

Effect of Therapeutic Heparin vs Prophylactic Heparin on Death, Mechanical Ventilation or Intensive Care Unit Admission in Moderately Ill Ward Patients with COVID-19: The RAPID Randomized Clinical Trial

Sholzberg et al.

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3. Supplementary Methods

3.1 Eligibility Criteria

The inclusion criteria:

- 1) Laboratory confirmed COVID-19 (diagnosis of SARS-CoV-2 via reverse transcriptase polymerase chain reaction as per the World Health Organization protocol or by nucleic acid based isothermal amplification). Positive test prior to hospital admission OR within first 5 days (i.e. 120 hours) after hospital admission;
- 2) Admitted to hospital for COVID-19;
- 3) One D-dimer value above ULN (within 5 days (i.e. 120 hours) of hospital admission) AND EITHER:
 - a. D-Dimer ≥ 2 times ULN OR
 - b. D-Dimer above ULN and Oxygen saturation $\leq 93\%$ on room air;
- 4) ≥ 18 years of age;
- 5) Informed consent from the patient (or legally authorized substitute decision maker).

The exclusion criteria:

- 1) pregnancy;
- 2) hemoglobin < 80 g/L in the last 72 hours;
- 3) platelet count $< 50 \times 10^9$ /L in the last 72 hours;
- 4) known fibrinogen < 1.5 g/L (if testing deemed clinically indicated by the treating physician prior to the initiation of anticoagulation);
- 5) known INR > 1.8 (if testing deemed clinically indicated by the treating physician prior to the initiation of anticoagulation);
- 6) patient already on intermediate dosing of LMWH that cannot be changed (determination of what constitutes an intermediate dose is to be at the discretion of the treating clinician taking the local institutional thromboprophylaxis protocol for high risk patients into consideration);
- 7) patient already on therapeutic anticoagulation at the time of screening (low or high dose nomogram UFH, LMWH, warfarin, direct oral anticoagulant (any dose of dabigatran, apixaban, rivaroxaban, edoxaban);
- 8) patient on dual antiplatelet therapy, when one of the agents cannot be stopped safely;
- 9) known bleeding within the last 30 days requiring emergency room presentation or hospitalization;
- 10) known history of a bleeding disorder of an inherited or active acquired bleeding disorder;
- 11) known history of heparin-induced thrombocytopenia;
- 12) known allergy to UFH or LMWH;
- 13) admitted to the intensive care unit at the time of screening;
- 14) treated with non-invasive positive pressure ventilation or invasive mechanical ventilation at the time of screening (of note: high flow oxygen delivery via nasal cannula is acceptable and is not an exclusion criterion);
- 15) Imminent death according to the judgement of the most responsible physician;
- 16) enrollment in another clinical trial of antithrombotic therapy involving pre-intensive care unit hospitalized patients.

3.2 Description of Therapeutic Heparin vs. Prophylactic Heparin

Therapeutic Heparin

Therapeutic anticoagulation with low molecular weight heparin (LMWH) or unfractionated heparin (UFH). The choice of LMWH versus UFH was at the clinician's discretion and dependent on local institutional supply. LMWH options are described in Table 1. UFH was administered using a weight-based nomogram (bolus plus continuous infusion) with activated partial thromboplastin time (aPTT) or UFH anti-Xa titration according to the center-specific institutional protocols as per venous thromboembolism treatment (i.e. high dose nomogram). UFH anti-Xa titration was preferred over aPTT if available as achieving a therapeutic aPTT may be challenging in patients with a pro-inflammatory state such as COVID-19. Therapeutic heparin was administered until hospital discharge, death, day 28 or study withdrawal. If the patient was admitted to the intensive care unit (ICU) or required mechanical ventilatory support (i.e. patient reached a component of the primary composite outcome), continuation of the allocated treatment was recommended, as long as the treating physician was in agreement.

Table 1. Therapeutic Heparin

Any of the following strategies could have been used for therapeutic anticoagulation:

CrCl	BMI	Enoxaparin	Dalteparin	Tinzaparin	UFH
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≥30	<40	1 mg/kg SC q12h OR 1.5 SC mg/kg q24h	200 units/kg SC q24h OR 100 IU/kg SC q12h	175 U/kg SC q24h	IV bolus, with continuous infusion to titrate to institution specific anti- Xa or aPTT values*
	≥40	1 mg/kg q12h ^{&}	100 units/kg SC q12h ^{&}	175 U/kg SC daily ^{&}	
<30	<40	UFH IV bolus, with continuous infusion to titrate to institution specific anti-Xa or aPTT values* or LMWH per hospital protocol taking BMI into consideration as above			
	≥40				

Abbreviations: CrCl = creatinine clearance; BMI = body mass index; * Initial bolus dose determined by sites, encouraging use of dosing algorithm designed for treatment of venous thromboembolism. UFH anti-Xa titration was preferred over aPTT if available as achieving a therapeutic aPTT may be challenging in patients with a pro-inflammatory state such as COVID-19

[&]For patients with BMI above 40, measurement of anti-Xa to confirm therapeutic effect was suggested.

Prophylactic Heparin

Administration of LMWH, UFH or fondaparinux at thromboprophylactic doses for acutely ill hospitalized medical patients, in the absence of contraindication, is generally considered standard care. The doses of thromboprophylaxis only included those listed below (Table 2).

Any of the following strategies could be used for prophylactic heparin doses above those listed was not considered as prophylactic. A lower dose of either LMWH or UFH than listed below was considered acceptable if due to extremely low weight/BMI, and considered as part of prophylactic heparin:

Table 2. Prophylactic Heparin

CrCl	BMI	Enoxaparin	Dalteparin	Tinzaparin	Fondaparinux	Unfractionated Heparin (UFH)
≥30	<40	40 mg SC q24h	5000 units SC q24h	4500 U SC q24h	2.5 mg SC q24h	5000 units SC q8- 12h
	≥40	40 mg SC q12h	5000 units SC q12h	9000 (+/- 1000) U SC q24h	not applicable	7500 units SC q8h
<30	<40	UFH 5000 units SC q8-12h or LMWH per hospital protocol taking BMI into consideration as above				
	≥40	UFH 7500 units SC q8h or LMWH per hospital protocol taking BMI into consideration as above				

Abbreviations: CrCl = creatinine clearance; BMI = body mass index

Full therapeutic dose anticoagulation (therapeutic dose UFH or LMWH) was permitted as rescue therapy in the event of suspected or confirmed thromboembolism.

3.3 Primary Outcome

Pre-specified primary composite outcome: ICU admission, non-invasive positive pressure ventilation, invasive mechanical ventilation or death at 28 days.

If a patient was discharged alive before 28 days, vital status was determined using a telephone follow-up. If a patient was discharged alive on mechanical ventilation (invasive or non-invasive) prior to day 28, a call to the patient or a doctor/nurse from the rehabilitation health facility was made to confirm ventilation status on day 28 and their last day of mechanical ventilation.

Pre-specified secondary outcomes, evaluated up to day 28, included:

- 1) All-cause death;
- 2) Composite of ICU admission or all-cause death;
- 3) Composite of mechanical ventilation or all-cause death;
- 4) Major bleeding as defined by the ISTH Scientific and Standardization Committee (ISTH-SSC) recommendation;¹
- 5) Red blood cell transfusion (≥1 unit);

- 6) Transfusion of platelets, frozen plasma, prothrombin complex concentrate, cryoprecipitate and/or fibrinogen concentrate;
- 7) Renal replacement therapy defined as continuous renal replacement therapy {CRRT} or intermittent hemodialysis {IHD};
- 8) Hospital-free days alive;
- 9) ICU-free days alive;
- 10) Ventilator-free days alive;
- 11) Organ support-free days alive;
- 12) Venous thromboembolism (defined as symptomatic or incidental, suspected or confirmed via diagnostic imaging and/or electrocardiogram where appropriate recognizing that access to diagnostic imaging may have been limited due to the COVID-19 pandemic, however confirmatory testing was encouraged);
- 13) Arterial thromboembolism (defined as suspected or confirmed via diagnostic imaging and/or electrocardiogram where appropriate recognizing that access to diagnostic imaging may have been limited due to the COVID-19 pandemic, however confirmatory testing was encouraged);
- 14) Heparin induced thrombocytopenia;
- 15) D-dimer at day 2+/- 24 hours.

In addition, the following pre-specified components of the primary composite outcome were pre-specified in the statistical analysis plan, but not in the protocol:

- 16) Proportion of subjects with ICU admission;
- 17) Proportion of subjects with the composite of invasive or non-invasive mechanical ventilation;
- 18) Proportion of subjects with invasive mechanical ventilation.

Outcome measures were obtained from participants' hospital medical records and where applicable through a telephone follow-up. The use of bi-level positive airway pressure (BIPAP) or continuous positive airway pressure (CPAP) at night or when sleeping for sleep apnea was not considered non-invasive mechanical ventilation or organ support for the purpose of this trial.

