





# Safety and efficacy of different prophylactic anticoagulation dosing regimens in critically and non-critically ill patients with COVID-19: a systematic review and meta-analysis of randomized controlled trials

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## Background

The clinical impact of different prophylactic anticoagulation regimens among hospitalized patients with coronavirus disease 2019 (COVID-19) remains unclear. We pooled evidence from available randomized controlled trials (RCTs) to provide insights on this topic.

## Methods and results

We searched for RCTs comparing treatment with an escalated-dose (intermediate-dose or therapeutic-dose) vs. a standard-dose prophylactic anticoagulation regimen in critically and non-critically ill COVID-19 patients requiring hospitalization and without a formal indication for anticoagulation. The primary efficacy endpoint was all-cause death, and the primary safety endpoint was major bleeding. Seven RCTs were identified, including 5154 patients followed on an average of 33 days. Compared to standard-dose prophylactic anticoagulation, escalated-dose prophylactic anticoagulation was not associated with a reduction of all-cause death [17.8% vs. 18.6%; risk ratio (RR) 0.96, 95% confidence interval (CI) 0.78–1.18] but was associated with an increase in major bleeding (2.4% vs. 1.4%; RR 1.73, 95%CI 1.15–2.60). Compared to prophylactic anticoagulation used at a standard dose, an escalated dose was associated with lower rates of venous thromboembolism (2.5% vs. 4.7%; RR 0.55, 95%CI 0.41–0.74) without a significant effect on myocardial infarction (RR 0.80, 95%CI 0.47–1.36), stroke (RR 0.94, 95%CI 0.43–2.09), or systemic arterial embolism (RR 1.20, 95%CI 0.29–4.95). There were no significant interactions in the subgroup analysis for critically and non-critically ill patients.

## Conclusions

Our findings provide comprehensive and high-quality evidence for the use of standard-dose prophylactic anticoagulation over an escalated-dose regimen as routine standard of care for hospitalized patients with COVID-19 who do not have an indication for therapeutic anticoagulation, irrespective of disease severity.

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## Study registration

This study is registered in PROSPERO (CRD42021257203).

## Keywords

Anticoagulant therapy • Coronavirus disease 2019 • Death • Thrombosis • Bleeding

## Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).<sup>1</sup> By August 24, 2021, >212 million cases of COVID-19 have been reported in 190 countries or regions, resulting in >4.96 million deaths.<sup>2</sup> Among hospitalized patients, COVID-19 infection has been associated with endotheliitis, intense endothelial activation, inflammation, and coagulopathy.<sup>1</sup> Patients with moderate or severe disease have consistently shown to have elevated D-dimer levels.<sup>1,3</sup> Moreover, autopsy studies have found a high incidence of macro- and microthrombi, with thromboembolic events representing an important clinical manifestation.<sup>3</sup> Accordingly, the use of prophylactic anticoagulation at a standard-dose regimen has been recommended for the prevention of thromboembolic events.<sup>3</sup> In addition to their effects on micro- and macrothromboembolism, heparin-based products have also been suggested to have anti-inflammatory and antiviral properties, including the ability to directly interact with the spike S1 protein of SARS-CoV-2.<sup>3</sup>

The occurrence of thromboembolic events despite standard-dose prophylactic anticoagulation and growing observations of heparin resistance have suggested the need for the use of prophylactic anticoagulation at an escalated dose for selected patients with COVID-19.<sup>4</sup> Observational studies and a meta-analysis of observational studies have suggested that the use of prophylactic anticoagulation at an escalated dose, composed of intermediate- or therapeutic-dosing regimens, is associated with reduced mortality in critically ill COVID-19 patients with coagulopathy.<sup>5,6</sup> However, randomized controlled trials (RCTs) assessing the safety and efficacy of prophylactic anticoagulation at an escalated dose compared with a standard dose have found contrasting results.<sup>7-13</sup> Of note, none of these RCTs were powered to test the superiority for individual clinical endpoints such as all-cause death or major bleeding. Meta-analyses of RCTs can provide a more precise and powered estimation of the benefit of a specific anticoagulation dosing regimen on such hard and clinically relevant endpoints. Moreover, such estimates can generate interim insights to guide clinical practice and future research.

We therefore performed a systematic review and meta-analysis of available RCTs to determine the safety and efficacy of escalated-dose prophylactic vs. standard-dose prophylactic anticoagulation on critically and non-critically ill hospitalized patients with COVID-19 without a formal indication for therapeutic anticoagulation.

## Methods

### Search strategy and selection criteria

This meta-analysis was done according to the Cochrane Collaboration and Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (see Supplementary material online, *Table S1*).<sup>14</sup> We included RCTs comparing treatment with escalated-dose (defined as

intermediate-dose or therapeutic-dose) vs. a standard-dose prophylactic anticoagulation regimen in critically and non-critically ill COVID-19 patients without a formal indication for anticoagulation.

