EVIDENCE SUMMARY

RESEARCH QUESTION: **Among COVID-19 patients, should anticoagulation be used for treatment?**

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RECOMMENDATIONS

Recommendations	Certainty of Evidence	Strength of Recommendation
We suggest the use of prophylactic over therapeutic dose anticoagulation among hospitalized adults with moderate, severe or critical COVID-19 disease unless there are any contraindications.	Low	Weak
We suggest the use of standard dose prophylactic anticoagulation over intermediate dose prophylactic anticoagulation among hospitalized adults with moderate, severe, or critical COVID-19 disease unless there are any contraindications.	Low	Weak
We suggest against the routine use of any anticoagulation among adults with mild COVID-19 in the outpatient setting unless there is a pre-existing non-COVID indication.	Low	Weak
We suggest the use of oral anticoagulation after hospital discharge among adults admitted for moderate, severe, or critical COVID-19 and who are suspected to have a high risk for VTE at-or-near hospital discharge.	Low	Weak
We suggest the use of prophylactic dose anticoagulation among hospitalized pregnant patients with moderate, severe, or critical COVID-19 disease unless there are any contraindications.	Very Low	Weak
We suggest prophylactic dose anticoagulation among hospitalized pediatric patients more than 12 years of age with moderate, severe, or critical COVID-19 or MIS-C unless there are any contraindications.	Very Low	Weak

Consensus Issues

The presence of moderate, severe, or critical COVID-19 infection increases the risk of microvascular thrombosis in patients hence the use of anticoagulation is suggested. In patients with no evidence of a pre-existing thrombotic event, a prophylactic standard dose is favored as the panel put heavier premium and emphasis on the potential for harm.

In the outpatient setting, mild COVID will carry a lower thrombotic risk compared to hospitalized patients, therefore in the absence of a known thrombotic event, anticoagulation must be considered only if there are indications since there is potential for serious adverse effects, limited monitoring, and added cost. Indications for its use may include but not limited to: left ventricular thrombus, atrial fibrillation, venous thromboembolism, or CVD infarct.

Only one trial with a low certainty of evidence was available for the use of oral anticoagulation post discharge. The study used Rivaroxaban 20mg tab once a day for 35 days given based on a VTE risk scoring system and D-dimer level prior to discharge.

The panel weakly suggests the use of prophylactic anticoagulation in children as the risk of thrombotic events seems higher for children more than 12 years old and this age group may benefit from the intervention.

KEY FINDINGS

- This updated review on the use of anticoagulants (AC) among patients with COVID-19 made use of evidence from twenty randomized control trials (RCTs), 12 of which are new studies not included in the previous recommendation.
- Overall, the certainty of evidence was low due to issues in blinding, allocation, imprecision, and significant heterogeneity especially in some of the critical outcomes.
- In the comparison of those receiving full dose (or therapeutic dose AC) versus prophylactic dose (standard low dose to intermediate dose AC), efficacy endpoints show no significant difference in terms of all-cause mortality, organ support-free days, and need for invasive mechanical ventilation while there was evidence to support therapeutic dose AC for incidence of any thrombotic events.
- Safety outcomes on the other hand show that prophylactic dose AC led to significantly less incidence of major bleeding episodes especially among those with severe COVID-19 disease.
- There was no significant difference for other bleeding events not considered major bleeding and heparin-induced thrombocytopenia.
- For those receiving intermediate dose versus standard dose AC, efficacy outcomes showed no significant difference in all-cause mortality and need for invasive mechanical ventilation.
- In preventing the incidence of any thrombotic events, overall, there was no difference between the two groups however in the subgroup of moderate disease, intermediate dose led to less incidence but this effect was highly influenced by one study.
- Safety outcomes showed no significant difference for major bleeding and any bleeding not considered major as well as for heparin-induced thrombocytopenia.
- For patients with mild disease in the outpatient setting, there was no significant difference in terms of efficacy (all-cause hospitalization, all-cause mortality, and any thrombotic events) for those that received AC and those that did not.
- Any bleeding episodes showed no significant difference but those receiving AC at best can receive minimal benefit but at worst can have increased risk of bleeding.
- One study showed that those who received AC while being admitted will benefit with receiving oral AC post discharge as it decreases pooled incidence of mortality and venous thrombotic events (VTE) with no occurrence of bleeding.
- For special populations, no direct evidence was seen among pregnant patients with COVID-19 however data from observational studies showed the same trend of increased risk for VTE for pregnant patients with COVID-19 compared to pregnant patients without the disease. Recommendations are thus based on the general population.
- For the pediatric population, a phase-2 non-randomized single-arm clinical trial showed the safety of enoxaparin use among pediatric patients with moderate to severe COVID-19 and MIS-C. Incidence of VTE and mortality among those receiving anticoagulation were lower in the pediatric population as compared to the adult population.

WHAT'S NEW IN THIS VERSION?

- Twelve new RCTs were added to the previous 8 to come up with the evidence presented in this review.
- Aside from the comparisons of therapeutic versus prophylactic dose anticoagulation, and intermediate dose and standard dose AC for hospitalized patients with moderate to severe COVID-19, we also present evidence for COVID-19 patients with mild disease in the outpatient setting and patients post-discharge.
- Similar recommendations are put forward in this review for the first two comparisons as with the previous review while evidence for non-benefit for outpatients and benefit for post-discharge are presented.
- Recommendation among pregnant women and pediatric populations are included in this review as well.

PREVIOUS RECOMMENDATIONS
As of 26 October 2021

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.

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 in cases among the general population hence its possible role in decreasing COVID-19 morbidity and mortality is being investigated [2].

REVIEW METHODS

For this update, a literature search was done in PubMed on November 1, 2022 to look for systematic reviews and meta-analysis with the following keywords: 1) COVID-19 or SARS-CoV-2 [MeSH], and 2) anticoagulation [MeSH]. Upon identifying the most recent, complete, and highest quality meta-analysis, its search methodology was used to do an updated search to look for RCTs published after the last day of the article search of the meta-analysis. This updated search was done on November 4, 2022. Whenever possible, comparisons in this review cover [1] therapeutic versus prophylactic dose anticoagulation and [2] intermediate versus standard dose prophylactic anticoagulation. Prophylactic dose AC in the first comparison include low standard dose AC and intermediate dose AC. COVID-19 disease severity from outpatient (mild) and hospitalized non-ICU and ICU (moderate to severe) was also considered in the analysis whenever possible.

RESULTS

The previous review included 8 studies which investigated therapeutic versus prophylactic anticoagulation (AC) from 6 studies [3–8] and intermediate dose vs standard dose AC from 2 studies [9,10]. Definitions of the doses covered are included below, but in summary a dose is considered therapeutic if it is given in the locally accepted therapeutic dose as indicated in a drug's formulation. Subtherapeutic doses are considered prophylactic and these are further divided into intermediate dose or standard dose with the latter also being based on local use/guideline for the drugs while intermediate dose is in between the standard dose and the therapeutic dose. Due to the high number of published studies, we first searched for meta-analysis answering our main research question. A high-quality meta-analysis assessed using the AMSTAR-II tool with last search done on May 23, 2022 was retrieved and used as the initial source document. It included 12 RCTs, 6 of which were included in our last recommendation and 6 new RCTs. We then did an updated search from May 23, 2022 to November 4, 2022 using the search strategy of the meta-analysis with additional filters for RCTs and the year 2022. We retrieved 6 more RCTs totaling to 12 new RCTs for this updated evidence review: 1 RCT in the intermediate vs standard dose comparison among admitted patients with moderate disease [11], 6 new RCTs investigating therapeutic versus prophylactic dose AC [12–17], 4 new RCTs investigating patients with mild COVID-19 disease in the outpatient setting [18–21], and one RCT investigating the use of AC after hospital discharge of patients previously given AC during their acute COVID-19 illness [22]. Among the new RCTs investigating therapeutic vs standard dose AC, 2 investigated patients with moderate disease using tinzaparin [16], and bemiparin [15] exclusively, 3 investigated patients with severe disease [13,14,17], while one investigated those who had moderate to severe disease [12]. The latter study provided separate results for the moderate and severe group and these were included in the subgroup analysis. The studies investigating mild COVID-19 patients all did majority of the monitoring and follow-up virtually, with one study doing all processes virtually from recruitment to follow-up without patient contact [20]. Two of these studies used oral rivaroxaban and apixaban [19,21], while two used enoxaparin for which the subjects had to administer the drug themselves subcutaneously [18,20]. All 4 RCTs investigating AC for mild COVID-19 patients were discontinued due to futility and slow recruitment hence statistical power for each individual study was small. Among the new RCTs, five studies had high risk of bias due to allocation concealment concerns, blinding of outcome assessors, and incomplete reporting of withdrawal and data results [11–13,15, 17], four had moderate risk of bias mainly due to blinding of outcome assessors, and some due to follow-up concerns especially those who had to self-administer the test drug [16,18,20,21], and three has low risk for bias [9,10,20].

Table 1. Definition of dose of anticoagulation used

Therapeutic dose	Dosing in included studies based on local guidelines for therapeutic dosing. Definitions include: Enoxaparin - twice daily dosing 0.8 to 1mg/kg adjusted to weight and BMI - once a day dosing1.5mg/kg Tinzaparin - 175U/kg q24 Dalteparin - 100u/kg q12 Bemiparin - 115 IU/kg q24 UFH - Titrate to institution-specific anti-Xa or aPTT values
Prophylactic dose AC considered to be dose lower than therapeutic dosage	
Intermediate dose	Enoxaparin

	- 0.5 – 1mg/kg once daily adjusted to weight and BMI - 40 mg BID for all Tinzaparin - 100IU/kg daily
Standard dose	Enoxaparin - 30-40mg OD, BID if BMI >30 or wt >120kg Tinzaparin - 4,500 IU daily
	Other AC agents (categorized in included studies as prophylactic dose) Fondaparinux - 2.5mg SC daily UFH - 5,000 – 7,500 U SC q8-1'2 adjusted to weight and BMI Dalteparin - 5,000 U q12 Tinzaparin - 9,000 U q24 Bemiparin - 3,500 IU once daily

A. Therapeutic dose versus prophylactic dose AC (12 RCTs, *6 new*)

The comparison between therapeutic dose and prophylactic dose made use of 12 RCTs. Of the 12 RCTs, eight trials made use of low standard dose while 4 trials made use of mixed intermediate to low standard prophylactic dose [4,5,8,16].

A.1 *All-cause mortality (12 RCTs, n=5618, Low certainty of evidence)*
All-cause mortality across all admitted population showed no significant difference among the two groups (RR 0.91; 95% CI 0.74-1.12). Subgroup analysis among disease severity also showed no significant difference for those with severe disease (RR 0.97, 95% CI 0.79-1.19, n=1,724), while the subgroups of moderate disease (RR 0.73, 95% CI 0.31-1.72, n=3,027), and mixed population (RR 1.07 95%CI 0.56-2.03, n=867) both showed inconclusive results.

A.2 *Any thrombotic events (11 RCTs, n=5,492, moderate certainty of evidence)*
The incidence of any thrombotic events were recorded in 11 RCTs and it showed a decreased risk among those receiving therapeutic dose AC compared to prophylactic dose AC with a relative risk of 0.59 (95%CI 0.48-0.71). This is true even among the subgroups of those who have severe (RR 0.63; 95%CI, 0.49-0.82; n=1,589) and moderate disease (RR 0.53; 95% CI 0.39-0.71; n=3,036). The two studies with mixed population showed inconclusive result but the trend was also in favor of those receiving therapeutic dose AC (RR 0.54; 95% CI, 0.27-1.06; n=467).

A.3 *Organ support-free days (3 RCTs, n=3,789, very low certainty of evidence)*
Effect of AC on organ support-free days was available from 3 studies similar to the last update. The over-all evidence showed no significant difference OR 1.11 (95% CI, 0.79-1.56) however, the subgroup of moderate disease shows some benefit towards prophylactic dose over therapeutic dose (OR 1.29; 95% CI 1.07-1.56), while the subgroup for severe disease shows some advantage (not significant) for therapeutic dose AC (OR 0.83; 95% 0.67-1.03).

A.4 *Need for invasive mechanical ventilation (3 RCTs, n=917, low certainty of evidence)*

In studies investigating moderate COVID-19 disease, the use of AC showed that using therapeutic versus prophylactic dose had no significant difference in progression to the need of invasive mechanical ventilation (RR 0.81; 95% CI 0.52-1.28).

A.5. *Major bleeding (12 RCTs, n=5,621, moderate certainty of evidence)*
Major bleeding was reported as the primary safety outcome among all included RCTs. The risk is significantly higher among those receiving therapeutic dose AC with a RR 1.76 (95% CI 1.16-2.68). Subgroups did not show this statistical significant difference but trends among the severe (RR 1.74; 95% CI 0.94-3.24; n=1,869), moderate (RR 1.43; 95% CI 0.62-3.29; n=3,138) and mixed group (RR 2.45; 95% CI 0.78- 7,73; n=614) all showed a trend towards increased bleeding among those receiving therapeutic dose AC

A.6 *Any bleeding not considered major bleeding (6 RCTs, n= 1635, very low certainty of evidence)*
Studies presenting data on bleeding episodes not considered major (i.e., minor bleeding and clinically relevant non-major bleeding needing physician's attention) showed no significant difference between the two groups (RR 2.34; 95% CI 0.67-8.17). Subgroup analysis also showed no statistically significant difference with severe disease showing less incidence among the prophylactic dose (RR 3.40; 95% CI 0.17-69.92), and moderate disease less incidence among therapeutic dose (RR 0.77; 95% CI 0.18-3.36); while the mixed population showed significantly less risk for those receiving prophylactic dose AC (RR 3.70, 95% CI 1.38-9.94).