3.4 Pre-specified Outcome Definition for Organ-support Free Days

Defined as the number of days that a patient was alive and free of organ support through 28 days after trial entry. Organ support was defined as receipt of non-invasive mechanical ventilation, high flow nasal cannula oxygen, invasive mechanical ventilation, or vasopressor therapy.

- Non-invasive mechanical ventilation was defined as BIPAP or CPAP when used for acute respiratory support.
- High Flow Nasal Cannula Oxygen was defined as receiving ≥ 30 l/min flow at $FiO_2 \geq 40\%$.
- Invasive mechanical ventilation was defined as positive pressure ventilation through endotracheal tube or tracheostomy.
- Vasopressor support included the infusion of any vasoactive or inotropic medication.
- A patient must have been extubated and not receiving mechanical ventilation for at least 2 days before being considered free of mechanical ventilation. If a patient was extubated and re-intubated and placed back on mechanical ventilation within 1 or 2 days, the patient was considered to be on mechanical ventilation during those 1 or 2 days before re-intubation.
- Any patient who died during the acute hospital stay was assigned 28 Day Organ-Support Free Days of -1 .
- If there was intervening time in which a patient was free of organ support, but went back on organ support, the intervening time did not count toward the organ support free days endpoint. Only time before organ support and after the last use of organ support was counted as "free days".
- If a patient was discharged alive without mechanical ventilation prior to Day 28, the patient was assumed to be free of organ support after hospital discharge for the remainder of the 28 days.
- If a patient was discharged alive on mechanical ventilation (invasive or non-invasive) prior to day 28, a call to the patient or a doctor/nurse from the rehabilitation health facility was made to confirm ventilation status on day 28 and their last day of mechanical ventilation.

3.5 Sample Size Considerations

462 patients (231 per group) were needed to detect a 15% risk difference, from 50% in the control group to 35% in the experimental group, with power of 90% at a two-sided alpha of 0.048.²⁻⁴ No attrition was expected. This calculation took two interim analyses into account. There was no inflation to account for losses to follow-up because we expected these to be very infrequent, and given the nature of the trial, included patients, and outcomes, we

concluded an absence of the primary outcome in patients discharged alive from hospital before 28 days with missing outcome data at day 28.

3.6 Extended Description of Statistical Methods

Statistical Analysis

Primary analyses were by the intention-to-treat population of all randomised patients in accordance with the allocated intervention. We conducted a chi-square test to derive a two-sided p-value for the main analysis of the primary outcome. We used logistic regression to derive odds ratios with 95% confidence intervals. In addition, we derived differences in proportions and 95% confidence interval from logistic regression using the observed risk of the primary outcome in the control group,⁵ and from a binomial model with identity link.

We conducted subgroup analyses accompanied by tests of interaction for the following variables: age, sex, BMI, time from COVID-19 symptom onset, diabetes mellitus, coronary artery disease, hypertension and race/ethnicity. Logistic regression and linear regression were used to analyse binary and continuous secondary outcomes after adjustment for age (used for stratification of randomization).

Secondary outcomes were exploratory and were not adjusted for multiple comparisons. A per-protocol analysis of the primary outcome was restricted to the per-protocol population of participants, defined as those who received experimental or control intervention as allocated during the first 48 hours after randomization.

If an outcome was missing in more than 5% of the patients, in addition to the pre-planned strategy of assuming no outcome if patients were discharged alive from hospital before 28 days, a complete case analysis, an inverse probability weighted analysis and multiple imputation on outcome was also conducted.

The statistical analysis plan was finalized prior to study closure without prior inspection of the data. All analyses were conducted in R version 3.6.2 and/or Stata version 15.1, or higher.

Interim Analysis

Interim analyses were done when approximately 25% and 75% of the originally planned number of participants reached determination of the primary outcome. A group sequential design was employed that applied a one-sided boundary. The boundary was based on a Hwang-Shih-DeCani spending function for efficacy. When approximately 75% of the originally planned number of participants reached determination of the primary endpoint, we performed a conditional power analysis.

If the conditional power given the accumulated data was <30% and there was robust evidence of harm – either a relevant increase in the risk of major bleeding in the experimental group and the lower limit of the 95% confidence interval for major bleeding excluded 5% on an absolute risk difference scale; or a relevant increase in the risk of all-cause death in the experimental group and the lower limit of the 95% confidence interval for death excluded 1% on an absolute risk difference scale - the protocol called for a non-binding recommendation to stop the trial by the Data and Safety Monitoring Board (DSMB). If the conditional power was <30%, but there was no robust evidence of harm, the protocol called for completing recruitment as planned. The rationale for this approach was that prevention of death (a component of the primary outcome) overrides short-term safety. If major bleeds led to bleeding related deaths to such an extent that no mortality benefit was likely to be realized, the trial would have been stopped. If the conditional power was ≥ 30 and <60%, the protocol called for completing recruitment as planned. If the conditional power was ≥ 60 and <80%, the protocol called for a non-binding recommendation to increase the sample size to achieve 80% power, if deemed feasible from a recruitment perspective. If the conditional power was ≥ 80 %, the protocol called for completing recruitment as planned, provided that the interim analysis against the one-sided boundary for efficacy was negative.

3.7 Adjudication

Outcomes were independently and blindly adjudicated by two clinical content experts for the English language source documentation, and two clinical content experts for the Portuguese source documentation from the Brazilian site.

The adjudicators reviewed de-identified and treatment allocation redacted, source documentation (e.g. clinical notes, discharge summary, diagnostic imaging, laboratory tests, autopsy reports etc.) to confirm the presence of clinical events specified in the protocol, and the date of occurrence for the following:

- 1) ISTH-defined major bleeding

- 2) Heparin induced thrombocytopenia (HIT)
- 3) Venous thromboembolism
- 4) Arterial thromboembolism
- 5) Mechanical ventilation, including whether invasive or non-invasive
- 6) Intensive care unit admission
- 7) Death, including cause of death

Each clinical event was reviewed in duplicate by two independent adjudicators who determined whether the event met the pre-specified criteria (per definitions in the protocol). The events were classified as a "Definite Event", "Probable Event" or "Not an Event" (see adjudication table from the adjudication manual below). The final adjudication result was based on consensus. If there was disagreement between the two adjudicators the medical monitors broke the tie. Additional source documentation could be requested.

Adjudication Checklist:

Adjudicator to complete:

Definite Event

Probable Event

Not an Event

If major hemorrhage, indicate which criterion of the ISTH definition was met:

1. Fatal bleeding, and/or
2. Symptomatic bleeding in critical area or organ (such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome, and/or
3. Bleeding causing a fall of hemoglobin level of 20g/L or more, or leading to transfusion of two or more units of whole blood or red cells.

If HIT, indicate if laboratory test proven Yes / No and if accompanied by a thrombotic event

Yes / No

If ATE, indicate if suspected ATE OR diagnostically confirmed ATE

If ATE, indicate type: ischemic stroke OR MI, OR limb ischemia OR other _____

If VTE, indicate if suspected VTE OR diagnostically confirmed VTE

If VTE, indicate if symptomatic VTE OR asymptomatic VTE OR unclear

If VTE, indicate type: PE OR DVT OR splanchnic VT OR cerebral VT OR other _____

If PE: indicate if segmental/beyond OR subsegmental

If DVT: indicate if proximal (above knee) OR distal (below knee)

If ICU admission, Yes, patient was admitted OR No, patient was not admitted OR unclear

