# Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

# 1 eAppendix: Investigators and Committees

Steering Committee

V. Labbé (principal investigator), A. Mekontso Dessap (scientific supervisor), E. Audureau (methodologist and biostatistician), and the sponsor's appointed representatives of the trial: Clinical Research Associate in charge of the project and project manager from URC Henri-Mondor university hospital ("*Unité de Recherche Clinique*") and project manager of Greater Paris Public hospitals DRCI ("*Direction de la Recherche Clinique et de l'Innovation*").

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***Hôpital Avicenne*, Bobigny, France :** W. Juguet, F. Mechai, C. Hugues, N. Hassold-Rugolino

Enrolled patients per site

***Centre Hospitalier Victor Dupouy, Argenteuil*, France, N=51**
***Hôpital Raymond Poincaré, Garches*, France, N=38**
***Hôpital Lariboisière*, Paris, France, N=31**
***Hôpitaux Universitaires Henri Mondor-Albert Chenevier, Créteil*, France, N=31**
***Centre Hospitalo-Universitaire de Poitiers*, Poitiers, France, N=28**
***Hôpital Saint Antoine*, Paris, France, N=25**
***Hôpital Tenon*, Paris, France, N=21**
***Hôpital Saint Camille, Bry-sur-Marne*, France, N=16**
***Hôpital Simone Veil, Centre Hospitalier de Cannes*, Cannes, France, N=15**
***Groupe Hospitalier Sud Ile de France, Melun*, France, N=12**
***Centre Hospitalo-Universitaire Gabriel-Montpied,* Clermont-Ferrand, France, N=11**
***Centre Hospitalo-Universitaire Lille*, Lille, France, N=11**
***Hôpital l'Archet 1*, Nice, France, N=11**
***Centre Hospitalier Saint Joseph-Saint Luc*, Lyon, France, N=10**
***Hôpital Louis Mourier*, Colombes, France, N=9**
***Hôpital Pitie Salpêtrière*, Paris, France, N=9**
***Centre Hospitalier Léon Binet, Provins*, France, N=8**
***Hôpital Larrey*, Toulouse, France, N=7**
***Hôpital Bichat*, Paris, France, N=3**
***Centre Hospitalier La Dracenie De Draguignan*, Draguignan, France, N=3**
***Hôpital Saint-Louis*, Paris, France, N=2**
***Hôpital Avicenne*, Bobigny, France, N=1**
***Centre Hospitalier Sud Francilien*, Corbeil-Essonnes, France, N=0**

## 2 eMethods 1. Study design, Interventions and Products

The trial was designed and led by an academic steering committee, and was conducted in 23 French hospitals, of which 22 enrolled participants.
The trial was coordinated by the Clinical Research and Innovation Department of Greater Paris Public Hospitals (Assistance Publique – Hôpitaux de Paris, AP-HP, France), the trial sponsor.
Each patient or next of skin provided written informed consent prior to inclusion. Eligible patients unable to receive information and for whom a substitute decision maker was not present could still be included through a process of deferred consent. After recovery, the patient's agreement to stay in the trial was sought.
Participants randomized to the LD-PA, HD-PA, and TA regimens were put on low weight molecular heparin (LMWH), preferably tinzaparin, whenever available, whilst taking into account its contraindications, recommended dose ranges and monitoring if applicable, as follows: LD-PA: 3,500 IU/24h; HD-PA: 7,000 IU/24h; TA: 175 IU/kg/24h.
The participating centres were allowed to use their available tinzaparin pre-filled syringe type, e.g. a 4,000 IU/24h dose instead of the 3,500 IU/24h in the LD-PA group given their similar indication in that regimen. If tinzaparin was not available, enoxaparin was indicated in a dose of: LD-PA: 4,000 IU/24h; HD-PA: 4,000 IU/12h; TA: 100 IU/kg/12h.
The choice of tinzaparin as first line LMWH was driven by the following arguments: i) it was used in all participating centres in routine care; ii) the single daily dose facilitated its use in clinical practice.
In case TA was clinically indicated, or serious anticoagulation-related adverse events occurred, the trial anticoagulation medicine was discontinued.
In case renal failure (creatinine clearance < 30 mL/min) occurred after randomization or if a patient needed invasive high-bleeding risk procedure, LMWH would be replaced by a continuous intravenous infusion of unfractionated heparin as follows: LD-PA:100 IU/kg/24h; HD-PA: 200 IU/kg/24h; TA: 500 IU/kg/24h, adapted to the anti-Xa activity (target between 0.3 and 0.6 IU/ml) as per the recommendations.

## 3 eMethods 1. Eligibility Criteria

### Inclusion criteria

- Age ≥ 18 years;
- Hypoxemic COVID-19 pneumonia, defined by:
    - A newly-appeared pulmonary parenchymal infiltrate; AND
    - A positive RT-PCR (either upper or lower respiratory tract) for COVID-19 (SARS-CoV-2); AND
    - WHO progression scale ≥ 5 on the WHO ordinal scale [1]

The WHO ordinal scale [1]

| Status of patient | Description | Points |
|---|---|---|
| Healed | No clinical infection, negative RT-PCR for COVID-19 | 0 |
| Not hospitalized | Asymptomatic with a positive RT-PCR for COVID-19 | 1 |
| | Symptomatic | 2 |
| | Symptomatic, in convalescent ward | 3 |
| Hospitalised in regular ward | No oxygen therapy | 4 |
| | Oxygen by mask or nasal prongs | 5 |
| Hospitalised in Intensive care unit | Requiring nasal high-flow oxygen therapy, noninvasive mechanical ventilation, or both | 6 |
| | Invasive mechanical, PaO2.FIO2 ≥ 150 | 7 |
| | Invasive mechanical, PaO2.FIO2 < 150 or catecholamine | 8 |
| | Requiring ECMO or dialysis | 9 |
| Death | Death | 10 |

    - Written informed consent (patient, next of skin, or emergency situation).

In view of the exceptional and urgent situation, affiliation to a social security scheme was not a criterion for inclusion.

### Exclusion criteria

- Pregnancy and breast feeding;
- Postpartum (6 weeks);
- Attaining the extremes of body weight (<40 kg or >100 kg);
- Hospital admission of more than 72 hours (if the WHO ordinal scale is 5 at time of inclusion) or intensive care unit admission of more than 72 hours (if the WHO ordinal scale is 6 or more at time of inclusion);
- Need for therapeutic anticoagulation (except for COVID-related pulmonary thrombosis);
- Bleeding event related to haemostasis disorders, acute clinically significant bleeding, presence of active gastrointestinal ulcer or any organic lesion with high risk for bleeding;
- Platelet count < 50 G/L;
- Within 15 days of recent surgery, within 24 hours of spinal or epidural anaesthesia;
- Past history of intracranial haemorrhage, enlarged acute ischemic stroke, known intracranial malformation or neoplasm, acute infectious endocarditis;
- Severe renal failure (creatinine clearance <30 mL/min);
- Iodine allergy;
- Hypersensitivity to heparin or its derivatives including low molecular weight heparin;
- Past history of type II heparin-induced thrombocytopenia;
- Chronic oxygen supplementation;
- Moribund patient or death expected from underlying disease during the current admission;

- Patient deprived of liberty and persons subject to institutional psychiatric care;
- Patients under guardianship or curatorship;
- Participation in another interventional research on anticoagulation.

## 4 eMethods 3. Definitions of Outcome Events

### Time to clinical improvement

Defined as the time from randomisation to an improvement of at least two points (from the status at randomisation), using a seven-category ordinal scale derived from the WHO recommended instrument, [1] as proposed by Coa et al [2].

