Anticoagulation among patients hospitalized for COVID-19. A Prospective Meta-analysis.

Group Information: The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group

The WHO Rapid Evidence Appraisal for COVID-19 Therapies [REACT] Working Group authors and collaborators are listed at the end of this article.

Manuscript Details
Key Findings: 122
Abstract: 347
Main article: 3729
Tables:0
Figures:4
References:40
Appendix: 1
Online Supplements: 7

Corresponding Author:

Srinivas Murthy, MD, MHSc
Faculty of Medicine, University of British Columbia, Vancouver, Canada
Srinivas.murthy@ubc.ca
604-445-7001

Key Points

Question Is administration of (1) therapeutic- vs prophylactic-dose; (2) therapeutic- vs intermediate-dose and (3) intermediate- vs prophylactic-dose anticoagulation associated with mortality within 28 days of randomization, need for invasive mechanical ventilation, thromboembolic disease, or major bleeding in patients hospitalized with COVID-19?

Findings Administration of therapeutic dose heparin reduced mortality, need for invasive mechanical ventilation, and thromboembolic events compared with prophylactic dose heparin in hospitalized patients with COVID-19. However, mortality was not lower for therapeutic- vs intermediate-dose or intermediate- vs prophylactic-dose anticoagulation. For each comparison, higher compared with lower dose anticoagulation was associated with fewer thromboembolic events but a greater risk of major bleeding.

Meaning There is high certainty evidence that therapeutic dose heparin, compared with prophylactic dose heparin, reduces 28-day mortality in hospitalized patients with COVID-19.

The WHO Rapid Evidence Appraisal for COVID-19 Therapies [REACT] Working Group

Authors and Members of the Writing Committee:

Claire L Vale; Peter J Godolphin; David Fisher; Julian PT Higgins; Alexandra McAleenan; Francesca Spiga; Tobias Tritschler; Pedro Barros; David D Berg; Jeffrey Berger; Lindsay R Berry; Behnood Bikdeli, Marc Blondon; Erin A Bohula; Marco Cattaneo; Riccardo Colombo; Valeria Coluccio; Maria DeSancho; Michael Farkouh; Valentin Fuster; Massimo Girardis; Judith S Hochman; Tom Jensen; Vivekanand Jha; Peter Jüni; Ajay Kirtane; Patrick Lawler; Gregoire Le Gal; Ramon Lecumberri; Steven R Lentz; Renato D Lopes; Elizabeth Lorenzi; Marco Marietta; Carlos Henrique Miranda; Nuccia Morici; Susan C Morpeth; David A Morrow; Zoe K McQuilten; Nuria Muñoz-Rivas; Matthew Neal; Suman Pant; Sahil A Parikh; Usha Perepu; Parham Sadeghipour; Sanjum Sethi; Michelle Sholzberg; Alex C Spyropoulos; Gregg W Stone; Azita H Talasaz; Steven Y C Tong; James Totterdell; Balasubramanian Venkatesh; Maddalena Alessandra Wu; Ryan Zarychanski; Stephane Zuily; Julie Viry; Jamie Rylance; Neill KJ Adhikari; Janet V Diaz; John C Marshall; Jonathan A C Sterne; and Srinivas Murthy.

Affiliations of The WHO Rapid Evidence Appraisal for COVID-19 Therapies [REACT] Working Group Authors and Members of the Writing Committee:

1. University College London, MRC Clinical Trials Unit at UCL, London, United Kingdom [Vale, Godolphin, Fisher]
2. Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, England [Sterne, Higgins, McAleenan, Spiga]
3. NIHR Bristol Biomedical Research Centre, Bristol, England [Higgins, Sterne]
4. Department of General Internal Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland [Tritschler]
5. Brazilian Clinical Research Institute (BCRI), Sao Paulo, Brazil (Barros, Lopes).
6. NYU Grossman School of Medicine, New York, USA [Berger]
7. Berry Consultants LLC, Austin, TX, United States [Berry, Jensen, Lorenzi]
8. TIMI Study Group, Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA [Berg, Bohula, Morrow]
9. Brigham and Women's Hospital, Boston USA [Bikdeli]
10. Faculty of Medicine and Geneva University Hospitals, Division of Angiology and Haemostasis [Blondon]
11. Università degli Studi di Milano, Dipartimento di Scienze della Salute [Cattaneo]
12. Division of Anesthesiology and Intensive Care, ASST Fatebenefratelli Sacco [Colombo]
13. Azienda Ospedaliero-Universitaria di Modena, Dipartimento Oncologia Ed Ematologia, Modena, Italy [Coluccio and Marietta]
14. Division of Hematology-Medical Oncology, Weill Cornell Medicine New York Presbyterian Hospital, Department of Medicine [DeSancho]

15. Toronto General Hospital Research Institute [Farkouh]
16. Academic Affairs, Cedars-SinaiHealth System, Los Angeles, California USA [Farkouh]
17. University Health Network [Farkouh, Lawler]
18. Icahn School of Medicine at Mount Sinai, New York, NY [Fuster, Stone]
19. Intensive Care Unit, University Hospital of Modena, Modena- Italy [Girardis]
20. NYU Grossman School of Medicine Department of Medicine [Hochman]
21. Imperial College, London, England, United Kingdom [Jha]
22. Nuffield Department of Population Health, Oxford, UK [Jüni]
23. Colombia University Department of Medicine [Kirtane, Parikh, Sethi]
24. Department of Medicine, University of Ottawa, Ottawa, Canada [Le Gal]
25. Servicio de Hematología, Clínica Universidad de Navarra, Pamplona, España. CIBER-CV, Madrid, España [Lecumberri]
26. Department of Internal Medicine, University of Iowa, USA [Lentz]
27. Duke University Medical Center, Duke Clinical Research Institute, Durham, USA [Lopes]
28. Monash University, Melbourne, Australia [McQuilten]
29. Monash Health, Melbourne, Australia [McQuilten]
30. University of Sao Paulo Department of Internal Medicine [Miranda]
31. IRCCS Fondazione Don Gnocchi, ONLUS, Milan, Italy [Morici]
32. Middlemore Hospital, Auckland, North Island, New Zealand [Morpeth]
33. Department of Internal Medicine, Infanta Leonor University Hospital, Complutense University of Madrid, Spain [Muñoz-Rivas]
34. Department of Surgery, University of Pittsburgh, Pittsburgh, PA [Neal]
35. Institute of Medicine, Tribhuvan University Teaching Hospital, Kathmandu, Bagmati, Nepal [Pant]
36. University of Iowa Department of Internal Medicine [Perepu]
37. Iran University of Medical Sciences Rajaie Cardiovascular Medical and Research Center, Iran University of Medical Sciences, Tehran, Iran [Sadeghipour, Talasaz]
38. Departments of Medicine, and Laboratory Medicine and Pathobiology, Li Ka Shing Knowledge Institute, St Michael's Hospital, University of Toronto, Toronto, Ontario, Canada [Sholzberg]
39. Northwell Health at Lenox Hill Hospital Department of Medicine New York, NY, USA and the Feinstein Institutes for Medical Research, Manhasset, NY, USA [Spyropoulos]
40. Victorian Infectious Diseases Service, The Royal Melbourne Hospital, at the Peter Doherty Institute for Infection and Immunity, Melbourne, Australia; Department of Infectious Diseases, The University of Melbourne at the Peter Doherty Institute for Infection and Immunity, Melbourne, Australia [Tong]
41. Faculty of Medicine and Health, The University of Sydney School of Public Health, Sydney [Totterdell]
42. University of Queensland, Brisbane, Australia; The George Institute for Global Health, Sydney, Australia; The Wesley Hospital, Brisbane, Queensland, Australia; University of New South Wales, Sydney, New South Wales, Australia [Venkatesh]
43. The George Institute for Global Health, Delhi, Delhi, India [Jha, Venkatesh]
44. Division of Internal Medicine, ASST Fatebenefratelli Sacco, Luigi Sacco Hospital, University of Milan, Milan, Italy [Wu]
45. Department of Biomedical and Clinical Sciences, University of Milan, Milan, Italy [Wu]
46. Max Rady College of Medicine University of Manitoba [Zarychanski]
47. University Hospital of Nancy Department of Vascular Medicine [Zuily]
48. Clinical Unit, Health Emergencies Programme, World Health Organization, Geneva, Switzerland [Diaz, Viry, Rylance]
49. Department of Critical Care Medicine, St. Michael's Hospital, University of Toronto, Toronto, Canada [Marshall]
50. Health Data Research UK South West [Sterne]
51. Department of Pediatrics, University of British Columbia, Vancouver, Canada [Murthy]

Abstract

Background Clinical trials assessing the efficacy of higher-dose anticoagulation in patients hospitalized for COVID-19 have variously reported benefit, no effect, and harm.

Purpose Estimate the association of higher- versus lower-dose anticoagulation with clinical outcomes

Data Sources Randomized trials were initially identified from searching the World Health Organization's International Clinical Trials Registry Platform (WHO ICTRP) and ClinicalTrials.gov in August 2020, combining search terms for COVID-19 and anticoagulation with no restriction by trial status or language. Searches were updated periodically until March 2023 when the final protocol was registered, with a final search in September 2024.

Study Selection Eligible trials randomly assigned patients hospitalized for COVID-19 to a higher- and a lower-dose anticoagulation strategy.

Data Extraction In this prospective meta-analysis, 18 trials met study selection criteria and provided data in a prospectively agreed format and 2 further studies were included based on published data. Risk of bias was assessed using the Cochrane Risk of Bias 2 tool. Primary analyses were inverse variance–weighted fixed-effects meta-analyses of odds ratios (ORs). The primary outcome was all-cause mortality 28 days after randomization. Secondary outcomes were progression to invasive mechanical ventilation (IMV) or death, thromboembolic events, and major bleeding.

