Journal Pre-proof

Thromboprophylaxis in Patients with COVID-19. A Brief Update to the CHEST Guideline and Expert Panel Report

Lisa K. Moores, MD, Tobias Tritschler, MD, MSc, Shari Brosnahan, MD, Marc Carrier, MD, Jacob F. Collen, MD, Kevin Doerschug, MD, MS, Aaron B. Holley, MD, Jonathan Iaccarino, MD, David Jimenez, MD, PhD, Gregoire LeGal, MD, PhD, Parth Rali, MD, Philip Wells, MD

PII: S0012-3692(22)00250-1

DOI: https://doi.org/10.1016/j.chest.2022.02.006

Reference: CHEST 4897

To appear in: *CHEST*

Received Date: 16 December 2021

Revised Date: 4 February 2022

Accepted Date: 7 February 2022

Please cite this article as: Moores LK, Tritschler T, Brosnahan S, Carrier M, Collen JF, Doerschug K, Holley AB, Iaccarino J, Jimenez D, LeGal G, Rali P, Wells P, Thromboprophylaxis in Patients with COVID-19. A Brief Update to the CHEST Guideline and Expert Panel Report, *CHEST* (2022), doi: https://doi.org/10.1016/j.chest.2022.02.006.

Thromboprophylaxis in Patients with COVID-19. A Brief Update to the CHEST Guideline and Expert Panel Report

Lisa K. Moores MD[1], Tobias Tritschler MD, MSc,[2] Shari Brosnahan MD[3], Marc Carrier MD[4], Jacob F. Collen MD[1,5], Kevin Doerschug MD, MS[6], Aaron B. Holley MD[5], Jonathan Iaccarino, MD[7,8], David Jimenez MD, PhD[9,10], Gregoire LeGal MD, PhD[4], Parth Rali MD[11], Philip Wells MD[4].

[1]Department of Medicine, F. Edward Hebert School of Medicine at the Uniformed Services University of the Health Science, Bethesda, MD
[2]Department of General Internal Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland
[3]Division of Pulmonary, Critical Care, and Sleep Medicine, New York University Langone Health System, New York, New York
[4]Department of Medicine, Ottawa Hospital Research Institute, University of Ottawa, Ottawa, Ontario, Canada
[5]Pulmonary, Critical Care and Sleep Medicine Service, Walter Reed National Military Medical Center, Bethesda, MD
[6]Pulmonary, Critical Care, and Occupational Medicine, University of Iowa, Iowa City, IA
[7]American College of Chest Physicians, Glenview, IL
[8]The Pulmonary Center, Boston University School of Medicine, Boston, MA
[9]Respiratory Medicine, Ramón y Cajal Hospital (IRYCIS), Madrid, Spain
[10]CIBER Enfermedades Respiratorias (CIBERES), Madrid, Spain
[11]Department of Thoracic Medicine and Surgery, Lewis Katz School of Medicine, Temple University, Philadelphia, PA

Correspondence to:

Lisa K. Moores MD, FCCP, MACP, FRCP
Associate Dean for Assessment and Professional Development
Professor of Medicine
F. Edward Hebert School of Medicine
The Uniformed Services University of the Health Sciences
Bethesda, MD
Email: lisa.moores@usuhs.edu

Conflict of Interest: None of the authors have any conflict of interest related to the content of this manuscript

Authors Roles:

LKM has full responsibility of the content and accuracy of the manuscript.

SB, MC, JC, KD, AH, DJ, GL, LKM, PR, TT, PW played an equal role in development of the PICO questions and drafting of the recommendations.

LKM drafted the initial manuscript. DJ prepared Table 1. TT prepared Table 2. PR prepared Table 3. JI performed the literature searches, ROB assessment, meta-analyses and evidence summaries.

SB, MC, JFC, KD, ABH, JI, DJ, GL, PR, TT, PW contributed equally to review and editing of the manuscript.

Word Count:

Abstract: 250

Main text: 3253

Key Words:

COVID-19, venous thromboembolism, deep vein thrombosis, pulmonary embolism, hypercoagulability, DIC

Abbreviations:

CI: Confidence Interval

COVID-19: coronavirus disease 2019

DVT: deep vein thrombosis

ICU: intensive care unit

LMWH: low-molecular-weight heparin

OR: Odds Ratio

OSFDs: Organ support free days

PE: pulmonary embolism

PICO: Population, Intervention, Comparator, Outcome

RCTs: Randomized Controlled Trials

RR: Relative Risk

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

UFH: unfractionated heparin

VTE: venous thromboembolism

Abstract:

Background:
Patients hospitalized with COVID-19 often exhibit markers of a hypercoagulable state and have an increased incidence of venous thromboembolism (VTE). In response, CHEST issued rapid clinical guidance regarding prevention of VTE. Over the past 18 months the quality of the evidence has improved. We thus sought to incorporate this evidence and update our recommendations as necessary.

Methods:

This update focuses on the optimal approach to thromboprophylaxis in hospitalized patients. The original questions were used to guide the search, using MEDLINE via PubMed. Eight randomized controlled trials and one observational study were included. Meta-analysis, using a random effects model, was performed. The panel created summaries using the GRADE Evidence-to-Decision framework. Updated guidance statements were drafted, and a modified Delphi approach was used to obtain consensus.

Results:
We provide separate guidance statements for VTE prevention for acutely (moderately) ill hospitalized patients and critically ill patients in the ICU. However, we divided each original question and resulting recommendation into two questions: standard prophylaxis vs. therapeutic (or escalated dose) prophylaxis and standard prophylaxis vs. intermediate dose prophylaxis. This led to a change in one recommendation, and an upgrading of three additional recommendations based upon higher quality evidence.

Conclusions:
Advances in care for patients with COVID-19 have improved overall outcomes. Despite this, rates of VTE in these patients remain elevated. Critically ill patients should receive standard thromboprophylaxis for VTE and moderately ill patients with a low bleeding risk might benefit from therapeutic heparin. We see no role for intermediate dose thromboprophylaxis in either setting.

Summary of Recommendations

Recommendation 1: In acutely ill hospitalized patients with COVID-19 who have low risk of bleeding, with consideration for the remarks below, we suggest therapeutic dose heparin (UFH or LMWH) over current standard dose anticoagulant thromboprophylaxis (conditional recommendation, ungraded consensus-based statement).

Remarks: Providers should carefully weigh the risks of thrombosis and bleeding in making this decision. Patients with an significantly elevated D-dimer level (studies have previously defined this as 2-4x the upper limit of normal), those with prior VTE, or other comorbidities known to be associated with VTE may be at increased risk of thrombosis. Patients with high risk of bleeding include, but are not limited to, those with known bleeding within the last 30 days requiring emergency room presentation or hospitalization, known history of an inherited or acquired bleeding disorder, active dual antiplatelet therapy, recent ischemic stroke, intracranial malignancy, history of bleeding diatheses (e.g., hemophilia), history of gastrointestinal bleeding within previous 3 months, thrombolysis within the previous 7 days, presence of an epidural or spinal catheter; recent major surgery <14 days, or uncontrolled hypertension (sBP >200 mmHg, dBP >120 mmHg).

