Results	Main Issues	Risk of Bias
Perepu	Yes	Open label design, outcome assessors NOT blinded, more patients received azithromycin in treatment arm (possible confounding)	Intention to treat analysis and sensitivity analysis done	Enrolment in other clinical trials allowed	high
Sadeghipour (INSPIRATION)	Yes	Open label design, outcome assessors blinded	Intention to treat analysis and sensitivity analysis done	None	low
Lopes (ACTION)	Yes	Open label design, outcome assessors blinded	Intention to treat analysis and sensitivity analysis done	Used different types of anticoagulants in treatment arm (not just LMLWH)	moderate
Goligher (REMAP-CAP, ACTIV-4a, ATTACC)	Yes	Open label design, outcome assessors blinded	Intention to treat analysis and sensitivity analysis done	None	low

Lawler (REMAP-CAP, ACTIV-4a, ATTACC)	Yes	Open label design, outcome assessors not specified if blinded	Intention to treat analysis NOT done; sensitivity analysis done	Inconsistent counts in some outcomes (used different number of population)	high
Sholzberg (RAPID)	Yes	Open label design, outcome assessors blinded	Intention to treat analysis and sensitivity analysis done, did not reach sample size	Underpowered number of participants	moderate
Lemos (HESACOVID)	Yes	Open label design, outcome assessors blinded	Intention to treat analysis and sensitivity analysis done, small sample size, small outcome events	wide confidence intervals due to small event outcome and sample size	Moderate
Spyropoulos (HEP-COVID)	Yes	Participants and outcome assessors blinded, those with direct care not blinded. Population chosen were those that had high risk for VTE and thus would likely benefit for anticoagulation use	Intention to treat analysis done, for safety outcome data was presented among ICU-admitted and non-ICU admitted patient while for efficacy outcomes this was not done	Recruited population are those that would benefit use of AC, allowed recruitment of those using AC or antiplatelet prior to randomization (for both groups), not all outcomes had the same subgroup (no explanation why only done on safety outcome and not on efficacy outcome), For both groups anytime CrCl went down to < 15, AC is shifted to therapeutic dose UFH then shifted back to original assignment once CrCl increases to more than 15 however no analysis and mention of data regarding this	high

Appendix 4. Grade Evidence Profile

Therapeutic dose AC compared to prophylactic dose AC for hospitalised COVID-19 patients?

Bibliography:

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With prophylactic dose AC	With therapeutic dose AC	Relative effect (95% CI)	Risk with prophylactic dose AC	Risk difference with therapeutic dose AC
Mortality- all population											
4730 (6 RCTs)	very serious[a,b]	serious[c]	not serious	serious[d]	none	⨁◯◯◯ Very low	363/2347 (15.5%)	351/2383 (14.7%)	**RR 0.90** (0.66 to 1.24)	155 per 1,000	**15 fewer per 1,000** (from 53 fewer to 37 more)
Venous Thromboembolism											
4730 (6 RCTs)	very serious[a,b,e]	not serious	not serious	not serious	none	⨁⨁◯◯ Low	98/2347 (4.2%)	55/2383 (2.3%)	**RR 0.56** (0.41 to 0.77)	42 per 1,000	**18 fewer per 1,000** (from 25 fewer to 10 fewer)
Organ support free days											
0 (3 RCTs)	very serious[a,b]	serious[c]	not serious	serious[f]	none	⨁◯◯◯ Very low			**OR 1.11** (0.79 to 1.56)	0 per 1,000	**1 fewer per 1,000** (from 2 fewer to 1 fewer)

Major bleeding

4730 (6 RCTs)	very serious[a,b]	not serious	not serious	not serious	none	⨁⨁◯◯ Low	32/2347 (1.4%)	60/2383 (2.5%)	**RR 1.82** (1.18 to 2.82)	14 per 1,000	**11 more per 1,000** (from 2 more to 25 more)

Minor bleeding

1793 (3 RCTs)	serious[a]	not serious	not serious	not serious	none	⨁⨁⨁◯ Moderate	8/938 (0.9%)	30/855 (3.5%)	**RR 3.77** (1.76 to 8.09)	9 per 1,000	**24 more per 1,000** (from 6 more to 60 more)

CI: confidence interval; **OR:** odds ratio; **RR:** risk ratio

Explanations

a. different severity of disease

b. differences in giving of intervention, such as shifting of kind of AC used, dose of AC used, etc

c. concern over I2, wide range of effect estimate in included studies

d. wide confidence interval

e. two study recruited patients with high risk for VTE

f. different result in studies, CI without overlap

Therapeutic dose AC compared to prophylactic dose AC for COVID-19 patients with critical illness?

Bibliography:

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With prophylactic dose AC	With therapeutic dose AC		Risk with prophylactic dose AC	Risk difference with therapeutic dose AC
Mortality											
1118 (2 RCTs)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ Moderate	205/574 (35.7%)	201/544 (36.9%)	**RR 0.84** (0.37 to 1.87)	357 per 1,000	**57 fewer per 1,000** (from 225 fewer to 311 more)
VTE											
1118 (2 RCTs)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ Moderate	12/574 (2.1%)	11/544 (2.0%)	**RR 0.96** (0.43 to 2.13)	21 per 1,000	**1 fewer per 1,000** (from 12 fewer to 24 more)

Major bleeding

1201 (3 RCTs)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ Moderate	13/612 (2.1%)	24/589 (4.1%)	**RR 1.85** (0.79 to 4.31)	21 per 1,000	**18 more per 1,000** (from 4 fewer to 70 more)

Minor bleeding

1118 (2 RCTs)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ Moderate	5/574 (0.9%)	14/544 (2.6%)	**RR 2.74** (1.03 to 7.26)	9 per 1,000	**15 more per 1,000** (from 0 fewer to 55 more)

CI: confidence interval; **RR:** risk ratio

Explanations

a. wide confidence interval; one study has low population and event outcome

Therapeutic dose AC compared to prophylactic dose AC for COVID-19 patient with non-critical disease?

