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Supplementary Methods

Trial-level aggregate data sharing agreements were established. Baseline and outcome data collection forms (Supplement 1) were subsequently verified by trial teams. Finalized data sets from contributing trials were received by February 4, 2022. Data on additional trials that did not respond to repeated requests to supply data were extracted from published reports. Trials were characterized based on the type of anticoagulant used (Heparin [including LMWH and UFH] or DOAC).

Secondary outcomes were chosen based on prioritization from guideline panels, including patient representatives. Thromboembolic events were defined by individual trials, while most trials used the definition of major bleeding from the International Society on Thrombosis and Haemostasis.(37)

Risk of bias assessments were based on the trial protocols and flowcharts following the Consolidated Standards of Reporting Trials together with information supplied by the investigators for each trial in a standard format. Risk of bias and GRADE assessments were done independently by at least two investigators (JH, AM, FS) with disagreements resolved through discussion.

Because outcome data were complete or nearly complete across trials, we restricted the analyses to trial participants with outcomes recorded. A ratio of ORs (ROR) equal to 1 corresponds to identical associations in the subgroups. The further the ROR is from 1, the greater is the difference between the estimated associations in the 2 subgroups. Some analyses used user-written Stata commands to conduct and graph the results of the meta-analyses.

In sensitivity analyses, treatment effects were estimated based on numbers of participants who did and did not experience each outcome according to intervention group, overall and in subgroups, and overall associations were estimated using random-effects meta-analyses with restricted maximum likelihood estimates of heterogeneity and Hartung-Knapp adjustment.(38-40)

Supplementary Results

One additional trial was identified in updated searches (5th October 2023) but as it had not been updated since original registration (June 2020), no data were sought for from investigators.

Absolute risk differences in patients with severe and critical disease

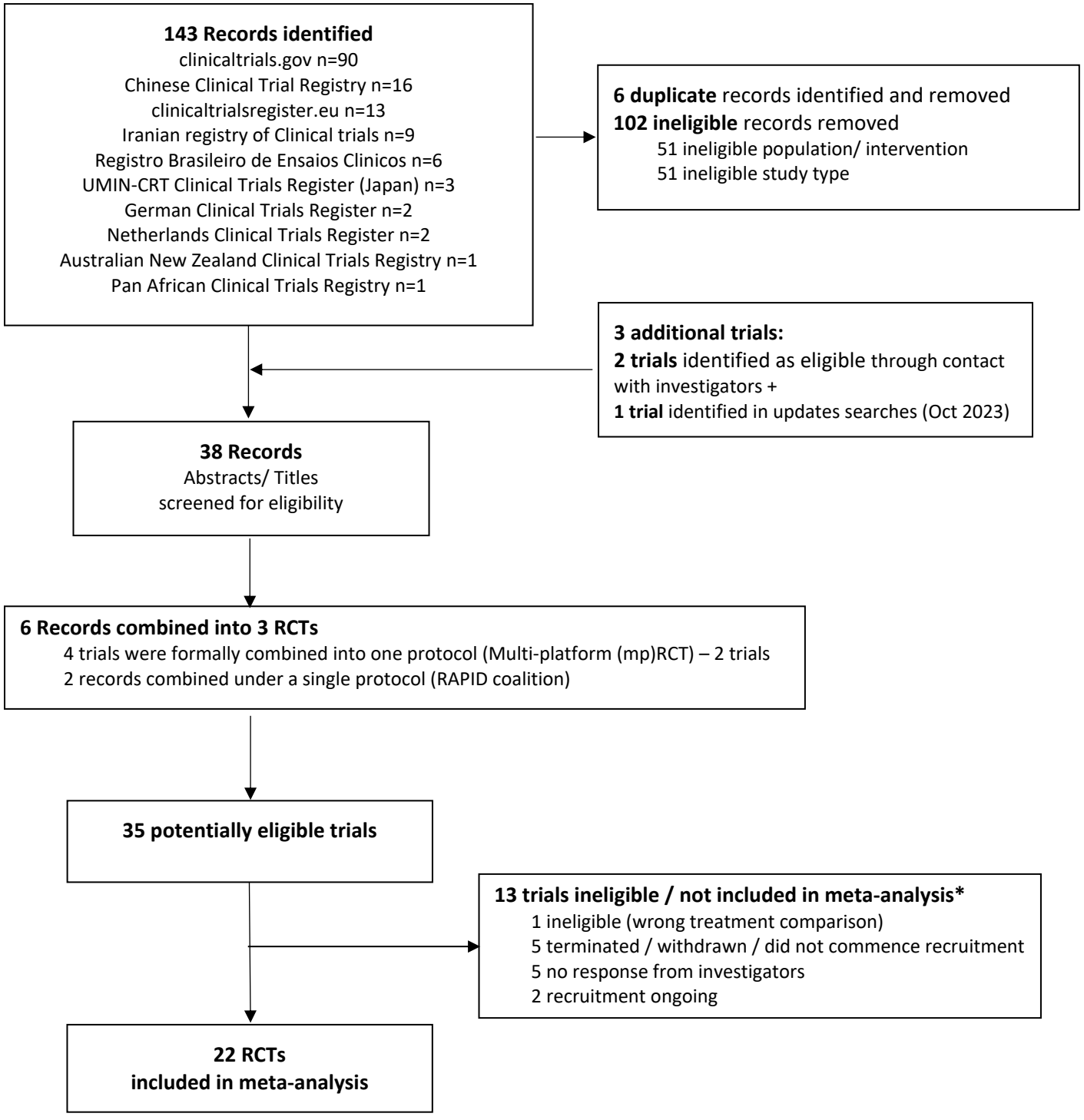
For therapeutic versus prophylactic dose anticoagulation, the corresponding absolute mortality risks were 5% for therapeutic- compared with an assumed 7% for prophylactic- dose anticoagulation among patients with severe disease, and 25% for therapeutic- compared with an assumed 30% for prophylactic-dose anticoagulation among patients with critical disease.

Comparisons within pre-defined subgroups

For therapeutic versus prophylactic dose anticoagulation, analyses of associations between treatment and outcomes within pre-specified patient subgroups were restricted to trials with available subgroup data in which all patients randomised to the comparator group received prophylactic dose anticoagulation. Data from 7 trials (1313 patients) were available for analyses of association according to levels of respiratory support at randomisation. The associations within subgroups defined by corticosteroid use, BMI, D-dimer status, age, sex and time period of randomization also appeared consistent across all outcomes (corticosteroid use: all p-values greater than 0.11; BMI: all p-values >0.31; D-Dimer: all p-values >0.46; age: all p-values >0.51; sex: all p-values >0.42; time period of randomization: all p-values >0.59, Table 2 and Supplements 3-6, section e).

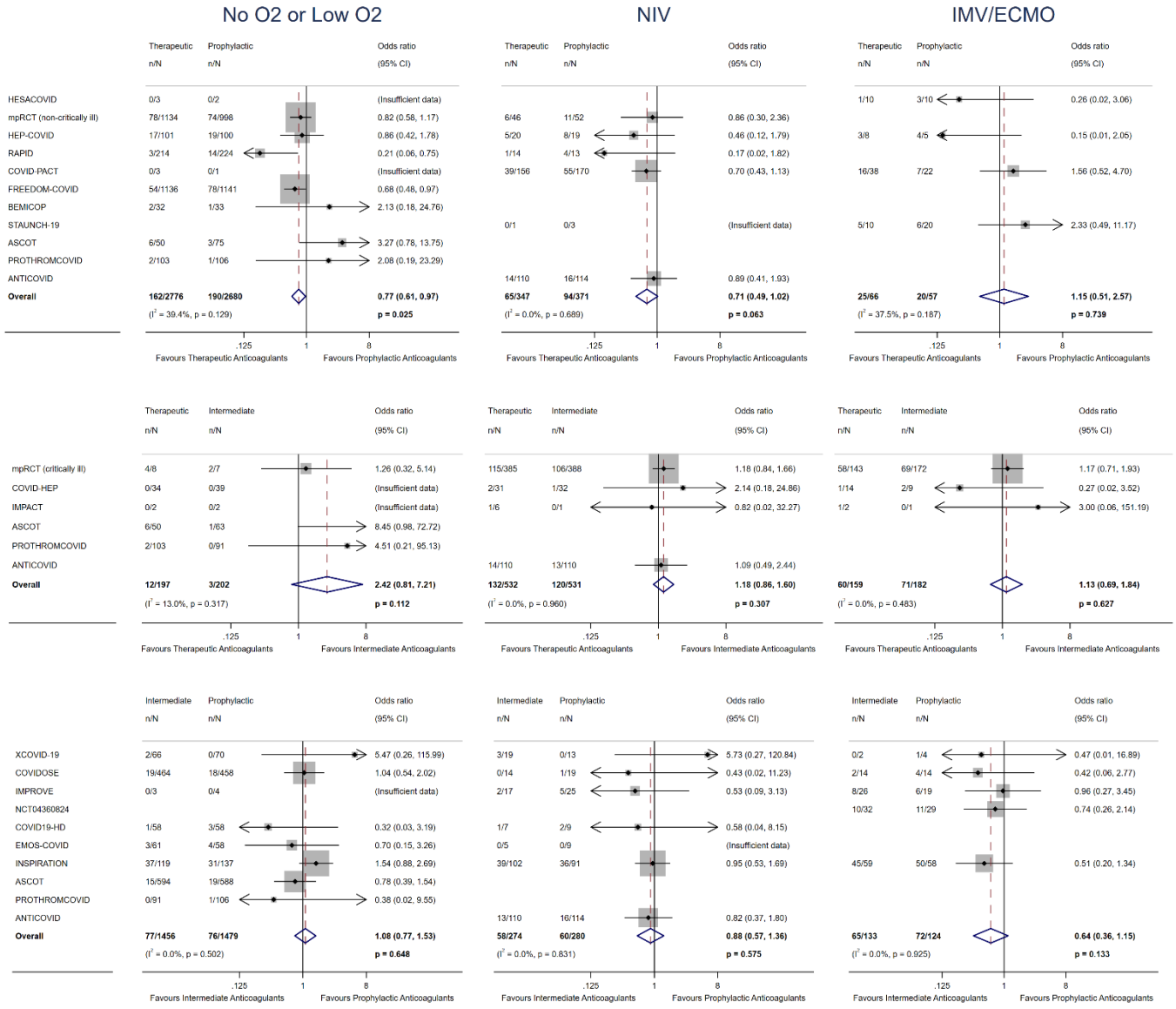
For intermediate versus prophylactic dose anticoagulation, analyses of associations between treatment and outcome within pre-defined patient subgroups, were restricted to trials with available subgroup data. Data from 9 trials (3383 patients) were available for analyses according to levels of respiratory support at randomisation. Associations with intermediate versus prophylactic dose anticoagulation appeared broadly consistent across pre-defined patient subgroups for all outcomes (corticosteroid use: all p-values >0.11; BMI: all p-values >0.11; D-Dimer: all p-values >0.27; age: all p-values >0.09; sex: all p-values >0.24; time period of randomization: all p-values >0.18, Table 2 and Supplements 3-6, section e).