A.7 *Heparin-induced thrombocytopenia (HIT) (2 RCTs, n=466, low certainty of evidence)*
Evidence for this outcome came from 2 studies, one investigating severe COVID-19 while the other those with moderate disease. One study did not show any incidence for both therapeutic and prophylactic group while the other study showed one incidence in the therapeutic dose while none in the prophylactic group (RR 3.0; 95%CI 0.15-59.89).

B. Intermediate versus standard dose prophylaxis (4 RCTs, *2 new)*

Comparisons between the intermediate versus standard prophylactic AC dose were based on 4 RCTs, 3 of which made use of enoxaparin while one used tinzaparin. Subgroup analysis of those who have severe and moderate disease was available and performed.

B.1 All-cause mortality (4 RCTs, n=1,113, low certainty of evidence)
The overall result for all-cause mortality showed no significant difference between the two comparison groups with an RR of 1.03 (95% CI 0.72-1.46). Subgroup analysis between those with severe and moderate disease maintained this result (RR 0.98; 95% CI, 0.73-1.32; n=735 and RR 2.67; 95%CI 0.68-10.38; n=378 respectively).

B.2 Thrombotic events (4 RCTs, n=1,115, low certainty of evidence)
There was no significant difference among thrombotic events among those that received intermediate dose AC compared to those that received standard dose (RR 0.77; 95%CI, 0.47-1.29). However on subgroup analysis it was shown that although those with severe disease had no difference in thrombotic events (RR 1.11; 95%CI, 0.62-1.99; n=735), this was the opposite for those with moderate disease which favored therapeutic dose AC (RR 0.22; 95% CI, 0.06-0.82; n= 380). For this subgroup though there is a considerable wide confidence interval among the two studies pooled possibly due to low event rates.

B.3 Need for invasive mechanical ventilation (2 RCTs, n=380, moderate certainty of evidence)
Two studies reported on the need for invasive mechanical ventilation among those with moderate disease and they showed no significant difference between those that received intermediate dose AC compared to standard dose AC (RR 1.02; 95%CI 0.36-2.88).

B.4 Major bleeding (4 RCTs, n=1,115, Low certainty of evidence)
Major bleeding had inconclusive results with an RR of 1.45 (95% CI, 0.55-3.80). This pooled result is maintained on subgroup analysis of severe (RR 1.52; 95% CI, 0.54-4.27; n=734) and moderate (RR 1.01; 95% CI, 0.06-15.92; n=380) disease.

B.5 Any bleeding not considered major bleeding (4 RCTs, n= 1,115, low certainty of evidence)
Pooled results from 4 RCTs showed that bleeding episodes not categorized as major bleeding did not differ significantly among those that received intermediate dose AC versus standard dose AC (RR 1.40, 95%CI 0.73-2.69). This is true even among the severe (RR 1.62, 95%CI 0.67-3.91) and moderate subgroups (RR 0.90, 95%CI 0.25-3.30).

B.6 Heparin-induced thrombocytopenia (2 RCTs, n=745, moderate certainty of evidence)
Two studies showed data for heparin induced coagulopathy. Thrombocytopenia among severe patients showed no significant difference for intermediate and standard dose AC (RR 0.94, 95%CI 0.71-1.24). Another study among moderate disease showed no events for the two groups.

C. Standard dose AC versus placebo in mild disease (4 new RCTs)

This comparison group was not available from the last recommendation since studies on AC for outpatients were still being done at that time. All-cause hospitalization showed no significant difference (4 RCTs, n=1,462; RR 0.96; 95% CI, 0.56-1.64) among those receiving AC versus standard of care (SoC) alone. The same result is seen for all- cause death (4 RCTs, n=1,462; RR 3.12; 95% CI, 0.33-29.83), any thrombotic events (2 RCTs, n=547; RR 1.09; 95% 0.07-17.14), and any bleeding (4 RCTs, n=1,562; RR 2.47; 95% CI 0.64-9.49). it is important to note that all pooled results had wide confidence intervals owing to low event rates and low sample sizes of the involved RCTs. Although not significant, any bleeding episodes showed a trend favoring the SoC group. Certainty of evidence for any thrombotic events was moderate while all-cause hospitalization, all-cause death, and any bleeding episodes have a low certainty of evidence.

D. AC post discharge (1 new RCT, n=320, Low certainty of evidence)

One issue raised during the last recommendation was for how long AC should be given among admitted COVID-19 patients who received AC during their admission. One RCT was able to provide data for this question. The RCT gave oral rivaroxaban to previously admitted COVID-19 patients up to 35 days after discharge to patients clinically suspected to have a high risk for VTE at hospital discharge. A high risk for VTE was defined by the international medical prevention registry (IMPROVE) VTE score of 2-3 and a D-dimer level > 500ng/mL or an IMPROVE score of 4 or more regardless of the D-dimer level. Result of the RCT showed that those receiving rivaroxaban had a significantly lower risk for the primary outcome which was a composite of fatal venous thromboembolism, any symptomatic or asymptomatic venous or arterial thrombotic event, and cardiovascular death at day 35 (RR 0.33; 95% CI, 0.12-0.90). Symptomatic and fatal VTE showed no difference for those that received the drug and those that didn't (RR 0.13; 95% CI, 0.02-0.99) while no bleeding was reported in both groups.

Anticoagulation for special populations

A. Pregnant patients

No studies show direct evidence of the benefit or harm of using AC for pregnant patients with COVID-19. Recommendations from different guidelines are based on the increased risk of thrombotic events among pregnant women with COVID-19 compared to normal pregnant women even if the incidence of these events are generally low [23,24]. Pregnant patients with COVID-19 admitted at the ICU are at a significantly higher risk to develop thrombotic events as is the case in the general population [25,26]. In a systematic review of clinical practice guidelines (CPGs) for management of pregnant patients with COVID-19, among the 28 included CPGs, 9 made a statement about thromboprophylaxis with 7 of these recommending the use of LMWH for symptomatic pregnant patients [27].

B. Pediatric patients

One single-arm multicenter, phase 2 clinical trial showed safety of thromboprophylaxis of subcutaneous enoxaparin among children [28]. Children hospitalized for either primary COVID-19 disease or MISC-C from 8 children's hospital in the Unites States were given enoxaparin at a starting dose of 0.5mg/kg SC every 12 hours to achieve a 4-hour post-dose antiXa level of 0.2-0.49

U/mL as recommended by ISTH. Since the trial is single arm, there is no randomization involved however outcome assessment was done by an independent group and results were monitored by an independent data and safety monitoring committee.

Bleeding
The primary outcome was clinically significant bleeding which includes major bleeding and clinically relevant non-major bleeding based on the ISTH criteria. There was no incidence of bleeding among all participants given enoxaparin (both those with primary COVID-19 illness and those with MISC-C).

Thrombosis
Two out of 38 patients (5.2%) receiving thromboprophylaxis developed VTE which were both central venous catheter-related. In comparison, one retrospective cohort study reported that thrombosis was seen in 2.1% of those with symptomatic COVID-19 and 6.5% among those with MIS-C. In this cohort study it was also reported that among those that had thrombotic events, incidence occurred mostly among children >12 years old (98%) and the same age group with MIS-C had the highest incidence to develop TE (19%) [29] . The incidence of thrombotic events among those given AC is comparable to the incidence of VTE among hospitalized adults who received prophylactic dose AC (8.8%) and those who received therapeutic dose AC (4.9%) based on our review's pooled data.

Mortality
One mortality was noted in a patient with primary COVID-19 illness (2.6%). This is similar to the reported mortality among children with either COVID-19 or MIS-C in the previously cited cohort study (2.3%). Among those that had TE, 28% died. This is lower compared to adult population which have a 14.3% and 15.2% mortality among those who received therapeutic and prophylactic dose AC.

RECOMMENDATIONS FROM OTHER GROUPS

Group or Agency	Recommendation	Strength of Recommendation/ Certainty/Quality of Evidence
American Society of Hematology (May 2021, January 2022) [33]	Suggest the use of prophylactic-intensity over intermediate intensity anticoagulation among patients with critical COVID-19 illness who do not have suspected or confirmed venous thromboembolism Suggest the use of therapeutic-intensity over prophylactic intensity anticoagulation for patients with COVID-19-related acute illness (admitted at the ward but not requiring ICU-level care) who do not have suspected or confirmed venous thromboembolism or another indication for anticoagulation	Conditional, low certainty of evidence Conditional, very low certainty of evidence
US NIH, COVID-19 treatment guideline panel (September 26, 2022) A= strong B= Moderate I - One or more RCT without major limitation	For those previously maintained on AC due to an underlying condition prior to their COVID-19 illness, continuation is recommended unless significant bleeding or other contraindications are present Patients with COVID-19 who are highly suspected to have thromboembolic disease but without a diagnostic imaging, therapeutic dose AC is recommended	AIII AIII AIIa

IIa - other randomized trials without major limitations or subgroup analysis of randomized trials IIb - nonrandomized or observational cohort III - expert opinion	In non-hospitalized patient, recommendation against the use of AC for prevention of VTE or arterial thrombosis except in a clinical trial Recommend against routine continuation of VTE prophylaxis after hospital discharge for patients with COVID-19 unless an indication is present or participating in a clinical trial For hospitalized patients, LMWH or UFH is preferred over oral anticoagulants Hospitalized patients not requiring ICU-level care: therapeutic dose heparin is recommended for patients whose D-dimer level are above the upper limit of normal, who require low-flow oxygen and who do not have an increased risk of bleeding (CIIa); prophylactic dose of heparin is recommended if therapeutic dose is not possible, unless a contraindication exists (AIIb) Hospitalized adult patients requiring ICU-level care: prophylactic dose AC for VTE prophylaxis is recommended unless a contraindication exists (AI); for patients on therapeutic dose AC in a non-ICU setting due to COVID-19 who are transferred to the ICU, recommended to switch to prophylactic dose heparin unless VTE is confirmed (BIII); recommend against using intermediate or therapeutic dose of AC for VTE prophylaxis except in a clinical trial (BI) Recommends the use of prophylactic dose AC for pregnant patients hospitalized for symptomatic COVID-19 unless a contraindication occurs (BIII) For children • With MISC-C AND moderate-to-severe left ventricular dysfunction, should receive therapeutic anticoagulation unless contraindicated due to bleeding risk • If with MISC-C but do not have large coronaries or ventricular dysfunction using of AC must be made on a case-to-case basis • Hospitalized due to COVID-19, if >12 years old, recommends prophylactic dose AC unless there are any contraindications • For younger than 12 years old, no evidence to support recommending for or against use of AC, instead, institutional standard regarding anticoagulation should be followed	AIII AIII CIIa, AIIb AI, BIII, BI, BIII AIII BIII
National Institute for Health and Care Excellence (NICE) (July 14, 2022) [34]	Standard prophylactic dose of LMWH as soon as possible and within 14 hours of admission to young people and adults with COVID-19 who need low-flow or high-flow oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation who do not have increased bleeding risk. Treatment should be given for a minimum of 7 days, including after discharge Consider a treatment dose of LMWH for young people and adults with COVID-19 who need low-flow oxygen and do not have an increased risk of bleeding	Moderate certainty of evidence Moderate certainty of evidence

ONGOING STUDIES AND RESEARCH GAPS

Although multiple studies have already presented evidence for anticoagulation use for COVID-19 patients, multiple RCTs are still being done. Current listed RCTs (15) are investigating different dosing regimens, use of different types of AC drugs specifically oral ACs, and in different populations.

ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (ETD) PHASE

COST, PATIENT'S VALUES AND PREFERENCE, EQUITY, ACCEPTABILITY, AND FEASIBILITY

There are currently no available studies directly investigating the cost-effectiveness of using anticoagulation among COVID-19 patients. Pre-pandemic studies have shown that VTE among medically admitted patients remain to be one of the most common preventable cause of death that is being suboptimally addressed [30,31]. Patients with a medium to high risk of developing DVTs are said to have the most to benefit from receiving AC while the primary prevention approach to VTEs is a cost effective approach over case screening of DVT [31]. However, some issues have been raised as some studies have shown that the risk of bleeding from AC use may actually increase hospital costs, length of hospital stay, and mortality among admitted patients [32]. The decision to give AC should always be balanced with the risk of bleeding.