Recommendation 2: In acutely ill hospitalized patients with COVID-19 who are not receiving therapeutic dose heparin (UFH or LMWH), we recommend current standard dose anticoagulant thromboprophylaxis over intermediate dose anticoagulation (defined as LMWH BID or increased weight-based dosing that is less than recommended therapeutic doses) (strong recommendation, ungraded consensus-based statement).

Recommendation 3: In critically ill patients with COVID-19, we suggest current standard dose anticoagulant thromboprophylaxis (with UFH or LMWH) over therapeutic dose anticoagulation (conditional recommendation, ungraded consensus-based statement).

Recommendation 4: In critically ill patients with COVID-19, we suggest current standard dose anticoagulant thromboprophylaxis over intermediate dose anticoagulation (defined as LMWH BID or increased weight-based dosing that is less than recommended therapeutic doses) (conditional recommendation, ungraded consensus-based statement).

Background

Within the first few months of the COVID-19 global pandemic, it was recognized that patients hospitalized with SARS-CoV-2 often exhibited markers of a hypercoagulable state and had an increased incidence of venous thromboembolism (VTE). Reports documented significantly elevated D-dimer levels that were associated with increased morbidity and mortality.[1,2] This led many professional societies, including CHEST[3], to develop rapid guidance documents regarding the optimal strategy for prophylaxis of VTE in these patients.[4-10] Initially, evidence was

extremely limited and consisted of fewer than 30 retrospective cohort studies of varying size that reported on patients from varied geographic regions and clinical settings. There was no universal approach to screening or diagnosis. Perhaps most importantly, the thromboprophylaxis regimens varied across studies and were sometimes not reported at all. Based upon the limited, low-quality evidence suggesting patients with COVID-19 pneumonia had a higher risk of thrombosis than similarly ill patients without COVID-19, societal guidelines were uniform in their recommendation that all hospitalized patients with COVID-19 pneumonia receive pharmacologic thromboprophylaxis in the absence of a contraindication. Recommendations regarding the optimal dosing, however, varied. Some, including CHEST, recommended standard dose prophylaxis for all patients, while a few suggested that intermediate or therapeutic dosing could be considered, especially in patients admitted to the intensive care unit. See **Table 1** for a summary of these early recommendations.

Since then, our understanding of the underlying pathophysiologic mechanisms of this prothrombotic state has advanced. While it is beyond the scope of this manuscript to describe these mechanisms in detail, it should be noted that there are two distinct but related processes: a hypercoagulable state that leads to large vessel macro thrombosis and a primary endotheliopathy that results in extensive in-situ, immunothrombosis. A more detailed review of these mechanisms has recently been published.[11] Over the past 15 months, we have also seen the emergence of randomized controlled trials (RCTs) focusing on the optimal dosing for thromboprophylaxis in both moderately ill hospitalized (non-ICU) and critically ill (ICU) patients. Here we provide updated guidance focused on prevention of thrombosis in hospitalized patients. We are not updating any prior guidance related to pre- or post-hospital prophylaxis, diagnosis, or treatment.

Methods

The panel followed standard CHEST process for the development of rapid guidance statements, as detailed in the first version of this guideline.[3] Conflict of interest declarations were reviewed for all panelists by the Professional Standards Committee. No panelist required any management for the topic areas being updated. The panel was aware of recently published or studies expected to be published soon regarding optimal thromboprophylaxis and thus chose to limit this update to guidance statements in this topic area. The original Population, Intervention, Comparator, Outcome (PICO) questions were used to guide the search, using MEDLINE via PubMed. Screening and full text selection were performed in duplicate by pairs of panel members. Additional studies were identified by panel members as they were published. Included studies[12-20] are outlined in **Table 2**.

Risk of bias was assessed by the methodologist using Version 2 of the Cochrane risk-of bias tool for randomized trials (RoB 2).[21] Data abstraction was done in duplicate. Any discrepancies were resolved through consensus. Primary outcomes included VTE (pulmonary embolism [PE] and deep vein thrombosis [DVT]), fatal PE, major bleeding, fatal bleeding, mortality, and organ support-free days (OSFDs). As our original guideline focused on VTE, we did not include arterial thrombosis as an outcome. A meta-analysis, using a random effects model, was performed.

The panel then created summaries using the GRADE Evidence-to-Decision framework.[22] These summaries were discussed by the entire group, and updated guidance statements were suggested and voted upon using a modified Delphi approach. This approach utilized several rounds of anonymous voting, with survey results and comments presented to the panel after each round until consensus was achieved. Per CHEST policy, consensus was defined as at least 80% agreement for each recommendation with at least 75% voting participation rate from the panel. Recommendation 1 was controversial and required four rounds of voting (see context comments below. Recommendation 2 reached consensus in three rounds of voting. Recommendations 3 and 4 each reached consensus after two rounds of voting.

Results and Recommendations

As in the first version of the guideline, we chose to provide separate guidance statements for VTE prevention for acutely ill hospitalized patients (also described as moderately ill, or non-ICU patients) and critically ill patients either hospitalized in the ICU or receiving ICU level care. However, we divided each original PICO question and resulting recommendation into two questions: standard prophylaxis vs. therapeutic (or escalated dose) prophylaxis and standard prophylaxis vs. intermediate dose prophylaxis.

Acutely Ill Hospitalized Patients

Question 1: Should acutely ill patients with COVID-19 be treated with therapeutic anticoagulation or thromboprophylaxis for prevention of VTE?

There were four studies reporting on 3475 patients addressing this question, the largest being the multiplatform ATTACC, ACTIV-4a, and REMAP-CAP study[12] that enrolled 2244 patients. Additional studies included the ACTION[16], RAPID[19], and HEP-COVID[20] trials. For both the multiplatform[12] and HEP-COVID[20] trials, we were only able to include PE as DVT rates were not mutually exclusive from PE. There was a reduction in any VTE in the therapeutic anticoagulation group (risk ratio [RR] 0.48 [95% CI 0.30-0.78]), at the expense of increased major bleeding (RR 1.79 [95% CI 1.01-3.16]) (Figure 1a/1b). No data regarding fatal PE could be extracted. Fatal bleeding was extremely rare and occurred in 0.3% (3/1180) of the therapeutic anticoagulation group compared to 0.1% (1/1047) in the thromboprophylaxis group in the multiplatform trial. The RAPID[19] trial reported no fatal bleeding in either group. There was no statistically significant difference in mortality between therapeutic and prophylactic anticoagulation (RR 0.75 [95% CI 0.41-1.37]) (Figure 1c). Therapeutic anticoagulation increased OSFDs compared to usual care with an OR of 1.27 (95% CI 1.03-1.58) in the multiplatform trial.[12] The RAPID[19] trial noted a statistically insignificant increased odds of OSFDs in the therapeutic group with an OR of 1.41 (95% CI 0.90-2.20) and the HEP-COVID[20] trial reported 7/84 (8.3%) in therapeutic group required mechanical ventilation compared to 13/86 (15.1%) in the thromboprophylaxis group. After considerable discussion and four rounds of voting, the panel reached consensus on the following recommendation.