Data Synthesis Administration of therapeutic- compared with prophylactic-dose anticoagulation with heparins was associated with lower 28-day mortality (OR 0.77, 95% CI 0.64-0.93; I^2=29%; 11 trials, 6297 patients, of whom 5456 required low or no oxygen at randomization). The ORs for 28-day mortality were 1.21 (95% CI 0.93-1.58; I^2=0%) for therapeutic- with intermediate-dose anticoagulation (6 trials, 1803 patients, 1043 receiving non-invasive ventilation at randomization) and 0.95 (95% CI 0.76-1.19; I^2=0%; 10 trials, 3897 patients, 2935 receiving no or low oxygen at randomization) for intermediate- versus prophylactic-dose anticoagulation. Associations between dose of anticoagulation and outcome appeared broadly consistent across pre-defined patient subgroups, although some analyses had limited power to detect interactions. For each comparison, higher- compared with lower-dose anticoagulation was associated with fewer thromboembolic events but a greater risk of major bleeding.

Conclusions Therapeutic- compared with prophylactic-dose anticoagulation reduced 28-day mortality. By contrast, mortality was similar for intermediate compared with prophylactic-dose anticoagulation and higher for therapeutic- compared with intermediate-dose anticoagulation, although this comparison was not estimated precisely.

Registration PROSPERO Identifier: CRD42020213461

Introduction

Hospitalized patients with COVID-19 have high rates of thrombosis and systemic inflammation. (1, 2) The role of thromboprophylaxis with anticoagulants, most commonly low-molecular weight heparins (LMWH), unfractionated heparin (UFH), and direct-acting oral anticoagulants (DOACs), has been investigated in randomized trials that variously reported clinical benefit, no benefit, and potential harm with varied doses and drugs for anticoagulation in patients with differing COVID-19 severity. The World Health Organization (WHO) Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group previously reported prospective meta-analyses evaluating corticosteroids, interleukin-6 antagonists and sodium-glucose cotransporter-2 (SGLT2) inhibitors in such patients. (3-5) We used a similar approach to estimate associations of higher- versus lower-dose anticoagulation with mortality by 28 days after randomization, progression to invasive mechanical ventilation or death, thromboembolic events and major bleeding in patients hospitalized for COVID-19. Secondary objectives were to estimate and compare associations within pre-specified subgroups.

Methods

Data Sources and Searches

Trials were identified through a systematic search of the World Health Organization's International Clinical Trials Registry Platform (WHO ICTRP) and ClinicalTrials.gov (25 August 2020). Searches were updated on 01 February 2021, and then periodically until the final version of the protocol was registered (06 March 2023), to ensure all relevant trials were identified. Additionally, research and WHO networks were asked for relevant trials. On the request of journal editors, additional searches were completed in October 2023 and September 2024 (sTable-1 Supplement 1).

Study Selection

Eligible trials randomly assigned hospitalized patients to higher versus lower doses of anticoagulants: queries regarding eligibility were resolved by consensus. The intensity of anticoagulant used was classified as prophylactic, intermediate, or therapeutic dosing, as defined in sTable-2 Supplement 1). All trials secured institutional review board (IRB) approval and obtained informed consent from participants.

In June 2021, principal investigators of potentially eligible trials were invited to participate in the prospective meta-analysis, and to join regular calls to develop the prospective meta-analysis protocol. The final protocol was registered on PROSPERO on 06 March 2023, before the current analyses were conducted (CRD42020213461).

Data Collection

Baseline and outcome data collection forms (Supplement 2) were requested for all eligible trials. Summary data for all outcomes was supplied by intervention group, overall and in pre-specified subgroups. Data were thoroughly checked, and trial investigators were asked to verify the final data prior to inclusion in the meta-analysis. Data on additional trials that did not respond to repeated requests to supply data were extracted from published reports by one reviewer (CLV) and checked by a second (PJG).

Data Synthesis and Analysis

The primary objective was to estimate intention-to-treat effects of: (1) therapeutic vs prophylactic; (2) therapeutic vs intermediate and (3) intermediate vs prophylactic dose (sTable-2 Supplement 1) anticoagulation in hospitalised patients with suspected or confirmed COVID-19. Trials with protocols that allowed a choice of prophylactic or intermediate doses in the comparator group were classified according to the dose received by the majority of patients (sTable-3 Supplement 1).

The primary outcome was all-cause mortality by 28 days after randomization. Secondary outcomes were: i) progression to invasive mechanical ventilation (IMV) or death, for those not requiring mechanical ventilation at the time of randomisation; ii) arterial or venous thromboembolic events; and iii) major bleeding as defined by the International Society of Thrombosis and Hemostasis (all by 28 days after randomization).

Severity of disease was defined based on respiratory support at randomization (no oxygen; oxygen flow <15 L/minute; non-invasive ventilation (NIV) including high-flow nasal oxygen (HFNO); invasive mechanical ventilation (IMV), noting that combining the first two groups corresponds to the WHO definition of 'severe' (severely or non-critically ill) and combining the second two corresponds to 'critical' (critically ill) patients. (6) Due to relatively low numbers of patients and/or few events in the 'no oxygen' category for the primary outcome (Therapeutic- vs prophylactic-dose: 1 event/296 patients; Therapeutic- vs intermediate-dose: 1 event /79 patients; Intermediate vs prophylactic dose: 23 events /908 patients), and because data on these two categories could not be separated in all included trials, we have combined them (i.e. no oxygen and oxygen flow <15 L/minute) for analysis. Furthermore, trials that did not provide or report summary results for respiratory support subgroups (7, 8) were categorised according to the level of oxygen support received by the majority of patients. Other patient subgroups were: 1) D-dimer level at randomization (Normal [<2× upper limit of normal (ULN)], Elevated [2-4× ULN], High [>4× ULN]); 2) Receipt of corticosteroids at randomization; 3) Sex; 4) Age (<70 and ≥70 years); 5) Body mass index (BMI; <30 and ≥30 kg/m^2) and 6) Epoch of randomization (Before June 2020; July-Dec 2020; Jan 2021 onwards).

The primary analyses were inverse-variance weighted fixed-effects meta-analyses of odds ratios (ORs). Inconsistency was quantified using I^2 statistics and heterogeneity p values using Cochran Q statistics. Precise p values were reported, without adjustment for multiple testing. No threshold for statistical significance was used. Trial-level treatment effect estimates were adjusted for adaptive randomization, where appropriate.

To obtain illustrative estimated absolute risk differences, risks of outcomes, overall and for patients with varying degrees of disease severity (defined by respiratory support required at randomisation), were assumed from approximate risks among eligible comparison (lower dose) group patients. Meta-analytic ORs were then applied to obtain the corresponding risk with higher-dose anticoagulants. Associations within subgroups were compared by calculating ratios of odds ratios (RORs) and corresponding interaction p-values. Comparisons between subgroups defined by patient characteristics were done by estimating trial-specific RORs comparing associations between subgroups and then combining these in meta-analyses (9, 10). To obtain specific treatment effects for subgroups defined by patient characteristics, we combined treatment effects in each patient subgroup across trials using inverse variance-weighted fixed-effects meta-analysis. In sensitivity analyses, we estimated subgroup effects that were adjusted so that they corresponded with the pooled RORs derived from the within-trial approach (9, 10). Analyses were conducted using Stata 18 (StataCorp. 2023) (11, 12). In sensitivity analyses we: (1) excluded trials in which <90% of patients in the comparator group received the same anticoagulation dose; (2) restricted analyses to trials at low risk of bias; (3) excluded trials at high risk of bias; and (4) restricted analyses to trials published or in press in peer reviewed journals.

To examine whether the severity of disease at randomisation (severe or critical as previously defined) modified the effect of anticoagulation dose, and to gain consistent estimates of treatment effect across the three dose comparisons incorporating both direct and indirect data from all included trials, we carried out an exploratory network meta-analysis (NMA) for all outcomes. Full methods and results for the NMA are provided in Supplement 3 (online only).

Quality Assessment

For each trial, the risk of bias (low risk, some concerns, or high risk) was assessed using the Cochrane Risk of Bias Assessment Tool version 2. (13) The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to assess the certainty of the evidence.

Results

Initial searches identified 143 potentially eligible trials, with two additional trials identified through contact with investigators. After removing duplicates and studies deemed ineligible based on population, intervention or study type, eligibility was assessed for 38 records, of which four (NCT04505774, NCT04359277, NCT04372589, NCT02735707) were combined into a multi-platform RCT within two populations defined by disease severity; one in non-critically ill patients (14) and one in critically ill patients (15). These were included separately. Two trials (NCT04444700, NCT04362085) were combined under the RAPID collaboration. (16)

Therefore, 35 trial investigators or groups were contacted and invited to participate, of which one trial was subsequently determined to be ineligible based on the interventions being assessed, 4 terminated early due to poor recruitment or did not commence recruitment and no data were provided, 7 did not respond to invitations to participate and one trial was still recruiting at the time of final data collection (Appendix eFigure-1 and sTable-4, Supplement 1). Among 22 trials and 11733 patients (98% of all randomised) with data available, data from two trials were extracted from publications (7, 8). Of 20 trials that supplied data, 17 are published (14-29; Appendix eTable-1).

Patients were recruited from 21 countries. Nineteen trials evaluated heparins, primarily enoxaparin, tinzaparin or dalteparin, or UFH. Our main findings therefore focus on anticoagulation using heparins. One trial (19) assessed compared therapeutic dose rivaroxaban with prophylactic dose heparins: its results are in supplementary materials (Supplement 4-7, online only).