Seven-category ordinal scale derived from the WHO recommended instrument (proposed by Coa et al.)

| Status of patient | Description | Points |
|---|---|---|
| Not hospitalized | Resumption of normal activities | 1 |
| | Unable to resume normal activities | 2 |
| Hospitalized | Not requiring supplemental oxygen | 3 |
| | Requiring supplemental oxygen | 4 |
| Intensive care unit | Requiring nasal high-flow oxygen therapy, noninvasive mechanical ventilation, or both | 5 |
| | Requiring invasive mechanical ventilation, ECMO, or both | 6 |
| Death | Death | 7 |

### Morbi-mortality and organ function

**All-cause death**

Death due to any cause

**Ventilator-free days**

Difference between total number of days the patient stayed alive post-randomization and total number of days spent on invasive mechanical ventilation, assigning a value of 0 ventilator-free days for patients who died before day 28. [3,4]

**Oxygen-free days**

Difference between total number of days the patient stayed alive post-randomization and total number of days spent on oxygen support, assigning a value of 0 oxygen-free days for patients who died before day 28. [3,4]

**Vasopressor-free days**

Difference between total number of days the patient stayed alive post-randomization and total number of days spent on vasopressor, assigning a value of 0 vasopressor-free days for patients who died before day 28. [3,4]

**Length of intensive care unit stay**

Total number of days spent in the intensive care unit

**Length of hospital stay**

Total number of days spent in the hospital

### Health-related quality of life measured at Day 90 using EuroQol 5-Dimension 5-Level (EQ-5D-5L) quality of life questionnaire [5]

The EQ-5D-5L consists of a descriptive system and the EQ visual analogue scale. The defined outcome measures were the EQ-5D-5L index value (a summary score based on the 5 domains reflecting health state according to the preference of general population; it ranges for 1.0 (perfect health) to values below zero (health states valued worse than death with zero defined as a state equivalent to death)) and EQ visual analogue scale. [5]

| Variable | Response (Please select the one sentence that best describes your health today) |
|---|---|
| Descriptive system | |
| MOBILITY | I have no problems in walking about<br>I have slight problems in walking about<br>I have moderate problems in walking about |

| | |
|---|---|
| | I have severe problems in walking about<br>I am unable to walk about |
| SELF-CARE | I have no problems washing or dressing myself<br>I have slight problems washing or dressing myself<br>I have moderate problems washing or dressing myself<br>I have severe problems washing or dressing myself<br>I am unable to wash or dress myself |
| USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)* | I have no problems doing my usual activities<br>I have slight problems doing my usual activities<br>I have moderate problems doing my usual activities<br>I have severe problems doing my usual activities<br>I am unable to do my usual activities |
| PAIN / DISCOMFORT | I have no pain or discomfort<br>I have slight pain or discomfort<br>I have moderate pain or discomfort<br>I have severe pain or discomfort<br>I have extreme pain or discomfort |
| ANXIETY / DEPRESSION | I am not anxious or depressed<br>I am slightly anxious or depressed<br>I am moderately anxious or depressed<br>I am severely anxious or depressed<br>I am extremely anxious or depressed |
| EQ visual analogue scale | |
| HEALTH TODAY | We would like to know how good or bad your health is TODAY. The scale is numbered from 0 to 100: 100 means the best health you can imagine; 0 means the worst health you can imagine. Please tell me the number to indicate how your health is TODAY. |

### Sepsis-induced Coagulopathy Score [6] [a]

| Category | Parameter | 0 point | 1 point | 2 points |
|---|---|---|---|---|
| Prothrombin time | PT-INR | ≤1.2 | >1.2 | >1.4 |
| Coagulation | Platelet count ($x10^9$/L) | ≥ 150 | <150 | <100 |
| Total SOFA [b] | SOFA four items | 0 | 1 | ≥3 |

Abbreviations: INR, internal normalization ratio; PT, prothrombin time: SOFA, Sequential Organ Failure Assessment.

[a] Sepsis-induced coagulopathy is diagnosed at a total score of 4 or more, with total score of prothrombin time and coagulation exceeding 2.

[b] Total SOFA is the sum of the four items (respiratory SOFA, cardiovascular SOFA, hepatic SOFA, and renal SOFA).

### Thrombotic events

**Ischemic stroke**

Acute focal cerebral, spinal, or retinal dysfunction associated with infarction detected on an imaging tool (computed tomography or magnetic resonance imaging); Haemorrhagic transformation of ischemic stroke should be classified as ischemic [7]

**Non-cerebrovascular arterial thrombotic event**

Acute vascular occlusion of the extremities or any non-cerebrovascular organ detected by one or more of the following: standard clinical and laboratory testing, operative findings, or autopsy findings [7]

**Deep venous thrombosis (DVT)**

Confirmed by venous duplex compression ultrasonography, and includes symptomatic lower extremity proximal DVT, upper extremity DVT, and asymptomatic proximal DVT of the lower extremities [8];

**Pulmonary artery thrombosis**

Truncular, lobar, segmental, or sub-segmental pulmonary thrombosis detected on CTPA

**Central venous catheter (CVC)-related DVT**

Event that prompted duplex ultrasound of the ipsilateral extremity in which an acute, proximal, large vein thrombosis was detected at time CVC was in or within 5 days of its removal.

**Venous thrombosis**

Composite of DVT, Pulmonary artery thrombosis, and CVC-related DVT

### Tolerance of anticoagulation

**Major bleeding event (ISTH definition, [9])**

Should meet ≥1 of the following criteria:

- Symptomatic bleeding in a critical area or organ, e.g., intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular with compartment syndrome;
- Reduction in haemoglobin of ≥2 g/dL (1.24 mmol/L) or leading to transfusion of ≥2 U of blood or packed cells;
- Fatal bleeding.

**Life-threatening bleeding event (RE-LY definition [10])**

Should meet ≥1 of the following criteria:

- Fatal bleeding;
- Symptomatic intracranial bleeding;
- Decrease in haemoglobin of ≥50 g/L, or bleeding requiring transfusion of ≥ 4 units of blood, or necessitating surgical, endoscopic, or endovascular procedures;
- Requiring surgical, endoscopic or endovascular haemostasis action.

**Intracranial bleeding (ISTH Definition, [9])**

Intracerebral bleedings, subdural bleedings, epidural bleedings, or subarachnoid bleedings.

**Fatal bleeding (ISTH Definition, [9])**

A bleeding event that is entangled as the primary cause of death or directly contributes to death.

**Any bleeding event**

Major and minor bleeding events. Minor bleeding events are defined as all non-major bleeding events.

**Heparin-induced thrombocytopenia (HIT)**

HIT is suspected if the platelet count reaches < 150 Giga/L and/or relatively falls by around 30 to 50% as compared with its level before any treatment.

Diagnosing HIT relies on:

- In vitro platelet aggregation tests and immunological tests;
- A hematology specialist's opinion to confirm or reject the diagnosis of HIT

### Net clinical outcome

Composite of all-cause death, thrombotic events, heparin-induced thrombocytopenia and ISTH-defined major bleeding events

## 5 eMethods 4. Statistical Aspects

**Sample size calculation**

Estimates, derived from prior studies led in similar populations [2], showed that a sample of at least 300 patients (100 per group) sufficed to achieve ≥80% power that is required to detect a statistically significant difference in the ranked composite primary endpoint. The analyses relied on 2-sided alpha of 0.017 using Bonferroni correction for multiple testing considering three pairwise comparisons between the randomised arms. Sample size calculation assumed having day-28 mortality of 24%, 21% and 18%, and time to clinical improvement of 16 +/-3 days (standard deviation), 14 days, and 12 days, with SD-PA, HD-PA, and TA, respectively. We hypothesized that the rate of positive CTPA would be 15% [11,12]. For such, we aimed to include 353 patients in order to randomise 300. Sample size calculation also considered the pairwise comparisons between the groups. For each performed comparison, 5,000 samples were simulated using R software. For the first component of the hierarchical primary endpoint (mortality), survival curves were simulated based on a Weibull distribution using the R package *simsurv*. For the second component of the hierarchical primary endpoint (time to clinical improvement) assessed in alive patients, two different approaches, taking into account the distribution of this parameter, were used to test the robustness of results in relation with the retained hypotheses. First, a normal distribution was hypothesized with means+/-SD of 16+/-3, 14+/-3, and 12+/-3 days in SD-PA, HD-PA, and TA, respectively. Second, incidence curves of clinical improvement were simulated based on Weibull distribution using the R package *simsurv*, with survival medians of 16, 14, and 12 days in SD-PA, HD-PA, and TA groups, respectively. With both approaches, 5% of patients were systematically identified through simulation as alive patients at day 28 but without achieving clinical improvement, which is consistent with Cao et al 2020 [2]. Standard deviation and mean number of days to clinical improvement, as well as shape and scale parameters of Weibull survival curves simulations were determined from Cao et al 2020 [2], considering median [interquartile range] survival time and Kaplan Meier curves. Within each sample/pairwise comparison, an individual score was calculated by comparing each patient in one group with all patients in the second group (23). These scores were then compared between groups using Mann-Whitney/Wilcoxon test in each of the 5,000 samples, and the *P*-value of each test was recorded. For each pairwise comparison, the percentage of tests with a *P*-value <0.017 was calculated, which gave an estimate of the achieved statistical power.