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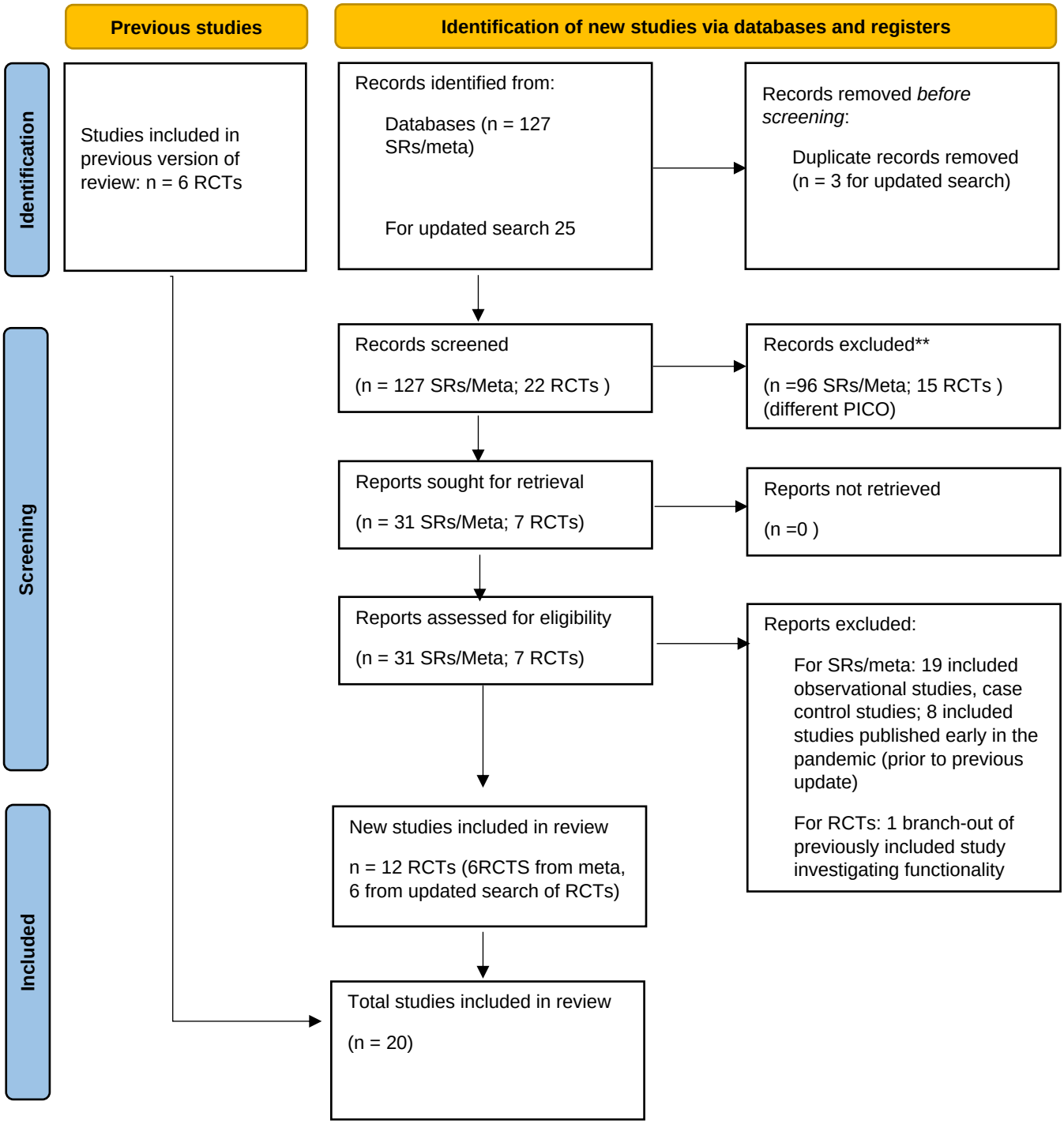
Appendix 1: Preliminary Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N=6/10)

FACTORS	JUDGEMENT				RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (6)			Relatively high **prevalence rate of venous thromboembolic events at 31%** among ICU patients with COVID-19
Benefits	Large	Moderate (3)	Small (2)	Varies (1)	**Therapeutic vs prophylactic dose: NO SIGNIFICANT DIFFERENCE** in all-cause mortality, organ support free-days, need for invasive mechanical ventilation. **Benefit [0.59 (0.48 to 0.71)] for therapeutic dose for incidence of any thrombotic event** **Intermediate vs standard dose: NO SIGNIFICANT DIFFERENCE** in outcomes including incidence of thrombotic events. [0.77 (0.47 to 1.29)] **Mild disease (outpatient): No significant difference in outcomes** **Special population:** **Children – incidence of 5.2% for thrombosis, and 2.6% for mortality** **Pregnant – no direct studies**
Harm	Large	Moderate (2)	Small (2)	Varies (2)	**Therapeutic vs prophylactic dose:** therapeutic dose led to significantly higher incidence of major bleeding episodes especially among those with severe COVID-19 disease. [1.76 (1.16 to 2.68)] **Intermediate vs standard dose: NO SIGNIFICANT DIFFERENCE** in safety outcomes **Mild disease (outpatient):** Any bleeding episode showed **no significant difference** **Special population:** **Children – no clinically significant bleeding event (1 study)** **Pregnant – no direct studies**
Certainty of Evidence	High	Moderate (2)	Low (4)	Very low	Prophylactic vs therapeutic: **LOW** Standard vs intermediate dose: **LOW** Mild disease/post discharge: **LOW** Special population (children/pregnant): **VERY LOW**

Balance of effects	Favors intervention	Probably favors intervention (2)	Does not favor intervention	Probably favors no intervention (2)	Favors no intervention	Varies (2)	**Favors standard dose prophylactic anticoagulation in patients with moderate, severe, and critical COVID-19.** While therapeutic dose can decrease the risk for any thrombotic event, there was no significant benefit for all-cause mortality, organ support-free days, and need for invasive mechanical ventilation WITH increased incidence of major bleeding. No significant benefit or harm for use. **In children, there is decreased incidence of mortality with no clinically significant bleeding events.**
Values	Important uncertainty or variability (1)	Possibly important uncertainty or variability (5)	Possibly NO important uncertainty or variability	No important uncertainty or variability			
Resources Required	Uncertain / Varies (1)	Large cost (1)	Moderate cost (4)	Negligible cost	Moderate savings	Large savings	Hospitalization cost for COVID-19: ₱51,000-200,000 **Enoxaparin cost** in the Philippines: ₱183-794 for 100mg/ml, 0.4mL pre-filled syringe (DOH drug price reference index)
Certainty of evidence of required resources	No included studies (3)	Very low	Low (3)	Moderate	High		**Higher costs** for those that develop bleeding caused by anticoagulants due to prolonged hospital stay and increased risk of mortality
Cost effectiveness	No included studies (2)	Probably / Favors the comparison (2)	Probably favors the intervention (1)	Favors the intervention	Varies (1)		
Equity	Varies (2)	Reduced	Probably reduced (2)	Probably no impact (1)	Probably increased (1)	Increased	
Acceptability	Varies (2)	No Probably no (1)	Yes	Probably yes (3)			For the use: 3 Against the use: 3
Feasibility	Varies (3)	No (1) Probably no (1)	Yes	Probably yes (1)			

Appendix 2: Search and Yield Results



Appendix 3: Characteristic of source meta-analysis

Author	Last search	Title	Search strategy	PICO
Kovacs	October 18 2021 then updated on May 23, 2022 journal	Higher Dose Anticoagulation Cannot Prevent Disease Progression in COVID-19 Patients: A Systematic Review and Meta-Analysis Aim: compare high dose thromboprophylaxis versus standard dose in COVID-19 patients	Database: CENTRAL, Embase, Medline, medRxviv language restriction: none strategy: outlined in the methodology exclusion criteria	Population: adults with clinically or laboratory confirmed COVID-19 infection Intervention: high dose thromboprophylaxis (intermediate and therapeutic dose according to ASH 2021*) versus standard dose thromboprophylaxis (low-dose preventive thromboprophylaxis) Outcome: primary: organ-support free-days, length of hospital stay, mortality (ICU, in-hospital, 30day) Safety outcomes: incidence of thrombotic events (arterial and venous), bleeding event rate (major bleeding, clinically relevant non major bleeding, minor bleeding as per defined by ISTH), requirement for transfusion Study designs: RCTs *ASH 2021: therapeutic dose enoxaparin 1.5mg/kg OD or 1mg/kg twice daily if CrCl >30mL/min and BMI < 40kg/m2 therapeutic dose UFH to target aPTT in therapeutic range per local guideline or anti-Xa activity 0.3-0.7 IU/mL intermediate dose enoxaparin 0.5mg/kg OD or 40mg (4000 U) twice daily for patients with CrCl> 30mL/min and BMI < 40kg/m2

Appendix 4: Assessment of quality using AMSTAR-2

AMSTAR Items	Kovacs 2022
Date of last search	*May 23, 2022*
Rating of overall confidence in the results of the review[§]	HIGH
1. Research questions, inclusion criteria include PICO components	Y
2.* Protocol registered before commencement of the review	Y
3. Selection of study designs to be included were explained	Y
4.* Adequacy of literature search	Y
5. Study selection done by at least 2 reviewers	Y
6. Data extraction done by at least 2 reviewers	Y
7.* Justification for excluding individual studies	Y
8. Described included studies in adequate detail	Y
9.* ROB from individual studies being included in the review	Y
10. Reported sources of funding for studies included	N
11.* Appropriateness of meta-analytical methods	Y
12. Potential impact of ROB in individual studies	Y
13.* Consideration of ROB when interpreting review results	Y
14. Sufficient explanation of heterogeneity	Y
15.* Assessment of presence and likely impact of publication bias	Y
16. Reported potential COI sources, funding they received	Y

Appendix 5: Characteristics of included studies (n=20)

Study ID	Study Design	Setting	Total Randomized	Population	Intervention	Comparator	Outcomes
Perepu (9)	multi-center, open-label RCT	three centers in the US	173	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 thrombosis past 3 months, acute or chronic renal insufficiency (CrCl < 30)	intermediate dose enoxaparin 1mg/kg SC daily, for BMI < 30 0.5mg/kg SC twice daily for BMI > 30 Until discharge from hospital	standard prophylactic dose enoxaparin 40mg SC daily for BMI < 30 30 or 40mg SC BID for BMI > 30 Until discharge from hospital	all-cause mortality at 30 days arterial/venous thromboembolism major bleeding minor bleeding
Sadeghipour (INSPIRATION) (10)	open label RCT	10 academic centers in Iran	600	adult COVID-19 patients admitted to the ICU *exclusion: life expectancy < 24hrs, established indication for therapeutic AC, weigh less than 40kg, pregnancy, history of heparin induced thrombocytopenia, platelet less than 50, and overt bleeding	intermediate dose enoxaparin <u>if CrCl >30</u> 1mg/kg SC daily if wt <120kg or BMI<35 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 given for 30 days	standard prophylactic AC <u>if CrCl >30</u> 40mg SC daily if wt <120kg or BMI<35 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	COMPOSITE of mortality within 30 days, venous/arterial thrombosis and treatment with ECMO major bleeding severe thrombocytopenia

Lopes (ACTION) (3)	multi-center, open-label RCT	31 hospitals in Brazil	614	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	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, 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 Until discharge	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

Goligher (REMAP-CAP, ACTIV-4a, ATTACC) (4)	open label, adaptive, multiplatform RCT	121 sites in 9 countries	1207	critically-ill patients with severe COVID-19 *exclusion- if admitted in ICU for 48hours or longer prior to randomisation OR admitted in hospital for 72 hours or longer, imminent risk of death, no commitment to organ support, high risk for bleeding, receiving dual antiplatelet therapy, has a non-covid indication for AC, or history of heparin sensitivity	therapeutic AC Enoxaparin 1mg/kg SC twice 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)
Lawler (REMAP-CAP, ACTIV-4a, ATTACC) (5)	open label, adaptive, multiplatform RCT	121 sites in 9 countries	2244	hospitalized COVID-19 patients not receiving critical care management (as above) *exclusion- if >72 hrs since admission or in hospital confirmation of COVID-19 to randomisation, or >14 days since admission, discharge expected within 72 hrs, clinical indication for therapeutic 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 thromboprophylaxis 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) (6)	multi-center, open-label RCT	28 sites in 6 countries	465	moderately ill hospitalised ward COVID-19 patients with elevated D-dimer within first five days of admission *exclusion- major bleeding risk, absolute indication for AC, any contraindication for use of heparin, pregnant,	therapeutic AC CrCl >30 if BMI < 40 enoxaparin1mg/kg SC q12 or 1.5mg/kg SC q24, dalteparin 200u/kg sc q 24 or 100u/kg q12, Tinzaparin 175U/kg q24	Prophylactic AC CrCl >30 if BMI < 40 enoxaparin 40mg SC q24, dalteparin 5000 U q 24, Tinzaparin 4500U q24, Fondaparinux 2.5mg q24,	composite of death, invasive and non-invasive mechanical ventilation, ICU admission major bleeding

				meet or imminent risk to develop component of primary outcome soon	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	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) (7)	open-label phase 2 RCT	single center in Brazil	20	COVID-19 patients with ARDS (by Berlin definition) requiring mechanical ventilation *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	therapeutic AC SC enoxaparin adjusted for age and CrCl *if CrCl worsened during study, transitioned to UFH 24h after last dose of enoxaparin up to14 days	prophylactic (according to doctor's judgment) UFH 5,000 IU TID (weight <120kg), 7500 IU TID (>120kg) OR enoxaparin 40mg OD (w<120kg), 40mg BID (w>120kg)	gas exchange over time (paO2/FiO2) at baseline, d7 and d14 time until weaning off MV, ventilator-free days

				of bleeding, participating in other RCTs, with indication for therapeutic AC other than COVID			
Spyropoulos (HEP-COVID) (8)	Multi-center RCT	12 academic centers in US	257	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 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	Therapeutic AC SC enoxaparin 1 mg/kg BID or 0.5mg/kg SC BID (if CrCl 15-29) Until discharge	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 Until discharge	Venous or arterial thromboembolism, death, major bleeding
Morici (X-COVID) (11)	Open-label, multicenter RCT	9 centers in Italy	183	Hospitalized adult patients with COVID-19 in the ward (direct ICU admissions excluded)	Intermediate dose Enoxaparin 40mg BID Until discharge from hospital	Standard dose Enoxaparin 30mg OD Until discharge	30-day mortality, venous thrombotic events, composite of venous thrombotic events and death, major bleeding
Blondon (COVID-HEP) (12)	Open-label, multicenter RCT	4 hospitals in Switzerland	159	Hospitalized COVID-19 patients presenting with severe disease defined as either an admission D-dimer of >1000ng/ml or admission to an immediate care/intensive care unit	Therapeutic dose Enoxaparin 1mg/kg twice daily or UFH with anti-Xa titration Until hospital discharge or at 30 days	Standard dose Enoxaparin 40mg OD or UFH 5000IU twice daily	Mortality, VTE, arterial thrombosis, disseminated intravascular coagulation