Most trials compared two anticoagulation doses, but three (8, 22, 23) compared three anticoagulation doses, so that relevant groups can be included in pairwise comparisons in each of the 3 meta-analyses. Trials with two groups in the same dose category were analysed as 2 group trials (19) and STAUNCH-19 unpublished). For two 3-group trials that included a randomisation to therapeutic dose heparin or apixaban (7), (18) we only included results from the comparison of therapeutic versus prophylactic dose heparin.

Therapeutic versus prophylactic dose anticoagulation

Data on patient characteristics and 28-day mortality were supplied for 6297 (99%) patients from 11 trials (Appendix eTable-1 and eTable-2). The range of median ages was 52-70 years and 3708 (57%) patients were male: 644 (15%) and 143 (3%) respectively of 4262 patients with data supplied received non-invasive ventilation and invasive mechanical ventilation at randomization. 275 comparator group patients from 2 trials (mpRCT-non-critically ill (14): 227 and COVID-HEP (24): 48 patients) received intermediate dose anticoagulation.

No trial results were judged as at high risk-of-bias. For 28-day mortality, risk of bias was judged as low in 9 trials (66.5% of the meta-analysis weight, Appendix eTable-3 and sFigure-1, Supplement 1).

Data on 28-day mortality were available for 3189 patients (252 deaths) receiving therapeutic dose and 3108 patients (304 deaths) receiving prophylactic dose anticoagulation (summary OR 0.77, 95% CI 0.64-0.93; I^2=29%; Figure 1). This corresponds to an absolute mortality risk of 7.2% for therapeutic- compared with an assumed 10% for prophylactic- dose anticoagulation (sTable-5, Supplement 1). Supplements 4-7 (online only) present further details and full results.

The summary odds ratios were 0.77 (95% CI 0.61-0.97; I^2=39%) among 5447 patients receiving no or low O2 at randomisation; 0.71 (95% CI 0.49-1.02; I^2=0%) among 714 patients receiving NIV or HFNO at randomisation and 1.15 (95% CI 0.51-2.57; I^2=38%) among 123 patients receiving IMV or ECMO at randomisation (p for interaction 0.57, Figure 2a; Appendix eFigure-2a).

Based on 10 trials, 711 of 5948 patients progressed to IMV or died by 28 days (summary OR 0.80 (95% CI 0.68-0.94; I^2=18%; Figure 1). Based on 11 trials, there were 222 thromboembolic events among 6289 patients (summary OR 0.48; 95% CI 0.36-0.64; I^2=0%; Figure 1) and 81 major bleeding events among 6298 patients (summary OR 1.90, 95% CI 1.19-3.05; I^2=0%; Figure 1). There was no strong evidence that the effects of anticoagulation differed by levels of respiratory support at randomisation for secondary outcomes (Appendix eFigures-3-8). Estimated absolute risks for secondary outcomes are in sTable-5, Supplement 1. Results of prespecified sensitivity analyses were broadly consistent with those reported above (sTable-6, Supplement 1). Comparisons within the remaining pre-defined patient subgroups are reported in Appendix eTable-4.

The GRADE assessment of the certainty of the evidence was high for each outcome except major bleeding, which was rated as moderate, due to imprecision (81 events) and some concerns about potential subjectivity in outcome assessment (sTable-7, Supplement 1).

Therapeutic versus intermediate dose anticoagulation

Data on patient characteristics and 28-day mortality were supplied for 1798 (93.7%) patients from 6 trials (Appendix eTable-1 and eTable-2). The range of median ages was 52-74 years and 1228 (64%) patients were male: 991 (55%) and 363 (20%) respectively were receiving non-invasive ventilation and invasive mechanical ventilation at randomization.

No trial results were judged as at high risk-of-bias. For 28-day mortality and progression to IMV or death, risk of bias was assessed as low in 2 trials (11% of the meta-analysis weight, with 4 trials judged to have some concerns, mostly due to missing reasons for excluding participants

or deviations from intended interventions. All 6 trial results were judged to have some concerns for the thromboembolic events and major bleeding (Appendix eTable-3 and sFigure-1, Supplement 1).

Data on 28-day mortality were available for 888 patients (204 deaths) receiving therapeutic dose and 915 patients (194 deaths) receiving intermediate dose anticoagulation (summary OR 1.21, 95% CI 0.93-1.58; I^2=0%; Figure 3). This corresponds to an absolute mortality risk of 27% for therapeutic- compared with an assumed risk of 24% for intermediate-dose anticoagulation (sTable-5, Supplement 1). Supplements 4-7 (online only) include further details and full results. The summary OR among 322 patients receiving no or low oxygen at randomisation was 2.42 (95% CI 0.81–7.21; I^2=13%); 1.18 (0.86-1.60; I^2=0%) among 1063 patients receiving NIV or HFNO at randomisation and 1.13 (95% CI 0.69-1.84; I^2=0%) for 341 patients receiving IMV or ECMO at randomisation (p-value for interaction 0.98,Figure 2b and Appendix eFigure-2b).

Based on 5 trials, 418 of 1242 patients progressed to IMV or death by 28 days (summary OR 1.30 (95% CI 1.00-1.71; I^2=2%; Figure 3). Based on 6 trials, there were 121 thromboembolic events among 1787 patients (summary OR 0.63; 95% CI 0.43-0.93; I^2=0%; Figure 3) and 46 major bleeding events among 1484 patients from 4 trials (summary OR 1.21; 95% CI 0.66-2.20; I^2=0%; Figure 3); two trials recorded no major bleeding events. There was no strong evidence that the effects of anticoagulation differed by levels of respiratory support at randomisation for secondary outcomes (Appendix eFigures 3b-8b). Estimated absolute risks for secondary outcomes are in sTable-5, Supplement 1. Results of the prespecified sensitivity analyses were broadly consistent with those reported above (sTable-6, Supplement 1). Insufficient data were available to assess the between-subgroup differences in associations of therapeutic- versus intermediate-dose anticoagulation between pre-defined patient subgroups.

The GRADE assessment of the certainty of the evidence was moderate for each outcome, with all judged to have some imprecision as well as potential subjectivity in assessment of major bleeding and thromboembolic events (sTable-7, Supplement 1).

Intermediate versus prophylactic dose anticoagulation

Data on patient characteristics and 28-day mortality were supplied for 3897 (98.9%) patients from 10 trials (Appendix eTable-1 and eTable-2). The range of median ages across trials was 48-65 years and 2449 (63%) patients were male. 496 (13%) and 250 (7%) of 2698 patients from 9 trials with data supplied received non-invasive ventilation and invasive mechanical ventilation respectively.

No trial results were judged as at high risk-of-bias. For 28-day mortality, risk of bias was judged as low in 8 trials (84% of the meta-analysis weight in the meta-analysis). One trial was judged to have some concerns for progression to IMV or death. Results for 9 trials (thromboembolic events) and 6 trials (major bleeding) were assessed as having some concerns, mainly because of potential for subjective outcome assessments (Appendix eTable-3 and sFigure-1, Supplement 1).

Data on 28-day mortality were available for 1939 patients (205 deaths) and 1958 patients (215 deaths) receiving intermediate and prophylactic dose anticoagulation respectively (summary OR 0.95; 95% CI 0.76-1.19; I^2=0%, Figure 4). This corresponds to little change in absolute mortality risk for intermediate- compared with an assumed 10% risk for prophylactic-dose anticoagulation (sTable-5, Supplement 1). Supplements 4-7 (online only) include further details and full results. The summary ORs were 1.08 (95% CI 0.77-1.53; I^2=0%) among 2928 patients receiving no or low oxygen support at randomisation; 0.88 (95% CI 0.57-1.36; I^2=0%) among 540 patients receiving NIV or HFNO at randomisation and 0.64 (95% CI 0.36-1.15; I^2=0%) among 257 patients receiving IMV or ECMO at randomisation (Test for interaction p=0.10 Figure 2c; Appendix eFigure-2c). Note that level of respiratory support was unknown for 151 patients from 5 trials.(23, 25-27, 29)

Based on 8 trials, the summary OR for progression to IMV or death by 28 days was 0.84 (95% CI 0.68-1.05; I^2 = 38%, Figure 4). Based on 10 trials, there were 121 thromboembolic events among 3847 patients (summary OR 0.67; 95% CI 0.45-1.00; I^2=37%; Figure 4) and 44 major

bleeding events among 3248 patients from 6 trials with data available (summary OR 1.22; 95% CI 0.66-2.25; I^2=0%; Figure 4). Three trials recorded no major bleeding events. There was no strong evidence that the effects of anticoagulation differed by levels of respiratory support at randomisation for secondary outcomes (Appendix eFigures-3c-8c). Estimated absolute risks for these secondary outcomes are in sTable-5, Supplement 1. Results of the prespecified sensitivity analyses were broadly consistent with those reported above (sTable-6, Supplement 1). Comparisons within the remaining pre-defined patient subgroups are reported in Appendix eTable-4.

The GRADE assessment of the certainty of the evidence was high for 28-day mortality and progression to IMV or death, and moderate for major bleeding and thromboembolic events, due to some imprecision and potential for subjective outcome assessment (sTable-7, Supplement 1).

Discussion

In this prospectively designed meta-analysis of randomized trials, administration of therapeutic- compared with prophylactic-dose anticoagulation with heparins to patients hospitalized for COVID-19 was associated with 23% lower 28-day mortality. Trials making this comparison were mainly conducted in patients requiring no or low oxygen at randomization. By contrast, mortality was higher for therapeutic- compared with intermediate-dose anticoagulation, although this comparison was not estimated precisely. The risk of 28-day mortality was similar for intermediate- versus prophylactic dose anticoagulation. Associations with progression to invasive mechanical ventilation or death were similar to those for 28-day mortality. For each comparison of higher and lower doses of anticoagulation, the risk of major bleeding was greater, but the risk of thromboembolic events was lower. Associations between dose of anticoagulation and outcome appeared broadly consistent across all pre-defined patient subgroups, although some analyses had limited power to detect interactions.

