



Clinical trial results:

Coagulopathy of COVID-19: A Pragmatic Randomized Controlled Trial of Therapeutic Anticoagulation versus Standard Care as a Rapid Response to the COVID-19 Pandemic (RAPID COVID COAG)

Summary

EudraCT number	2020-002190-10
Trial protocol	IE
Global end of trial date	14 October 2021

Results information

Result version number	v1 (current)
This version publication date	04 October 2022
First version publication date	04 October 2022

Trial information

Trial identification

Sponsor protocol code	UCDCRC/20/03
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04362085
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University College Dublin
Sponsor organisation address	Belfield, Dublin 4, Dublin, Ireland,
Public contact	Clinical Trials Information, University College Dublin, +353 1716 4593, crc.monitoring@ucd.ie
Scientific contact	Clinical Trials Information, University College Dublin, +353 1716 4593, crc.monitoring@ucd.ie

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	09 June 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 May 2021
Global end of trial reached?	Yes
Global end of trial date	14 October 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary Objective:

To determine the effect of therapeutic anticoagulation, with LMWH (enoxaparin sodium), compared to standard care in hospitalized patients admitted for COVID-19 with an elevated D-dimer on the composite outcome of intensive care unit (ICU) admission, non-invasive positive pressure ventilation, invasive mechanical ventilation or death at 28 days.

Protection of trial subjects:

This study was conducted according to Good Clinical Practice and the EU CT Directive 2001/20/EC and GCP Commission Directive 2005/28/EC. All participants or their legal representatives provided written informed consent before undergoing any trial related procedures. Authorized research ethics committees approved the trial at all participating sites.

The global study was monitored by an independent data safety monitoring board (DSMB) including a biostatistician, a hematologist, a general internist and intensive care specialist assigned by the global trial sponsor United Health Toronto – St. Michael's Hospital.

Background therapy: -

Evidence for comparator:

Those allocated to the control arm received prophylactic heparin (LMWH or UFH). 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. Prophylactic dose level was defined based on the best available evidence from clinical trials and expert consensus, and took body mass index and creatinine clearance into consideration.

Actual start date of recruitment	01 February 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Ireland: 23
Country: Number of subjects enrolled	Brazil: 105
Country: Number of subjects enrolled	Canada: 150
Country: Number of subjects enrolled	Saudi Arabia: 147
Country: Number of subjects enrolled	United Arab Emirates: 13
Country: Number of subjects enrolled	United States: 27
Worldwide total number of subjects	465
EEA total number of subjects	23

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	276
From 65 to 84 years	164
85 years and over	25

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 28 sites across 6 countries. From May, 2020 through April, 2021, a total of 3975 patients were screened and 465 were randomized.

Pre-assignment

Screening details:

Participants were adults admitted to hospital wards for Covid-19 with laboratory confirmed SARS-CoV-2 infection and elevated D-dimer within the first 5 days of admission. During screening, conformance with inclusion/exclusion criteria was assessed.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Blinding of participants, clinical research staff, and clinicians was not possible due to the nature of the intervention. However, important clinical outcomes were adjudicated by independent, blinded, clinical content experts.

Arms

Are arms mutually exclusive?	Yes
Arm title	Therapeutic Heparin

Arm description:

Patients allocated to the experimental arm received therapeutic low molecular weight heparin (LMWH) or unfractionated heparin (UFH). UFH, if used in the experimental arm, was administered intravenously using a weight-based nomogram and the activated partial thromboplastin time (aPTT) or UFH anti-Xa titration according to center-specific venous thromboembolism (VTE) treatment protocols.

Arm type	Experimental
Investigational medicinal product name	Low molecular weight heparin (LMWH) or unfractionated heparin (UFH)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection/infusion
Routes of administration	Intravenous use, Subcutaneous use

Dosage and administration details:

Therapeutic heparin was administered until hospital discharge, death, day 28 or study withdrawal.

Choice of LMWH vs UFH was at clinician's discretion and dependent on local institutional supply. LMWH dose regimens were dependent on CrCl (creatinine clearance) and BMI. e.g. for Enoxaparin:

CrCl \geq 30 and BMI <40 1 mg/kg SC q12h OR 1.5 SC mg/kg q24h Enoxaparin

CrCl \geq 30 and BMI \geq 40 1 mg/kg q12h* Enoxaparin

CrCl <30 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

*For BMI above 40, measurement of anti-Xa to confirm therapeutic effect could be used.

UFH, if used in the experimental arm, 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)

Arm title	Prophylactic Heparin
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Arm description:

Subjects allocated to prophylactic heparin (control arm) received dose-capped prophylactic subcutaneous heparin (LMWH or UFH) adjusted for body mass index and creatinine clearance.

Prophylactic dose level was defined based on the best available evidence from clinical trials and expert consensus, and took body mass index and creatinine clearance into consideration.

Arm type	Active comparator
Investigational medicinal product name	Low molecular weight heparin (LMWH), unfractionated heparin (UFH) or fondaparinux
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection/infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

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. Prophylactic dose level was defined based on the best available evidence from clinical trials and expert consensus, and took BMI and creatinine clearance (CrCl) into consideration.

e.g. for Enoxaparin:

≥30 CrCl and BMI <40: 40 mg SC q24h

≥30 CrCl and BMI ≥40: 40 mg SC q12h

<30 CrCl and BMI <40: UFH 5000 units SC q8-12h or LMWH per hospital protocol taking BMI into consideration

<30 CrCl and BMI ≥40: UFH 7500 units SC q8h or LMWH per hospital protocol taking BMI into consideration as above

Full therapeutic dose anticoagulation (therapeutic dose LMWH) was permitted as rescue therapy in the event of suspected or confirmed thromboembolism. Additional rescue therapy, in the form of thrombolysis (with tissue plasminogen activator), was also permitted if deemed clinically warranted.