There was no restriction on the type of anticoagulation used. We included heparinoids [unfractionated heparin (UFH), low-molecular weight heparin (LMWH), or pentasaccharides], vitamin K antagonists (VKAs), direct oral anticoagulants (DOACs), and non-oral direct anticoagulants. Therapeutic, intermediate, or standard doses of anticoagulation regimens used for prophylaxis were defined according to the definitions of the trials [i.e. therapeutic-dose prophylactic anticoagulation: enoxaparin 1 mg/kg twice daily or UFH 10 000 UI subcutaneous (SC) three times a day, or rivaroxaban 20 mg daily; intermediate-dose prophylactic anticoagulation: enoxaparin 1 mg/kg SC daily or UFH 10 000 units SC twice daily; and standard-dose prophylactic anticoagulation: enoxaparin 40 mg SC daily or UFH 5000 units SC twice daily. If indicated, all doses were adjusted by creatinine clearance and body mass index]. For this meta-analysis, therapeutic- and intermediate-dosing regimens were pooled into one group and defined as escalated dose, which was compared to the standard-dose regimen. The rationale for this approach is that both the therapeutic and intermediate doses provide superior anticoagulant effect compared to the standard dose.<sup>15</sup>

Preprint (not peer-reviewed) status was not considered as exclusion criteria. In line with other meta-analysis related to COVID-19 treatment, we considered this strategy acceptable because of the urgency for timely evidence regarding effective treatment of COVID-19 patients.<sup>16</sup> If a preprint article became published during the performance of this study, the analysis was updated with published data. From June 1 to July 15, 2021, we did a systematic digital search using MEDLINE (via PubMed), Cochrane, Embase, Web of Science databases, and medRxiv. In addition, we searched preprints, abstracts, presentations, unpublished data from annual meetings of the following societies: European Society of Cardiology, European Association of Percutaneous Cardiovascular Interventions, American Heart Association, American College of Cardiology, Transcatheter Cardiovascular Therapeutics, and Society of Cardiovascular Angiography and Interventions. Search terms were 'COVID-19', 'SARS-CoV-2', 'anticoagulation', 'prophylactic', 'hospitalized', 'severe', 'critically-ill', 'non-critically-ill', 'therapeutic', 'moderate', 'intensive care unit', 'clinical trial', in addition to combinations of these terms (see Supplementary material online, *Table S2* for the full search strategy). An experienced medical librarian reviewed literature search terms. Two investigators (L.O.P., M.G.) independently screened titles and abstracts for eligibility as well as the full text, supplementary material, online appendices, and reference lists of each eligible study to confirm the inclusion criteria and to identify further published studies. The same two investigators independently performed data extraction. There were no restrictions with respect to the language used, publication status, or publication date. Disagreements were solved by consensus.

### Data analysis

The risk of bias was independently assessed by two investigators (L.O.P., M.G.) according to the Cochrane Collaboration risk-of-bias-tool 2 (RoB 2).<sup>17</sup> The primary efficacy endpoint was all-cause death at the

longest follow-up available in the respective trials. Secondary efficacy endpoints were venous thromboembolism (VTE) (deep vein thrombosis or pulmonary embolism), myocardial infarction (MI), stroke, and systemic arterial embolism. The primary safety endpoint was major bleeding. Secondary safety outcomes were any bleeding and minor bleeding. Major, minor, or any bleeding were defined according to trial definitions. We prioritized the Bleeding Academic Research Consortium definition when available.<sup>18</sup> If not reported, we chose the Thrombolysis in Myocardial Infarction criteria or International Society on Thrombosis and Haemostasis. Details on endpoint definitions are provided in the appendix (see Supplementary material online, *Table S3*).

Risk ratios (RRs) with 95% confidence intervals (95% CIs) were calculated with RevMan software version 5.3 (Cochrane Collaboration) to provide a practical interpretation of effect estimates. The Cochran's Q test and Higgins'  $I^2$  statistics were used to estimate heterogeneity among studies, with  $I^2$  less than 25% indicating low heterogeneity, 25–50% indicating moderate heterogeneity, and more than 50% indicating high heterogeneity.<sup>17</sup> For moderate-to-high heterogeneity, the random-effects model with inverse variance weighting was used, whereas the Mantel-Haenszel fixed-effect model was used for low heterogeneity. *P*-values less than 0.05 were considered significant.

All analyses were run according to the pre-specified subgroups of critically vs. non-critically ill patients to provide both an overall and a specific treatment effect estimate according to clinical status. A difference between the estimates of these subgroups was considered significant for  $P_{\text{interaction}} < 0.10$ .<sup>19</sup>

To explore whether a single study significantly affected our overall findings, we ran a sensitivity analysis by sequentially removing each single study from the pooled effect estimates. Moreover, to address varying durations of follow-up across studies, we also performed a further sensitivity analysis by using incidence risk ratios (IRRs) and associated 95% CIs using R 3.6 (The R Project for Statistical Computing, Vienna). Furthermore, fixed- and random-effects meta-regression analyses were performed to evaluate the impact of concomitant antiplatelet therapy use on the treatment effects of anticoagulation regimens. The 'number needed to treat' (NNT) or the 'number needed to harm' (NNH) to prevent or cause an adverse event were calculated according to the absolute risk differences. The presence of publication bias was investigated by visual estimation of funnel plots. This study is registered with PROSPERO (CRD42021257203).

