UiT The Arctic University of Norway

Faculty of Health Sciences

Efficacy and safety of escalated versus standard prophylactic anticoagulation in patients with Covid-19: A literature review and meta-analysis

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1 Preface

The aim of this master thesis is to summarize and create an overview of the available randomized controlled trials (RCTs) studying the clinical effect and safety of escalated prophylactic doses compared to standard prophylactic doses in hospitalized COVID-19 patients.

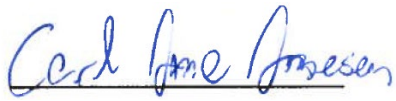
My interest in clinical epidemiology and venous thromboembolism started in 2018, when I was accepted to the integrated research program at the medical studies in Tromsø. I had a full year of research in 2019/2020 as a part of K.G Jebsen – Thrombosis Research and Expertise Center (TREC). The Coronavirus pandemic began during my research year, and after the national lockdown commenced in March 2020, I started working at the Corona Centre in Tromsø municipality as an infection tracker. I chose to take advantage of my experience with both venous thromboembolism (VTE) and the Coronavirus pandemic when choosing the subject for my master thesis.

The writing of this thesis has given me the opportunity to learn more about the methodological and statistical considerations that are involved in literature reviews and meta-analyses. I am certain that this thesis has provided me with valuable knowledge and skills that I will take advantage of in my future scientific and clinical work.

I would like to thank my supervisor, Professor Sigrid Kufaas Brækkan, for great help and constructive feedback during the writing process, especially during the latter stages. She is always available for feedback and guidance, no matter how busy her schedule is, and has been essential in both the writing of this thesis and my other research work.

Finally, I am grateful and privileged to be part of the TREC-team.

Carl Arne Løchen Arnesen



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2 Summary

Background: Coronavirus disease 2019 (COVID-19) is known to increase the risk of venous thromboembolism (VTE), and studies have shown a three-fold increase in VTE-risk in hospitalized COVID-19 patients compared to similar respiratory infections. Standard dose thromboprophylaxis is recommended in all hospitalized COVID-19 patients. However, despite prophylaxis, VTE incidence remains high. Several randomized controlled trials (RCTs) have studied the effect of escalated doses of thromboprophylaxis, but they have produced conflicting results, and have not been adequately powered to assess the outcomes VTE, major bleeding and all-cause mortality.

Aim: To conduct a literature review and meta-analysis of RCTs, comparing the effect of escalated versus standard doses of prophylactic anticoagulation in hospitalized COVID-19 patients admitted to an intensive care unit (ICU) or non-ICU, focusing on VTE, major bleeding and all-cause mortality.

Methods: A structured literature search was performed to retrieve RCTs investigating the safety and efficacy of escalated versus standard doses of prophylactic anticoagulation in hospitalized COVID-19-patients. The trials were analyzed in overall populations, and subgroups based on clinical setting (ICU/non-ICU). Risk ratios (RRs) with 95% Confidence intervals (95% CI) for VTE, death and major bleeding were extracted, and pooled results were calculated and displayed in forest plots.

Results: In the meta-analysis, 9 RCTs were included (n=5,658). Compared to standard dose, escalated dose prophylactic anticoagulation was associated with an overall reduction in VTE risk (RR: 0.49, 95% CI: 0.38-0.64), an increase in major bleeding risk (RR: 1.76, 95% CI: 1.19-2.59) and no difference in mortality (RR: 0.98, 95% CI: 0.88-1.09). In subgroup analysis based on clinical setting, estimates indicated a further reduction in VTE risk and all-cause mortality in non-ICU-patients compared to ICU-patients. However, these differences did not reach statistical significance.

Conclusion: Escalated doses of prophylactic anticoagulation was associated with a reduction in VTE-risk, increased major bleeding and no effect on all-cause mortality.

3 Abbreviations

95% CI – 95% confidence interval

ARDS – Acute respiratory Distress Syndrome

ASH – American society of hematology

AT – Antithrombin

ATE – Arterial thromboembolism

COPD – Chronic obstructive pulmonary disease

COVID-19 – Coronavirus disease 2019

DIC – Disseminated intravascular coagulation

DOAC – Direct oral anticoagulant

DVT – Deep vein thrombosis

ECMO - Extracorporeal membrane oxygenation

HR – Hazard ratio

ICU – Intensive care unit

LMWH – low-molecular weight heparin

OR – Odds ratio

PICOS – Population, Intervention, Comparison, Objective, Study design

PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses

RAM – Risk assessment model

RCT – Randomized controlled trial

RR – Risk ratio

SARS-CoV-2 – Severe acute respiratory syndrome coronavirus 2

UFH – unfractionated heparin

VTE – Venous thromboembolism

4 Introduction

4.1 Covid-19

Coronavirus disease 2019 (COVID-19) is a respiratory and vascular disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1). The disease was discovered in Wuhan, China in December 2019, and quickly spread worldwide, leading to the COVID-19 pandemic (2). As of April 30th 2022 there are more than 500 million confirmed cases, and more than 6.2 million confirmed deaths associated with the virus (3). SARS-CoV-2 is a virus of the Corona group which primarily attacks the epithelium and can result in acute respiratory distress syndrome (ARDS) (4). The virus can also infect many other cell types, causing systemic inflammation with cytokine release and affects multiple critical organs besides the lungs in severe cases (4). The most common symptoms are fever, cough, tiredness and loss of taste or smell, while more serious symptoms are shortness of breath, chest pain, loss of mobility and confusion (5). The severity of disease has varied greatly between individuals from the start (6). Chinese data from February 2020 indicated that around 80% of infections were mild or asymptomatic, 15% developed severe infections with need for oxygen treatment, while less than 5% got critically ill and were in need of ventilation treatment (6). Official American estimates from May 2020 reported that 14% of all who tested positive were hospitalized, 2 % were admitted to the intensive care unit (ICU) and 5% died (7). The most vulnerable are people with advanced age and comorbidities such as cancer, heart conditions and respiratory illnesses such as asthma and chronic obstructive pulmonary disease (COPD) (6). Cardiovascular complications and thromboembolic events have been particularly common and contributed to increased mortality and morbidity (8, 9). The severity of COVID has diminished considerably with time due to more knowledge about the disease, better treatment, virus mutation, infection-induced immunity, and vaccine immunity (10).

The treatment of COVID-19 is still a topic of some discussion, but some effective treatments have been identified (illustration 1) (11). A meta-analysis of randomized controlled trials (RCT) conducted in critically ill COVID-patients, found that the glucocortico-steroid dexamethasone reduced mortality compared to standard care with an odds ratio of 0.66 (95% confidence interval (95% CI): 0.53-0.82) (12). Furthermore, the antiviral therapies remdesivir, tocilizumab and baricitinib have shown possible clinical benefits (13), while prophylactic

anticoagulation, NSAIDs and oxygen treatment are viewed as important additional treatment in hospitalized COVID-patients (11).

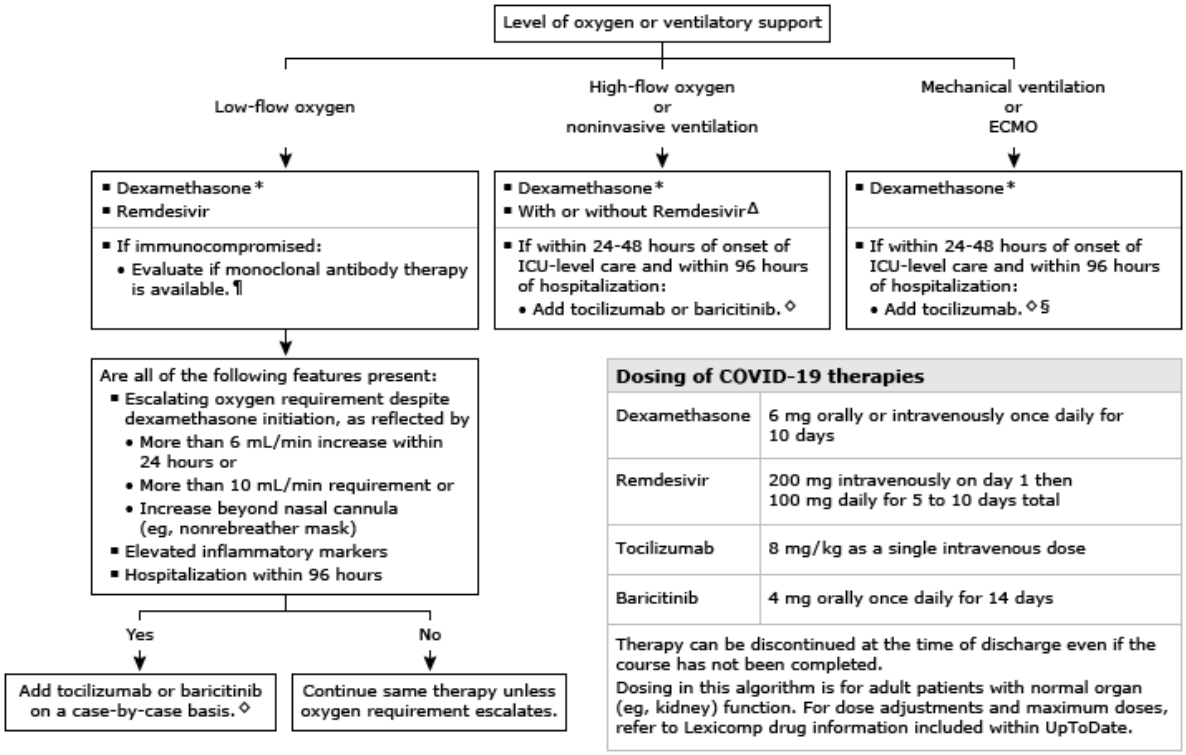

Illustration 1: Treatment algorithm for COVID-19 (11)

4.2 Venous thromboembolism

Venous thromboembolism (VTE) is a common disorder that has an annual incidence of 1-2 per 1000 individuals in the general population. Although it can occur at all ages, the incidence increases markedly with age (14, 15). VTE is a major cause of morbidity and mortality and is the third most common life-threatening cardiovascular disease after myocardial infarction and stroke (16). Common risk factors for VTE are cancer, infection, surgery, immobility, trauma and pregnancy (14), and it is a condition that often affects critically ill patients, and severely affects their potential to recover (17).

