Therapeutic Anticoagulation in Non-Critically Ill Patients with Covid-19

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Abstract

Background
Thrombo-inflammation may contribute to morbidity and mortality in Covid-19. We hypothesized that therapeutic-dose anticoagulation may improve outcomes in non-critically ill patients hospitalized for Covid-19.

Methods
In an open-label adaptive multiplatform randomized controlled trial, non-critically ill patients hospitalized for Covid-19, defined by the absence of critical care-level organ support at enrollment, were randomized to a pragmatic strategy of therapeutic-dose anticoagulation with heparin or usual care pharmacological thromboprophylaxis. The primary outcome combined survival to hospital discharge and days free of organ support through 21 days, which was evaluated with Bayesian statistical models according to baseline D-dimer.

Results
The trial was stopped when prespecified criteria for superiority were met for therapeutic-dose anticoagulation in groups defined by high (≥2-fold elevated) and low (<2-fold elevated) D-dimer. Among 2219 participants in the final analysis, the probability that therapeutic anticoagulation increased organ support-free days compared to thromboprophylaxis was 99.0% (adjusted odds ratio 1.29, 95% credible interval 1.04 to 1.61). The adjusted absolute increase in survival to hospital discharge without organ support with therapeutic-dose anticoagulation was 4.6% (95% credible interval 0.7 to 8.1). In the primary adaptive stopping groups, the final probabilities of superiority for therapeutic anticoagulation were 97.3% in the high D-dimer group and 92.9% in the low D-dimer group. Major bleeding occurred in 1.9% and 0.9% of participants randomized to therapeutic anticoagulation and thromboprophylaxis, respectively.

Conclusions
In non-critically ill patients with Covid-19, an initial strategy of therapeutic-dose anticoagulation with heparin increases the probability of survival to hospital discharge with reduced use of organ support.

Trial registration numbers: NCT02735707, NCT04505774, NCT04359277, NCT04372589

Background

The clinical course of Covid-19 is characterized by an initial period of mild to moderate symptoms, followed by progressive respiratory failure and requirement for intensive care unit (ICU)-level organ support or death in some patients.[1,2] The majority of patients requiring hospitalization are moderately ill, not initially requiring ICU-level organ support.[3-5] Limited therapies are available to prevent clinical progression to ICU-level organ support and death among moderately ill hospitalized patients.

Patients with Covid-19 have a notable incidence of macro- and microvascular thrombosis and inflammation in association with poor clinical outcomes.[6,7] Given the anti-thrombotic, anti-inflammatory, and possible anti-viral properties of heparins,[8-10] it has been hypothesized that anticoagulation with heparin administered at doses higher than conventionally used for venous thromboprophylaxis may improve outcomes.[11] Further, elevated D-dimer is associated with vascular thrombosis and poor clinical outcomes,[6,12] and thus some have advocated using D-dimer to guide anticoagulant dosing in patients with Covid-19. In the absence of data from randomized trials, clinical guideline recommendations[13] and practice[14] vary widely.

To determine whether an initial strategy of therapeutic-dose anticoagulation with heparin improves survival to hospital discharge with reduced use of ICU-level organ support in hospitalized, non-critically ill patients with Covid-19, we conducted an international, adaptive, multiplatform randomized controlled trial (mpRCT).

Methods

Trial Design and Oversight

To accelerate evidence generation, three adaptive randomized controlled trial protocols
evaluating therapeutic-dose anticoagulation with heparin in patients hospitalized for Covid-19
were integrated into a single mpRCT. Alignment of eligibility criteria, interventions, outcome
measures, and data collection was prospectively undertaken. A joint analysis plan was
implemented involving periodic evaluation of statistical stopping criteria (**Protocol Appendix**).
Independent data and safety monitoring boards (DSMBs) oversaw the platforms using a
collaborative cross-platform DSMB interaction plan. The participating platforms were
Antithrombotic Therapy To Ameliorate Complications of Covid-19 (ATTACC; NCT04372589),[15]
Accelerating Covid-19 Therapeutic Interventions and Vaccines-4 Antithrombotics Inpatient
platform trial (ACTIV-4a, NCT04505774; which included a vanguard/pilot, NCT04359277), and
Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired
Pneumonia (REMAP-CAP, NCT02735707).[16] The trial was approved by relevant ethics
committees and conducted in accordance with Good Clinical Practice guidelines and the
Declaration of Helsinki. Written or verbal informed consent, in accordance with regional
regulations, was obtained from all participants or their surrogates. The trial was supported by
multiple international funding organizations which had no role in the design, analysis, or
reporting of the trial results, apart from the ACTIV-4a protocol which received input on design
from the National Institutes of Health professional staff and peer reviewers.

Participants

The mpRCT enrolled patients hospitalized for Covid-19. The investigators hypothesized that the benefits and risks of therapeutic-dose anticoagulation with heparin may vary according to disease severity. As such, the design prospectively stratified participants into severe (ICU-level of care; critically ill) and moderate (hospitalized; non-critically ill) disease severity states at enrollment. Moderate disease severity was defined as hospitalization for Covid-19 without the requirement for ICU-level of care. ICU-level of care was defined by use of respiratory or cardiovascular organ support (high flow nasal oxygen, non-invasive or invasive mechanical ventilation, vasopressors, or inotropes) in an ICU. In ACTIV-4a, where definitions of an ICU were thought challenging to operationalize during the pandemic, receipt of organ support, irrespective of hospital setting, was used to define ICU-level of care. Participants admitted to an ICU but without the receipt of qualifying organ support were considered moderately ill. Participants with moderate disease severity were further stratified by their baseline D-dimer: high D-dimer group (D-dimer ≥2 times the upper limit of normal per local assay); low D-dimer group (D-dimer <2 times the upper limit of normal per local assay); or unknown D-dimer group. Patients were ineligible for enrollment beyond 72 hours after hospital admission for Covid-19 or in-hospital SARS-CoV-2 confirmation (ATTACC, ACTIV-4a) or after 14 days following admission (REMAP-CAP). In addition, patients were excluded if discharge was expected within 72 hours, or if they had a clinical indication for therapeutic anticoagulation, high risk for bleeding, required dual antiplatelet therapy, or had a history of heparin allergy including heparin-induced thrombocytopenia (HIT). Detailed exclusion criteria are provided in the **Protocol Appendix**.

Randomization

Using central web-based systems, participants were randomized to receive an initial pragmatic strategy of therapeutic-dose anticoagulation with heparin or usual care pharmacological thromboprophylaxis in an open label fashion. Therapeutic-dose low molecular weight or unfractionated heparin was administered according to local protocols used for the treatment of acute venous thromboembolism for up to 14 days or until recovery (defined as hospital discharge, or liberation from supplemental oxygen for ≥24 hours). Thromboprophylaxis was provided according to local practice.

A subset of REMAP-CAP participants were randomized in other platform domains, including an antiplatelet domain. Treatment assignments were initially randomized in a 1:1 ratio. The ATTACC and REMAP-CAP designs specified the possibility for response-adaptive randomization, whereby blinded randomization allocation ratios could be modified during the trial based on adaptive analyses to favor allocation of participants to the treatment arm demonstrating greater benefit. In participants with moderate severity Covid-19, response-adaptive randomization was implemented for ATTACC participants on December 15, 2020.