Oliynyk (13)	Double-blind RCT	One center in Ukraine	126	ICU admitted, non-intubated COVID-19 patients with COVID-19 associated coagulopathy	Therapeutic dose Enoxaparin 100 antiXa IU/kg twice daily or UFH titrated to aPTT 40-70s	Standard dose Enoxaparin of 50anti Xa IU/kg once daily	28-day mortality, rate of intubation
Rashidi (14)	Open-label pilot RCT (3-arm study, only applicable data included)	2 centers in Iran	10	ICU admitted adult patients	therapeutic dose UFH 5000 IU every 8 hours	Standard dose UFH titrated until aPTT 5-70	Improvement in PaO2/FiO2 ratio, 30-day all-cause mortality, SOFA score improvement, rate of ICU/hospital discharge, thrombotic events, major bleeding
Marcos-Jubilar (BEMICOP) (15)	Open-label, muticenter RCT	5 hospitals in Spain	65	Hospitalized, non-ICU admitted COVID-19 patients with elevated D-dimer	Therapeutic dose Bemiparin 115 IU/kg daily	Standard dose Bemiparin 3500 IU SC daily	Composite: death, ICU admission, mechanical ventilation, moderate/severe ARDS, symptomatic venous or arterial thromboembolism
Muñoz-Rivas (PROTHROMCOVID) (16)	Open-label, multicenter RCT	Hospital wards of 18 academic hospitals in Spain	300	Adults admitted to non-ICU wards due to COVID-19 pneumonia if (1) baseline O2 <95%, (2) D-dimer >1000ug/L, CRP > 150mg/L, or IL6> 40pg/mL	Therapeutic dose Tinzaparin 175 IU/kg once daily Until 7 days after discharge then at discretion of physician	Intermediate dose TInzaparin 100 IU/kg once daily Standard dose Tinzaparin 4500 IU once daily Until 7 days after discharge then at discretion of physician	Composite endpoint of death, need for invasive and non-invasive mechanical ventilation, venous or arterial thrombosis within 30 days of randomization safety outcome major bleeding, clinically relevant non-major bleeding based on ISTH
Bohula (COVID-PACT) (17)	multi-center 2x2 factorial, open label, randomized controlled	34 centers in US	382	>18 year old patients who have an acute SARS-CoV2 infection requiring intensive care unit level of care </ 96hrs before randomization without any indication for	full-dose AC (n=191) UFH IV targeting apTT 1.5-2.5x control OR enoxaparin 1mg/kg SC q12 OR others (Bivalirudin,	standard dose prophylactic AC (n=191) enoxaparin 50mg SC OD if CrCl>/30mL/min, 30mg SC OD if	Hierarchical composite of venous and arterial thrombotic events including death Safety outcome fatal or life-threatening bleeding

	trial with blinded end point adjudication			a full dose anticoagulation	Argatroban, Fondaparinux) clopidogrel 300mg PO OD on day1 followed by maintenance of 75mgPO OD until day 28 or hospital discharge	CrCl<30ml/min OR heparin 5000 U SC 3x daily OR fondaparinux 2.5mg SC OD no antiplatelet	
Barco (OVID) (18)	randomized, open-label, parallel group, multi-center, investigator initiated phase 3 trial	8 centers in Switzerland and Germany	472	outpatients with age ranging from 50 above who presented with acute COVID-19 symptoms (respiratory symptoms or body temp >37.5) and who tested positive for SARS-CoV-2 in the previous 5 days	subcutaneous enoxaparin 40mg OD x 14 days (n=234	standard of care (no thromboprophylaxis) (n= 238)	Primary outcome: composite of any untoward hospitalisation and all-cause death within 30 days of randomization Primary safety outcome: major bleeding and non-major clinically relevant bleeding
Ananwaranich (19)	phase 2b, randomized, double-blind, study	13 outpatient clinics in 7 US states and 1 virtual site enrolling participants from 40 states	497	>18 years old with mild COVID-19 symptoms confirmed to have SARS-CoV-2 infection (PCR test within 10 days of screening with at least 1 COVID ssx within 7 days of enrolment) but have risk factors for COVID-19 progression (based on age, BMI, or comorbidity)	oral rivaroxaban 10mg (n=246) OD x 21 days follow-up to 35 days, 12 telemedicine visits throughout	placebo (n=251)	Death, major bleeding, clinically relevant non-major bleeding, progressions, hospitalization
Cools (ETHIC) (20)	Open-label, multicentre, randomized, controlled, phase 3b trial	15 centers in 6 countries (Belgium, Brazil, India, South Africa, Spain, UK)	219	outpatients at least 30 years of age who has not received a COVID vaccine and has symptomatic, COVID-19 confirmed mild disease with at least one risk factor for severe disease	SC enoxaparin 40 mg once per day x 21 days if <100kg or twice per day if > 100kg (n=105), self-administered, follow-up up to 90 days	standard of care (no enoxaparin) (n=114)	primary efficacy: composite of all-cause mortality and hospitalisation at 21 days incidence of VTE bleeding

							adverse events
Connors (Activ-4B) (21)	Double-blind RCT with 4 study arms	13 outpatient clinics in 7 US states and 1 virtual site enrolling participants from 40 states	657	symptomatic but clinically stable OUTPATIENTS with COVID-19 aged 40-80 years old	group A: aspirin 81mg OD n=164 group B: prophylactic dose apixaban (2.5mg PO, BID), n=165 group C: therapeutic dose apixaban (5mg PO, BID), n =164 duration: 45 days, follow-up period 30 days	group D: placebo, n =164	primary outcome: composite of all-cause mortality, symptomatic venous or arterial thromboembolism, myocardial infarction, stroke, or hospitalization for cardiovascular or pulmonary cause primary safety: major bleeding
Ramaciotti (MICHELLE) (22)	Open-label, multicenter, randomized trial	14 centers in Brazil	318	Patients discharged after getting admitted for COVID-19 and who were identified to be at high risk for venous thromboembolism (IMPROVE VTE score of >/4 OR 2-3 with D-dimer >500ng/mL) and were given standard dose heparin as thromboprophylaxis during admission	rivaroxaban 10mg/day x 35 days (n= 160)	no anticoagulation x 35 days (n=160)	Primary efficacy outcome: composite at day 35 of symptomatic or fatal VTE, asymptomatic VTE on bilateral lower-limb venous ultrasound and pulmonary CT angiogram, symptomatic arterial thromboembolism, cardiovascular death Primary safety outcome major bleeding

Appendix 6: Assessment of risk of bias of included studies

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)	Low
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	Low
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	Low
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	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	High

		likely benefit for anticoagulation use		(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	
New studies included					
Study ID	**Directness**	**Validity**	**Results**	**Main Issues**	**Risk of Bias**
X-COVID	YES	Open label design, separate group assigned for data management and statistical analysis	Intention to treat analysis with sensitivity analysis of different components of the composite outcome	Small sample size, and slow recruitment prompted early termination of study; slightly longer median duration of treatment for interventional group as compared to control group (9 vs 7 days)	Low
COVID-HEP	Yes	Open label design, outcome assessors blinded	Intention to treat analysis for efficacy outcomes and per protocol analysis for safety outcomes	Small event rate and slow recruitment due to increased vaccination drives and decrease in cases led to early termination of the study (80% of planes sample size)	Low
Olinyk	Yes	Open label design, no mention of blinding of assessors, no mention of allocation concealment	No direct mention of intention to treat or per protocol analysis, no mention of withdrawals and reason for such	Incomplete reporting of methodology and results	High

Rashidi	Yes	Open label, no mention of allocation concealment and blinding of assessors	No description of fall-outs/withdrawals from study, very small sample size	Small sample size with some concerns in blinding and randomization process	High
BEMICOP	Yes	Open label, allocation concealment, no mention of blinding of outcome assessors	intention to treat analysis; early termination due to slow recruitment rate and futility	Allocation concealment and blinding of outcome assessors	High
PROTHROMCOVID	Yes	Open label, outcome assessor not blinded,	Intention to treat analysis, sensitivity analysis done, early termination due to drop in recruitment rate and futility	Low sample size due to early termination	Moderate
COVID-PACT	Yes (some concern as after randomization to AC, further randomization to receive antiplatelet also occurred)	Open label, no mention of allocation concealment, outcome assessors blinded	intention to treat analysis included but report highlighted on-treatment analysis; early termination due to slow recruitment from decreasing ICU admissions	majority of patients were already receiving some form of anticoagulation prior to randomization (different doses from, intermediate dose, to high)	High
OVID	Yes	Open label, allocation concealed, outcome assessors not blinded	Intention to treat analysis done	Giving of enoxaparin after the initial dose was not witnessed by investigators (either self-administered/ administered by contact of patient); early termination due to futility	Moderate
Ananworanich	Yes	Open label design, no mention of allocation concealment, no mention of blinding of outcome assessors	Intention to treat analysis with sensitivity analysis	All processes were done virtually	High
ETHIC	Yes	Open label design, no allocation concealment, blinded outcome assessors	Intention to treat analysis with sensitivity analysis	All processes were done virtually; Self administration of enoxaparin	Moderate

ACTIV-4B	Yes	Double blinded, allocation concealment, outcome assessors blinded	Not ITT	Early termination due to low event rate	Moderate
MICHELLE	Yes	Open label design, blinded adjudication	Intention to treat analysis done,	Low number of participants	Low
COVAC-TP	Yes	Open-label, single-arm multi-center study; outcome assessors blinded	Intention to treat	No randomization since single-arm design,	Moderate

Appendix 7: Forest Plots

Study or Subgroup	therapeutic dose Events	Total	prophylactic dose Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Severe disease						
COVID-HEP 2022	3	44	3	44	1.7%	1.00 [0.21, 4.69]
COVID-PACT 2022	36	191	32	191	13.0%	1.13 [0.73, 1.73]
Goligher et al 2021	199	534	200	564	25.6%	1.05 [0.90, 1.23]
HESACOVID 2020	1	10	3	10	1.0%	0.33 [0.04, 2.69]
Oliynyk 2021	17	84	14	42	8.5%	0.61 [0.33, 1.11]
Rashidi et al 2021	2	5	4	5	2.9%	0.50 [0.16, 1.59]
Subtotal (95% CI)		**868**		**856**	**52.7%**	**0.97 [0.79, 1.19]**
Total events	258		256			
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 5.72$, df = 5 (P = 0.33); $I^2 = 13\%$						
Test for overall effect: Z = 0.30 (P = 0.76)						
1.1.2 Moderate disease						
BEMICOP 2022	2	32	1	33	0.8%	2.06 [0.20, 21.64]
COVID-HEP 2022	0	35	0	36		Not estimable
Lawler et al 2021	86	1171	86	1048	19.0%	0.89 [0.67, 1.19]
PROTHROMCOVID 2022	3	103	2	104	1.3%	1.51 [0.26, 8.88]
RAPID 2021	4	228	18	237	3.4%	0.23 [0.08, 0.67]
Subtotal (95% CI)		**1569**		**1458**	**24.5%**	**0.73 [0.31, 1.72]**
Total events	95		107			
Heterogeneity: $Tau^2 = 0.39$; $Chi^2 = 6.85$, df = 3 (P = 0.08); $I^2 = 56\%$						
Test for overall effect: Z = 0.72 (P = 0.47)						
1.1.3 mixed population						
ACTION 2021	35	310	23	304	10.9%	1.49 [0.90, 2.46]
HEP-COVID 2021	25	129	31	124	11.9%	0.78 [0.49, 1.23]
Subtotal (95% CI)		**439**		**428**	**22.8%**	**1.07 [0.56, 2.03]**
Total events	60		54			
Heterogeneity: $Tau^2 = 0.16$; $Chi^2 = 3.54$, df = 1 (P = 0.06); $I^2 = 72\%$						
Test for overall effect: Z = 0.20 (P = 0.84)						
Total (95% CI)		**2876**		**2742**	**100.0%**	**0.91 [0.74, 1.12]**
Total events	413		417			
Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 17.67$, df = 11 (P = 0.09); $I^2 = 38\%$						
Test for overall effect: Z = 0.86 (P = 0.39)						
Test for subgroup differences: $Chi^2 = 0.51$, df = 2 (P = 0.78), $I^2 = 0\%$						