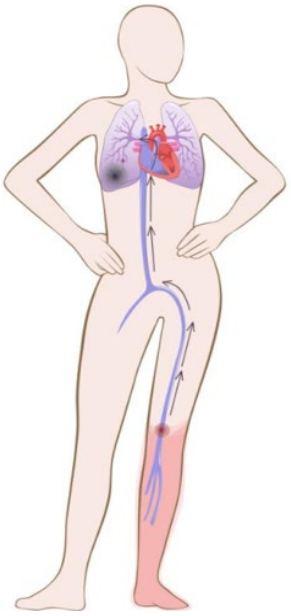

Illustration 2: Venous thromboembolism

VTE usually manifests as either deep vein thrombosis (DVT) or pulmonary embolism (PE). DVT refers to the formation of a blood clot (thrombus) in the deep veins, and usually affects the large veins of the leg or thigh (illustration 2) (18). PE occurs when a blood clot dislodges from its original site and embolize to

the arterial blood supply of the lungs (18). Both conditions are collectively referred to as VTE, since they share the same underlying pathology, and often occur simultaneously in both locations, though often clinically silent in one of the locations (19). VTE has a one-week fatality rate of 5-10%, and especially PE is a potentially deadly condition, with 25% of all cases of PE essentially presenting as sudden death (20).

4.3 Medical conditions, hospitalization and VTE

Hospitalization for medical conditions is a well-established risk factor for VTE (21). Studies have indicated that 22% of all VTE events occur in relation to current or recent hospital admission for acute medical illness and is thus considered preventable (22). Additionally, more than 70% of all VTE-related deaths are estimated to result from hospital-acquired VTE (23), and three-quarters of these deaths occur in medical patients (24). The prevalence of VTE in patients hospitalized with respiratory diseases such as COPD has been estimated to be as high as 25% (24). Additionally, 15% of patients hospitalized due to an infectious disease without prophylactic treatment sustained a VTE, and several studies have reported that respiratory diseases are associated with a two-fold increase in VTE risk (24-27).

4.4 Medical thromboprophylaxis

Medical thromboprophylaxis is a treatment that aims to prevent the development of thrombi in patients that are considered at risk (22). Due to the substantial morbidity and mortality risk of VTE, medical thromboprophylaxis is recommended (22) and used (28) in the treatment of hospitalized patents, and studies have shown a significant reduction in VTE-incidence when using medical thromboprophylaxis (29). Anticoagulants, which works through targeting coagulation factors in the coagulation cascade (illustration 3), is the recommended treatment for hospitalized patients (30). However, any anticoagulant treatment is associated with an increased risk of major bleeding (4 per 1000) (31). Therefore, risk assessment of patients based on known VTE risk factors is recommended to evaluate the need for thromboprophylaxis

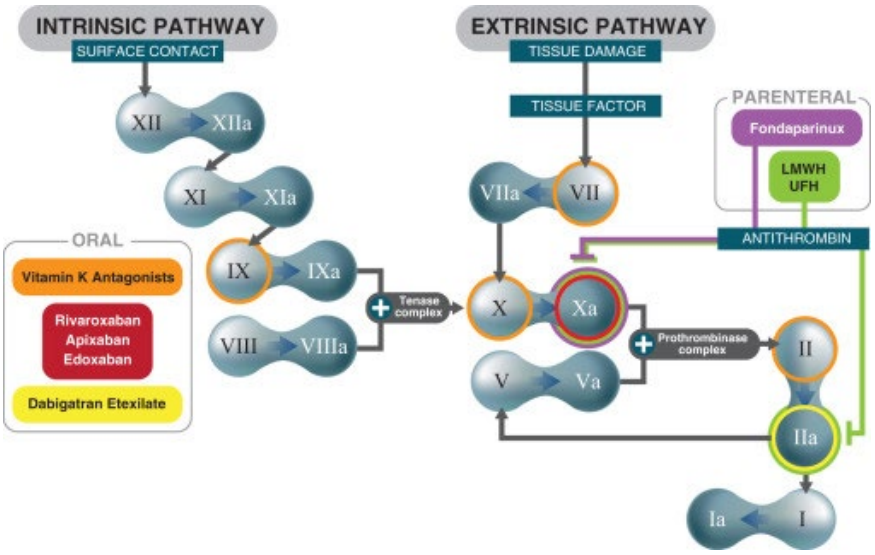

Illustration 3: Coagulation cascade and targets for medication

There are several risk assessment models (RAMs) that can be used for risk stratification of hospitalized medical patients (32). The RAM recommended in Norway is the Padua Risk Score (illustration 4), which identifies patient at high (Padua score ≥4) and low risk (Padua score <4) (32). The Padua score was validated in a cohort study which reported a 32-fold higher risk of VTE in patients at high risk of VTE (33). Furthermore, high-risk patients (Padua score ≥4) who received anticoagulation had a significant reduction in VTE risk (HR: 0.13, 95% CI: 0.04-0.4) compared to high-risk patients who received placebo (33). In hospitalized patients at low risk of VTE, the risk of bleeding relative to VTE risk (4 per 1000) is too high to warrant prophylaxis (31, 32). Consequently, a universal approach to prevention among hospitalized patients is not recommended (34).

VTE risk factor	Points
Decreased mobility	3
Thrombophilia	3
Previous trauma or surgery within the last month	2
Age ≥70	1
Heart or respiratory failure	1
Ischemic stroke or acute myocardial Infarction	1
Acute rheumatologic disorder and/or acute infection	1
Obesity	1
Hormonal therapy	1

VTE: venous thromboembolism
Low risk: score <4
High risk: score ≥4

Illustration 4: Padua risk score

The preferred anticoagulant prophylactic treatment in-hospital is low-molecular weight heparins (LMWH), and the most frequently used LMWH agents are dalteparin and enoxaparin (32). Norwegian and international guidelines recommend 40 mg enoxaparin during the hospital stay or until full mobilization as prophylactic anticoagulation. In contrast, therapeutic anticoagulation (i.e. treatment of a first VTE to prevent recurrence) demands a higher, weight-

dependent dosage of 1.5mg/kg enoxaparin (22, 32). LMWH mostly acts by binding to antithrombin (AT), which inhibits coagulation factors Xa and IIa, and thus prevents the formation of thrombi (29). LMWH targets the same biological agent as unfractionated heparin (UFH), but due to its low molecular weight it has some favorable functions. LMWH is easier to monitor and dose, has fewer side effects, its pharmacokinetic effect is linear, it is easy to administer, and it is more cost-effective than UFH (35, 36). LMWH is metabolized in the liver, but unlike UFH it is more dependent upon renal clearance and is therefore contraindicated in patients with a glomerular filtration rate under 30 (36). The effect of LMWH and UFH can be reversed with the antidote protamine sulphate (37). Furthermore, heparin has been suggested to have anti-inflammatory and antiviral properties, including the ability to directly interact with specific spike proteins of the COVID-19 virus (38). An alternative to heparins is direct oral anticoagulants (DOACs). DOACs directly inhibit Factor Xa, and like LMWH they are easy to administer and monitor (22). However, guidelines generally recommend the use of LMWH as prophylaxis due to an increased risk for major bleeding when using DOACs (22).

4.5 Covid-19 and VTE

At the advent of the pandemic, a high number of thromboembolic events in Covid-19 patients was observed (39). Covid-related VTE risk increased with disease severity and additional predisposing risk factors for VTE such as cancer, surgery and immobilization (40). A systematic review and meta-analysis consisting of 66 studies with more than 28,000 patients reported an overall VTE prevalence of 14.1% in Covid-19 patients (41). The prevalence was 7.9% in non-ICU-patients and 22.7% in ICU-patients (41), suggesting that VTE is a frequent complication in Covid-19 patients, and that a coagulation disruption is especially common in severely ill patients with COVID-19. A later meta-analysis by Mansory et al. included more studies, and found similar risks overall, but a sensitivity analysis of 20% of the included studies, chosen based on sample size, showed a VTE prevalence in all patients, ICU and non-ICU patients of 5.5%, 15.7% and 5.6%, respectively (42). Piroth et al. compared the rates of VTE and PE in COVID-19 patients versus influenza patients (for influenza the rates were assessed during the year before the COVID-19 outbreak). They found that the rates of VTE were 4.9% in COVID-19 patients versus 1.7% in influenza patients, while the corresponding PE rates were 3.4% versus 0.9%, respectively (43). Additionally, Poissy et al. found a PE incidence of 20.6% in COVID-

patients admitted to an ICU in 2020, which was more than three times higher than the PE incidence in influenza patients admitted to the ICU in 2019 (44).