eFigure-1: PRISMA flow diagram showing the identification of eligible and participating trials



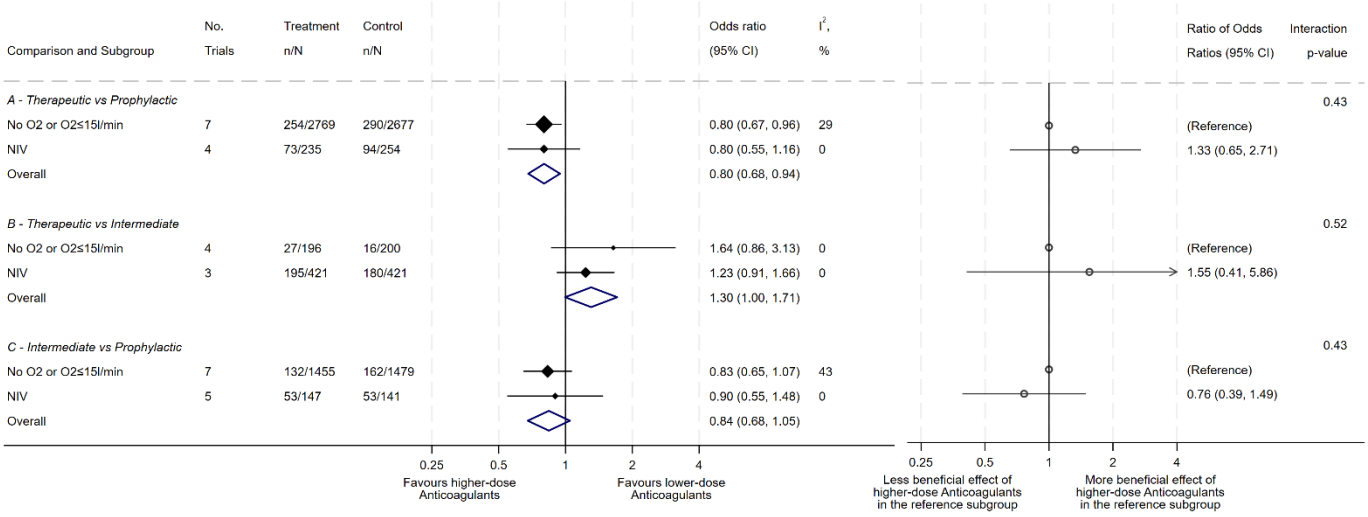
*Details of trials not included are supplied in eTable-4

eFigure-2: 28-day mortality according to levels of respiratory support required at randomisation (a) therapeutic- versus prophylactic- dose; (b) therapeutic- versus intermediate-dose anticoagulation; (c) intermediate- versus prophylactic-dose anticoagulation. Trials are listed in order of date of first randomisation.



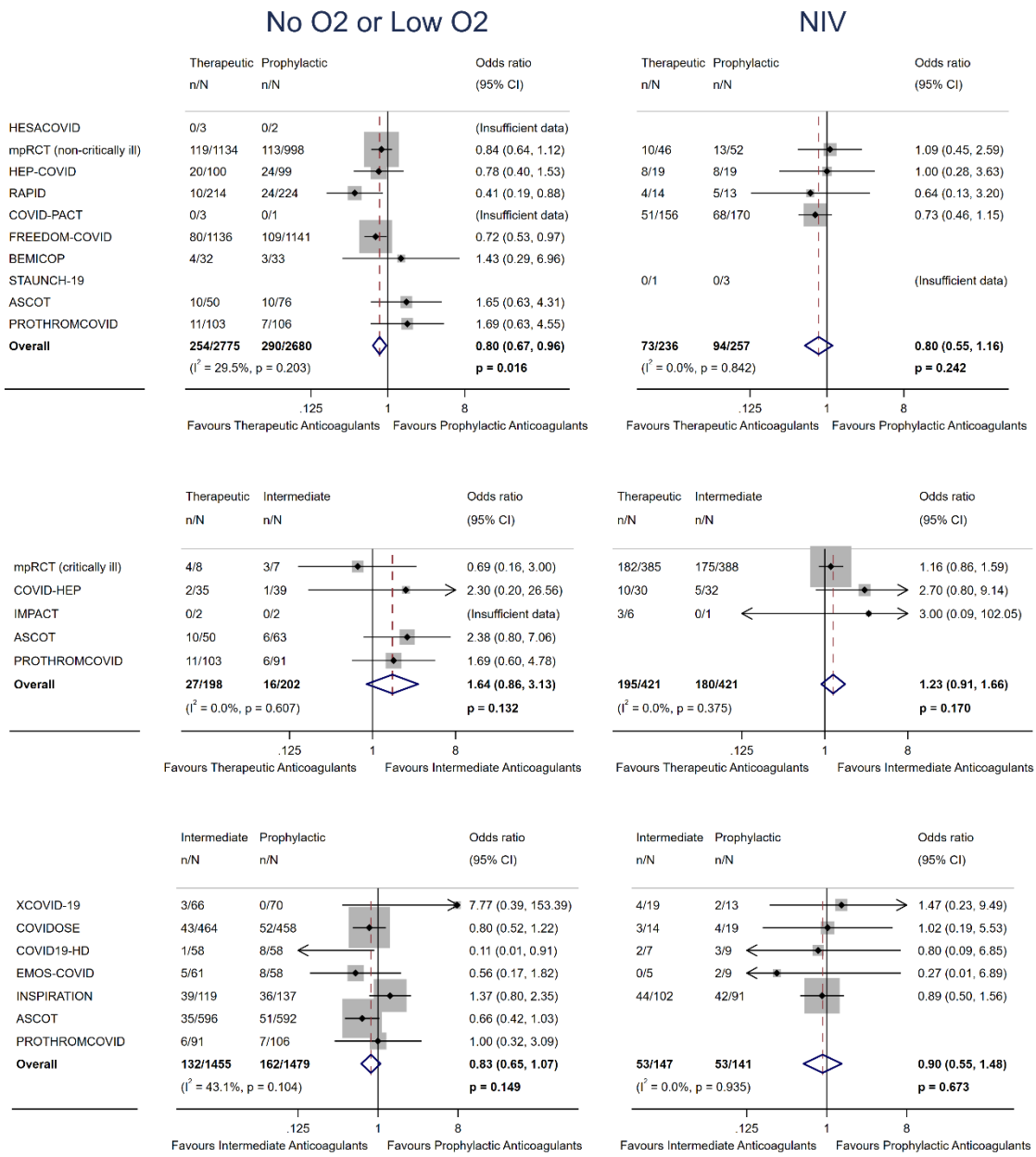
*Anticovid trial: 225/334 (67%) of participants received NIV or HFNO at the time of randomisation; 32/225 (14%) IMV; 77/334 (23%) mask or nasal catheter only

eFigure-3. Associations of anticoagulation with progression to IMV, ECMO or death (in patients not receiving IMV or ECMO at randomization) at 28-days, 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.

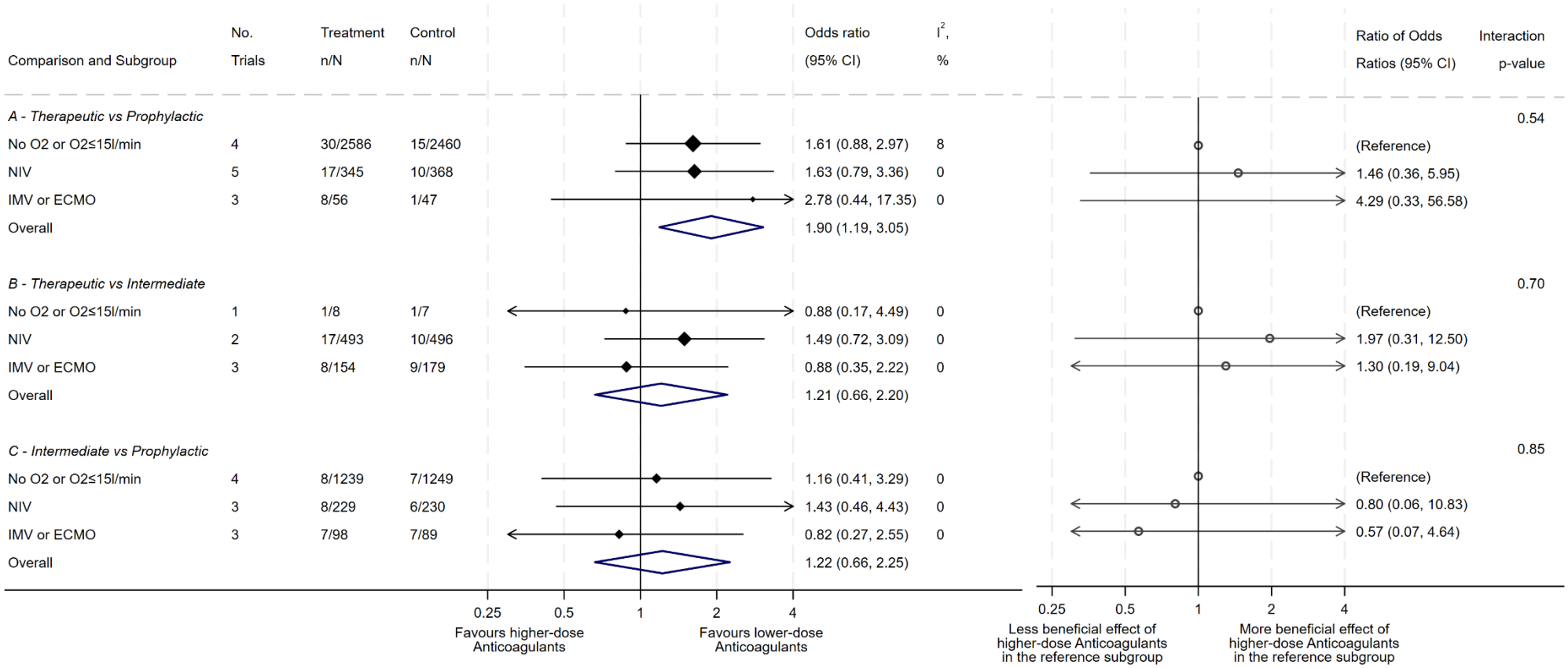


Footnote: The p-values for interaction test the null hypothesis that the odds ratios across respiratory support subgroups are the same and are based on chi-squared statistics with 1 degree of freedom. Trials unable to supply subgroup data, and those with no events, are not included in the summary counts of trials, events/patients, nor do they contribute to the pooled OR estimate. For full details including all trials, see Appendix eFigure-4.