Recommendation 1: In acutely ill hospitalized patients with COVID-19 who have low risk of bleeding, with consideration for the remarks below, we suggest therapeutic dose heparin (UFH or LMWH) over current standard dose anticoagulant thromboprophylaxis (conditional recommendation, ungraded consensus-based statement).

Remarks: Providers should carefully weigh the risks of thrombosis and bleeding in making this decision. Patients with an significantly elevated D-dimer level (studies have previously defined this as 2-4x the upper limit of normal), those with prior VTE, or other comorbidities known to be associated with VTE may be at increased risk of thrombosis. Patients with high risk of bleeding include, but are not limited to, those with known bleeding within the last 30 days requiring emergency room presentation or hospitalization, known history of an inherited or acquired bleeding disorder, active dual antiplatelet therapy, recent ischemic stroke, intracranial malignancy, history of bleeding diatheses (e.g., hemophilia), history of gastrointestinal bleeding within previous 3 months, thrombolysis within the previous 7 days, presence of an epidural or spinal catheter; recent major surgery <14 days, or uncontrolled hypertension (sBP >200 mmHg, dBP >120 mmHg).

Context:

The panel struggled to come to consensus on this recommendation. From a pure VTE perspective, these trials are consistent with historical trials---therapeutic heparin, either intravenous UFH or full dose LMWH, reduces VTE at the cost of increased bleeding, without any benefit in overall mortality. The reporting of decreased OSFDs in the multiplatform trial[12] deserves notice but is not a typical outcome used in VTE studies. That said, in balance, the benefits of therapeutic vs. prophylactic dosing appears to favor the former. Several nuanced issues beyond this were discussed. The ACTION[16] trial, which was the only to use therapeutic doses of rivaroxaban as opposed to heparin, showed no overall benefit. To explain this, we might invoke that there are additional pleiotropic and/or anti-inflammatory effects of heparin that are beneficial beyond the benefits of thromboprophylaxis. While plausible, studies in similarly ill patients without COVID-19 have been inconclusive. The panel also noted the inconsistency in effect between acutely (moderately) ill hospitalized patients and critically ill patients, with the OSFD benefit only being seen in the former. This invokes a hypothesis regarding timing of the initiation. Perhaps early administration of therapeutic heparin does indeed affect the underlying pathophysiologic mechanisms in a way that reduces macro and microthrombosis, but once patients develop more severe end-organ damage, the harmful effects outweigh any benefit. This is also plausible, but not fully studied. Another concern raised was the likelihood of ascertainment bias (patients in the therapeutic arm of an open label trial may be less likely to undergo diagnostic testing for VTE). Finally, the panel raised concern that the extremely low rate of bleeding in these trials does not match real world rates, perhaps because patients with high risk of bleeding were excluded, and thus assessment of bleeding risk is paramount in decision making. Panel members also pointed out the heterogeneous populations included in the trials and the known changes in standard

management over time. Given all of this, the panel voted to make a conditional recommendation in favor of therapeutic anticoagulation, while noting in the remarks that the decision should be based upon the risk of thrombosis (those with higher D-Dimer levels or other risks for VTE may be at higher risk) and the risk of bleeding (see **Table 3** for a more extensive list of factors associated with an increased risk of bleeding). Although consensus was reached, one panel member strongly disagreed with this recommendation.

Question 2: Should patients with COVID-19 hospitalized in the ward setting be treated with intermediate dose anticoagulation or thromboprophylaxis?

There were no randomized trials addressing this question. The only study to inform this question was an observational cohort that reported on rates of VTE stratified by thromboprophylaxis received.[14] The rate of VTE in the intermediate dosing group was 7/33 (21%) and in the prophylactic dose group, 20/67 (30%). Bleeding estimates were not reported. Given our original recommendation against intermediate dosing in these patients, the evidence already presented above for consideration of therapeutic dosing in this cohort, and the lack of any evidence suggesting clear benefit of this approach, the panel voted to endorse the prior recommendation, with consensus reached after one round of voting.

Recommendation 2: In acutely ill hospitalized patients with COVID-19 who are not receiving therapeutic dose heparin (UFH or LMWH), we recommend current standard dose anticoagulant thromboprophylaxis over intermediate dose anticoagulation (defined as LMWH BID or increased weight-based dosing that is less than recommended therapeutic doses) (strong recommendation, ungraded consensus-based statement).

Context

Given the lack of RCTs to address this question, there was unanimous agreement regarding this recommendation. Panel members also noted that 'intermediate dose anticoagulation' leaves too much room for error and confusion in clinical practice.

<u>Critically Ill Patients</u>

Question 3: Should critically ill patients with COVID-19 be treated with therapeutic anticoagulation or thromboprophylaxis for prevention of VTE?

For this analysis, we chose to include all studies that compared standard thromboprophylaxis dosing to “escalated” dosing (intermediate or therapeutic). This was done because the panel recognized that common practice in many ICU settings includes varying escalated dosing protocols. There were five studies to inform this question, which included a total of 1947 patients. Again, the largest was the multiplatform ATTACC, ACTIV-4a, and REMAP-CAP[13] trial which accounted for 1089 patients. Additional studies included the HESACOVID[15], INSPIRATION[18], HEP-COVID[20], and Perepu[17] studies. It should be noted that the multiplatform trial and the HEP-COVID trial reflect PE data only. There were additional patients with DVT in

each group, but we could not determine if these patients overlapped those with PE, thus they were excluded from analysis. Perepu[17] and Sadeghipour[18] used intermediate dose anticoagulation in the "therapeutic anticoagulation" group. These were included in this analysis as this was a higher than standard dosing. There was a non-significant reduction in VTE (RR 0.65 [95% CI 0.35-1.19]) (Figure 2a). None of these studies reported fatal PE. There was a non-significant increase in major bleeding (RR 1.70 [95% CI 0.97-2.98]) (Figure 2b). The INSPIRATION[18] trial had 2/276 patients with fatal bleeding in the intermediate anticoagulation group compared to 0/286 in the thromboprophylaxis group and the HESACOVID[15] had no fatal bleeding in either group. The multiplatform trial reported a non-significant reduction in OSFDs (OR 0.83 [95%CI 0.67-1.03]). The HESACOVID[15] trial reported 15 (6-16) ventilator-free days in the therapeutic dose cohort vs. 0 (0-11) ventilator-free days in the prophylactic group, which was significant (p=0.028). In the HEP-COVID[20] trial, 10/38 (26.3%) in the therapeutic group required mechanical ventilation compared to 8/35 (22.9%) in the thromboprophylaxis group. Six trials were included in the mortality analysis. In addition to the trials mentioned above, the ACTION[16] trial also included a small number of critically ill patients (n=39) that were incorporated in the analysis. There was no significant difference in mortality between the two groups (RR 1.03 [95%CI 0.91-1.15]) (Figure 2c).