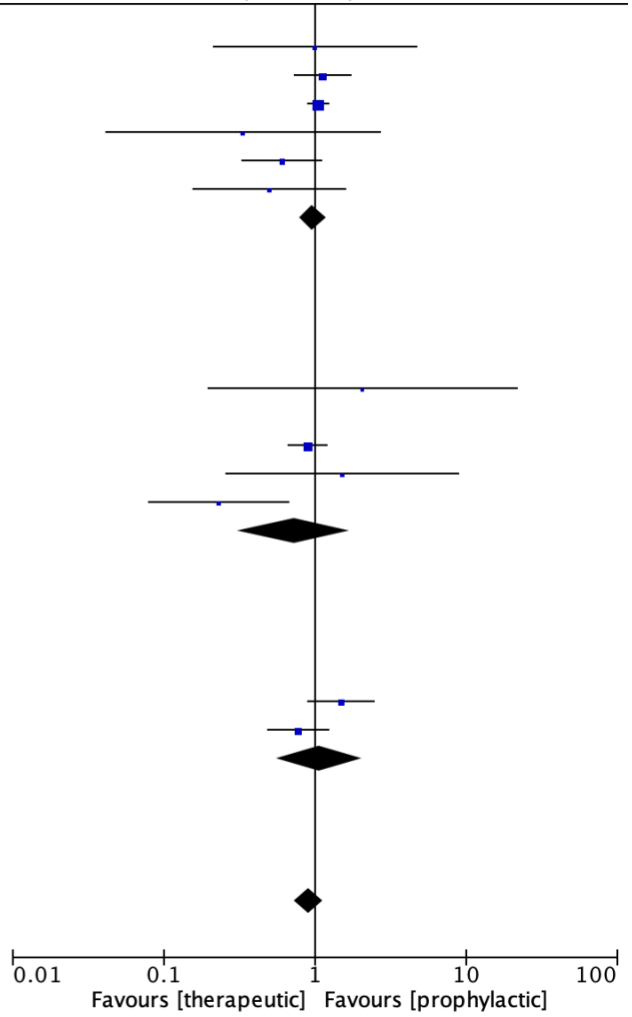


Figure 1. All-cause mortality therapeutic vs prophylactic dose AC

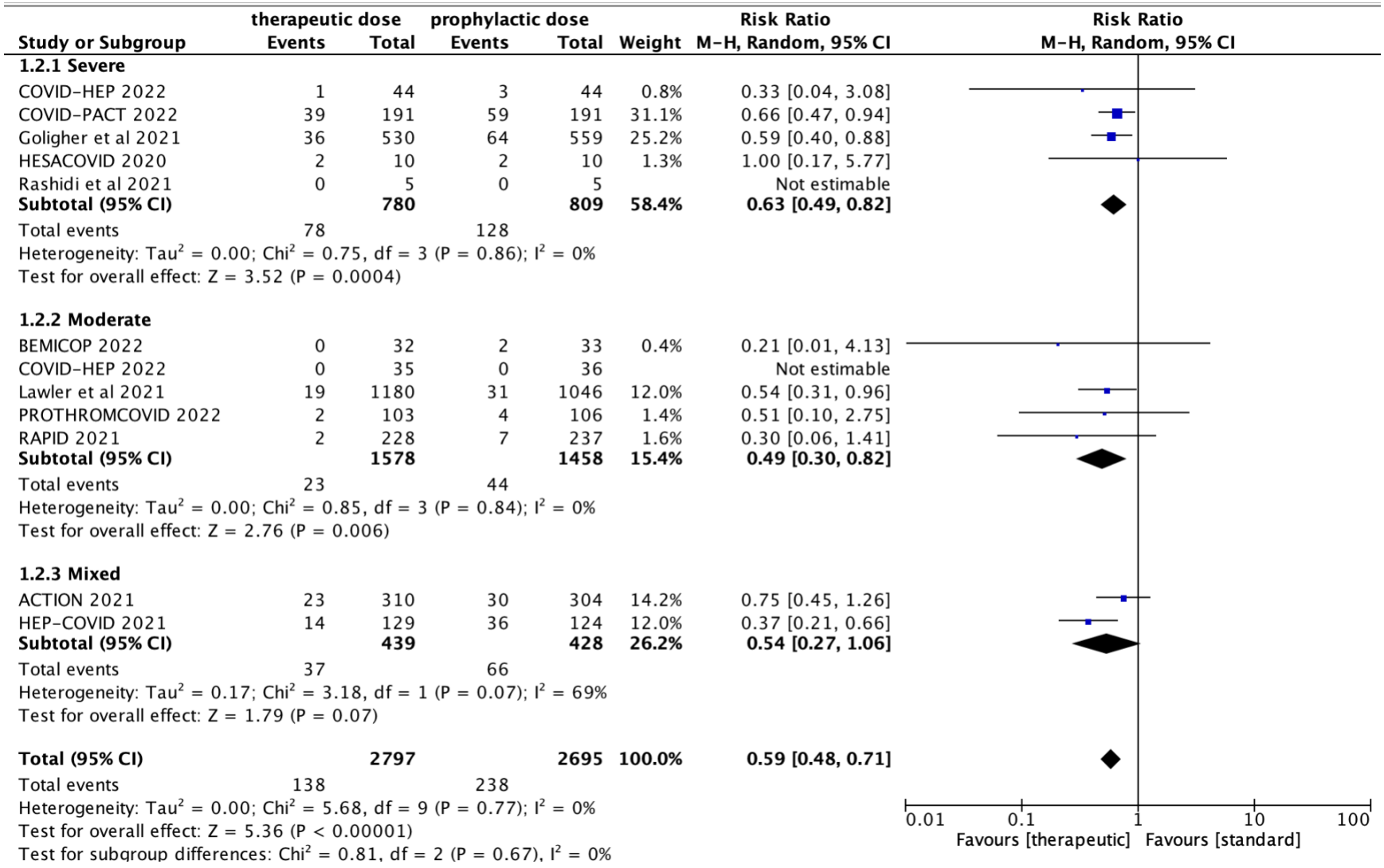


Figure 2. Any thrombotic events among those receiving therapeutic vs prophylactic AC

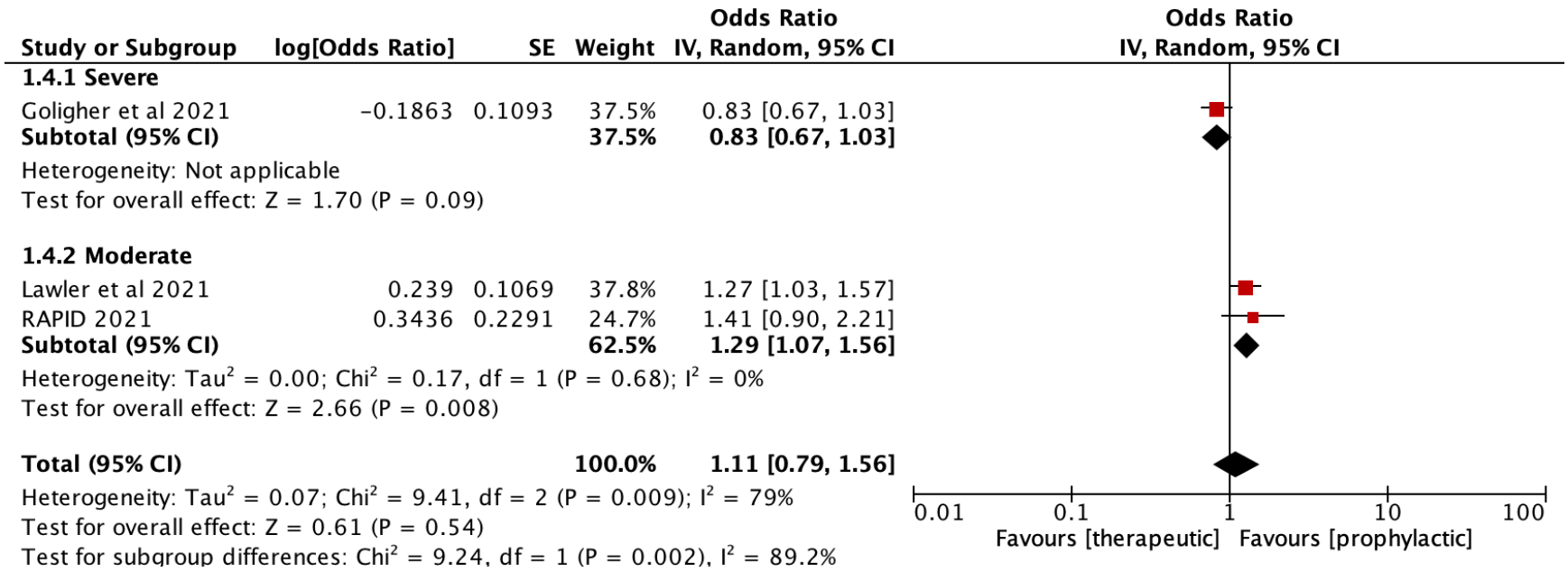


Figure 3. Organ support-free days among those receiving therapeutic vs prophylactic dose AC

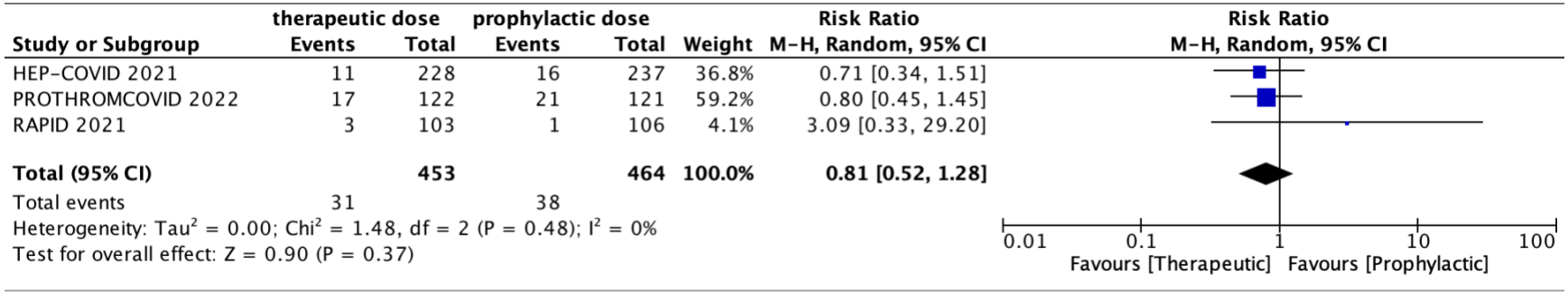


Figure 4. Need for invasive mechanical ventilation among patients with moderate COVID-19

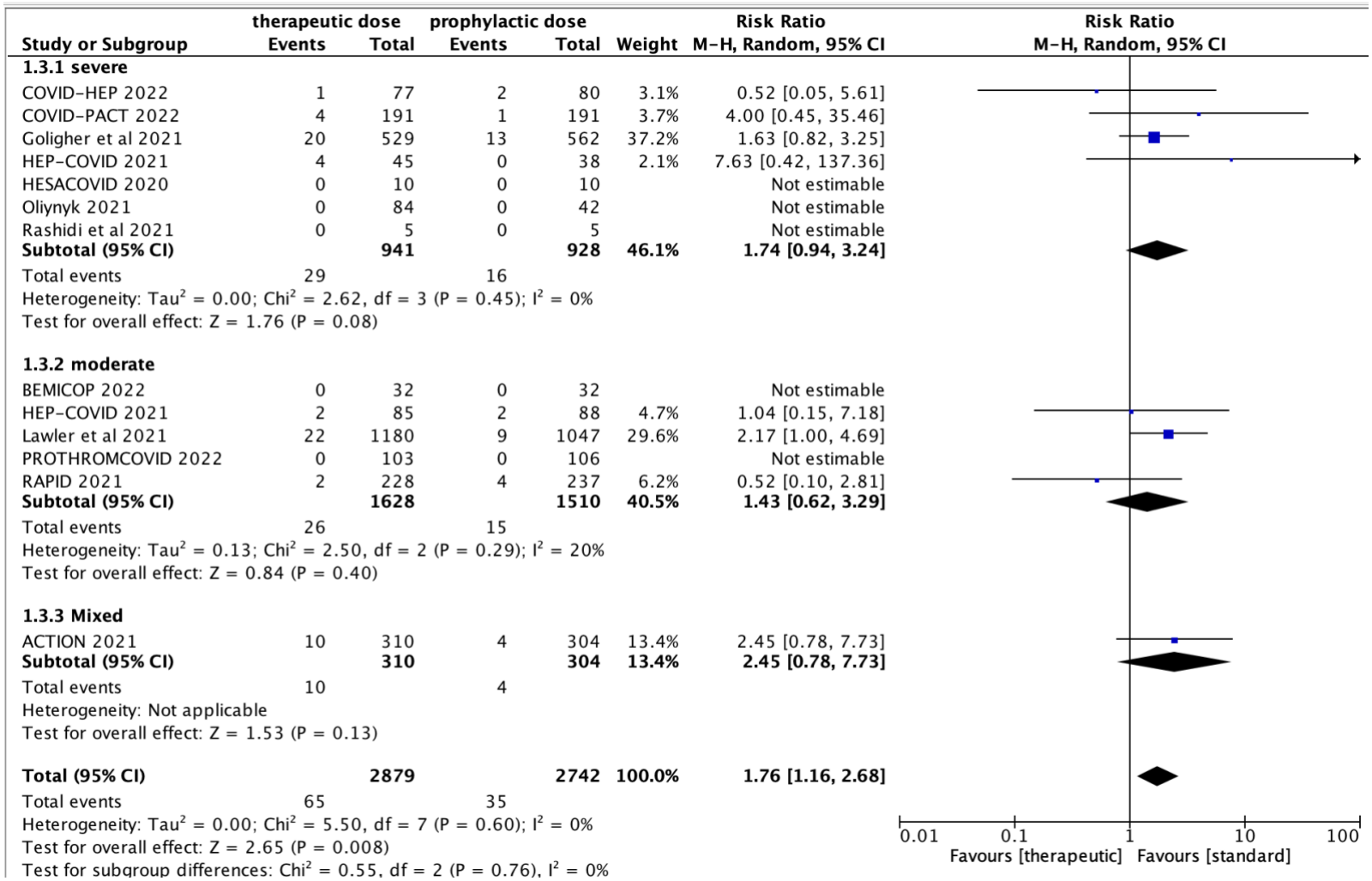


Figure 5. Major bleeding among those given therapeutic dose AC versus prophylactic dose AC