Number of subjects in period 1	Therapeutic Heparin	Prophylactic Heparin
Started	228	237
Completed	188	193
Not completed	40	44
Lost to follow-up	12	12
Protocol deviation	28	32

Baseline characteristics

Reporting groups

Reporting group title	Therapeutic Heparin
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Reporting group description:

Patients allocated to the experimental arm received therapeutic low molecular weight heparin (LMWH) or unfractionated heparin (UFH). UFH, if used in the experimental arm, was administered intravenously using a weight-based nomogram and the activated partial thromboplastin time (aPTT) or UFH anti-Xa titration according to center-specific venous thromboembolism (VTE) treatment protocols.

Reporting group title	Prophylactic Heparin
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Reporting group description:

Subjects allocated to prophylactic heparin (control arm) received dose-capped prophylactic subcutaneous heparin (LMWH or UFH) adjusted for body mass index and creatinine clearance. Prophylactic dose level was defined based on the best available evidence from clinical trials and expert consensus, and took body mass index and creatinine clearance into consideration.

Reporting group values	Therapeutic Heparin	Prophylactic Heparin	Total
Number of subjects	228	237	465
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	60.4	59.6	
standard deviation	± 14.1	± 15.5	-
Gender categorical Units: Subjects			
Female	105	96	201
Male	123	141	264
Race/Ethnicity			
Note: 'Other' category encompasses: American Indian, Alaska Native, First Nations, Indigenous/Aboriginal or Metis			
Units: Subjects			
White - European	97	96	193
White - Middle Eastern, North African	65	67	132
Asian	27	38	65
Black or African American	18	23	41
Hispanic or Latino	14	10	24
Native Hawaiian or Other Pacific Islander	1	0	1
Other	0	1	1

disease			
Includes chronic restrictive pulmonary disease, chronic obstructive pulmonary disease, and asthma.			
Units: Subjects			
Yes	36	27	63
No	192	210	402
Medical History - Chronic kidney disease			
Units: Subjects			
Yes	20	13	33
No	208	224	432
Medical History - Chronic liver disease			
Units: Subjects			
Yes	5	9	14
No	223	228	451
Medical History - Cancer			
Units: Subjects			
Yes	13	19	32
No	215	218	433
Medical History - Immunodeficiency			
Units: Subjects			
Yes	1	2	3
No	227	235	462
Medical History - Autoimmune disease			
Units: Subjects			
Yes	6	11	17
No	222	226	448
Medical History - Cognitive impairment			
Units: Subjects			
Yes	12	11	23
No	216	226	442
Mental illness			
Units: Subjects			
Yes	18	13	31
No	210	224	434
Medical History - Active smoking			
Units: Subjects			
Yes	5	7	12
No	223	230	453
Medication history - Systemic corticosteroid			
Note: No patients were on remdesivir or tocilizumab at baseline.			
Units: Subjects			
Yes	161	162	323
No	67	75	142
Medication history - Antiplatelet agent			
Note: No patients were on remdesivir or tocilizumab at baseline.			
Units: Subjects			
Yes	24	29	53
No	204	208	412
Laboratory values - D-dimer positivity			
Note: 6 patients in the therapeutic heparin group and 5 prophylactic heparin group did not meet eligibility criteria pertaining to D-dimer at the time of randomization due to a delay in protocol harmonization with Brazil.			

Units: Subjects			
Yes	222	232	454
No	6	5	11
Laboratory values - D-dimer (categorized levels)			
D-dimer levels are calculated relative to ULN (Upper limit of normal) and categorized accordingly.			
Units: Subjects			
D-dimer <2 times ULN	115	112	227
D-dimer > 2 - 3 times ULN	61	55	116
D-dimer > 3 - 4 times ULN	25	27	52
D-dimer > 4 times ULN	27	43	70
Country			
Units: Subjects			
Brazil	54	51	105
Canada	72	78	150
Ireland	11	12	23
Saudi Arabia	71	76	147
United Arab Emirates	7	6	13
United States of America	13	14	27
Body mass index			
Body-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.			
Units: kg/m ²			
arithmetic mean	30.3	30.2	-
standard deviation	± 6.4	± 7	-
Duration of symptoms prior to hospitalization			
Data regarding duration of symptoms prior to hospitalization was missing for 1 patients in the therapeutic heparin group and 5 for the prophylactic heparin group.			
Units: Days			
arithmetic mean	7.1	7.1	-
standard deviation	± 5.1	± 5.2	-
Duration of hospitalization before randomization			
Units: Days			
arithmetic mean	1.5	1.4	-
standard deviation	± 1.1	± 1.0	-
Laboratory values - D-dimer times ULN*			
*ULN = Upper limit of normal			
Units: Relative to upper limit of normal			
geometric mean	2.1	2.5	-
standard deviation	± 0.7	± 0.9	-
Laboratory values - Creatinine			
Data regarding creatinine was missing for 14 patients in the therapeutic heparin group and 23 patients in the prophylactic heparin group.			
Units: µmol/L			
arithmetic mean	84.6	85.9	-
standard deviation	± 44.1	± 58.2	-
Laboratory values - platelet count			
Data regarding platelet count was missing for 16 patients in the therapeutic heparin group and 24 patients in the prophylactic heparin group			
Units: 10 ⁹ /L			

arithmetic mean	233.7	237.8	
standard deviation	± 95.7	± 95.3	-

End points

End points reporting groups

Reporting group title	Therapeutic Heparin
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Reporting group description:

Patients allocated to the experimental arm received therapeutic low molecular weight heparin (LMWH) or unfractionated heparin (UFH). UFH, if used in the experimental arm, was administered intravenously using a weight-based nomogram and the activated partial thromboplastin time (aPTT) or UFH anti-Xa titration according to center-specific venous thromboembolism (VTE) treatment protocols.

Reporting group title	Prophylactic Heparin
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Reporting group description:

Subjects allocated to prophylactic heparin (control arm) received dose-capped prophylactic subcutaneous heparin (LMWH or UFH) adjusted for body mass index and creatinine clearance. Prophylactic dose level was defined based on the best available evidence from clinical trials and expert consensus, and took body mass index and creatinine clearance into consideration.

Primary: ICU admission, non-invasive positive pressure ventilation, invasive mechanical ventilation or death at 28 days

End point title	ICU admission, non-invasive positive pressure ventilation, invasive mechanical ventilation or death at 28 days
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End point description:

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.

End point type	Primary
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End point timeframe:

From randomisation to 28 days

End point values	Therapeutic Heparin	Prophylactic Heparin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	228	237		
Units: None				
Yes	37	52		
No	191	185		

Statistical analyses

Statistical analysis title	Primary analysis
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Statistical analysis description:

Primary analyses were by the intention-to-treat population of all randomized patients in accordance with the allocated intervention. A chi-square test was conducted to derive a two-sided p-value for the main analysis of the primary outcome. A logistic regression model was fitted to derive odds ratios with 95% confidence intervals.

Comparison groups	Therapeutic Heparin v Prophylactic Heparin
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Number of subjects included in analysis	465
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.12
Method	Chi-squared
Parameter estimate	Odds ratio (OR)
Point estimate	0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	1.1

Statistical analysis title	Per protocol analysis
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Statistical analysis description:

The per protocol set was restricted those who received the experimental or control intervention as allocated during the first 48 hours after randomization. A logistic regression model was fitted to derive an odds ratio with 95% confidence intervals. The per protocol set includes 216 patients in the therapeutic heparin arm (34 met the primary endpoint) and 227 patients in the prophylactic heparin arm (47 met the primary endpoint).

Comparison groups	Therapeutic Heparin v Prophylactic Heparin
Number of subjects included in analysis	465
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	1.17

Statistical analysis title	Sensitivity analysis 1
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Statistical analysis description:

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; 11 patients in therapeutic heparin group and 12 patients in the prophylactic heparin group. 37/217 met this endpoint in the therapeutic heparin arm and 52/225 met this endpoint in the prophylactic heparin arm. Logistic regression was used to derive odds ratios with 95% confidence intervals.

Comparison groups	Therapeutic Heparin v Prophylactic Heparin
Number of subjects included in analysis	465
Analysis specification	Post-hoc
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	0.68

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	1.1

Statistical analysis title	Sensitivity analysis 2
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Statistical analysis description:

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). 36/222 met this endpoint in the therapeutic heparin arm and 48/231 met this endpoint in the prophylactic heparin arm. Logistic regression was used to derive odds ratios with 95% confidence intervals.

Comparison groups	Therapeutic Heparin v Prophylactic Heparin
Number of subjects included in analysis	465
Analysis specification	Post-hoc
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	0.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	1.19

Statistical analysis title	Sensitivity analysis 3
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Statistical analysis description:

Sensitivity analysis 3 was conducted using logistic regression to derive odds ratios with 95% confidence intervals, excluding 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; 17 patients in the therapeutic heparin group and 18 patients in the prophylactic heparin group. 36/211 met the primary endpoint in the therapeutic heparin arm and 48/219 in the prophylactic heparin arm

Comparison groups	Therapeutic Heparin v Prophylactic Heparin
Number of subjects included in analysis	465
Analysis specification	Post-hoc
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	1.19

Statistical analysis title	Age-adjusted intention-to-treat analysis
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Statistical analysis description:

Intention-to-treat analysis of the primary endpoint adjusted for age, taking into account that

randomization was stratified by age. An odds ratio with 95% confidence interval was estimated by logistic regression.

Comparison groups	Therapeutic Heparin v Prophylactic Heparin
Number of subjects included in analysis	465
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	0.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	1.08

Statistical analysis title	ITT analysis adjusted for time
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Statistical analysis description:

This intention-to-treat analysis of the primary endpoint was repeated to adjust for time. 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 randomized 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

Comparison groups	Therapeutic Heparin v Prophylactic Heparin
Number of subjects included in analysis	465
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Odds ratio (OR)
Point estimate	0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	1.1

Secondary: Death from any cause

End point title	Death from any cause
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End point description:

If a patient was discharged alive before 28 days, vital status was determined using a telephone follow-up.