Reported results of some of the studies included in this meta-analysis have suggested that therapeutic anticoagulation doses are preferable in patients not requiring intensive care unit (ICU) levels of care (14, 16) but not in those requiring ICU care (15, 20), and have informed current guidelines to varying extents (31-34). This includes one of the largest trials, which found that effects of therapeutic versus non-therapeutic anticoagulation on its primary composite outcome (organ support–free days, evaluated on an ordinal scale) differed between severely and critically ill patients (30). These results have informed guidelines to varying extents (31-34). Results of our subgroup analysis on effect of therapeutic vs prophylactic doses of anticoagulation on 28-day all-cause mortality in patients on IMV or ECMO at randomization were inconclusive because of small numbers of patients. However, we did not identify clear differences between patients requiring different levels of respiratory support. It is possible that effects on non-mortality components of organ support-free days, not considered in this study, differ by disease severity. Larger sample sizes are required to identify between-subgroup differences for all-cause mortality than on an ordinal composite outcome.

Interpretation of these results is difficult because of the different doses of anticoagulation compared, and because severity of illness at randomization differed for different dose comparisons. In trials comparing therapeutic with prophylactic dose anticoagulation, 5543 (88.2%) of 6286 patients did not require IMV or ECMO at randomization, compared with 386 (21.4%) of 1803 patients in trials comparing therapeutic with intermediate dose anticoagulation. The association of therapeutic versus intermediate dose anticoagulation with higher 28-day mortality could therefore relate either to the different dosing regimens or to the differing distributions of COVID-19 severity between patients recruited to the different dose comparisons. Flexible dosing of comparison groups (sTable-3, Supplemnent 1) meant that in some trials a significant minority of comparison group patients received a different dose to that specified for the comparison. In the mpRCT, 29% of 1050 non-critically ill comparison group patients received intermediate or sub-therapeutic dose anticoagulation (14), while 40% of 567 critically ill comparison group patients (15) received prophylactic dose anticoagulation. The lack of dose-

dependency of the treatment effect is possibly explained both by the varied patients recruited and doses assessed within trials, and by the balance between risks and benefits. Therapeutic dose plausibly has higher benefit on efficacy outcomes, but higher adverse event rates, while intermediate dose has relatively less benefit on efficacy outcomes, but relatively lower adverse event rates.

Prospective meta-analyses (PMAs) designed in conjunction with trial investigators before trial results are known can provide comprehensive information based on all available evidence for outcomes of primary interest, overall and in pre-specified subgroups, particularly in the face of a pandemic. (35) They can rapidly provide evidence informing clinical decision-making and identify key knowledge gaps (36). In this example, we were not able to provide rapid evidence largely due to the complexity of analysis, and because some large trials, important to the evidence base, reported independently and were not able to collaborate in this endeavour.

Our study has further several limitations. First, only one trial examined a DOAC, so our results apply to anticoagulation with heparins. Second, inconsistencies in reporting severe adverse events meant we only examined major bleeding as the adverse event of primary interest. Data on the relative impact of specific adverse events such as thromboembolic events or haemorrhages were lacking, acknowledging the varied impacts of these events. Third, as we did not achieve collaboration for all trials, some data were extracted from publications (7, 8). This has resulted in some missing outcome data, inability to separate patients receiving different degrees of respiratory support at randomisation, and lack of doses studied for certain populations resulting in reductions in power to detect subgroup effects. Unsuccessful attempts to obtain data directly contributed to a considerable delay to the reporting of this prospective meta-analysis. Fourth, the majority of the data were for therapeutic vs prophylactic dose comparisons, particularly in populations with low or no oxygen requirement at randomization, with comparisons involving intermediate-dosing having fewer numbers randomized. Fifth, while collection of summary data meant that while we could assess the interaction of individual patient characteristics (e.g. D-Dimer levels or respiratory support level) with treatment effects,

we are not able to consider the impact of multiple factors (e.g. D-Dimer levels and respiratory support levels) on treatment effects: this would require collection and analysis of individual participant data. Finally, as with much of the work on COVID19 therapeutics, evolving disease and population factors decrease the generalizability of these trials, largely conducted earlier in the pandemic, to current practice.

Conclusions

In this prospective meta-analysis of clinical trials examining doses of anticoagulation for hospitalized patients with COVID-19, therapeutic- compared with prophylactic-dose anticoagulation reduced 28-day mortality. By contrast, mortality was higher for therapeutic compared with intermediate dose anticoagulation, although this comparison was not estimated precisely, and similar for intermediate compared with prophylactic dose anticoagulation. For each comparison, higher compared with lower dose anticoagulation was associated with fewer thromboembolic events but a greater risk of major bleeding.

Figures and tables

Figure 1. Association of therapeutic- versus prophylactic-dose anticoagulation with (a) 28-day mortality, (b) progression to invasive mechanical ventilation or death, (c) thromboembolic events, and (d) major bleeding.
Footnote: Trials are listed in order of date of first randomisation.

Figure 2. Associations of anticoagulation with 28-day mortality, based on inverse-variance weighted meta-analyses, according to level of respiratory support at the time of randomisation, together with ratios of odds ratios comparing associations across respiratory support subgroups.
Footnote: The p-values for interaction test the null hypothesis that the odds ratios across respiratory support subgroups are the same and are based on chi-squared statistics with 2 degrees of freedom. Trials unable to supply subgroup data, and those with no events, are not included in the summary counts of trials, events/patients, nor do they contribute to the pooled OR estimate. For full details see Appendix eFigure-3.

Figure 3. Association of therapeutic- versus intermediate-dose anticoagulation with (a) 28-day mortality, (b) progression to invasive mechanical ventilation or death, (c) thromboembolic events, and (d) major bleeding.
Footnote: Trials are listed in order of date of first randomisation.

Figure 4. Association of intermediate- versus prophylactic-dose anticoagulation with (a) 28-day mortality, (b) progression to invasive mechanical ventilation or death, (c) thromboembolic events, and (d) major bleeding.
Footnote: Trials are listed in order of date of first randomisation.

Author Contributions:

Drs Murthy, Vale, Sterne had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Drs Murthy and Sterne are equal contributors.

Concept and design*:* Murthy, Vale, Godolphin, Fisher, Tritschler, Sterne, Diaz, Marshall

Trial design and provision of data*:* Berg, Berry, Blondon, Bohula, Cattaneo, Coluccio; DeSancho, Farkouh, Girardis, Hochman, Jensen, Jüni, Kirtane, Lawler, Lawler, Le Gal, Lecumberri, Lopes, Lorenzi, Marietta, Miranda, Morici, Morrow, Muñoz-Rivas, Neal, Parikh, Perepu, Sadeghipour, Bikdeli, Sethi, Sholzberg, Spyropoulos, Wu, Zarychanski, Zuily

Acquisition, analysis, or interpretation of data*:* Data collection forms were designed by Vale, Sterne, Murthy, Godolphin, and Fisher. Assessing risk of bias and certainty in the evidence [GRADE]: Higgins, McAleenan, Spiga. All authors contributed to the analysis and interpretation of data.

Drafting of the manuscript*:* Murthy, Vale and Sterne generated the first draft of the manuscript. All authors provided revisions towards the final draft.

Critical revision of the manuscript for important intellectual content*:* All authors.

Statistical analysis*:* Vale, Godolphin, Fisher, Sterne

Obtained funding*:* Sterne, Murthy, Diaz, Marshall.

Administrative, technical, or material support*:* Murthy, Vale, Sterne, Diaz, Marshall.

Supervision: Sterne, Murthy, Vale, Godolphin, Higgins, Diaz, Marshall.

Conflict of Interest Disclosures:

CLV, PJG and DJF are supported by the UKRI Medical Research Council (https://mrc.ukri.org/) Grant number: MC_UU_00004/06.

JACS is supported the NIHR Bristol Biomedical Research Centre at University Hospitals Bristol and Weston NHS Foundation Trust and by Health Data Research UK South West. The views expressed in this article are those of the authors and do not necessarily represent those of the NHS, the NIHR, MRC, or the Department of Health and Social Care.

JPTH and FS are supported by the NIHR Bristol Evidence Synthesis Group. JPTH is an NIHR Senior Investigator (NIHR203807) and is also supported by the NIHR Applied Research Collaboration West (ARC West) at University Hospitals Bristol and Weston NHS Foundation Trust.

PJ serves as unpaid member of steering group or executive committee of trials funded by Abbott Vascular, Astra Zeneca, Biotronik, Biosensors, St. Jude Medical, Terumo and The Medicines Company, has received research grants to the institution from Appili Therapeutics, Astra Zeneca, Biotronik, Biosensors International, Eli Lilly, The Medicines Company, and honoraria to the institution for participation in advisory boards and/or consulting from Amgen, Ava and Fresenius, but has not received personal payments by any pharmaceutical company or device manufacturer. PJ was a Tier 1 Canada Research Chair in Clinical Epidemiology of Chronic Diseases. This research was completed, in part, with funding from the Canada Research Chairs Programme.

BB is supported by the Scott Schoen and Nancy Adams IGNITE Award from the Mary Horrigan Connors Center for Women's Health and Gender Biology at Brigham and Women's Hospital and a Career Development Award from the American Heart Association (#938814). BB reports that he is a consulting expert, on behalf of the plaintiff, for litigation related to two specific brand models of IVC filters.