If yes, indicate rationale for transfer to ICU _____ OR unclear

If mechanically ventilated, indicate if non-invasive OR invasive

If patient died, indicate cause of death: _____ OR unclear

Adjudicator signature + date: _____

Adjudication Manual

EVENT TYPE	INFORMATION NEEDED	DOCUMENTS REQUIRED (EXAMPLES)
Death	<input type="checkbox"/> Date of death <input type="checkbox"/> Cause of death	Medical notes, death certificate, discharge summary
ICU admission	<input type="checkbox"/> Date of transfer to ICU <input type="checkbox"/> Rationale for transfer	Medical notes, medical orders
Invasive Mechanical ventilation	<input type="checkbox"/> Stat date of invasive mechanical ventilation (i.e. endotracheal intubation with mechanical ventilation) <input type="checkbox"/> Rationale for invasive mechanical ventilation (e.g. hypoxemic respiratory failure, airway protection due to compromised neurologic status) <input type="checkbox"/> Max FiO ₂ (e.g. 0.80 or 80%) <input type="checkbox"/> Stop date (if applicable)	Medical notes, medical orders, respiratory therapy notes Diagnostic imaging: Chest Xray indicating placement of endotracheal tube
Noninvasive Mechanical Ventilation (Positive pressure ventilation)	<input type="checkbox"/> Start date <input type="checkbox"/> BIPAP or CPAP <input type="checkbox"/> Rationale for noninvasive mechanical ventilation (e.g. hypoxemic respiratory failure) <input type="checkbox"/> Max FiO ₂ (e.g. 0.80 or 80%) <input type="checkbox"/> Stop date (if applicable)	Medical notes, medical orders, respiratory therapy notes, nursing notes
Major bleeding*	<input type="checkbox"/> Date of onset <input type="checkbox"/> Date of resolution (if applicable) <input type="checkbox"/> Transfusion (# of red cell units and date transfused) <input type="checkbox"/> Location of bleed in critical area or organ (e.g. intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial, or intramuscular with compartment syndrome) <input type="checkbox"/> Fatal bleeding (yes or no) <input type="checkbox"/> Fall in hemoglobin by ≥ 20 g/L	Medical notes, medical orders, nursing notes (e.g. transfusion order/nursing documentation of transfusion administration), surgical note (if applicable) Lab result: fall in hemoglobin by ≥ 20 g/L (if applicable) Diagnostic imaging reports (if available): CT, MRI, Ultrasound report
Heparin-induced thrombocytopenia	<input type="checkbox"/> Date of onset <input type="checkbox"/> Date of resolution (if applicable) <input type="checkbox"/> Laboratory confirmation of heparin-induced thrombocytopenia <input type="checkbox"/> Evidence of secondary thromboembolism (if applicable) <input type="checkbox"/> Treatment given (medication order)	Medical notes, medical orders Lab results: <ul style="list-style-type: none"> - 5-day trend of platelet count <u>AND</u> - Immunologic based assay (ELISA or LIA) assay evaluating for heparin-PF4 antibodies and/or Serotonin release assay Diagnostic imaging (per venous thromboembolism and arterial thromboembolism categories below if patient experienced secondary thromboembolism)

Venous thromboembolism	<input type="checkbox"/> Date of onset <input type="checkbox"/> Date of resolution (if applicable) <input type="checkbox"/> Type (PE, DVT, splanchnic vein thrombosis, cerebral vein thrombosis, or other) <ul style="list-style-type: none"> ○ If PE: segmental/beyond or subsegmental ○ If DVT: distal (below knee) or proximal (above knee) <input type="checkbox"/> Symptomatic or asymptomatic <input type="checkbox"/> Suspected or confirmed <input type="checkbox"/> Treatment given (medication order)	Medical notes, medical orders Lab result: D-dimer (if available) from date of onset Diagnostic imaging reports (if available): CT, Doppler Ultrasound, MRI, ventilation/perfusion lung scan
Arterial thromboembolism	<input type="checkbox"/> Date of onset <input type="checkbox"/> Date of resolution (if applicable) <input type="checkbox"/> Type (ischemic stroke, MI, or limb ischemia, other) <input type="checkbox"/> Suspected or confirmed <input type="checkbox"/> Treatment given (medication order)	Medical notes, medical orders Lab results (if available) from date of onset: <ul style="list-style-type: none"> - Troponin - Lactate (venous or arterial) Diagnostic imaging reports (if available): Doppler ultrasound, ultrasound, angiogram, ECG, CT, MRI, echocardiogram
Organ Support via High-Flow Nasal Cannula	<input type="checkbox"/> Start date <input type="checkbox"/> Stop date (if applicable) <input type="checkbox"/> Max O2 flow rate (should be >30 L/min to qualify, per our trial definition, as HFNC) <input type="checkbox"/> Max FiO2 value (e.g. 0.80 or 80%)	Medical notes, respiratory therapy notes, nursing notes
Organ Support via Vasopressor/Inotropic therapy	<input type="checkbox"/> Start date <input type="checkbox"/> Stop date (if applicable) <input type="checkbox"/> Vasopressor/inotrope examples: <ul style="list-style-type: none"> ▪ Norepinephrine (Levophed, Levo) ▪ Epinephrine (Epi) ▪ Vasopressin (Vaso) ▪ Dopamine (Dop) ▪ Dobutamine (Dobu) 	Medical notes, nursing notes, medical orders

*Major bleeding defined by ISTH Scientific and Standardization Committee (ISTH-SSC) recommendation:

- 1) Fatal bleeding, and/or
- 2) symptomatic bleeding in critical area or organ (such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome, and/or
- 3) bleeding causing a fall of hemoglobin level of 20g/L or more, or leading to transfusion of two or more units of whole blood or red cells.

3.8 Data and Safety Monitoring Board

The DSMB acted in an advisory capacity to the principal investigators to monitor participant safety, data quality and evaluate the progress of the trial. The DSMB was composed of a biostatistician, a hematologist, a general internist and an intensive care specialist. The four members were not study investigators. The DSMB convened meetings at the formal interim analyses mentioned above (section 3.6), and also when approximately 10% and 50% of the originally planned number of participants reached determination of the primary outcome. When 10%, 25% and 50% of the originally planned number of participants reached determination of the primary outcome, this recommendation was at the discretion of the DSMB. When approximately 75% of the originally planned number of participants reached determination of the primary outcome, the DSMB was required to also take into account the conditional power when doing the safety review. The recommendations were made by a formal majority vote based on safety concerns as evidenced by statistical and clinical judgment, progress of the trial including data quality and

accrual/retention, and new scientific or therapeutic developments that may have an impact on the safety. The DSMB was immediately informed of any serious adverse events (SAEs) which were potentially study drug related. Moreover, the DSMB chair was notified within 24 hours of any major bleed or occurrence of heparin induced thrombocytopenia. The Data Management and Coordination Center (DMCC) was responsible for the data analysis and the DMCC statistician provided the interface with DSMB members. The DSMB received reports of enrollment and events, including events as reported by the site and had full access to the data.

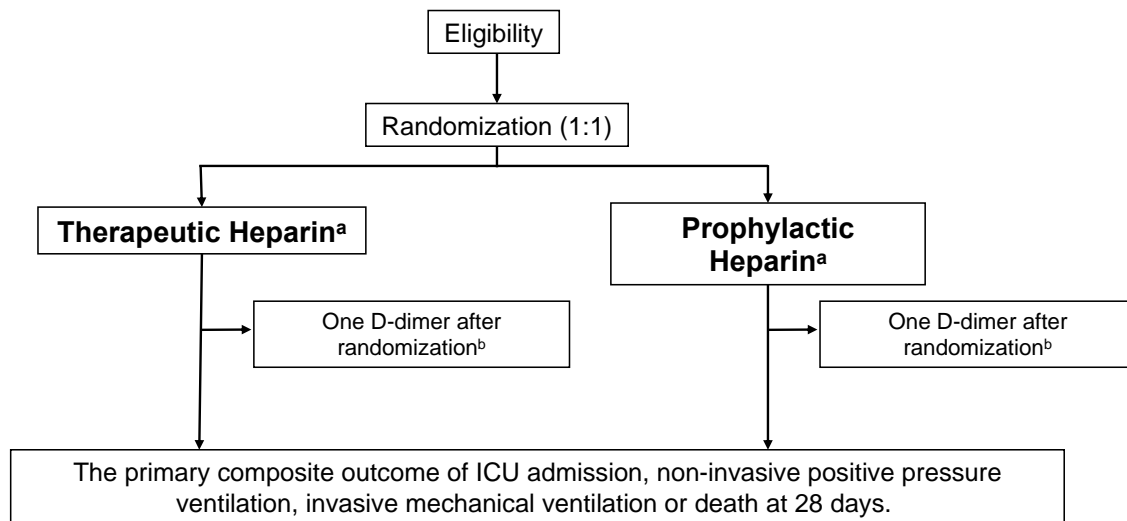
3.9 Trial Administration

Protocols in English (NCT04362085) and Portuguese (NCT04444700) were harmonized in all aspects, except for an initial material difference in eligibility criteria: between July 3, 2020, and October 22, 2020, patients in the single Brazilian site of the trial were eligible if they had normal D-Dimer levels, but an oxygen saturation of $\leq 93\%$ on room air. This led to the initial inclusion of 11 patients in Brazil with normal D-Dimer levels at baseline. These patients were included in the intention-to-treat analysis. From October 23, 2020 onwards, protocols were fully harmonized, requiring elevated D-Dimer levels at baseline in all patients. Data from all sites, including the site in Brazil, were entered in a common database and managed centrally by the trial's data coordination centre (Applied Health Research Centre, St. Michael's Hospital, University of Toronto) according to a single set of standard operating procedures.

The original protocol of RAPID BRAZIL initially approved on June 17, 2020 by the Institutional Research Ethics Board and Brazilian National Research Ethics Commission is version 3.0. All subsequent versions were anchored from version 3.0. The latest version of the protocol is version 5.2 approved on April 13, 2021.