eFigure-4: Progression to IMV or death by 28 days according to levels of respiratory support required at randomisation (a) therapeutic- versus prophylactic- dose; (b) therapeutic- versus intermediate-dose; (c) intermediate- versus prophylactic-dose anticoagulation

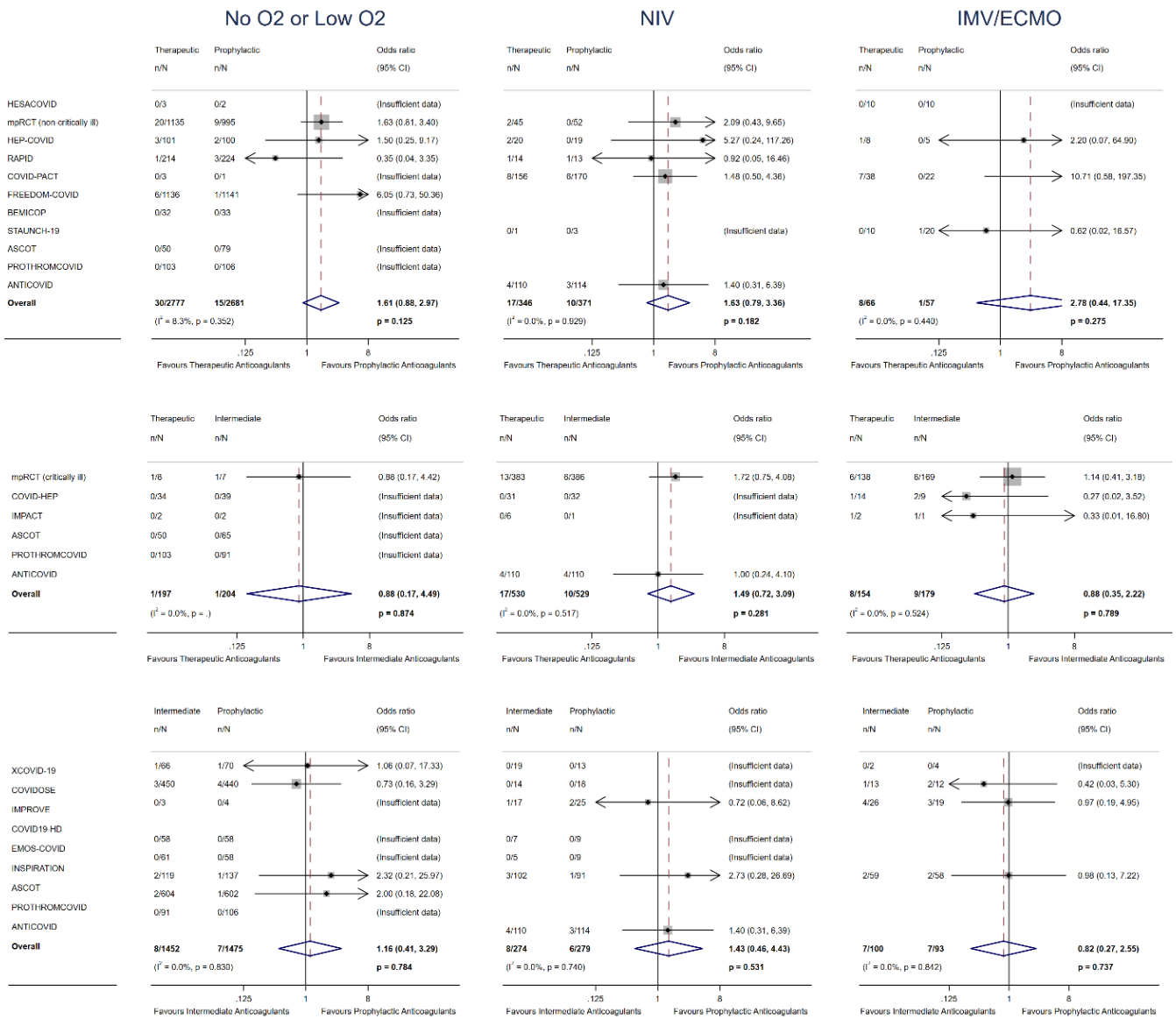


eFigure-5. Associations of anticoagulation with major bleeding at 28-days, based on inverse-variance weighted meta-analyses, according to level of respiratory support at the time of randomisation, together with ratios of odds ratios comparing associations across respiratory support subgroups.

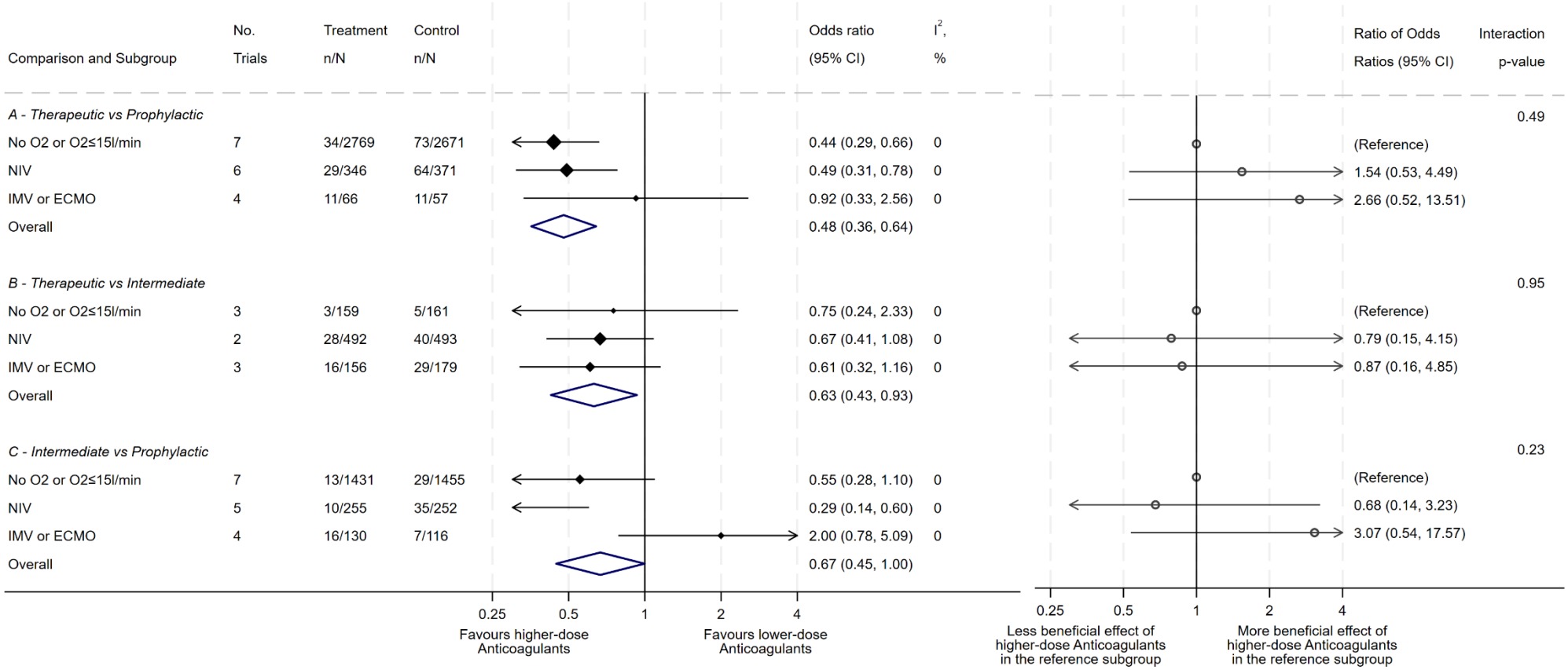


Footnote: The p-values for interaction p-value the null hypothesis that the odds ratios across respiratory support subgroups are the same and are based on chi-squared statistics with 2 degrees of freedom. Trials unable to supply subgroup data, and those with no events, are not included in the summary counts of trials, events/patients, nor do they contribute to the pooled OR estimate. For full details including all trials, see Appendix eFigure-5.

eFigure-6: Major bleeding according to levels of respiratory support required at randomisation (a) therapeutic- versus prophylactic- dose; (b) therapeutic- versus intermediate- dose; (c) intermediate- versus prophylactic-dose anticoagulation