Outcome Measures

The primary outcome was organ support-free days, an ordinal outcome composed of survival to hospital discharge and, among survivors, the number of days free of ICU-level organ support through day 21. Any death during the index hospitalization through 90 days was assigned –1. This endpoint thus reflects both utilization of critical care therapies and survival. Higher values for organ support-free days indicate better outcomes.

Pre-specified secondary efficacy outcomes included survival, survival without receipt of organ support, survival without receipt of invasive mechanical ventilation, mechanical respiratory support-free days (days free of invasive or non-invasive mechanical ventilation), time-to-hospital discharge, survival without symptomatic major thrombotic events (a composite of freedom from myocardial infarction, pulmonary embolism, ischemic stroke, systemic arterial embolism, and in-hospital death), and survival without any macrovascular thrombotic event (the components of major thrombotic events and symptomatic deep venous thrombosis) (**Supplementary Appendix**). Pre-specified secondary safety outcomes assessed during the treatment period were major bleeding, as defined by the International Society of Thrombosis and Haemostasis,[17] and laboratory-confirmed HIT. All reported bleeding and thrombotic events were adjudicated in a blinded fashion by clinical endpoints committees using consensus definitions (**Supplementary Appendix**).

Statistical Analysis

The primary analysis was a Bayesian cumulative logistic model that calculated the posterior probability distribution for the proportional odds ratio for therapeutic-dose anticoagulation compared with thromboprophylaxis on organ support-free days in participants with microbiologically confirmed SARS-CoV-2 infection. The primary model incorporated weakly-informative Dirichlet prior distributions for organ support-free days proportions, and was adjusted for age, sex, site, D-dimer group, and enrollment time period. The model was fit using a Markov Chain Monte Carlo algorithm with 100,000 samples from the joint posterior distribution, allowing calculation of the posterior distributions for the proportional odds ratios,

including medians and 95% credible intervals (CrIs), and the posterior probabilities of

superiority and futility for therapeutic-dose anticoagulation compared with usual care

thromboprophylaxis. In this report, odds ratios >1.0 favor therapeutic-dose anticoagulation.

The primary model estimated treatment effects for each of the disease severity-defined

groups (severe and moderate, the latter stratified by baseline D-dimer), utilizing a Bayesian

hierarchical approach. The treatment effects of anticoagulation for the groups were nested in a

hierarchical prior distribution centered on an overall intervention effect estimated with a

neutral prior, but distinct group-specific effects were estimated. When consistent effects were

observed for the groups, the posterior distribution for each intervention group effect is shrunk

towards the overall estimate (dynamic borrowing).[18] The stopping criteria for treatment

superiority (>99% probability of odds ratio >1.0) and futility (<5% probability of odds ratio >1.2)

were evaluated monthly by an independent statistical analysis committee and could be reached

within the low and/or high D-dimer groups at each adaptive analysis. Sensitivity analyses of the

primary model assuming independent treatment effects (without dynamic borrowing) in each

D-dimer group are also reported. Additionally, analyses are presented from the overall

moderate severity cohort assuming a single treatment effect irrespective of D-dimer.

Subgroup analyses assessed whether treatment effect varied according to age, sex,

baseline respiratory support, and thromboprophylaxis dosing. Protocol adherence was defined

by the anticoagulant dose equivalent administered within the first 24-48 hours following

randomization (**Supplementary Appendix** for consensus dosing categories). Doses categorized

as therapeutic and subtherapeutic heparin qualified as adherent in the therapeutic-dose

anticoagulation arm, and low- and intermediate prophylactic-dose anticoagulants qualified as

adherent in the thromboprophylaxis arm. The analysis of this dataset was pre-specified in a statistical analysis plan (**Protocol Appendix**).

Results

The first participant was randomized on April 21, 2020. On January 22, 2021, enrollment was discontinued on advice from the DSMBs after planned adaptive analyses of 1398 moderate severity participants demonstrated that the pre-specified stopping criteria for superiority of therapeutic-dose anticoagulation had been reached in both the high and low D-dimer groups (**Supplementary Appendix Table S1**). By that time, 2245 moderate severity participants had been randomized. The primary analysis population consisted of 2219 participants with SARS-CoV-2 confirmation for whom the primary outcome was known (**Figure 1**). Parallel enrollment of patients with severe Covid-19 ran through December 19, 2020; these results are reported separately.[19]

Participants

Baseline characteristics were similar between treatment arms (**Table 1**), including within each D-dimer group (**Supplementary Appendix Table S2**). Participants in the high D-dimer and unknown D-dimer groups were generally older with a higher prevalence of comorbid diseases compared to those in the low D-dimer group. Concomitant therapies at enrollment included antiplatelet agents (12%), corticosteroids (62%), and remdesivir (36%).

Adherence to protocol-assigned anticoagulation dose on the day following randomization was 88.3% in the therapeutic-dose anticoagulation arm and 98.3% in the thromboprophylaxis

arm (**Supplementary Appendix Table 3**). Among participants randomized to therapeutic-dose

heparin, 94.7% (1035/1093) received a low molecular weight heparin, most commonly

enoxaparin. Among participants allocated to usual care thromboprophylaxis, 71.7% (613/855)

received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis.

Primary Outcome

Among 2219 participants in the overall moderate severity cohort, the posterior probability that

therapeutic-dose anticoagulation increased organ support-free days compared to usual care

thromboprophylaxis was 99.0% (median adjusted odds ratio 1.29, 95% CrI 1.04 to 1.61) (**Figure**

2 and **Figure 3**). The proportion of participants in the thromboprophylaxis arm surviving to

hospital discharge without receipt of organ support during the first 21 days (control event

frequency) was 76.4% (247/1048). The median adjusted absolute improvement in this

proportion with therapeutic-dose anticoagulation was 4.6% (95% CrI 0.7 to 8.1). In the primary

adaptive analysis groups, the final posterior probability for superiority of therapeutic-dose

anticoagulation compared with usual care thromboprophylaxis was 97.3% (adjusted odds ratio

1.31, 95% CrI 1.00 to 1.76) in the high D-dimer group (n=630) and 92.9% (adjusted odds ratio

1.22, 95% CrI 0.93 to 1.57) in the low D-dimer group (n=1075) (**Figure 3** and **Supplementary**

Appendix Figure S1). The posterior probability of superiority of therapeutic-dose

anticoagulation in the unknown D-dimer group (n=514) was 97.3% (adjusted odds ratio 1.32,

95% CrI 1.00 to 1.86). The results were consistent in sensitivity analyses (**Supplementary**

Appendix Table S4).

In the overall moderate severity cohort, the treatment effect did not vary meaningfully by age, respiratory support at enrollment, or thromboprophylaxis dosing. There was a 95.5% probability that the odds ratio associated with therapeutic-dose anticoagulation was higher in men compared to women (**Supplementary Appendix Figure S2**).