Recommendation 3: In critically ill patients with COVID-19, we suggest current standard dose anticoagulant thromboprophylaxis (with UFH or LMWH) over therapeutic dose anticoagulation (conditional recommendation, ungraded consensus-based statement).

Context

There was no disagreement about the direction of the recommendation. The data supporting thromboprophylaxis for the critically ill is quite robust. Other than the effect on PE seen in the multiplatform trial, there was insufficient evidence to suggest deviation from standard thromboprophylaxis. When all outcomes in the multiplatform trial, and not just PE, are factored in, the case against therapeutic anticoagulation is quite strong. Further, although the risk of VTE is likely lower on therapeutic anticoagulation (absolute risk reduction approximately 5%), the risk of major bleeding is higher (absolute risk increase approximately 1-2%), and there is no effect on mortality. Considering the risk of ascertainment bias for VTE in these open-label trials, the incomplete reporting of VTE events (no DVTs reported) and the high probability of inferiority of therapeutic anticoagulation compared to usual thromboprophylaxis for OSFDs in the multiplatform trial, the data thus far support continued use of existing guidelines.

Question 4: Should critically ill patients with COVID-19 be treated with intermediate dose anticoagulation or thromboprophylaxis for prevention of VTE?

For this question, we chose to focus on studies primarily designed specifically to evaluate intermediate dose thromboprophylaxis, as opposed to a combination of escalated doses. There were two studies to inform this question, the INSPIRATION[18] and Perepu[17] trials. 725 patients were included in the analysis. There was no difference in VTE (RR 1.00 [95%CI 0.51-1.96]),

major bleeding ((RR 1.53 [95%CI 0.54-4.28]), or mortality (RR 0.98 [95%CI 0.73-1.32]) (Figure 3). No data was reported regarding fatal PE. The INSPIRATION[18] trial reported that there was no difference between the two groups in ventilator-free days.

Recommendation 4: In critically ill patients with COVID-19, we suggest current standard dose anticoagulant thromboprophylaxis over intermediate dose anticoagulation (defined as LMWH BID or increased weight-based dosing that is less than recommended therapeutic doses) (conditional recommendation, ungraded consensus-based statement).

Context

There was no disagreement in the direction of the recommendation. The panel noted that the INSPIRATION[18] trial, the largest, did not show a benefit in VTE reduction and yet there was a potential increase in bleeding risk (statistically not significant). Therefore, the panel considered upgrading the recommendation from conditional to strong. Some felt this was perhaps premature given some methodological issues of the study. Ultimately the panel chose to maintain the conditional recommendation in favor of standard thromboprophylaxis in this cohort.

Discussion and Limitations

This manuscript serves as a brief update to the original guidance statement. Although we have better quality evidence, many questions remain. Despite this, our panel felt that it was important to share our thoughts regarding the new evidence, especially as one recommendation differs in direction from the original publication, and the others have more evidence to support them. The decision to change the recommendation was not an easy one. While the new trials are higher quality evidence, the interpretation of the results is not without controversy. Progression of respiratory failure due to COVID-19 is a different endpoint than preventing VTE. In the end, we felt that it was an important endpoint.

Some may question our decision not to include arterial thrombotic events as a primary outcome. These are clearly important to patients and clinicians. Our original publication, however, was focused on VTE and this was designed as an update to that publication. In addition, a recent meta-analysis that did include these events would not likely have changed our recommendations.[23]

Questions remain and should guide further research. Does the timing of heparin administration affect the ultimate outcome? Should patients admitted to the ICU during their admission continue therapeutic heparin? Does heparin indeed have anti-inflammatory, antiviral, or other pleiotropic effects in COVID-19? Which mechanisms of the prothrombotic state are prominent, and does this influence the optimal approach? Are current standard therapies changing the baseline risk of VTE? Should the approach to vaccinated patients be any different than unvaccinated patients?

Conclusions and Future Directions

We have learned quite a bit regarding thrombosis in patients with COVID-19 pneumonia. Although advances in care have improved overall outcomes, current evidence supports that the rates of VTE are higher in these patients, at least in the ICU.[24,25] At this time, we believe critically ill patients should still receive standard thromboprophylaxis for VTE and moderately ill patients with a low bleeding risk might benefit from therapeutic heparin. We see no role for intermediate dose thromboprophylaxis in either setting. The World Health Organization plans to perform a meta-analysis that includes several small trials along with the studies included here, and their findings may inform practice (PROSPERO registration ID is CRD42020213461). In addition, results from recently published trials examining the effect of pre- and post-hospital prophylaxis may lead to additional guideline updates.

References

1. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost.* 2020;18(5):1094-1099.
2. Tang N, Pan Y, Xu C, Li D. Characteristics of emergency patients with markedly elevated D-dimer levels. *Sci Rep.* 2020;10(1):7784.
3. Moores LK, Tritschler T, Brosnahan S, et al. Prevention, Diagnosis, and Treatment of VTE in Patients With Coronavirus Disease 2019: CHEST Guideline and Expert Panel Report. *Chest.* 2020;158(3):1143-1163.
4. NICE COVID-19 management. 2021; https://www.guidelines.co.uk/infection/nice-covid-19-management/455939.article. Accessed 6/03/2021.
5. COVID-19 clinical management: living guidance. World Health Organization. 2021; https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-1. Accessed June 03, 2021.
6. Bikdeli B, Madhavan MV, Jimenez D, et al. COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-Up: JACC State-of-the-Art Review. *J Am Coll Cardiol.* 2020;75(23):2950-2973.
7. Cuker A, Tseng EK, Nieuwlaat R, et al. American Society of Hematology 2021 guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19. *Blood Adv.* 2021;5(3):872-888.
8. Gerotziafas GT, Catalano M, Colgan MP, et al. Guidance for the Management of Patients with Vascular Disease or Cardiovascular Risk Factors and COVID-19: Position Paper from VAS-European Independent Foundation in Angiology/Vascular Medicine. *Thromb Haemost.* 2020;120(12):1597-1628.
9. Panel C-TG. Coronavirus Disease 209 (COVID-19) Treatment Guideines. National Institutes of Health. 2021; https://www.covid19treatmentguidelines.nih.gov. Accessed 11/30/2021.
10. Spyropoulos AC, Levy JH, Ageno W, et al. Scientific and Standardization Committee communication: Clinical guidance on the diagnosis, prevention, and treatment of venous thromboembolism in hospitalized patients with COVID-19. *J Thromb Haemost.* 2020;18(8):1859-1865.
11. Poor HD. Pulmonary Thrombosis and Thromboembolism in COVID-19. *Chest.* 2021;160(4):1471-1480.
12. Investigators A, Investigators AC-a, Investigators R-C, et al. Therapeutic Anticoagulation with Heparin in Noncritically Ill Patients with Covid-19. *N Engl J Med.* 2021;385(9):790-802.
13. Investigators R-C, Investigators AC-a, Investigators A, et al. Therapeutic Anticoagulation with Heparin in Critically Ill Patients with Covid-19. *N Engl J Med.* 2021;385(9):777-789.
14. Bellmunt-Montoya S, Riera C, Gil D, et al. COVID-19 Infection in Critically Ill Patients Carries a High Risk of Venous Thrombo-embolism. *Eur J Vasc Endovasc Surg.* 2021;61(4):628-634.