Bibliography:

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With prophylactic dose AC	With therapeutic dose AC	Relative effect (95% CI)	Risk with prophylactic dose AC	Risk difference with therapeutic dose AC
Mortality											
2684 (2 RCTs)	serious [a,b]	serious [c]	not serious	serious [d]	none	⨁◯◯◯ Very low	104/1285 (8.1%)	90/1399 (6.4%)	**RR 0.50** (0.13 to 1.88)	81 per 1,000	**40 fewer per 1,000** (from 70 fewer to 71 more)
VTE											
2684 (2 RCTs)	serious [a,b]	not serious	not serious	not serious	none	⨁⨁⨁◯ Moderate	33/1285 (2.6%)	18/1399 (1.3%)	**RR 0.51** (0.29 to 0.90)	26 per 1,000	**13 fewer per 1,000** (from 18 fewer to 3 fewer)
Major bleeding											
2854 (3 RCTs)	serious [a,b]	not serious	not serious	serious [d]	none	⨁⨁◯◯ Low	15/1371 (1.1%)	26/ 1483 (1.8%)	**RR 1.43** (0.61 to 3.32)	11 per 1,000	**5 more per 1,000** (from 4 fewer to 25 more)

CI: confidence interval; **RR:** risk ratio

Explanations

a. one study with inconsistent event counts

b. one study is underpowered (did not reach adequate sample size)

c. concerns with I2, CI did not overlap

d. wide confidence interval

Intermediate dose prophylactic AC compared to standard dose AC for severe COVID-19 patients?

Bibliography:

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With standard dose AC	With intermediate dose prophylactic AC	Relative effect (95% CI)	Risk with standard dose AC	Risk difference with intermediate dose prophylactic AC
All-cause mortality at 30 days											
731 (2 RCTs)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ low	135/371 (36.4%)	132/360 (36.7%)	**RR 1.00** (0.78 to 1.28)	364 per 1,000	**0 fewer per 1,000** (from 80 fewer to 102 more)
Venous thromboembolism											
731 (2 RCTs)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ low	16/371 (4.3%)	16/360 (4.4%)	**RR 1.03** (0.52 to 2.02)	43 per 1,000	**1 more per 1,000** (from 21 fewer to 44 more)
Major Bleeding											
731 (2 RCTs)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ low	6/371 (1.6%)	9/360 (2.5%)	**RR 1.54** (0.55 to 4.31)	16 per 1,000	**9 more per 1,000** (from 7 fewer to 54 more)

Intermediate dose prophylactic AC compared to standard dose AC for severe COVID-19 patients?

Bibliography:

Certainty assessment							Summary of findings				
Minor bleeding											
731 (2 RCTs)	serious [a]	not serious	not serious	serious [b]	none	⨁◯◯ low	11/371 (3.0%)	18/360 (5.0%)	**RR 1.62** (0.67 to 3.91)	30 per 1,000	**18 more per 1,000** (from 10 fewer to 86 more)

CI: confidence interval; **RR:** risk ratio

Explanations

a. one study allowed the participation of patients who are enrolled in other clinical trials (n= 37);

b. wide confidence interval (>25% range on each side)