Secondary Outcomes

Secondary outcomes are shown in **Figure 3, Figure 4**, and **Supplementary Appendix Table S5.** In the overall moderate severity cohort, the posterior probabilities that therapeutic-dose anticoagulation increased survival without organ support or survival without invasive mechanical ventilation through 28 days were 99.1% and 92.2%, respectively. The posterior probability that therapeutic-dose anticoagulation improved survival to hospital discharge compared with thromboprophylaxis was 87.1% (median adjusted odds ratio 1.21, 95% CrI 0.87 to 1.68; median adjusted absolute improvement 1.3%, 95%CrI -1.1 to 3.2%).

A major thrombotic event or death in-hospital occurred in 8.0% (94/1180) of participants randomized to therapeutic-dose anticoagulation and 9.9% (104/1046) of participants randomized to thromboprophylaxis (**Figure 3** and **Supplementary Appendix Tables S5** and **S6**). The composite secondary thrombosis outcome including deep vein thrombosis is reported in **Supplementary Appendix Table S5**. Major bleeding occurred in 1.9% (22/1180) of participants randomized to therapeutic-dose anticoagulation and 0.9% (9/1047) of participants randomized to thromboprophylaxis (**Supplementary Appendix Table S7**). Fatal bleeding occurred in three participants randomized to therapeutic-dose anticoagulation and one participant randomized

to thromboprophylaxis. No episodes of intracranial bleeding or confirmed HIT occurred during the treatment window.

Discussion

In this randomized trial report of non-critically ill patients hospitalized for Covid-19, therapeutic-dose anticoagulation with heparin increased the probability of surviving to hospital discharge with reduced need for ICU-level organ support, including invasive and non-invasive mechanical ventilation. Therapeutic-dose anticoagulation with heparin was beneficial irrespective of baseline D-dimer. Major bleeding occurred infrequently.

Several non-randomized cohort studies have observed favorable associations between anticoagulant use and survival from Covid-19, although these studies are at risk of bias.[20-22] Because SARS-CoV-2 infection incites a dysregulated inflammatory response that may cascade to activation of coagulation and widespread thrombin generation,[23] potentially contributing to organ failure,[24-26] heparins may reduce the requirement for organ support by limiting thrombo-inflammation through anti-thrombotic, anti-inflammatory, and potentially anti-viral mechanisms.[8-10,27] The results from this mpRCT show that empiric therapeutic-dose anticoagulation with heparin provided to patients hospitalized prior to the receipt of ICU-level organ support improved outcomes.

In contrast, in a parallel enrolling group of the mpRCT comprised of critically-ill patients (receiving ICU-level of care at enrollment), empiric therapeutic-dose anticoagulation was not beneficial.[19] In a separate randomized trial in critically-ill patients with Covid-19, intermediate-dose heparin was likewise not beneficial.[28] Differential treatment effects based on illness

severity and the time course of SARS-CoV-2 infection have been reported in randomized trials of other Covid-19 therapies.[29-31] It is possible that therapeutic-dose heparin is unable to influence the thrombo-inflammatory cascade and organ injury in patients with advanced disease and its sequale.[32-34] Among moderately-ill participants in this mpRCT, those in the high D-dimer group were at increased risk for mortality and receipt of organ support compared with those in the low D-dimer group and, accordingly, adjusted absolute treatment benefits were more apparent. Participants in the high D-dimer group were generally older with a higher prevalence of comorbid diseases.

Strengths of our trial design include elements incorporated to speed evidence generation. First, we adopted a novel prospective mpRCT design, whereby three collaborating platforms developed and administered harmonized trial protocols across complementary global networks of sites to increase efficiency and reliability of evidence generation. Second, the trial employed an adaptive Bayesian design which accounted for uncertainties in the pandemic. This approach allowed for trial conclusions to be reached simultaneously or sequentially in groups defined by illness severity and D-dimer through periodic adaptive analyses. Dynamic borrowing was incorporated to enable the trial to reach conclusions more quickly across the stopping groups where treatment effects were similar, and to mitigate the influence of outlying treatment effects by shrinking similar treatment estimates together. Response-adaptive randomization allowed randomization probabilities to be modified as the trial acquired knowledge about treatment effects. Response-adaptive randomization may lead to imbalances in baseline covariates between treatment arms over time, and as such the primary models of treatment effect are necessarily adjusted for age, sex, site, D-dimer group, and time. Given the importance

of accounting for these factors under this design, absolute risk reductions based on adjusted treatment effects and observed control event rates are presented. The adjusted absolute improvement in outcomes presented is a median; patients at higher baseline risk, including older age, male sex, and higher baseline D-dimer may derive greater absolute benefit.

Although the open-label design of the mpRCT represents a potential limitation, the primary outcome involving survival and receipt of organ support was selected to minimize bias and to function across a spectrum of illness severity. The potential for ascertainment bias cannot be excluded for the secondary outcomes of major bleeding or thrombosis. This, along with the absence of protocolized screening for venous thrombosis, exclusion of patients at increased bleeding risk, and changing disease epidemiology over time may have contributed to lower thrombotic event rates than have been previously reported.[35] The treatment effect was attenuated in the final analysis relative to the adaptive stopping results; nevertheless, a high probability of benefit persisted in all D-dimer groups.

In conclusion, in hospitalized, non-critically ill patients with Covid-19, an initial strategy of therapeutic-dose anticoagulation with heparin improves organ support-free days. Therapeutic-dose anticoagulation increases the probability of survival to hospital discharge with reduced use of critical care-level organ support.

Acknowledgements

References

1. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395(10229):1054-1062.

2. Mody A, Lyons PG, Guillamet CV, et al. The Clinical Course of COVID-19 Disease in a US Hospital System: a Multi-state Analysis. American Journal of Epidemiology 2021;190(4):539-552.

3. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. JAMA 2020;323(20):2052-2059.

4. Lewnard JA, Liu VX, Jackson ML, et al. Incidence, clinical outcomes, and transmission dynamics of severe coronavirus disease 2019 in California and Washington: prospective cohort study. BMJ 2020;369:m1923.

5. Garibaldi BT, Fiksel J, Muschelli J, et al. Patient Trajectories Among Persons Hospitalized for COVID-19 : A Cohort Study. Annals of Internal Medicine 2021;174(1):33-41.

6. Bilaloglu S, Aphinyanaphongs Y, Jones S, Iturrate E, Hochman J, Berger JS. Thrombosis in Hospitalized Patients With COVID-19 in a New York City Health System. JAMA 2020;324(8):799-801.

7. Godoy LC, Goligher EC, Lawler PR, Slutsky AS, Zarychanski R. Anticipating and managing coagulopathy and thrombotic manifestations of severe COVID-19. CMAJ : Canadian Medical Association Journal 2020 192(40):E1156-E1161.

8. Clausen TM, Sandoval DR, Spliid CB, et al. SARS-CoV-2 Infection Depends on Cellular Heparan Sulfate and ACE2. Cell 2020;183(4):1043-1057.

9. Buijsers B, Yanginlar C, Maciej-Hulme ML, de Mast Q, van der Vlag J. Beneficial non-anticoagulant mechanisms underlying heparin treatment of COVID-19 patients. EBioMedicine 2020;59:102969.