15. Lemos ACB, do Espirito Santo DA, Salvetti MC, et al. Therapeutic versus prophylactic anticoagulation for severe COVID-19: A randomized phase II clinical trial (HESACOVID). *Thromb Res.* 2020;196:359-366.
16. Lopes RD, de Barros ESPGM, Furtado RHM, et al. Therapeutic versus prophylactic anticoagulation for patients admitted to hospital with COVID-19 and elevated D-dimer concentration (ACTION): an open-label, multicentre, randomised, controlled trial. *Lancet.* 2021;397(10291):2253-2263.
17. Perepu US, Chambers I, Wahab A, et al. Standard prophylactic versus intermediate dose enoxaparin in adults with severe COVID-19: A multi-center, open-label, randomized controlled trial. *J Thromb Haemost.* 2021;19(9):2225-2234.
18. Sadeghipour P, Talasaz AH, Rashidi F, et al. Effect of Intermediate-Dose vs Standard-Dose Prophylactic Anticoagulation on Thrombotic Events, Extracorporeal Membrane Oxygenation Treatment, or Mortality Among Patients With COVID-19 Admitted to the Intensive Care Unit: The INSPIRATION Randomized Clinical Trial. *Jama.* 2021;325(16):1620-1630.
19. Sholzberg M, Tang GH, Rahhal H, et al. Effectiveness of therapeutic heparin versus prophylactic heparin on death, mechanical ventilation, or intensive care unit admission in moderately ill patients with covid-19 admitted to hospital: RAPID randomised clinical trial. *BMJ.* 2021;375:n2400.
20. Spyropoulos AC, Goldin M, Giannis D, et al. Efficacy and Safety of Therapeutic-Dose Heparin vs Standard Prophylactic or Intermediate-Dose Heparins for Thromboprophylaxis in High-risk Hospitalized Patients With COVID-19: The HEP-COVID Randomized Clinical Trial. *JAMA Intern Med.* 2021.
21. Sterne JAC, Savovic J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ.* 2019;366:l4898.
22. Alonso-Coello P, Oxman AD, Moberg J, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: Clinical practice guidelines. *BMJ.* 2016;353:i2089.
23. Ortega-Paz L, Galli M, Capodanno D, et al. Safety and efficacy of different prophylactic anticoagulation dosing regimens in critically and non-critically ill patients with COVID-19: A systematic review and meta-analysis of randomized controlled trials. *Eur Heart J Cardiovasc Pharmacother.* 2021.
24. Jimenez D, Garcia-Sanchez A, Rali P, et al. Incidence of VTE and Bleeding Among Hospitalized Patients With Coronavirus Disease 2019: A Systematic Review and Meta-analysis. *Chest.* 2021;159(3):1182-1196.
25. Mai V, Tan BK, Mainbourg S, et al. Venous thromboembolism in COVID-19 compared to non-COVID-19 cohorts: A systematic review with meta-analysis. *Vascul Pharmacol.* 2021;139:106882.

FIGURES AND TABLES

Table 1: Early Societal Guidelines Regarding Thromboprophylaxis in COVID-19

	Outpatient	**In-hospital Non critically ill**	**In-hospital Critically ill**	**Post discharge**
Global COVID-19 Thrombosis Collaborative Group[6] (17 April 2020)	In the absence of high-quality data, pharmacological prophylaxis should be reserved for those patients at highest risk, including those with limited mobility and history of prior VTE or active malignancy	Prophylactic daily LMWH or twice daily subcutaneous UFH	Prophylactic daily LMWH or twice daily subcutaneous UFH	it is reasonable to employ individualized risk stratification for thrombotic and hemorrhagic risk, followed by consideration of **extended prophylaxis** (for up to 45 days) for patients with elevated risk of VTE who have low risk of bleeding
International Society of Thrombosis and Haemostasis[10] (27 May 2020)	NA	A universal strategy of routine thromboprophylaxis with standard-dose UFH or LMWH should be used after careful assessment of bleed risk, with LMWH as the preferred agent. **Intermediate-dose LMWH may also be considered**	Routine thromboprophylaxis with prophylactic-dose UFH or LMWH should be used after careful assessment of bleed risk. **Intermediate-dose LMWH can also be considered in high-risk patients**	**Extended post-discharge thromboprophylaxis** should be considered for all hospitalized patients with COVID-19 that meet high VTE risk criteria
Chest Guideline and Expert Panel Report[3] (2 June 2020)	NA	In acutely ill hospitalized patients with COVID-19, we recommend current standard dose anticoagulant thromboprophylaxis over intermediate or full treatment dosing, per existing guidelines	In critically ill patients with COVID-19, we suggest current standard dose anticoagulant thromboprophylaxis over intermediate or full treatment dosing, per existing guidelines	In patients with COVID-19, we recommend inpatient thromboprophylaxis only over inpatient plus extended thromboprophylaxis after hospital discharge
VAS-European Independent Foundation in Angiology/Vascular Medicine[8] (13 September 2020)	NA	**Routine thromboprophylaxis with weight-adjusted intermediate doses of LMWH** (unless contraindication)	Routine thromboprophylaxis with weight-adjusted **intermediate doses of LMWH** (unless contraindication)	Evaluation of the risk of VTE before hospital discharge using the IMPROVE-D-dimer score and **prolonged post-discharge thromboprophylaxis** with rivaroxaban, betrixaban, or LMWH
World Health Organization[5] (25 January 2021)	NA	In hospitalized patients with COVID-19, without an established indication for higher dose anticoagulation, we suggest administering standard thromboprophylaxis dosing of anticoagulation rather than therapeutic or intermediate dosing	In hospitalized patients with COVID-19, without an established indication for higher dose anticoagulation, we suggest administering standard thromboprophylaxis dosing of anticoagulation rather than therapeutic or intermediate dosing	NA
American Society of Hematology[7] (8 February 2021)	NA	Prophylactic-intensity over intermediate-intensity or therapeutic-intensity anticoagulation for patients with COVID-19–related acute illness who do not have suspected or confirmed VTE	Prophylactic-intensity over intermediate-intensity or therapeutic-intensity anticoagulation for patients with COVID-19–related critical illness who do not have suspected or confirmed VTE	NA
National Institutes of Health[9] (11 February 2021)	For nonhospitalized patients with COVID-19, anticoagulants and	Hospitalized nonpregnant adults with COVID-19 should receive	Hospitalized nonpregnant adults with COVID-19 should receive	Hospitalized patients with COVID-19 should not routinely be discharged