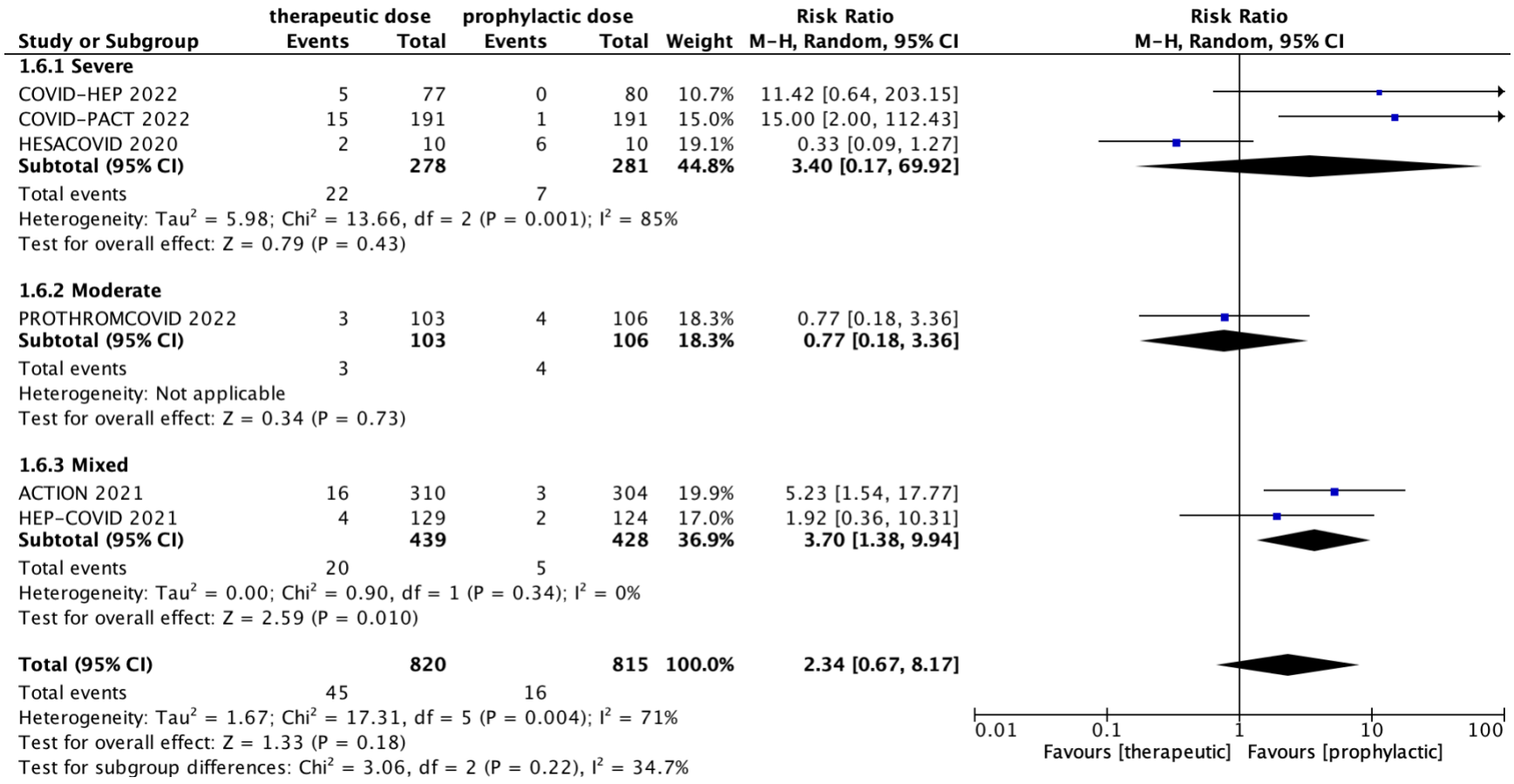


Figure 6. Any bleeding episode not considered major bleeding among those receiving therapeutic vs prophylactic dose AC

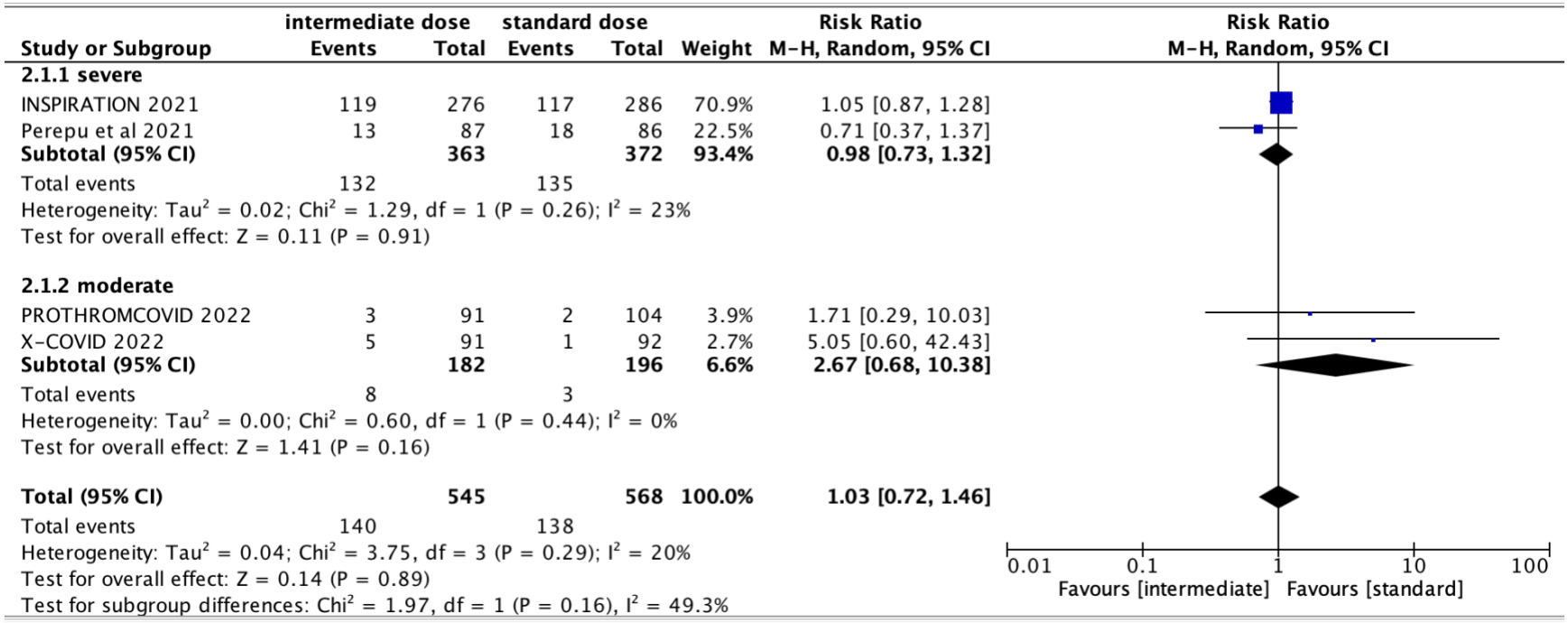


Figure 7. All-cause mortality among those receiving intermediate dose vs standard dose AC

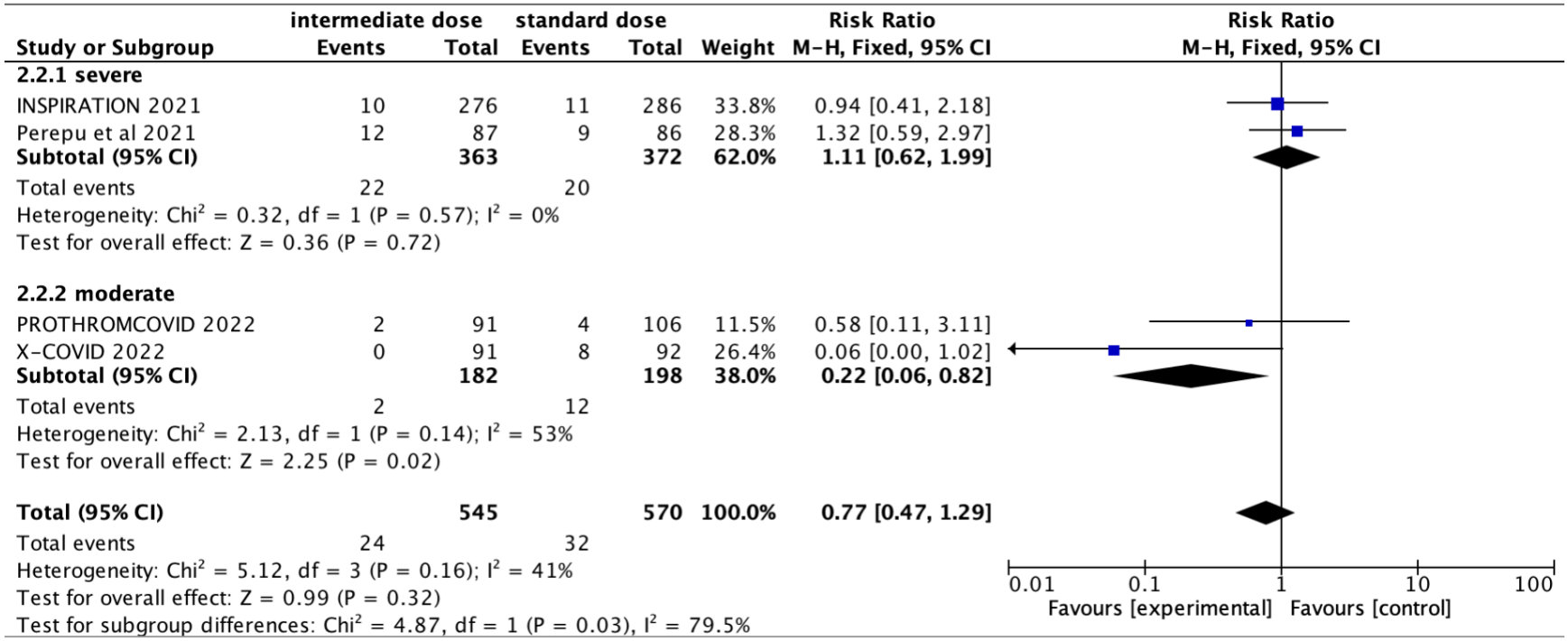


Figure 8. Thrombotic events among those receiving intermediate dose versus standard dose AC

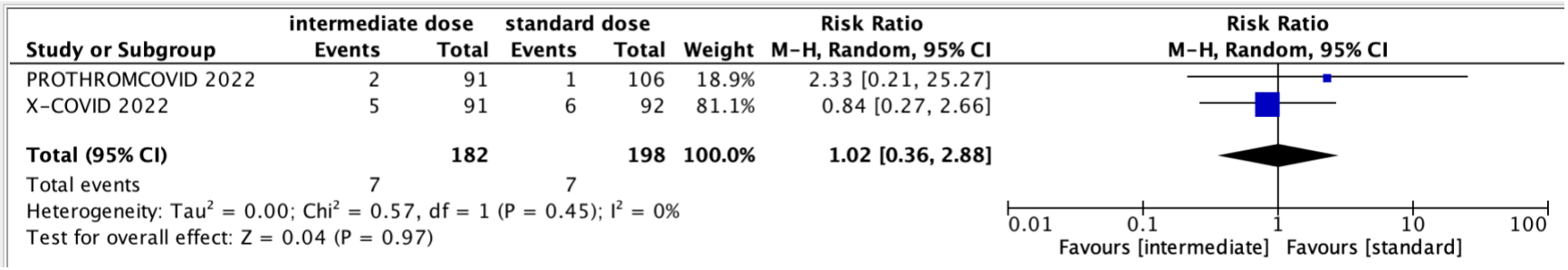


Figure 9. Need for invasive mechanical ventilation for moderate COVID-19 patients receiving intermediate vs standard dose AC