4. Supplementary Figures and Tables

Figure S1. Trial Schematic



^aAdministered until hospital discharge, death or day 28, if the patient is admitted to the ICU or required ventilatory support, we recommended continuation of the allocated treatment as long as the treating physician was in agreement.

^bA single D-dimer test (if not collected through standard of care) on day 2 after randomization (± 24 hours) was collected for participants in both study arms (considering the day of randomization as day 1).

Table S1. Recruitment Numbers By Site

Country and Name of Site	Therapeutic Heparin (N=228)	Prophylactic Heparin (N=237)
	no. of patients (%)	
Brazil		
Hospital das Clinicas HCFMUSP	54 (23.7)	51 (21.5)
Canada		
Hôpital Charles Lemoyne	15 (6.6)	18 (7.6)
William Osler Health System ^a	15 (6.6)	15 (6.3)
Mount Sinai Hospital	7 (3.1)	9 (3.8)
Trillium Health Partners ^a	7 (3.1)	7 (3.0)
St. Joseph's Health Centre Toronto	7 (3.1)	7 (3.0)
Alberta Health Services ^a	7 (3.1)	7 (3.0)
The Ottawa Hospital ^a	5 (2.2)	5 (2.1)
Hôpital du Sacré-Coeur de Montréal	2 (0.9)	4 (1.7)
Michael Garron Hospital	3 (1.3)	2 (0.8)
St. Michael's Hospital	3 (1.3)	1 (0.4)
University of Alberta Hospital	0 (0.0)	2 (0.8)
Southlake Regional Health Centre	1 (0.4)	0 (0.0)
Hospital Maisonneuve-Rosemont	0 (0.0)	1 (0.4)
Queen Elizabeth II Health Sciences Centre	0 (0.0)	0 (0.0)
Ireland		
Mater Misericordiae University Hospital	11 (4.8)	12 (5.1)
Saudi Arabia		
King Saud University Medical City	29 (12.7)	31 (13.1)
King Fahad Medical City	28 (12.3)	28 (11.8)
King Faisal Specialist Hospital	14 (6.1)	17 (7.2)
United Arab Emirates		
Al Ain Hospital	7 (3.1)	6 (2.5)
United States of America		
Versiti	12 (5.3)	13 (5.5)
University of Vermont Medical Center	1 (0.4)	1 (0.4)
Barnes Jewish Hospital	0 (0.0)	0 (0.0)

^aSome RAPID trial sites include multiple hospitals. There were 28 total recruiting sites.

Table S2. Means and Medians and Measures of Dispersion of Continuous Baseline Characteristics

Characteristic	Therapeutic Heparin (N=228)	Prophylactic Heparin (N=237)
Age (years)		
Mean (SD)	60.4 (14.1)	59.6 (15.5)
Median (IQR)	60.0 (51.8, 70.0)	60.0 (49.0, 70.0)
Body mass index (kg/m ²) ^a		
Mean (SD)	30.3 (6.4)	30.2 (7.0)
Median (IQR)	28.8 (25.8, 33.1)	29.3 (25.8, 33.0)
Duration of symptoms prior to hospitalization (days) ^b		
Mean (SD)	7.1 (5.1)	7.1 (5.2)
Median (IQR)	7.0 (3.0, 10.0)	7.0 (3.0, 10.0)
Duration of hospitalization before randomization (days)		
Mean (SD)	1.5 (1.1)	1.4 (1.0)
Median (IQR)	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)
Platelet count (10 ⁹ /L) ^c		
Mean (SD)	233.7 (95.7)	237.8 (95.3)
Median (IQR)	220.5 (169.0, 276.0)	221.0 (171.0, 288.0)
Creatinine (μmol/L) ^d		
Mean (SD)	84.6 (44.1)	85.9 (58.2)
Median (IQR)	77.0 (64.0, 91.0)	75.1 (62.2, 94.6)
D-dimer ratio (D-dimer x ULN)		
Geometric mean (SD) ^e	2.1 (0.7)	2.5 (0.9)
Median (IQR)	2.0 (1.4, 2.9)	2.0 (1.4, 3.4)

Abbreviations: IQR, interquartile range; SD, standard deviation; ULN, upper limit of normal.

^aBody-mass index (BMI) is the weight in kilograms divided by the square of the height in meters; Data regarding BMI was missing for 6 participants in the therapeutic heparin group and 4 participants in the prophylactic heparin group.

^bData regarding duration of symptoms prior to hospitalization were missing for 1 patient in the therapeutic heparin group and 5 for the prophylactic heparin group.

^cData regarding platelet count was missing for 16 patients in the therapeutic heparin group and 24 patients in the prophylactic heparin group.

^dData regarding creatinine was missing for 14 patients in the therapeutic heparin group and 23 patients in the prophylactic heparin group.

^eSD for the natural logarithm of D-dimer ratios (D-dimer levels x ULN).

Table S3. Duration and Type of Heparin Used

Heparin	Therapeutic Heparin	Prophylactic Heparin
	(N=228)	(N=237)
	no. of patients (%)	
Duration of anticoagulation (days) ^a		
Mean (SD)	6.5 (5.4)	6.3 (5.4)
Median (IQR)	6.0 (3.0, 8.0)	5.0 (3.0, 8.0)
Dalteparin	25 (11.0)	25 (10.5)
Enoxaparin	188 (82.5)	183 (77.2)
Fondaparinux	0 (0.0)	1 (0.4)
Tinzaparin	11 (4.8)	13 (5.5)
Unfractionated heparin	3 (1.3)	14 (5.9)

Abbreviations: SD, standard deviation. IQR, interquartile range.

^aData on the duration of anticoagulation were missing for 4 patients in the therapeutic heparin group and 5 patients in the prophylactic heparin group.

Table S4. Concomitant Treatments Received

	Therapeutic Heparin		Prophylactic Heparin	
	No Death (N=224)	Death (N=4)	No Death (N=219)	Death (N=18)
	no. of patients (%)			
Systemic Corticosteroid	172 (76.8)	3 (75.0)	167 (76.3)	14 (77.8)
Remdesivir	30 (13.4)	1 (25.0)	27 (12.3)	3 (16.7)
Tocilizumab	10 (4.5)	0 (0.0)	11 (5.0)	2 (11.1)

Treatments received over course of study duration, pre- and post-randomization combined. See Table 1 for medication use at baseline.

Table S5. Means and Medians and Measures of Dispersion of Continuous Outcomes

Outcome	Therapeutic Heparin (N=228)	Prophylactic Heparin (N=237)	Odds Ratio or Ratio of Geometric Means (95% CI)	P value
Ventilator-free days alive (days)				
Mean (SD)	26.5 (5.6)	24.7 (8.5)	1.77 (1.02, 3.08)	0.042
Median (IQR)	28.0 (28.0, 28.0)	28.0 (28.0, 28.0)		
Organ support-free days alive (days)				
Mean (SD)	25.8 (6.2)	24.1 (8.8)	1.41 (0.90, 2.21)	0.13
Median (IQR)	28.0 (28.0, 28.0)	28.0 (28.0, 28.0)		
ICU-free days alive (days)				
Mean (SD)	26.0 (6.1)	24.2 (8.8)	1.51 (0.94, 2.41)	0.087
Median (IQR)	28.0 (28.0, 28.0)	28.0 (28.0, 28.0)		
Hospital-free days alive (days)				
Mean (SD)	19.8 (7.3)	18.4 (9.2)	1.09 (0.79, 1.50)	0.59
Median (IQR)	22.0 (18.0, 25.0)	22.0 (18.0, 25.0)		
D-dimer ratio (D-dimer x ULN)				
Geometric mean (SD) ^a	1.9 (0.7)	2.4 (0.9)	0.88 (0.78, 0.99)	0.032
Median (IQR)	1.8 (1.3, 2.6)	2.0 (1.2, 3.6)		

Abbreviations: IQR, interquartile range; SD, standard deviation; ULN, upper limit of normal.

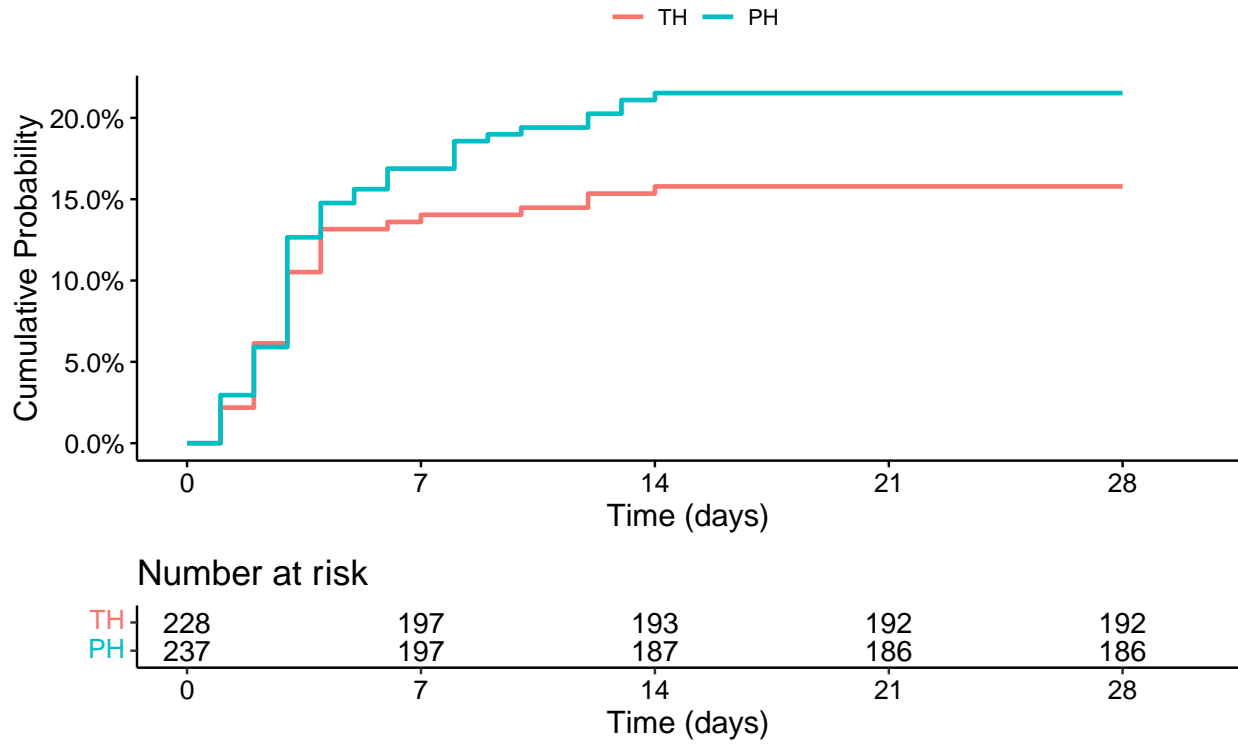
^aRatio of geometric means of D-dimer ratios (D-dimer x ULN) of day 2±24h post-randomization, adjusted for baseline geometric means of D-dimer ratios using analysis of covariance. SD for the natural logarithm of D-dimer ratios. The day 2±24 hours D-dimer was missing for 66 in the therapeutic heparin group and 64 in the prophylactic heparin group.

Table S6. Primary Cause of Death

Cause	Therapeutic Heparin	Prophylactic Heparin
	(N=228)	(N=237)
	no. of patients (%)	
Hypoxemic respiratory failure	4 (100.0)	13 (72.2)
Multi-system organ failure	0 (0.0)	5 (27.8)

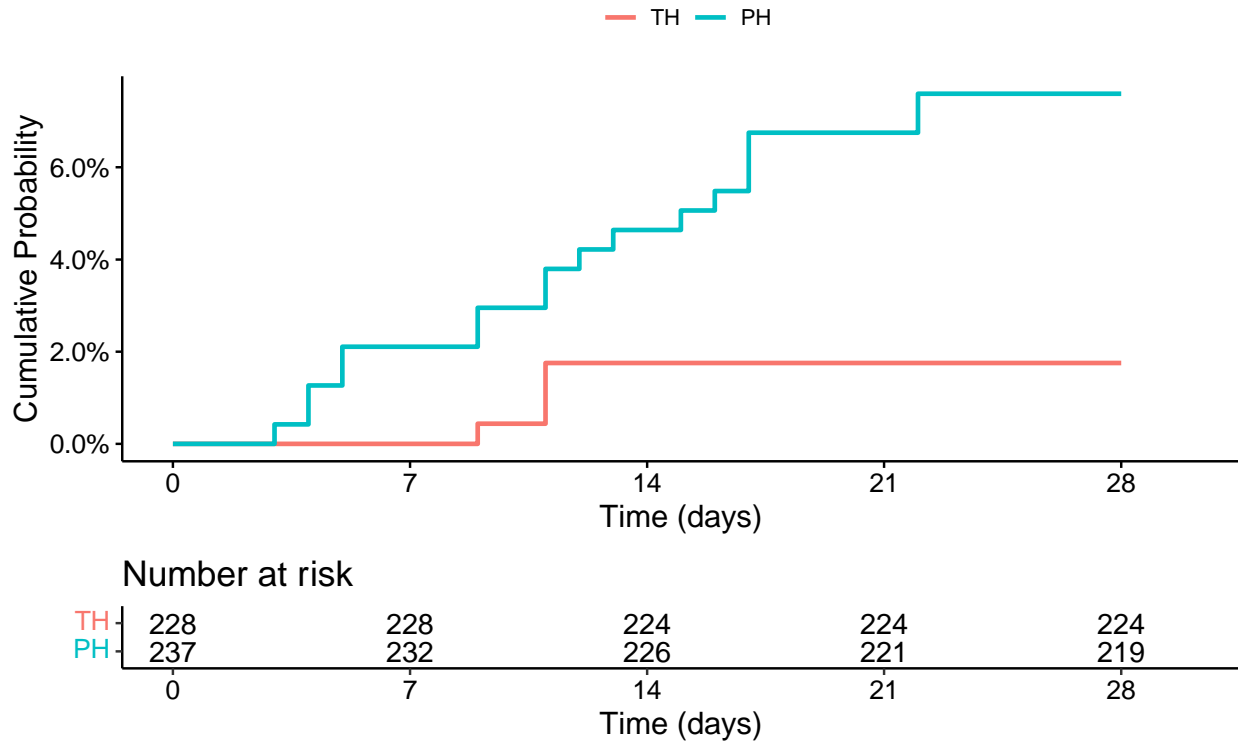
There were no cases of sudden, unexplained death.

Figure S2. Time-to-event Analyses of the Primary Composite Outcome



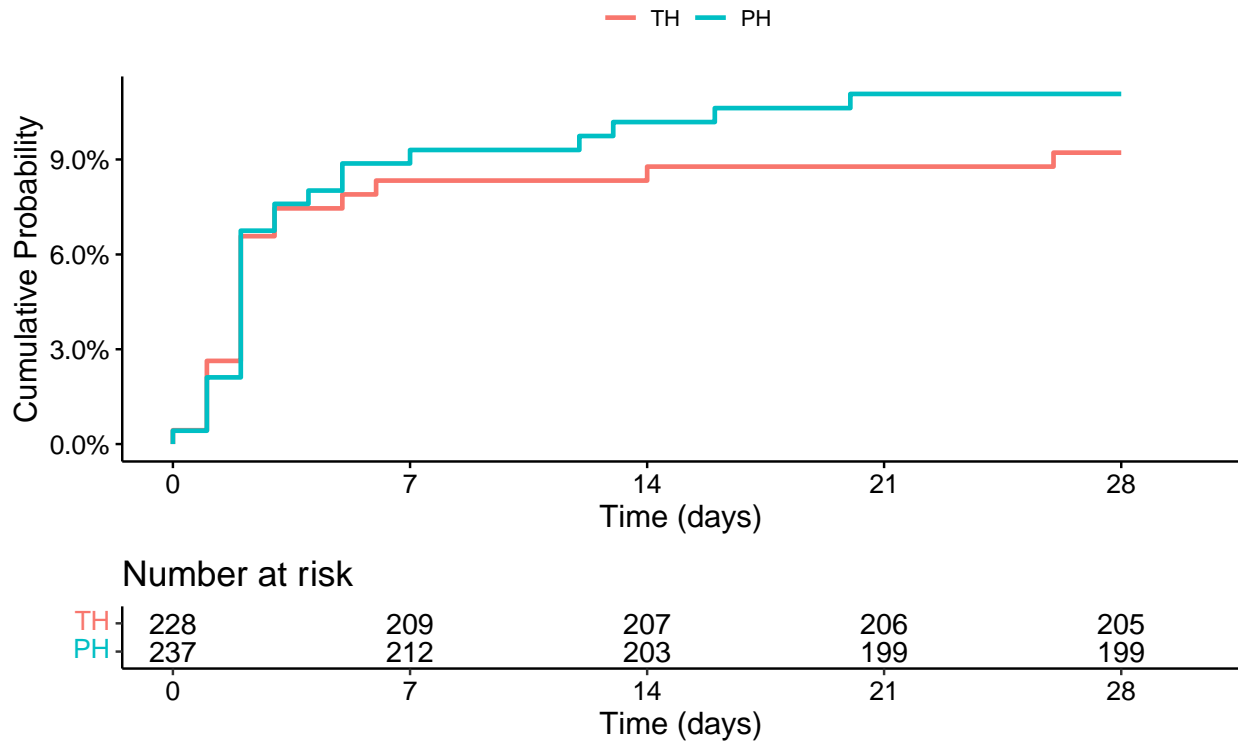
The hazard ratio comparing therapeutic with prophylactic heparin was 0.72 (95% confidence interval, 0.47 to 1.10).
 Abbreviations: TH, therapeutic heparin. PH, prophylactic heparin. Primary composite outcome defined as death, invasive mechanical ventilation, non-invasive (bilevel or continuous positive airway pressure) mechanical ventilation or ICU admission. Cumulative primary composite outcome curves through 28 days in the two study groups.

Figure S3. Time-to-event Analyses of All-cause Death



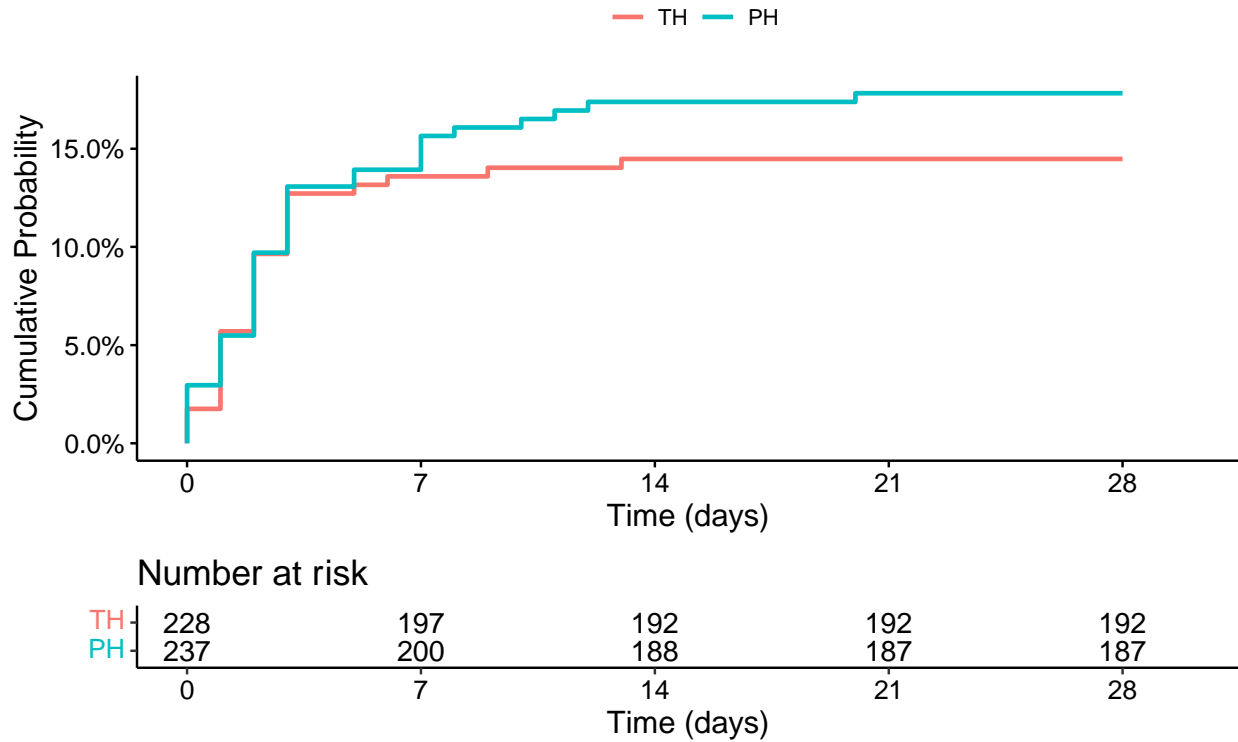
The hazard ratio comparing therapeutic with prophylactic heparin was 0.23 (95% confidence interval, 0.08 to 0.66).
 Abbreviations: TH, therapeutic heparin. PH, prophylactic heparin. Cumulative all-cause death curves through 28 days in the two study groups.

Figure S4. Time-to-event Analyses of Mechanical Ventilation



The hazard ratio comparing therapeutic with prophylactic heparin 0.83 (95% confidence interval, 0.47 to 1.48).
 Abbreviations: TH, therapeutic heparin. PH, prophylactic heparin. Cumulative invasive or non-invasive (bilevel or continuous positive airway pressure) mechanical ventilation curves through 28 days in the two study groups.

Figure S5. Time-to-event Analyses of Intensive Care Unit Admission



The hazard ratio comparing therapeutic with prophylactic heparin 0.81 (95% confidence interval, 0.51 to 1.28). Abbreviations: TH, therapeutic heparin. PH, prophylactic heparin. Cumulative ICU admission curves through 28 days in the two study groups.

Table S7. Thromboembolism

Event	Therapeutic Heparin (N=228) no. of patients (%)	Prophylactic Heparin (N=237)
Venous		
Deep vein thrombosis ^a	1 (0.4)	1 (0.4)
Pulmonary embolism ^b	1 (0.4)	5 (2.1)
Arterial		
Myocardial infarction	0 (0.0)	1 (0.4)

^a1 patient in the therapeutic heparin group (symptomatic, diagnostically confirmed, proximal deep vein), 1 patient in the prophylactic heparin group (incidental deep venous thrombosis, diagnostically confirmed, proximal deep vein).

^b1 patient in the therapeutic heparin group (symptomatic, diagnostically confirmed, segmental pulmonary artery or beyond), 5 patients in the prophylactic heparin group (all symptomatic, all diagnostically confirmed, 4 segmental pulmonary artery or beyond, 1 sub-segmental pulmonary artery).

Table S8. ISTH Major Bleeding Events

	Randomised treatment allocation	Anticoagulation received 24 hours prior to event	Fatal bleeding	Symptomatic bleeding in critical area or organ ^a	Bleeding causing a fall of hemoglobin of 20g/L or more	Bleeding leading to transfusion of two or more units of whole blood or red cells	Relatedness ^b	Concomitant medications
Patient 1	Therapeutic Heparin	Therapeutic dose LMWH	No	Intramuscular	Yes	Yes	Not related	Systemic corticosteroid
Patient 2	Therapeutic Heparin	Prophylactic dose LMWH	No	No	Yes	Yes	Unlikely	Systemic corticosteroid, Antiplatelet agent
Patient 3	Prophylactic Heparin	Intermediate dose LMWH	No	No	Yes	Yes	Unlikely	Systemic corticosteroid
Patient 4	Prophylactic Heparin	Prophylactic dose LMWH	No	No	Yes	Yes	Unlikely	Systemic corticosteroid, Antiplatelet agent
Patient 5	Prophylactic Heparin	Prophylactic dose LMWH	No	Retroperitoneal	Yes	Yes	Probable	Antiplatelet agent
Patient 6	Prophylactic Heparin	None*	No	No	Yes	Yes	Unlikely	Systemic corticosteroid

Major bleeding defined by the International Society on Thrombosis and Haemostasis (ISTH) Scientific and Standardization Committee.¹; LMWH = low molecular weight heparin.

^aAll non-critical area/organ bleeding events were gastrointestinal in origin.

^bRelatedness was independently and blindly adjudicated.

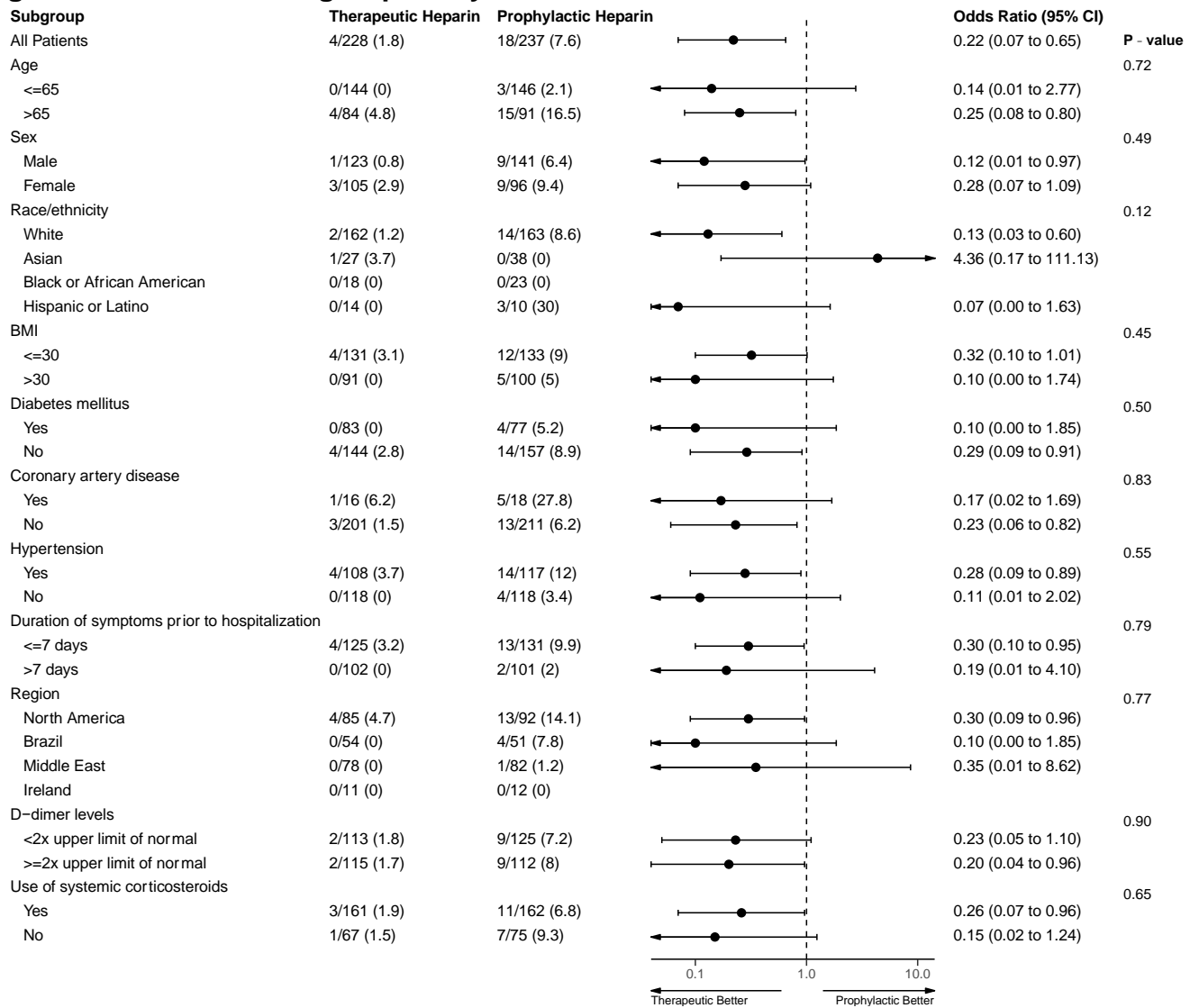
*This event occurred 11 days post-hospital discharge.

Table S9. Bleeding Events by Concomitant Treatments Received

	Therapeutic Heparin	Prophylactic Heparin
	no. of patients (%)	
Major Bleeding	2	4
Systemic corticosteroid only	2 (100.0)	2 (50.0)
Antiplatelet agent only	0 (0.0)	1 (25.0)
Antiplatelet and systemic corticosteroid	0 (0.0)	1 (25.0)
No antiplatelet and systemic corticosteroid	0 (0.0)	0 (0.0)
No major bleeding	226	233
Systemic corticosteroid only	125 (55.3)	129 (55.4)
Antiplatelet agent only	8 (3.5)	13 (5.6)
Antiplatelet and systemic corticosteroid	25 (11.1)	24 (10.3)
No antiplatelet and systemic corticosteroid	68 (30.1)	67 (28.8)

Major bleeding defined by the International Society on Thrombosis and Haemostasis Scientific and Standardization Committee.¹

Figure S6. Post-Hoc Subgroup Analysis of All-Cause Death



Subgroup-specific odds ratios derived from logistic regression. Point estimates are plotted as dark circles; the horizontal lines represent the 95% confidence intervals. Odds ratio less than 1.0 favors therapeutic heparin. BMI, body mass index in kg/m².

Table S10. Per Protocol Analysis of the Primary Outcome and Its Components

Outcome	Therapeutic Heparin (N=216) no. of patients (%)	Prophylactic Heparin (N=227) no. of patients (%)	Odds Ratio (95% CI)
Primary Composite Outcome ^a	34 (15.7)	47 (20.7)	0.72 (0.44, 1.17)
Components of the primary composite outcome			
Death from any cause	4 (1.9)	17 (7.5)	0.23 (0.08, 0.71)
Invasive mechanical ventilation	9 (4.2)	13 (5.7)	0.72 (0.30, 1.71)
Any mechanical ventilation ^b	18 (8.3)	22 (9.7)	0.85 (0.44, 1.63)
Intensive care unit admission	30 (13.9)	37 (16.3)	0.83 (0.49, 1.40)

Per protocol analysis excluded patients who did not receive their allocated treatment during the first 48 hours after randomization.

^aDefined as death, invasive mechanical ventilation, non-invasive mechanical ventilation or ICU admission.

^bInvasive or non-invasive (bilevel or continuous positive airway pressure) mechanical ventilation.

Table S11. Sensitivity Analysis 1 of the Primary Outcome and Its Components

Outcome	Therapeutic Heparin (N=224) no. of patients (%)	Prophylactic Heparin (N=230) no. of patients (%)	Odds Ratio (95% CI)
Primary Composite Outcome ^a	37 (16.5)	52 (22.6)	0.68 (0.42, 1.08)
Components of the primary composite outcome			
Death from any cause	4 (1.8)	18 (7.8)	0.21 (0.07, 0.64)
Invasive mechanical ventilation	11 (4.9)	16 (7.0)	0.69 (0.31, 1.53)
Any mechanical ventilation ^b	21 (9.4)	26 (11.3)	0.81 (0.44, 1.49)
Intensive care unit admission	33 (14.7)	42 (18.3)	0.77 (0.47, 1.27)

Sensitivity analysis 1 excluded patients who did not meet a component of the primary composite outcome and did not have a follow-up up to day 28; 4 patients in therapeutic heparin group and 7 patients in the prophylactic heparin group.

^aDefined as death, invasive mechanical ventilation, non-invasive mechanical ventilation or ICU admission.

^bInvasive or non-invasive (bilevel or continuous positive airway pressure) mechanical ventilation.

Table S12. Sensitivity Analysis 2 of the Primary Outcome and Its Components

Outcome	Therapeutic Heparin	Prophylactic Heparin	Odds Ratio (95% CI)
	(N=222) no. of patients (%)	(N=231)	
Primary Composite Outcome ^a	36 (16.2)	48 (20.8)	0.74 (0.46, 1.19)
Components of the primary composite outcome			
Death from any cause	4 (1.8)	17 (7.4)	0.23 (0.08, 0.70)
Invasive mechanical ventilation	10 (4.5)	14 (6.1)	0.73 (0.32, 1.69)
Any mechanical ventilation ^b	20 (9.0)	23 (10.0)	0.90 (0.48, 1.68)
Intensive care unit admission	32 (14.4)	39 (16.9)	0.83 (0.50, 1.38)

Sensitivity analysis 2 excluded those who did not satisfy all eligibility criteria (i.e. those with a negative d-dimer; 6 patients in the therapeutic heparin group and 5 in the prophylactic heparin group).

^aDefined as death, invasive mechanical ventilation, non-invasive mechanical ventilation or ICU admission.

^bInvasive or non-invasive (bilevel or continuous positive airway pressure) mechanical ventilation.

Table S13. Sensitivity Analysis 3 of the Primary Outcome and Its Components

Outcome	Therapeutic Heparin	Prophylactic Heparin	Odds Ratio (95% CI)
	(N=218)	(N=224)	
	no. of patients (%)		
Primary Composite Outcome ^a	36 (16.5)	48 (21.4)	0.73 (0.45, 1.17)
Components of the primary composite outcome			
Death from any cause	4 (1.8)	17 (7.6)	0.23 (0.08, 0.69)
Invasive mechanical ventilation	10 (4.6)	14 (6.2)	0.72 (0.31, 1.66)
Any mechanical ventilation ^b	20 (9.2)	23 (10.3)	0.88 (0.47, 1.66)
Intensive care unit admission	32 (14.7)	39 (17.4)	0.82 (0.49, 1.36)

Sensitivity analysis 3 excluded patients who did not meet a component of the primary composite outcome, did not have a follow-up up to day 28 and those who did not satisfy all eligibility criteria; 10 patients in the therapeutic heparin group and 13 patients in the prophylactic heparin group.

^aDefined as death, invasive mechanical ventilation, non-invasive mechanical ventilation or ICU admission.

^bInvasive or non-invasive (bilevel or continuous positive airway pressure) mechanical ventilation.

Table S14. Intention-to-Treat Analysis of the Primary Outcome and Its Components Adjusted for Age

Outcome	Therapeutic Heparin	Prophylactic Heparin	Odds Ratio (95% CI)
	(N=228)	(N=237)	
	no. of patients (%)		
Primary Composite Outcome ^a	37 (16.2)	52 (21.9)	0.68 (0.42, 1.08)
Components of the primary composite outcome			
Death from any cause	4 (1.8)	18 (7.6)	0.19 (0.06, 0.61)
Invasive mechanical ventilation	11 (4.8)	16 (6.8)	0.69 (0.31, 1.53)
Any mechanical ventilation ^b	21 (9.2)	26 (11.0)	0.82 (0.45, 1.50)
Intensive care unit admission	33 (14.5)	42 (17.7)	0.78 (0.47, 1.29)

Intention-to-treat analysis of the primary outcome and its components adjusted for age taking into account that randomization was stratified by age.

^aDefined as death, invasive mechanical ventilation, non-invasive mechanical ventilation or ICU admission.

^bInvasive or non-invasive (bilevel or continuous positive airway pressure) mechanical ventilation.

Table S15. Intention-to-Treat Analysis of the Primary Outcome with Time-by-Treatment Interaction

Analysis	Therapeutic Heparin	Prophylactic Heparin	Odds Ratio (95% CI)
	(N=228)	(N=237)	
	no. of patients (%)		
Primary Analysis	37 (16.2)	52 (21.9)	0.69 (0.43, 1.10)
Analysis adjusted for time	37 (16.2)	52 (21.9)	0.69 (0.43, 1.10)

Intention-to-treat analysis of the primary outcome according to primary analysis and adjusted for time, including a time-by-treatment interaction.

Primary outcome defined as death, invasive mechanical ventilation, non-invasive mechanical ventilation or ICU admission.

To address changes in co-interventions over time due to emerging evidence from Covid-19 clinical trials, a logistic regression model was used to fit a time by treatment interaction where time was days since first randomised subject. Time was modelled with a restricted cubic spline having 3 knots. Three knots were chosen because of the modest number of events.

The model with splines and interactions revealed little evidence for an interaction ($p = 0.85$) or non-linearity ($p = 0.95$). Given these results a linear additive model was fit to estimate the time adjusted treatment effect. In this model there was strong evidence of a time effect ($p=0.0086$) while the evidence for a treatment effect was identical to the unadjusted analysis (p for treatment effect= 0.12).

Table S16. Intention-to-Treat Analysis of the Primary Outcome Estimating Risk Differences

Analysis	Therapeutic Heparin (N=228)	Prophylactic Heparin (N=237)	Risk Difference (95% CI)
	no. of patients (%)		
Estimated from logistic regression	37 (16.2)	52 (21.9)	-5.7% (-11.2%, 1.7%)
Estimated from binomial model	37 (16.2)	52 (21.9)	-5.7% (-12.9%, 1.4%)

Intention-to-treat analysis of the primary outcome estimating risk differences from logistic regression and a binomial model with identity link.

Primary outcome defined as death, invasive mechanical ventilation, non-invasive mechanical ventilation or ICU admission.

The primary outcome was reanalysed with a binary model and identity link to estimate the absolute risk difference. This analysis yielded nearly identical results to the logistic regression and risk difference estimated from that model. The evidence for a treatment effect was similar to the evidence based on logistic regression (p for treatment effect=0.12).

Table S17. Sensitivity Analyses of D-Dimer Levels at Day 2

Analysis	Ratio of Geometric Means (95% CI)
Primary analysis (complete case)	0.88 (0.78, 0.99)
Inverse probability weighted analysis	0.87 (0.78, 0.98)
Multiple Imputation	0.91 (0.81, 1.03)

D-dimer levels at day 2±24 hours post-randomization were missing for 66 (29.0%) in the therapeutic heparin group and 64 (27.0%) in the prophylactic heparin groups. As pre-specified, we therefore used an inverse probability weighted analysis and multiple imputation to derive ratios of geometric means.

Ratio of geometric means of D-dimer level x ULN of day 2±24h post-randomization, adjusted for baseline geometric means of D-dimer levels x ULN using analysis of covariance. SD for the natural logarithm of D-dimer levels x ULN.

Table S18. Study Drug Not Received as Allocated within the First 48 hours

	Therapeutic Heparin (N=228)	Prophylactic Heparin (N=237)
	no. of patients (%)	
Any change	6 (2.6)	5 (2.1)
Discontinued	2 (0.9)	1 (0.4)
Prophylactic	2 (0.9)	-
Intermediate	2 (0.9)	1 (0.4)
Therapeutic	-	3 (1.3)

Study drug not received as allocated defined as not received as allocated within the first 48 hours post randomization or changed without clear clinical indication.

Table S19. Study Drug Change within the First 48 hours With and Without Clear Clinical Indication

	Therapeutic Heparin (N=228)	Prophylactic Heparin (N=237)
	no. of patients (%)	
Clear clinical indication		
Suspected or Confirmed Thromboembolism	0 (0.0)	5 (2.1) ^b
Change in Creatinine Clearance	1 (0.4) ^a	0 (0.0)
Bleeding	1 (0.4) ^a	1 (0.4) ^a
Intensive care unit admission	2 (0.9) ^a	0 (0.0)
Palliative care		1 (0.4) ^a
No clear clinical indication		
Clinician discretion	4 (1.8) ^a	5 (2.1) ^c
Patient refusal	2 (0.9) ^a	0 (0.0)

Heparin dose change lasting over 24 hours within the first 48 hours of study treatment period. ^aHeparin dose decreased or heparin discontinued. ^bHeparin dose increased. ^c3 patients received therapeutic dose heparin, 1 received intermediate dose heparin, 1 had their heparin discontinued.

Table S20. Primary and Secondary Outcomes until Hospital Discharge

Outcome	Therapeutic Heparin	Prophylactic Heparin	Odds Ratio or Ratio of Geometric Means (95% CI)	p value
	(N=228)	(N=237)		
	<i>no. of patients (%)</i>			
Primary composite outcome ^a	36 (15.8)	51 (21.5)	0.68 (0.43, 1.10)	0.11
Components of the primary composite outcome				
Death from any cause	4 (1.8)	17 (7.2)	0.23 (0.08, 0.70)	0.009
Invasive mechanical ventilation	10 (4.4)	15 (6.3)	0.68 (0.30, 1.55)	0.36
Any mechanical ventilation ^b	20 (8.8)	25 (10.5)	0.82 (0.44, 1.52)	0.52
ICU admission	32 (14.0)	41 (17.3)	0.78 (0.47, 1.29)	0.33
Death or any mechanical ventilation	22 (9.6)	37 (15.6)	0.58 (0.33, 1.01)	0.056
Death or ICU admission	35 (15.4)	49 (20.7)	0.70 (0.43, 1.12)	0.14
Renal replacement therapy ^c	1 (0.4)	4 (1.7)	0.26 (0.03, 2.33)	0.23
Thromboembolism ^d				
Venous	2 (0.9)	6 (2.5)	0.34 (0.07, 1.71)	0.19
Arterial	0 (0.0)	1 (0.4)	-	-
Bleeding				
ISTH major bleeding ^e	2 (0.9)	3 (1.3)	0.69 (0.11, 4.19)	1.0
Red blood cell transfusion (≥ 1 unit)	2 (0.9)	8 (3.4)	0.25 (0.05, 1.21)	0.11
Transfusion of other blood components or products ^f	0 (0.0)	0 (0.0)	-	-
Heparin induced thrombocytopenia	0 (0.0)	0 (0.0)	-	-

Abbreviations: ICU, intensive care unit; CI, confidence interval; SD, standard deviation; ISTH, International Society on Thrombosis and Hemostasis.

^aDefined as death, invasive mechanical ventilation, non-invasive mechanical ventilation or ICU admission.

^bInvasive or non-invasive (bilevel or continuous positive airway pressure) mechanical ventilation.

^cContinuous renal replacement therapy or intermittent hemodialysis.

^dAll diagnostically confirmed except for 1 symptomatic deep vein thrombosis in the prophylactic heparin group, which could not be definitively confirmed as diagnostic imaging was not done during acute symptomatic period.

^eMajor bleeding defined by the ISTH Scientific and Standardization Committee

^fTransfusion of platelets, frozen plasma, prothrombin complex concentrate, cryoprecipitate and/or fibrinogen concentrate; 17 patients received convalescent plasma and were not included in the count.

5. References

1. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *Journal of Thrombosis and Haemostasis*. 2005;3(4):692-694. doi:10.1111/j.1538-7836.2005.01204.x
2. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost*. 18(5):1094-1099. doi:10.1111/jth.14817
3. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *The Lancet*. 2020;395(10229):1054-1062. doi:10.1016/S0140-6736(20)30566-3
4. Sholzberg M, Tang GH, Negri E, et al. Coagulopathy of hospitalised COVID-19: A Pragmatic Randomised Controlled Trial of Therapeutic Anticoagulation versus Standard Care as a Rapid Response to the COVID-19 Pandemic (RAPID COVID COAG – RAPID Trial): A structured summary of a study protocol for a randomised controlled trial. *Trials*. 2021;22(1):202. doi:10.1186/s13063-021-05076-0
5. Doi SA, Furuya-Kanamori L, Xu C, Lin L, Chivese T, Thalib L. Questionable utility of the relative risk in clinical research: a call for change to practice. *J Clin Epidemiol*. Published online November 7, 2020. doi:10.1016/j.jclinepi.2020.08.019