End point type	Secondary
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End point timeframe:

From randomisation to 28 days

End point values	Therapeutic Heparin	Prophylactic Heparin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	228	237		
Units: None				
Yes	4	18		
No	224	219		

Statistical analyses

Statistical analysis title	Intention-to-treat analysis
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Statistical analysis description:

This analysis was conducted on the ITT population. Logistic regression was used to derive odds ratios with 95% confidence intervals. Secondary outcomes were exploratory and were not adjusted for multiple comparisons.

Comparison groups	Therapeutic Heparin v Prophylactic Heparin
Number of subjects included in analysis	465
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	0.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.07
upper limit	0.65

Statistical analysis title	Per protocol analysis
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Statistical analysis description:

The per protocol set was restricted those who received the experimental or control intervention as allocated during the first 48 hours after randomization. A logistic regression model was fitted to derive an odds ratio with 95% confidence intervals. The per protocol set includes 216 patients in the therapeutic heparin arm (4 experienced death from any cause within 28 days) and 227 patients in the prophylactic heparin arm (17 experienced death from any cause within 28 days)

Comparison groups	Therapeutic Heparin v Prophylactic Heparin
Number of subjects included in analysis	465
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.08
upper limit	0.71

Statistical analysis title	Sensitivity analysis 1
Statistical analysis description:	
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; 11 patients in therapeutic heparin group and 12 patients in the prophylactic heparin group. 4/217 met this endpoint in the therapeutic heparin arm and 18/225 met this endpoint in the prophylactic heparin arm. Logistic regression was used to derive odds ratios with 95% confidence intervals.	
Comparison groups	Therapeutic Heparin v Prophylactic Heparin
Number of subjects included in analysis	465
Analysis specification	Post-hoc
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	0.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.07
upper limit	0.65

Statistical analysis title	Sensitivity analysis 2
Statistical analysis description:	
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). 4/222 met this endpoint in the therapeutic heparin arm and 17/231 met this endpoint in the prophylactic heparin arm. Logistic regression was used to derive odds ratios with 95% confidence intervals.	
Comparison groups	Therapeutic Heparin v Prophylactic Heparin
Number of subjects included in analysis	465
Analysis specification	Post-hoc
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.08
upper limit	0.7

Statistical analysis title	Sensitivity analysis 3
Statistical analysis description:	
Sensitivity analysis 3 was conducted using logistic regression to derive an odds ratio with a 95% confidence interval, excluding 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; 17 patients in the therapeutic heparin group and 18 patients in the prophylactic heparin group. 4/211 met the endpoint within the therapeutic heparin arm and 17/219 in the prophylactic heparin arm	
Comparison groups	Therapeutic Heparin v Prophylactic Heparin

Number of subjects included in analysis	465
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.08
upper limit	0.7

Statistical analysis title	Age-adjusted intention-to-treat analysis
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Statistical analysis description:

Intention-to-treat analysis of the primary endpoint components were adjusted for age, taking into account that randomization was stratified by age. An odds ratio with 95% confidence interval was estimated by logistic regression.

Comparison groups	Therapeutic Heparin v Prophylactic Heparin
Number of subjects included in analysis	465
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.06
upper limit	0.61

Secondary: Invasive mechanical ventilation

End point title	Invasive mechanical ventilation
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End point description:

End point type	Secondary
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End point timeframe:

Up to 28 days post-randomisation

End point values	Therapeutic Heparin	Prophylactic Heparin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	228	237		
Units: Subjects				
Yes	11	16		
No	217	221		

Statistical analyses

Statistical analysis title	Intention-to-treat analysis
Statistical analysis description:	
This analysis was conducted on the ITT population. Logistic regression was used to derive odds ratios with 95% confidence intervals. Secondary outcomes were exploratory and were not adjusted for multiple comparisons.	
Comparison groups	Therapeutic Heparin v Prophylactic Heparin
Number of subjects included in analysis	465
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.32
upper limit	1.55

Statistical analysis title	Per protocol analysis
Statistical analysis description:	
The per protocol set was restricted those who received the experimental or control intervention as allocated during the first 48 hours after randomization. A logistic regression model was fitted to derive an odds ratio with 95% confidence intervals. The per protocol set includes 216 patients in the therapeutic heparin arm (9 met this endpoint) and 227 patients in the prophylactic heparin arm (13 met this endpoint).	
Comparison groups	Therapeutic Heparin v Prophylactic Heparin
Number of subjects included in analysis	465
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	1.71

Statistical analysis title	Sensitivity analysis 1
Statistical analysis description:	
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; 11 patients in therapeutic heparin group and 12	

patients in the prophylactic heparin group. 11/217 met this endpoint in the therapeutic heparin arm and 16/225 met this endpoint in the prophylactic heparin arm. Logistic regression was used to derive odds ratios with 95% confidence intervals.

Comparison groups	Therapeutic Heparin v Prophylactic Heparin
Number of subjects included in analysis	465
Analysis specification	Post-hoc
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.32
upper limit	1.54

Statistical analysis title	Sensitivity analysis 2
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Statistical analysis description:

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). 10/222 met this endpoint in the therapeutic heparin arm and 14/231 met this endpoint in the prophylactic heparin arm. Logistic regression was used to derive odds ratios with 95% confidence intervals.