## Results

### Studies and patient characteristics

Using our search strategy, we screened 2408 potentially relevant articles. The PRISMA flow diagram describing the search and study selection process is available in Supplementary material online, *Table S4*. Seven relevant studies were identified. Our analyses included a total of 5154 patients: 562 from INSPIRATION<sup>7</sup> comparing intermediate vs. standard prophylactic dose with LMWH/UFH in critically ill patients; 614 from ACTION<sup>8</sup> comparing therapeutic- vs. standard-dose prophylactic anticoagulation with rivaroxaban (non-critically ill patients) or enoxaparin (critically ill patients); 1098 from REMAP-CAP, ACTIV-4a, and ATTACC<sup>12</sup> comparing therapeutic- vs. standard-dose prophylactic anticoagulation with LMWH/UFH in critically ill patients; 2219 from REMAP-CAP, ACTIV-4a, and ATTACC<sup>13</sup> comparing therapeutic- vs. standard-dose prophylactic anticoagulation with LMWH/UFH in non-critically ill patients; 20 from HESACOV

19 comparing therapeutic- vs. standard-dose prophylactic anticoagulation with LMWH/UFH in critically ill patients; RAPID<sup>10</sup> comparing therapeutic- vs. standard-dose prophylactic anticoagulation with LMWH/UFH in non-critically ill patients; and 176 from Perepu et al.<sup>11</sup> comparing intermediate- vs. standard-dose prophylactic anticoagulation with LMWH/UFH in critically ill patients. The mean follow-up duration was 33 days. INSPIRATION had the longest follow-up (90 days), whereas HESACOV had the shortest (14 days). COVID-19 infection was confirmed by a polymerase chain reaction in the majority of trials. The median time from hospital admission to randomization was 4 days (interquartile range 2–4 days). The main trial characteristics are shown in *Table 1*. A summary of baseline and clinical characteristics of each trial is shown in Supplementary material online, *Table S5*. A detailed list of the different anticoagulation regimens and outcomes definitions are shown in Supplementary material online, *Table S3*. In the pooled analysis, the rate of treatment with LMWH was 87.4%; enoxaparin was used in 83.1% of patients treated with LMWH (see Supplementary material online, *Table S6*). The risk of bias for each study and estimate of the overall risk of bias are reported in Supplementary material online, *Table S7* and publication bias by visual inspection of funnel plots in Supplementary material online, *Table S8*.

### Primary outcomes

Seven studies were included for the primary outcomes of all-cause death and major bleeding. Overall, the incidence of all-cause death was 17.8% (466/2616) in the escalated-dose and 18.6% (473/2535) in the standard-dose prophylactic anticoagulation group. The incidence of major bleeding was 2.4% (63/2620) and 1.4% (36/2532) in the escalated-dose and standard-dose anticoagulation groups, respectively. Compared to standard-dose prophylactic anticoagulation, escalated-dose prophylactic anticoagulation was not associated with a reduction of all-cause death (RR 0.96, 95%CI 0.78–1.18,  $I^2 = 56\%$ ) but was associated with an increase in major bleeding (RR 1.73, 95%CI 1.15–2.60,  $I^2 = 0\%$ ) (*Figure 1*).

### Secondary outcomes

Seven studies were included for the outcome of VTE. The incidence of VTE was 2.5% (66/2621) with the escalated-dose and 4.7% (119/2528) with the standard-dose prophylactic anticoagulation. An escalated-dose regimen was associated with lower rates of VTE events compared to the standard dose (RR 0.55, 95%CI 0.41–0.74,  $I^2 = 0\%$ ) (*Figure 2*). Moreover, when compared to prophylactic anticoagulation at the standard dose, the reduction in VTE events in patients treated with the escalated dose was mainly driven by a significant lower rate of PE (RR 0.39, 95%CI 0.26–0.58,  $I^2 = 0\%$ ), without any effect on the rate of deep venous thrombosis (RR 1.03, 95%CI 0.60–1.75,  $I^2 = 0\%$ ) (see Supplementary material online, *Table S9*).

Six trials were included for the outcome of MI. The incidence of MI was 0.9% (23/2611) and 1.2% (29/2518) in the escalated-dose and standard-dose groups, respectively, resulting in no significant differences between regimens (RR 0.80, 95%CI 0.47–1.36,  $I^2 = 0\%$ ) (*Figure 2*).

Four trials were included for the outcomes of stroke and systemic arterial embolism. The incidence of stroke was 0.5% (11/2296) and 0.5% (12/2195) in the escalated-dose and standard-dose groups,

**Table 1. General characteristics of the seven randomized controlled trials on escalated-dose vs. standard-dose prophylactic anticoagulation in hospitalized COVID-19 patients.**

Study	Methodology	Treatment arms	Time period	Location	Clinical status	Confirmed by rt-PCR (%)	Sample size	Follow-up Duration (days)
INSPIRATION	Open label, RCT	Intermediate-dose (enoxaparin/UFH) vs. standard-dose prophylactic anticoagulation <sup>b</sup>	From July 29, to November 19, 2020	Iran	Critically ill	100	562	90
ACTION	Open label, RCT	Therapeutic-dose anticoagulation with rivaroxaban (stable patients) or enoxaparin (unstable patients) vs. standard-dose (enoxaparin/UFH) prophylactic anticoagulation <sup>b</sup>	From June 24, 2020, to February 26, 2021	Brazil	Non-critically ill (94%) and critically ill (6%)	100	614	30
REMAP-CAP, ACTIV-4a, and ATTACC	Open label, RCT	Therapeutic-dose (enoxaparin/UFH) vs. standard-dose prophylactic anticoagulation <sup>c</sup>	From April 21, to December 19 2020	UK, USA, Canada, Brazil, and other	Critically ill	91.6	1098	21
REMAP-CAP, ACTIV-4a, and ATTACC	Open label, RCT	Therapeutic-dose (enoxaparin/UFH) vs. standard-dose prophylactic anticoagulation <sup>c</sup>	From April 21, 2020 to January 22, 2021	UK, USA, Canada, Brazil, and other	Non-critically ill	NA	2219	21
HESACOVID	Open label, RCT	Therapeutic-dose (enoxaparin/UFH) vs. standard-dose (enoxaparin/UFH) prophylactic anticoagulation <sup>b</sup>	From April 2020 to July 2020	Brazil	Critically ill	100	20	14
RAPID <sup>a</sup>	Open label, RCT	Intermediate-dose (enoxaparin/UFH) vs. standard-dose prophylactic anticoagulation <sup>b</sup>	From May 2020 to April 2021	Canada, Saudi Arabia, Brazil, and other	Non-critically ill	100	465	28
Perepu et al.	Open label, RCT	Therapeutic-dose (enoxaparin/UFH) vs. standard-dose prophylactic anticoagulation (enoxaparin/UFH) <sup>b</sup>	From April 2020 to January 2021	USA	Critically ill	100	176	30