	antiplatelet therapy should not be initiated for the prevention of VTE or arterial thrombosis unless the patient has other indications for the therapy or is participating in a clinical trial	prophylactic dose anticoagulation	prophylactic dose anticoagulation	from the hospital while on VTE prophylaxis. Continuing anticoagulation with a Food and Drug Administration-approved regimen for extended VTE prophylaxis after hospital discharge can be considered for patients who are at low risk for bleeding and high risk for VTE
National Institute for Health and Care Excellence[4] (06 March 2021)	Consider pharmacological prophylaxis if the risk of VTE outweighs the risk of bleeding	Consider a **treatment dose** of a LMWH, unless contraindicated, for young people and adults with COVID-19 who: i) are likely to be in hospital for the next 3 days; ii) need supplemental oxygen and who are not yet receiving high-flow oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation	For young people and adults who are already receiving high-flow oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation and are on a standard prophylactic dose of a LMWH for VTE prophylaxis: i) consider increasing anticoagulation to an **intermediate dose**; ii) reassess VTE and bleeding risks daily	Treatment should be for a minimum of 14 days or until discharge

Abbreviations: COVID-19, Coronavirus Disease 2019; VTE, venous thromboembolism; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin; NA, not available; VAS, Angiology Vascular Medicine.

Table 2: Included Studies

	mpRCT (critically ill)[13]	**mpRCT (non-critically ill)[12]**	**ACTION[16]**	**RAPID[19]**	**INSPIRATION[18]**	**HEP-COVID[20]**	**HESACOVID[15]**	**Perepu[17]**
Design	Adaptive, multinational, open-label RCT	Adaptive, multinational, open-label RCT	Multicenter (Brazil), open-label RCT	Multinational, open-label RCT	Multicenter (Iran), open-label RCT with 2x2 factorial design*	Multicenter (US), open-label RCT	Single-center (Brazil), open-label RCT	Multicenter (US), open-label RCT
Intervention	Therapeutic-dose heparin until discharge or day 14	Therapeutic-dose heparin until discharge or day 14	Rivaroxaban 20 mg daily for 30 days†	Therapeutic-dose heparin until discharge or day 28	Intermediate-dose heparin for 30 days	Therapeutic-dose heparin until discharge	Therapeutic-dose heparin for ≥4 to 14 days	Intermediate-dose enoxaparin until discharge
Comparator	Usual-care pharmacological thromboprop	Usual-care pharmacological thromboprop	BMI-adjusted prophylactic-dose	BMI-adjusted prophylactic-dose	Weight- and BMI-adjusted prophylacti	Usual-care pharmacological thromboprop	Weight-adjusted prophylact	BMI-adjusted prophylactic-dose

	hylaxis (up to intermediate-dose heparin) until discharge	hylaxis (up to intermediate-dose heparin) until discharge	heparin until discharge ‡	heparin until discharge or day 28	c-dose heparin for 30 days	hylaxis (up to intermediate-dose heparin) until discharge	ic-dose heparin	enoxaparin until discharge
Primary outcome	Organ support-free days up to day 21	Organ support-free days up to day 21	Hierarchical composite of time to death, duration of hospitalization, or duration of supplemental oxygen use through 30 days.	Composite of ICU admission, non-invasive or invasive mechanical ventilation, or death up to 28 days	Composite of acute VTE, arterial thrombosis, treatment with ECMO, or mortality within 30 days	Composite of VTE, ATE or death from any cause within 30 ±2 days	Change in PaO2/FiO2 ratio from baseline to day 14	Mortality at 30 days
Major bleeding criteria	ISTH	ISTH	ISTH	ISTH	BARC (type 3 or 5)	ISTH	TIMI	ISTH
Screening ultrasound for DVT	No	No	No	No	No	10 +4 days or at discharge	No	No
Eligibility based on D-dimer	No	No	>ULN	≥2x ULN or >ULN and oxygen saturation ≤93%	No	>4x ULN	>1000 µg/L	No
No. of randomized participants	1207§	2244¶	615	465	598	257	20	176
No. of participants included in primary analysis	1103	2219	614	465	562	253	20	173
Age (years)	61 (mean)	59 (mean)	57 (mean)	60 (mean)	62 (median)	67 (mean)	57 (mean)	64 (median)
Women, no./total no. (%)	331/1103 (30)	921/2231 (41)	247/615 (40)	201/465 (43)	237/562 (42)	117/253 (46)	4/20 (20)	76/173 (44)
BMI ≥30 kg/m², no./total no. (%)	Median 30 kg/m^2	Median 30 kg/m^2	264/615 (43)	191/455 (42)	123/535 (23)	Mean 31 kg/m^2	Mean 34 kg/m^2	106/173 (61)
D-dimer ≥2x ULN, no./total no. (%)	207/433 (48)	630/1705 (37)	≥3 ULN: 167/615 (27)	227/465 (49)	94/188 (50)	253/253 (100)	NR	NR
Oxygen support at baseline								
None	0	279/2231 (13)**	155/615 (25)	††	0	9/253 (3.6)	0	NR‡‡
Low-flow nasal	15/1103 (1.4)	1485/2231 (67)**	369/615 (60)	††	256/562 (46)	192/253 (76)	0	NR‡‡

cannula or mask, no./total no. (%)								
High-flow nasal cannula, no./total no. (%)	358/1103 (32)	53/2231 (2.4)	48/615 (7.8)	27/465 (5.8)	15/562 (2.7)	§§	0	NR‡‡
Noninvasive positive pressure ventilation, no./total no. (%)	415/1103 (38)	45/2231 (2.0)	5/615 (0.1)	0	178/562 (32)	§§	0	NR‡‡
Invasive ventilation, no./total no. (%)	315/1103 (29)	0	38/615 (6.2)	0	113/562 (20)	13/253 (5.1)	20/20 (100)	40/173 (23)
Co-treatment at baseline								
Antiplatelet agent, no./total no. (%)	75/979 (7.7)¶¶	259/2153 (12)***	48/615 (7.8)	53/465 (11)	172/562 (31)	64/253 (25)	0	NR
Glucocorticoids, no./total no. (%)	884/1077 (82)	894/1447 (62)	510/615 (83)	323/465(69)	524/562 (93)	204/250 (82)	14/20 (70)	130/173 (75)†††
Remdesivir, no./total no. (%)	346/1096 (32)	811/2226 (36)	NR	0	338/562 (60)	178/253 (70)	0	105/173 (61)†††
Tocilizumab, no./total no. (%)	20/1096 (32)	13/2148 (0.6)	NR	0	74/562 (13)	NR	0	NR