10. Mycroft-West CJ, Su D, Pagani I, et al. Heparin Inhibits Cellular Invasion by SARS-CoV-2: Structural Dependence of the Interaction of the Spike S1 Receptor-Binding Domain with Heparin. Thrombosis and haemostasis 2020;120(12):1700-1715.

11. Chowdhury JF, Moores LK, Connors JM. Anticoagulation in Hospitalized Patients with Covid-19. The New England Journal of Medicine 2020;383(17):1675-1678.

12. Short SAP, Gupta S, Brenner SK, et al. D-dimer and Death in Critically Ill Patients With Coronavirus Disease 2019. Critical Care Medicine 2021;49(5):e500-e511.

13. Flaczyk A, Rosovsky RP, Reed CT, Bankhead-Kendall BK, Bittner EA, Chang MG. Comparison of published guidelines for management of coagulopathy and thrombosis in critically ill patients with COVID 19: implications for clinical practice and future investigations. Critical Care 2020;24(1):559.

14. Rosovsky RP, Sanfilippo KM, Wang TF, et al. Anticoagulation Practice Patterns in COVID-19: A Global Survey. Research and Practice in Thrombosis and Haemostasis 2020; 4(6):969-983.

15. Houston BL, Lawler PR, Goligher EC, et al. Anti-Thrombotic Therapy to Ameliorate Complications of COVID-19 (ATTACC): Study design and methodology for an international, adaptive Bayesian randomized controlled trial. Clin Trials 2020;17(5):491-500.

16. Angus DC, Berry S, Lewis RJ, et al. The REMAP-CAP (Randomized Embedded Multifactorial Adaptive Platform for Community-acquired Pneumonia) Study. Rationale and Design. Ann Am Thorac Soc 2020;17(7):879-891.

17. Schulman S, Kearon C, Subcommittee on Control of Anticoagulation of the S, Standardization Committee of the International Society on T, Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005;3(4):692-4.

18. McGlothlin AE, Viele K. Bayesian Hierarchical Models. JAMA 2018;320(22):2365-2366.

19. https://www.medrxiv.org/content/10.1101/2021.03.10.21252749v1.full.

20. Nadkarni GN, Lala A, Bagiella E, et al. Anticoagulation, Bleeding, Mortality, and Pathology in Hospitalized Patients With COVID-19. J Am Coll Cardiol 2020;76(16):1815-1826.

21. Ionescu F, Jaiyesimi I, Petrescu I, et al. Association of anticoagulation dose and survival in hospitalized COVID-19 patients: A retrospective propensity score-weighted analysis. Eur J Haematol 2021;106(2):165-174.

22. Frohlich GM, Jeschke E, Eichler U, et al. Impact of oral anticoagulation on clinical outcomes of COVID-19: a nationwide cohort study of hospitalized patients in Germany. Clinical Research in Cardiology 2021;Jan 8:1-10.

23. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. Blood 2020;135(23):2033-2040.

24. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. The New England Journal of Medicine 2020;383(2):120-128.

25. Hanley B, Naresh KN, Roufosse C, et al. Histopathological findings and viral tropism in UK patients with severe fatal COVID-19: a post-mortem study. The Lancet Microbe 2020;1(6):e245-e253.

26. Rapkiewicz AV, Mai X, Carsons SE, et al. Megakaryocytes and platelet-fibrin thrombi characterize multi-organ thrombosis at autopsy in COVID-19: A case series. EClinicalMedicine 2020;24:100434.

27. Liu J, Li J, Arnold K, Pawlinski R, Key NS. Using heparin molecules to manage COVID-2019. Research and practice in thrombosis and haemostasis 2020;4(4):518-523.

28. 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.

29. Horby P, Lim WS, Emberson JR, et al. Dexamethasone in Hospitalized Patients with Covid-19. The New England Journal of Medicine 2021;384(8):693-704.

30. Libster R, Perez Marc G, Wappner D, et al. Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults. The New England Journal of Medicine 2021;384(7):610-618.

31. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 - Final Report. The New England Journal of Medicine 2020;383(19):1813-1826.

32. Xue M, Zeng Y, Qu HQ, et al. Heparin-binding protein levels correlate with aggravation and multiorgan damage in severe COVID-19. ERJ Open Research 2021;7(1):00741-2020.

33. White D, MacDonald S, Bull T, et al. Heparin resistance in COVID-19 patients in the intensive care unit. Journal of thrombosis and thrombolysis 2020;50(2):287-291.

34. Fisher J, Linder A. Heparin-binding protein: a key player in the pathophysiology of organ dysfunction in sepsis. Journal of Internal Medicine 2017;281(6):562-574.

35. 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.

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline[a]		
Characteristic	**Therapeutic-dose anticoagulation (N=1181)[b]**	**Usual care pharmacological thromboprophylaxis (N=1050)[b]**
Age – year	59.0 (14.1)	58.8 (13.9)
Male Sex – no. (%)	713/1181 (60.4)	597/1050 (56.9)
Race		
White – no. (%)	622/994 (62.6)	564/845 (66.7)
Asian – no. (%)	41/994 (4.1)	43/845 (5.1)
Black – no. (%)	219/994 (22)	162/845 (19.2)
First Nations/American Indian – no. (%)	118/965 (12.2)	82/819 (10.0)
Other – no. (%)	17/1109 (1.5)	16/968 (1.7)
Hispanic or Latino ethnicity – no. (%)	574/1004 (57.2)	537/879 (61.1)
Body mass index, kg/m2	29.8 (26.3–34.7)	30.3 (26.7–34.9)
	N = 979	N = 860
Pre-existing conditions		
Hypertension – no. (%)	546/1023 (53.4)	447/892 (50.1)
Diabetes mellitus – no. (%)	352/1181 (29.8)	311/1049 (29.6)
Severe cardiovascular disease[c] – no. (%)	123/1165 (10.6)	123/1165 (10.6)
Chronic kidney disease – no. (%)	83/1173 (7.1)	69/1037 (6.7)
Chronic respiratory disease[d] – no. (%)	249/1132 (22)	212/988 (21.5)
Immunosuppressive disease – no. (%)	105/1143 (9.2)	103/1005 (10.2)
Baseline treatments		
Antiplatelet agent[e] – no. (%)	148/1140 (13.0)	111/1013 (11.0)
Remdesivir – no. (%)	428/1178 (36.3)	383/1048 (36.5)
Corticosteroids – no. (%)	479/791 (60.6)	415/656 (63.3)
Tocilizumab – no. (%)	6/1178 (0.5)	7/1048 (0.7)
Baseline respiratory support – n/N (%)		
None – no. (%)	156/1181 (13.2)	123/1050 (11.7)
Low flow nasal cannula/face mask – no. (%)	789/1181 (66.8)	696/1050 (66.3)
High flow nasal cannula – no. (%)	25/1181 (2.1)	28/1050 (2.7)
Non-invasive mechanical ventilation – no. (%)	21/1181 (1.8)	24/1050 (2.3)
Unspecified[f] – no. (%)	190/1181 (16.1)	179/1050 (17.1)
Laboratory values		
D-dimer relative to site upper limit of normal	1.6 (0.9–2.6)	1.5 (1–2.7)
	N = 900	N = 779
Platelets x10^9/L	221 (171–290)	218 (172.5–289)
	N = 1160	N = 1031
Lymphocytes x10^9/L	0.9 (0.7–1.3)	1 (0.7–1.4)
	N = 1032	N = 908
Creatinine (mg/dL)	0.9 (0.7–1.1)	0.9 (0.7–1.1)
	N = 1144	N = 1012
Platform of enrollment[g]		
ATTACC[h] – no. (%)	650/1181 (55.0)	509/1050 (48.5)
ACTIV-4a – no. (%)	387/1181 (32.8)	392/1050 (37.3)
REMAP-CAP – no. (%)	144/1181 (12.2)	149/1050 (14.2)
Country of enrollment		