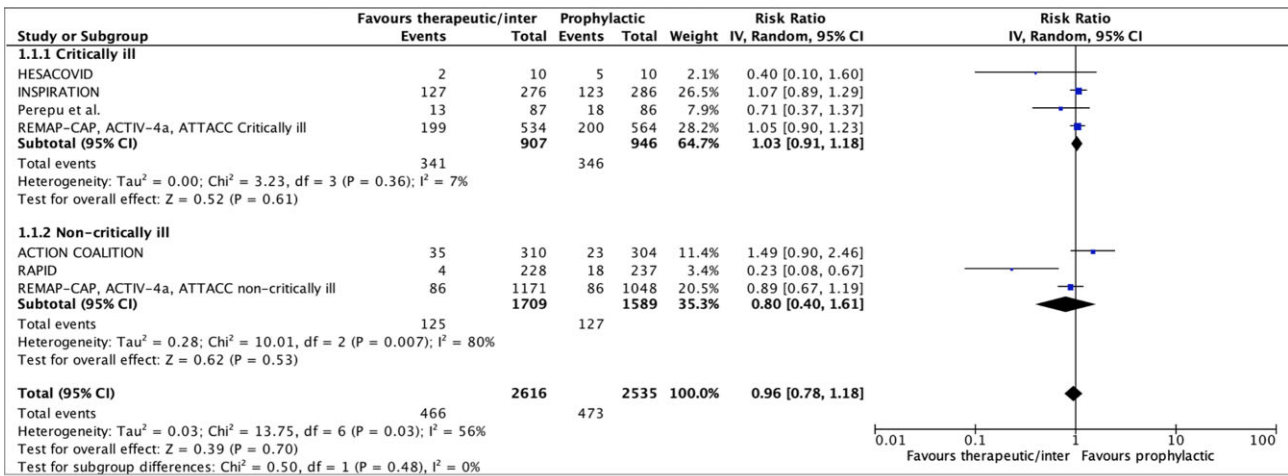
RCT, randomized controlled trial; UFH, unfractionated heparin; UK, United Kingdom; USA, United States of America; rt-PCR, reverse transcription polymerase chain reaction; NA, not available.

<sup>a</sup> Preprint manuscript.

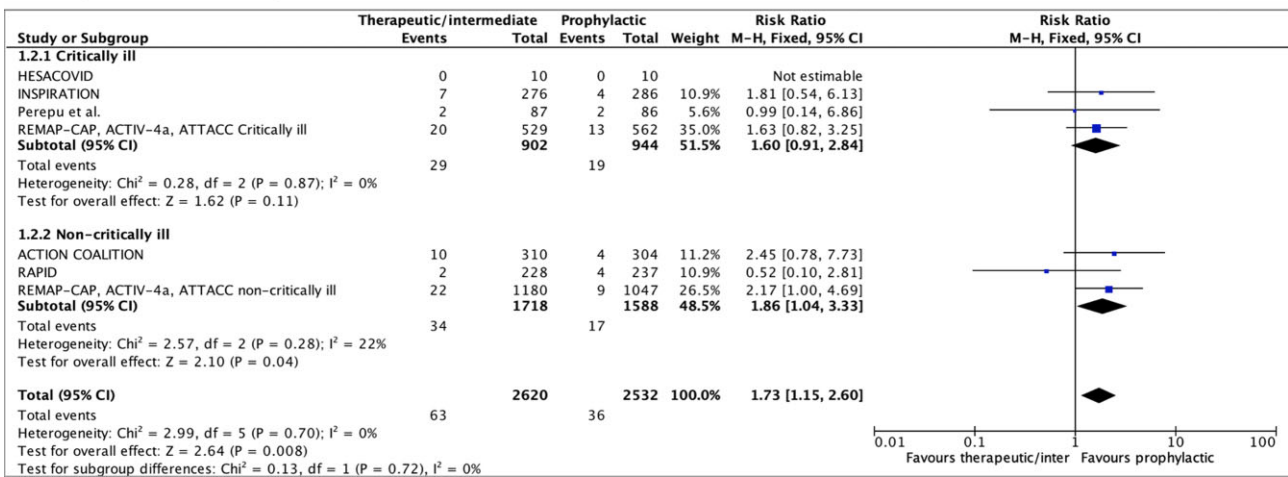
<sup>b</sup> Defined according to trial protocol.

<sup>c</sup> Standard-dose prophylactic anticoagulation was defined according to local site protocols.