**Detailed statistical analyses**

Descriptive statistical analyses were conducted on the whole study population, in particular the randomised groups to describe their general and baseline characteristics, demographics, past history, as well as numbers of premature study withdrawals. Quantitative variables are presented as mean (±standard deviation) or median ($25^{th}$-$75^{th}$ percentiles) according to the normality of their distribution as assessed by Shapiro-Wilk tests and graphical methods. Qualitative variables are presented as numbers (%).

Primary endpoint analyses were performed according to randomization group on intention-to-treat (ITT) basis. The main analyses did not include patients with no follow-up information after early consent withdrawal or those excluded earlier for violation of eligibility criteria. Additional supportive analyses were performed on the per protocol (PP) population who did not deviate from the protocol, i.e. have complete information on the primary endpoint and a >75% adherence to the initially allocated treatment from randomization to day 14 (or until developing thrombotic event or major bleeding event or hospital discharge or weaning of supplemental oxygen for 48 consecutive hours, whichever comes first).

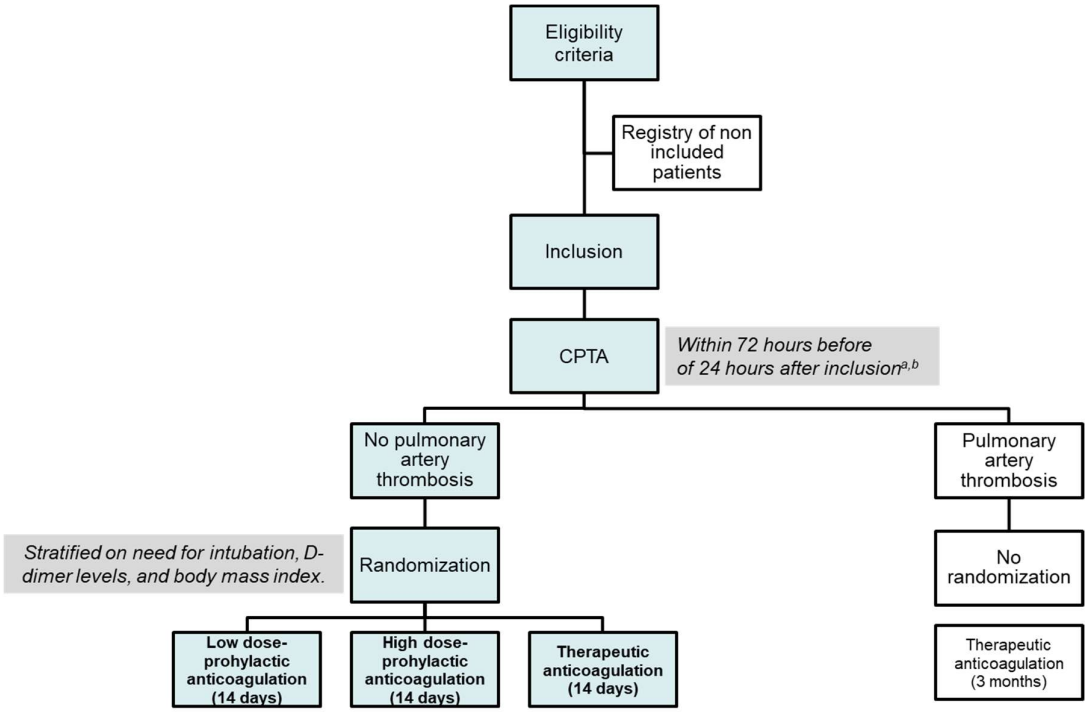
For the ranked composite primary endpoint analysis, each patient was compared with every other patient in the study and assigned a score (equality: 0, win: +1, loss: −1) for each pairwise comparison based on who fared better. If a patient survived and the other did not, the former was attributed +1 and the latter −1 for that pairwise comparison. If both patients survived, the score depended on who needed more time (days) to clinically improve: fewer days meant a score of +1 and more days meant a score of −1. If both patients survived and had the same number of days to clinical improvement or if both died, they were scored 0 for that pairwise comparison. For each patient, the scores of all pairwise comparisons were summed to obtain a cumulative score. The cumulative scores were ranked and compared between the three groups via non-parametric Mann-Whitney test.[32] Effect size was reported using the probabilistic index, an estimate of the probability that a patient randomly selected from one randomized arm will have a more favorable outcome than a patient randomly selected from the other arm.[33] The probabilistic index is mathematically equivalent to the area under the receiver operating characteristic curve for the non-parametric Mann-Whitney U test. The 95% confidence intervals (95% CIs) were computed using the method from Newcombe.[34]

Secondary outcomes of randomized groups were compared using Chi square or Fisher's exact tests, according to expected numbers in crossings, for categorical variables, and using t-test or non-parametric Mann-Whitney test (pairwise comparisons), and ANOVA or Kruskal Wallis tests (comparisons of >2 groups) for quantitative

variables, as appropriate. Effect sizes were reported as the absolute differences in proportions with asymptotic 95% CIs for binary endpoints (e.g., composite thrombotic event) and as the median difference between treatments and corresponding 95% CIs calculated from Hodges-Lehman estimate for continuous endpoints (e.g., ventilator-free days). Analyses of time-to-event endpoints took into account the competing risks of hospital discharge (for mortality evaluation and net clinical outcome) and death or discharge (for time to first bleeding or thrombosis). Cumulative incidence curves were plotted for each treatment group and compared using Gray test. Tolerance analysis examined the intervention-related adverse events according to their period of appearance and the concerned randomized group to compare rates and time of occurrence. Information on the primary endpoint was complete for the ITT analysis, while analyses of secondary endpoints were performed on a complete cases basis, with no imputation of missing information.

All analyses were performed according to a predefined statistical analysis plan, using Stata v16.1 (StataCorp, College Station, TX, USA) and R 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria). A two-tailed P-value of $<0.05$ indicated statistical significance.