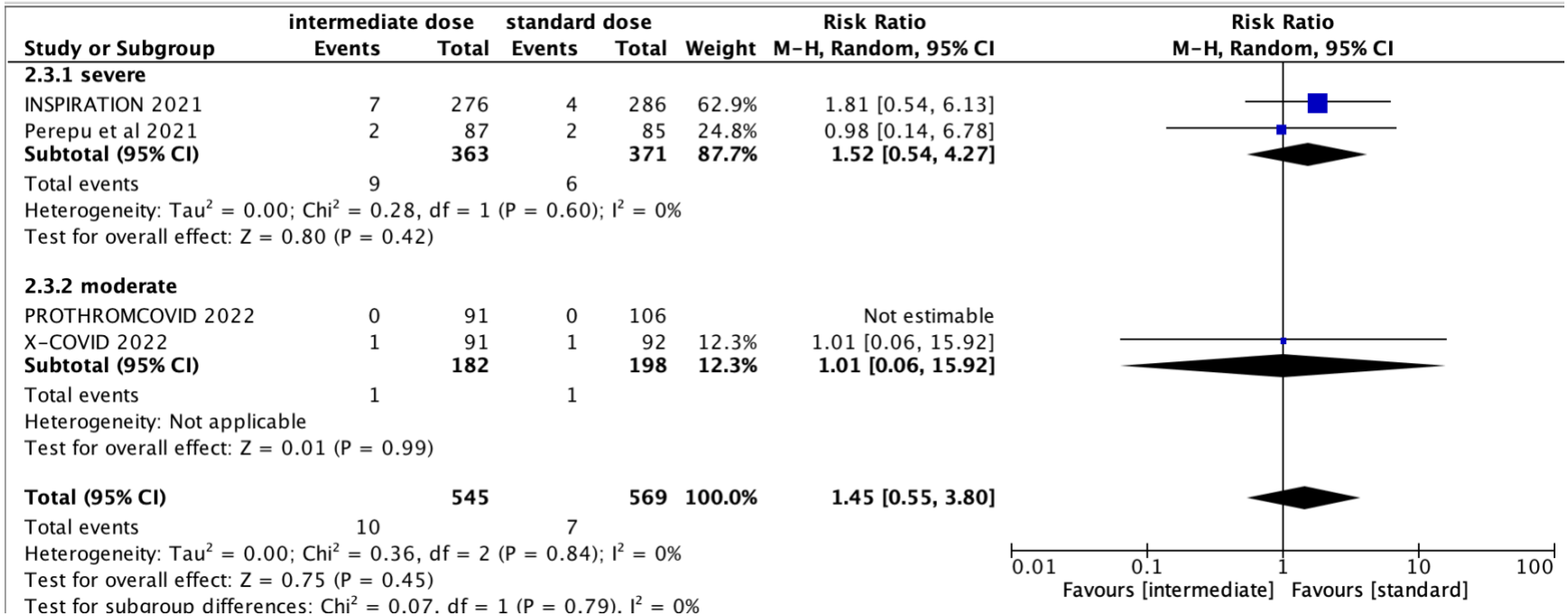


Figure 10. Major bleeding among those receiving intermediate vs standard dose AC

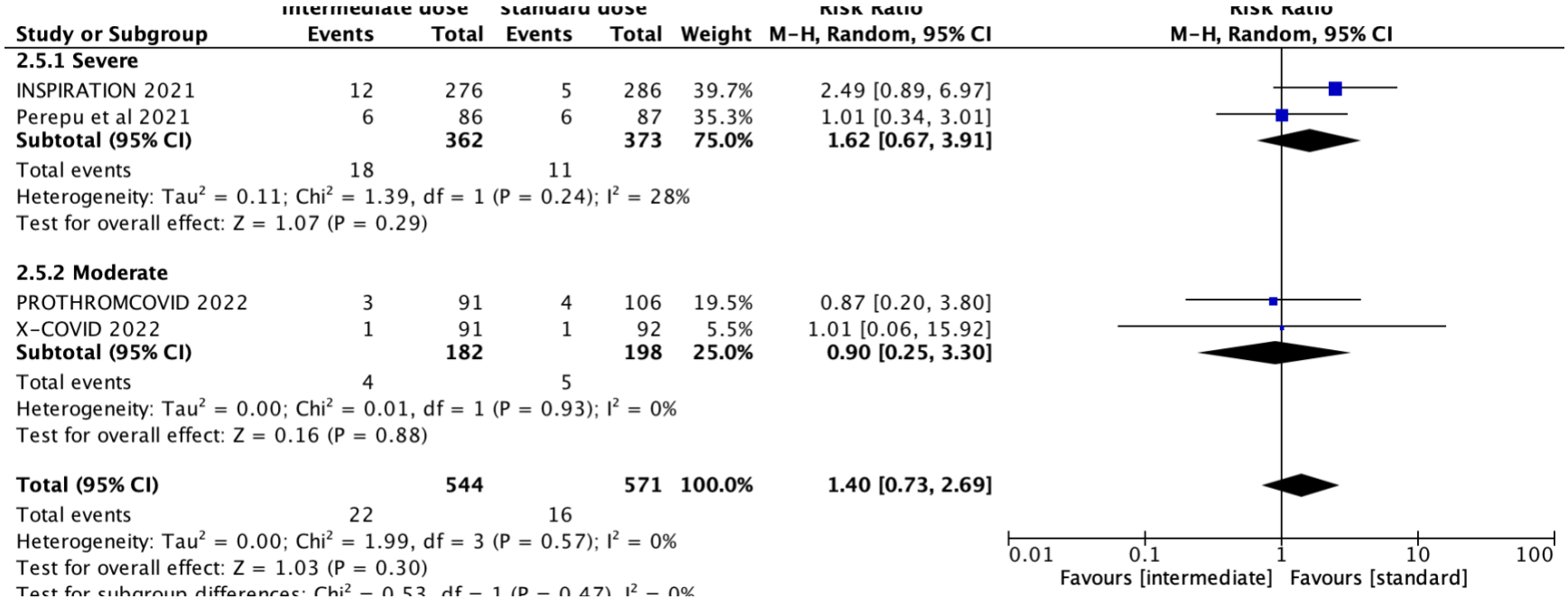


Figure 11. Any bleeding not considered major among those receiving intermediate dose vs standard dose AC

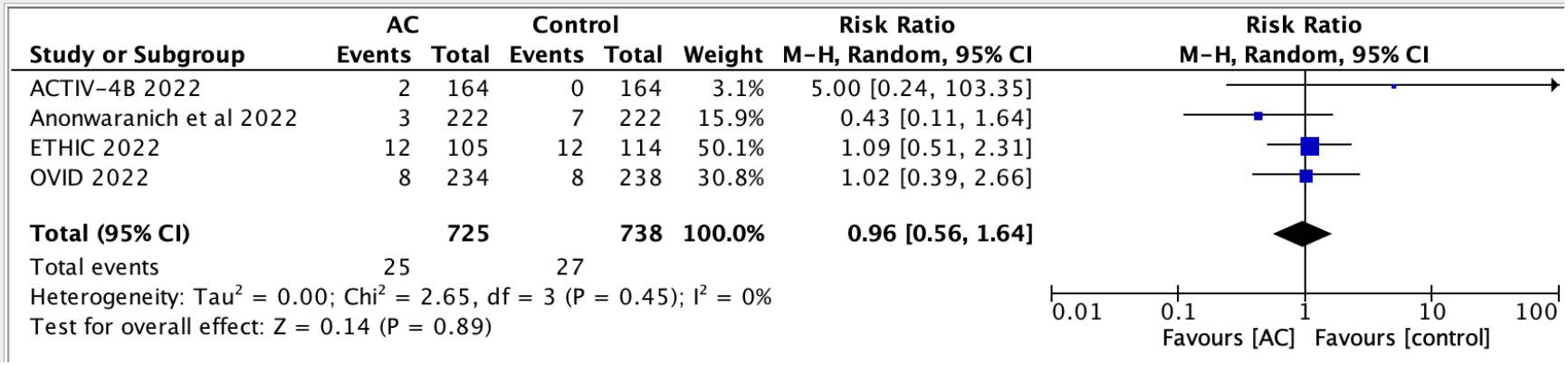


Figure 12. All-cause hospitalization for patients with mild COVID-19 receiving AC versus standard of care (SoC)

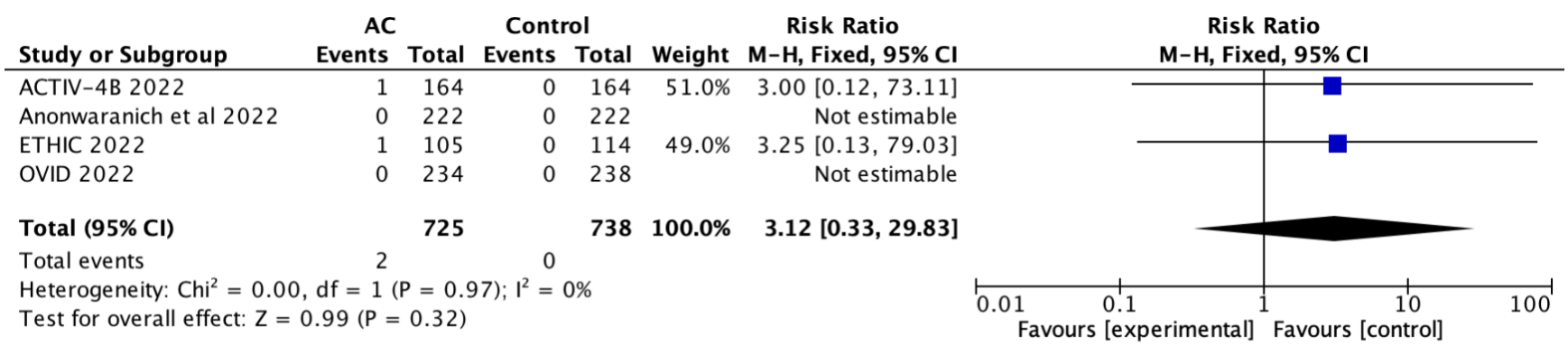


Figure 13. All-cause mortality among patients with mild COVID-19 receiving AC versus SoC

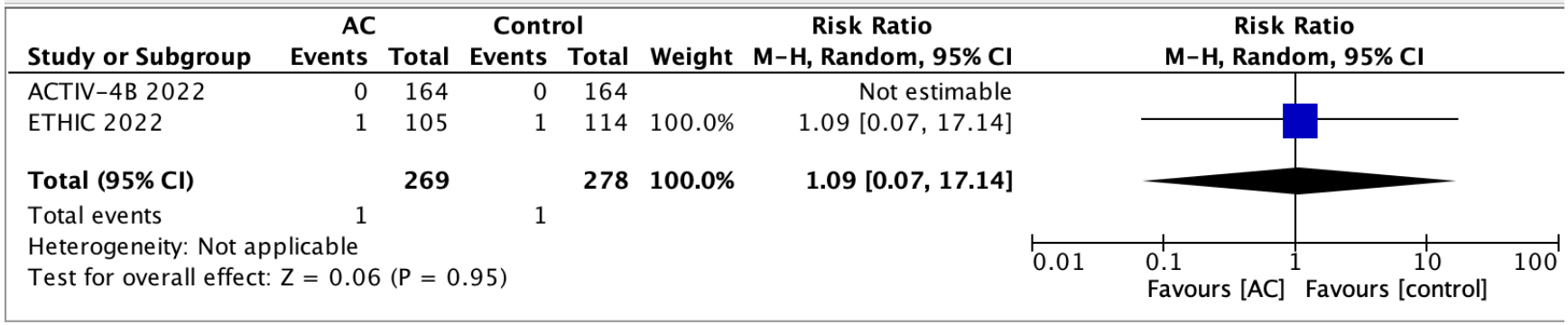


Figure 14. Any thrombotic events among those with mild COVID-19 given AV vs SoC

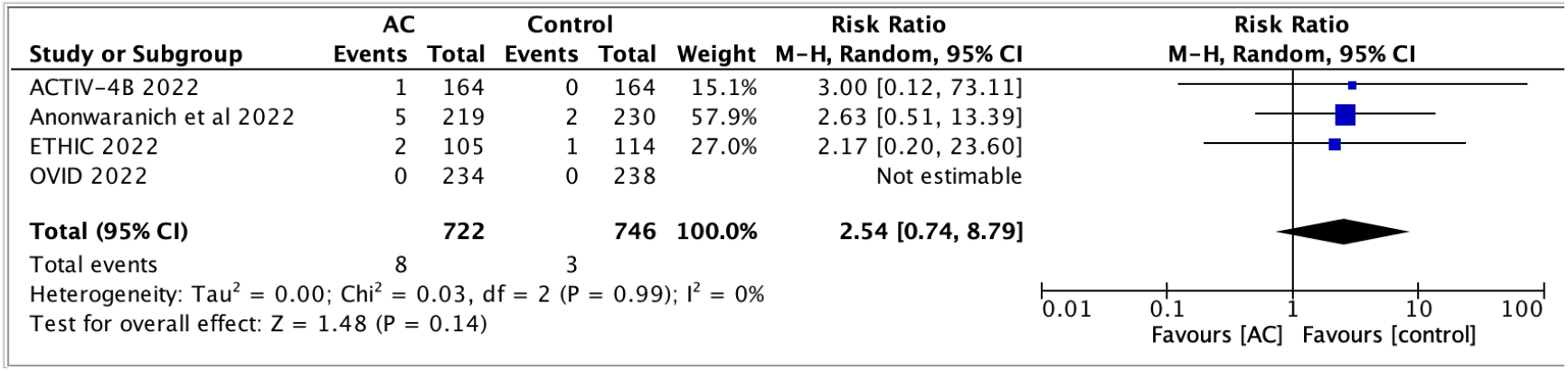


Figure 15. Any bleeding events among mild COVID-19 patients receiving AC vs SoC

Appendix 8: GRADE Evidence Profile Tables

Table 2. GRADE evidence profile for critical outcomes among those receiving therapeutic dose AC versus prophylactic dose AC