Comparison groups	Therapeutic Heparin v Prophylactic Heparin
Number of subjects included in analysis	465
Analysis specification	Post-hoc
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.32
upper limit	1.69

Statistical analysis title	Sensitivity analysis 3
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Statistical analysis description:

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; 17 patients in the therapeutic heparin group and 18 patients in the prophylactic heparin group. 10/211 received invasive mechanical ventilation in the therapeutic heparin group and 14/219 in the prophylactic heparin group.

Comparison groups	Prophylactic Heparin v Therapeutic Heparin
Number of subjects included in analysis	465
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	0.73

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.32
upper limit	1.68

Statistical analysis title	Age-adjusted ITT analysis
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Statistical analysis description:

Intention-to-treat analysis of invasive mechanical ventilation adjusted for age taking into account that randomization was stratified by age.

Comparison groups	Therapeutic Heparin v Prophylactic Heparin
Number of subjects included in analysis	465
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.31
upper limit	1.53

Secondary: Any mechanical ventilation

End point title	Any mechanical ventilation
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End point description:

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

End point type	Secondary
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End point timeframe:

Up to 28 days post-randomisation

End point values	Therapeutic Heparin	Prophylactic Heparin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	228	237		
Units: Subjects				
Yes	21	26		
No	207	211		

Statistical analyses

Statistical analysis title	Intention-to-treat analysis
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Statistical analysis description:

This analysis was conducted on the ITT population. Logistic regression was used to derive odds ratios with 95% confidence intervals. Secondary outcomes were exploratory and were not adjusted for multiple comparisons.

Comparison groups	Therapeutic Heparin v Prophylactic Heparin
Number of subjects included in analysis	465
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	1.51

Statistical analysis title	Per protocol analysis
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Statistical analysis description:

The per protocol set was restricted those who received the experimental or control intervention as allocated during the first 48 hours after randomization. A logistic regression model was fitted to derive an odds ratio with 95% confidence intervals. The per protocol set includes 216 patients in the therapeutic heparin arm (18 with any mechanical ventilation) and 227 patients in the prophylactic heparin arm (22 with any mechanical ventilation).

Comparison groups	Therapeutic Heparin v Prophylactic Heparin
Number of subjects included in analysis	465
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	1.63

Statistical analysis title	Sensitivity analysis 1
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Statistical analysis description:

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; 11 patients in therapeutic heparin group and 12 patients in the prophylactic heparin group. 21/217 met this endpoint in the therapeutic heparin arm and 26/225 met this endpoint in the prophylactic heparin arm. Logistic regression was used to derive odds ratios with 95% confidence intervals.

Comparison groups	Therapeutic Heparin v Prophylactic Heparin
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Number of subjects included in analysis	465
Analysis specification	Post-hoc
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	1.51

Statistical analysis title	Sensitivity analysis 2
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Statistical analysis description:

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). 20/222 met this endpoint in the therapeutic heparin arm and 23/231 met this endpoint in the prophylactic heparin arm. Logistic regression was used to derive odds ratios with 95% confidence intervals.

Comparison groups	Therapeutic Heparin v Prophylactic Heparin
Number of subjects included in analysis	465
Analysis specification	Post-hoc
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	1.68

Statistical analysis title	Sensitivity analysis 3
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Statistical analysis description:

Sensitivity analysis 3 was conducted using logistic regression to derive an odds ratio with a 95% confidence interval, excluding 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; 17 patients in the therapeutic heparin group and 18 patients in the prophylactic heparin group.

Comparison groups	Therapeutic Heparin v Prophylactic Heparin
Number of subjects included in analysis	465
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	1.68

Statistical analysis title	Age-adjusted ITT analysis
Statistical analysis description: Intention-to-treat analysis of any mechanical ventilation adjusted for age taking into account that randomization was stratified by age.	
Comparison groups	Therapeutic Heparin v Prophylactic Heparin
Number of subjects included in analysis	465
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	1.5

Secondary: ICU admission

End point title	ICU admission
End point description:	
End point type	Secondary
End point timeframe: Up to 28 days post-randomization	

End point values	Therapeutic Heparin	Prophylactic Heparin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	228	237		
Units: Subjects				
Yes	33	42		
No	195	195		

Statistical analyses

Statistical analysis title	Intention-to-treat analysis
Statistical analysis description: This analysis was conducted on the ITT population. Logistic regression was used to derive odds ratios with 95% confidence intervals. Secondary outcomes were exploratory and were not adjusted for multiple comparisons.	
Comparison groups	Therapeutic Heparin v Prophylactic Heparin

Number of subjects included in analysis	465
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	1.29

Statistical analysis title	Per protocol analysis
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Statistical analysis description:

The per protocol set was restricted those who received the experimental or control intervention as allocated during the first 48 hours after randomization. A logistic regression model was fitted to derive an odds ratio with 95% confidence intervals. The per protocol set includes 216 patients in the therapeutic heparin arm (30 admitted to the ICU) and 227 patients in the prophylactic heparin arm (37 admitted to ICU).

Comparison groups	Therapeutic Heparin v Prophylactic Heparin
Number of subjects included in analysis	465
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	1.4

Statistical analysis title	Sensitivity analysis 1
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Statistical analysis description:

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; 11 patients in therapeutic heparin group and 12 patients in the prophylactic heparin group. 33/217 met this endpoint in the therapeutic heparin arm and 42/225 met this endpoint in the prophylactic heparin arm. Logistic regression was used to derive odds ratios with 95% confidence intervals.