### All-cause death



### Major bleeding



**Figure 1.** Forest plots according to pre-specified subgroups (critically vs. non-critically ill) of escalated-dose vs. standard-dose prophylactic anticoagulation for the primary efficacy (all-cause death) and safety (major bleeding) endpoints. CI = confidence intervals; M-H = Mantel-Haenszel; IV = inverse variance.

respectively, resulting in no significant differences between regimens (RR 0.94, 95%CI 0.43–2.09, I<sup>2</sup> = 0%) (Figure 2). The incidence of systemic arterial embolism was 0.4% (9/2296) and 0.3% (6/2195) in the escalated-dose and standard-dose groups, respectively, resulting in no significant differences between regimens (RR 1.20, 95%CI 0.29–4.95, I<sup>2</sup> = 27%) (Figure 2).

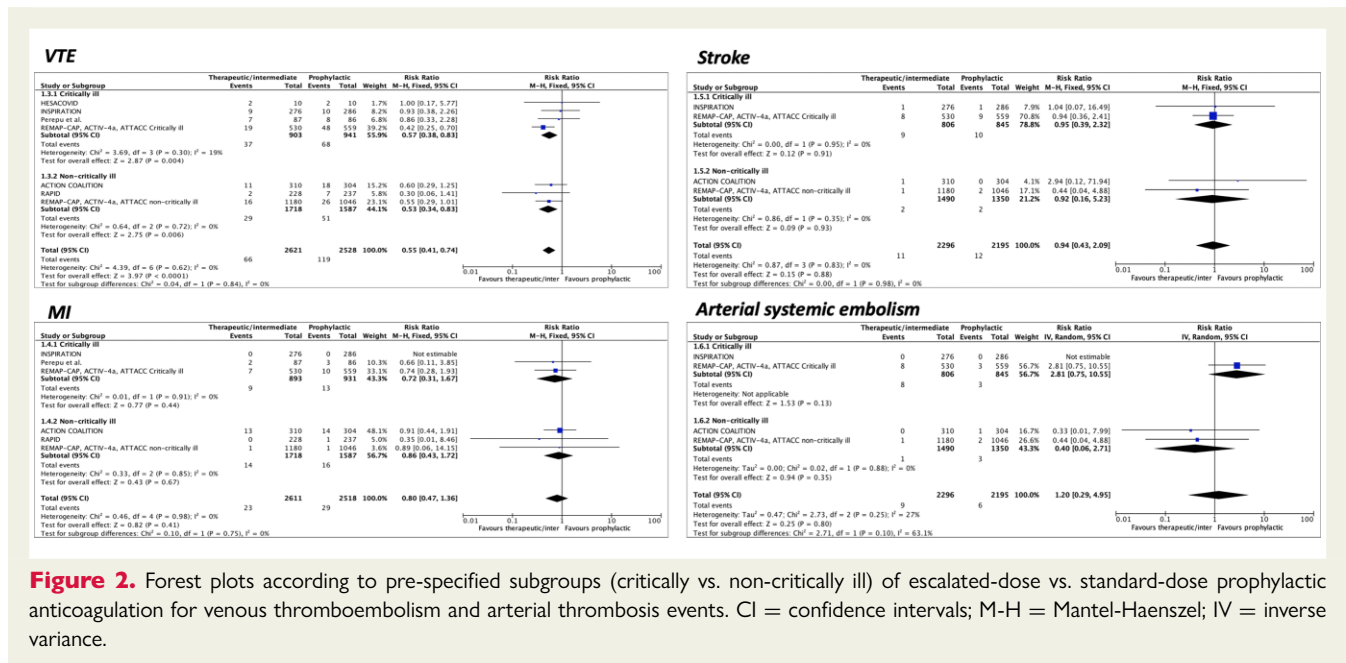
Four studies were included for the outcome of any bleeding and minor bleeding. The incidence of any bleeding was 9.5% (65/683) with prophylactic anticoagulation at the escalated dose and 4.2% (29/686) at the standard dose. The incidence of minor bleeding was 5.3% (36/683) and 2.2% (15/686) in the escalated-dose and standard-dose groups, respectively. Prophylactic anticoagulation at the escalated dose was associated with higher rates of any bleeding (RR 2.01, 95%CI 1.08–3.74, I<sup>2</sup> = 47%) and minor bleeding (RR 2.23, 95%CI 1.04–4.81, I<sup>2</sup> = 30%) compared to prophylactic anticoagulation at the standard dose (Figure 3).

### Sensitivity and subgroup analyses

Sensitivity analysis by sequentially excluding one trial at a time showed that individual study data did not generally influence any of the included outcomes. Exceptions were major bleeding after exclusion of REMAP-CAP, ACTIV-4a, and ATTACC non-critically ill patients. While after exclusion of the HESACOVID, ACTION, or INSPIRATION trial, the results of the outcomes any and minor bleeding were affected (see Supplementary material online, Table S10).

Subgroup analysis showed consistent results for all included outcomes among both critically ill and non-critically ill patients, except for any bleeding, which was significantly higher in non-critically ill, but not in critically ill patients (P<sub>interaction</sub> = 0.03) (Figures 1–3).

The results were consistent in the sensitivity analyses performed with IRR (see Supplementary material online, Table S11).



**Figure 2.** Forest plots according to pre-specified subgroups (critically vs. non-critically ill) of escalated-dose vs. standard-dose prophylactic anticoagulation for venous thromboembolism and arterial thrombosis events. CI = confidence intervals; M-H = Mantel-Haenszel; IV = inverse variance.

At meta-regression analysis, we did not find any association between the concomitant use of antiplatelet therapy and the treatment effects of the anticoagulation regimens in both fixed-effects and random-effects models (see Supplementary material online, Table S12).