Appendix 5. Forest plots of comparisons of outcomes

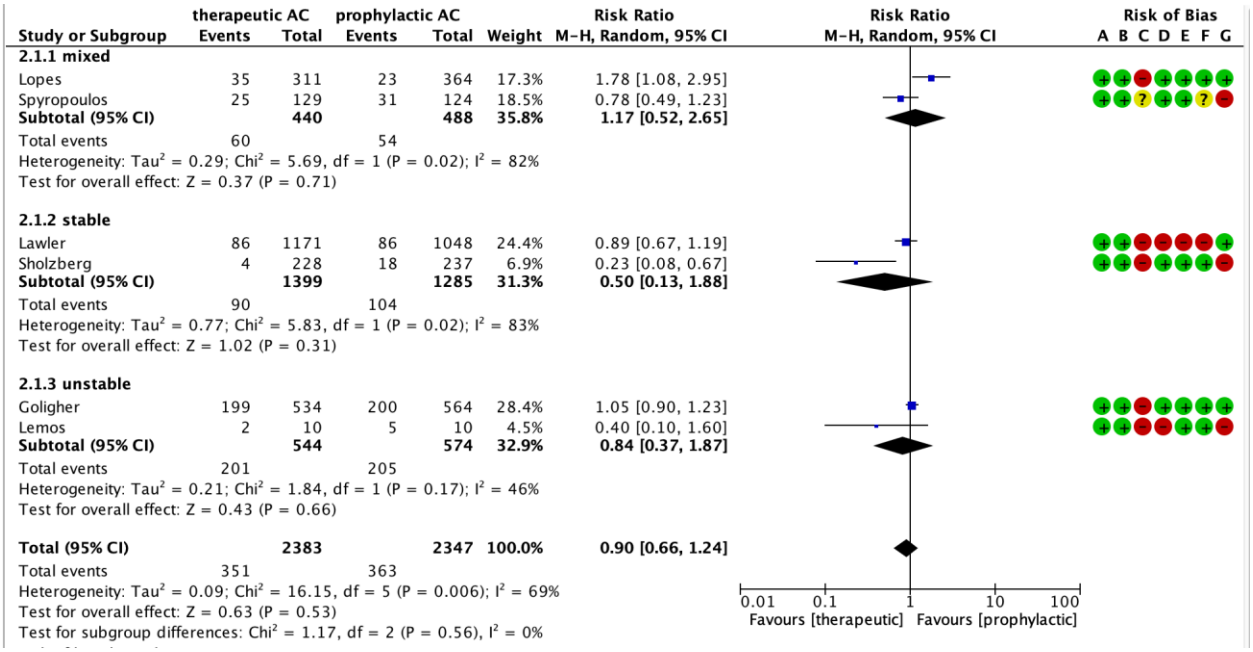


Figure 1. Risk of Mortality comparing therapeutic versus prophylactic AC

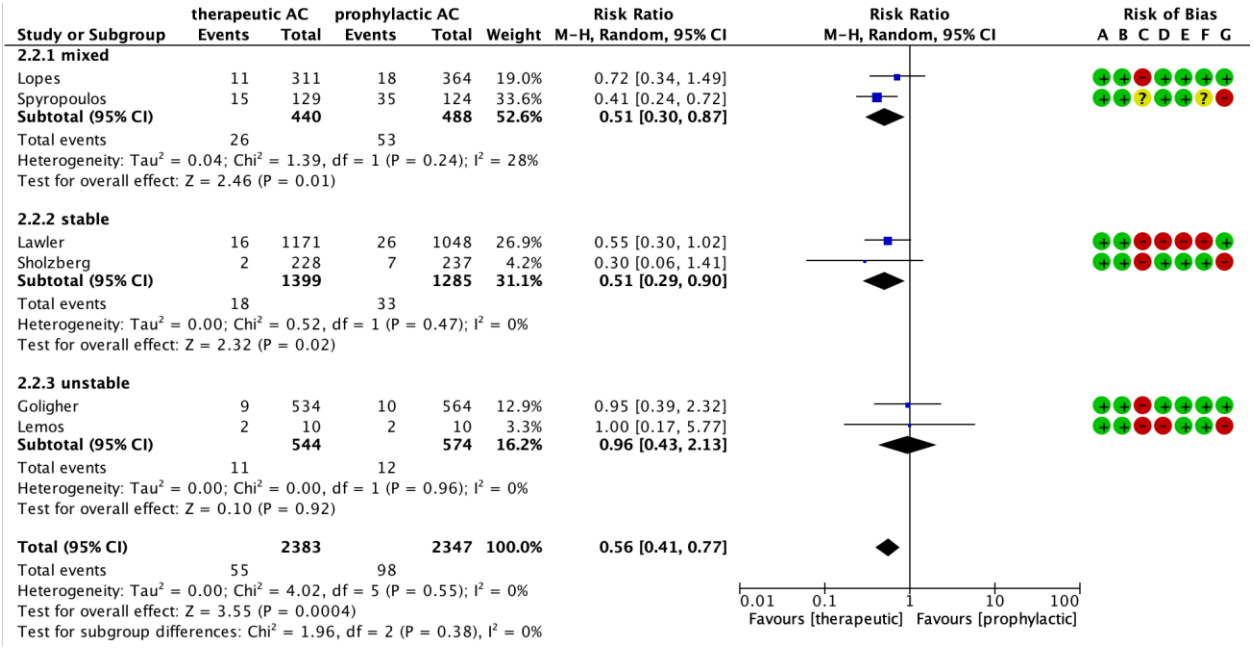


Figure 2. Comparing incidence of VTE in therapeutic versus prophylactic AC

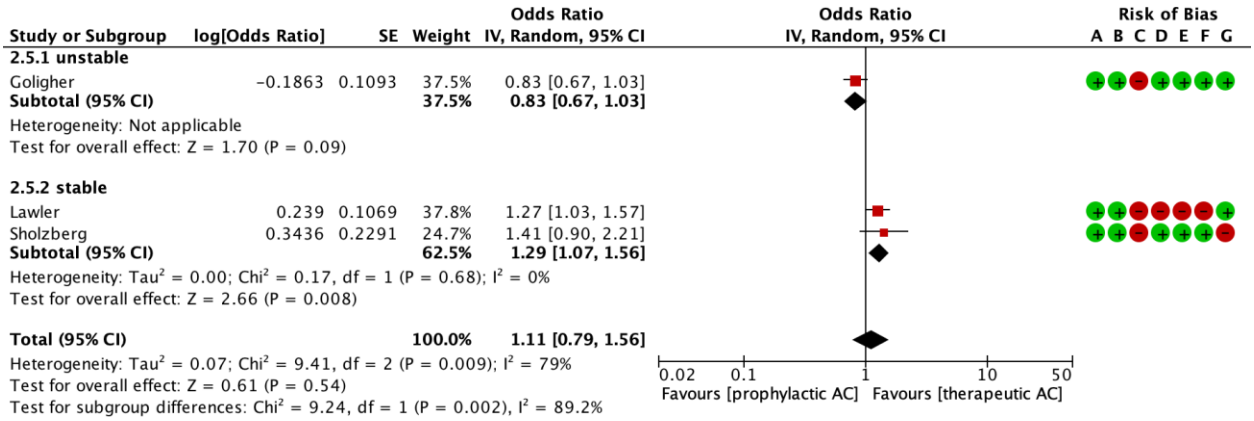


Figure 3. Comparing organ support-free days between therapeutic versus prophylactic AC