MTD is Panel Member American Society of Hematology Practice guidelines for anticoagulation in COVID-19 and on advisory board of Pharmacosmos.

GS has received speaker honoraria from Medtronic, Pulnovo, Infraredx, Abiomed, Amgen, Boehringer Ingelheim; has served as a consultant to Abbott, Daiichi Sankyo, Ablative Solutions,

CorFlow, Cardiomech, Robocath, Miracor, Vectorious, Apollo Therapeutics, Elucid Bio, Cardiac Success, Valfix, TherOx, HeartFlow, Neovasc, Ancora, Occlutech, Impulse Dynamics, Adona Medical, Millennia Biopharma, Oxitope, HighLife, Elixir, Remote Cardiac Enablement, Aria; and has equity/options from Cardiac Success, Ancora, Cagent, Applied Therapeutics, Biostar family of funds, SpectraWave, Orchestra Biomed, Aria, Valfix, Xenter. Dr. Stone's employer, Mount Sinai Hospital, receives research grants from Shockwave, Abbott, Abiomed, Bioventrix, Cardiovascular Systems Inc, Phillips, Biosense-Webster, Vascular Dynamics, Pulnovo, V-wave.

RZ receives operating grants from the Canadian Institutes of Health Research (CIHR) and research support as the Lyonel G Israels Research Chair in Hematology at the University of Manitoba.

ACS receives grants from the Agency for Healthcare Research and Quality and the Broxmeyer Fellowship in Clinical Thrombosis

TT is supported by grants from the Canadian Venous Thromboembolism Research Network (CT-12359) and the CTU Bern, University of Bern.

SM receives operating grants from the Canadian Institutes of Health Research (CIHR) and research support as the Innovative Medicines Canada and Health Research Foundation chair in pandemic preparedness research at the University of British Columbia.

Funding/Support: Funding for administrative and communications support was provided by the World Health Organization.

Role of the Funder/Sponsor: The World Health Organization [WHO] contributed to the design and conduct of the study by convening the WHO COVID-19 Clinical Management and Characterization Working Group. This group assembled information on ongoing trials and invited trial investigators to participate in this prospective meta-analysis. The WHO chief scientist invited trial investigators to participate and provided a secure portal for submission of

data. Other than the contributions of Dr Diaz as a co-author, the WHO had no role in the preparation, review, or approval of the manuscript. The WHO had no role in the decision to submit the manuscript for publication.

Disclaimer: The views expressed in this article are those of the authors and not necessarily those of the UK National Institute for Health Research or the UK Department of Health and Social Care.

Data Access Statement

Protocol: Registered with PROSPERO (available at: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020213461)
Statistical Code: Available on request from the authors
Data: Please see individual trials for data sharing policies. All summary results used in this meta-analysis are presented either in the article or are included in the online supplementary material.

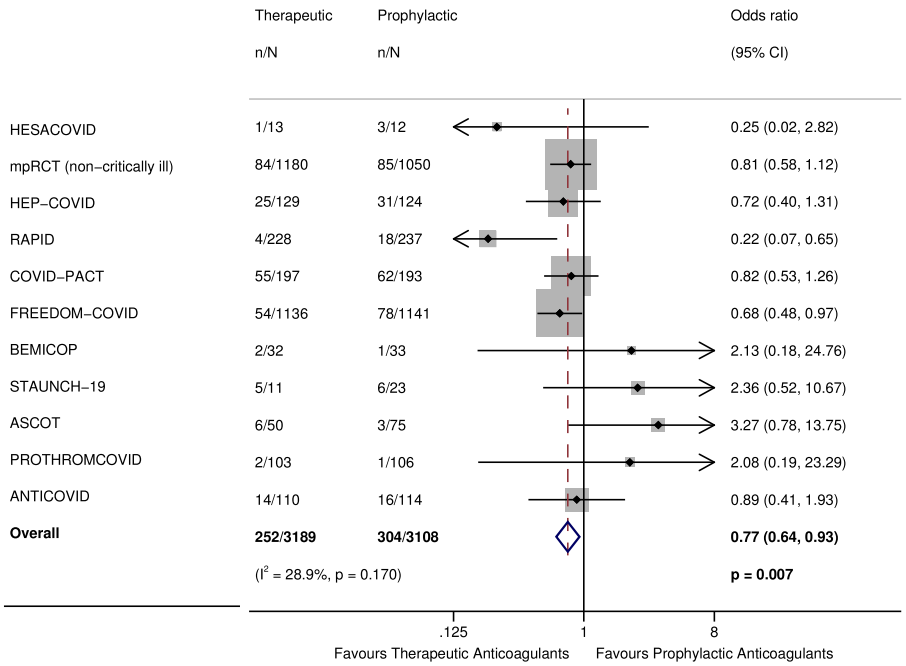
References

1. Jiménez D, García-Sanchez A, Rali P, Muriel A, Bikdeli B, Ruiz-Artacho P, et al. Incidence of VTE and Bleeding Among Hospitalized Patients With Coronavirus Disease 2019: A Systematic Review and Meta-analysis. Chest. 2021;159:1182-96.
2. Voicu S, Bonnin P, Stépanian A, Chousterman BG, Le Gall A, Malissin I, et al. High Prevalence of Deep Vein Thrombosis in Mechanically Ventilated COVID-19 Patients. J Am Coll Cardiol. 2020;76:480-2.
3. WHO Rapid Evidence Appraisal for COVID-19 Therapies Working Group**.** Association Between Administration of IL-6 Antagonists and Mortality Among Patients Hospitalized for COVID-19: A Meta-analysis. JAMA. 2021;326:499-518.
4. WHO Rapid Evidence Appraisal for COVID-19 Therapies Working Group, Sterne JAC, Murthy S, Diaz JV, Slutsky AS, Villar J, et al. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. JAMA. 2020.
5. Vale C, Godolphin PJ, Fisher D, Horby PW, Kosiborod MN, Hochman JS, et al. Sodium-glucose co-transporter 2 inhibitors (SGLT2i) for hospitalised patients with COVID-19: prospective meta-analysis of randomised trials. The Lancet Diabetes and Endocrinology. 2024;S2213-8587(24)00219-5.
6. World Health Organization 2023;Pageshttps://app.magicapp.org/#/guideline/j1WBYn on 16 February 2024.
7. Stone GW, Farkouh ME, Lala A, Tinuoye E, Dressler O, Moreno PR, et al. Randomized Trial of Anticoagulation Strategies for Noncritically Ill Patients Hospitalized With COVID-19. J Am Coll Cardiol. 2023;81:1747-62.
8. Labbé V, Contou D, Heming N, Megarbane B, Razazi K, Boissier F, et al. Effects of Standard-Dose Prophylactic, High-Dose Prophylactic, and Therapeutic Anticoagulation in Patients With Hypoxemic COVID-19 Pneumonia: The ANTICOVID Randomized Clinical Trial. JAMA Intern Med. 2023;183(520-531).
9. Fisher DJ, Carpenter JR, Morris TP, Freeman SC, Tierney JF**.** Meta-analytical methods to identify who benefits most from treatments: daft, deluded, or deft approach? BMJ. 2017;356:j573.
10. Godolphin PJ, White IR, Tierney JF, Fisher DJ**.** Estimating interactions and subgroup-specific treatment effects in meta-analysis without aggregation bias: A within-trial framework. . Research Synthesis Methods. 2022;14:68-78.
11. Fisher DJ**.** Two-stage individual participant data meta-analysis and generalized forest plots. Stata Journal. 2015;15(2):369-96.
12. Fisher D, Harris R, Bradburn M, Deeks J, Harbord R, Altman D, et al. METAN: Stata module for fixed and random effects meta-analysis. Statistical Software Components S456798,: Boston College Department of Economics; 2006.
13. Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4989.
14. Lawler PR, Goligher EC, Berger JS, Neal MD, McVerry BJ, Nicolau JC, et al. Therapeutic Anticoagulation with Heparin in Noncritically Ill Patients with Covid-19 N Engl J Med. 2021;26(9):790-802.
15. Goligher EC, Bradbury CA-O, McVerry BA-O, Lawler PA-O, Berger JS, Gong MN, et al. Therapeutic Anticoagulation with Heparin in Critically Ill Patients with Covid-19. New England Journal of Medicine. 2021 385:777-89.
16. Sholzberg MA-O, Tang GH, Rahhal H, AlHamzah M, Kreuziger LB, Áinle FN, 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.
17. Lemos ACB, do Espírito Santo DA, Salvetti MC, Gilio RN, Agra LB, Pazin-Filho A, Miranda CH**.** Therapeutic versus prophylactic anticoagulation for severe COVID-19: A randomized phase II clinical trial (HESACOVID). Thromb Res. 2020;193(359-366).