## Numbers needed to treat

The NNT and NNH calculations reflecting the number of treated patients needed to prevent or cause each outcome are shown in Figure 4. The NNT for all-cause death was 119, whereas the NNT for VTE was 46. The NNH for major, minor, and any bleeding events were 102, 32, and 16, respectively.

## Discussion

In this comprehensive meta-analysis including all available RCTs comparing prophylactic anticoagulation at an escalated vs. standard dose in hospitalized COVID-19 patients without a formal indication to be on therapeutic anticoagulation, we found that the escalated dosing regimen: (1) was not associated with lower risk of all-cause death; (2) was associated with significantly higher rates of any, major, and minor bleeding; (3) was associated with significantly lower rates of VTE, driven by a reduction in PE, but not of arterial thrombotic events; (4) showed consistent safety and efficacy profiles among both critically and non-critically ill patients.

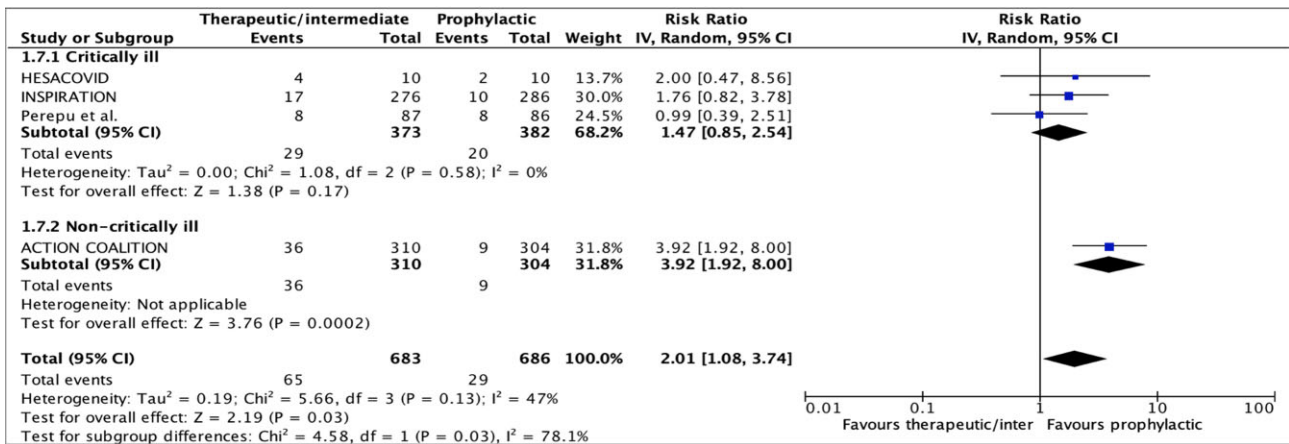
Thromboprophylaxis is a guideline-recommended therapy for preventing VTE in selected hospitalized medical and surgical patients without an indication for anticoagulation therapy.<sup>20</sup> Current evidence suggests that thromboprophylaxis reduces the risk of VTE in hospitalized patients with risk factors.<sup>21</sup> However, thromboprophylaxis does not eliminate the risk of VTE or VTE-related death. Of note, in acutely ill medical patients, thromboprophylaxis does not reduce mortality.<sup>21</sup> The potential clinical benefits of thrombo-

prophylaxis on VTE prevention are associated with an increase in major and non-major bleeding, especially in the presence of risk factors such as frailty, active gastroduodenal ulcer, previous bleeding, and low platelet count.<sup>22</sup> Nevertheless, a risk-balance assessment suggests that the benefits outweigh the risks, and therefore, it is considered a standard of care in selected patients.<sup>20</sup>

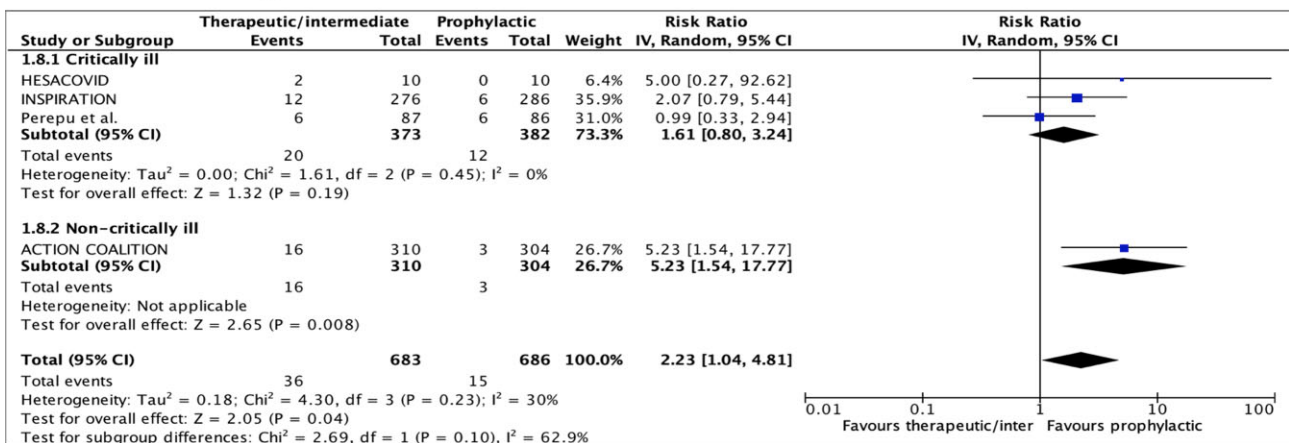
Because of the pro-coagulant state and increased risk of thromboembolic events in COVID-19 patients, the use of anticoagulation for prophylactic purposes is recommended.<sup>23</sup> Anticoagulation can indeed be of potential benefit for the treatment and prevention of venous and arterial micro- and macrothrombosis.<sup>1</sup> An early finding suggested that using an escalated rather than a standard prophylactic anticoagulant dosing regimen decreased mortality in patients with severe COVID-19 and coagulopathy.<sup>5</sup> However, this study was not randomized, it excluded patients with bleeding diathesis, and included only patients from China. A meta-analysis of observational studies including 25 719 hospitalized COVID-19 patients found that an escalated prophylactic anticoagulant dosing regimen was associated with a 50% reduction in in-hospital mortality.<sup>6</sup> Nevertheless, the absence of data from RCTs is a major limitation of these findings. Several RCTs were designed worldwide to address the critical clinical question on the safety and efficacy of anticoagulation in COVID-19 patients.<sup>7-9</sup> However, none of these trials were powered for testing the superiority of treatment regimens with respect to all-cause death or major bleeding.