Comparison groups	Therapeutic Heparin v Prophylactic Heparin
Number of subjects included in analysis	465
Analysis specification	Post-hoc
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	1.29

Statistical analysis title	Sensitivity analysis 2
Statistical analysis description:	
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). 32/222 met this endpoint in the therapeutic heparin arm and 39/231 met this endpoint in the prophylactic heparin arm. Logistic regression was used to derive odds ratios with 95% confidence intervals.	
Comparison groups	Therapeutic Heparin v Prophylactic Heparin
Number of subjects included in analysis	465
Analysis specification	Post-hoc
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	1.38

Statistical analysis title	Sensitivity analysis 3
Statistical analysis description:	
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; 17 patients in the therapeutic heparin group and 18 patients in the prophylactic heparin group. 32/211 subjects were admitted to the ICU in the therapeutic heparin arm and 39/219 in the prophylactic heparin arm	
Comparison groups	Therapeutic Heparin v Prophylactic Heparin
Number of subjects included in analysis	465
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	1.38

Statistical analysis title	Age-adjusted ITT analysis
Statistical analysis description:	
Intention-to-treat analysis ICU admission adjusted for age taking into account that randomization was stratified by age.	
Comparison groups	Therapeutic Heparin v Prophylactic Heparin

Number of subjects included in analysis	465
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	1.29

Secondary: Death or any mechanical ventilation

End point title	Death or any mechanical ventilation
End point description:	
End point type	Secondary
End point timeframe:	
Up to 28 days post-randomization	

End point values	Therapeutic Heparin	Prophylactic Heparin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	228	237		
Units: Subjects				
Yes	23	38		
No	205	199		

Statistical analyses

Statistical analysis title	Intention-to-treat analysis
Statistical analysis description:	
This analysis was conducted on the ITT population. Logistic regression was used to derive odds ratios with 95% confidence intervals. Secondary outcomes were exploratory and were not adjusted for multiple comparisons.	
Comparison groups	Therapeutic Heparin v Prophylactic Heparin
Number of subjects included in analysis	465
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.34
upper limit	1.02

Secondary: Death or ICU admission

End point title	Death or ICU admission
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End point description:

End point type	Secondary
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End point timeframe:

Up to 28 days post-randomization

End point values	Therapeutic Heparin	Prophylactic Heparin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	228	237		
Units: Subjects				
Yes	36	50		
No	192	187		

Statistical analyses

Statistical analysis title	Intention-to-treat analysis
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Statistical analysis description:

This analysis was conducted on the ITT population. Logistic regression was used to derive odds ratios with 95% confidence intervals. Secondary outcomes were exploratory and were not adjusted for multiple comparisons.

Comparison groups	Therapeutic Heparin v Prophylactic Heparin
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Number of subjects included in analysis	465
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Analysis specification	Pre-specified
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Analysis type	superiority
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Parameter estimate	Odds ratio (OR)
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Point estimate	0.7
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Confidence interval

level	95 %
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sides	2-sided
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lower limit	0.44
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upper limit	1.13
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Secondary: Ventilator-free days alive

End point title	Ventilator-free days alive
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End point description:

End point type	Secondary
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End point timeframe:

Up to 28 days post-randomization

End point values	Therapeutic Heparin	Prophylactic Heparin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	228	237		
Units: days				
arithmetic mean (standard deviation)	26.5 (± 5.6)	24.7 (± 8.5)		

Statistical analyses

Statistical analysis title	Intention-to-treat analysis
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Statistical analysis description:

This analysis was conducted on the ITT population. Ordinal logistic regression was used to derive odds ratios with 95% confidence intervals. Death up to 28 days was assigned the worst outcome (a value of -1) in these analyses. Secondary outcomes were exploratory and were not adjusted for multiple comparisons.

Comparison groups	Therapeutic Heparin v Prophylactic Heparin
Number of subjects included in analysis	465
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	1.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.02
upper limit	3.08

Secondary: Organ support-free days alive

End point title	Organ support-free days alive
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End point description:

Organ support was defined as receipt of non-invasive mechanical ventilation, high flow nasal cannula oxygen, invasive mechanical ventilation, or vasopressor therapy. 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.

End point type	Secondary
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End point timeframe:

Defined as the number of days that a patient was alive and free of organ support through 28 days after trial entry.

End point values	Therapeutic Heparin	Prophylactic Heparin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	228	237		
Units: days				
arithmetic mean (standard deviation)	25.8 (± 6.2)	24.1 (± 8.8)		

Statistical analyses

Statistical analysis title	Intention-to-treat analysis
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Statistical analysis description:

This analysis was conducted on the ITT population. Ordinal logistic regression was used to derive odds ratios with 95% confidence intervals. Death up to 28 days was assigned the worst outcome (a value of -1) in these analyses. Secondary outcomes were exploratory and were not adjusted for multiple comparisons.

Comparison groups	Prophylactic Heparin v Therapeutic Heparin
Number of subjects included in analysis	465
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	1.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	2.21

Secondary: ICU-free days alive

End point title	ICU-free days alive
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End point description:

End point type	Secondary
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End point timeframe:

Up to 28 days post-randomization

End point values	Therapeutic Heparin	Prophylactic Heparin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	228	237		
Units: days				
arithmetic mean (standard deviation)	26.0 (± 6.1)	24.2 (± 8.8)		

Statistical analyses

Statistical analysis title	Intention-to-treat analysis
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Statistical analysis description:

This analysis was conducted on the ITT population. Ordinal logistic regression was used to derive odds ratios with 95% confidence intervals. Death up to 28 days was assigned the worst outcome (a value of -1) in these analyses. Secondary outcomes were exploratory and were not adjusted for multiple comparisons.