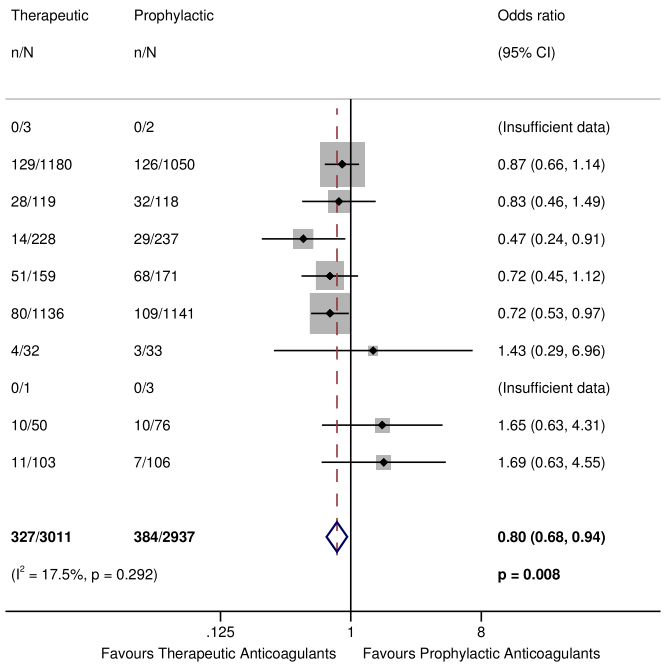
18. Spyropoulos AC, Goldin M, Giannis D, Diab W, Wang J, Khanijo S, et al. Efficacy and Safety of Therapeutic-Dose Heparin vs Standard Prophylactic or Intermediate-Dose Heparins for Thromboprophylaxis in High-risk Hospitalized Patients With COVID-19: The HEP-COVID Randomized Clinical Trial. JAMA Intern Med. 2021;181(1612-1620).
19. Lopes RD, de Barros ESPGM, Furtado RHM, Macedo AVS, Bronhara B, Damiani LP, 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(2253-2263).
20. Bohula EA-O, Berg DA-O, Lopes MA-O, Connors JA-OX, Babar I, Barnett CA-O, et al. Anticoagulation and Antiplatelet Therapy for Prevention of Venous and Arterial Thrombotic Events in Critically Ill Patients With COVID-19: COVID-PACT. Circulation. 2022;146:1344-56.
21. Marcos-Jubilar M, Carmona-Torre F, Vidal R, Ruiz-Artacho PA-O, Filella D, Carbonell C, et al. Therapeutic versus Prophylactic Bemiparin in Hospitalized Patients with Nonsevere COVID-19 Pneumonia (BEMICOP Study): An Open-Label, Multicenter, Randomized, Controlled Trial. Thromb Haemost. 2021;122(295-299).
22. Muñoz-Rivas NA-OX, Aibar JA-O, Gabara-Xancó C, Trueba-Vicente Á, Urbelz-Pérez AA-O, Gómez-Del Olmo V, et al. Efficacy and Safety of Tinzaparin in Prophylactic, Intermediate and Therapeutic Doses in Non-Critically Ill Patients Hospitalized with COVID-19: The PROTHROMCOVID Randomized Controlled Trial. J Clin Med. 2022;11:5632.
23. McQuilten Z, Venkatesh B, Jha V, Roberts J, Morpeth S, Totterdell J, et al. ASCOT ADAPT study of COVID-19 therapeutics in hospitalised patients: an international multicentre adaptive platform trial. NEJM Evidence. 2023;2.
24. Blondon M, Cereghetti S, Pugin J, Marti C, Darbellay Farhoumand P, Reny JL, et al. Therapeutic anticoagulation to prevent thrombosis, coagulopathy, and mortality in severe COVID-19: The Swiss COVID-HEP randomized clinical trial. . Res Pract Thromb Haemost. 2022;18(4):e12712.
25. Morici NA-O, Podda G, Birocchi S, Bonacchini L, Merli MA-O, Trezzi M, et al. Enoxaparin for thromboprophylaxis in hospitalized COVID-19 patients: The X-COVID-19 Randomized Trial. Eur J Clin Invest. 2022;52:e13735.
26. Zuily S, Lefèvre B, Sanchez O, Empis de Vendin O, de Ciancio G, Arlet JB, et al. Effect of weight-adjusted intermediate-dose versus fixed-dose prophylactic anticoagulation with low-molecular-weight heparin on venous thromboembolism among noncritically and critically ill patients with COVID-19: the COVI-DOSE trial, a multicenter, randomised, open-label, phase 4 trial. EClinicalMedicine. 2023;60:102031.
27. Perepu US, Chambers I, Wahab A, Ten Eyck P, Wu C, Dayal SA-O, 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(2225-2234).
28. Sadeghipour P, Talasaz AH, Rashidi F, Sharif-Kashani B, Beigmohammadi MT, Farrokhpour M, 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(1620-1630).
29. Wu MA-O, Del GC, Colombo R, Dolci G, Arquati M, Vicini R, et al. Low-molecular-weight heparin for the prevention of clinical worsening in severe non-critically ill COVID-19 patients: a joint analysis of two randomized controlled trials. Intern Emerg Med. 2024;19(1970-9366 (Electronic)):71-9.
30. Goligher EC, Lawler PR, Jensen TP, Talisa V, Berry LR, Lorenzi E, et al. Heterogeneous Treatment Effects of Therapeutic-Dose Heparin in Patients Hospitalized for COVID-19. JAMA. 2023;329(13):1066-77.
31. COVID-19 Treatment Guidelines Panel**.** Coronavirus Disease 2019 (COVID-19) Treatment Guidelines.: National Institutes of Health; 2023.

32. Cuker A, Tseng EK, Nieuwlaat R, Angchaisuksiri P, Blair C, Dane K, et al. American Society of Hematology living guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19: May 2021 update on the use of intermediate-intensity anticoagulation in critically ill patients. Blood Advances. 2021;5(20):3951-9.
33. Condliffe R, Bunclark K, Church C, hurdman J, Kiely D, Maclean R, et al. 2021;Pages. Accessed at British Thoracic Society at https://www.brit-thoracic.org.uk/quality-improvement/covid-19/covid-19-information-for-the-respiratory-community/ on 20 February 2024 2024.
34. Kyriakoulis KG, Kollias A, Kyriakoulis IG, Kyprianou IA, Papachrysostomou C, Makaronis P, et al. Thromboprophylaxis in Patients with COVID-19: Systematic Review of National and International Clinical Guidance Reports. Current Vascular Pharmacology. 2022;20(1):96-110.
35. Tierney JF, Fisher DJ, Vale CL, Burdett S, Rydzewska LH, Rogozińska E, et al. A framework for prospective, adaptive meta-analysis (FAME) of aggregate data from randomised trials. PLoS Medicine. 2021;18(5):e1003629.
36. Godolphin PJ, Rogozińska E, Fisher DJ, Vale CL, Tierney JF. Meta-analyses based on summary data can provide timely, thorough and reliable evidence: don't dismiss them yet. Nature Medicine. 2022;28(3):429-30.
37. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost. 2005;3(692-4)(4)doi:10.1111/j.1538-7836.2005.01204.x.
38. Langan D, Higgins JPT, Jackson D, et al. A comparison of heterogeneity variance estimators in simulated random-effects meta-analyses. Research synthesis methods. 2019/03/01 2019;10(1):83-98. doi:https://doi.org/10.1002/jrsm.1316
39. Nikolakopoulou A, Mavridis D, Salanti G. Demystifying fixed and random effects meta-analysis. Evidence Based Mental Health. 2014;17(2):53. doi:10.1136/eb-2014-101795
40. Serghiou S, Goodman SN. Random-Effects Meta-analysis: Summarizing Evidence With Caveats. JAMA. 2019;321(3):301-302. doi:10.1001/jama.2018.19684.