## 6 eFigure 1. Study Design



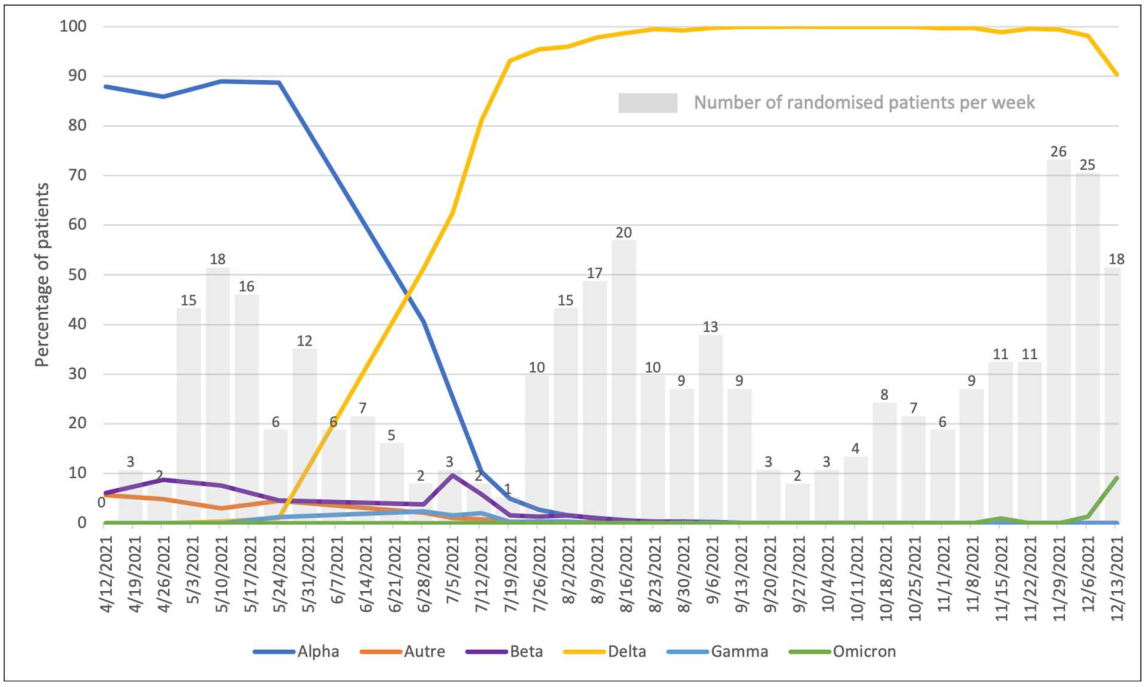

Abbreviations: CTPA= computed tomography with pulmonary angiogram.

[a] If the patient had no pulmonary artery thrombosis but presented clinical signs of deep venous thrombosis at inclusion, complete duplex ultrasound (CDUS) of the lower extremities was performed. If the CDUS was negative, the patient was randomized.

[b] If CTPA was performed within 7 days of inclusion and the likelihood of pulmonary artery thrombosis was deemed unchanged by the clinician (its reasoning was mainly based on hypoxemia, hemodynamic status, right ventricle function if echocardiography performed, or D-dimer level if measured), the result of that CTPA could be considered at the time of inclusion. Of the 353 included patients, 12 (3.4%) had an initial CTPA performed earlier than 72 hours before inclusion (4 days, n=10; 5 days, n=2). Only one randomized patient who underwent initial CTPA earlier than 72 hours before inclusion had pulmonary artery thrombosis during the 28 days of follow-up.

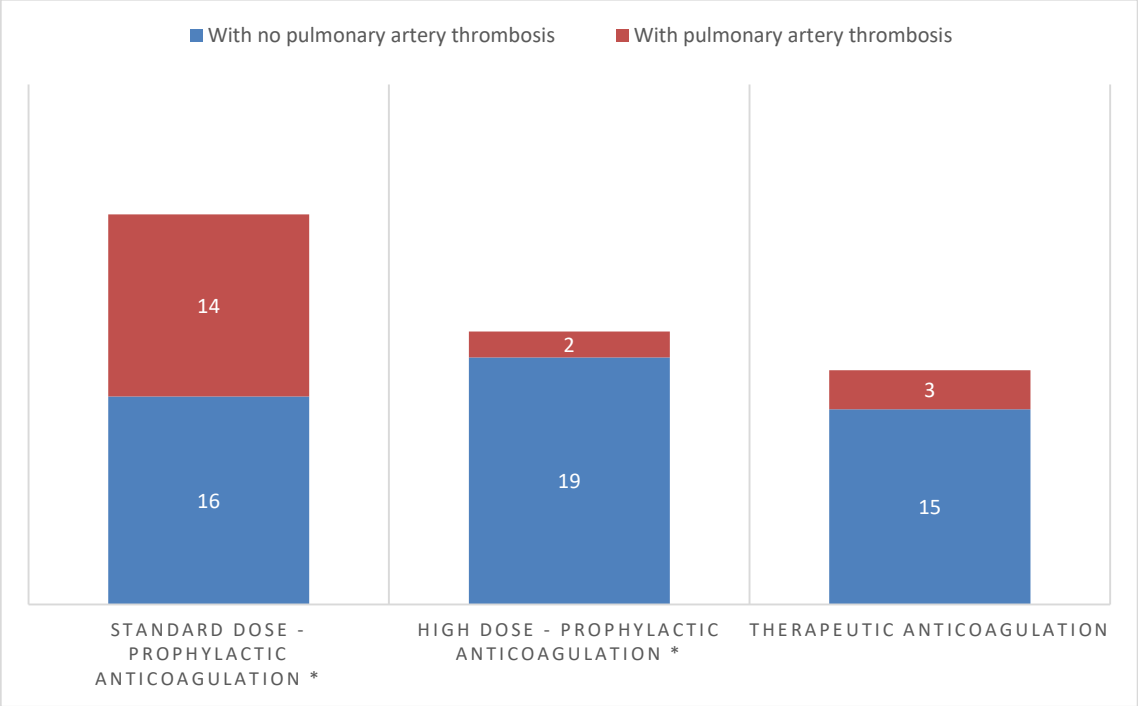
## 7 eFigure 2. Proportion of Variant of Concern in France during the Study Period of Inclusion [a]

Of note, 71% of patients were included from July 19 to December 13, 2021, a period during which the variant Delta represented over 90% of the viruses sequenced in France.



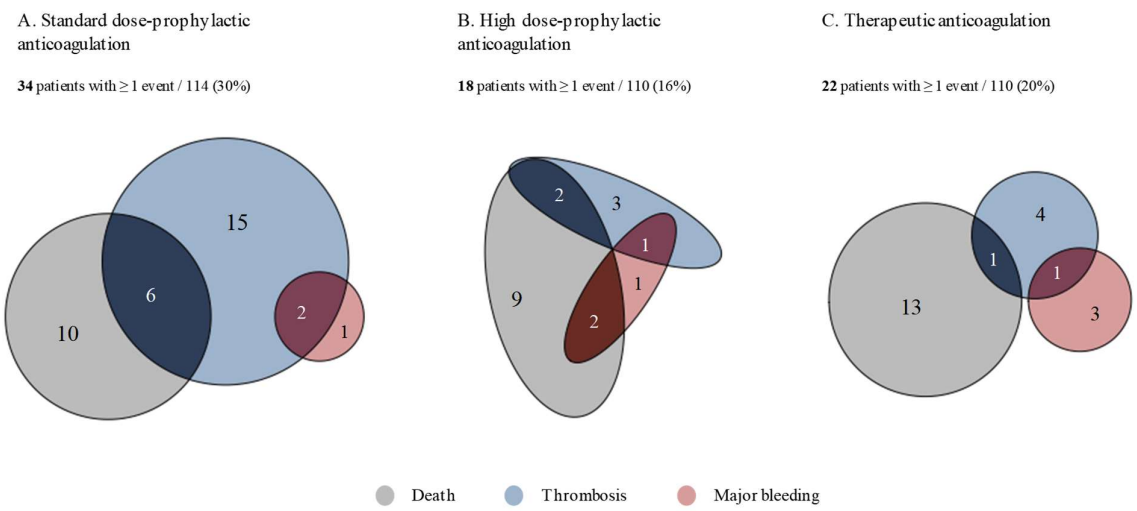

[a] Sequencing data from the Flash surveys of *Sante publique France* and ANRS | Emerging Infectious Diseases **Santé publique France, données EMERGEN.**[13]

## eFigure 3 Computed Tomography with Pulmonary Angiogram Screening for Thrombosis Performed from Randomization to Day 28




*Because of unstable hemodynamics precluding patient's transport, it was not possible to localise the site of pulmonary artery thrombosis with computed tomography in one case in the SD-PA group and one case in the HD-PA group; the diagnosis of pulmonary artery thrombosis was adjudicated based on echocardiography in these two cases.