In this meta-analysis including 5154 hospitalized COVID-19 patients from 7 RCTs, we found that the use of prophylactic anticoagulation at an escalated dose was not associated with a significant reduction in all-cause death compared to the standard dose regardless of the clinical status (i.e. critically and non-critically ill patients). Heterogeneity among trials for all-cause death was high (56%) possibly reflecting multiple causes of death including both bleeding and thromboembolic events. Compared to the standard prophylactic anticoagulant dose, the escalated-dosing regimen

### Any bleeding



### Minor bleeding

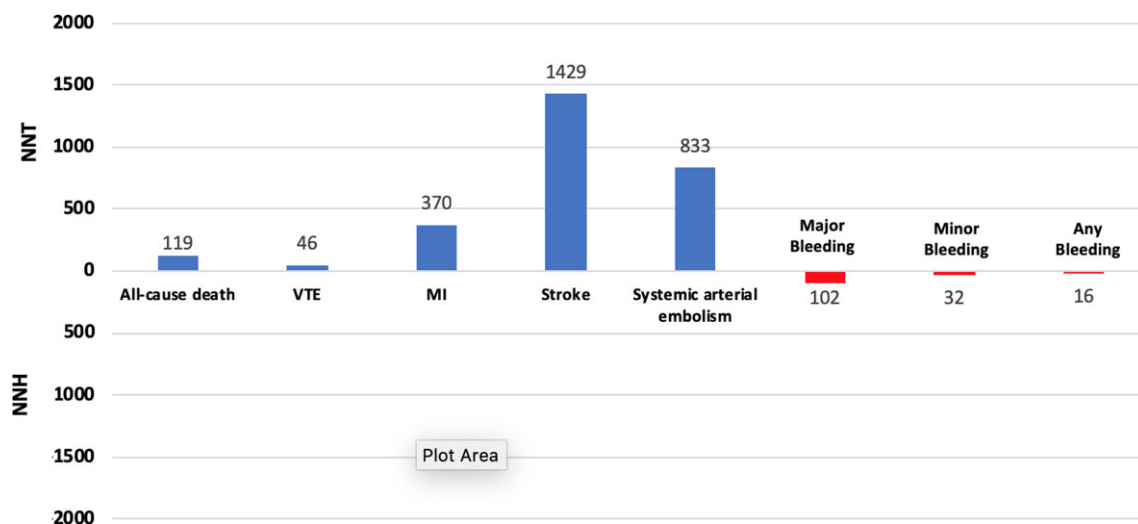


**Figure 3.** Forest plots according to pre-specified subgroups (critically vs. non-critically ill) of escalated-dose vs. standard-dose prophylactic anticoagulation for any and minor bleeding. CI = confidence intervals; M-H = Mantel-Haenszel, IV = inverse variance.

significantly reduced VTE, with an NNT of 46, but significantly increased the risk of bleeding, with an NNH of 102. There were no significant differences on arterial thrombotic events. Overall, the cumulative evidence to support the routine use of escalated-dose prophylactic anticoagulation in clinical practice is limited. An escalated dose might be considered only on an individual basis, when thrombotic risk is deemed too heavily outweigh the bleeding risk. It should be highlighted that of the included trial, the REMAP-CAP, ACTIV-4a, and ATTACC non-critically ill patients met its primary composite endpoint of organ support—free days.<sup>13</sup> However, this endpoint was not included in this analysis because it was only measured in the REMAP-CAP, ACTIV-4a, and ATTACC trials.

COVID-19 patients may exhibit complex coagulopathy states. While at the beginning of the disease patients may exhibit a pro-thrombotic state, those who advance to severe forms of the disease may exhibit a disseminated intravascular coagulopathy (DIC)-like state.<sup>24</sup> Therefore, as the severity of the COVID-19 increase, the bleeding risk may also increase. In the present analysis, major bleeding and VTE were both more frequent among critically

vs. non-critically ill patients (2.6% vs. 1.5% for bleeding and 5.7% vs. 2.4% for VTE), but critical-illness status did not significantly interact with treatment effects on these outcomes. Timing of administration of anticoagulation may be crucial. On average, the median time from symptom onset to randomization in the included trials was close to 10 days (7–8 days from symptom onset to hospitalization and 2–4 days from hospitalization to randomization). At this time point, some patients can be ending the pro-coagulant state and transitioning into a DIC-like state, albeit bleeding rates are not as high. Thus, in patients in whom the predominant state is pro-coagulant, prophylactic anticoagulation at an escalated dose may be potentially beneficial. However, in patients who advance to a DIC-like state, such escalated regimen may be harmful. Of note, observational studies have reported that major bleeding events may be related to higher risk of death in COVID-19 patients and should be considered as important as thrombotic events.<sup>25</sup> Optimizing patient selection and the window for treatment with anticoagulant therapy can be challenging and warrants further research. The application of prediction models to identify patients at higher risk of thrombotic