United Kingdom – no. (%)	95/1181 (8)	103/1049 (9.8)
United States – no. (%)	573/1181 (48.5)	506/1049 (48.2)
Canada – no. (%)	102/1181 (8.6)	83/1049 (7.9)
Brazil – no. (%)	234/1181 (19.8)	209/1049 (19.9)
Other[i] – no. (%)	177/1181 (15)	148/1049 (14.1)

Median [IQR] or proportions. **Abbreviations**: No. = number.

Footnotes:

a. all moderate severity participants; **Supplementary Appendix Table S2** for baseline characteristics stratified by D-dimer group;

b. Unequal denominators due to response-adaptive randomization

c. defined in REMAP-CAP as a baseline history of New York Heart Association class IV symptoms; defined in ACTIV-4a and ATTACC as a baseline history of heart failure, myocardial Infarction, coronary artery disease, peripheral arterial disease, or cerebrovascular disease (stroke or transient ischemic attack);

d. defined as a baseline history of asthma, chronic obstructive pulmonary disease, bronchiectasis, interstitial lung disease, primary lung cancer, pulmonary hypertension, active tuberculosis, or through the receipt of home oxygen therapy;

e. not included in this summary are 74 participants co-enrolled in the REMAP-CAP Antiplatelet Domain (39 in the therapeutic anticoagulation arm and 35 in the usual care thromboprophylaxis arm);

f. in REMAP-CAP, levels of oxygen support, including no support, below high flow nasal cannula were not differentiated;

g. imbalanced randomization due to implementation of response-adaptive randomization in ATTACC on December 15, 2020;

h. 215 patients enrolled by the ATTACC platform were funded by the ACTIV4a platform from the National Heart Lung and Blood Institute of the NIH;

i. other participating countries included: Mexico, Nepal, Australia, Netherlands, and Spain.

Figure Legends

Figure 1. Screening, enrollment, randomization, and inclusion in analysis. **Footnotes**: **a.** sites used varying screening and documentation practices during the pandemic to identify eligible patients (**Protocol Appendix**); as reported, 3799 assessed for eligibility in ACTIV-4a, 7202 assessed for eligibility in ATTACC, and 2372 assessed for eligibility in REMAP-CAP; **b.** potentially used for covariate adjustment and dynamic borrowing; **c.** may be imbalanced due to response adaptive randomization; **d.** reasons (number of participants) for non-inclusion of Moderate severity participants assigned to receive therapeutic anticoagulation in the modified intention to treat primary analysis population included: withdrawal of consent (9), SARS-CoV-2 not confirmed (9), and outcome not available (1); **e.** reasons (number of participants) for non-inclusion of Moderate severity participants assigned to receive usual care pharmacological thromboprophylaxis in the modified intention to treat primary analysis population included: withdrawal of consent (2), SARS-CoV-2 not confirmed (3), and outcome not available (2).

Figure 2. Organ support-free days to day 21. **Upper panel**) the cumulative proportion (y-axis) for each intervention group along the ordinal scale (x-axis). The ordinal scale ranges from –1 (in-hospital death; the worst possible outcome) through 0 to 21 (among survivors, the numbers of days alive without organ support; intermediate outcomes), to 22 (survival to hospital discharge without receipt of organ support; the best possible outcome). The height of each curve at any point, for example, at day = 10, indicates the proportion of participants with organ support-free days (OSFD) of 10 or lower (i.e., 10 or worse). The difference in height of the two curves at any point represents the difference in the cumulative probability of having a value for OSFDs less than or equal to that point on the x-axis. **Lower panel**) Organ support-free days are shown as horizontally stacked proportions by intervention group, with possible outcomes as: in-hospital death with or without the receipt of organ support (dark red; the worst possible outcome, corresponding to an ordinal scale score of -1); survival, requiring ICU-level organ support (red to blue gradient shading based on number of days alive without organ support; intermediate outcomes, corresponding to an ordinal scale scores of 0-21); and survival to hospital discharge, without requiring ICU-level organ support (dark blue; the best possible outcome, corresponding to an ordinal scale score of 22). The median adjusted proportional odds ratio for therapeutic dose vs. thromboprophylaxsis among all moderate severity participants in the modified intention-to-treat analysis was 1.29 (95% credible interval 1.04 to 1.61; posterior probability of superiority 99.0%).

Figure 3. Primary and secondary outcomes. Median adjusted proportional odds ratios and 95% credible intervals are shown, along with the corresponding probabilities for superiority (adjusted odds ratio >1.0), the control event proportion, and the mean adjusted improvement in absolute risk. Forest plots are shown such that values >1.0 favor therapeutic heparin and values <1.0 favor usual care pharmacological thromboprophylaxis. The High D-dimer group is defined as moderate severity participants with baseline D-dimer ≥2 times local upper limit of normal for assay, the Low D-dimer group as moderate severity participants with baseline D-

dimer <2 times local upper limit of normal for assay, and the baseline Unknown D-Dimer
defined as moderate severity participants without available baseline D-dimer. Additional
secondary endpoints are reported in **Figure 4** and **Supplementary Appendix Table S5**.
Abbreviations: CrI = credible interval. **Footnotes**: **a.** effect estimates are adjusted for age, sex,
site, D-dimer group, and time epoch, and are computed so that a value greater than 1 indicates
benefit from therapeutic anticoagulation; **b.** calculated from the adjusted treatment effect and
control event frequency; **c.** the primary analysis includes 630 High D-dimer moderate severity
participants, 1075 Low D-dimer moderate severity participants, and 514 Unknown D-dimer
moderate severity participants; the primary analysis uses dynamic borrowing across illness
severity and D-dimer groups, whereby observations from one group are used to inform
treatment effect estimation in other groups where effect is observed to be similar (results from
a sensitivity analysis assuming independent treatment effects between D-dimer-defined groups
are shown in **Supplementary Appendix Table S5**); treatment effects also reported for the
overall moderate severity cohort (n=2219) assuming a single treatment effect irrespective of D-
dimer; **d.** includes dynamic borrowing between D-dimer groups as derives from the primary
model; other secondary outcomes do not employ dynamic borrowing; **e.** similar results were
obtained from a time-to-event model of survival through 28 days: adjusted hazard ratio of 1.20
(95% CrI, 0.88-1.61; posterior probability of superiority 87.8%); **f.** dichotomous endpoint;
similar results obtained following the exclusion of 52 participants receiving organ support at
baseline (median adjusted odds ratio 1.30, 95% CrI 1.06-1.62; posterior probability of
superiority 99.3%); **g.** ordinal outcome with death as the worst possible outcome.

Figure 4. Effect of therapeutic anticoagulation on mortality, organ and respiratory support, in
the overall moderate severity cohort. Unadjusted proportions are shown by treatment group.
The posterior probability of superiority of therapeutic anticoagulation with heparin in
comparison to usual care thromboprophylaxis is shown for the combined probabilities of death
and receipt of either organ support, or the subsets of mechanical respiratory support (non-
invasive or invasive mechanical ventilation), or intubation. **Abbreviations**: IV = invasive
ventilation; NIV = non-invasive ventilation; Pr = probability. **Footnote**: Models analyzed as
follows: survival without organ support through 28 days (dichotomous outcome); mechanical
respiratory support-free days (ordinal outcome based on days free of support, with in-hospital
death assigned as 0) through 28 days; and survival free of invasive mechanical ventilation
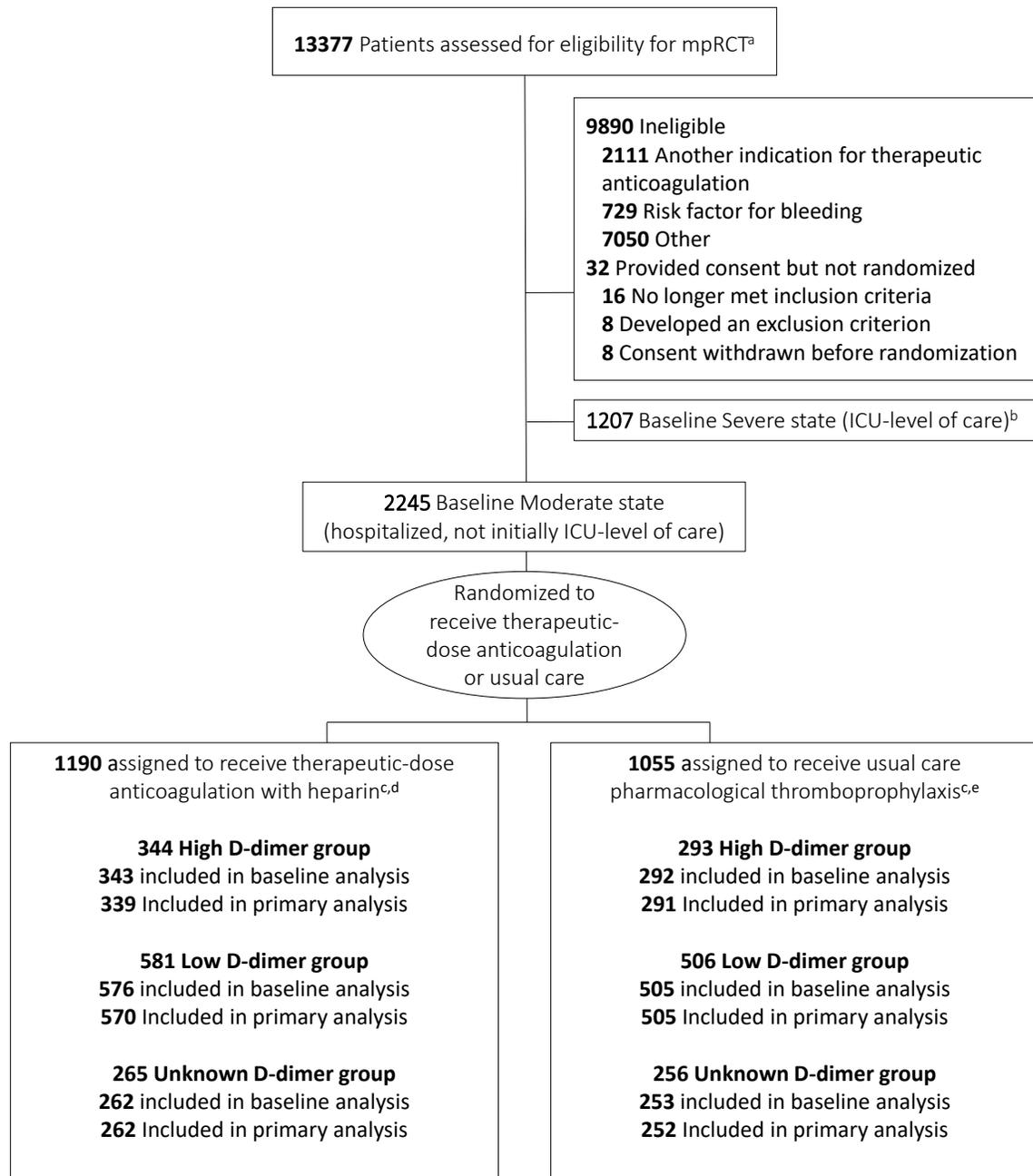through 28 days (ordinal, death as the worse outcome).

Figure 1

13377 Patients assessed for eligibility for mpRCT[a]

9890 Ineligible
    2111 Another indication for therapeutic anticoagulation
    729 Risk factor for bleeding
    7050 Other
32 Provided consent but not randomized
    16 No longer met inclusion criteria
    8 Developed an exclusion criterion
    8 Consent withdrawn before randomization

1207 Baseline Severe state (ICU-level of care)[b]

2245 Baseline Moderate state
(hospitalized, not initially ICU-level of care)

Randomized to receive therapeutic-dose anticoagulation or usual care

1190 assigned to receive therapeutic-dose anticoagulation with heparin[c,d]

    344 High D-dimer group
    343 included in baseline analysis
    339 Included in primary analysis

    581 Low D-dimer group
    576 included in baseline analysis
    570 Included in primary analysis

    265 Unknown D-dimer group
    262 included in baseline analysis
    262 Included in primary analysis

1055 assigned to receive usual care pharmacological thromboprophylaxis[c,e]