## 9 eFigure 4: Net Clinical Outcome




Euler diagrams showing the overlapped numbers of patients with thrombotic event, ISTH-defined major bleeding, and all-cause death of the three randomised groups (upper panels). Euler diagrams are Venn diagrams showing only the required intersections, not all (even empty ones). The circles or ellipses areas in the diagrams are proportional to the input.

## 10 eTable 1. Baseline Characteristics and Medication

| | No. (%) | | |
|---|---|---|---|
| | Standard dose prophylactic anticoagulation (n =114) | High dose prophylactic anticoagulation (n =110) | Therapeutic anticoagulation (n =110) |
| Body mass index ≥ 30 kg/m$^2$ | 36 (32) | 30 (27) | 36 (33) |
| Comorbidities | | | |
| Chronic obstructive pulmonary disease | 4 (4) | 4 (4) | 4 (4) |
| Coronary artery disease | 4 (4) | 2 (2) | 8 (7) |
| Angioplasty | 3 (3) | 2 (2) | 5 (5) |
| Coronary artery bypass graft | 0 | 0 | 2 (2) |
| Chronic heart Failure | 1 (<1) | 2 (2) | 0 |
| LVEF < 45% | 0 | 1 (<1) | 0 |
| LVEF ≥ 45% | 1 (<1) | 1 (<1) | 0 |
| Peripheral artery disease | 3 (3) | 4 (4) | 2 (2) |
| Acquired immunodeficiency syndrome | 2 (2) | 2 (2) | 0 |
| Solid organ transplantation | 3 (3) | 2 (2) | 1 (<1) |
| Past history of pulmonary embolism | 1 (<1) | 0 | 1 (<1) |
| Past history of deep vein thrombosis | 2 (2) | 1 (<1) | 2 (2) |
| Past history of ischemic stroke | 1 (<1) | 1 (<1) | 2 (2) |
| Past history of non-cerebral arterial thrombo-embolism | 1 (<1) | 0 | 0 |
| Solid cancer | 4 (4) | 2 (2) | 5 (5) |
| Solid cancer with metastasis | 1 (<1) | 0 | 2 (2) |
| Acute malignant haemopathy | 7 (6) | 2 (2) | 5 (5) |
| Past history of haemorrhagic stroke | 0 | 0 | 0 |
| Past history of gastro-duodenal ulcer | 1 (<1) | 1 (<1) | 2 (2) |
| Baseline medication | | | |
| Antiplatelet therapy | 17 (15) | 22 (20) | 16 (15) |
| Non steroid anti-inflammatory drug | 3 (3) | 4 (4) | 1 (<1) |
| ACE-I or ARB | 13 (11) | 17 (15) | 23 (21) |
| Immunosuppressive treatment | 26 (23) | 29 (27) | 20 (18) |
| Glucocorticoid | 21 (23) | 20 (23) | 16 (19) |
| Others | 8 (9) | 9 (10) | 4 (5) |
| Medication prior randomisation | | | |
| Other antiviral treatment than Remdesivir | 1 (<1) | 2 (2) | 0 |
| Other immunomodulator treatment than Tocilizumab | 5 (15) | 6 (18) | 5 (15) |

Abbreviations: ACE-I=angiotensin-converting enzyme inhibitor. ARB=angiotensin II receptor blocker. CTPA=chest computed tomography with pulmonary angiogram. LVEF=left ventricular ejection fraction.

## 11 eTable 2. Compliance with Study Protocol

| | No. (%) or Median (IQR) | | |
|---|---|---|---|
| | Standard dose-prophylactic anticoagulation (n =114) | High dose-prophylactic anticoagulation (n =110) | Therapeutic anticoagulation (n =110) |
| Study drug (first dose) | | | |
| Low molecular weight heparin | 111 (97) | 107 (97) | 105 (95) |
| Tinzaparin | 21 (18) | 54 (49) | 77 (70) |
| Enoxaparin | 90 (79) | 53 (48) | 28 (25) |
| Unfractionated heparin | 3 (3) | 3 (3) | 5 (5) |
| Received first dose as per protocol | 109 (96) | 101 (92) | 106 (96) |
| Time on assigned treatment, %[a] | 100 (93 - 100) | 100 (75 - 100) | 100 (92 - 100) |
| Time on assigned treatment | | | |
| <50% | 13 (11) | 13 (12) | 6 (5) |
| 50-74% | 9 (8) | 15 (14) | 10 (9) |
| ≥75% | 92 (81) | 82 (75) | 94 (85) |

[a] from randomization to day 14 (or until reaching thrombosis or major bleeding or heparin-induced thrombocytopenia or hospital discharge or weaning of supplemental oxygen for 48 consecutive hours, whichever comes first)

## 12 eTable 3. Secondary Efficacy and Safety Outcomes

| Parameters | No. (%) | | |
|---|---|---|---|
| | SD-PA (n=114) | HD-PA (n=110) | TA (n=110) |
| Efficacy outcomes | | | |
| Deep vein thrombosis | 5 (4) | 1 (<1) | 1 (<1) |
| CVC-related deep vein thrombosis | 2 (2) | 1 (<1) | 0 |
| Ischemic stroke | 3 (3) | 1 (<1) | 1 (<1) |
| Non-cerebrovascular arterial thrombosis | 2 (2) | 0 | 1 (<1) |
| Modified seven-category scale | | | |
| 1-2, Hospital discharge [a] | 78 (68) | 67 (61) | 72 (65) |
| 3, Hospitalised with no oxygen therapy | 2 (2) | 5 (5) | 3 (3) |
| 4, Hospitalised with oxygen by mask or nasal catheter | 4 (4) | 7 (6) | 10 (9) |
| 5, Hospitalised with non-invasive ventilation or high-flow oxygen | 3 (3) | 3 (3) | 2 (2) |
| 6, Hospitalised with invasive mechanical ventilation, ECMO, or both | 11 (10) | 15 (14) | 9 (8) |
| 7, Death | 16 (14) | 13 (12) | 14 (13) |
| Safety outcomes | | | |
| Life-threatening bleeding event (RE-LY definition) | 3 (3) | 1 (<1) | 0 |
| Fatal bleeding | 2 (2) | 1 (<1) | 0 |
| Any bleeding [b] | 4 (4) | 4 (4) | 8 |
| Heparin induced thrombocytopenia | 0 | 0 | 0 |

Abbreviations: CVC=central venous catheter. ECMO=extracorporeal membrane oxygenation. HD-PA=High dose prophylactic anticoagulation. RE-LY= Randomised Evaluation of Long-Term Anticoagulation Therapy. SD-PA=standard dose prophylactic anticoagulation. TA=therapeutic anticoagulation.

[a] Home nasal oxygen therapy was prescribed at discharge for 10 patients (SD-PA, n=1; HD-PA, n=4; TA, n=5).

[b] Includes all ISTH-defined major bleedings and non-ISTH defined major bleedings.

## 13 eTable 4. Anatomical Localization of Adjudicated Pulmonary Artery Thrombosis

| Parameters | No. (%) | | |
|---|---|---|---|
| | SD-PA (n=15) | HD-PA (n=3) | TA (n=3) |
| Pulmonary artery thrombosis[a] | | | |
| Sub segmental or segmental | 5 (36) [n=14] | 1 (50) [n=2] | 2 (67) |
| Lobar or truncular | 9 (64) [n=14] | 1 (50) [n=2] | 1 (33) |
| Unilateral | 4 (29) [n=14] | 2 (100) [n=2] | 2 (67) |
| Bilateral | 10 (71) [n=14] | 0 [n=2] | 1 (33) |
| Right ventricular dilatation | 2 (13) | 1 (33) | 1 (33) |

Abbreviations: HD-PA=High dose prophylactic anticoagulation. SD-PA=standard dose prophylactic anticoagulation. TA=therapeutic anticoagulation.