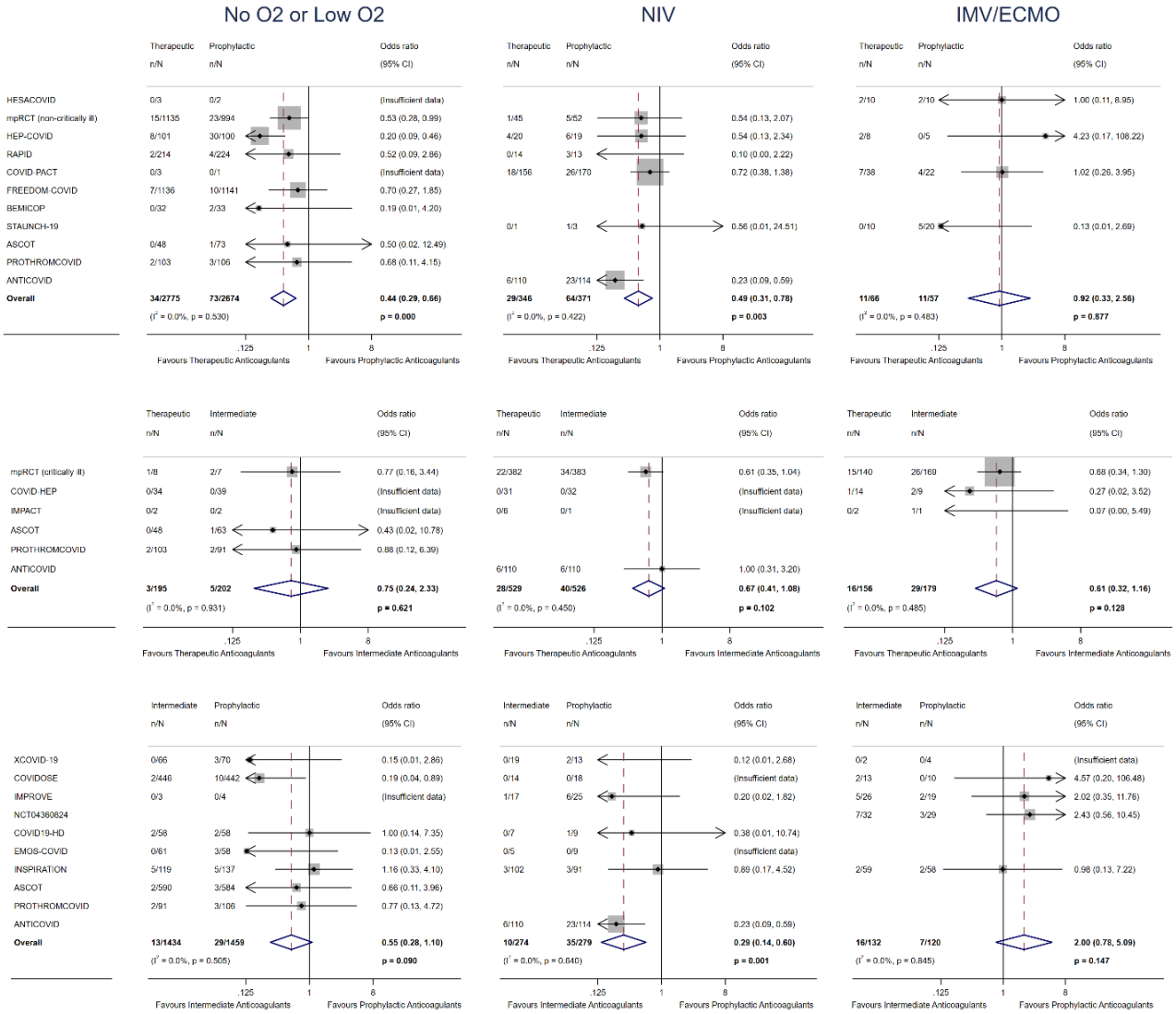


eFigure-7. Associations of anticoagulation with thromboembolic events at 28-days, based on inverse-variance weighted meta-analyses, according to level of respiratory support at the time of randomisation, together with ratios of odds ratios comparing associations across respiratory support subgroups.



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 including all trials, see Appendix eFigure-6.

eFigure-8: Thromboembolic events according to levels of respiratory support required at randomisation (a) therapeutic- versus prophylactic- dose; (b) therapeutic- versus intermediate- dose; (c) intermediate- versus prophylactic-dose anticoagulation



eTable-1: Description of included trials in each meta-analysis comparison

Comparison 1: Therapeutic dose anticoagulants vs prophylactic dose anticoagulants							
Trial	**Recruitment period**	**Experimental arm: Anticoagulant Dose / Schedule**	**Control arm: Anticoagulant Dose / Schedule**	**Duration of intervention**	**Population**	**Location(s) of trial**	**Patients (analysed for PMA primary outcome)**
HESACOVID(17)	Apr 2020– Jul 2020	Enoxaparin 1mg/Kg adjusted by age/ creatinine clearance. Maximum dose 140 mg BID / 14 days	Weight-adjusted: Enoxaparin 40 mg/day (>120 kg: 40 mg BID) OR UFH 5000 units /8h (>120 kg: 7500 units/8h)	Up to 14 days	Patients with severe COVID-19 requiring mechanical ventilation	Brazil	25 (25)
*mpRCT – NON-CRITICALLY ILL(14) (ACTIV-4A, REMPA-CAP, ATTACC and PROTECT)	April 2020 – Jan 2021	Enoxaparin: 1 mg/kg q12h or 1.5 mg/kg q24h Tinzaparin: 175 units/kg q24h Dalteparin: 200 units/kg q24h or 100 units/kg q12h UFH (target aPTT 1.5-2.5x the reference)	Local standard care (Local standard thromboprophylaxis)	14 days or discharge or liberation from the need for supplemental oxygen (whichever comes first)	Hospitalised patients with confirmed COVID-19, either: • Severe disease (ICU-level care or critically ill) or Moderate disease (hospitalized but noncritically ill)	USA, UK	2244 (2219)
RAPID COVID COAG(16)	May 2020 – Apr 2021	Enoxaparin 1 mg/kg q12h or 1.5 mg/kg q24h Tinzaparin 175 units/kg q24h Dalteparin 200 units/kg q24h or 100 units/kg q12h UFH (center-specific protocol)	Prophylactic LMWH, UFH or fondaparinux (no specific drug/doses reported) (From RAPID Brazil): Enoxaparin 40 mg q24h; or 60 mg q24h UFH 5000 q12h or q8h	Until discharge, 28 days or death	Patients admitted to hospital wards with laboratory confirmed SARS-CoV-2 infection and elevated D-dimer levels (> upper limit of normal (ULN) of the local hospital in the presence of oxygen saturation ≤93% on room air, or ≥2 times the ULN irrespective of oxygen saturation) within the first 5 days of admission.	Brazil, Canada, Ireland, Saudi Arabia, Switzerland, UAE, USA	465 (465)
†HEP-COVID(18)	May 2020-May 2021	Enoxaparin 1 mg/kg q12h (0.5 mg/kg q12h if CrCl 15-30 mL/min)	Enoxaparin up to 0.5 mg/kg q12h Dalteparin up to 5000 units q24h UFH up to 7500 units q8h	Until discharge	Hospitalised patients with a respiratory rate > 20	USA	253 (253)

					and an oxygen saturation < 92% on room air with either elevated D-Dimers or SIC score of ≥4		
Action NCT04394377(19)	Jun 2020 – Feb 2021	Enoxaparin 1 mg/kg q12h UFH Rivaroxaban 20 mg q24h (or 15 mg if CrCl 30-49 mL/min and or concomitant use of azithromycin)	Enoxaparin 40 mg q24h	30 days	Adult patients hospitalised with a confirmed diagnosis of COVID-19, symptoms for up to 14 days before randomisation, and elevated D-dimer concentration	Brazil	615 (614)
COVID-PACT(20)	Aug 2020 – Mar 2022	• UFH (i.v.) with a nomogram targeting an aPTT of 1.5-2.5 x control • Enoxaparin 1 mg/kg (s.c.) every 12 hours (if CrCl≥30 ml/min)	• Enoxaparin 40mg administered (s.c.) once daily (if CrCl≥30 ml/min)* • Enoxaparin 30mg (s.c.) once daily (if CrCl<30 ml/min) • Heparin 5,000 units (s.c.) three times daily *Enoxaparin 30-40 mg administered SC twice daily may also be considered if CrCl≥30ml/min and BMI ≥35 kg/m2	Until discharge, 28 days or death	At least 18 years of age, acute infection with SARS-CoV2 requiring ICU for ≤96 hours before randomization, and no indication for full-dose anticoagulation.	USA	390 (390)
‡FREEDOM COVID(7)	Aug 2020 - Sept 2022	Enoxaparin 1 mg/kg sc q 12 hours; (1 mg/kg sc / day for creatinine clearance <30 mL/min) OR Apixaban 5mg oral twice daily; (2.5 mg every 12 hours for patients with at least 2 of 3 of age ≥80 years, weight ≤60 kg, or serum creatinine ≥1.5 mg/dL).	Prophylactic-dose enoxaparin (40 mg subcutaneously every day; 30 mg subcutaneously every day for creatinine clearance <30 mL/min	Until discharge or death	Age 18 years or greater; hospitalized within 48 hours with symptoms consistent with COVID-19 or confirmed disease (positive PCR or antigen test) and informed consent	USA, Brazil, Columbia, Hong Kong, India, Italy, Mexico, Panama, Poland, Spain	2277 (2277)
BEMICOP(21)	Oct 2020 - May 2021	Therapeutic bemiparin	Bemiparin 3,500 q24h	10 days	Adult patients hospitalized with non-severe COVID-19 pneumonia and elevated D-dimers.	Spain	66 (65)
STAUNCH-19 (unpublished)	Nov 2020 – Jun 2021	Unfractionated heparin at therapeutic dosages plus	Group 1: Enoxaparin at standard prophylactic dose	Until ICU discharge	Adult patients with confirmed COVID-	Italy	210 (34)

		methylprednisolone.	Group 2: Enoxaparin at standard prophylactic dose and methylprednisolone		19, requiring positive pressure ventilation (either non-invasive or invasive) from > 24 hours or invasive mechanical ventilation from < 96 hours and elevated D-Dimers		
‡PROTHROMCOVID(22)	Feb 2021 - Sept 2021	Tinzaparin 175 UI/kg	Tinzaparin 4500 UI	Until discharge or death	Adults (50–100 kg) who required admission to a conventional (non-critical) hospital ward due to COVID-19 pneumonia plus any of the following criteria: (a) baseline oxygen saturation ≤ 94%; D-dimer > 1000 µg/L; C-Reactive Protein (CRP) > 150 mg/L; IL-6 > 40 pg/mL	Spain	215 (209)
‡ASCOT(23)	Feb 2021 – Oct 2021	Enoxaparin (1mg/kg q12h or 1.5mg/kg q 24h;) or Tinzaparin (175IU/kg per 24h) Or Dalteparin (100IU/kg q12h or 200IU/kg q24h)	Enoxaparin (50-120kg: 40mg/ 24h; <50kg:20mg/24h; >120kg:60mg/24h) or Tinzaparin (75IU/kg per 24h) Or Dalteparin (40-120kg: 5000IU q12h; <40kg: 5000IU q4h; >120kg: 7500IU q24h)	Until discharge or death	Hospitalised adults with PCR confirmed, symptomatic, SARS-CoV-2 infection, within 14 days of symptom onset.	Australia, New Zealand, India, Nepal	129 (125)
‡ANTICOVID(8)	Apr 2021 - Dec 2021	Therapeutic Anticoagulation: LMWH (preferably tinzaparin) 175 IU/kg/24h	LMWH (preferably tinzaparin) 3,500 IU/24h	14 days	Age ≥ 18 years; - Hypoxemic COVID-19 pneumonia, defined by a newly-appeared pulmonary parenchymal infiltrate; a positive RT-PCR for COVID-19 (SARS-CoV-2) and ≥ 5 on the WHO	France	