Abbreviations: ATE, arterial thromboembolism; BARC, Bleeding Academic Research Consortium; BMI, body mass index; DVT, deep vein thrombosis; ECMO, extracorporeal membrane oxygenation; FiO2, fraction of inspired oxygen; ICU, intensive care unit; ISTH, International Society on Thrombosis and Haemostasis; mpRCT, multiplatform randomized controlled trial; NR, not reported; PaO2, partial pressure of arterial oxygen; TIMI, Thrombolysis in Myocardial Infarction; ULN, upper limit of normal; VTE, venous thromboembolism.

* INSPIRATION was an RCT with a 2x2 factorial design comparing intermediate-dose vs prophylactic-dose anticoagulation and statin therapy vs matching placebo.
† In patients with a creatinine clearance of 30-49 mL/min or those taking azithromycin, rivaroxaban 15 mg daily was used (66 of 280 patients taking rivaroxaban, 24%). Unstable patients received enoxaparin 1 mg/kg subcutaneous twice daily or therapeutic-dose intravenous unfractionated heparin (30 of 311 patients, 9.6%).
‡ Extended prophylaxis beyond hospital discharge was prescribed in 38 of 304 (13%) patients allocated to the comparator group.
§ A total of 81 patients were excluded, because they did not have confirmed COVID-19.
¶ A total of 12 patients were excluded, because they did not have confirmed COVID-19.
** In REMAP-CAP, levels of oxygen support (including no support) below the level of high-flow nasal cannula were not reported.
†† Levels of oxygen support below the level of high-flow nasal cannula were not reported.
‡‡ Levels of oxygen support other than mechanical ventilation were not reported. At baseline, 107 (62%) patients were admitted to an intensive care unit.
§§ A total of 45 of 253 (18%) patients were on either high-flow or noninvasive positive-pressure ventilation.
¶¶ Not listed are 113 patients who were coenrolled in the REMAP-CAP Antiplatelet Domain (47 in the therapeutic-dose anticoagulation group and 66 in the usual-care pharmacologic thromboprophylaxis group).
*** Not listed are 74 patients who were coenrolled in the REMAP-CAP Antiplatelet Domain (39 in the therapeutic-dose anticoagulation group and 35 in the usual-care pharmacologic thromboprophylaxis group).
††† Treatment during trial period.

Table 3: High bleeding risk Patients *

Bleeding within last 30 days needing acute care setting
History of inherited or acquired bleeding disorder
Recent ischemic stroke
History of intracranial hemorrhage
Presence of epidural or spinal catheter
Intracranial malignancy
History of bleeding diathesis (i.e. hemophilia)
Recent gastrointestinal bleeding (within 3 months)
Thrombolysis in previous 7 days
Recent major surgery (within 14 days)
Uncontrolled hypertension (sBP >200 mmHg or dBP>120 mmHg)
Baseline INR > 2.0 or aPTT > 50 seconds
Hemoglobin < 8 g/dL
Platelet count < 50 x 10^9/L
Dual antiplatelet agents

*Bleeding risk should be individualized and discussed on case-by-case basis.