[a]Because of unstable hemodynamics precluding patient's transport, it was not possible to localise the site of pulmonary artery thrombosis with computed tomography in one case in the SD-PA group and one case in the HD-PA group; the diagnosis of pulmonary artery thrombosis was adjudicated based on echocardiography in these two cases.

## 14 eTable 5. Description of Major Bleeding Events at Day 28 as per ISTH Definition

| N | Age | Sex | Assigned anticoagulation regimen | Time from randomization, days | Concomitant therapeutic anticoagulation | Concomitant antiplatelet therapy | Source | Severity criteria [a] | Haemostasis action reported [b] | Life-threatening bleeding [c] | Fatal |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 67 | M | SD-PA | 19 | Yes | No | Haemoptysis | 0 | Yes | Yes | Yes |
| 2 | 69 | M | HD-PA | 27 | Yes | No | Lower gastro-intestinal | 1 | No | No | No |
| 3 | 54 | F | TA | 12 | Yes | No | Haemoptysis | 1 | No | No | No |
| 4 | 75 | M | SD-PA | 10 | No | Yes | Upper gastro-intestinal | 1 | No | Yes | Yes |
| 5 | 66 | F | TA | 25 | Yes | No | Upper gastro-intestinal | 1 | No | No | No |
| 6 | 41 | F | HD-PA | 12 | Yes | Yes | Haemoptysis | 1 | No | No | No |
| 7 | 64 | M | SD-PA | 26 | Yes | No | Intramuscular with compartment syndrome | 0 | Yes | Yes | No |
| 8 | 81 | M | TA | 1 | Yes | No | Urinary | 1 | No | No | No |
| 9 | 61 | M | HD-PA | 7 | No | No | Diffuse Alveolar Haemorrhage | 0 | No | No | No |
| 10 | 73 | F | TA | 10 | Yes | No | Epistaxis | 1 | No | No | No |
| 11 | 56 | F | HD-PA | 10 | No | No | Intra-spinal | 0 | No | Yes | Yes |

Abbreviations: HD-PA=High dose prophylactic anticoagulation, ISTH=International Society on Thrombosis and Haemostasis, SD-PA=standard dose prophylactic anticoagulation, TA=therapeutic anticoagulation.
[a] Severity parameters: 1 = Bleeding associated with a reduction in haemoglobin of at least 2 g/dL or leading to transfusion of two or more units of blood or packed cells; 2 = Bleeding associated with a reduction in haemoglobin of at least 5 g/dL or leading to transfusion of at least four units of blood or packed cells.
[b] Surgical, endoscopic, or endovascular haemostasis action.
[c] According to the Randomised Evaluation of Long-Term Anticoagulation Therapy (RE-LY) definition [10].

## 15 eTable 6. Intention-to-treat and Subgroup Analysis of the Primary Outcome [a]

| | HD-PA % (95% CI) | SD-PA % (95% CI) | *P*-value | TA % (95% CI) | SD-PA % (95% CI) | *P*-value | TA % (95% CI) | HD-PA % (95% CI) | *P*-value |
|---|---|---|---|---|---|---|---|---|---|
| Intention-to-treat population | 47.3 (39.9 to 54.8) | 52.7 (45.2 to 60.1) | 0.48 | 50.9 (43.4 to 58.3) | 49.1 (41.7 to 56.6) | 0.82 | 53.5 (45.8 to 60.9) | 46.5 (39.1 to 54.2) | 0.37 |
| ICU hospitalised at randomisation | | | | | | | | | |
| Yes | 46.8 (39.0 to 54.7) | 53.2 (45.3 to 61.0) | 0.40 | 48.0 (40.1 to 56.0) | 52.0 (44.0 to 59.9) | 0.62 | 51.1 (43.1 to 59.0) | 48.9 (41.0 to 56.9) | 0.80 |
| No | 58.1 (34.5 to 78.2) | 41.9 (21.8 to 65.5) | 0.52 | 67.2 (44.7 to 83.3) | 32.8 (16.7 to 55.3) | 0.13 | 60.7 (36.7 to 80.0) | 39.3 (20.0 to 63.3) | 0.40 |
| Body-mass index. kg/m2 | | | | | | | | | |
| >30 | 45.2 (32.2 to 59.0) | 54.8 (41.0 to 67.8) | 0.50 | 55.1 (41.9 to 67.5) | 44.9 (32.5 to 58.1) | 0.45 | 59.6 (45.6 to 72.0) | 40.4 (28.0 to 54.4) | 0.18 |
| ≤30 | 48.1 (39.3 to 57.0) | 51.9 (43.0 to 60.7) | 0.68 | 48.2 (39.3 to 57.3) | 51.8 (42.7 to 60.7) | 0.71 | 50.3 (41.3 to 59.3) | 49.7 (40.7 to 58.7) | 0.95 |
| D-dimer level, ng/L [b] | | | | | | | | | |
| > 3000 | 55.2 (33.5 to 74.9) | 44.8 (25.1 to 66.5) | 0.66 | 51.8 (31.1 to 71.8) | 48.2 (28.2 to 68.9) | 0.88 | 42.4 (22.8 to 65.2) | 57.6 (34.8 to 77.2) | 0.54 |
| ≤ 3000 | 46.5 (38.7 to 54.5) | 53.5 (45.5 to 61.3) | 0.39 | 51.1 (43.1 to 59.0) | 48.9 (41.0 to 56.9) | 0.79 | 54.5 (46.5 to 62.3) | 45.5 (37.7 to 53.5) | 0.27 |
| Invasive mechanical ventilation | | | | | | | | | |
| Yes | 60.8 (37.1 to 79.9) | 39.2 (20.1 to 62.9) | 0.39 | 63.0 (38.0 to 82.1) | 37.0 (17.9 to 62.0) | 0.32 | 51.3 (29.1 to 72.8) | 48.8 (27.2 to 70.9) | 0.92 |
| No | 46.0 (38.3 to 54.0) | 54.0 (46.0 to 61.7) | 0.32 | 49.9 (42.1 to 57.7) | 50.1 (42.3 to 57.9) | 0.98 | 53.7 (45.6 to 61.5) | 46.3 (38.5 to 54.4) | 0.37 |

Abbreviations: SD-PA=Standard dose prophylactic anticoagulation. HD-PA=High dose prophylactic anticoagulation. TA=Therapeutic anticoagulation.

[a] Probability of more favourable outcome, also known as the probabilistic index, is the estimated probability that a patient randomly selected from one randomised arm will have a more favourable outcome than a patient randomly selected from the other arm.

[b] D-dimer upper limit of the normal range was 500 ng/ml.

## 16 eTable 7. Day 28 Outcomes taking onto account home nasal oxygen after hospital discharge [a]

| | No. (%) or Median (IQR) | | | HD-PA vs. SD-PA | TA vs. SD-PA | TA vs. HD-PA |
|---|---|---|---|---|---|---|
| | SD-PA (n=114) | HD-PA (n=110) | TA (n=110) | | | |
| **Primary outcome** | | | | Effect size (95%CI), *P* value | | |
| Probability of more favorable outcome, a ranked composite incorporating death and time to clinical improvement in survivors[b] | NA[c] | | | 46.0% (38.6 to 53.5), 0.29 | 49.4% (41.9 to 56.9), 0.88 | 53.2% (45.6 to 60.6), 0.41 |
| **Secondary efficacy outcomes** | | | | Absolute difference (95%CI), p value | | |
| Time to clinical improvement, days [d] | 8 (5-13) | 9 (6-13) | 8 (5-14) | 0.0 (2.0 to -1.0), 0.85 | -1.0 (1.0 to -2.0), 0.49 | -1.0 (1.0 to -2.0), 0.40 |

Abbreviations: HD-PA= high dose prophylactic anticoagulation. NA= Not applicable. SD-PA= standard dose prophylactic anticoagulation. TA=therapeutic anticoagulation.