While much is still unknown, some pathophysiological factors have been identified that may explain the high incidence of thromboembolic events in COVID-19 patients. There is a known association between activation of an inflammatory response and activation of the coagulation system known as thrombo-inflammation, which leads to an elevated risk of thromboembolic events in patients with infectious disease (40). SARS-CoV-2 does not itself appear to have direct procoagulant effects, but research suggests that the virus attacks the respiratory epithelium and endothelium using angiotensin-converting enzyme-receptors, which leads to coagulopathy and an increased risk of thromboembolism (45). Additionally, COVID-19 is associated with many well established VTE risk factors, such as immobilization due to disease, hospitalization, need for intensive care treatment, cancer and obesity, which in themselves increase the risk of a thromboembolic event (9, 40).

Early in the pandemic, a Chinese study using the Padua risk score reported that 40% of hospitalized patients with Covid-19 were at high risk of VTE (46). Due to the high disease burden and potentially fatal outcome of VTE, the use of thromboprophylaxis was viewed as a key component in medical care of COVID-19 patients, with international guidelines supporting the use of prophylactic anticoagulation in hospitalized COVID-19 patients (30, 47-50). An observational cohort study found that patients receiving prophylactic anticoagulation had lower mortality (Hazard ratio (HR): 0.73, 95% CI: 0.66-0.81) compared to those who did not receive anticoagulation (51). Despite this, Helms et al. reported a higher VTE incidence than expected in critically ill COVID ARDS patients compared to non-COVID ARDS patients, mainly due to increased PE incidence (11.7 vs. 2.1%) even when receiving standard prophylactic doses of LMWH (52). Therefore, some hospitals implemented a treatment regimen where escalated doses of anticoagulants were used. An early meta-analysis of retrospective observational studies found a 43% reduction in mortality among patients receiving escalated doses (53). However, increased doses were also associated with a 2.5-fold increase in risk of bleeding, and the findings were based on low-quality evidence due to the non-randomized nature of the included studies (53). Consequently, it was important to fill the knowledge gap, and procure high-quality evidence on the efficacy and safety of escalated prophylactic doses compared to standard doses in acutely ill and critically ill COVID-19 patients through RCTs (54). Several RCTs

were performed, but the size of these studies was limited and many used composite primary outcomes and were thus not powered to assess the impact of escalated doses of anticoagulation on important secondary outcomes such as VTE, major bleeding and death. By pooling data from published RCTs, we can provide more robust assessments of effect and risk. We therefore conducted a meta-analysis of RCTs comparing escalated and standard doses of thromboprophylactic anticoagulation in hospitalized COVID-19 patients in both ICU and non-ICU patients to assess whether the overall population and these subgroups would benefit from escalated thromboprophylactic intervention.

5 Aim of the thesis

The overall aim of the present thesis is to provide a comprehensive literature review and meta-analysis of randomized controlled trials comparing escalated and standard doses of thromboprophylaxis in Covid-19-treatment in ICU and non-ICU patients, especially focusing on the impact on VTE, major bleeding and all-cause mortality.

6 Methods

A structured literature search was constructed and performed to retrieve randomized controlled trials investigating the use of escalated and standard doses of thromboprophylaxis in treatment of Covid-19, and especially in the prevention of VTE.

6.1 Databases and search strategy

The bibliographic databases Embase and Medline were used to conduct our search. Access to both databases were secured through the Ovid search software.

The structured searches in Medline and Embase are presented in Supplementary Table 1-2. For VTE, the following search terms were entered: *exp thromboembolism / exp thrombosis / exp venous thromboembolism / deep vein thrombosis*/Pulmonary embolism**. The search-terms for thromboprophylaxis were: *prophy* / thromboprophy* / anticoagul* /*. Additional search terms were: *exp randomized controlled trial / exp covid-19 / exp animals/ not humans / limit to English language* and *Year 2019-2022*.

After the systematic searches were executed and duplicates removed, all citations and references were imported to EndNote X9 (Thomson Reuters, Toronto, Canada) to help manage and organize the literature. The final search was conducted on April 1st, 2022.

6.2 Inclusion and exclusion criteria

Inclusion criteria for being included in the meta-analysis were defined using the PICOS process (55), and were:

Population: Hospitalized patients with confirmed COVID-19

Intervention: Escalated doses of thromboprophylaxis (≥40 mg enoxaparin daily, or equal/higher dose of other anticoagulant treatment)

Comparison: Standard dose of thromboprophylaxis (40 mg enoxaparin daily, or equal dose of other anticoagulant treatment believed to give similar prophylactic effect)

Outcomes: VTE, all-cause mortality and major bleeding

Study design: RCT

Searches were limited to articles published between January 1st 2019 and April 1st 2022. Only articles written in English language and studies consisting of at least 50 participants were eligible for inclusion. Studies included in the meta-analysis were RCTs. Studies on post hospital-discharge prophylaxis and animal studies were excluded.

Studies were first screened by title, then by abstract and finally by full text assessment. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart for the search is shown in figure 1. The figure shows the number of identified articles and reasons for exclusion.

6.3 Extraction of data

Relevant articles were read, and the following variables were extracted to be presented in a pre-defined table: First author and year of publication, study design, type of intervention, number of study participants, outcomes, setting, main results, and conclusions. A narrative summarization for all included studies were conducted and can be found in the supplementary material. Data on VTE, death and major bleeding was extracted directly from either main text or supplementary material.

6.4 Data analysis

We performed a meta-analysis to determine the effect of escalated versus standard doses of prophylactic anticoagulants on the risk of VTE, mortality and major bleeding. The trials were analyzed in overall populations and subgroups based on whether they were conducted in an ICU or non-ICU setting. Risk ratios (RRs) with 95% Confidence intervals (95% CI) for VTE, death and major bleeding were extracted, and pooled results were calculated with Revman 5.4.1 (Cochrane Collaboration, London, United Kingdom) and displayed in forest plots. Risk estimates for the overall hospitalized population and subgroups (ICU, non-ICU) were reported for all study outcomes. Cumulative incidence and pooled incidence of VTE, death and major bleeding was calculated based on the reported number of events and total number at risk. Risk of bias assessment was also performed for all studies using the risk-of-bias tool developed by the Cochrane collaboration (56), and figures were created using the Robvis-tool (57).

7 Results

Nine full-text randomized controlled trials on in-hospital use of thromboprophylaxis in COVID-19 patients were identified from the structured search and included in the thesis. Of the nine trials, 5 were exclusively performed in a non-ICU-setting (58-62), while 3 were performed exclusively in an ICU-setting (63-65), and 1 study included both ICU- and non-ICU patients (62).

The main type of anticoagulant used was LMWH and UFH. The LMWH enoxaparin was the main study intervention in the REMAP-CAP, ACTIV-4a and ATTACC (henceforth only referred to as "ATTACC")(58, 64), HEP-COVID(66), RAPID (62), X-COVID-19 (61), INSPIRATION (63) and Perepu (65) studies. The ACTION study was conducted with the direct factor Xa-inhibitor Rivaroxaban as the main type of intervention (59).

Six randomized controlled studies enrolled non-critically ill hospital patients (N=3,742). Information on main type of treatment, location, number of participants, length of follow up and primary outcome is found in table 1. The trials were conducted in Brazil, UK, Spain, USA, Canada, Italy, and Saudi Arabia. The number of participants ranged from 65 to 2,244 and the primary outcomes were in-hospital incidence of VTE, arterial thromboembolism (ATE), death, organ-support free days and composite outcome of death, hospital stay and duration of oxygen therapy, ICU admission, oxygen therapy, ARDS, VTE or ATE.

Four randomized controlled studies enrolled ICU patients (N=1,916). Information on main type of treatment, location, number of participants and length of follow-up is found in table 2. The trials were conducted in Iran, UK, USA, Canada, and Brazil. Number of participants ranged from 83 to 1,098 and primary outcomes were all-cause mortality, organ support-free days, composite outcomes of VTE, ATE or death, and VTE, ATE, Extracorporeal membrane oxygenation (ECMO) or death.

7.1 Risk of bias

In the risk of bias assessment of the non-ICU RCTs (figure 5), all studies were open label. The ATTACC (58) and BEMICOP (60) studies were assessed as being at a high risk of bias. The ATTACC study was vulnerable crossover bias due to lack of rigidity in the treatment of both groups: There was a major degree of crossover with over 20% of the escalated dose group receiving less than the planned doses, and almost 30% of the usual-care group receiving more than standard dose of prophylaxis. The BEMICOP study was not blinded for outcome assessment, introducing outcome bias. The risk of bias in the X-COVID-19 study was unclear, due to a big difference in treatment length between study groups, and a high number of unexplained exclusions that might introduce selection bias. The HEP-COVID, RAPID and ACTION studies were assessed as having an overall low risk of bias.

All the ICU-studies (figure 6) were open label. The ATTACC study (64) on critically ill patients had a high crossover rate. In the control group, 60% received higher doses than standard doses of thromboprophylaxis, while more than 20% in the escalated dose group received smaller doses than planned. Additionally, the Perepu study had a high risk of outcome bias due to lack of blinding for outcome, unclear reporting, and high, unaccounted for exclusion rate. The INSPIRATION and HEP-COVID studies were assessed as having an overall low risk of bias.