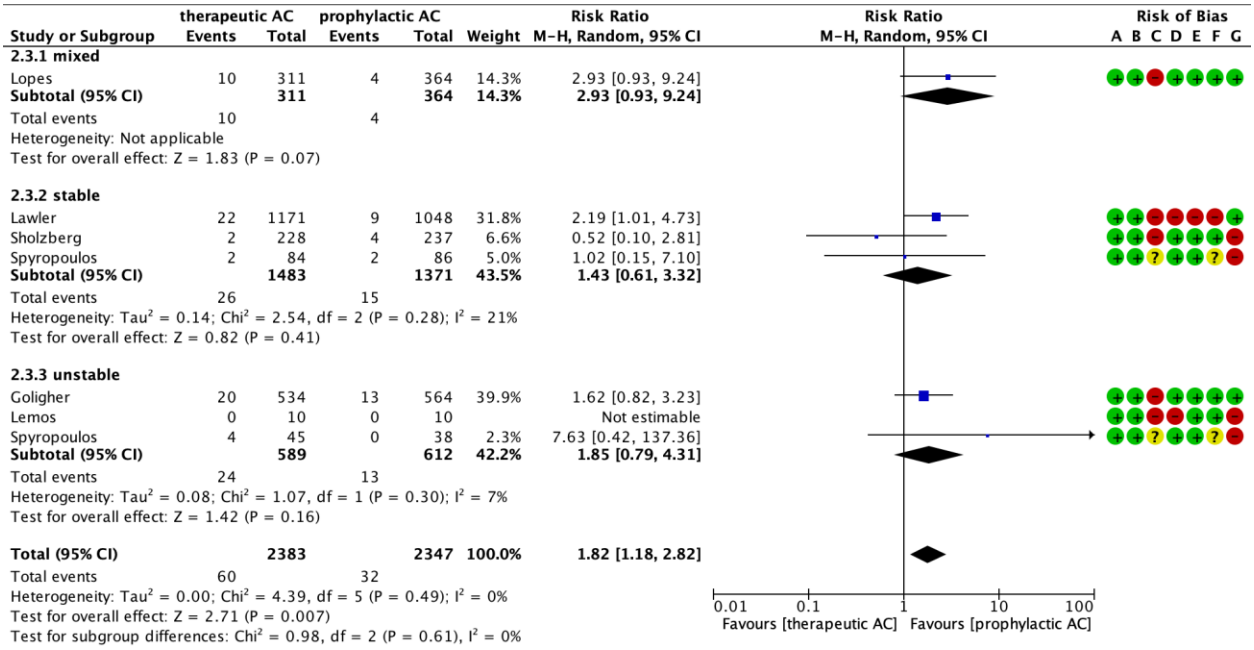


Figure 4. Comparing major bleeding risk between therapeutic versus prophylactic AC