[a] Home nasal oxygen therapy was prescribed at discharge for 10 patients (SD-PA, n=1; HD-PA, n=4; TA, n=5).

[b] Probability of more favorable outcome, also known as the probabilistic index, is the estimated probability that an individual randomly selected from one treatment group will have a higher score (more favorable outcome) than an individual randomly selected from the other group. It is mathematically equivalent to the area under the receiver operating characteristic curve of Mann-Whitney.

[c] No absolute value is reported for the primary endpoint effect estimate, i.e. probability of more favorable outcome, because the probability for either group is itself the comparator effect estimate; their combined probability equals 100%.

[d] Clinical improvement was defined as a decline of two points on the modified seven-category ordinal scale of clinical status [14].

## 17 eTable 8. Day 28 Secondary Outcomes of the Intensive Care Unit Subgroup

| | No. (%) or Median (IQR) | | | Absolute difference (95%CI), *P* value | | |
|---|---|---|---|---|---|---|
| | **SD-PA (n=101)** | **HD-PA (n=101)** | **TA (n=97)** | **HD-PA vs. SD-PA** | **TA vs. SD-PA** | **TA vs. HD-PA** |
| **Secondary efficacy outcome** | | | | | | |
| Composite thrombotic event | 22 (22) | 5 (5) | 6 (6) | -16.8 (-7.7 to -25.9), 0.001 | -15.6 (-6.2 to -25.0), 0.002 | 1.2 (7.6 to -5.2), 0.76 |
| Venous thrombosis | 19 (19) | 4 (4) | 4 (4) | -14.9 (-6.3 to -23.4), 0.001 | -14.7 (-6.1 to -23.3), 0.001 | 0.2 (5.7 to -5.3), 1.00 |
| Deep vein thrombosis (including CVC-related) | 7 (7) | 2 (2) | 1 (1) | -5.0 (0.7 to -10.6), 0.17 | -5.9 (-0.6 to -11.2), 0.06 | -0.9 (2.4 to -4.3), 1.00 |
| Pulmonary artery thrombosis | 14 (14) | 2 (2) | 3 (3) | -11.9 (-4.6 to -19.1), 0.003 | -10.8 (-3.2 to -18.3), 0.01 | 1.1 (5.5 to -3.3), 0.68 |
| Arterial thrombosis | 5 (5) | 1 (1) | 2 (2) | -4.0 (0.7 to -8.6), 0.21 | -2.9 (2.2 to -8.0), 0.44 | 1.1 (4.5 to -2.4), 0.62 |
| All-cause death | 14 (14) | 11 (11) | 13 (13) | -3.0 (6.1 to -12.0), 0.67 | -0.5 (9.1 to -10.0), 1.00 | 2.5 (11.6 to -6.6), 0.67 |
| Time to clinical improvement, d [a] | 9 (6-14) | 9 (6-14) | 8 (5-15) | 0.0 (2.0 to -1.0), 0.78 | 0.0 (2.0 to -2.0), 0.84 | 0.0 (2.0 to -2.0), 0.67 |
| Supplemental oxygen-free days, d | 17 (0-23) | 16 (0-22) | 16 (0-22) | 0.0 (1.0 to -2.0), 0.70 | 0.0 (1.0 to -2.0), 0.54 | 0.0 (1.0 to -2.0), 0.76 |
| Ventilator-free days, d | 28 (14-28) | 28 (14-28) | 28 (10-28) | 0.0 (0.0 to 0.0), 0.81 | 0.0 (0.0 to 0.0), 0.48 | 0.0 (0.0 to 0.0), 0.62 |
| Vasopressors-free days, d | 28 (26-28) | 28 (27-28) | 28 (26-28) | 0.0 (0.0 to 0.0), 0.84 | 0.0 (0.0 to 0.0), 0.75 | 0.0 (0.0 to 0.0), 0.60 |
| Sepsis-induced coagulopathy Score at day 7 [b] | 2 (2-2) [n=35] | 2 (2-2) [n=35] | 2 (2-3) [n=39] | 0.0 (0.0 to 0.0), 0.53 | 0.0 (0.0 to 0.0), 0.18 | 0.0 (0.0 to 0.0), 0.43 |
| D-dimer at day 7, ng/mL [c] | 1983 (1169-5229) [n=54] | 1991 (994-5589) [n=55] | 1685 (765-3315) [n=52] | -209.5 (520.0 to -1006.0), 0.63 | -640.0 (40.0 to -1444.0), 0.06 | -413.5 (233.0 to -1199.0), 0.21 |
| Length of intensive care unit stay, d | 15 (9-22) | 17 (11-30) | 14 (9-27) | 2.0 (5.0 to -1.0), 0.15 | 1.0 (4.0 to -2.0), 0.67 | -2.0 (1.0 to -5.0), 0.24 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Length of hospital stay, d | 15 (9-22) | 17 (11-30) | 14 (9-27) | 2.0 (5.0 to -1.0), 0.11 | 1.0 (4.0 to -2.0), 0.68 | -2.0 (1.0 to -5.0), 0.17 |
| EuroQol 5-Dimension 5-Level index value at day 90 [d] | 1 (1-1) [n=56] | 1 (1-1) [n=66] | 1 (1-1) [n=63] | 0.0 (0.0 to 0.0), 0.51 | 0.0 (0.0 to 0.0), 0.21 | 0.0 (0.0 to 0.0), 0.34 |
| EuroQol 5-Dimension 5-Level General Health Visual analogue scale at day 90 [e] | 80 (70 - 95) [n=53] | 81 (70 - 90) [n=64] | 80 (60 - 90) [n=58] | 0.0 (5.0 to -5.0), 0.71 | -5.0 (0.0 to -10.0), 0.12 | -5.0 (0.0 to -10.0), 0.13 |
| All-cause death at day 90. | 19 (19) | 20 (20) | 17 (18) | 1.0 (11.9 to -9.9), 1.00 | -1.1 (9.7 to -11.9), 0.86 | -2.1 (8.8 to -13.0), 0.72 |
| **Safety outcomes** | | | | | | |
| Major bleeding (ISTH definition) | 3 (3) | 4 (4) | 4 (4) | 1.0 (6.0 to -4.1), 1.00 | 1.2 (6.3 to -4.0), 0.72 | 0.2 (5.7 to -5.3), 1.00 |
| **Combined efficacy and safety outcome** | | | | | | |
| Net clinical outcome [f] | 31 (31) | 16 (16) | 21 (22) | -14.9 (-3.4 to -26.3), 0.019 | -9.0 (3.1 to -21.2), 0.20 | 5.8 (16.7 to -5.0), 0.36 |

Abbreviations: CVC= central venous catheter. ECMO= extracorporeal membrane oxygenation. HD-PA= high dose prophylactic anticoagulation. ISTH = International Society on Thrombosis and Haemostasis. NA= Not applicable. SOFA=Sequential Organ Failure Assessment. SD-PA= standard dose prophylactic anticoagulation. TA=therapeutic anticoagulation.

[a] Clinical improvement was defined as a decline of two points o the modified seven-category ordinal scale of clinical status [14].

[b] The assessment scores from 0 to 2 each of the following variables: platelet count, PT ratio and total SOFA (sum of the four items: respiratory SOFA, cardiovascular SOFA, hepatic SOFA, renal SOFA) [6].

[c] D-dimer upper limit of the normal range was 500 ng/ml.

[d] Preference-based health-related quality of life measured with one question for each of the five dimensions, including mobility, self-care, usual activities, pain and discomfort, and anxiety and depression. The index values vary from 1.0 (perfect health) to below zero (health condition valued worse than death), and zero (a state equivalent to death) [5].

[e] Scale numbered from 0 to 100: 100 means the best health the patient can imagine; 0 means the worst health the patient can imagine.

[f] Composite outcome including any composite thrombotic event, ISTH-defined major bleeding, and all-cause death.