					ordinal scale. Written informed consent		

Comparison 2: Therapeutic dose anticoagulants vs intermediate dose anticoagulants							
Trial		Experimental arm: Anticoagulant Dose / Schedule	Control arm: Anticoagulant Dose / Schedule	Duration of intervention	Population	Location(s) of trial	Patients (analysed for PMA primary outcome)
[§]**mpRCT – CRITICALLY ILL(15)** **(ACTIV-4A, REMPA-CAP, ATTACC and PROTECT)**	Apr 2020 - Dec 2020	Enoxaparin: 1 mg/kg q12h or 1.5 mg/kg q24h Tinzaparin: 175 units/kg q24h Dalteparin: 200 units/kg q24h or 100 units/kg q12h UFH (target aPTT 1.5-2.5x the reference)	Local standard care (Local standard thromboprophylaxis)	14 days or discharge or liberation from the need for supplemental oxygen (whichever comes first)	Hospitalised patients with confirmed COVID-19, either: • Severe disease (ICU-level care or critically ill) or Moderate disease (hospitalized but noncritically ill)	USA, UK	1207 (1098)
[||]**COVID-HEP(24)**	Apr 2020 – Jun 2021	Enoxaparin 1 mg/kg q12h UFH (target anti-Xa 0.3-0.7)	Prophylactic dosing – enoxaparin 40mg q24h (60mg if >100kg) ; UFH 5000IU q12h (q8h if >100kg) Intermediate dosing (in ICU) – enoxaparin 40mg q12h (60mg if >100kg) ; UFH 5000IU q8h (10000IU q12h if >100kg)	Until the earliest of discharge, clinical recovery or 30 days	Hospitalized adults with proven COVID-19 infection in a severe state with elevated D-dimer (>2x), or in a critical state	Switzerland	159 (159)
IMPACT (unpublished)	Jul 2020 – Jul 2021	Enoxaparin 1 mg/kg q12h UFH (target anti-Xa level 0.3 -0.7 IU/mL or aPTT according to institutional protocol) Argatroban (if HIT, dosed according to institutional protocol) Fondaparinux (if HIT, dosed by weight)	Enoxaparin 0.5 mg/kg q12h (q24h if CrCl <30 mL/min) UFH 7,500 units q8h Fondaparinux 2.5 mg q24h	28 days	• Critically ill patients with COVID-19, either admitted to ICU or non-ICU patients in receipt of IMV, BiPAP, 100% non-rebreather mask, or high flow oxygen or supplemental oxygen of at least 4l/minute nasal cannula. Elevated D-Dimer status	USA	14 (14)

‡PROTHROMCOVID(22)	Feb 2021 - Sept 2021	Tinzaparin 175 UI/kg	Tinzaparin 100 UI/kg	Until discharge or death	Adults (50–100 kg) who required admission to a conventional	Spain	201 (194)
‡ASCOT(23)	Feb 2021 – Oct 2021	Enoxaparin (1mg/kg q12h or 1.5mg/kg q 24h;) or Tinzaparin (175IU/kg per 24h) Or Dalteparin (100IU/kg q12h or 200IU/kg q24h)	Enoxaparin (50-120kg: 40mg/ 12h; <50kg:40mg/24h; >120kg:60mg/12h) or Tinzaparin (125IU/kg per 24h) Or Dalteparin (40-120kg: 5000IU/12h; <40kg: 5000IU/24h; >120kg: 7500IU/24h)	Until discharge or death	Hospitalised adults with PCR confirmed, symptomatic, SARS-CoV-2 infection, within 14 days of symptom onset.	Australia, New Zealand, India, Nepal	115 (113)
‡ANTICOVID(8)	Apr 2021- Dec 2021	Therapeutic Anticoagulation: LMWH (preferably tinzaparin) 175 IU/kg/24h	Tinzaparin 7,000 IU/24h	14 days	Age ≥ 18 years; - Hypoxemic COVID-19 pneumonia, defined by a newly-appeared pulmonary parenchymal infiltrate; a positive RT-PCR for COVID-19 (SARS-CoV-2) and ≥ 5 on the WHO ordinal scale. Written informed consent	France	223 (220)

Comparison 3: Intermediate dose anticoagulants versus prophylactic dose anticoagulants							
Trial		Experimental arm: Anticoagulant Dose / Schedule	Control arm: Anticoagulant Dose / Schedule	Duration of intervention	Population	Location(s) of trial	Patients (analysed for PMA primary outcome)
X-Covid 19(25)	Apr 2020 – May 2021	Enoxaparin 40 mg q12h	Enoxaparin 40 mg q24h	Until discharge	Adult patients with COVID-19 admitted to general ward	Italy	186 (183)
COVI-DOSE(26)	May 2020 - Apr 2021	Weight-based intermediate-dose LMWH, e.g: Enoxaparin: <50kg: 40 mg q12h 50-70kg: 50 mg q12h 70-100kg: 60 mg q12h >100kg: 70 mg q12h	Prophylactic LMWH (augmented in ICU patients)	Discharge (up to 28 days)	Adult patients with COVID19 hospitalized in medical wards or intensive care units	France	996 (996)

IMPROVE (unpublished)	May 2020 – May 2021	eGFR ≥ 30 mL/min: Enoxaparin 1mg/kg (SC) daily or UFH at 10 units/kg/hour eGFR <30 mL/min or acute kidney injury or CRRT: UFH 10units/kg/hour (minimum 500 units/hour if CRRT)	eGFR ≥30 mL/min: < 40 kg/m^2: Enoxaparin 40 mg SC/day 40-50 kg/m^2: Enoxaparin 40 mg SC q12h 50 kg/m2: Enoxaparin 60 mg SC q12h eGFR < 30 mL/min or acute kidney injury: 50-120 kg: UFH 5000 units SC q8h >120 kg: UFH 7500 units SC q8h If CRRT: UFH infusion pre-filter at 500 units/hour	Duration of ICU stay or until endpoint reached	Adult patients with COVID-19, new admissions to ICU within 5 days	USA	94 (94)
NCT04360824(27)	May 2020 – Apr 2021	Enoxaparin 1 mg/kg q24h (0.5 mg/kg if BMI ≥30)	Enoxaparin 40 mg q12h (30 mg q12h or 40 mg q12h if BMI ≥30)	Discharge	Adult patients hospitalized with COVID19	USA	176 (170)
INSPIRATION(28)	Jul 2020 – Nov 2020	Enoxaparin 1 mg/kg q24h or UFH 10,000 units q12h	Enoxaparin 40 mg q24h or UFH 5000 units q12h	30 days	Adult patients with COVID-19 admitted to the ICU	Iran	566 (566)
COVID-19 HD(29)	Jul 2020 – Apr 2021	Enoxaparin 0.7 mg/kg q12h	Enoxaparin 40 mg q24h	Until discharge	Hospitalized patients with severe covid-19 pneumonia and coagulopathy	Italy	132 (132)
EMOS-COVID(29)	Jul 2020 – Jul 2021	Enoxaparin <65kg: 40 mg q12h ≥65 Kg: 60 mg q12h ≥100 Kg: 80 mg q12h	Enoxaparin 40 mg q24h - if >100 kg: 60 mg q24h	Until discharge; prophylactic dose for 30 days after discharge	COVID-19 infected patients with moderate-severe respiratory failure (PaO2/FiO2<250) and/or increased D-dimer levels	Italy	136 (136)
‡PROTHROMCOVID(22)	Feb 2021-Sept 2021	Tinzaparin 100 UI/kg	Tinzaparin 4500 UI	Until discharge or death	Adults (50–100 kg) who required admission to a conventional	Spain	206 (197)
‡ASCOT(23)	Feb 2021 – Oct 2021	Enoxaparin (50-120kg: 40mg q 12h; <50kg:40mg q24h; >120kg:60mg q12h) or Tinzaparin (125IU/kg q 24h) Or Dalteparin (40-120kg: 5000IU q12h; <40kg: 5000IU q24h; >120kg: 7500IU q24h)	Enoxaparin (50-120kg: 40mg q24h; <50kg:20mg q24h; >120kg:60mg q24h) or Tinzaparin (75IU/kg q24h) Or Dalteparin (40-120kg: 5000IU q12h; <40kg: 5000IU q4h; >120kg: 7500IU q24h)	Until discharge or death	Hospitalised adults with PCR confirmed, symptomatic, SARS-CoV-2 infection, within 14 days of symptom onset.	Australia, New Zealand,	1223 (1199)

‡ANTICOVID(8)	April 2021 - Dec 2021	Tinzaparin 7,000 IU/24h	LMWH (preferably tinzaparin) 3,500 IU/24h	14 days	Age ≥ 18 years; - Hypoxemic COVID-19 pneumonia, defined by a newly-appeared pulmonary parenchymal infiltrate; a positive RT-PCR for COVID-19 (SARS-CoV-2) and ≥ 5 on the WHO ordinal scale. Written informed consent	France	227 (224)

***** 73% of patients with severe (non-critical) disease at randomisation in the mpRCT received prophylactic dose anticoagulation on the control arm

† 61% of control arm received prophylactic anticoagulation, remainder (39%) intermediate dose ‡Prothromcovid. ANTICOVID and ASCOT are 3-arm trials, split here into each of the separate pairwise comparisons.

‡Total pts randomised across 3 arms: Prothromcovid =311; ANTICOVID 339 (334); ASCOT = 1276 (1259).

FREEDOM COVID is also a 3-arm trial however only the two enoxaparin arms are considered in this meta-analysis (total patients randomised in 2 arms=2277)

§ 54% of patients with critical disease at randomisation in the mpRCT received intermediate dose anticoagulation on the control group

|| 41 (51%) critically ill patients (i.e. requiring ICU-level care) were randomised to intermediate dose anticoagulation and 39 (49%) non-critically ill patients received prophylactic dose in the control group

UFH- Unfractionated Heparin; BID- bi-daily; LMWH- Low molecular weight heparin; SIC -Sepsis-induced coagulopathy; CrCl-creatinine clearance; SC- subcutaneous; eGFR - estimated glomerular filtration rate; CRRT – continual renal replacement therapy; ICU – Intensive Care Unit; IL-6 - interleukin 6

eTable-2: Selected characteristics of included trials [a]

Trial	Group[a]	Patients randomized (analysed)	Median age (IQR)	Sex (n, % Male)	BMI ≤30 (n, %)	D-Dimers			Concomitant therapy at the time of randomisation[b]				
									Oxygenation and ventilation n (%)				Corticosteroids n (%)
						Normal <2xULN	2xULN to ≤4x ULN	>4 x ULN	None	<15l/min	Non-invasive ventilation	Invasive mechanical ventilation	
Comparison 1: Therapeutic dose anticoagulants vs prophylactic dose anticoagulants													
HESACOVID REBEC RBR949z6v	Therapeutic dose anticoagulation	13	58 (49-67)	10 (77%)	6 (46%)	0	5 (38%)	8 (62%)	0	3 (23%)	0	10 (77%)	7 (54%)
	Prophylactic dose anticoagulation	12	62 (50-69)	9 (75%)	7 (58%)	0	7 (58%)	5 (42%)	0	2 (17%)	0	10 (83%)	7 (58%)
mpRCT – non-critically ill	Therapeutic dose anticoagulation	1190 (1171)	59[e] (45-73)	713 (60%)	-	579	343[f]		156 (13%)	789 (67%)	46 (4%)	0	479/791 (61%)
	Prophylactic dose anticoagulation	1054 (1048)	59[e] (45-73)	597 (57%)	-	505	292[f]		123 (12%)	696 (66%)	52 (5%)	0	415/656 (63%)
RAPID NCT04362085N CT04444700	Therapeutic dose anticoagulation	228	60	123 (54%)	130 (57%)	119 (52%)	82 (36%)	27 (12%)	14 (6%)	200 (88%)	14 (6%)	0	161 (71%)
	Prophylactic dose anticoagulation	237	60	141 (60%)	132 (56%)	118 (50%)	76 (32%)	43 (18%)	17 (7%)	207 (87%)	13 (6%)	0	162 (68%)
HEP-COVID	Therapeutic dose anticoagulation	129	67 (56-75)	68 (53%)	65 (50%)	0	0	125 (97%)	5 (4%)	96 (74%)	20 (16%)	8 (6%)	111 (86%)
	Prophylactic dose anticoagulation	124	69 (59-78)	68 (55%)	78 (63%)	0	0	124 (100%)	4 (3%)	96 (77%)	19 (15%)	5 (4%)	93 (75%)
Action NCT04394377	Therapeutic dose anticoagulation	311 (310)	-	192 (62%)	-	-	-	-	75 (24%)	185 (59%)	28 (9%)	23 (7%)	257 (83%)
	Prophylactic dose anticoagulation	304	-	176 (58%)	-	-	-	-	80 (26%)	184 (61%)	25 (8%)	15 (5%)	253 (83%)
COVID-PACT NCT04409834	Therapeutic dose anticoagulation	197	59 (51-70)	122 (62%)	70 (36%)	108 (55%)	39 (20%)	40 (20%)	0	3 (2%)	156 (79%)	38 (19%)	178 (90%)
	Prophylactic dose anticoagulation	193	62 (51-68)	109 (56%)	56 (59%)	95 (49%)	42 (22%)	36 (19%)	0	1 (1%)	170 (88%)	22 (11%)	177 (92%)
FREEDOM COVID NCT04512079	Therapeutic dose anticoagulation[c]	1136	52 (40-64)	674 (59%)	-	-	-	-	-	-	-	-	240 (21%)
	Prophylactic dose anticoagulation	1141	53 (39-64)	678 (59%)	-	-	-	-	-	-	-	-	238 (21%)
BEMICOP NCT04604327	Therapeutic dose anticoagulation	33 (32)	63 (49-77)	17 (53%)	27 (84%)	21 (66%)	11 (34%)	0	12 (38%)	20 (63%)	0	0	32 (100%)
	Prophylactic dose	33	62	24 (73%)	29	23 (70%)	9 (27 %)	1 (3%)	15 (46%)	18 (55%)	0	0	30 (91%)

	anticoagulation		(50-74)		(88%)								
STAUNCH-19[d] NCT04528888	Therapeutic anticoagulation	11	70 (61-73)	8 (73%)	7 (64%)	0	0	11 (100%)	0	0	1 (9%)	10 (91%)	11 (100%)
	Prophylactic dose anticoagulation (1)	12	65 (47-73)	9 (75%)	4 (36%)	0	0	12 (100%)	0	0	2 (8%)	10 (92%)	12 (100%)
	Prophylactic dose anticoagulation (2)	11	56 (55-69)	8 (73%)	7 (64%)	0	0	11 (100%)	0	0	1 (9%)	10 (91%)	11 (100%)
Prothromcovid NCT04730856	Therapeutic dose anticoagulation	103	59 (49-69)	62 (60%)	60 (58%)	74 (72%)	14 (14%)	3 (3%)	17 (17%)	86 (84%)	-	-	5 (5%)
	Prophylactic dose anticoagulation	106	54 (45-66)	63 (59%)	67 (63%)	79(75%)	63 (69%)	7 (7%)	13 (12%)	93(88%)	-	-	2 (2%)
ASCOT	Therapeutic dose anticoagulation	50	59 (46- 69)	25 (50%)	-	-	-	-	24 (48%)	26 (52%)	0	0	-
	Prophylactic dose anticoagulation	79 (75)	59 (46- 69)	25 (50%)	-	-	-	-	31 (39%)	48 (61%)	0	0	-
Anticovid NCT04808882	Therapeutic dose anticoagulation	112 (110)	60 (53-70)	84 (76%)	-	-	-	-	-	26 (24%)	74 (67%)	10 (9%)	100 (91%)
	Prophylactic dose anticoagulation	116 (114)	57 (50-67)	71 (65%)	-	-	-	-	-	28 (25%)	76 (67%)	10 (9%)	103 (90%)
Comparison 2: Therapeutic dose anticoagulants vs intermediate dose anticoagulants													
mpRCT – critically ill	Therapeutic dose anticoagulation	591 (536)	60 (47-73)[e]	387 (72%)	-	-	100/210 (48%)[f]		0	8 (2%)	385 (72%)	143 (27%)	426/522 (82%)
	Intermediate dose anticoagulation	616 (567)	62 (49-14)[e]	385 (68%)	-	-	107/223 (48%)[f]		0	7 (1%)	388 (69%)	172 (30%)	458/555 (83%)
COVID-HEP NCT04345848	Therapeutic dose anticoagulation	79	60 (55-73)	56 (71%)	45 (57%)	17 (22%)	44 (56%)	14 (18%)	2 (3%)	33 (42%)	30 (38%)	14 (18%)	77 (98%)
	Intermediate dose anticoagulation	80	64 (56-71)	55 (69%)	59 (74%)	21 (26%)	35 (44%)	18 (23%)	3 (4%)	36 (45%)	32 (40%)	9 (11%)	73 (91%)
IMPACT IRB Protocol #: 20-04021936	Therapeutic dose anticoagulation	10	74	6 (60%)	7 (70%)	0	1 (10%)	9 (90%)	0	2 (20%)	6 (60%)	2 (20%)	7 (70%)
	Intermediate dose anticoagulation	4	66	2 (50%)	4 (100%)	0	1 (25%)	3 (75%)	0	2 (50%)	1 (25%)	1 (25%)	4 (100%)
Prothromcovid	Therapeutic dose anticoagulation	103	59 (49-69)	62 (60%)	60 (58%)	74 (72%)	14 (14%)	3 (3%)	17 (17%)	86 (84%)	-	-	5 (5%)
	Intermediate dose anticoagulation	91	55 (46-67)	57 (63%)	57 (63%)	63 (69%)	18 (20%)	6 (7%)	11 (12%)	80 (88%)	-	-	4 (4%)
ASCOT	Therapeutic dose anticoagulation	50	59 (46-69)	25 (50%)	-	-	-	-	24 (48%)	26 (52%)	0	0	-

	Intermediate dose anticoagulation	65 (63)	52 (37-70)	35 (54%)	-	-	-	-	22 (34%)	43 (66%)	0	0	-
Anticovid NCT04808882	Therapeutic dose anticoagulation	112 (110)	60 (53-70)	84 (76%)	-	-	-	-	-	26 (24%)	74 (67%)	10 (9%)	100 (91%)
	Intermediate dose anticoagulation	111 (110)	58 (49-68)	74 (62%)	-	-	-	-	-	23 (21%)	75 (68%)	12 (11%)	105 (95%)
Comparison 3: Intermediate dose anticoagulants versus prophylactic dose anticoagulants													
XCOVID-19 EudraCT: 2020-001708-41	Intermediate dose anticoagulation	91	63 (49-77)	56 (62%)	63 (69%)	60 (66%)	8 (9%)	4 (4%)	28 (26%)	42 (38%)	16 (15%)	0	15 (17%)
	Prophylactic dose anticoagulation	92	60 (44-76)	59 (64%)	70 (76%)	60 (65%)	3 (3%)	3 (3%)	34 (31%)	41 (38%)	11 (10%)	0	9 (10%)
COVIDOSE NCT04373707	Intermediate dose anticoagulation	500	62 (53-71)	326 (66%)	308 (62%)	205 (41%)	142 (29%)	52 (11%)	62 (13%)	404 (82%)	14 (3%)	14 (3%)	435 (87.9%)[h]
	Prophylactic dose anticoagulation	496	62 (52-71)	333 (67%)	327 (66%)	208 (42%)	133 (27%)	67 (14%)	57 (12%)	400 (81%)	19 (4%)	14 (3%)	446 (89.9%)[h]
IMPROVE	Intermediate dose anticoagulation	46	62.6	23 (50%)	24 (35%)	14 (30%)	10 (22%)	13 (28%)	2 (4%)	1 (2%)	17 (37%)	26 (57%)	37 (80%)
	Prophylactic dose anticoagulation	48	63.3	27 (56%)	26 (54%)	29 (60%)	7 (15%)	8 (17%)	2 (4%)	2 (4%)	25 (52%)	19 (40%)	42 (88%)
NCT04360824	Intermediate dose anticoagulation	87 (85)	65 (24-86)	47 (54%)	37 (43%)	20 (24%)	30 (35%)	33 (39%)	0	0	0	19 (22%)	63 (72%)
	Prophylactic dose anticoagulation	86 (85)	64 (30-85)	50 (58%)	30 (35%)	23 (27%)	25 (29%)	37 (44%)	0	0	0	19 (22%)	67 (78%)
INSPIRATION NCT04486508	Intermediate dose anticoagulation	280	62 (51-70)	163 (58%)	207 (74%)	51 (18%)	22 (8%)	32 (11%)	0	119 (43%)	102 (36%)	59 (21%)	266 (95%)
	Prophylactic dose anticoagulation	286	61 (47-71)	163 (57%)	207 (72%)	50 (17%)	17 (6%)	24 (8%)	0	137 (48%)	91 (32%)	58 (20%)	262 (92%)
COVID19-HD EudraCT: 2020-001972-13	Intermediate dose anticoagulation	65	61	49 (75%)	32 (49%)	40 (62%)	15 (23%)	8 (12%)	58 (89%)[g]		7 (11%)	0	53 (82%)
	Prophylactic dose anticoagulation	67	60	47 (70%)	35 (52%)	38 (57%)	20 (30%)	8 (12%)	58 (87%)[g]		9 (13%)	0	54 (81%)
EMOS-COVID NCT04646655	Intermediate dose anticoagulation	68	64 (56-71)	46 (68%)	17 (25%)	35 (52%)	21 (31%)	8 (12%)	5 (7%)	48 (71%)	13 (19%)	0	68 (100%)
	Prophylactic dose anticoagulation	68	63 (54-71)	54 (79%)	24 (35%)	40 (59%)	16 (36%)	4 (6%)	3 (4%)	43 (63%)	21 (31%)	0	68 (100%)
Prothromcovid	Intermediate dose anticoagulation	91	55 (46-67)	57 (63%)	57 (63%)	63 (69%)	18 (20%)	6 (7%)	11 (12%)	80 (88%)	-	-	4 (4%)

	Prophylactic dose anticoagulation	106	54 (45-66)	63 (59%)	67 (63%)	79(75%)	63 (69%)	7 (7%)	13 (12%)	93(88%)	-	-	2 (2%)
ASCOT	Intermediate dose anticoagulation	613 (603)	48 (37-61)	387 (63%)	-	-	-	-	363 (59%)	241 (39%)	0	0	-
	Prophylactic dose anticoagulation	610 (596)	48 (37-60)	354 (58%)	-	-	-	-	350 (57%)	252 (41%)	0	0	-
Anticovid NCT04808882	Intermediate dose anticoagulation	111 (110)	58 (49-68)	74 (62%)	-	-	-	-	-	23 (21%)	75 (68%)	12 (11%)	105 (95%)
	Prophylactic dose anticoagulation	116 (114)	57 (50-67)	71 (65%)	-	-	-	-	-	28 (25%)	76 (67%)	10 (9%)	103 (90%)

Footnotes:

(a) Dose categories as defined in the PMA protocol. Full details in eTable 2

(b) Use of concomitant therapy at the point of randomisation. Corticosteroids include dexamethasone, methylprednisolone, prednisolone and hydrocortisone

(c) Therapeutic dose enoxaparin group only

(d) Two arms of STAUNCH-19 assigned anticoagulation at prophylactic dose (as defined by the PMA protocol) and were combined for meta-analysis. See Table 2 for further details.

(e) Age range for mpRCT is +/- 1 SD (not IQR)

(f) Includes all patients with D-Dimer >=2x ULN (no upper cut-off presented)

(g) Totals include patients receiving no O2 support or O2 <15l/min at randomisation.

(h) Defined as above 10mg/day

eTable-3: Risk of bias assessments for all trials (all outcomes)

Study	Randomization process	Deviations from intended intervention	Missing data	Outcome assessment	Selection of the reported result	Overall
1. 28-day all-cause mortality						
Comparison 1: Therapeutic dose anticoagulants vs prophylactic dose anticoagulants						
HESACOVID	Low	Low	Low	Low	Low	Low
mpRCT*	Low	Some concerns	Low	Low	Low	Some concerns
RAPID	Low	Low	Low	Low	Low	Low
HEP-COVID	Low	Some concerns	Low	Low	Low	Low
ACTION	Low	Low	Low	Low	Low	Low
COVID-PACT	Low	Low	Low	Low	Low	Low
FREEDOM	Low	Low	Low	Low	Low	Low
BEMICOP	Low	Some concerns	Low	Low	Low	Low
STAUNCH-19	Low	Low	Low	Low	Low	Low
PROTHROMCOVID	Low	Low	Low	Low	Low	Low
ASCOT	Low	Low	Some concerns	Low	Low	Some concerns
ANTICOVID	Low	Low	Low	Low	Low	Low
Comparison 2: Therapeutic dose anticoagulants vs intermediate dose anticoagulants						
mpRCT*	Low	Some concerns	Low	Low	Low	Some concerns
COVID-HEP	Low	Low	Some concerns	Low	Low	Some concerns
IMPACT	Some concerns	Some concerns	Low	Low	Low	Some concerns
PROTHROMCOVID	Low	Low	Low	Low	Low	Low
ASCOT	Low	Low	Some concerns	Low	Low	Some concerns
ANTICOVID	Low	Low	Low	Low	Low	Low
Comparison 3: Intermediate dose anticoagulants versus prophylactic dose anticoagulants						
XCOVID-19	Low	Some concerns	Low	Low	Low	Low
COVIDOSE	Low	Low	Low	Low	Low	Low
IMPROVE	Some concerns	Low	Low	Low	Low	Some concerns
NCT04360824	Low	Some concerns	Low	Low	Low	Low
INSPIRATION	Low	Low	Low	Low	Low	Low
COVID-19 HD	Low	Low	Low	Low	Low	Low
EMOS-COVID	Low	Low	Low	Low	Low	Low
PROTHROMCOVID	Low	Low	Low	Low	Low	Low
ASCOT	Low	Low	Some concerns	Low	Low	Some concerns
ANTICOVID	Low	Low	Low	Low	Low	Low

2. Progression to IMV or death						
Comparison 1: Therapeutic dose anticoagulants vs prophylactic dose anticoagulants						
HESACOVID	Low	Low	Low	Low	Low	Low
mpRCT*	Low	Some concerns	Low	Low	Low	Some concerns
RAPID	Low	Low	Low	Low	Low	Low
HEP-COVID	Low	Some concerns	Low	Low	Low	Low
ACTION	Low	Low	Low	Low	Low	Low
COVID-PACT	Low	Low	Low	Low	Low	Low
FREEDOM	Low	Low	Low	Low	Low	Low
BEMICOP	Low	Some concerns	Low	Low	Low	Low
STAUNCH-19	Low	Low	Low	Low	Low	Low
PROTHROMCOVID	Low	Low	Low	Low	Low	Low
ASCOT	Low	Low	Low	Low	Low	Low
Comparison 2: Therapeutic dose anticoagulants vs intermediate dose anticoagulants						
mpRCT*	Low	Some concerns	Low	Low	Low	Some concerns
COVID-HEP	Low	Low	Some concerns	Low	Low	Some concerns
IMPACT	Some concerns	Some concerns	Low	Low	Low	Some concerns
PROTHROMCOVID	Low	Low	Low	Low	Low	Low
ASCOT	Low	Low	Low	Low	Low	Low
Comparison 3: Intermediate dose anticoagulants versus prophylactic dose anticoagulants						
XCOVID-19	Low	Some concerns	Low	Low	Low	Low
COVIDOSE	Low	Low	Low	Low	Low	Low
NCT04360824	Low	Some concerns	Some concerns	Low	Low	Some concerns
INSPIRATION	Low	Low	Low	Low	Low	Low
COVID-19 HD	Low	Low	Low	Low	Low	Low
EMOS-COVID	Low	Low	Low	Low	Low	Low
PROTHROMCOVID	Low	Low	Low	Low	Low	Low
ASCOT	Low	Low	Low	Low	Low	Low
3. Thromboembolic events						
Comparison 1: Therapeutic dose anticoagulants vs prophylactic dose anticoagulants						
HESACOVID	Low	Low	Low	Some concerns	Low	Some concerns
mpRCT*	Low	Some concerns	Low	Some concerns	Low	Some concerns
RAPID	Low	Low	Low	Some concerns	Low	Some concerns
HEP-COVID	Low	Some concerns	Low	Low	Low	Low
ACTION	Low	Low	Low	Low	Some concerns	Some concerns
COVID-PACT	Low	Low	Low	Low	Low	Low
FREEDOM	Low	Low	Low	Low	Low	Low

BEMICOP	Low	Some concerns	Low	Some concerns	Low	Some concerns
STAUNCH-19	Low	Low	Low	Some concerns	Low	Some concerns
PROTHROMCOVID	Low	Low	Low	Some concerns	Low	Some concerns
ASCOT	Low	Low	Some concerns	Some concerns	Low	Some concerns
ANTICOVID	Low	Low	Low	Some concerns	Low	Some concerns
Comparison 2: Therapeutic dose anticoagulants vs intermediate dose anticoagulants						
mpRCT*	Low	Some concerns	Low	Some concerns	Low	Some concerns
COVID-HEP	Low	Low	Some concerns	Low	Low	Some concerns
IMPACT	Some concerns	Some concerns	Low	Some concerns	Low	Some concerns
PROTHROMCOVID	Low	Low	Low	Some concerns	Low	Some concerns
ASCOT	Low	Low	Some concerns	Some concerns	Low	Some concerns
ANTICOVID	Low	Low	Low	Some concerns	Low	Some concerns
Comparison 3: Intermediate dose anticoagulants versus prophylactic dose anticoagulants						
XCOVID-19	Low	Some concerns	Low	Low	Low	Low
COVIDOSE	Low	Low	Low	Some concerns	Low	Some concerns
IMPROVE	Some concerns	Low	Low	Low	Low	Some concerns
NCT04360824	Low	Some concerns	Low	Some concerns	Low	Some concerns
INSPIRATION	Low	Low	Low	Some concerns	Low	Some concerns
COVID-19 HD	Low	Low	Low	Some concerns	Low	Some concerns
EMOS-COVID	Low	Low	Low	Some concerns	Low	Some concerns
PROTHROMCOVID	Low	Low	Low	Some concerns	Low	Some concerns
ASCOT	Low	Low	Some concerns	Some concerns	Low	Some concerns
ANTICOVID	Low	Low	Low	Some concerns	Low	Some concerns
4. Major bleeding						
Comparison 1: Therapeutic dose anticoagulants vs prophylactic dose anticoagulants						
HESACOVID	Low	Low	Low	Some concerns	Low	Some concerns
mpRCT*	Low	Some concerns	Low	Some concerns	Low	Some concerns
RAPID	Low	Low	Low	Low	Low	Low
HEP-COVID	Low	Some concerns	Low	Low	Low	Low
ACTION	Low	Low	Low	Low	Low	Low
COVID-PACT	Low	Low	Low	Low	Low	Low
FREEDOM	Low	Low	Low	Low	Low	Low
BEMICOP	Low	Some concerns	Low	Some concerns	Low	Some concerns
STAUNCH-19	Low	Low	Low	Some concerns	Low	Some concerns
PROTHROMCOVID	Low	Low	Low	Some concerns	Low	Some concerns
ASCOT	Low	Low	Low	Some concerns	Low	Some concerns
ANTICOVID	Low	Low	Low	Some concerns	Low	Some concerns

Comparison 2: Therapeutic dose anticoagulants vs intermediate dose anticoagulants						
mpRCT*	Low	Some concerns	Low	Some concerns	Low	Some concerns
COVID-HEP	Low	Low	Some concerns	Low	Low	Some concerns
IMPACT	Some concerns	Some concerns	Low	Some concerns	Low	Some concerns
PROTHROMCOVID	Low	Low	Low	Some concerns	Low	Some concerns
ASCOT	Low	Low	Low	Some concerns	Low	Some concerns
ANTICOVID	Low	Low	Low	Some concerns	Low	Some concerns
Comparison 3: Intermediate dose anticoagulants versus prophylactic dose anticoagulants						
XCOVID-19	Low	Some concerns	Low	Low	Low	Low
COVIDOSE	Low	Low	Low	Low	Low	Low
IMPROVE	Some concerns	Low	Low	Low	Low	Some concerns
INSPIRATION	Low	Low	Low	Some concerns	Low	Some concerns
COVID-19 HD	Low	Low	Low	Some concerns	Low	Some concerns
EMOS-COVID	Low	Low	Low	Low	Low	Low
PROTHROMCOVID	Low	Low	Low	Some concerns	Low	Some concerns
ASCOT	Low	Low	Low	Some concerns	Low	Some concerns
ANTICOVID	Low	Low	Low	Some concerns	Low	Some concerns

*Assessment applies to both mpRCT critically ill and non-critically ill

eTable-4. Associations of anticoagulation with 28-day mortality; progression to invasive mechanical ventilation (IMV) or death; thromboembolic events and major bleeding with other patient characteristics ascertained at the time the patient was randomised. (Per protocol analysis excluding trials that allowed a choice of dosing (intermediate or prophylactic) on the control arm)

Treatment comparison*		Therapeutic dose (TD)- vs Prophylactic dose (PD) anticoagulation					Intermediate dose (ID) vs Prophylactic dose (PD) anticoagulation				
Subgroup		**No. of events / No. of patients**		**I^2**	**OR (95% CI)**	**Test for interaction p value**	**No. of events / No. of patients**		**I^2**	**OR (95% CI)**	**Test for interaction p value**
		TD	**PD**				**ID**	**PD**			
28-day mortality											
Corticosteroids at randomization	No corticosteroids	9/104	10/111	37%	1.07 (0.35-3.28)	0.227	43/624	41/648	41%	1.13 (0.70-1.81)	0.111
	Corticosteroids	60/480	81/493	31%	0.74 (0.50-1.10)		133/584	138/589	35%	0.95 (0.70-1.28)	
Sex	Female	28/267	42/281	31%	0.63 (0.36-1.11)	0.671	71/678	64/702	0%	1.21 (0.81-1.81)	0.237
	Male	47/367	52/398	19%	0.98 (0.60-1.58)		121/1150	135/1141	0%	0.85 (0.63-1.14)	
Age	<70	38/465	51/522	45%	0.79 (0.49-1.29)	0.523	117/1403	105/1402	0%	1.12 (0.82-1.52)	0.215
	≥70	37/169	43/157	0%	0.62 (0.34-1.13)		75/426	94/442	10%	0.77 (0.50-1.17)	
BMI	<30	32/300	41/303	23%	0.67 (0.38-1.18)	0.857	117/767	119/789	0%	0.98 (0.72-1.34)	0.765
	≥30	36/276	49/291	0%	0.81 (0.48-1.34)		47/403	53/398	0%	0.96 (0.60-1.54)	
D-Dimers	Normal (<2x ULN)	20/285	26/286	54%	0.69 (0.35-1.37)	0.971	27/475	35/515	0%	0.89 (0.50-1.58)	0.357
	Elevated (2 to 4x ULN)	21/177	26/157	23%	0.69 (0.34-1.38)		22/283	14/249	0%	1.40 (0.67-2.94)	
	Elevated (>4x ULN)	23/100	30/131	42%	0.94 (0.48-1.85)		32/163	36/168	0%	0.76 (0.42-1.3^)	
Time Period of Randomisation	≤31/12/2020	26/157	32/156	0%	0.71 (0.37-1.37)	0.964	160/698	161/715	0%	1.07 (0.81-1.41)	0.453
	≥01/01/2021	49/477	62/523	47%	0.89 (0.57-1.38)		32/1131	38/1129	0%	0.78 (0.48-1.28)	
Progression to IMV or death 28 days after randomization											
Corticosteroids at randomization	No corticosteroids	9/94	18/105	45%	0.52 (0.20-1.36)	0.633	52/572	61/594	9%	0.89 (0.60-1.31)	0.487
	Corticosteroids	71/432	89/447	11%	0.78 (0.54-1.13)		102/484	109/490	8%	0.91 (0.66-1.27)	
Sex	Female	32/248	47/266	54%	0.75 (0.44-1.28)	0.823	64/610	70/647	0%	0.99 (0.68-1.45)	0.451
	Male	58/328	70/362	23%	0.82 (0.54-1.24)		127/1067	152/1047	7%	0.77 (0.59-1.00)	
Age	<70	51/423	69/481	50%	0.83 (0.55-1.25)	0.645	126/1305	140/1322	0%	0.91 (0.70-1.18)	0.379
	≥70	39/153	48/147	0%	0.61 (0.34-1.10)		64/373	82/373	49%	0.73 (0.47-1.18)	
BMI	<30	34/279	48/284	0%	0.60 (0.36-1.01)	0.527	95/677	119/707	24%	0.80 (0.59-1.09)	0.109
	≥30	45/240	58/258	63%	0.75 (0.46-1.23)		48/345	45/331	0%	1.11 (0.69-1.80)	
D-Dimers	Normal (<2x ULN)	36/275	42/281	0%	0.83 (0.50-1.37)	0.839	37/446	51/469	0%	0.71 (0.45-1.13)	0.496
	Elevated (2x to 4x ULN)	25/162	31/142	0%	0.63 (0.33-1.19)		27/256	27/230	0%	1.00 (0.55-1.84)	
	Elevated (>4x ULN)	18/73	23/100	70%	0.86 (0.39-1.92)		15/123	23/128	9%	0.58 (0.28-1.21)	
Time Period of Randomisation	≤31/12/2020	26/133	30/131	0%	0.72 (0.38-1.36)	0.640	122/580	119/586	0%	1.05 (0.78-1.42)	0.179
	≥01/01/2021	64/443	87/497	38%	0.83 (0.57-1.22)		68/1098	103/1109	0%	0.65 (0.47-0.90)	
Thromboembolic events											
Corticosteroids at randomization	No corticosteroids	7/104	4/111	0%	1.72 (0.47-6.30)	0.112	19/607	18/631	39%	1.08 (0.52-2.23)	0.207
	Corticosteroids	24/480	46/493	0%	0.55 (0.32-0.93)		17/582	29/584	0%	0.65 (0.35-1.19)	
Sex	Female	10/267	16/280	0%	0.73 (0.32-1.65)	0.744	18/830	17/693	0%	0.99 (0.48-2.02)	0.998
	Male	21/365	35/397	0%	0.63 (0.35-1.14)		22/975	35/1123	7%	0.81 (0.45-1.46)	
Age	<70	25/464	37/520	0%	0.80 (0.46-1.38)	0.309	26/1395	37/1391	0%	0.69 (0.40-1.16)	0.477

	≥70	6/168	14/157	0%	0.40 (0.15-1.08)		14/411	15/426	0%	1.14 (0.51-2.55)	
BMI	<30	9/300	19/303	0%	0.47 (0.21-1.08)	0.404	23/755	26/772	4%	0.98 (0.53-1.82)	0.371
	≥30	22/276	31/291	5%	0.83 (0.45-1.53)		14/397	23/392	6%	0.68 (0.33-1.40)	
D-Dimers	Normal (<2x ULN)	8/285	8/286	0%	1.03 (0.38-2.81)	0.558	4/471	12/506	0%	0.51 (0.16-1.57)	0.925
	Elevated (2x to 4x ULN)	7/177	11/157	0%	0.60 (0.23-1.58)		9/277	12/243	3%	0.56 (0.20-1.58)	
	Elevated (>4x ULN)	13/100	26/131	0%	0.62 (0.29-1.32)		10/159	13/164	0%	0.86 (0.35-2.13)	
Time Period of Randomisation	≤31/12/2020	7/157	9/156	0%	0.85 (0.39-2.48)	0.586	28/687	31/703	2%	1.00 (0.58-1.73)	0.651
	≥01/01/2021	24/475	42/521	0%	0.63 (0.37-1.08)		12/1119	21/1114	0%	0.50 (0.23-1.05)	
Major bleeding											
Corticosteroids at randomization	No corticosteroids	3/104	2/111	60%	1.24 (0.14-10.73)	0.987	7/532	7/559	0%	0.95 (0.32-2.85)	0.594
	Corticosteroids	14/480	9/493	0%	1.66 (0.70-3.93)		10/576	9/571	0%	1.13 (0.44-2.86)	
Sex	Female	5/267	5/282	0%	1.23 (0.36-1.29)	0.507	6/636	8/665	0%	0.72 (0.24-2.24)	0.362
	Male	12/367	6/401	36%	1.93 (0.66-5.58)		14/1101	9/1085	0%	1.42 (0.57-3.54)	
Age	<70	11/465	7/525	0%	1.72 (0.65-4.53)	0.956	13/1376	9/1380	0%	1.39 (0.59-3.24)	0.764
	≥70	6/169	4/158	55%	0.93 (0.16-5.46)		7/362	8/371	0%	0.99 (0.33-2.92)	
BMI	<30	9/300	4/303	59%	1.70 (0.43-6.71)	0.311	12/722	8/741	0%	1.58 (0.64-3.94)	0.236
	≥30	8/276	7/291	0%	1.41 (0.50-3.93)		5/348	8/339	0%	0.59 (0.19-1.87)	
D-Dimers	Normal (<2x ULN)	5/285	2/286	0%	2.40 (0.46-12.63)	0.463	4/452	6/484	0%	0.95 (0.25-3.57)	0.266
	Elevated (2x to 4x ULN)	6/177	1/157	64%	2.35 (0.27-20.23)		1/250	4/219	0%	0.24 (0.04-1.59)	
	Elevated (>4x ULN)	4/100	6/131	0%	0.95 (0.27-3.41)		5/126	2/126	0%	1.93 (0.37-10.14)	
Time Period of Randomisation	≤31/12/2020	8/157	3/156	37%	2.36 (0.57-9.86)	0.666	9/604	10/621	0%	1.17 (0.44-3.08)	0.437
	≥01/01/2021	9/477	8/527	0%	1.26 (0.47-3.36)		11/1134	7/1130	0%	1.21 (0.45-3.22)	

202 *Subgroup effects not estimated for the comparison of therapeutic versus intermediate dose due to low numbers of events /patients with available data