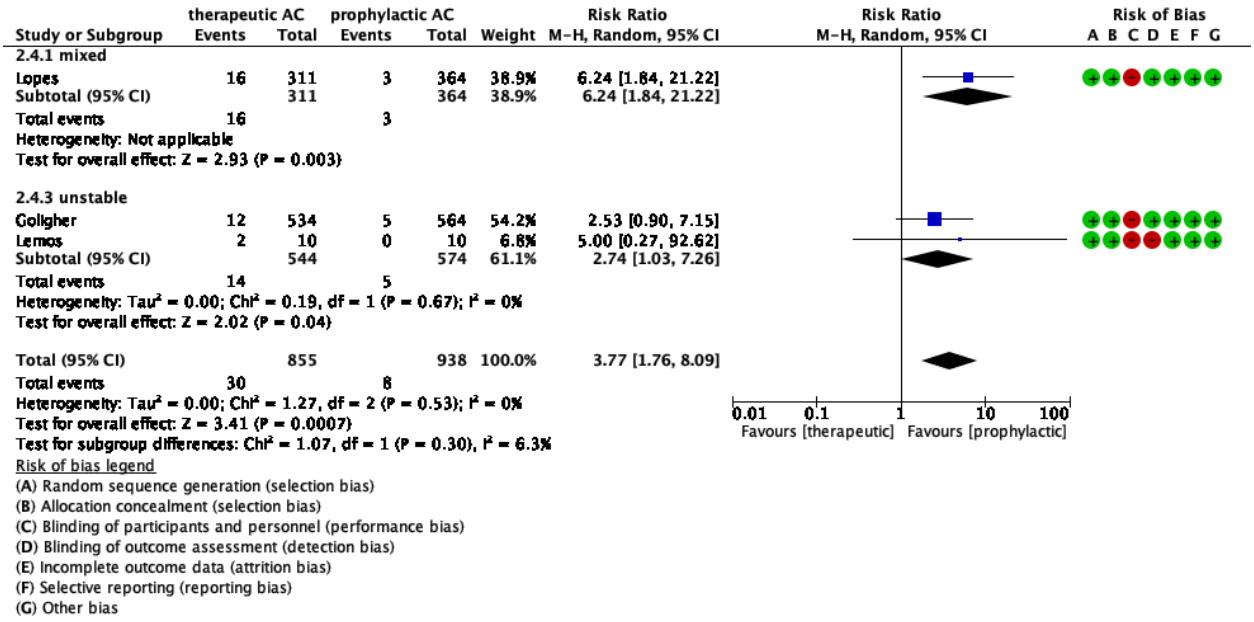


Figure 5. Comparing risk of minor bleeding between therapeutic versus prophylactic AC

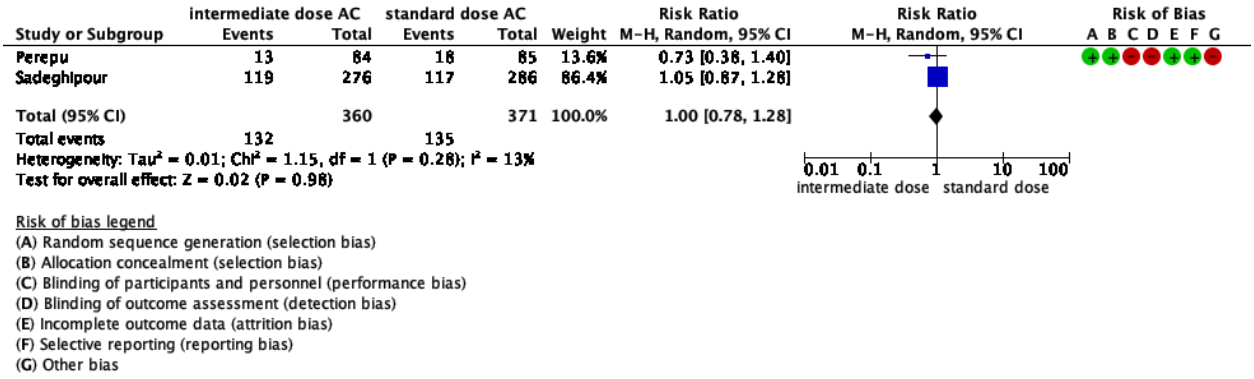


Figure 6. Comparison of risk of mortality between intermediate dose versus prophylactic dose AC

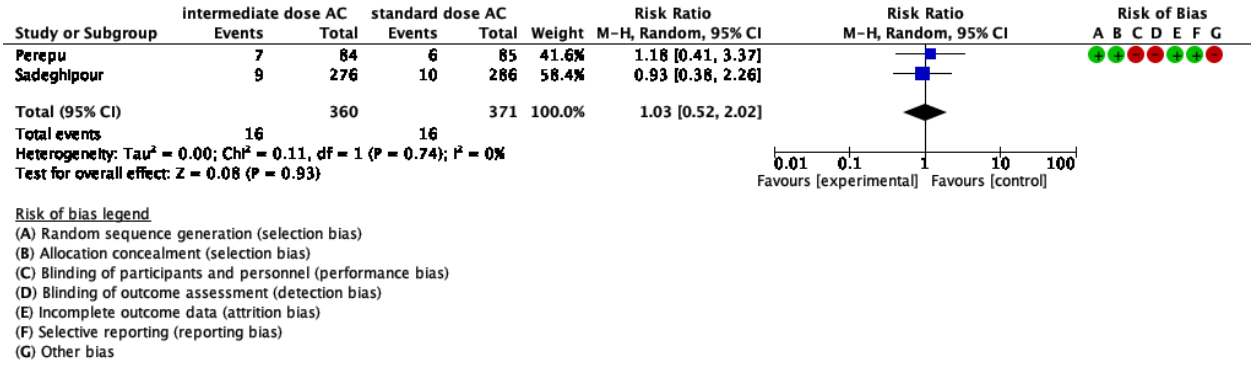


Figure 7. Comparison of incidence of VTE between intermediate dose versus prophylactic dose AC

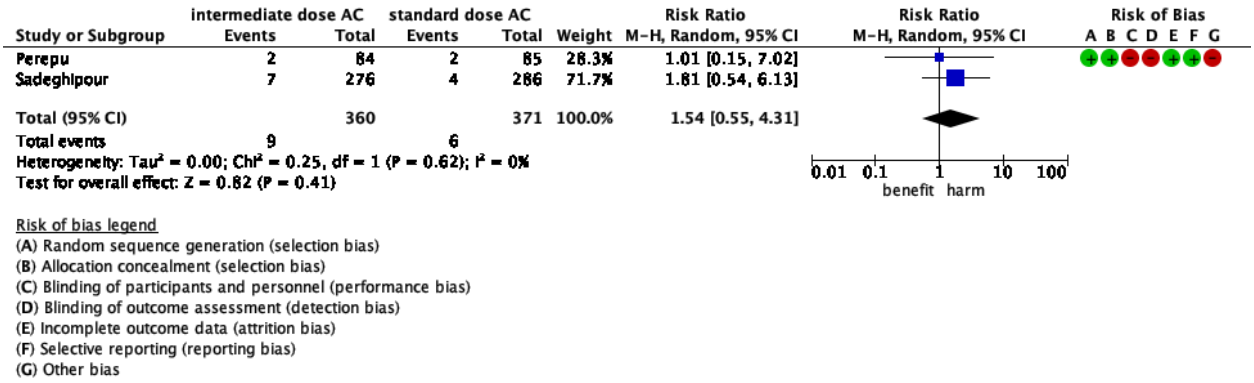


Figure 8. Comparison of risk of major bleeding between intermediate dose versus prophylactic dose AC