    293 High D-dimer group
    292 included in baseline analysis
    291 Included in primary analysis

    506 Low D-dimer group
    505 included in baseline analysis
    505 Included in primary analysis

    256 Unknown D-dimer group
    253 included in baseline analysis
    252 Included in primary analysis

Figure 2

Figure 3

	Adjusted odds ratio (95% CrI)[a]	Posterior probability of superiority	Control event proportion	Adjusted improvement in absolute risk (95% CrI)[b]
● Organ support free days (primary endpoint)[c]				
High D-dimer	1.31 (1.00 to 1.76)	97.3%	-	-
Low D-dimer	1.22 (0.93 to 1.57)	92.9%	-	-
Unknown D-dimer	1.32 (1.00 to 1.86)	97.3%	-	-
All moderate participants	1.29 (1.04 to 1.61)	99.0%	-	-
■ Survival to hospital discharge (secondary endpoint)[d,e]				
High D-dimer	1.16 (0.79 to 1.71)	78.6%	260/291 (89.3)	1.3% (−2.5, 4.2)
Low D-dimer	1.19 (0.81 to 1.74)	81.7%	477/505 (94.5)	0.8% (−1.2, 2.3)
Unknown D-dimer	1.20 (0.81 to 1.83)	82.1%	225/252 (89.3)	1.6% (−2.2, 4.6)
All moderate participants	1.21 (0.87 to 1.68)	87.1%	962/1048 (91.8)	1.3% (−1.1, 3.2)
▲ Survival without organ support through 28 days (secondary endpoint)[f]				
High D-dimer	1.40 (0.96 to 2.03)	96.0%	205/290 (70.7)	6.5% (−0.9, 12.3)
Low D-dimer	1.22 (0.90 to 1.65)	89.4%	396/503 (78.7)	3.1% (−1.0, 7.2)
Unknown D-dimer	1.31 (0.87 to 1.99)	90.2%	188/253 (74.3)	6.0% (−2.1, 12.2)
All moderate participants	1.30 (1.05 to 1.61)	99.1%	789/1046 (75.4)	4.5% (0.9, 7.7)
▼ Survival without intubation through 28 days (secondary endpoint)[g]				
High D-dimer	1.14 (0.71 to 1.84)	71.3%	253/292 (86.6)	1.4% (−4.5, 5.6)
Low D-dimer	1.20 (0.80 to 1.83)	80.9%	457/505 (90.5)	1.5% (−2.1, 4.1)
Unknown D-dimer	1.29 (0.79 to 2.18)	84.3%	213/253 (84.2)	3.1% (−3.4, 7.9)
All moderate participants	1.22 (0.93 to 1.59)	92.2%	923/1050 (87.9)	2.0% (−0.8, 4.1)
○ Survival to hospital discharge without major thrombosis (secondary endpoint)				
High D-dimer	1.29 (0.78 to 2.13)	84.1%	253/292 (86.6)	2.7% (−3.2, 6.6)
Low D-dimer	1.27 (0.78 to 2.07)	83.0%	473/505 (93.7)	1.3% (−1.6, 3.2)
Unknown D-dimer	1.64 (0.92 to 3.00)	95.2%	216/249 (86.7)	4.7% (−1.0, 8.4)
All moderate participants	1.39 (1.02 to 1.88)	98.0%	942/1046 (90.1)	2.6% (0.2, 4.4)
◆ Freedom from major bleeding (secondary endpoint)				
High D-dimer	0.62 (0.23 to 1.67)	17.7%	288/292 (98.6)	−0.8% (−4.4, 0.6)
Low D-dimer	0.43 (0.16 to 1.08)	3.7%	503/505 (99.6)	−0.5% (−2.0, 0.0)
Unknown D-dimer	1.30 (0.36 to 4.83)	65.5%	247/250 (98.8)	0.3% (−2.1, 0.9)
All moderate participants	0.56 (0.27 to 1.11)	4.8%	1038/1047 (99.1)	−0.7% (−2.4, 0.1)

Adjusted Odds Ratio (95% CrI)