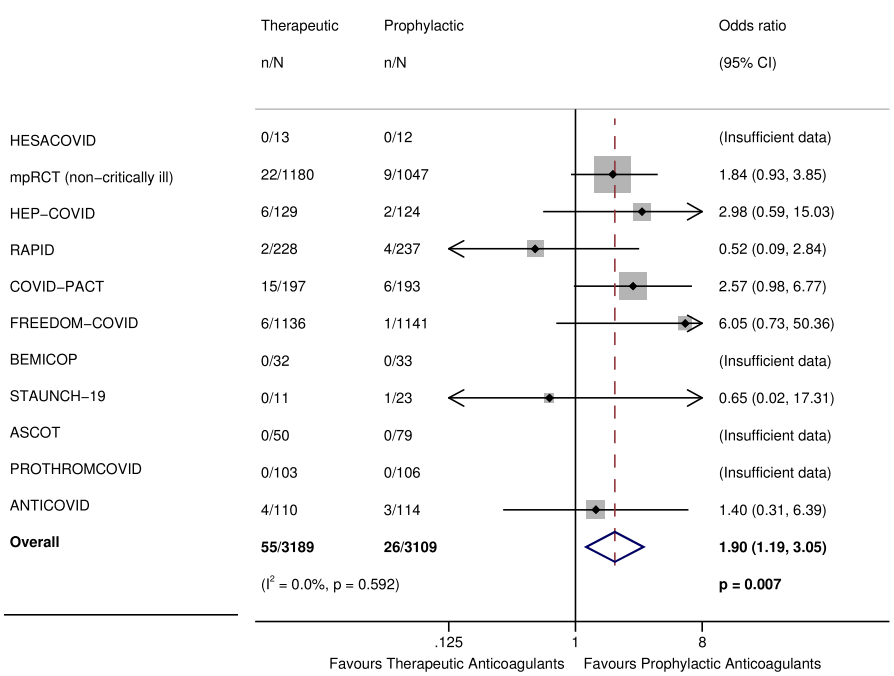
28–day mortality



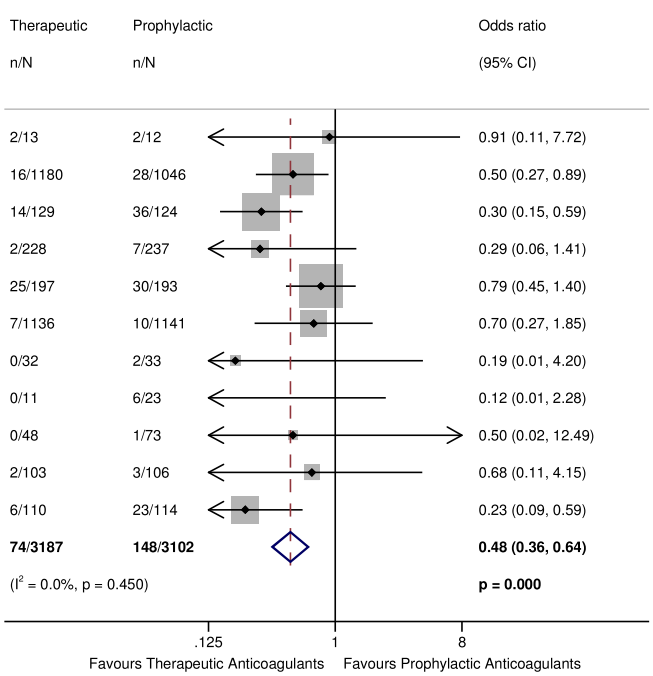
Progression to IMV or death

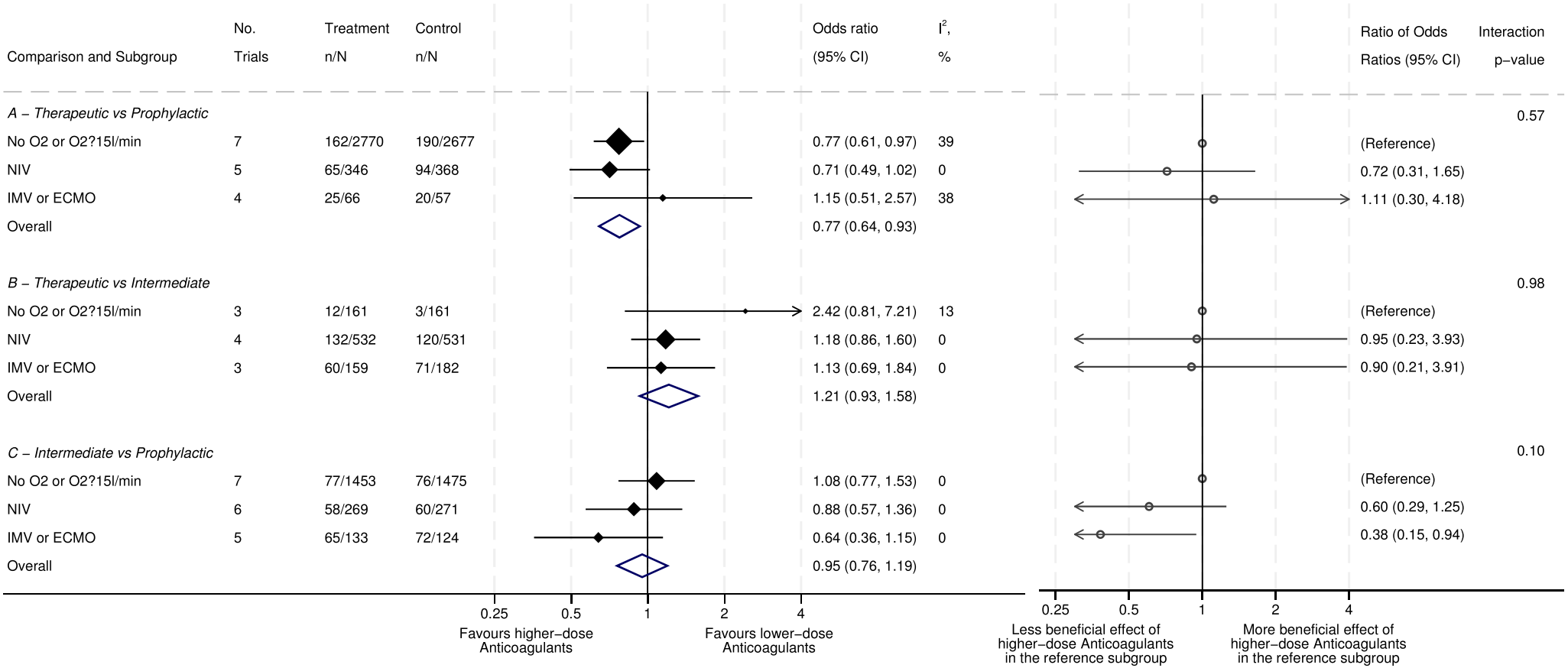


Major bleeding

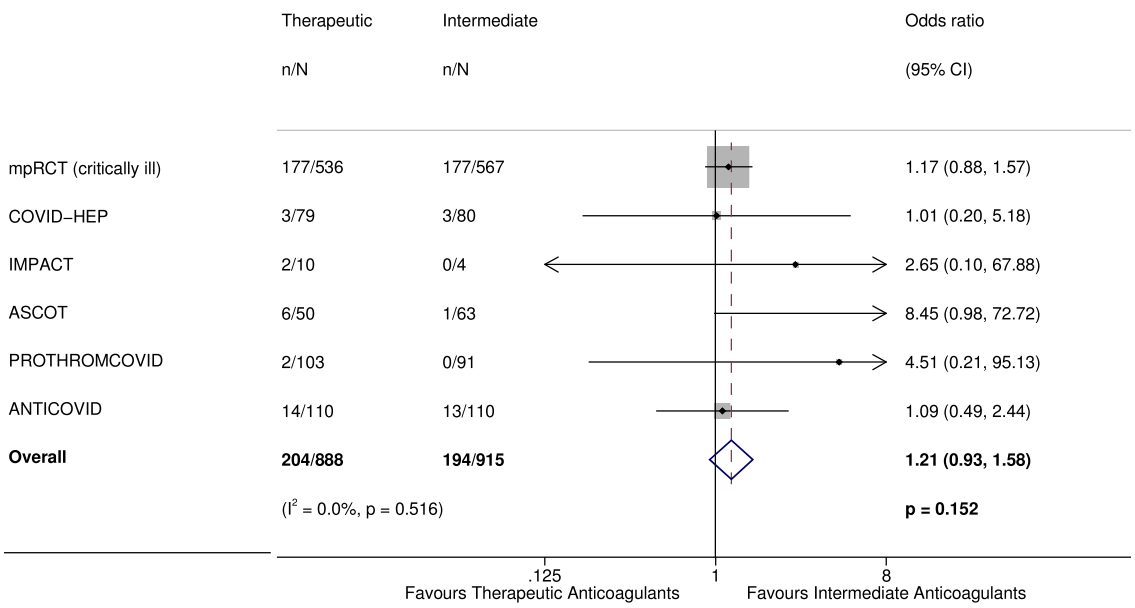


Thromboembolic events

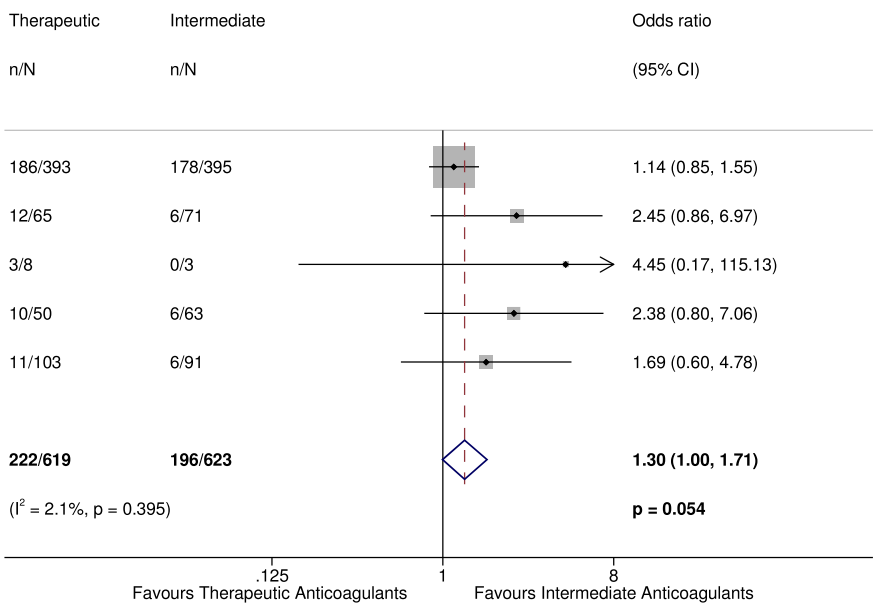



Comparison and Subgroup
No. Trials
Treatment n/N
Control n/N
Odds ratio (95% CI)
I², %
Ratio of Odds Ratios (95% CI)
Interaction p–value
A – Therapeutic vs Prophylactic
0.57
No O2 or O2?15l/min 7 162/2770 190/2677 0.77 (0.61, 0.97) 39 (Reference)
NIV 5 65/346 94/368 0.71 (0.49, 1.02) 0 0.72 (0.31, 1.65)
IMV or ECMO 4 25/66 20/57 1.15 (0.51, 2.57) 38 1.11 (0.30, 4.18)
Overall 0.77 (0.64, 0.93)
B – Therapeutic vs Intermediate
0.98
No O2 or O2?15l/min 3 12/161 3/161 2.42 (0.81, 7.21) 13 (Reference)
NIV 4 132/532 120/531 1.18 (0.86, 1.60) 0 0.95 (0.23, 3.93)
IMV or ECMO 3 60/159 71/182 1.13 (0.69, 1.84) 0 0.90 (0.21, 3.91)
Overall 1.21 (0.93, 1.58)
C – Intermediate vs Prophylactic
0.10
No O2 or O2?15l/min 7 77/1453 76/1475 1.08 (0.77, 1.53) 0 (Reference)
NIV 6 58/269 60/271 0.88 (0.57, 1.36) 0 0.60 (0.29, 1.25)
IMV or ECMO 5 65/133 72/124 0.64 (0.36, 1.15) 0 0.38 (0.15, 0.94)
Overall 0.95 (0.76, 1.19)
0.25
0.5
1
2
4
Favours higher–dose Anticoagulants
Favours lower–dose Anticoagulants
Less beneficial effect of higher–dose Anticoagulants in the reference subgroup
More beneficial effect of higher–dose Anticoagulants in the reference subgroup