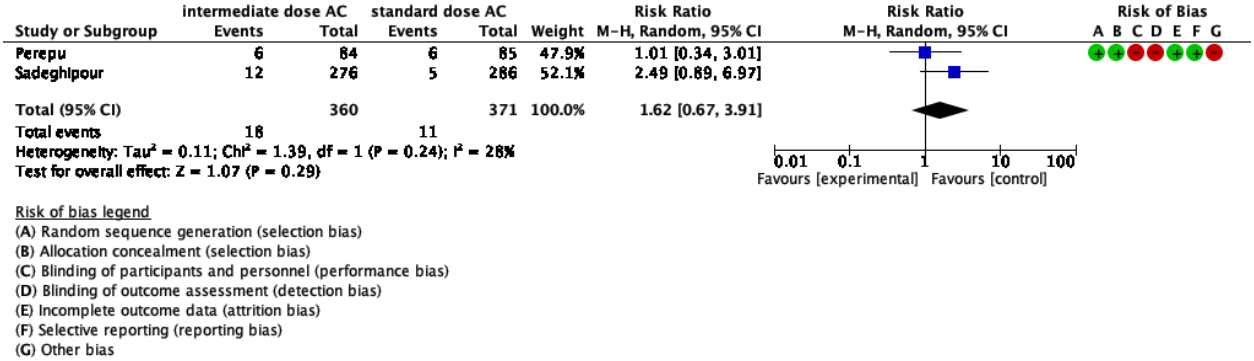


Figure 9. Comparison of risk of minor bleeding between intermediate dose versus prophylactic dose AC

Appendix 6. Study Characteristics of Ongoing Active trials (n=19)

Title Identifier Expected completion date	Intervention	Comparator	Patients/population recruited	Outcome
ANTIcoagulation in severe COOVID-19 patients (ANTICOVID) December 1,2021 https://ClinicalTrials.gov/show/NCT04808882	Drug: Tinzaparin,Therapeutic anticoagulation	DrugTinzaparin, Low dose prophylactic anticoagulation Drug: Tinzaparin, High dose prophylactic anticoagulation	18 Years and older with severe COVID-19 pneumonia	All-cause mortality|Number of days to clinical improvement|Score on WHO Ordinal Scale|Number of days alive and free from supplemental oxygen at Day-28|Proportion of patients needing intubation at Day-28|Number of days alive and free from invasive mechanical ventilation at Day-28|Number of days alive and free from vasopressors at Day-28|Length of intensive care unit stay|Length of hospital stay|Quality of life and disability at assessed using a quality of life questionnaire|All-cause deaths|Proportion of patients with at least one thrombotic event at Day-28|D-dimers|Proportion of patients with at least one major bleeding event (MBE) at Day-28|Proportion of patients with at least one life-threatening bleeding event at Day-28|Proportion of patients with any bleeding event at Day-28|Proportion of patients with Heparin Induced Thrombocytopenia (HIT) at Day-28|7-points ordinal scale|Sepsis-Induced Coagulopathy Score (SCS)
Anticoagulation in Patients Suffering From COVID-19 Disease (The ANTI-CO Trial) March 28, 2021 (no posted results) https://ClinicalTrials.gov/show/NCT04445935	Bivalirudin Injection	standard anticoagulation with LMWH/UFH	18years to 99 years old with COVID-19 ARDS	P/F ratio Kidney function
Anticoagulation in Critically Ill Patients With COVID-19 (The IMPACT Trial) December 2022 https://ClinicalTrials.gov/show/NCT04406389	Therapeutic dose Drug: Enoxaparin sodium| Drug: Unfractionated heparin| Drug: Fondaparinux|	Intermediate Dose Prophylaxis Drug: Enoxaparin sodium| Drug: Unfractionated heparin| Drug: Fondaparinux|	18 years old and older COVID-19 patients with critical illness	30-day mortality|Length of Intensive Care Unit (ICU) Stay in Days|Number of documented venous thromboembolism (VTE), arterial thrombosis (stroke, myocardial infarction, other) and microthrombosis events|Number of major and clinically relevant non-major bleeding events