0.125 0.25 0.5 1 2 4
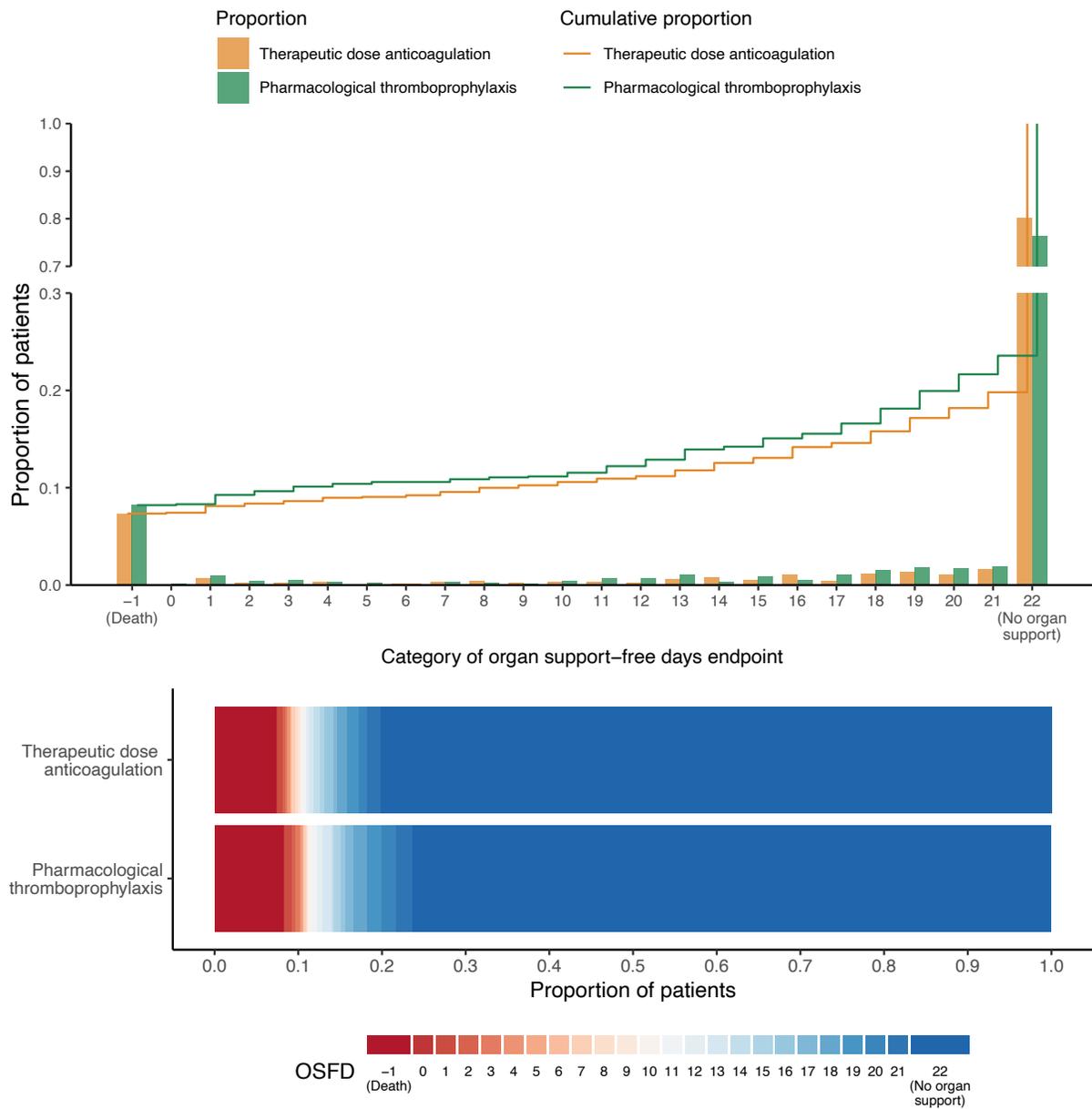
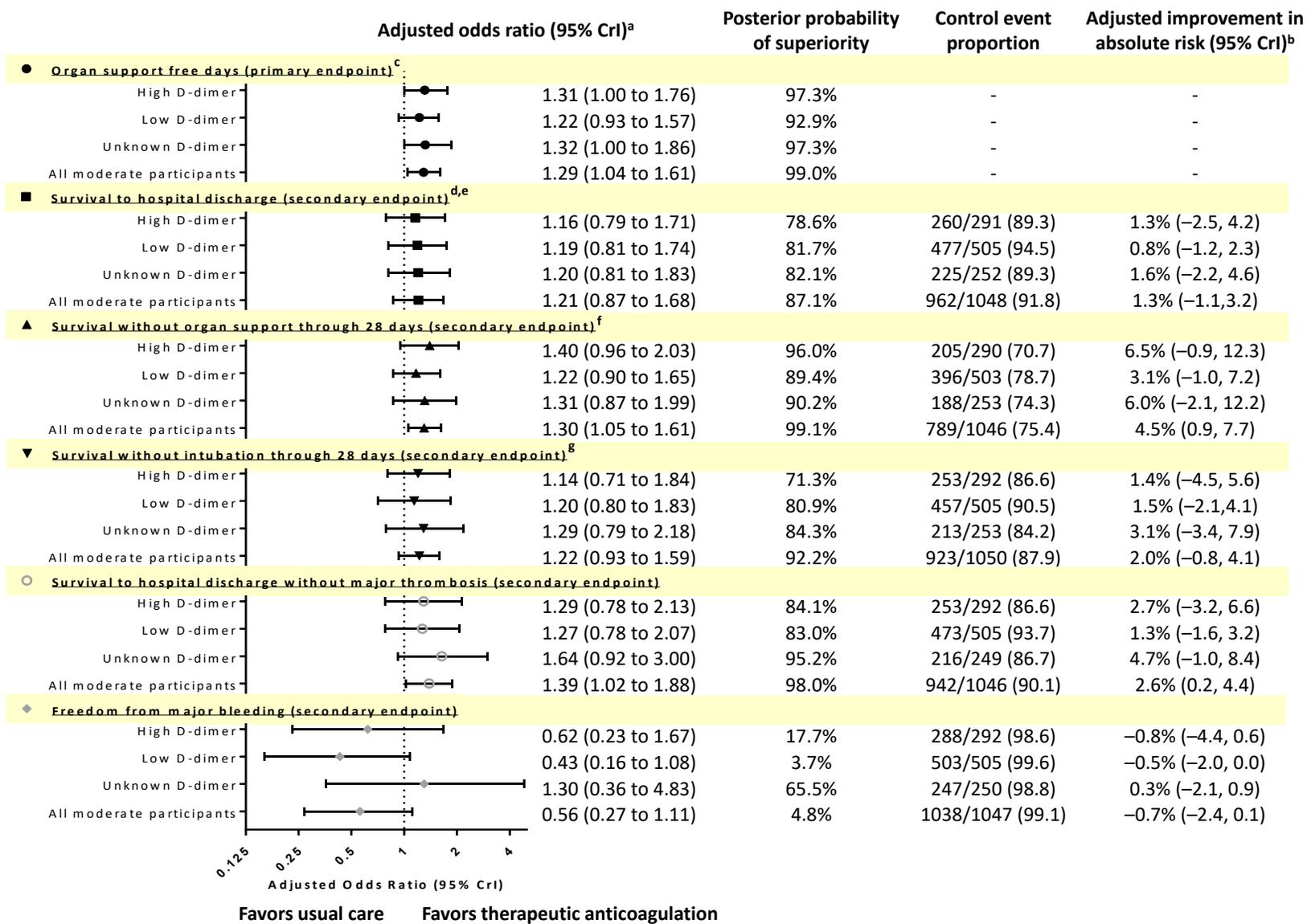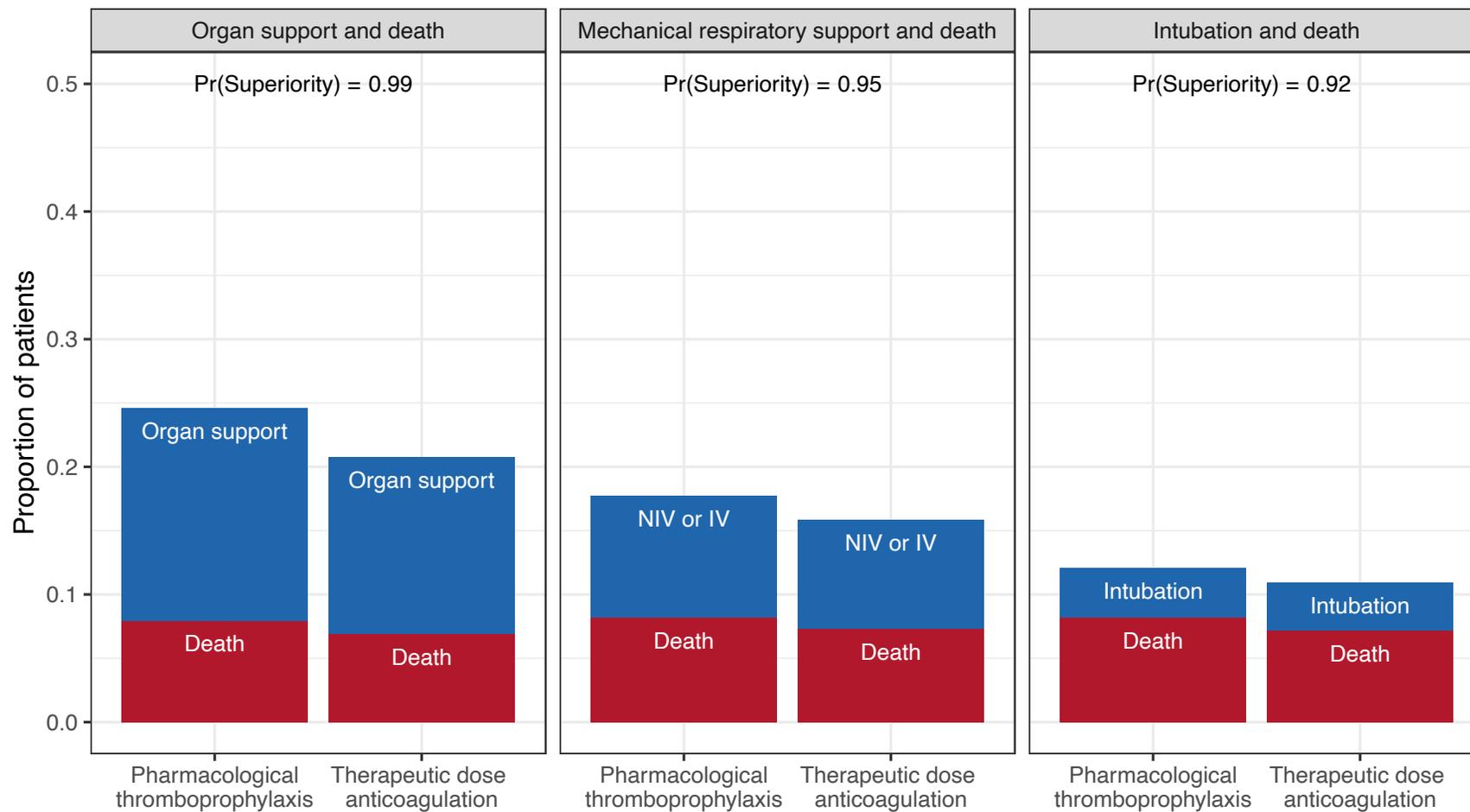Favors usual care   Favors therapeutic anticoagulation

Figure 4

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