Figure 1a. VTE

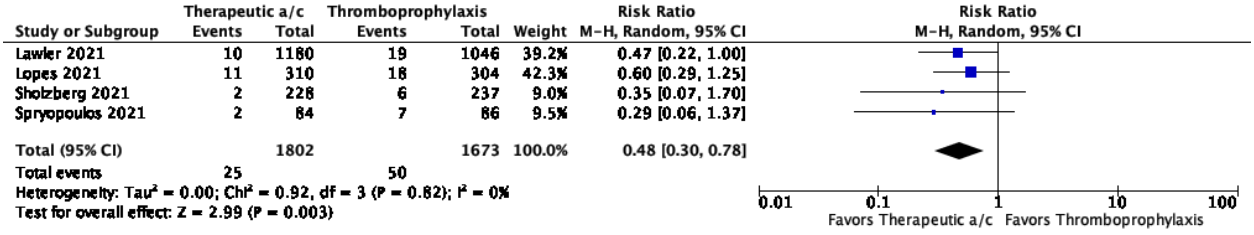

Figure 1b. Major Bleeding

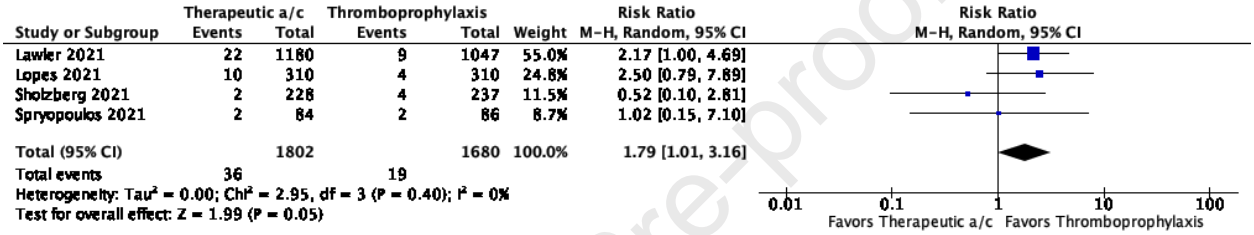

Figure 1c. Mortality

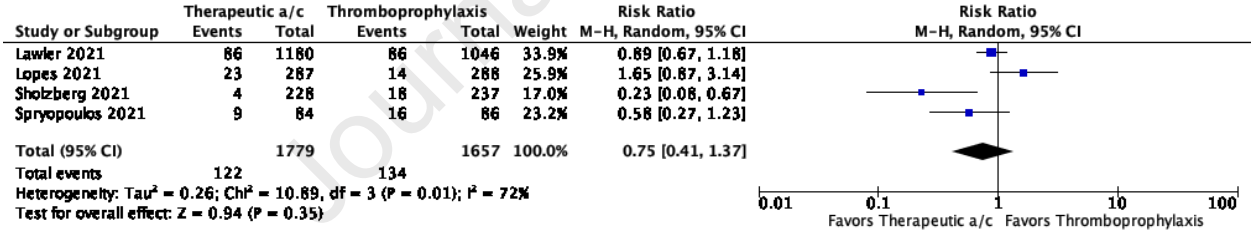

Figure 2a. VTE

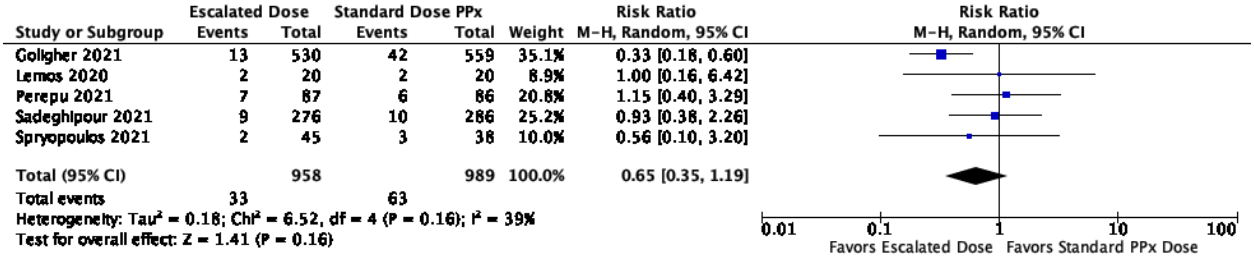

Figure 2b. Major Bleeding

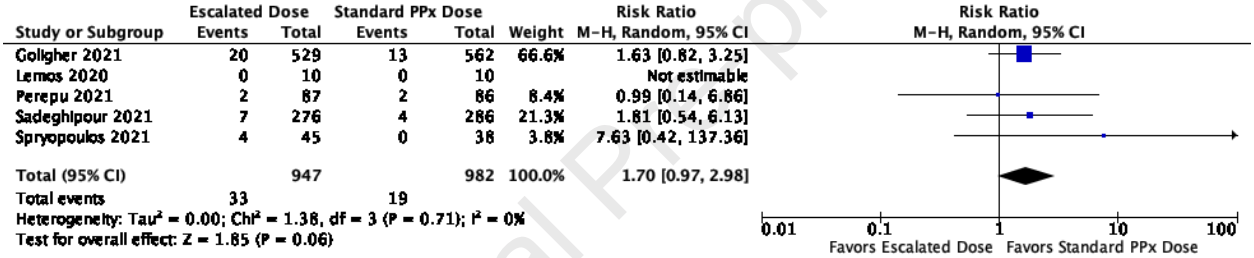

Figure 2c. Mortality

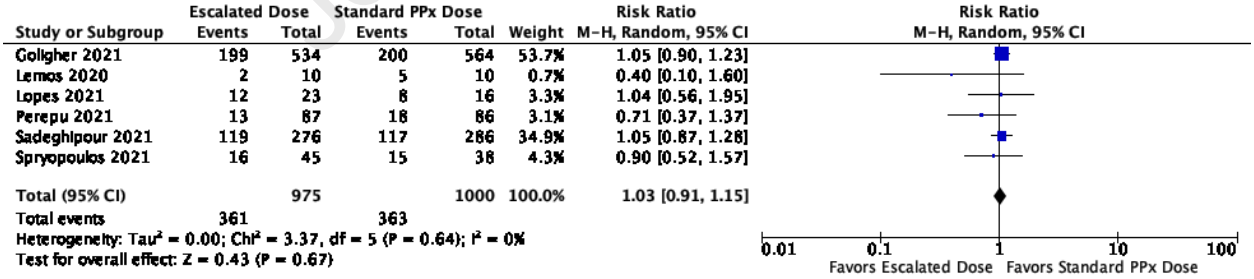

Figure 3a. VTE

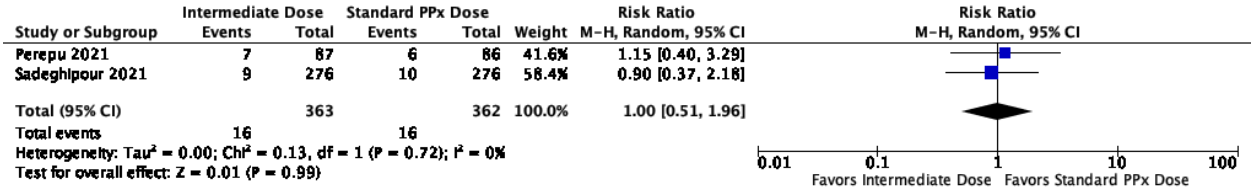

Figure 3b. Major Bleeding

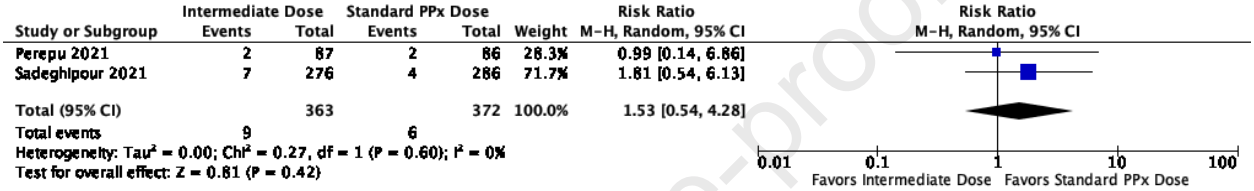

Figure 3c. Mortality

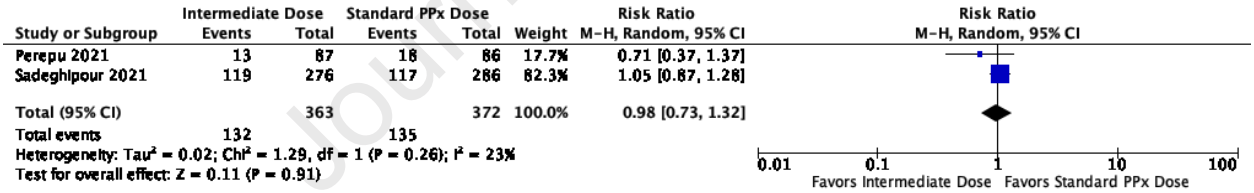

FIGURE LEGENDS

Figure 1: Outcomes in Moderately Ill Hospitalized Patients receiving Therapeutic Anticoagulation vs. Standard Thromboprophylaxis

Figure 2: Outcomes in Critically Ill Patients Receiving Increased-Dose Anticoagulation vs. Standard Thromboprophylaxis

Figure 3: Outcomes in Critically Ill Patients Receiving Intermediate Dose Thromboprophylaxis vs. Standard Thromboprophylaxis