	Drug: Argatroban			
Hamburg Edoxaban for Anticoagulation in COVID-19 Study (HERO-19) September 30, 2021 https://ClinicalTrials.gov/show/NCT04542408	Anticoagulation Agents (Edoxaban and/or high dose LMWH)	Drug: Low dose Low molecular weight heparin or Placebo	18 Years and older COVID-19 patients	Combined endpoint: all-cause mortality and/ or venous thromboembolism and/ or arterial thromboembolism|All-cause mortality|Mortality related to venous thromboembolism|Mortality related to arterial thromboembolism|Rate of venous and/ or arterial thromboembolism|Rate and length of mechanical ventilation|Length of initial stay at ICU after application of IMP|Rehospitalisation|Rate and length of renal replacement therapy|Cardiac arrest/ CPR
Effect of Anticoagulation Therapy on Clinical Outcomes in COVID-19 (COVID-PREVENT) January 31, 2022 https://ClinicalTrials.gov/show/NCT04416048	Drug: Rivaroxaban|	Standard Of Care (SOC)	18 Years and older COVID-19 patients	Composite endpoint of venous thromboembolism (DVT and/or fatal or non-fatal PE), arterial thromboembolism, new myocardial infarction, non-hemorrhagic stroke, all-cause mortality or progression to intubation and invasive ventilation|Development of disseminated intravascular coagulation (DIC) according to the ISTH criteria|Number of days requiring invasive ventilation|Number of days requiring non-invasive ventilation|Improvement on a seven-category ordinal scale recommended by the WHO as clinical improvement scale for patients with respiratory infections
Regional Anticoagulation Modalities in Continuous Venous Venous Hemodialysis in Patients With COVID-19 (CoV-Hep Study) August 2021 https://ClinicalTrials.gov/show/NCT04487990	Patients on continuous hemodialysis (blood flow 150 ml / min, dose of 30 ml / kg / h) receiving anticoagulation with sodium citrate at 4 mmol / l associated with unfractionated heparin at 10U / Kg / h.	Patients on continuous hemodialysis (blood flow 150 ml / min, dose of 30 ml / kg / h) receiving anticoagulation with sodium citrate at 4 mmol / l.	18 Years and older with acute kidney injury	Clotted dialyzers|Time-free of clotting|Number of dialyzers used|Pressure variation|Urea sieving|Downtime of dialysis
Safety and Efficacy of Therapeutic Anticoagulation on Clinical Outcomes	Enoxaparin (therapeutic dose)	Standard dose anticoagulation	18 Years and older with cardiovascular disease	Number of patients with the composite efficacy endpoint of death, cardiac arrest, symptomatic deep venous thrombosis, pulmonary embolism,

in Hospitalized Patients With COVID-19 January 1, 2022 https://ClinicalTrials.gov/show/NCT04377997				arterial thromboembolism, myocardial infarction, or hemodynamic shock.|Number of patients with a major bleeding event according to the International Society on Thrombosis and Haemostasis (ISTH) definition
Intermediate or Prophylactic-Dose Anticoagulation for Venous or Arterial Thromboembolism in Severe COVID-19 (IMPROVE) April 2021 (recruiting) https://ClinicalTrials.gov/show/NCT04367831	Drug: Heparin SC| Drug: Enoxaparin/Lovenox Intermediate Dose	Enoxaparin Prophylactic Dose| Drug: Heparin Infusion|	18 years to 80 years old COVID-19 patients with venous or arterial thrombosis	Total Number of Patients with Clinically Relevant Venous or Arterial Thrombotic Events in ICU|Total Number of Patients with In hospital Clinically Relevant Venous or Arterial Thrombotic Events|ICU Length of Stay|Total Number of Patients with the Need for Renal Replacement Therapy in the ICU|Total Number of Patients with Major bleeding in the ICU|Hospital
FREEDOM COVID-19 Anticoagulation Strategy (FREEDOM COVID) March 2022 https://ClinicalTrials.gov/show/NCT04512079	Drug: Enoxaparin (full dose) Drug: Apixaban	Drug: Enoxaparin (prophylactic dose)	18 years and older with COVID-19	Time to first event|Number of in-hospital rate of BARC 3 or 5|Number of participants with Myocardial infarction|Number of participants with Deep Vein Thrombosis|Number of participants requiring Ventilation|Number of All Death|Cause of Death|Number of participants with Stroke|Number of participants with Pulmonary Emboli|Number of participants with Systemic
Standard vs High Prophylactic Doses or Anticoagulation in Patients With High Risk of Thrombosis Admitted With COVID-19 Pneumonia (PROTHROMCOVID) July 31, 2021 https://ClinicalTrials.gov/show/NCT04730856	Drug: Tinzaparin (high dose)	Drug: Tinzaparin (standard dose)	18 years and older with COVID-19 related thrombosis	Reduction of suspicion of systemic thrombotic symptomatic events|Use of Mechanical ventilation|Progression on the WHO Progression Scale during follow-up.|Overall survival at 30 days.|Length of hospital stay (days)|Length of ICU stay (days)|Number of bleedings and adverse
Tenecteplase in Patients With COVID-19 December 2021	Drug: Tenecteplase	Drug: Placebo	18 to 75years old with COVID-19 related ARDS	Number of participants free of respiratory failure|Number of occurrences of bleeding|Number of participants with in-hospital deaths at 14 days|Number of participants with death at 28 days|Number of ventilator-free days|Number of respiratory