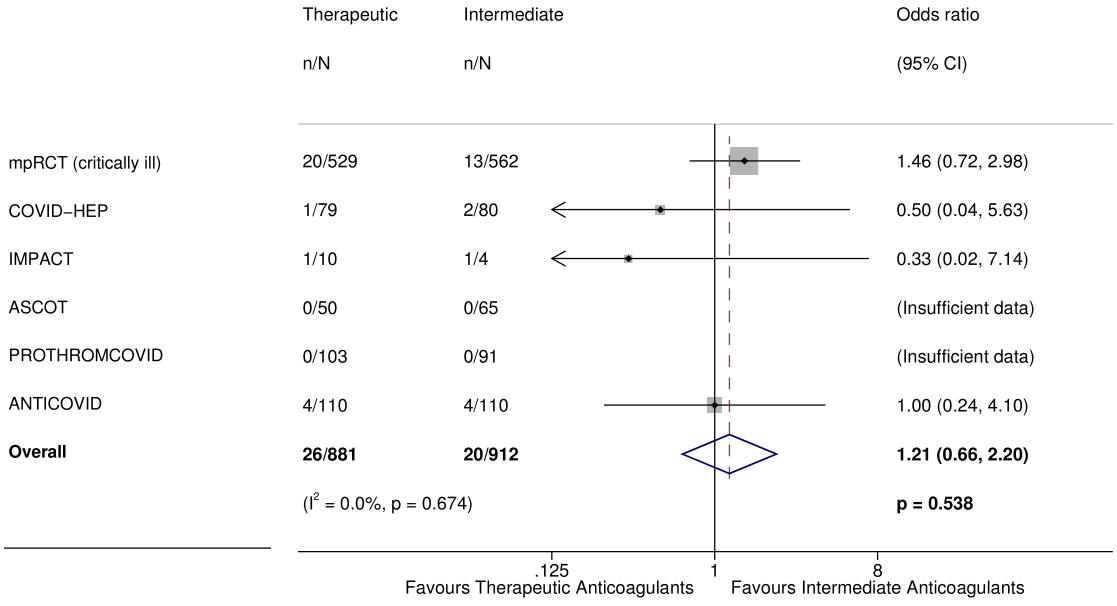
28–day mortality



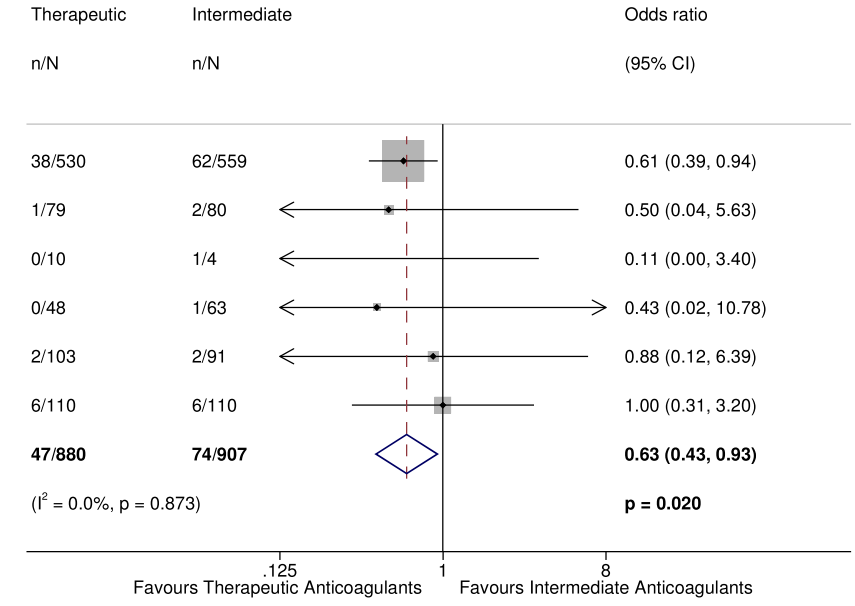
Progression to IMV or death



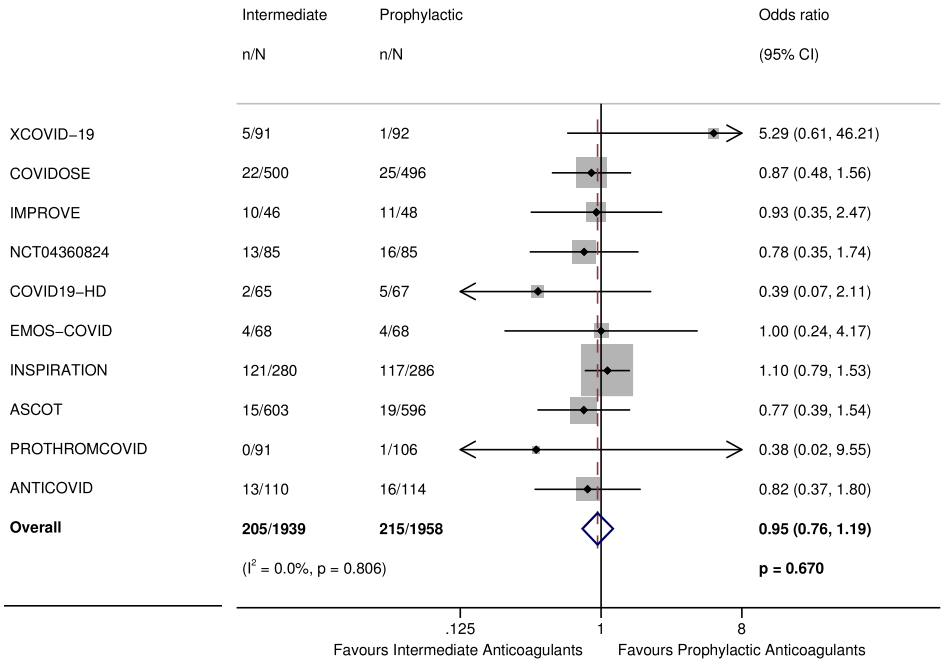
Major bleeding



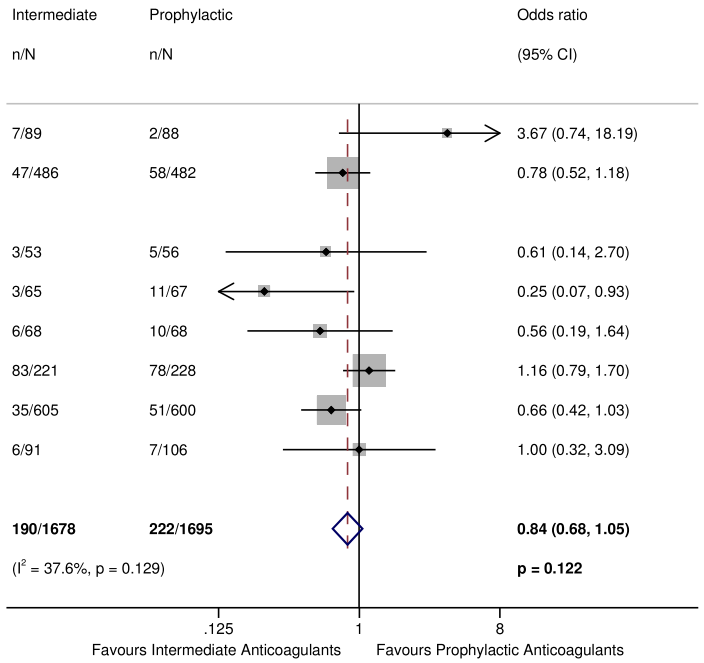
Thromboembolic events



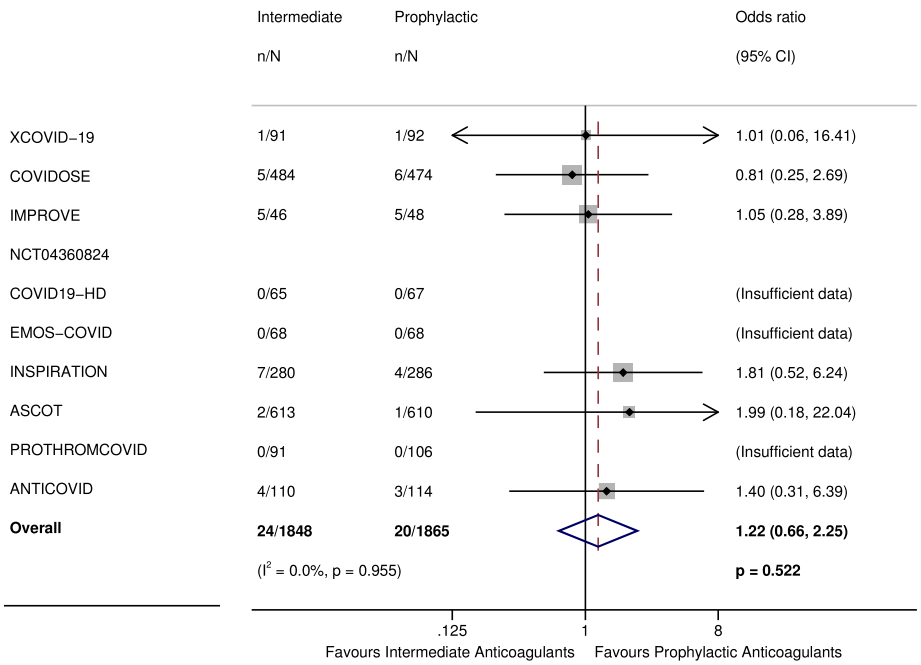
28–day mortality



Progression to IMV or death



Major bleeding



Thromboembolic events