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Therapeutic dose	prophylactic dose AC	Relative (95% CI)	Absolute (95% CI)		
all-cause mortality												
12	randomised trials	serious[a]	not serious	not serious	serious[b]	none	413/2876 (14.4%)	417/2742 (15.2%)	**RR 0.91** (0.74 to 1.12)	**14 fewer per 1,000** (from 40 fewer to 18 more)	⨁⨁◯◯ Low	CRITICAL
Any Thrombotic events												
11	randomised trials	serious[a]	not serious	not serious	not serious	none	138/2797 (4.9%)	238/2695 (8.8%)	**RR 0.59** (0.48 to 0.71)	**36 fewer per 1,000** (from 46 fewer to 26 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
Major Bleeding												
12	randomised trials	serious[a]	not serious	not serious	not serious	none	65/2879 (2.3%)	35/2742 (1.3%)	**RR 1.76** (1.16 to 2.68)	**10 more per 1,000** (from 2 more to 21 more)	⨁⨁⨁◯ Moderate	CRITICAL

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

Explanations

a. some studies included have moderate to high risk of bias due to allocation concealment issues, blinding of outcome assessors and reporting of results

Table 3. GRADE evidence profile for other outcomes among those receiving therapeutic versus prophylactic dose AC

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Therapeutic dose	prophylactic dose AC (continuation)	Relative (95% CI)	Absolute (95% CI)		
organ support-free days												
3	randomised trials	serious[a]	serious[b]	not serious	serious[c]	none	organ support free-days on day 21 reported among the 3 studies with OR of 1.11 (95% CI, 0.79- 1.56),				⨁◯◯◯ Very low	IMPORTANT
Need for invasive mechanical ventilation												
3	randomised trials	serious[d]	not serious	not serious	serious[c]	none	31/453 (6.8%)	38/464 (8.2%)	**RR 0.81** (0.52 to 1.28)	**16 fewer per 1,000** (from 39 fewer to 23 more)	⨁⨁◯◯ Low	CRITICAL
Bleeding not considered major												
6	randomised trials	serious[e]	serious[b]	not serious	serious[c]	none	45/820 (5.5%)	16/815 (2.0%)	**RR 2.34** (0.67 to 8.17)	**26 more per 1,000** (from 6 fewer to 141 more)	⨁◯◯◯ Very low	IMPORTANT

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

Explanations

a. ones study with high risk of bias for concerns for attrition and selective reporting bias which contributed to a third of the total weight of the pooled result
b. different trends among studies
c. wide confidence interval
d. one study contributing to more than a third of the weight of the pooled result had a high risk of bias due to concerns for selective reporting and enrollment of participants more likely to benefit from intervention
e. two studies with high risk of bias
c. one study contributing to more than a third of the weight of the pooled result had a high risk of bias due to concerns for selective reporting and enrollment of participants more likely to benefit from intervention
d. two studies with high risk of bias

Table 4. GRADE evidence profile for critical outcomes among those receiving intermediate dose versus standard dose AC

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intermediate dose	standard dose prophylaxis	Relative (95% CI)	Absolute (95% CI)		
all-cause mortality												
4	randomised trials	serious[a]	not serious	not serious	serious[b]	none	140/545 (25.7%)	138/568 (24.3%)	**RR 1.03** (0.72 to 1.46)	**7 more per 1,000** (from 68 fewer to 112 more)	⨁⨁◯◯ Low	CRITICAL
any thrombotic event												
4	randomised trials	serious[a]	not serious	not serious	serious[b]	none	24/545 (4.4%)	32/570 (5.6%)	**OR 0.76** (0.44 to 1.31)	**13 fewer per 1,000** (from 31 fewer to 16 more)	⨁⨁◯◯ Low	CRITICAL
major bleeding												
4	randomised trials	serious[a]	not serious	not serious	serious[c]	none	10/545 (1.8%)	7/569 (1.2%)	**RR 1.45** (0.55 to 3.80)	**6 more per 1,000** (from 6 fewer to 34 more)	⨁⨁◯◯ Low	CRITICAL

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

Explanations

a. one study had a high risk of bias for selection bias as they enrolled patients who are also part of other covid-19 trials, and also at high risk for detection bias. This study had the second highest weight among the pooled results so downgrading is deemed necessary
b. wide confidence interval for overall result. One study had only one event for both the treatment and control arm. Another study had no events

Table 5. Other outcomes for those receiving intermediate dose versus standard dose AC

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intermediate dose	standard dose prophylaxis (continuation)	Relative (95% CI)	Absolute (95% CI)		
Need for invasive mechanical ventilation												
2	randomised trials	not serious	not serious	not serious	serious[a]	none	7/182 (3.8%)	7/198 (3.5%)	**RR 1.02** (0.36 to 2.88)	**1 more per 1,000** (from 23 fewer to 66 more)	⨁⨁⨁◯ Moderate	CRITICAL
Any bleeding not considered major bleeding												
4	randomised trials	serious[b]	not serious	not serious	serious[a]	none	22/544 (4.0%)	16/571 (2.8%)	**RR 1.40** (0.73 to 2.69)	**11 more per 1,000** (from 8 fewer to 47 more)	⨁⨁◯◯ Low	IMPORTANT
Heparin induced thrombocytopenia (HIT)												
2	randomised trials	not serious	not serious	not serious	serious[c]	none	70/367 (19.1%)	77/378 (20.4%)	**RR 0.94** (0.71 to 1.24)	**12 fewer per 1,000** (from 59 fewer to 49 more)	⨁⨁⨁◯ Moderate	IMPORTANT

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

Explanations

a. wide confidence interval due to low event rates
b. one study with high risk of bias due to concerns for selection and detection bias contributing to a third of the weight of the pooled result
c. one study with no event for both groups (i.e. inestimable effect), result mainly form one study

Table 6. GRADE evidence profile for AC use among patients with mild COVID-19

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	AC	placebo in outpatient setting	Relative (95% CI)	Absolute (95% CI)		
all-cause hospitalization												
4	randomised trials	serious[a]	not serious	not serious	serious[b]	none	25/725 (3.4%)	27/738 (3.7%)	**RR 0.96** (0.56 to 1.64)	**1 fewer per 1,000** (from 16 fewer to 23 more)	⨁⨁◯◯ Low	CRITICAL
all-cause death												
4	randomised trials	serious[a]	not serious	not serious	serious[b]	none	2/725 (0.3%)	0/738 (0.0%)	**OR 3.15** (0.33 to 30.48)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁⨁◯◯ Low	CRITICAL
thrombotic events												
2	randomised trials	not serious	not serious	not serious	serious[c]	none	1/269 (0.4%)	1/278 (0.4%)	**RR 1.09** (0.07 to 17.14)	**0 fewer per 1,000** (from 3 fewer to 58 more)	⨁⨁⨁◯ Moderate	CRITICAL
any bleeding												
4	randomised trials	serious[a]	not serious	not serious	serious[d]	none	8/722 (1.1%)	3/746 (0.4%)	**RR 2.54** (0.74 to 8.79)	**6 more per 1,000** (from 1 fewer to 31 more)	⨁⨁◯◯ Low	CRITICAL

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

Explanations

a. one study had high risk of bias for selection and detection bias, while three studies had moderate risk of bias for selection, detection and attrition bias
b. wide confidence interval
c. wide confidence interval overall, one study had no events for both groups while the other study had one event per comparison group
d. wide confidence interval due to overall low event rate

Table 7. GRADE evidence profile for AC use post-discharge

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	anticoagulation	no anticoagulation	Relative (95% CI)	Absolute (95% CI)		
Pooled fatal, symptomatic or asymptomatic venous or arterial thrombotic events at day 35												
1	randomised trials	not serious	not serious	not serious	serious[a]	publication bias strongly suspected[b]	5/159 (3.1%)	15/159 (9.4%)	**RR 0.33** (0.13 to 0.90)	**63 fewer per 1,000** (from 82 fewer to 9 fewer)	⨁⨁◯◯ Low	IMPORTANT
symptomatic and fatal VTE												
1	randomised trials	not serious	not serious	not serious	serious[a]	publication bias strongly suspected[b]	1/159 (0.6%)	8/159 (5.0%)	**RR 0.13** (0.02 to 0.99)	**44 fewer per 1,000** (from 49 fewer to 1 fewer)	⨁⨁◯◯ Low	CRITICAL
Major bleeding												
1	randomised trials	not serious	not serious	not serious	not serious	publication bias strongly suspected[b]	No bleeding events noted among two groups				⨁⨁⨁◯ Moderate	CRITICAL

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

Explanations

a. wide confidence interval
b. based only on one study

Table 8. GRADE evidence profile for AC use among pediatric population

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Significant bleeding									
1	randomised trials	serious[a]	not serious	not serious	serious[b]	publication bias strongly suspected[c]	no patients developed significant bleeding episodes	⊕◯◯◯ Very low	CRITICAL
VTE									
1	randomised trials	serious[a]	not serious	not serious	serious[b]	publication bias strongly suspected[c]	2 of 38 developed VTE (5.2%)	⊕◯◯◯ Very low	CRITICAL
Mortality									
1	randomised trials	serious[a]	not serious	not serious	serious[b]	publication bias strongly suspected[c]	1 of 38 died due to primary COVID-19 (2.6%)	⊕◯◯◯ Very low	CRITICAL

CI: confidence interval

Explanations

a. single-arm, no randomization
b. low sample size
c. basis only from one study

Appendix 9: Ongoing studies (n=16)

Title Identifier Expected completion date	Intervention	Comparator	Patients/population recruited	Outcome
ANTIcoagulation in severe COVID-19 patients (ANTICOVID) Completed March 13, 2022 but no results posted https://ClinicalTrials.gov/show/NCT04808882	Drug: Tinzaparin, Therapeutic anticoagulation	Drug Tinzaparin, 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 Critically Ill Patients With COVID-19 (The IMPACT Trial) December 2023 https://ClinicalTrials.gov/show/NCT04406389	Therapeutic dose Drug: Enoxaparin sodium| Drug: Unfractionated heparin| Drug: Fondaparinux| Drug: Argatroban	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
Hamburg Edoxaban for Anticoagulation in COVID-19 Study (HERO-19) September 2022 (current status: recruiting) 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

Safety and Efficacy of Therapeutic Anticoagulation on Clinical Outcomes in Hospitalized Patients With COVID-19 June 1, 2022 (current status: recruiting) https://ClinicalTrials.gov/show/NCT04377997	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, 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) Completed but report ongoing quality control review 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) July 2022 (current status: recruiting) 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	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

Admitted With COVID-19 Pneumonia (PROTHROMCOVID) Completed, last update posted September 15, 2022 no posted results/report yet https://ClinicalTrials.gov/show/NCT04730856				
Tenecteplase in Patients With COVID-19 Completed, last update posted July 2022 but no result/report posted yet https://ClinicalTrials.gov/show/NCT04505592	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 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
Australasian COVID-19 Trial ADAptive Platform Trial (ASCOT ADAPT) December 31, 2024 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
Clinical Efficacy of Heparin and Tocilizumab in Patients With Severe COVID-19 Infection (HEPMAB) completed but no result posted (last update March 18, 2022) 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
Hemostasis in COVID-19: an Adaptive Clinical Trial May 30,2022 Current status: recruiting, last update posted June 9, 2021 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
Factor Xa inhibitor versus SoC Heparin in Hospitalized patients with COVID-19 (XACT trial) Recruitment status completed, last update poted June 30, 2021	Drug: Enoxaparin Subcutaneous enoxaparin While hospitalized only.	Active Comparator: Adaptive Dosing: Enoxaparin Low 40mg subcutaneous (SQ) daily	18 Years to 100 Years	Death or 30-day all-cause mortality Mechanical ventilation, intubation Transfer to ICU setting

No results posted NCT04640181	Drug: Rivaroxaban Oral rivaroxaban While hospitalized and through discharge for a total of 28 days.	Intermediate 40mg SQ q12 hours, or Therapeutic 1mg/kg SQ q12 hours Intervention: Drug: Enoxaparin Active Comparator: Adaptive Dosing: Rivaroxaban low 10mg po daily Intermediate 10mg po daily Therapeutic 20mg po daily		
COVID-19 Post-hospital Thrombosis Prevention Trial: An Adaptive, Multicenter, Prospective, Randomized Platform Trial Evaluating the Efficacy and Safety of Antithrombotic Strategies in Patients With COVID-19 Following Hospital Discharge Completed: September 23, 2022 (no result posted yet) Activ4CC NCT04650087	Apixaban 2.5mg	Placebo	18 Years and older hospitalized for two or more days	Composite outcome of symptomatic deep vein thrombosis, pulmonary embolism, other venous thromboembolism, ischemic stroke, myocardial infarction, other arterial thromboembolism, and all-cause mortality as measured by hospital records. [Time Frame: 30 days after hospital discharge]

HElping Alleviate the Longer-term Consequences of COVID-19 (HEAL-COVID): a National Platform Trial HEAL-COVID NCT04801940 Current status: recruiting Expected completion: January 31, 2024	Apixaban Atorvastatin	Standard of care	18 years and older, hospitalized but expected to be discharged within 5 days	Hospital free survival