https://ClinicalTrials.gov/show/NCT04505592				failure-free days|Number of vasopressor-free days|Vasopressor doses at 24 hours|Vasopressor doses at 72 hours|P/F ratio at 24 hours|P/F ratio at 72 hours|Number of ICU-free days|Hospital length of stay|Number of participants with new-onset renal failure|Number of participants with need for renal replacement therapy
Apixaban for PrOphyLaxis of thromboemboLic Outcomes in COVID-19 (APOLLO) December 2021 https://ClinicalTrials.gov/show/NCT04746339	Drug: Apixaban	Drug: Placebo	18 years and older with COVID-19	Number of days alive and out of hospital or emergency department|Hospitalization due to bleeding|Hospitalizations for cardiopulmonary causes|All-cause hospitalization|All-cause death|Days free of venous thromboembolism|Major cardiovascular events (MACE)
Prevention of Arteriovenous Thrombotic Events in Critically-Ill COVID-19 Patients Trial (COVID-PACT) November 2021 https://ClinicalTrials.gov/show/NCT04409834	Drug: Unfractionated Heparin IV Drug: Enoxaparin 1 mg/kg|Drug: Clopidogrel|	Drug: Enoxaparin 40 Mg/0.4 mL Injectable Solution Drug: Unfractionated heparin SC|	18 years and older with COVID-19 critical illness	Venous or arterial thrombotic events|Key secondary endpoint: Clinically evident venous or arterial thrombotic events
Nebulized Heparin for COVID19-associated Acute Respiratory Failure March 31, 2022 https://ClinicalTrials.gov/show/NCT04842292	Drug: Heparin|	Drug: Placebo	18 to 80 years old COVID-19 patients	Mean PaO2/FiO2 ratio|Clinically Significant Bleeding|Incidence of venous thromboembolism
Australasian COVID-19 Trial ADAptive Platform Trial (ASCOT ADAPT) December 31, 2022 https://ClinicalTrials.gov/show/NCT04483960	Drug: Nafamostat Mesilate|Biological: Hyperimmune Globulin|Drug: Enoxaparin|Drug: Dalteparin|Drug: Tinzaparin	Drug: Nafamostat Mesilate|Biological: Hyperimmune Globulin|Drug: Enoxaparin|Drug: Dalteparin|Drug: Tinzaparin	18 years and older COVID-19 patients	Death from any cause or requirement of new intensive respiratory support (invasive or non-invasive ventilation) or vasopressor/inotropic support.|Time to clinical recovery|WHO 8-point ordinal outcome scale|All-cause mortality|Days alive and free of hospital|Days alive and free of invasive or non-invasive ventilation|Shortness of breath|Quality of life|Antiviral domain-specific outcome: Viral clearance|Antiviral domain-specific outcome: Viral load|Antiviral domain-specific outcome: Safety (Liver enzymes)|Antiviral domain-specific

				outcome: Safety (potassium)|Antiviral domain-specific outcome: Safety (sodium)|Antiviral domain-specific outcome: Safety (bleeding)|Antiviral domain-specific outcome: Safety (thrombophlebitis)|Antiviral domain-specific outcome: serious adverse reactions|Antibody domain-specific outcome: Serious treatment-related adverse events|Antibody domain-specific outcome: Haemolysis|Antibody domain-specific outcome: Confirmed arterial thrombosis|Antibody domain-specific outcome: Confirmed venous thrombosis|Anticoagulation domain-specific outcome: Confirmed deep venous thrombosis|Anticoagulation domain-specific outcome: Confirmed pulmonary embolus|Anticoagulation domain-specific outcome: Confirmed acute myocardial infarction|Anticoagulation domain-specific outcome: Confirmed ischemic cerebrovascular event|Anticoagulation domain-specific outcome: Major bleeding|Anticoagulation domain-specific outcome: Clinically relevant non-major bleeding|Anticoagulation domain-specific outcome: Heparin-induced thrombocytopenia (HIT)|Anticoagulation domain-specific outcome: Other confirmed thrombotic event
Low-Dose Tenecteplase in Covid-19 Diagnosed With Pulmonary Embolism December 31, 2021 https://ClinicalTrials.gov/show/NCT04558125	Tenetecplase	Placebo	18 to 75 years with COVID-19 related pulmonary embolism	Percent improvement in shock index (defined as heart rate divided by systolic blood pressure) 6 hours after the TNK/placebo bolus.|1. Clinical status at 24 hours after administration of TNK / placebo based upon 7-point scale.
Clinical Efficacy of Heparin and Tocilizumab in Patients With Severe COVID-19 Infection (HEPMAB) December 31,2021 https://ClinicalTrials.gov/show/NCT04600141	Drug: Tocilizumab|Drug: Heparin - Therapeutic dosage|	Drug: Tocilizumab| Drug: Heparin - Prophylactic dosage	18 years and older with COVID-19	Proportion of patients with clinical improvement|Hospital and ICU length of stay;|Duration of invasive mechanical ventilation|Duration of vasopressor use|Renal failure by AKIN criteria|Incidence of cardiovascular complications|Incidence of venous thromboembolism|Mortality

COVID-19 Positive Outpatient Thrombosis Prevention in Adults Aged 40-80 September 2021 https://ClinicalTrials.gov/show/NCT04498273	Drug: Apixaban 2.5 MG|Drug: Apixaban 5MG|Drug: Aspirin|	Drug: Placebo	40 to 80years old with mild COVID-19	Hospitalization for cardiovascular/pulmonary events
Hemostasis in COVID-19: an Adaptive Clinical Trial May 30,2022 https://ClinicalTrials.gov/show/NCT04466670	|Drug: Unfractionated heparin nebulized	Drug: acetylsalicylic acid	18 years and older with COVID-19	Hospital discharge - alive / death|Length of mechanical ventilation free days|Length of renal replacement therapy free days|Number of documented venous thromboembolism or arterial thrombosis