**Figure 4.** Number needed to treat (NNT) and number needed to harm (NNH). VTE = venous thromboembolism; MI = myocardial infarction.

events may improve patient selection who can benefit from escalated doses of prophylactic anticoagulation.<sup>26</sup> Moreover, special populations such as the elderly may benefit from tailored dose anticoagulation to minimize the risk of adverse events.<sup>27</sup> However, this approach should be tested in dedicated RCTs.

In clinical practice, knowing the inflammatory status of an individual patient may be of potential utility given its association with the risk of bleeding. Observational studies have suggested that high C-reactive protein levels may be associated with an increased bleeding risk.<sup>28</sup> Therefore, it may be hypothesized that anti-inflammatory therapies may modulate the risk of bleeding. Given the pro-inflammatory status which characterizes patients with COVID-19, the link between anti-inflammatory therapies and bleeding outcomes is important and warrants further investigation.

Prophylactic anticoagulation at an escalated dosing regimen was associated with a lower rate of VTE, driven by a reduction in PE, without any effect on arterial thrombotic events. Although arterial thrombotic events occur less frequently than VTE, they have greater impact on adverse prognosis.<sup>29,30</sup> This may be attributed to the fact that VTE is commonly represented by in situ PE in COVID-19 patients.<sup>1,31</sup> Taking into consideration the differential prognostic impact of venous vs. arterial thrombotic events, including all-cause death, it appears that VTE prevention does not compensate for the increase in bleeding risk associated with the use of prophylactic anticoagulation at an escalated-dosing regimen.

Ultimately, we performed a subgroup analysis according to clinical status (i.e. critically and non-critically ill). The rationale for this analysis is that several factors differ from critically and non-critically ill patients, including indication for VTE prophylaxis, vital prognosis, coagulopathy state, bleeding risk profile, drug selection, via of drug administration, and drug interactions. We only found a significant interaction between subgroups in the endpoint of any bleeding. However, we believe this interaction should be considered cautiously because the endpoint of any bleeding was reported by only three trials including critically ill patients and one trial including non-critically

ill patients. Moreover, this significant interaction was not found for the outcomes of major or minor bleeding endpoints. Overall, all results were consistent independently of the clinical status of the patient. This finding has important clinical implications because previous observational data suggested that critically ill patients may benefit more from an escalated anticoagulant dosing regimen than non-critically ill patients.<sup>6</sup> The results of this meta-analysis of RCTs do not support these findings.

## Limitations

This meta-analysis has limitations. First, trial-level rather than individual-level data were used to assess outcomes. Second, due to the limited size of specific groups, we did not perform detailed subgroup analyses according to baseline characteristics. However, all analyses were performed according to a pre-specified subgroup analysis by clinical status (critically vs. non-critically ill), which is the main prognostic determinant. Third, ACTION was the only trial using a DOAC (i.e. rivaroxaban) as anticoagulation strategy compared to the other trials (using UFH/LMWH). Nevertheless, we ran sensitivity analyses for all the endpoints removing the ACTION trial, and the overall study findings remained consistent. Fourth, the INSPIRATION and Perepu et al. trials used an intermediate dose of anticoagulation (enoxaparin/UFH) rather than a full anticoagulant dose. However, the study findings were consistent even after the exclusion of the INSPIRATION or Perepu et al. trials results. Fifth, one preprint trial was included in this meta-analysis. Nonetheless, there is a low probability of a change in the raw data during the peer-review process and, in light of the urgent status due to the pandemic, it is essential to provide in a timely fashion updated evidence to guide clinical practice. Sixth, since we performed a meta-analysis of aggregated data, we cannot rule out the risk of ecological bias. Moreover, since less than 10 studies were included in this analysis, the accuracy of funnel plots as well of meta-regression analyses may be debated. Therefore, we cannot rule out the presence of publication and reporting bias of the studied outcomes. Ultimately,



over 30 RCTs are still enrolling patients with the aim of comprehensively evaluating the role of anticoagulation in COVID-19 patients using a wide variety of drugs at different regimens in diverse clinical settings.<sup>32</sup> Therefore, once these further studies will be available, future updated meta-analyses, possibly performed at a patient-level, including a network design, and multivariate rather than univariate analyses, will play an essential role in defining the safety and efficacy of therapeutic vs. standard prophylactic anticoagulation in critically and non-critically ill patients with COVID-19.

## Conclusions

In hospitalized patients with COVID-19 without an indication for therapeutic anticoagulation, although the use of prophylactic anticoagulation at an escalated dose was associated with a reduction in the risk of VTE compared to a standard dose, it was not associated with a reduction in all-cause death or other adverse ischemic events but with a significant increase in major bleeding. These findings were consistent among critically and non-critically ill patients. The overall findings of this meta-analysis of RCTs do not support the routine use of prophylactic anticoagulation at an escalated over a standard dose in hospitalized patients with COVID-19.

## Supplementary material

Supplementary material is available at *European Heart Journal—Cardiovascular Pharmacotherapy* online.

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**Data availability statement:** Extracted data are available on request to the corresponding author.

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