Comparison groups	Therapeutic Heparin v Prophylactic Heparin
Number of subjects included in analysis	465
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	1.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.94
upper limit	2.41

Secondary: Hospital-free days alive

End point title	Hospital-free days alive
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End point description:

End point type	Secondary
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End point timeframe:

Up to 28 days post-randomization

End point values	Therapeutic Heparin	Prophylactic Heparin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	228	237		
Units: days				
arithmetic mean (standard deviation)	19.8 (± 7.3)	18.4 (± 9.2)		

Statistical analyses

Statistical analysis title	Intention-to-treat analysis
Statistical analysis description: This analysis was conducted on the ITT population. Ordinal logistic regression was used to derive odds ratios with 95% confidence intervals. Death up to 28 days was assigned the worst outcome (a value of -1) in these analyses. Secondary outcomes were exploratory and were not adjusted for multiple comparisons.	
Comparison groups	Therapeutic Heparin v Prophylactic Heparin
Number of subjects included in analysis	465
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	1.5

Secondary: Renal replacement therapy

End point title	Renal replacement therapy
End point description: Renal replacement therapy was defined as continuous renal replacement therapy {CRRT} or intermittent hemodialysis {IHD};	
End point type	Secondary
End point timeframe: Up to 28 days post-randomization	

End point values	Therapeutic Heparin	Prophylactic Heparin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	228	237		
Units: Subjects				
Yes	2	5		
No	226	232		

Statistical analyses

Statistical analysis title	Intention-to-treat analysis
Statistical analysis description: This analysis was conducted on the ITT population. Logistic regression was used to derive odds ratios with 95% confidence intervals. Secondary outcomes were exploratory and were not adjusted for multiple comparisons.	
Comparison groups	Therapeutic Heparin v Prophylactic Heparin

Number of subjects included in analysis	465
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Log odds ratio
Point estimate	0.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.08
upper limit	2.15

Secondary: Venous thromboembolism

End point title	Venous thromboembolism
End point description:	
Thromboembolism was 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.	
End point type	Secondary
End point timeframe:	
Up to 28 days post-randomization	

End point values	Therapeutic Heparin	Prophylactic Heparin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	228	237		
Units: Subjects				
Yes	2	7		
No	226	230		

Statistical analyses

Statistical analysis title	Intention-to-treat analysis
Statistical analysis description:	
This analysis was conducted on the ITT population. Logistic regression was used to derive odds ratios with 95% confidence intervals. Secondary outcomes were exploratory and were not adjusted for multiple comparisons.	
Comparison groups	Therapeutic Heparin v Prophylactic Heparin
Number of subjects included in analysis	465
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	0.29

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.06
upper limit	1.42

Secondary: Arterial thromboembolism

End point title	Arterial thromboembolism
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End point description:

Thromboembolism was all 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.

End point type	Secondary
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End point timeframe:

Up to 28 days post-randomization.

End point values	Therapeutic Heparin	Prophylactic Heparin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	228	237		
Units: Subjects				
Yes	0	1		
No	228	236		

Statistical analyses

No statistical analyses for this end point

Secondary: Heparin induced thrombocytopenia

End point title	Heparin induced thrombocytopenia
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End point description:

End point type	Secondary
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End point timeframe:

Up to 28 days post-randomization.

End point values	Therapeutic Heparin	Prophylactic Heparin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	228	237		
Units: Subjects				
Yes	0	0		
No	228	237		

Statistical analyses

No statistical analyses for this end point

Secondary: D-dimer x ULN

End point title	D-dimer x ULN
End point description:	
<p>Since D-dimer assays differed across sites, D-dimer levels were analyzed as the logarithm of D-dimer x ULN by taking the natural logarithm of the ratio of the actual d-dimer value divided by the ULN for the assay used. SD reported is for the natural logarithm of D-dimer levels x ULN. The day 2±24 hours D-dimer was missing for 66 in the therapeutic heparin group and 64 in the prophylactic heparin group. In accordance with the statistical analysis plan, because this outcome had missing data for more than 5% of the subjects, the main analysis was a complete case analysis , with sensitivity analysis by inverse probability weighted analysis and multiple imputation.</p>	
End point type	Secondary
End point timeframe:	
D-dimer level at 2 days ± 24 hours post-randomization	

End point values	Therapeutic Heparin	Prophylactic Heparin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	228	237		
Units: D-dimer level x ULN				
geometric mean (standard deviation)	1.9 (± 0.7)	2.4 (± 0.9)		

Statistical analyses

Statistical analysis title	Complete case analysis (primary analysis)
Statistical analysis description:	
<p>Ratio of geometric means of D-dimer levels x ULN of day 2±24h post-randomization, adjusted for baseline geometric means of D-dimer levels x ULN using analysis of covariance. The day 2±24 hours D-dimer was missing for 66 in the therapeutic heparin group and 64 in the prophylactic heparin group.</p>	
Comparison groups	Therapeutic Heparin v Prophylactic Heparin

Number of subjects included in analysis	465
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Ratio of geometric means
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	0.99

Statistical analysis title	Inverse probability weighted analysis
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Statistical analysis description:

Sensitivity analysis. 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. 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. Inverse probability weighted analysis used to account for missing data.