## 18 eTable 9. Day 28 Outcomes in the Per-Protocol Cohort

| | No. (%) or Median (IQR) | | | HD-PA vs. SD-PA | TA vs. SD-PA | TA vs. HD-PA |
|---|---|---|---|---|---|---|
| | SD-PA (n=92) | HD-PA (n=82) | TA (n=94) | | | |
| **Primary outcome** | | | | Effect (95%CI), *P* value | | |
| Probability of more favourable outcome, a ranked composite incorporating death and time to clinical improvement in survivors [a] | NA [b] | | | 47.0% (38.7 to 55.5), 0.49 | 48.8% (40.7 to 57.1), 0.78 | 51.8% (43.4 to 60.1), 0.68 |
| **Secondary efficacy outcome** | | | | Absolute difference (95%CI), *P* value | | |
| Composite thrombotic event | 19 (21) | 5 (6) | 6 (6) | -14.6 (-4.8 to -24.3), 0.007 | -14.3 (-4.6 to -23.9), 0.005 | 0.3 (7.4 to -6.9), 1.000 |
| Venous thrombosis | 16 (17) | 4 (5) | 4 (4) | -12.5 (-3.5 to -21.6), 0.016 | -13.1 (-4.4 to -21.9), 0.004 | -0.6 (5.6 to -6.8), 1.00 |
| Deep vein thrombosis (including CVC-related) | 4 (4) | 2 (2) | 1 (1) | -1.9 (3.4 to -7.2), 0.68 | -3.3 (1.4 to -7.9), 0.21 | -1.4 (2.6 to -5.3), 0.60 |
| Pulmonary artery thrombosis | 12 (13) | 2 (2) | 3 (3) | -10.6 (-3.0 to -18.3), 0.011 | -9.9 (-2.1 to -17.6), 0.016 | 0.8 (5.6 to -4.1), 1.00 |
| Arterial thrombosis | 5 (5) | 1 (1) | 2 (2) | -4.2 (1.0 to -9.4), 0.21 | -3.3 (2.2 to -8.8), 0.28 | 0.9 (4.7 to -2.9), 1.00 |
| All-cause death | 14 (15) | 10 (12) | 12 (13) | -3.0 (7.2 to -13.2), 0.66 | -2.5 (7.5 to -12.4), 0.68 | 0.6 (10.4 to -9.2), 1.00 |
| Time to clinical improvement, days [c] | 8 (5-12) | 8 (6-12) | 8 (5-14) | 1.0 (2.0 to -1.0), 0.46 | 0.0 (2.0 to -2.0), 0.80 | 0.0 (1.0 to -2.0), 0.64 |
| Supplemental oxygen-free days, days | 18 (0-23) | 16 (0-22) | 18 (0-22) | 0.0 (1.0 to -3.0), 0.57 | 0.0 (1.0 to -2.0), 0.83 | 0.0 (2.0 to -1.0), 0.75 |
| Ventilator-free days, days | 28 (12-28) | 28 (14-28) | 28 (10-28) | 0.0 (0.0 to 0.0), 0.91 | 0.0 (0.0 to 0.0), 0.65 | 0.0 (0.0 to 0.0), 0.71 |
| Vasopressors-free days, days | 28 (26-28) | 28 (27-28) | 28 (26-28) | 0.0 (0.0 to 0.0), 0.74 | 0.0 (0.0 to 0.0), 0.87 | 0.0 (0.0 to 0.0), 0.60 |
| Sepsis-induced coagulopathy Score at day 7 [d] | 2 (2-2) [n=33] | 2 (2-2) [n=26] | 2 (2-3) [n=37] | 0.0 (0.0 to 0.0), 0.67 | 0.0 (0.0 to 0.0), 0.28 | 0.0 (0.0 to 0.0), 0.13 |
| D-dimer at day 7, ng/mL [e] | 1780 (980-4790) [n=51] | 1935 (1180-5589) [n=42] | 1595 (770-3270) [n=50] | 18.5 (801.0 to -823.0), 0.95 | -420.0 (230.0 to -1150.0), 0.17 | -458.0 (271.0 to -1312.0), 0.22 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Length of intensive care unit stay, days | 14 (9-22) | 16 (10-30) | 14 (9-27) | 2.0 (5.0 to -2.0), 0.30 | 1.0 (4.0 to -2.0), 0.49 | -1.0 (2.0 to -4.0), 0.62 |
| Length of hospital stay, days | 14 (8-22) | 15 (10-30) | 13 (8-24) | 2.0 (5.0 to -1.0), 0.20 | 0.0 (3.0 to -2.0), 0.73 | -1.5 (1.0 to -4.0), 0.28 |
| EuroQol 5-Dimension 5-Level index value at day 90 [f] | 1 (1-1) [n=49] | 1 (1-1) [n=53] | 1 (1-1) [n=58] | 0.0 (0.0 to 0.0), 0.42 | 0.0 (0.0 to 0.0), 0.32 | 0.0 (0.0 to 0.0), 0.57 |
| EuroQol 5-Dimension 5-Level General Health Visual analogue scale at day 90 [g] | 80 (70-95) [n=47] | 80 (70-90) [n=51] | 80 (60-90) [n=52] | 0.0 (5.0 to -6.0), 0.73 | -5.0 (0.0 to -10.0), 0.25 | -2.0 (1.0 to -10.0), 0.30 |
| All-cause death at day 90 | 18 (20) | 18 (22) | 16 (17) | 2.4 (14.5 to -9.7), 0.71 | -2.2 (9.0 to -13.4), 0.85 | -4.6 (7.3 to -16.4), 0.57 |
| **Safety outcomes** | | | | | | |
| Major bleeding (ISTH definition) | 2 (2) | 1 (1) | 4 (4) | -1.0 (2.9 to -4.8), 1.00 | 2.1 (7.1 to -3.0), 0.68 | 3.0 (7.8 to -1.7), 0.37 |
| **Combined efficacy and safety outcome** | | | | Absolute difference (95%CI), *P* value | | |
| Net clinical outcome [h] | 29 (32) | 13 (16) | 20 (21) | -15.7 (-3.3 to -28.0), 0.02 | -10.2 (2.3 to -22.8), 0.13 | 5.4 (16.9 to -6.0), 0.44 |

Abbreviations: CVC= central venous catheter. ECMO= extracorporeal membrane oxygenation. HD-PA= high dose prophylactic anticoagulation. ISTH= International Society on Thrombosis and Haemostasis. NA= Not applicable. RE-LY= Randomised Evaluation of Long-Term Anticoagulation Therapy. SOFA=Sequential Organ Failure Assessment. SD-PA= standard dose prophylactic anticoagulation. TA=therapeutic anticoagulation.

[a] Probability of more favourable outcome, also known as the probabilistic index, is the estimated probability that an individual randomly selected from one treatment group will have a higher score (more favourable outcome) than an individual randomly selected from the other group. It is mathematically equivalent to the area under the receiver operating characteristic curve of Mann-Whitney.

[b] No absolute value is reported for the primary endpoint effect estimate, i.e. probability of more favourable outcome, because the probability for either group is itself the comparator effect estimate; their combined probability equals 100%.

[c] Clinical improvement was defined as a decline of two points on the modified seven-category ordinal scale of clinical status [14].

[d] The assessment scores from 0 to 2 each of the following variables: platelet count, PT ratio, and total SOFA (sum of the four items: respiratory SOFA, cardiovascular SOFA, hepatic SOFA, and renal SOFA) [6].

[e] D-dimer upper limit of the normal range was 500 ng/ml.

[f] Preference-based health-related quality of life measured with one question for each of the five dimensions, including mobility, self-care, usual activities, pain and discomfort, and anxiety and depression. The index values vary from 1.0 (perfect health) to below zero (health condition valued worse than death), and zero (state equivalent to death) [5].

[g] Scale numbered from 0 to 100: 100 means the best health the patient can imagine; 0 means the worst health the patient can imagine.

[h] Composite outcome including any composite thrombotic event, ISTH-defined major bleeding, and all-cause death.

## 19 eReferences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