7.2 VTE

7.2.1 Non-ICU

All non-ICU studies except the HEP-COVID trial investigated VTE as an outcome. The individual study results as well as the pooled results from the meta-analysis are found in figure 2. All studies used LMWH as the main intervention (58, 61, 62, 64, 66, 67), except for the ACTION study which used a DOAC (Rivaroxaban)(59). In the ACTION study, the therapeutic anticoagulation group had a VTE risk reduction of 40% (RR: 0.60, 95% CI: 0.29-1.25) compared to standard dose, which was not statistically significant (59). Similar findings were reported in the ATTACC study (RR: 0.52, 95% CI: 0.26-1.03) (58), the BEMICOP study (RR: 0.21, 95% CI: 0.01-4,13) (60), the RAPID study (RR: 0.35, 95% CI: 0.07-1.70) (62) and X-COVID-19 study (RR: 0.08, 95% CI: 0.00-1.36) (61).

The pooled incidence of VTE (Figure 2) in the non-ICU subgroup was 1.4% (26/1851) in patients receiving escalated doses and 3.1% (54/1720) in patients receiving standard doses.

Escalated doses of anticoagulation were associated with a substantial, statistically significant reduction in VTE (RR: 0.46, 95% CI: 0.29-0.73) compared to prophylactic anticoagulation in non-ICU patients.

7.2.2 ICU

VTE outcome data was reported in three of the four studies that included ICU-patients (Figure 2). Comparing escalated versus standard dose thromboprophylaxis, the ATTACC study reported a considerable, statistically significant reduction in VTE risk of nearly 60% (RR:0.42, 95% CI: 0.25-0.70). The INSPIRATION (RR: 0.93, 95% CI: 0.38-2.26) and Perepu (RR: 1.15, 95% CI: 0.40-3.29) studies reported no difference between the groups.

The pooled incidence of VTE in the ICU subgroup was 3.9% (35/897) and 6.8% (64/936) in the escalated and standard group, respectively (Figure 2). The pooled results of the meta-analysis indicated that escalated dosages of thromboprophylaxis were associated with a significant reduction of more than 40% in VTE incidence compared to standard dosages in ICU patients (RR: 0.57, 95% CI: 0.38-0.85).

7.2.3 Overall

Overall, the pooled incidence of VTE in all studies was 2.6% (76/2877) in patients receiving escalated doses of anticoagulants and 5.5% (153/2780) in patients receiving standard doses. The reported VTE events in the HEP-COVID-study did not distinguish between ICU and non-ICU patients and was therefore only included in the overall results. Escalated-dose prophylactic anticoagulation was associated with reduced risk of VTE regardless of ICU status (RR: 0.49, 95% CI: 0.38-0.64) (Figure 2).

7.3 Major bleeding

7.3.1 Non-ICU

All six studies that included non-ICU patients reported on major bleeding in a non-ICU setting. The individual study results as well as the pooled results from the meta-analysis are found in figure 3. The ACTION (RR: 2.45, 95% CI: 0.78-7.73) and ATTACC (RR:2.17, 95% CI: 1.00-4.69) studies reported considerable increased risk of major bleeding for escalated versus standard dose anticoagulation, while the RAPID study (RR: 0.52, 95% CI: 0.10-2.81) reported a decreased risk of major bleeding in the escalated dose study arm. HEP-COVID (RR: 1.02, 95%

CI: 0.15-2.81) and X-COVID-19 (RR: 0.99, 95% CI: 0.06-15.58) studies reported no difference between the groups.

The pooled incidence of major bleeding was 1.9% (37/1926) and 1.1% (20/1798) in the escalated and standard dose group, respectively (Figure 3). Overall, an increased risk of major bleeding in patients on therapeutic dosages was identified in the non-ICU setting (RR:1.74, 95% CI: 1.01-3.00).

7.3.2 ICU

All four studies that included ICU patients reported on major bleeding. Escalated-dose anticoagulation was associated with considerable risk of major bleeding in the HEP-COVID (RR: 7.63, 95% CI: 0.42-137.36), INSPIRATION (RR: 1.81, 95% CI: 0.54-6.13) and ATTACC (RR: 1.63, 95% CI: 0.82-3.25) trials, however, none of the results were statistically significant (Figure 3). The Perepu trial found no difference in bleeding risk (RR: 1.01, 95% CI: 0.15-7.02).

The pooled incidence of major bleeding across all studies of ICU patients was 3.5% (33/936) with escalated-dose anticoagulation and 1.9% (19/973) with standard dose anticoagulation (Figure 3). The pooled risk ratio showed an increased risk of major bleeding in patients receiving escalated prophylaxis in an ICU-setting (RR: 1.78, 95% CI: 1.02-3.09).

7.3.3 Overall

Overall, pooled incidence of major bleeding across all studies was 2.4% (70/2862) in patients receiving escalated dose anticoagulation, and 1.4% (39/2771) in patients receiving standard dose anticoagulation regardless of ICU status (Figure 3). The risk of major bleeding was significantly increased in patients receiving escalated doses of thromboprophylaxis (RR: 1.76, 95% CI: 1.19-2.59).

7.4 Mortality

7.4.1 Non-ICU

Five studies of non-ICU patients reported on mortality, and information on the number of events, RRs and study population can be found in figure 4. The ACTION (RR: 1.49, 95% CI: 0.90-2.46) and BEMICOP trials (RR:2.06, 95% CI: 0.20-21.64) found an increased risk of death in patients receiving escalated doses, but the findings were not statistically significant. The X-Covid-19 trial reported a reduced risk in the escalated-dose group (RR: 0.20, 95% CI: 0.02-

1.66), while the ATTACC trial (RR: 0.89, 95% CI: 0.67-1.18) found no difference between the groups.

The pooled mortality in non-ICU patients was 6.9% (128/1842) among patients receiving escalated-dose anticoagulation, and 7.8% (133/1711) in patients receiving standard-dose prophylactic anticoagulation (Figure 4). No difference in mortality rates for escalated and standard prophylactic treatment regimens was found (RR: 0.89, 95% CI: 0.70-1.12).

7.4.2 ICU

Three studies reported on all cause death in an ICU setting. The Perepu trial (RR: 0.71, 95% CI: 0.37-1.37) reported a reduced mortality risk in the escalated dose group, but the finding was not significant (Figure 4). The ATTACC (RR: 1.05, 95% CI: 0.90-1.23) and INSPIRATION trials (RR: 1.05, 95% CI: 0.87-1.28) did not report any difference in mortality.

The pooled incidence of mortality in ICU patients receiving escalated prophylactic dose thromboprophylaxis was 36.9% (331/897) compared to 35.8% (335/936) in ICU patients receiving standard anticoagulation (Figure 4). No significant difference in mortality risk was found (RR: 1.03, 95% CI: 0.92-1.17).

7.4.3 Overall

Overall, the pooled incidence of mortality across all studies was 16.9% (484/2868) and 18.0% (499/2771) in the escalated and standard dose group, respectively (Figure 4). No difference in mortality was found (RR: 0.98, 95% CI: 0.88-1.09). The HEP-COVID trial did not distinguish between non-ICU and ICU patients and was therefore only included in the pooled analysis.

8 General discussion

In the present thesis, the effect of escalated versus standard dose prophylactic anticoagulation on VTE, major bleeding and mortality in hospitalized COVID-19 patients was evaluated in the form of a review and meta-analysis. The pooled results from our meta-analysis suggested that escalated doses of prophylactic anticoagulation were associated with a substantial reduction in VTE risk of almost 50%. However, escalated doses of thromboprophylaxis were associated with a considerable increase in risk of major bleeding of 75% and escalated doses of thromboprophylaxis had no impact on all-cause mortality. In the analyses based on clinical setting, estimates indicated a lower risk of VTE and all-cause mortality in non-ICU patients receiving escalated doses of prophylactic anticoagulation compared to ICU patients. However, these results were not statistically significant.

Due to the increased VTE rates in COVID-19 compared to other respiratory infections, international guidelines support the use of standard dose prophylactic anticoagulation in all hospitalized COVID-19 patients who do not have a contraindication to treatment (30, 68). However, despite prophylactic anticoagulation, there has still been a considerable incidence of thromboembolic events, suggesting that standard doses might be insufficient to prevent VTE at the same rate as it does for other respiratory conditions, such as influenza (43). Therefore, many institutions have employed escalated doses of thromboprophylaxis in the treatment of hospitalized COVID-19 patients (48). Our meta-analysis of studies comparing escalated versus standard dose of thromboprophylaxis identified an overall reduction in VTE risk of 51%, (95% CI: 0.38-0.64), which does support an improved effect of escalated dose anticoagulation. Whether acutely ill and critically ill COVID-19 patients should be treated differently has been debated (30). In hospitalized medical patients, anticoagulant prophylaxis has been shown to be more beneficial for patients at high risk of VTE (32), and therefore, one would expect that escalated doses of thromboprophylaxis would be more impactful in critically ill ICU-patients than in non-ICU patients. The results of our meta-analysis do not support this, as there was no difference in the risk reduction of VTE between ICU and non-ICU patients. Of note, the risk estimates indicated a larger risk reduction of VTE in non-ICU patients (RR: 0.46, 95% CI: 0.29-0.73) than ICU-patients (RR: 0.57, 95% CI: 0.38-0.85). In critically ill COVID-19 patients, thrombus formation is driven by what is commonly known as a “cytokine storm”, where a high activation of immune cells and inflammatory cytokines leads to thrombi,

pulmonary edema, alveolar destruction and severe coagulopathy (69). These surface-bound complexes of cytokines, activated complement, platelets, endothelial and inflammatory cells and fibrin-bound thrombin are rather resistant to antithrombin-inhibition, the key cofactor in heparin and LMWH (70). Thus, it has been proposed that these mechanisms are less active in non-ICU patients, and could explain the observed benefit of escalated doses in non-ICU patients (70).

Considering the high rate of VTE-, and especially PE cases in hospitalized COVID-patients, one might expect that escalated doses of prophylactic anticoagulation could lead to a decrease in mortality (71). Overall, we found no benefit on risk of death in the escalated dose group (RR: 0.98, 95% CI: 0.88-1.09). In the analysis based on clinical setting, the pooled estimates indicated a slight reduction in mortality among non-ICU patients (RR: 0.89, 95% CI: 0.70-1.12), while no such benefit was found in ICU-patients (1.03, 95% CI: 0.92-1.17), although the confidence intervals overlapped and included 1. This may be because patients with severe illness has likely progressed further from the procoagulant state into a disseminated intravascular coagulopathy (DIC)-state, and the antithrombotic effect might be much less impactful (70). Therefore, timing of the anticoagulant treatment may be essential (70). Of note, a recently updated guideline from the American Society of Hematology (ASH) suggests the use of escalated prophylactic doses of anticoagulants in acutely ill COVID-patients (72), while they suggest using standard dose prophylaxis in critically ill COVID-patients (73).

The risk of bleeding is known to increase with increasing doses of anticoagulants (30). A Cochrane review published in 2014 found that standard prophylactic treatment with heparin in medical patients was associated with an increase in bleeding risk of 65-83% compared to no prophylaxis (29). Our meta-analysis found that the overall increase in bleeding risk of 76% in patients receiving escalated thromboprophylaxis compared to standard treatment. There was no difference in bleeding risk in ICU (RR: 1.78, 95% CI: 1.02-3.09) and non-ICU (RR:1.74, 95% CI: 1.01-3.00) patients given escalated doses.

In the subgroups based on clinical setting, the estimates for VTE and all-cause mortality indicated marginal benefits in non-ICU patients receiving escalated prophylactic anticoagulation. However, these findings were not statistically significant. Considering the similarity in risk of bleeding, two questions arise. 1) Should escalated doses of prophylactic anticoagulation be used in all hospitalized COVID-19-patients? And if no; 2) Should escalated

doses of prophylactic anticoagulation be given to acutely ill COVID-19 patients? International guidelines do not recommend escalated doses in all hospitalized COVID-patients (72), mainly due to increased bleeding risk, and low-certainty evidence showing a potential increase in all-cause mortality in critically ill patients (73). The results from our meta-analysis do not provide any evidence that suggests a different course, especially due to the lack of benefit on all-cause mortality in critically ill patients. However, whether acutely ill patients should receive escalated doses merits further discussion. As mentioned, ASH has recently suggested the use of intermediate doses in acutely ill patients (72). However, they do cite low certainty in available evidence, and a need for individualized decision-making. This can potentially be done using the IMPROVE-DD RAM (74), developed for use in hospitalized COVID-19 patients, but bleeding risk must also but taken into account before escalated doses are used (72). Our meta-analysis also indicates a possible benefit in all-cause mortality and a clear reduction in VTE risk. However, a lot of the available evidence was gathered early in the pandemic (no patient enrolled in any included study after May 2021), and in the presence of improved treatment of COVID-19, herd immunity, new virus variants and vaccine coverage, the baseline risk of VTE might have changed substantially. Therefore, the findings of the initial studies summarized in our meta-analysis might not be generalizable to hospitalized COVID-patients in 2022.

The studies included in our meta-analysis had some limitations. In total, 4 studies were assessed as being at a high risk of bias (58, 60, 61, 64). All studies were open-label studies which may increase the risk of differential bias related to outcome assessment. However, all studies included in the meta-analysis except one attempted to minimize the risk of outcome bias introduced by the open-label design through blinded adjudication of outcomes. The BEMICOP study did not perform blinded adjudication of outcomes and was therefore at high risk of outcome bias (60). Additionally, the BEMICOP and Perepu studies deemed many potential participants ineligible, without documenting why, which might have led to selection bias, thereby weakening the generalizability of their findings (60, 65). The two largest studies included in the meta-analysis, the ATTACC studies for non-critically (58) and critically ill (64) COVID-19 patients, were at high risk of regression dilution bias due to a substantial crossover in both the treatment and comparison groups. The treatment crossover was especially large, and unbalanced in the study on ICU-patients, where almost 60% of the comparison group received escalated doses, and this may have diluted a potential effect of escalated dose

prophylactics. Additionally, the BEMICOP, Perepu and X-COVID were terminated due to poor recruitment, and therefore smaller than planned, which also puts the study at high risk of selection bias (60, 61, 65).

This methodological approach of this master thesis has some limitations. First, due to time constraints, we used a restricted search strategy. Therefore, we may potentially have missed some relevant studies. However, we cross-checked references of included studies to ensure that our data gathering was as comprehensive as possible. Second, the screening, selection of studies and risk of bias assessment was only conducted by one person. Ideally two people should have independently conducted the screening, but this was not feasible for this thesis. Third, subgroup analysis was performed by clinical setting, but the criteria for how ill a patient had to be for ICU eligibility varied from study to study, and thus some misclassification may have occurred. Additionally, any RCTs published or not indexed in the Embase or Medline after April 22, 2022, was not included.

This thesis focused on in-hospital thromboprophylaxis to COVID-19 patients. In addition, post-hospitalization prophylactic anticoagulation has been a subject of much debate. The MICHELLE trial (75) investigated the effect of rivaroxaban, given at a prophylactic dose to both ICU and non-ICU patients at high risk of VTE for a period of 35 days after hospital discharge. The study indicated that standard dose prophylactic anticoagulation given to patients at high risk of VTE and concomitant low risk of bleeding, was effective and safe. Additionally, the ACTION study treated patients in-hospital and post-discharge with escalated doses of rivaroxaban (59). They concluded that such an approach was not superior to prophylactic-dose heparin treatment solely until hospital discharge, due to marginal effect on VTE risk and increased risk of bleeding, indicating that higher doses of rivaroxaban post-discharge is not beneficial. More studies on post-hospitalization anticoagulation are still needed.

9 Conclusion

This review and meta-analysis of studies comparing escalated doses with standard doses of thromboprophylaxis identified a moderately decreased risk of VTE, little to no reduction in death and an increase in risk of major bleeding when using escalated doses compared to standard prophylactic doses of anticoagulants. There was no difference in treatment benefit in ICU patients compared to non-ICU patients. However, the estimates might indicate a slight advantage of escalated doses in non-ICU patients. Many RCTs on prophylactic anticoagulation to COVID-19 patients are still ongoing, and knowledge on the subject is quickly evolving.

10 References

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11 Tables and figures

TABLE 1. Randomized controlled trials conducted in a non-intensive care unit (ICU) setting comparing escalated versus standard dose prophylactic anticoagulation.

STUDY, YEAR	TREATMENT (MAIN)	LOCATION	N (N=3,742)	FOLLOW-UP DURATION	PRIMARY OUTCOME
ACTION (59), 2021	Escalated: 20 mg rivaroxaban Standard: 40 mg enoxaparin x1 Treatment duration: Day 30 in escalated arm, discharge in standard arm	Brazil	615	30 days	Composite outcome: Death, length of hospital stay, oxygen therapy duration
ATTACC (58), 2021	Escalated: 40 mg x2 enoxaparin Standard: Usual care Treatment duration: 14 days in therapeutic arm, up to clinician in prophylactic arm	UK, USA, Canada, Brazil	2,244	21 days	Organ support-free days
BEMICOP (60), 2021	Escalated: 115 IU/kg bemiparin x1 Standard: 3500 IU bemiparin x1 Treatment duration: 10 days	Spain	65	10 days	Composite outcome: Death, ICU[a] admission, oxygen therapy, ARDS[b], VTE[c], ATE[d]
HEP-COVID (66), 2021	Escalated: 1 mg/kg Enoxaparin x2 Standard: 40 mg enoxaparin x1 Treatment duration: Hospital stay	USA and more	170	30 days	VTE[c], ATE[d] or death
RAPID (62), 2021	Escalated: 1 mg/kg Enoxaparin x2 Standard: 40 mg enoxaparin x1 Treatment duration: Discharge, day 28 or death	Canada and more	465	28 days	Death, mechanic ventilation or ICU admission
X-COVID-19 (61), 2021	Escalated: 40 mg enoxaparin x2 Standard: 40 mg enoxaparin x1 Treatment duration: Until discharge	Italy	183	30 days	In-hospital incidence of VTE

[a] ICU: Intensive care unit
[b] ARDS: Acute respiratory distress syndrome
[c] VTE: Venous thromboembolism
[d] ATE: Arterial thromboembolism

TABLE 2. Randomized controlled trials conducted in an intensive care unit setting comparing escalated versus standard dose prophylactic anticoagulation.

STUDY, YEAR	TREATMENT (MAIN)	LOCATION	N	FOLLOW-UP DURATION	PRIMARY OUTCOME
ATTACC (64), 2021	Escalated: 40 mg x2 enoxaparin Standard: Usual care Treatment duration: 14 days in therapeutic arm, up to clinician in prophylactic arm	UK and more.	1,098	21 days	Organ support-free days
HEP-COVID (66), 2021	Escalated: 1 mg/kg Enoxaparin x2 Standard: 40 mg enoxaparin x1 Treatment duration: Hospital stay	USA and more	83	30 days	VTE[a], ATE[b] or death
INSPIRATION (63), 2021	Escalated: 1 mg/kg enoxaparin x1 Standard: 40 mg enoxaparin x1 Treatment duration: 30 days	Iran	562	90 days	VTE[a], ATE[b], ECMO[c] or death
PEREPU (65), 2021	Escalated: 40 mg enoxaparin x2 Standard: 40 mg enoxaparin x1 Treatment duration: Hospital stay	USA	173	30 days	All-cause mortality

[a] VTE: Venous thromboembolism

[b] ATE: Arterial thromboembolism

[c] ECMO: Extracorporeal membrane oxygenation

Figure 1. Modified PRISMA flow diagram illustrating the process of the structured search.

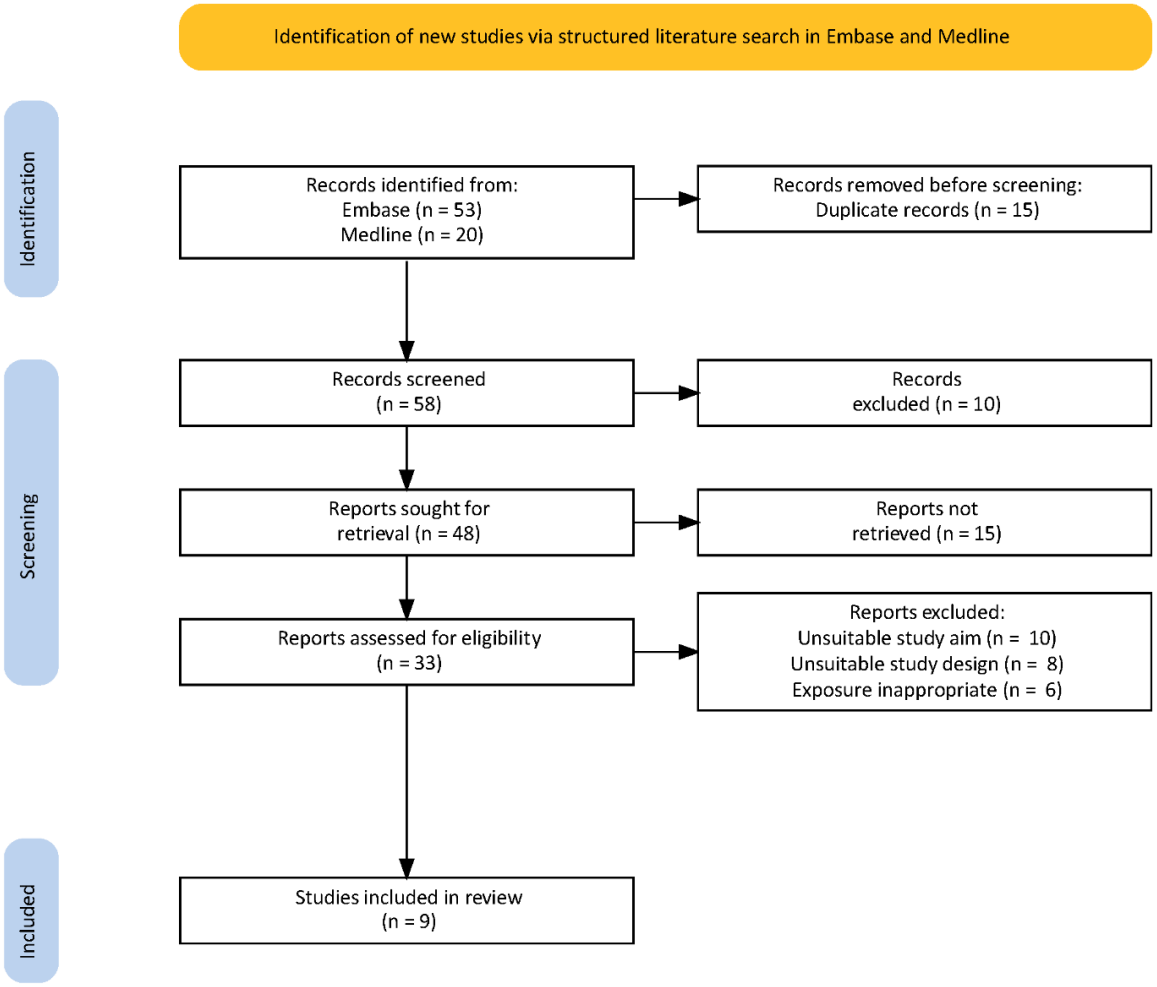
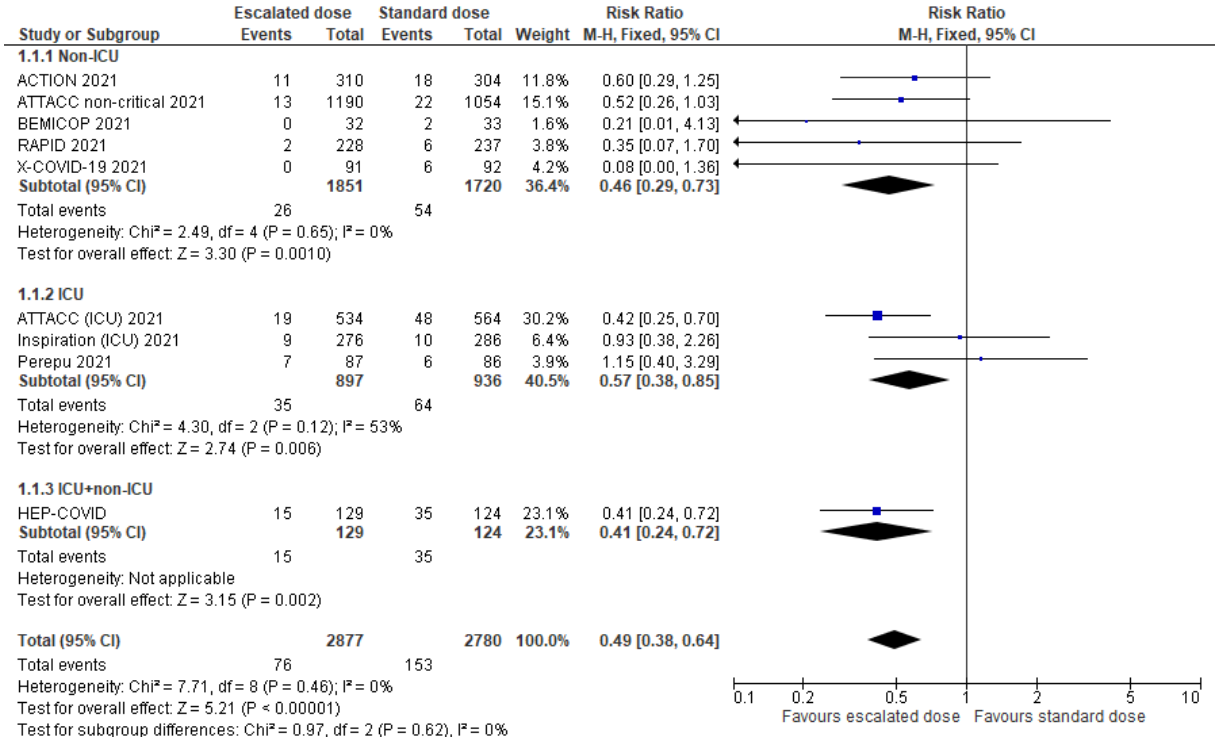
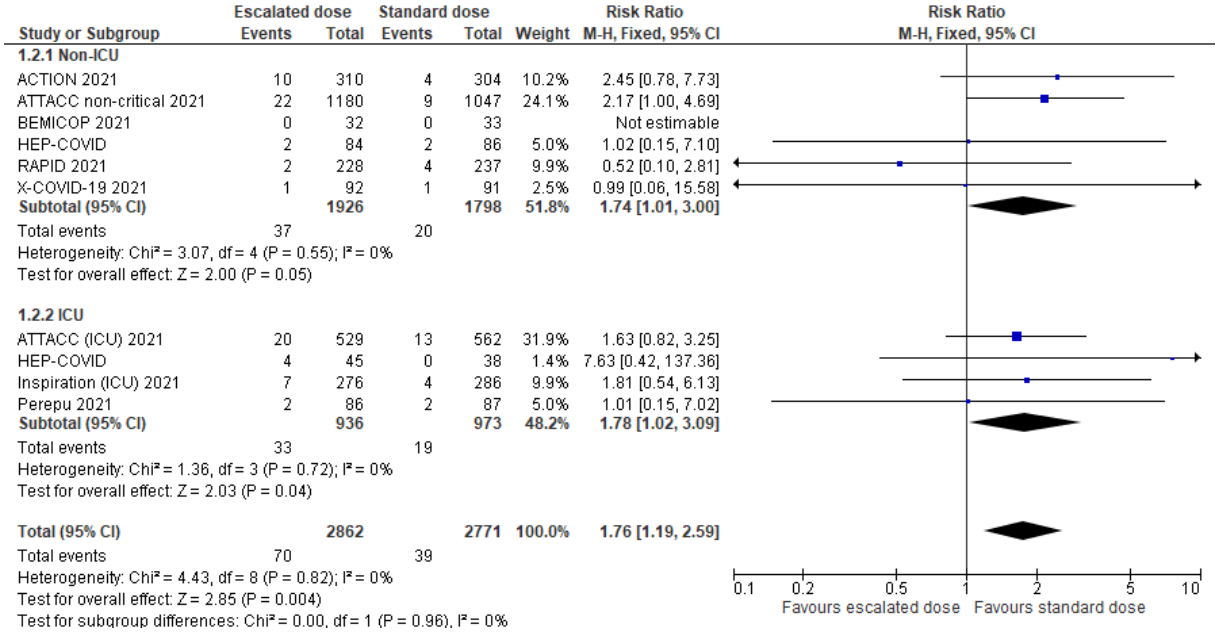


Figure 2. Forest plot of comparison. Thromboprophylaxis escalated versus standard prophylactic dose, outcome: Venous thromboembolism.



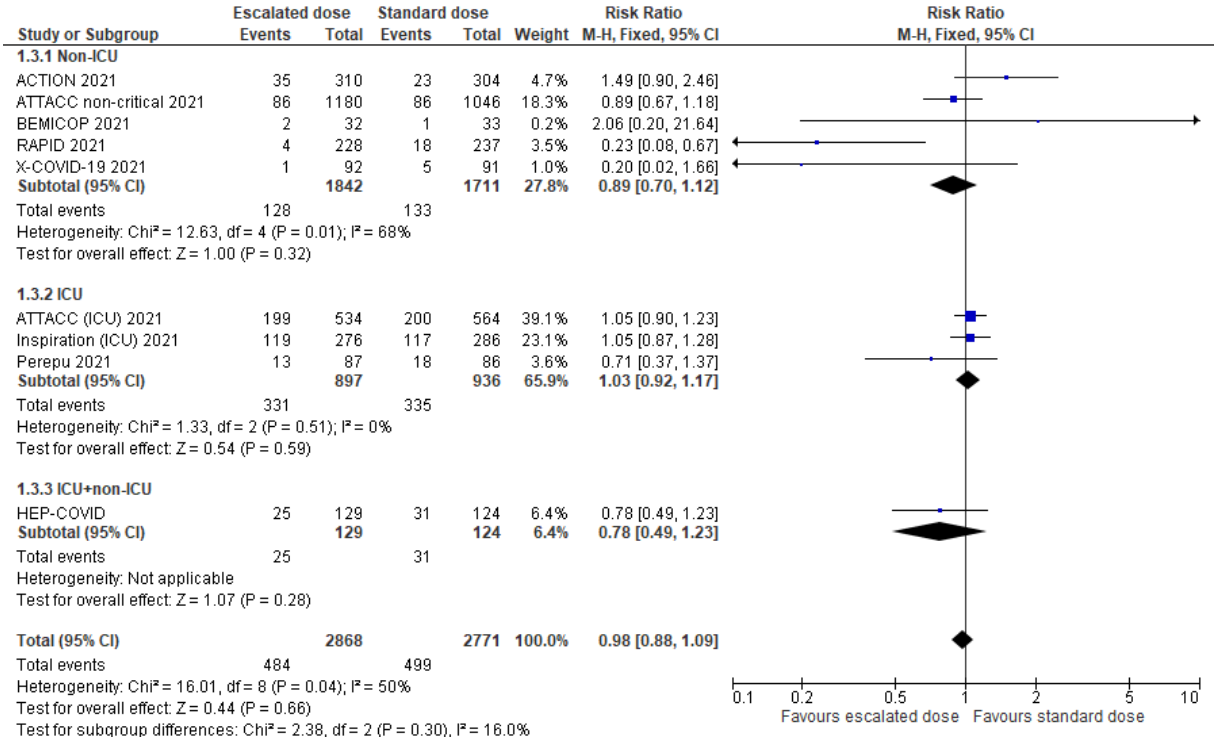
M-H: Mantel Haenszel
ICU: Intensive care unit
CI: Confidence interval

Figure 3. Forest plot of comparison. Thromboprophylaxis escalated versus standard prophylactic dose, outcome: Major bleeding.



M-H: Mantel Haenszel
ICU: Intensive care unit
CI: Confidence interval

Figure 4. Forest plot of comparison. Thromboprophylaxis escalated versus standard prophylactic dose, outcome: All-cause mortality



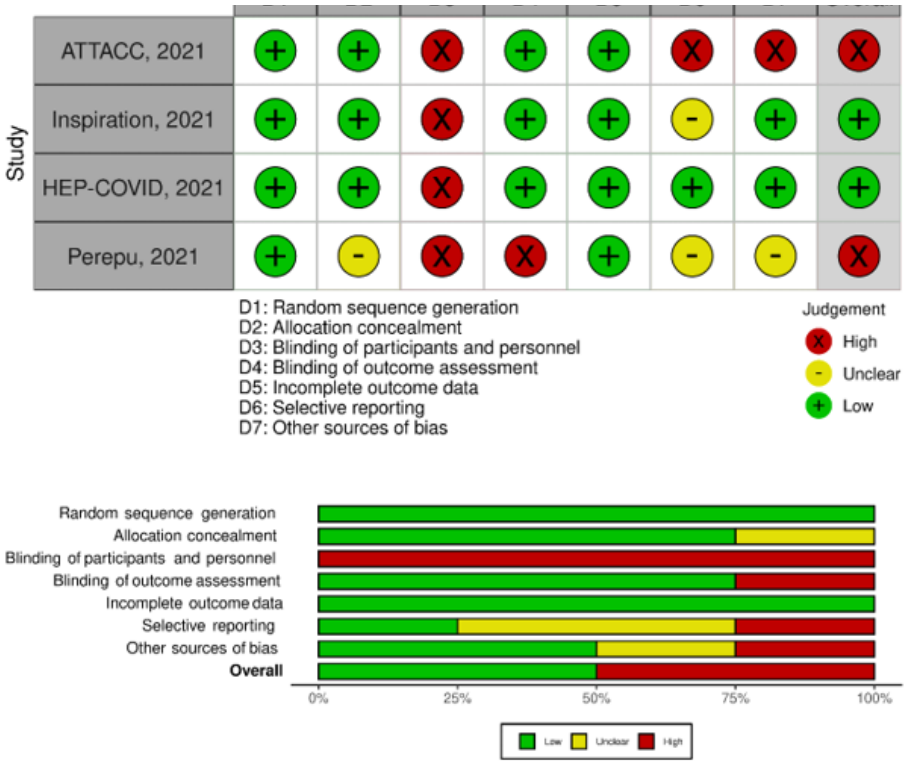
M-H: Mantel Haenszel

ICU: Intensive care unit

CI: Confidence interval

Figure 5. Risk of bias assessment of non-intensive care unit randomized controlled trials.

Figure 6. Risk of bias assessment of intensive care unit randomized controlled trials.



12 Supplementary material

Results table. Randomized controlled trials on therapeutic and prophylactic thromboprophylaxis in ICU patients.

Study Name	Intervention	Comparison	Goal	Number of participants	Results	Conclusions
REMAP-CAP, ACTIV-4a and ATTACC	Intermediate: 40 mg x2 or 1 mg/kg x1/0.5 mg/kg x2 Enoxaparin	Standard: 40 mgx1 enoxaparin	Does therapeutic anticoagulation with heparin in critically ill patients with Covid-19 improve outcomes?	Escalated dose: 534 usual care: 564	Primary outcome: Intermediate: 1 day Standard: 4 days OR: 0.83, 95% CI: 0.67-1.03 Survival: Intermediate 62.7% 335 Standard: 64.5% 364 OR: 0.84, 95 CI: 0.64-1.11 Major thrombotic events: PE (some patients had more than one event): Therapeutic: 13 Standard: 42 DVT: Therapeutic 6, Standard: 6 Major bleeding: Intermediate 3.8%, Standard: 2.3%	Initial strategy of therapeutic-dose anticoagulation with unfractionated or low-molecular-weight heparin was not associated with a greater probability of survival to hospital discharge or a greater number of days free of cardiovascular or respiratory organ support than was usual-care pharmacologic thromboprophylaxis.
REMAP-CAP, ACTIV-4a and ATTACC	Intermediate: 40 mg x2 or 1 mg/kg x1/0.5 mg/kg x2 Enoxaparin	Standard: 40 mgx1 enoxaparin	Does therapeutic anticoagulation with heparin in non-critically ill patients with Covid-19 improve outcomes?	escalated: 1190 Usual care: 1054	Primary outcome: OR: 1.27, 95% CI: 1.03-1.58 Survival: Therapeutic 92.7% Standard: 91.8% without organ support: Therapeutic 79.3%, Standard: 75.4% Major thrombotic event: Therapeutic: 1.1% Standard: 2.1% Major bleeding: Therapeutic: 1.9% Standard: 0.9%	In noncritically ill patients with Covid-19, an initial strategy of therapeutic-dose anticoagulation with heparin increased the probability of survival to hospital discharge with reduced use of cardiovascular or respiratory organ support as compared with usual-care thromboprophylaxis.

ACTION	Therapeutic intensity: 20 or 15 mg rivaroxaban Alt:1 mg/kg enoxaparin	Standard: 40 mg enoxaparin	comparison of efficacy and safety of therapeutic versus prophylactic anticoagulation in patients hospitalised with COVID, elevated D-dimer and symptoms for at least 2 weeks before randomization Primary outcome:Mortality, length of hospital stay, or duration of oxygen therapy at the end of a 30-day follow-up Safety outcome: Major or clinically relevant bleeding	Escalated: 311 Standard: 304	The primary efficacy outcome was not different between patients assigned therapeutic or prophylactic anticoagulation, (win ratio 0·86 [95% CI 0·59–1·22], p=0·40).	In patients hospitalised with COVID-19 and elevated D-dimer concentration, in-hospital therapeutic anticoagulation with rivaroxaban or enoxaparin followed by rivaroxaban to day 30 did not improve clinical outcomes and increased bleeding compared with prophylactic anticoagulation.
BEMICOP	Escalated dose: Bemiparin 115 IU/kg daily	Standard: Bemiparin 3500 IU daily	Evaluate the effect of therapeutic doses of bemiparin (LMWH) vs. Standard prophylaxis with bemiparin The primary efficacy outcome was a composite of death, intensive care unit admission, need of mechanical ventilation support, development of moderate/severe acute respiratory distress, and venous or arterial thrombosis within 10 days	Therapeutic: 32 Standard: 33	The primary efficacy outcome occurred in 7 patients (22%) in the therapeutic-dose group and 6 patients (18%) in the prophylactic group (absolute risk difference 3.6% [95% confidence interval [CI], –16% – 24%]; odds ratio 1.26 [95% CI, 0.37–4.26]; p¼0.95). Discharge in the first 10 days was possible in 66 and 79% of patients, respectively. No major bleeding event was registered.	Therefore, in patients with COVID-19 hospitalized with nonsevere pneumonia but elevated D-dimer, the use of a short course of therapeutic-dose bemiparin does not appear to improve clinical outcomes compared with standard prophylactic doses.

X-COVID-19	40 mg x2 enoxaparin	40 mg x1 enoxaparin	Evaluate the efficacy and safety of higher doses of anticoagulants than reccomended for thromboprophylaxis in general wards Primary efficacy outcome: In-hospital incidence of VTE Safety outcome: Major bleeding	183 patients 91 in x2-group 92 in x1-group	x1 group: 6 PEs x2 group: 0 PEs The incidence of DVT was reasonably low both in patients treated with standard prophylactic doses of anticoagulation and patients treated with higher doses. The incidence of pulmonary artery occlusions was higher than that of DVT and tended to be higher in patients treated with prophylactic doses, compared to patients treated with higher doses of anticoagulants. In general, high doses of anticoagulants did not improve the general clinical outcomes of the patients, with the only exception on noncritically ill patients enrolled in the Multiplatform RCT.	No DVT developed in COVID-19 patients hospitalized in general wards, independently of enoxaparin dosing used for thromboprophylaxis. Pulmonary artery occlusions developed only in the o.d. group. Our trial is underpowered and with few events.
Perepu	Therapeutic: 40 mg x2	Standard: 40 mg enoxaparin	To compare outcomes in hospitalized adults with severe COVID- 19 treated with standard prophylactic versus intermediate dose enoxaparin.	176 patients randomized 99 males 77 females	In the intention- to- treat population, all-cause mortality at 30 days was 15% for intermediate dose enoxaparin and 21% for standard prophylactic dose enoxaparin (odds ratio, 0.66; 95% confidence interval, 0.30– 1.45 Arterial or venous thrombosis occurred in 13% of patients assigned to intermediate dose enoxaparin and 9% of patients assigned to standard dose enoxaparin. Major bleeding occurred in 2% of patients in each arm.	In hospitalized adults with severe COVID- 19, standard prophylactic dose and intermediate dose enoxaparin did not differ significantly in preventing death or thrombosis at 30 days.

RAPID	LMWH or UFH Dosage adjusted by BMI and creatinine clearance Prophylactic group smaller dosages	Evaluate the effects of therapeutic heparin compared with prophylactic heparin among moderately ill patients admitted to hospital wards Brazil, Canada, Ireland, Saudi Arabia, UAE and US Primary outcome was death, mekanisk ventilasjon eller innleggelse på ICU	Escalated: 228 Standard: 237	Primary composite outcome had occured in: Therapeutic: 37/228 patients (16.2%) 4 deaths (1.8%) prophylactic: 52/237 (21.9%) 18 deaths (7.6%) Primary OR=0.69, CI 0.43-1.10 Death OR: 0.22 CI 0.07 to 0.65 VTE: Therapeutic: 2 (0.9%), prophylactic: 6 (2.5%) OR: 0.37, CI: 0.07-1.71 Major bleeding occurred in two patients (0.9%) assigned to therapeutic heparin and four (1.7%) assigned to prophylactic heparin (0.52, 0.09 to 2.85)	In moderately ill patients with covid-19 and increased D-dimer levels admitted to hospital wards, therapeutic heparin was not significantly associated with a reduction in the primary outcome but the odds of death at 28 days was decreased. The risk of major bleeding appeared low in this trial.
HEP-COVID	LMWH or UFH Dosage adjusted by creatinine clearance 1 mg/kg or 0.5mg/kg Prophylactic group smaller dosages prophylactic: Enoxaparin 40 mg or less intermediate: 30-40 mg x2	Evaluate effects of therapeutic-dose LMWH vs. Prophylactic or intermediate dose heparins for thromboprophylaxis in high risk hospitalized patients (D-dimer >4 upper normal limit or sepsis-induced coagulopathy) Primary efficacy outcome: VTE, ATE or death Safety outcome: Major bleeding	124 patients in the standard dose-group 129 in the therapeutic dose-group	Primary efficacy outcome: Prophylactic group=41.9% total VTE: 28.2%, DVT 17.7%, PE: 8.1% ATE: 3.2%, Death: 25 % Therapeutic group= 28.7% total VTE: 11.7%, DVT 7.0%, PE 3.1%, ATE: 3.2%, Death: 19.4% A significant difference—driven by reduction in thromboembolism—that was not seen in critically ill patients. The primary efficacy outcome was reduced in non-ICU patients (36.1% vs 16.7%; RR, 0.46; 95% CI, 0.27-0.81; P = .004) but not ICU patients (55.3%vs 51.1%; RR, 0.92; 95% CI, 0.62-1.39; P = .71). Major bleeding: Prophylactic=1.6%, therapeutic=4.7%, RR= 2.88, CI 0.59-14.02	Therapeutic-dose LMWH reduced major thromboembolism and death compared with institutional standard heparin thromboprophylaxis among inpatients with COVID-19 with very elevated D-dimer levels. The treatment effect was not seen in ICU patients.

Inspiration trial	intermediate: 1 mg/kg enoxaparin prophylactic: 40 mg enoxaparin	What are the effects of intermediate-dose compared with standard-dose prophylactic anticoagulation in patients with COVID-19 admitted to the intensive care unit (ICU)? Primary efficacy outcome: VTE, ATE, ECMO or death within 30 days Safety outcome: major bleeding	562 patients Escalated:276 Standard: 286	Therapeutic: primary outcome= 45.7% Major bleeding in 2.5% prophylactic: Primary outcome=44.1% Major bleeding: 1.4% Comparison Primary outcome: OR=1.06, CI 0.76-1.48) Major bleeding: OR= 1.83, CI: 0.00-5.93	Among patients admitted to the ICU with COVID-19, intermediate-dose prophylactic anticoagulation, compared with standard-dose prophylactic anticoagulation, did not result in a significant difference in the primary outcome of a composite of adjudicated venous or arterial thrombosis, treatment with extracorporeal membrane oxygenation, or mortality within 30 days.

Supplementary table 1. Structured literature search in Ovid Embase for randomized controlled trials comparing different doses of thromboprophylaxis in Covid-19 patients.

#	Search	Text results
1	exp thromboembolism/	641573
2	exp thrombosis/	439920
3	exp venous thromboembolism/	187353
4	deep vein thrombosis*.ab,ti,kw.	30959
5	pulmonary embolism*.ab,ti,kw.	65535
6	1 or 2 or 3 or 4 or 5	647717
7	exp covid-19/	216413
8	prophy*.ab,ti,kw.	293194
9	thromboprophy*.ab,ti,kw.	9920
10	anticoagul*.ab,ti,kw.	179880
11	or/8-10	463944
12	exp randomized controlled trial/	712406
13	6 and 7 and 11 and 12	83
14	exp animals/ not humans/	12867246
15	13 not 14	54
16	limit 15 to (english language and yr="2019-2022")	53

Supplementary table 2. Structured literature search in Ovid Medline for randomized controlled trials comparing different doses of thromboprophylaxis in Covid-19 patients.

#	Search	Text results
1	exp thromboembolism/	61800
2	exp thrombosis/	138972
3	exp venous thromboembolism/	14017
4	deep vein thrombosis*.ab,ti,kw.	19241
5	pulmonary embolism*.ab,ti,kw.	39813
6	1 or 2 or 3 or 4 or 5	221336
7	exp covid-19/	161833
8	prophy*.ab,ti,kw.	183032
9	thromboprophy*.ab,ti,kw.	5976
10	anticoagul*.ab,ti,kw.	108577
11	or/8-10	286993
12	exp randomized controlled trial/	570251
13	6 and 7 and 11 and 12	20
14	exp animals/ not humans/	5009122
15	13 not 14	20
16	limit 15 to (english language and yr="2019-2022")	20