Comparison groups	Therapeutic Heparin v Prophylactic Heparin
Number of subjects included in analysis	465
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Ratio of geometric means
Point estimate	0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	0.98

Statistical analysis title	Multiple imputation analysis
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Statistical analysis description:

Sensitivity analysis. 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. 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. Multiple imputation used to account for missing data.

Comparison groups	Therapeutic Heparin v Prophylactic Heparin
Number of subjects included in analysis	465
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Ratio of geometric means
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	1.04

Secondary: ISTH major bleeding

End point title	ISTH major bleeding
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End point description:

End point type	Secondary
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End point timeframe:

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

End point values	Therapeutic Heparin	Prophylactic Heparin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	228	237		
Units: Subjects				
Yes	2	4		
No	226	233		

Statistical analyses

Statistical analysis title	Intention-to-treat analysis
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Statistical analysis description:

This analysis was conducted on the ITT population. Logistic regression was used to derive odds ratios with 95% confidence intervals. Secondary outcomes were exploratory and were not adjusted for multiple comparisons.

Comparison groups	Therapeutic Heparin v Prophylactic Heparin
Number of subjects included in analysis	465
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.09
upper limit	2.85

Secondary: Bleeding - red blood cell transfusion (>=1 unit)

End point title	Bleeding - red blood cell transfusion (>=1 unit)
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End point description:

End point type	Secondary
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End point timeframe:
Up to 28 days post-randomization

End point values	Therapeutic Heparin	Prophylactic Heparin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	228	237		
Units: Subjects				
Yes	3	9		
No	225	228		

Statistical analyses

Statistical analysis title	Intention-to-treat analysis
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Statistical analysis description:

This analysis was conducted on the ITT population. Logistic regression was used to derive odds ratios with 95% confidence intervals. Secondary outcomes were exploratory and were not adjusted for multiple comparisons.

Comparison groups	Therapeutic Heparin v Prophylactic Heparin
Number of subjects included in analysis	465
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Odds ratio (OR)
Point estimate	0.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.09
upper limit	1.27

Secondary: Bleeding - Transfusion of hemostatic blood components or products

End point title	Bleeding - Transfusion of hemostatic blood components or products
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End point description:

End point type	Secondary
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End point timeframe:

Up to 28 days post-randomization

End point values	Therapeutic Heparin	Prophylactic Heparin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	228	237		
Units: Subjects				
Yes	1	0		
No	227	237		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The AE reporting period began on the day of randomization and ended with the final study (follow-up) visit.

Adverse event reporting additional description:

Investigators and study staff assessed the occurrence of AEs and SAEs at all subject evaluation time points during the study. Adverse events were recorded in the subject's medical records and on applicable AE source documents. Regulatory authorities, REBs and investigators were notified of SAEs in accordance with applicable requirements.

Assessment type	Systematic
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Dictionary used

Dictionary name	Not applicable
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Dictionary version	N/A
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Reporting groups

Reporting group title	Therapeutic Heparin
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Reporting group description:

Patients allocated to the experimental arm received therapeutic low molecular weight heparin (LMWH) or unfractionated heparin (UFH). UFH, if used in the experimental arm, was administered intravenously using a weight-based nomogram and the activated partial thromboplastin time (aPTT) or UFH anti-Xa titration according to center-specific venous thromboembolism (VTE) treatment protocols.

Reporting group title	Prophylactic Heparin
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Reporting group description:

Those allocated to the control arm received prophylactic heparin (LMWH or UFH). Prophylactic dose level was defined based on the best available evidence from clinical trials and expert consensus, and took body mass index and creatinine clearance into consideration.

Serious adverse events	Therapeutic Heparin	Prophylactic Heparin	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 228 (3.07%)	10 / 237 (4.22%)	
number of deaths (all causes)	4	18	
number of deaths resulting from adverse events			
Blood and lymphatic system disorders			
Anaemia	Additional description: Note that the event occurring in the standard-of-care arm (prophylactic heparin) was classified as 'Probably' related to treatment.		
subjects affected / exposed	1 / 228 (0.44%)	1 / 237 (0.42%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thromboembolism			
subjects affected / exposed	1 / 228 (0.44%)	0 / 237 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Gastrointestinal bleeding subjects affected / exposed	0 / 228 (0.00%)	1 / 237 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory Failure/Hypoxia subjects affected / exposed	7 / 228 (3.07%)	6 / 237 (2.53%)	
occurrences causally related to treatment / all	0 / 7	0 / 6	
deaths causally related to treatment / all	0 / 3	0 / 3	
Renal and urinary disorders			
Acute kidney injury subjects affected / exposed	0 / 228 (0.00%)	1 / 237 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Infections and infestations			
COVID progression subjects affected / exposed	1 / 228 (0.44%)	1 / 237 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Therapeutic Heparin	Prophylactic Heparin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 228 (15.35%)	49 / 237 (20.68%)	
Respiratory, thoracic and mediastinal disorders			
Respiratory failure/Hypoxia subjects affected / exposed	35 / 228 (15.35%)	49 / 237 (20.68%)	
occurrences (all)	35	49	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported