Supplement – Baseline Risk Study Characteristics

Study ID	Study Design	Location Study Period	Population	COVID-19 diagnosis	Age	Male (%)	Prior VTE (%)	Anticoagulation prior to hospitalization (%)	D-dimer	Still in ICU at end of study (%)	Still in hospital at end of study (%) (May include ICU, if not specified.)	Number of patients on prophylactic intensity (N)	Prophylactic intensity description (drug, dose, duration)	RoB
Pavoni 2020	Single-centre, retrospective, observational study	Italy; 28 Feb 2020 - 10 Apr 2020	Adult patients (≥ 18 years old) with severe COVID-19 admitted to ICU	Confirmed diagnosis	Mean (SD): 61 (13.00)	60	NR	NR	Mean (SD): 1556 (1090.00)	NR	NR	40	Enoxaparin, 3000-4000 units daily, NR	Low risk of bias for all relevant outcome(s), except for PE, DVT, and IVM
Maatman 2020	Retrospective cohort	USA; 12 Mar 2020 - 31 Mar 2020	Patients with severe laboratory-confirmed SARS-CoV-2 infection who were treated in ICU.	Positive SARS-CoV-2 test only	Mean (SD): 61 (16.00)	56.88	NR	NR	Median (IQR): 84506 (321,973)	2.75	3.66	109	5,000 U subcutaneous heparin every 8 hours, 40 mg enoxaparin daily, or 30 mg enoxaparin bid.	Low risk of bias for all relevant outcome(s)
Longchamp 2020	Observational study	Switzerland; 08 Mar 2020 - 04 Apr 2020	Critically ill patients admitted to ICU for hypoxemic respiratory failure	Confirmed diagnosis	Mean (SD): 68 (11.00)	64	0.00	8.00	Median (IQR): 2071 (953,3606)	8.00	NR	25	Thromboprophylactic regimen, either with continuous intravenous heparin infusion (15 000 IU/24 h, or 20 000 IU/24 h for patients >100 kg), or once-daily subcutaneous enoxaparin injections (40 mg, or 60 mg for patients >100 kg)	Low risk of bias for all relevant outcome(s)
Mei 2020*	Retrospective study	China; 01 Jan 2020 - 23 Mar 2020	COVID-19 pneumonia patients admitted to a tertiary regional medical center (critically and acutely ill patients)	Confirmed diagnosis	Median (IQR): 55.5 (0.5,87)	51.17	0.00	NR	Median (IQR): 510 (310,830)	NR	NR	45	All patients received VTE prophylaxis following standard protocols with LMWH or UFH or mechanical intermittent pneumatic compression device if contraindicated to anticoagulant	Low risk of bias for all relevant outcome(s)
Klok 2020	NR	Netherlands; 07 Mar 2020 - 22 Apr 2020	Critically ill patients with proven COVID-19 pneumonia	Not reported	Mean (SD): 64 (12.00)	75.54	NR	NR	NR	75.54	NA	184	Varies between hospitals: Nadroparin 2850 IU sc OD or 5700 IU OD if body weight > 100 kg OR Nadroparin 5700 IU OD; nadroparin 5700 IU sc BID from April 4th 2020 and onwards OR 2850 IU sc OD or 5700 IU OD if body weight > 100 kg; nadroparin 5700 IU sc OD from March	Low risk of bias for all relevant outcome(s)

													30th 2020 and onwards	
Al-Samkari 2020	Retrospective cohort study	USA; 01 Mar 2020 - 05 Apr 2020	All patients aged 18 years or more with confirmed COVID-19 who had a D-dimer test performed on initial presentation (critically ill patients)	Confirmed diagnosis	Median (IQR): 65 (32,97)	64.6	NR	NR	NR	NR	68.75	144	Enoxaparin, 40mg SC daily (or every 12 hours for BMI ≥41 or weight >120 kg) OR Unfractionated heparin 5000U SC every 8-12 hours (or 5000-7500 U SC every 8 hours for BMI ≥41 or weight >120 kg)	Low risk of bias for all relevant outcome(s)
Lemos 2020	Randomized, controlled, open-label, single-center, phase II study	Brazil; 01 Apr 2020 - 30 Jul 2020	Patients with age over 18 years-old, SARS-CoV-2 infection confirmed, acute respiratory distress syndrome (ARDS), severe clinical presentation with respiratory failure requiring mechanical ventilation, D-dimer levels greater than 1000 µg/L; prothrombin time/international normalized ratio (INR) < 1.5; activated partial thromboplastin time (aPTT)/ratio < 1.5, and platelet count greater than 100,000/mm3.	Positive SARS-CoV-2 test only	Mean (SD): 56.5 (13.08)	80	NR	55.00	Mean (SD): 3792 (3410.51)	NA	NA	10	Subcutaneous unfractionated heparin (UFH) at a dose of 5000 IU TID (if weight < 120 kg) and 7500 IU TID (if weight > 120 kg) or enoxaparin at a dose of 40 mg OD (if weight < 120 kg) and 40 mg BID (if weight > 120 Kg)	Low risk of bias for all relevant outcome(s)
Shah 2020	Retrospective observational	UK; 15 Mar 2020 - 05 May 2020	All patients admitted to adult ICUs	Combination (ie confirmed and suspected)	Mean (Range): 57 (49,64)	66.3	5.50	NR	Mean (Range): 2587 (950, 10000)	17.64	NR	187	80% received prophylactic (standard weight-based low molecular weight heparin thromboprophylaxis	Medium or high risk of bias for all relevant outcome(s)
Fujiwara 2021	retrospective cohort study	Japan; 01 Feb 2020 - 31 Aug 2020	All adult patients with COVID-19 admitted to ICU during the defined timeframe.	Confirmed diagnosis	Median (IQR): 63 (51,68)	91.4	NR	NR	NR	NR	NR	20	Prophylactic anticoagulants (unfractionated intravenous heparin, subcutaneous heparin calcium, direct oral anticoagulants, and warfarin)	Low risk of bias for all relevant outcome(s)
Dutch COVID & Thrombosis Coalition 2021	Cohort study	Netherlands; 01 Sep 2020 - 30 Nov 2020	All adults COVID-19 patients	Combination (ie confirmed and suspected)	Mean (SD): 64 (12.00)	74	5.30	11.00	NR	NR	NR	96	Dalteparin 5000 IU/d or 5000 IU BID if body weight >100 kg; OLVG: nadroparin 5700 IU for <100 kg, nadroparin 7600 IU/d for 100 kg	Low risk of bias for all relevant outcome(s)
Moll 2020	Retrospective cohort study	USA; 07 Mar 2020 - 13 Apr 2020	COVID positive pts spending time in the ICU at any point during admission	Positive SARS-CoV-2 test only	Mean (SD): 64.61 (14.86)	57.8	3.90	NR	Median (IQR): 1456.5 (732.75,2660 .25)	NR	18.60	102	Enoxaparin 40mg sc daily, or Unfractioned heparin 5000 IU sc BID or TID	Low risk of bias for all relevant outcome(s)

Taboada 2020	Prospective observational cohort study	Spain; 21 Mar 2020 - 19 Apr 2020	Critically ill patients with COVID-19 admitted to the anesthesia ICUs of 7 hospitals in Galicia, Northwest Spain	Confirmed diagnosis	Median (IQR): 69 (61,73)	63.9	NR	7.20	Median (IQR): 1204 (7523,2159)	9.28	NR	16	Prophylactic-dose anticoagulant. No description of drug and/or dose used.	Low risk of bias for all relevant outcome(s)
Nadeem 2021	Retrospective Cohort	UAE; NR	All adult patients with confirmed COVID-19 infection admitted to the ICU of Dubai hospital	Confirmed diagnosis	Mean (SD): 50.7 (11.30)	86.5	NR	NR	Mean (SD): 4600 (9000)	NR	NR	34	Prophylactic Enoxaparin (without description of dose)	Low risk of bias for all relevant outcome(s)
Piazza 2020	Retrospective observational cohort analysis	USA; 13 Mar 2020 - 03 Apr 2020	Consecutive patients 18 years or older and who tested positive for SARS-CoV-2 infection based on SARS	Confirmed diagnosis	Mean (SD): 67.70 (1.00)	62.3	5.30	89.40	Mean (SD): 2515.60 (7913.30)	NR	28.80	170	Prophylactic dosages not specified, thromboprophylaxis with LMWH, UFH, Rivaroxaban	Low risk of bias for all relevant outcome(s)
Faqihi 2021	Retrospective study	Saudi Arabia; 01 Apr 2020 - 30 May 2020	COVID-19 patients that were admitted to intensive care unit (ICU)	Confirmed diagnosis	Median (IQR): 49 (39,58)	78.1	5.00	NR	Median (IQR): 2700 (1200,8900)	NR	NR	160	Low-molecular-weight heparin thromboprophylaxis unless contraindicated (enoxaparin 20 mg once daily if <50 kg, enoxaparin 40 mg once daily if 50–100 kg, 40 mg twice daily if 101–150 kg, and 60 mg twice daily if >150 kg) as per hospital protocol	Low risk of bias for all relevant outcome(s) except for PE, DVT, major bleeding, intracranial hemorrhage, renal replacement therapy
Stattin 2020	Prospective observational study	Sweden; 13 Mar 2020 - 14 Apr 2020	All adult patients with COVID-19 admitted to the ICU with thromboelastography results	Positive SARS-CoV-2 test only	Median (IQR): 65 (51,70)	81	3.00	NR	Mean (SD): 1940 (2460)	NR	NR	31	COVID-19 patients with body weight below 70 kg were given 5000 IU Dalteparin, those with body weight 70–90 kg were given 7500 IU Dalteparin and those above 90 kg were given 10,000 IU Dalteparin.	Low risk of bias for all relevant outcome(s) except for PE, DVT, and IVM
Martinelli 2021	Observational cohort	Italy; 09 Mar 2020 - 07 Apr 2020	Hospitalized patients in ICU	Positive SARS-CoV-2 test only	Median (IQR): 55 (47,62)	73	NR	NR	Median (IQR): 1493 (578,7642)	NR	NR	20	Standard dose: enoxaparin 40 mg daily increased to 60 mg daily in obese.	Low risk of bias for all relevant outcome(s) except for VTE and major bleeding
Helms 2021	Before and after study	France; 03 Mar 2020 - 30 May 2020	COVID-19 patients admitted to ICUs for ARDS	Positive SARS-CoV-2 test only	Median (IQR): 62 (51,70)	72.6	5.00	NR	NR	0.00	NR	108	Low molecular weight heparin LMWH-enoxaparin—up to 6000 IU/12 h SC in obese patients or unfractionated heparin UFH 200 IU/kg/24 h if creatinine clearance<30 mL/min	Low risk of bias for all relevant outcome(s) except for PE, DVT, VTE, Stroke, Major bleeding

Bellmunt-Montoya 2020	Prospective cohort (according to registered protocol)	Spain; 01 Apr 2020 - 30 Apr 2020	All adult patients had confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.	Confirmed diagnosis	Median (IQR): 61.8 (55,67)	77	1.30	2.60	Median (IQR): 2135 (1051,4610)	69.56	NA	230	Standard dose = Enoxaparin 40 mg once daily or 0.5 mg/kg once daily (n=127), intermediate dose = Enoxaparin 60 mg once daily or 1 mg/kg once daily (n=33), or therapeutic dose =Enoxaparin 1 mg/kg bid. No AC (only mechanical prophylaxis) = 3	Low risk of bias for all relevant outcome(s) except for PE
Roger 2021	Prospective multicentre, cohort study	France; 02 Apr 2020 - 03 Jul 2020	All patients admitted to the intensive care unit for a diagnosis of probable or confirmed SARS-CoV-2 infection	Combination (ie confirmed and suspected)	Median (IQR): 66 (58,73)	75	NR	8.00	Median (IQR): 1560 (821,3690)	NR	32.00	607	Prophylactic dosing	Low risk of bias for all relevant outcome(s)
Bikdeli 2021 (INSPIRATION)	Multicenter, open-label, randomized trial with a 2 × 2 factorial design	Iran; 29 Jul 2020 - 19 Sep 2020	Adult patients (≥18 years), with PCR-confirmed COVID-19 admitted to ICU within 7 days of initial hospitalization, who do not have another firm indication for anticoagulation (such as mechanical valve, high-risk AF, VTE, or left ventricular thrombus)	Positive SARS-CoV-2 test only	Median (IQR): 62 (50,71)	57.8	0.00	0.00	Mean (SD): 972 (394)	39.00	NR	286	Enoxaparin, 40mg daily, was the control group standard-dose prophylactic anticoagulation regimen.	Low risk of bias for all relevant outcome(s)
Perepu 2021*	Randomized, open-label, interventional study	USA; 26 Apr 2020 - 06 Jan 2021	Adult patients with SARS-CoV-2 infection requiring hospitalization who were admitted to an ICU and/or had a modified ISTH Overt DIC score ≥3.	Confirmed diagnosis	Mean (Range): 64 (24,86)	56	NR	NR	Median (IQR): 1680 (920,3980)	NR	NR	53	The standard dose was 40 mg SC daily if the body mass index (BMI) was <30 kg/m2 and either 30 mg SC twice daily or 40 mg SC twice daily if the BMI was ≥30.	Low risk of bias for all relevant outcome(s) except PE, DVT, VTE
Goligher 2021 (ATTACC, ACTIV-4a, REMAP-CAP)	Open-label, international multiplatform randomized clinical trial with response-adaptive randomization	International (United States, Canada, the United Kingdom, Brazil, Mexico, Nepal, Australia, the Netherlands, and Spain); 21 Apr 2020 – 19 Dec 2020	Severe COVID-19 leading to receipt of ICU-level respiratory or cardiovascular organ support. Exclusion criteria: admitted to ICU >48h, admitted to hospital >72 hours, imminent risk for death, high risk of bleeding, factors prohibiting heparin	Positive SARS-CoV-2 test only	Mean (SD): 61.07 (12.81)	69.9	NR	0.00	48% with >=2xULN *(no measurement in 61% of all patients)*	NR	NR	616	Usual care pharmacological thromboprophylaxis, according to **local practice** which included either standard low-dose thromboprophylaxis or enhanced intermediate-dose thromboprophylaxis	Low risk of bias for all relevant outcome(s)
Oliynyk 2021	Randomized control trial	Ukraine; 01 Jul 2020 - 01 Mar 2021	Confirmed SARS-CoV-2 infection patients with presence of bilateral interstitial pneumonia on a computed tomography (CT) scan, respiratory failure with arterial partial pressure of oxygen (PaO2) < 60 mm Hg with room air, a D-dimer level > 3 mg/L, a platelet count < 120 × 109/L.	Positive SARS-CoV-2 test only	Mean (SD): 70.33 (2.80)	60.32	NR	NR	Mean (SD): 4862.22 (3331.62)	NR	NR	42	LMWH—enoxaparin at a preventive dose of 50 anti-Xa IU/kg QD subcutaneously	Low risk of bias for all relevant outcome(s)

*Baseline characteristics were based on the study's overall population and also included non-ICU hospitalized patients. HEP-COVID was not included in the BLR analysis as many patients were not on prophylactic intensity anticoagulation with population being indirect and at very high risk of VTE

Study ID	Study Design	Location Study Period	Population	COVID-19 diagnosis	Age	Male (%)	Prior VTE (%)	Anticoagulation prior to hospitalization (%)	D-dimer	Still in ICU at end of study (%)	Still in hospital at end of study (%) (May include ICU, if not specified.)	Anticoagulation group (N)	Anticoagulation description (drug, dose, duration)	Risk of Bias
Spyropoulos 2021 (HEP-COVID)*	Open-label, multi-center randomized active control trial with pseudo-blinding mechanisms.	United states of America; 08 May 2020 – 14 May 2021	Hospitalized nonpregnant adults 18 years or older with COVID-19 diagnosed by nasal swab or serologic testing who needed supplemental oxygen per investigator judgment with plasma D-dimer level greater than 4 times the upper limit of normal based on local laboratory criteria or a sepsis-induced coagulopathy score of 4 or greater were included. Exclusion criteria: high bleeding risk, antiplatelet need, contraindication study drug	Confirmed diagnosis	Mean (SD): 66.70 (14.00)	53.8	3.10	94.94	100% with >=4xULN	NR	NR	Therapeutic intensity (N= 45)	**Enoxaparin 1mg/kg** sc BID if CrCl was 30 mL/min/1.73m2 or greater **or 0.5 mg/kg BID** if CrCl was 15-29 mL/min/ 1.73m2	Some concerns for all relevant outcome(s)
												Prophylactic intensity (N= 38)	**Prophylactic or intermediate-dose heparin** regimens per local standard and could include UFH, up to 22,500 IU sc (BID or TID); enoxaparin, 30 mg or 40 mg sc OD or BID (weight based enoxaparin 0.5mg/kg sc BID was permitted but strongly discouraged); or dalteparin, 2500 IU or 5000 IU sc daily	
Goligher 2021 (ATTACC, ACTIV-4a, REMAP-CAP)	Open-label, international multiplatform randomized clinical trial with response-adaptive randomization	International (United States, Canada, the United Kingdom, Brazil, Mexico, Nepal, Australia, the Netherlands, and Spain); 21 Apr 2020 – 19 Dec 2020	Severe COVID-19 leading to receipt of ICU-level respiratory or cardiovascular organ support. Exclusion criteria: admitted to ICU >48h, admitted to hospital >72 hours, imminent risk for death, high risk of bleeding, factors prohibiting heparin	Positive SARS-CoV-2 test only	Mean (SD): 61.07 (12.81)	69.9	NR	0.00	48% with >=2xULN *(no measurement in 61% of all patients)*	NR	NR	Therapeutic intensity (N= 534)	Initial pragmatic strategy of therapeutic-dose anticoagulation with heparin, according **to local protocols used for the treatment of acute VTE** for up to 14 days or until recovery	High risk of bias for all relevant outcome(s)
												Prophylactic intensity (N= 564)	Usual care pharmacological thromboprophylaxis, according to **local practice** which included either standard low-dose thromboprophylaxis or enhanced intermediate-dose thromboprophylaxis	

*Reported population characteristics were based on the study's overall population and included non-ICU hospitalized patients.