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Anticoagulation in patients with severe COVID-19: protocol for a multicenter, parallel-group, open-label, randomized controlled trial

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ABSTRACT

Introduction: Coronavirus disease 2019 (COVID-19) induces venous, arterial, and microvascular thrombosis, involving several distinct pathophysiological processes. In severe COVID-19 patients without initial macrovascular thrombotic event, dose escalation with high-dose preventive anticoagulation (HD-PA) or therapeutic anticoagulation (TA) could be beneficial by limiting the extension of microvascular thrombosis and the evolution of the lung and multi-organ microcirculatory dysfunction. In the absence of data from randomized trials in this setting, recommendations and clinical practice vary widely.

Methods and analysis: This is a multicenter, parallel-group, open-label, randomized controlled superiority trial to compare the efficacy and safety of three anticoagulation strategies in COVID-19 patients. Patients with oxygen dependant COVID-19 pneumoniae and a computed tomography with pulmonary angiogram showing no pulmonary artery thrombosis will be randomized to receive either low-dose preventive anticoagulation (LD-PA), HD-PA, or TA for 14 days. Patients with extreme weights and those with severe renal failure will not be included. Three hundred patients will be randomised with a 1:1:1 ratio, stratified by center, receiving invasive mechanical ventilation, D-dimer levels and body mass index. The primary endpoint is a hierarchical criterion assessed at day-28, including all-cause mortality, followed by the time to clinical improvement defined as the time from randomization to an improvement of at least two points, using an ordinal clinical scale. Secondary outcomes include thrombotic events and major bleeding events at day-28, individual components of the composite ranked primary endpoint, number of oxygen-, ventilator- and vasopressor-free days at day 28, D-dimers and Sepsis-Induced Coagulopathy Score at day-7, ICU and hospital length of stay at day-28 and day-90, and all-cause death and quality of life at day-90.

Ethics and dissemination: The study has been approved by an ethics committee and patients will be included after obtention of informed consent. The results will be submitted for publication in a peer-reviewed journals.

Trial registration number: NCT04808882

Strengths and limitations of the study

►This randomized controlled trial may contribute to establish strong recommendations with a high level of evidence on the best anticoagulation strategy to limit the extension of microvascular thrombosis and the evolution of the lung and multi-organ microcirculatory dysfunction in severe COVID-19 patients without initial macrovascular thrombosis.

►Eligibility criteria differ from previous published studies on anticoagulation strategies in COVID-19 patients with the systematic screening for macro-thrombosis before randomization and exclusion of obese patients and patients with renal failure to minimize baseline bleeding risk.

►Limitation: Individual study assignments will not be masked.

INTRODUCTION

Background and rationale

Coronavirus disease 2019 (COVID-19), a viral respiratory illness caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), may predispose patients to thrombotic disease [1] due to a combination of intense inflammation, platelet activation, and endothelial dysfunction leading to respiratory distress and increased mortality [2–4].

The incidence of macrovascular thrombotic events varies from 10 to 30% in COVID-19 hospitalized patients depending on the type of thrombosis, arterial or venous and the severity of illness [2–4]. Based on the observational data in patients receiving routine low-dose prophylactic anticoagulation (LD-PA), several institutions released guidance statements in order to prevent macrovascular thrombotic events using dose escalation anticoagulation [5,6]. In these recommendations, high-dose prophylactic anticoagulation (HD-PA) and therapeutic anticoagulation (TA) can be employed either empirically or based on various criteria like the body mass index or the D-dimer concentration [5–7]. However, other conflicting recommendations challenge this approach [6,8].

Microvascular thrombotic events are also of major concern in patients with COVID-19. A large review of autopsy findings in COVID-19-related deaths reported micro thrombi in small pulmonary vessels [9]. COVID-19-induced endothelitis and coagulopathy across vascular beds of different organs leads to widespread microvascular thrombosis [2,10,11]. Thus, in severe COVID-19 patients without initial macrovascular thrombotic event, HD-PA or TA could be beneficial by limiting the extension of microvascular thrombosis and the evolution of the lung and multi-organ microcirculatory dysfunction.

To date, no randomized clinical trial has evaluated the best anticoagulation strategy in severe COVID-19 patients in whom an initial macrovascular thrombotic event has been systematically excluded. It seems important to rationalize and compare anticoagulation strategies in this population.

Hypothesis

Our hypothesis is dual, in patients with severe COVID-19 pneumonia and free of macrovascular thrombosis: i) first, that TA and HD-PA strategies mitigate microthrombosis and each limit the progression of COVID-19, including respiratory failure and multi-organ dysfunction, leading to decreased mortality and duration of disease, as compared to a low-dose PA; ii) second, that TA outperforms HD-PA in this setting.

Objectives

Primary objective

The main objective is to compare the efficacy of three strategies (LD- PA, HD-PA, and TA) to reduce the mortality and the time to clinical improvement.

Secondary objectives

The secondary objectives are to compare the benefit and risks of the three strategies (LD-PA, HD-PA, and TA) regarding: i) mortality, morbidity and organ dysfunction; ii) thrombotic events, bleeding events, and net clinical benefit.

Ancillary study

An ancillary study will assess clinical and biological characteristics of severe COVID-19 pneumonia with or without pulmonary embolism to establish a scoring system for COVID-19 related pulmonary embolism diagnosis.

METHODS AND ANALYSIS

Trial design

This is a multicenter, parallel-group, open-label, randomized controlled superiority trial to compare the efficacy and safety of three anticoagulation strategies (LD- PA, HD-PA, and TA) in patients with COVID-19 pneumonia. This trial protocol follows the Standard Protocol Items: Recommendations for Interventional Trial (CONSORT) reporting guidelines.

Study setting

This study will take place in more than 30 units (23 intensive care units and 8 conventional care units) in at least 23 hospitals in France.

Eligibility criteria

Inclusion criteria

Adult patients (age ≥ 18 years) admitted to the hospital will be eligible as soon as they meet all of the following criteria:

1. Severe COVID-19 pneumonia, defined by: i) new pulmonary parenchymal infiltrate; and ii) positive RT-PCR (either upper or lower respiratory tract) for SARS-CoV-2; and iii) WHO (World Health Organisation) ordinal scale ≥ 5 [12];
2. Written informed consent as per French law (patient, next of kin or differed consent in an emergency situation).

Non-inclusion criteria

Patients fulfilling one of the following criteria will not be included:

1. Pregnant or breast-feeding woman;
2. Postpartum (6 weeks);
3. Extreme weights (<40 kg or >100 kg);
4. Patients admitted since more than 72 hours to the hospital (if the WHO ordinal scale is 5 at the time of inclusion) or since more than 72 hours to the intensive care unit (if the WHO ordinal scale is 6 or more at time of inclusion);
5. Need for TA;
6. Bleeding event related to hemostasis disorders, acute clinically significant bleed, current gastrointestinal ulcer or any organic lesion with high risk for bleeding;
7. Platelet count < 50 G/L;
8. Within 15 days of recent surgery, within 24 hours of spinal or epidural anaesthesia;
9. Any prior intracranial hemorrhage, large acute ischemic stroke, known intracranial malformation or neoplasm, acute infectious endocarditis;
10. Severe renal failure (creatinine clearance <30 mL/min);
11. Iodine allergy;
12. Hypersensitivity to heparin or its derivatives including low-molecular-weight heparin;
13. History of type II heparin-induced thrombocytopenia;
14. Chronic oxygen supplementation;
15. Moribund patient or death expected from underlying disease during the current admission;
16. Patient deprived of liberty and persons subject to institutional psychiatric care;

17. Patients under guardianship or curatorship;
18. Participation to another interventional research on anticoagulation.

Intervention

A systematic daily check of all patients hospitalized with a positive RT-PCR (either upper or lower respiratory tract) for COVID-19 (SARS-CoV-2) in the participating centers will be performed, looking for inclusion and non-inclusion criteria. The number of patients who do not meet the inclusion criteria will be reported prospectively on a paper register by each of the participating centers. A patient identification number as well as the reason for non-inclusion will be noted (local register of non-inclusion in each of the centers).

Inclusion (D0) is performed as soon as possible, within 72 hours of hospital admission (if the WHO ordinal scale is 5 at time of inclusion, [12]) or within 72 hours of intensive care unit admission (if the WHO ordinal scale is 6 or more at time of inclusion, [12]).

A chest computed tomography with pulmonary angiogram (CTPA) will be performed within 72 hours before **(**or up to 24 hours after**)** inclusion; If a CTPA was performed within 7 days of inclusion and the likelihood of pulmonary artery thrombosis is deemed unchanged by the clinician, the result of that CTPA may be considered at time of inclusion (Figure 1).

- If CTPA demonstrates the existence of a pulmonary artery thrombosis, the patient will not be randomized and will receive TA following current guidelines [13].
- If CTPA does not demonstrate the existence of a pulmonary artery thrombosis, the patient will be randomised to receive either LD-PA, HD-PA or TA for 14 days (or until hospital discharge or weaning of supplemental oxygen during 48 consecutive hours, whichever occurs first). If the patient has no pulmonary artery thrombosis but presents with clinical signs suggestive of deep venous thrombosis at inclusion, a complete duplex ultrasound (CDUS) of the lower extremities will be performed [14]; If CDUS demonstrates the existence of deep venous thrombosis, the patient will not be randomized and will receive TA according to current guidelines; If the CDUS is negative, the patient will be randomized.

LD-PA, HD-PA, and TA will be initiated immediately after randomization in all patients with low weight molecular heparin (LMWH) tinzaparin at the dose of 3500 IU/24h, 7000 IU/24h, or 175 IU/kg/24h, respectively; if tinzaparin is not available, enoxaparin may be used at the dose of: 4000 IU/24h, 4000 IU/12h, and 100 IU/kg/12h, respectively.

In case of renal failure (creatinine clearance < 30 mL/min) occurring after randomization or in case of invasive procedure at high risk of bleeding, LMWH may be replaced by a continuous intravenous infusion of unfractioned heparin as follows: i) LD-PA: 100 IU/kg/24h; ii) HD-PA: 200 IU/kg/24h; iii) TA: 500 IU/kg/24h, adapted to the anti-Xa activity (target between 0.3 and 0.6 IU/ml) as per current guidelines.

After day-14, or hospital discharge, or in case of a clinical indication for TA, or of serious adverse event related to anticoagulation, the investigational anticoagulation strategy will be discontinued and anticoagulation treatment will be left at the discretion of attending physicians.

In all groups, current recommendations for the management of COVID-19 pneumonia will be followed, including the use of dexamethasone [15].

Criteria and procedure for premature withdrawal of a participant from the study

In accordance with the usual management of patients with severe COVID-19 pneumonia, anticoagulation will be discontinued in the following cases:

- Occurrence of major bleeding event according to the ISTH definition (see annex 5);
- Occurrence of a large acute ischemic stroke;
- Skin necrosis at the injection site;
- Occurrence of a type II heparin induced thrombocytopenia;
- Occurrence of an allergic reaction;
- Hospital discharge prior to day-14.

The TA strategy will be temporarily interrupted if any of the following conditions is met, prior to the maximum treatment period (14 days from randomisation); the study drug will be administered again at least 6 hours after the resolution of the anomaly:

- Clinical need for TA;
- Need for lumbar puncture, spinal or epidural anaesthesia;
- Need for surgery.

Outcomes

Primary outcome

The primary endpoint is a hierarchical criterion assessed at day-28, including all-cause mortality, followed by the time to clinical improvement calculated in such a manner that death constitutes a worse outcome than delay to clinical improvement.

The time (number of days) to clinical improvement is defined as the time from randomization to an improvement of at least two points (from the status at randomization), using a seven-category ordinal scale derived from the WHO recommended instrument [12], as proposed by Coa et al [16] (**table 1**). Since all included patients will at least require oxygen supplementation, live discharge from hospital will represent a minimal 2-points decrease in the 7-points scale, thus a clinical improvement.

Secondary outcomes

Secondary outcome will include the following:

(1) Efficacy on morbi-mortality and organ function

- Individual components of the composite ranked primary endpoint, including time to clinical improvement and all-cause death at day-28;
- All-cause death at day-90;
- Score on WHO ordinal scale and 7-points ordinal scale at day-28;
- D-dimers and Sepsis-Induced Coagulopathy Score (SCS) (see detailed definition in **Table** 2) at day-7;
- Proportion of patients needing invasive mechanical ventilation at day-28;
- Number of days alive and free from supplemental oxygen at day-28;
- Number of days alive and free from invasive mechanical ventilation at day-28;
- Number of days alive and free from vasopressors at day-28;
- Length of intensive care unit stay at day-28 and day-90;
- Length of hospital stay at day-28 and day-90;
- Quality of life assessed using a quality-of-life questionnaire (EQ5D5L) [17] at day-90.

(2) ***Efficacy on thrombotic events***: proportion of patients with at least one thrombotic event at day-28 including ischemic stroke, non-cerebrovascular arterial thrombotic

event, deep venous thrombosis, pulmonary embolism, or central venous catheter-related deep venous thrombosis (**see detailed definition in Annex 5**);

(3) Tolerance of anticoagulation

- Proportion of patients with at least one major bleeding event (MBE) at day-28 according to the international Society on Thrombosis and Haemostasis (ISTH) definition (**see details definition in Annex 5**);
- Proportion of patients with at least one life-threatening bleeding event at day-28 according to the RE-LY definition (**see details definition in Annex 5**);
- Proportion of patients with any bleeding event at day-28 including major and minor bleeding events; minor bleeding events will be defined as all non-major bleeding events;
- Proportion of patients with Heparin Induced Thrombocytopenia (HIT) at day-28.

(4) Net clinical benefit of anticoagulation

- Composite endpoint at day-28 including of all-cause death, thrombotic event, and MBE.

Classification of the severity of thrombotic and bleeding events will be carried out by an adjudication committee.

Sample size and its statistical justification

The required number of participants is 300 randomized patients (353 included patients).
Using estimates derived from prior studies led in similar populations [16], a sample of at least 300 patients (100 per group) was needed to provide ≥80% power to detect a statistically significant difference in the primary ranked composite outcome with 2-sided alpha of 0.017 using a Bonferroni correction for multiple testing considering 3 pairwise comparisons between randomized arms. Sample size calculations assumed 28-day mortality of 24%, 21% and 18%, and time to clinical improvement of 16 +/- 3 days (standard deviation), 14 days and 12 days, with LD-PA, HD-PA, and TA, respectively. We hypothesize a 15% rate of positive CTPA [18,19]. In order to randomize 300 patients, we aim to include 353 patients.

Sample size calculation was carried out by considering pairwise comparisons between the groups. For each performed comparison, 5000 samples were simulated using R software. For the first component of the hierarchical primary endpoint (i.e. mortality), survival curves were simulated based on a Weibull distribution using the R package simsurv. For the second component of the hierarchical primary endpoint (i.e. days until clinical improvement) assessed in alive patients, two different approaches were used regarding the distribution of this parameter to test the robustness of the results depending on retained hypotheses. First, a normal distribution was hypothesized with means+/-SD of 16+/-3, 14+/-3 and 12+/-3 days in LD-PA, HD-PA and TA, respectively. Second, incidence curves for clinical improvement were simulated based on a Weibull distribution using the R package simsurv, with survival medians of 16, 14 and 12 days in LD-PA, HD-PA and TA, respectively. For both approaches, a systematic 5% rate of patients were identified through simulation as alive patients at D28 but without achieving clinical improvement, consistent with Cao et al 2020 [16]. Standard deviation and mean number of days until clinical improvement, as well as shape and scale parameters for the Weibull survival curves simulations were determined from Cao et al 2020 [16], considering median [interquartile range] survival times and Kaplan Meier curves. Within each sample/pairwise comparison, each patient's score was calculated based on comparing each patient in one group to all patients in the second group (23). These scores were then compared between groups by a Mann-Whitney / Wilcoxon test in each of the 5000 samples and the p-value of each test recorded. For each pairwise comparison, the proportion of tests with a p-value <0.017 was calculated, providing an estimate for the statistical power achieved.

Recruitment

The expected duration of patient enrolment is 18 months, starting in April 2021. The chronogram of the study is as follows: i) december 2020: industrial grant award; ii) December 2020: Promotion by the Assistance Publique Hôpitaux de Paris; iii) March 2021: approval by an independent ethics committee; iv) April 2021-October 2022: inclusion of patients; iv) 2022-2023: end of inclusions, monitoring of participating centres and queries to investigators; cleaning and closure of the database; blind review to determine protocol violation, to define intention-to-treat and per-protocol analysis populations; ; v) 2022-2023: data analysis, writing of the manuscript and submission for publication.

Assignment of intervention and data collection

After obtaining consent from the patient or her/his relative, all inclusion/exclusion criteria will be checked by the investigator before randomization. Centralized blocked randomization according to a 1:1:1 ratio will be prepared by the Clinical Research Unit before the start of the trial. It will be carried out in balanced blocks and stratified by hospital center and according to the following criteria at inclusion: need for intubation (yes or no), D-dimer levels (upper or lower than 3 µg/ml), and body mass index (upper or lower than 30 kg/m2). Randomization will be carried out by connecting to the centralized e-CRF website "Cleanweb" provided by Telemedicine technologies. Data will be entered into the e-CRF by a trained investigator or research assistant at each centre. Patient follow-up and data collected are detailed in the study flow chart **(Table 3).**

Statistical methods

All the analyses will be performed by the study statistician 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 less than 0.05 will be considered as indicating statistical significance.

In accordance with the CONSORT statement, a flow diagram will describe the progress of patients of the three groups throughout the different phases of the trial (enrolment, intervention allocation, intervention received, follow-up, and data analysis). The analysis will be performed on an intention-to-treat basis. In case of premature stop or withdrawal from the study, patients won't be substituted. Missing value will be described and, according to nature and frequency, multiple imputation methods will be used. A per-protocol analysis will be held as sensitivity analysis, excluding patients wrongly randomised or who didn't receive the allocated intervention.

Comparative analysis will systematically be done with (main analysis) and without adjustment on randomisation stratification factors. No interim analysis is planned. The primary efficacy endpoint will be analyzed using the intention to treat (ITT) population. Supportive analyses in the per protocol (PP) population will be carried out, so as to document the patients excluded from PP, investigate the impact on ITT analysis and eventually check whether similar results are obtained for a robust interpretation. All analyses of secondary endpoints will be conducted on both ITT and PP populations to assess the robustness of the results.

Descriptive analysis

Descriptive statistical analyses will be conducted overall and regarding the randomized groups in terms of general characteristics, demographics, history and baseline characteristics, as well as numbers of prematurely study treatment withdrawals. Quantitative variables will be presented as mean (±standard deviation) or median (25^{th}-75^{th} percentiles) according to the normality of their distribution as assessed by means of Shapiro-Wilk tests and graphical methods, and qualitative variables will be presented as numbers (%).

Analysis of the primary outcome

The prespecified primary end point will be a ranked composite score that incorporates death and time to clinical improvement, calculated in such manner that death constitutes a worse outcome than more days to clinical improvement. Each patient will be compared with every other patient in the study and assigned a score (tie: 0, win: +1, loss: −1) for each pairwise comparison based on whom fared better. If one patient survived and the other did not, scores of +1 and −1 will be assigned, respectively, for that pairwise comparison. If both patients in the pairwise comparison survived, the assigned score will depend on which patient had more days to clinical improvement: the patient with fewer days will receive a score of +1, while the patient with more days will receive a score of −1. If both patients survived and had the same number of days to clinical improvement, or if both patients died, they both will be assigned a score of 0 for that pairwise comparison. For each patient, scores for all pairwise comparisons will be summed, resulting in a cumulative score for each patient. These cumulative scores will be ranked and compared between treatment groups via a non-parametrical Mann-Whitney test.

Analysis of secondary outcomes

Comparisons between randomized groups at given timepoints will be conducted by use of the Chi square test or the Fisher's exact test, according to expected numbers in crossings, for categorical variables and by use of t-tests or non-parametrical Mann-Whitney tests (pairwise comparisons), and ANOVA or Kruskal Wallis tests (global comparisons for>2 groups) for quantitative variables, as appropriate. Pairwise comparisons within groups (i.e. across timepoints) will be conducted using tests for paired data, i.e. McNemar tests for qualitative data, and t-tests for paired data or Wilcoxon signed ranks tests for continuous data, as appropriate.

Individual components of the composite primary endpoint will be assessed as secondary endpoints, i.e. all-cause mortality at 28-day follow-up and number of days until clinical improvement. To do so, methods for time-to-event endpoints based on follow-up censored data will be conducted, accounting for the competing risks of hospital discharge (for mortality evaluation) and death (for time to clinical improvement). Kaplan-Meier survival curves and cumulative incidence curves will be plotted for each treatment group, and Fine-Gray regression models will be used to calculate subhazard ratios along with their 95% confidence intervals and corresponding P-values.

Analyses of independent determinants of quantitative secondary endpoints will be performed using multivariable linear regression analyses adjusting for baseline characteristics and, for global longitudinal analysis using generalized linear regression mixed models, testing interaction between time, group and prespecified predictors and entering patient level as a random effect to account for the hierarchical structure of repeated data.

Tolerance analysis will be carried out according to the period of appearance and randomization group on the detailed adverse events relating to the treatment, comparing the rates of occurrence and time of occurrence.

Data monitoring

The trial will be overseen by a steering committee (principal investigator, senior investigator and methodologist) regarding the progression and monitoring of the study. Research assistants will regularly monitor all the centres on site to check protocol adherence and accuracy of the recorded data. An investigator at each centre will be responsible for daily patient screening, patient enrolment, adherence to the protocol and completing the electronic case-report form. Since three strategies are currently used in routine practice, no data safety monitoring board was required by the ethical committee.

ETHICS AND DISSEMINATION

Consent to participate

Patients will be included after having provided a written informed consent. If the patient is not able to understand the information given, he/she can be included if the same procedure is completed with a next of kin. Eligible patients unable to receive information and for whom a substitute decision maker won't be present may be included through a process of deferred

consent. After the patient's recovery, she/he will be asked if she/he agrees to continue the trial.

Confidentiality

Data will be handled according to French law on data protection and European General Data Protection Regulation (GDPR). All original records will be archived at trial sites for 15 years.

Declaration of interest

This study was funded by a grant from the LEO Pharma. The sponsor is Assistance Publique – Hôpitaux de Paris, AP-HP (Délégation à la Recherche Clinique et à l'Innovation, DRCI).

Access to data

Investigators will make the documents and individual data required for monitoring, quality control and audit of the study available to dedicated persons, in accordance with the law.

Dissemination policy

Findings will be published in peer-reviewed journals and presented at national and international meetings. Communications, reports and publication of the results of the study will be placed under the responsibility of the principal investigator-coordinator of the study and the steering committee. Reporting will follow CONOSRT statement and rules of publication will follow the international recommendations according to *The Uniform Requirements for Manuscripts* (ICMJE, April 2010).

Patient and public involvement

Patients and/or the public were not involved in the development of this study.

DISCUSSION

Up to now, there are no randomized controlled trials available on the best anticoagulation strategy to mitigate microvascular thrombosis and the evolution of the lung and multi-organ microcirculatory dysfunction in COVID-19 patients without initial macrovascular thrombosis.

Some recent trials studied various anticoagulation strategies with heparin in COVID-19 patients [8]. In the Iranian INSPIRATION trial [20], Sadeghipour et al. compared the efficacy of a standard LD-PA (40 mg once daily enoxaparin) to a weight-based higher dose-PA (1 mg/kg enoxaparin) among severe COVID-19 patients admitted to intensive care unit. Higher dose-PA did not result in a significant difference in the primary outcome (a composite of adjudicated venous or arterial thrombosis, treatment with extracorporeal membrane oxygenation, or mortality within 30 days), as compared to standard-dose PA. The risk of bleeding was also similar between both groups. In an international, multiplatform, randomized clinical trial that combined data from patients who were enrolled in one conventional randomized trial (ACTIV-4a) and in two trials that used response-adaptive randomization (REMAP-CAP and ATTACC), the potential benefits and risks of TA against standard PA (at a lower or higher dose based on local practice) depended on the initial severity of patients [21,22]. In critically-ill patients, TA did not improve the primary outcome of organ support–free days at day-21 and was associated with more major bleedings (3.8% vs 2.3%) than PA [22]. In non-critically-ill patients, TA appeared to increase the probability of survival to hospital discharge with reduced use of cardiovascular or respiratory organ. However, major bleeding occurred in 1.9% of the patients receiving TA and in 0.9% of those receiving PA (1.9% vs. 0.9%) [21].

However, the ANTICOVID study differs from these studies for several methodological and clinical reasons. The inclusion criteria differ because of systematic (ANTICOVID) vs. non-systematic (INSPIRATION, REMAPCAP, ACTIV-4, ATTACC) CTPA to exclude macro-thrombosis, which is de facto an indication for curative anticoagulation. By excluding macro-thrombosis from randomization, ANTICOVID will provide an answer to the specific question of micro-thrombosis. On the other hand, in contrast to other trials, ANTICOVID explicitly excludes patients with renal failure (creatinine clearance < 30 ml/min) which has been shown to be an independent risk factor for bleeding in critically-ill patients requiring TA [23]. In addition ANTICOVID excludes patients with extreme body weights, for whom LMWH dosing has not been assessed. In particular, obese patients have a lower proportion of lean body mass as a percentage of total body weight. As a result, LMWH dosing based on total body weight could cause supra-therapeutic anticoagulation [24]. Therefore, ANTICOVID will allow evaluation of anticoagulation dose escalation in a population with a minimized baseline bleeding risk. Lastly, our study is the only one to investigate in separate arms, lower and higher prophylactic doses, as compared to curative anticoagulation. Therefore, the

ANTICOVID trial is needed in order to explore the lowest effective dose (given the bleeding risk of anticoagulation) and to answer the key question of dose escalation anticoagulation among COVID-19 patients without initial macrovascular thrombosis.

In summary, the ANTICOVID trial is an open label randomized controlled trial testing the efficacy of three routinely used anticoagulation strategies (LD-PA, HD-PA, and TA) to limit the extension of microvascular thrombosis in severe COVID-19 patients without initial macrovascular thrombosis. The trial targets a well-selected population (notably at lower risk of bleeding), with a suitable primary objective and experimental design, to provide a robust response (lowest effective dose with respect to the bleeding risk of anticoagulation). Therefore, this trial may help establish international recommendations with a high level of evidence for the efficacy and safety of anticoagulation dose escalation needed to improve outcomes in severe COVID-19 patients.

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Table 1: Seven-category ordinal scale derived a WHO recommended instrument (proposed by Coa et al [16])

Statut 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

Table 2: sepsis-induced Coagulopathy Score [25]

Variable		**Points**
INR	≤1.2	0
	>1.2 to 1.4	1
	>1.4	2
Platelet count, cells x 10^9/L	≥150	0
	100 to <150	1
	<100	2
Total SOFA score [a]	0	0
	1	1
	≥2	2

[a] Summation of the SOFA score's respiratory, cardiovascular, hepatic, and renal SOFA components.

Table 3: Study flow chart

Procedures and assessments (C= care; R= research)	day-0 (inclusion)	day-1 (randomization)	day-7	day-2 to day-14	day-15 to day-28 (or hospital discharge)	day-90 +/- 10 days (End of study)
Inclusion and non-inclusion criteria	R					
Enrolment						
Informed consent	R					
CTPA		C				
Intervention						
Low dose prophylactic anticoagulation strategy		C		C		
High dose prophylactic anticoagulation strategy		C		C		
Therapeutic anticoagulation		C		C		
Assessments						
Characteristics of the patient [a]	C					
Seven-category ordinal scale [b] and its components		C		C	C	
D-dimers and platelet count		C	C	C		
Sepsis coagulopathy score and its components [c]		C	C			
Adverse event		C		C	C	R
ICU stay and hospital stay						
Vital status		C		C	C	R

Abbreviations: CPTA, chest computed tomography with pulmonary angiogram; ICU, intensive care unit

[a] Characteristics of the patient include age, gender, height, weight, severity score indicated by the Simplified Acute Physiological Score II and the Sepsis-related Organ Failure Assessment score, pre-existing conditions (chronic cardio-vascular, respiratory, renal, liver, or gastric diseases, arterial hypertension, diabetes mellitus, thrombotic or bleeding event, stroke, neoplasia, Human Immunodeficiency Virus, solid organ transplantation), treatments for COVID-19 at baseline, baseline organ support

[b] derived from the WHO scale [12]

[c] international normal ratio, platelet count, Sepsis-related Organ Failure Assessment score [25]

Figure 1: Experimental schema

Abbreviations: CT scan, chest computed tomography

Trial registration number: NCT04808882

Contributors

VL and AMD designed the study and wrote the manuscript. EA provided substantial contributions to the conception and design of the study, and wrote the statistical analysis plan and estimated the sample size. All authors contributed for drafting the work, revising it critically for important intellectual content and approved the final version of the manuscript. All authors give their agreement to be accountable for all aspects of the work, and ensure the accuracy and integrity of any part of the work.

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Disclaimer

None

Competing interests

AMD reports lectures for Leo Pharma.

AE reports personal fees from GBT, personal fees from Hemanext unrelated with the present study

GV received research grant from Bio-Mérieux, SOS Oxygène, Janssen unrelated to the present study; and advisory board fees from BioMérieux unrelated to the present study.

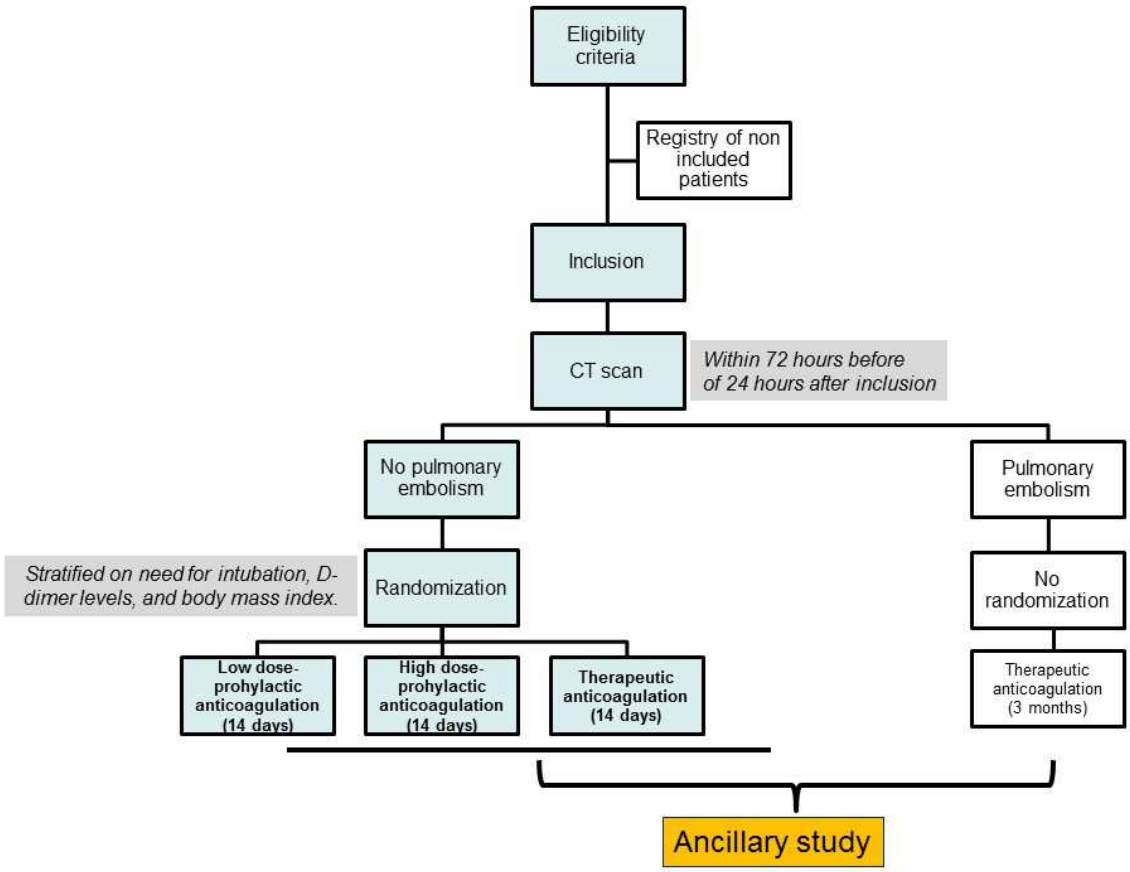
VL receives advisory board fees from Amomed unrelated with the present study

Ethics approval

The study has been approved by an independent ethics committee (Ethics Committee Ile de France VII, Paris, France) with the registration number 2020-A03531-38.

Provenance and peer review

Not commissioned; externally peer reviewed.



CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	4
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	6
	2b	Specific objectives or hypotheses	7
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	7, 9,14
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	8
	4b	Settings and locations where the data were collected	14
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	9
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	11
	6b	Any changes to trial outcomes after the trial commenced, with reasons	na
Sample size	7a	How sample size was determined	12-13
	7b	When applicable, explanation of any interim analyses and stopping guidelines	na
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	14
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	14
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	na
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	14
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	na

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	10
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	14-15-16
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	na
	13b	For each group, losses and exclusions after randomisation, together with reasons	na
Recruitment	14a	Dates defining the periods of recruitment and follow-up	na
	14b	Why the trial ended or was stopped	na
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	na
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	na
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	na
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	na
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	na
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	na
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	na
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	na
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	na
Other information			
Registration	23	Registration number and name of trial registry	26
Protocol	24	Where the full trial protocol can be accessed, if available	na
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	26

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

Comparison of standard prophylactic, intermediate prophylactic and therapeutic anticoagulation in patients with severe COVID-19: protocol for the ANTICOVID multicenter, parallel-group, open-label, randomized controlled trial

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Primary Subject Heading:	Infectious diseases
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Comparison of standard prophylactic, intermediate prophylactic and therapeutic anticoagulation in patients with severe COVID-19: protocol for the ANTICOVID multicenter, parallel-group, open-label, randomized controlled trial

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ABSTRACT

Introduction: Coronavirus disease 2019 (COVID-19) induces venous, arterial, and microvascular thrombosis, involving several pathophysiological processes. In patients with severe COVID-19 without macrovascular thrombosis, escalating into high-dose prophylactic anticoagulation (HD-PA) or therapeutic anticoagulation (TA) could be beneficial in limiting the extension of microvascular thrombosis and forestalling the evolution of lung and multi-organ microcirculatory dysfunction. In the absence of data from randomized trials, clinical practice varies widely.

Methods and analysis: This is a French multicenter, parallel-group, open-label, randomized controlled superiority trial to compare the efficacy and safety of three anticoagulation strategies in patients with COVID-19. Patients with oxygen-treated COVID-19 showing no pulmonary artery thrombosis on computed tomography with pulmonary angiogram will be randomized to receive either low-dose prophylactic anticoagulation (LD-PA), HD-PA, or TA for 14 days. Patients attaining the extremes of weight and those with severe renal failure will not be included. We will recruit 353 patients. Patients will be randomised on a 1:1:1 basis, and stratified by center, use of invasive mechanical ventilation, D-dimer levels, and body mass index. The primary endpoint is a hierarchical criterion at day 28 including all-cause mortality followed by the time to clinical improvement defined as the time from randomization to an improvement of at least two points on the ordinal clinical scale. Secondary outcomes include thrombotic and major bleeding events at day 28, individual components of the primary endpoint, number of oxygen-, ventilator- and vasopressor-free days at day 28, D-dimer and sepsis-induced coagulopathy score at day 7, intensive care unit and hospital stay at day 28 and day 90, and all-cause death and quality of life at day 90.

Ethics and dissemination: The study has been approved by an ethical committee (Ethics Committee, *Ile de France* VII, Paris, France; reference 2020-A03531-38). Patients will be included after obtaining their signed informed consent. The results will be submitted for publication in peer-reviewed journals.

Trial registration number: NCT04808882.

Strengths and limitations of this study

►This randomized controlled trial may contribute to establish solid recommendations with a high level of evidence on the best anticoagulation strategy to limit the extension of microvascular thrombosis and to forestall the evolution of lung and multi-organ microcirculatory dysfunction in patients with severe COVID-19 without initial macrovascular thrombosis.

►Eligibility criteria differ from those retained by previous published studies on anticoagulation strategies in patients with COVID-19 given the systematic pre-randomization screening for macro-thrombosis and the exclusion of obese and renal failure patients to minimize baseline bleeding risk.

►One limitation of the trial is that it is not blinded.

INTRODUCTION

Background and rationale

Coronavirus disease 2019 (COVID-19), a respiratory viral infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), may predispose patients to thrombotic complication [1] incurred by a combination of intense inflammation, platelet activation, and endothelial dysfunction leading to respiratory distress and high mortality [2–4].

The incidence of macrovascular thrombotic events varies from 10 to 30% in COVID-19 hospitalized patients depending on the type of thrombosis, arterial or venous, and the severity of the illness [2–4]. Based on observational data of patients receiving routine low-dose prophylactic anticoagulation (LD-PA), several institutions released guidance statements recommending escalated anticoagulant doses to prevent macrovascular thrombotic events [5,6]. In these recommendations, high-dose prophylactic anticoagulation (HD-PA) and therapeutic anticoagulation (TA) can be employed either empirically or based on various criteria like body mass index or D-dimer concentration [5–7]. However, other conflicting recommendations challenge this approach [6,8].

Microvascular thrombotic events are another major concern in COVID-19 patients. A large review screened the autopsy findings of COVID-19-related deaths and reported the presence of micro-thrombi in small pulmonary vessels [9]. COVID-19-induced endothelitis and coagulopathy across vascular beds of different organs precipitate widespread microvascular thrombosis [2,10,11]. Thus, in critically ill COVID-19 patients without initial macrovascular thrombotic event, HD-PA or TA could be beneficial in limiting the extension of microvascular thrombosis and forestalling lung and multi-organ microcirculatory dysfunction.

To date, no randomized clinical trial has evaluated the best anticoagulation strategy in patients with severe COVID-19, in whom an initial macrovascular thrombotic event is systematically excluded. It seems important to rationalize and compare anticoagulation strategies in this population.

Hypothesis

Our hypotheses are formulated in patients who have severe COVID-19 pneumonia and are macrovascular-thrombosis free to assess: i) First, that TA and HD-PA strategies mitigate microthrombosis, and each thwarts COVID-19 progression to respiratory failure and multi-organ dysfunction, thus decreases mortality and disease duration, as compared with LD-PA; ii) second, that TA outperforms HD-PA in this setting.

Objectives

Primary objective

The main objective is to compare the efficacy of the three strategies (LD- PA, HD-PA, and TA) in reducing mortality and time to clinical improvement.

Secondary objectives

The secondary objectives are to compare the benefits and risks of the three strategies (LD-PA, HD-PA, and TA) in terms of: i) mortality, morbidity, and organ dysfunction; ii) thrombotic events, bleeding events, and net clinical benefit.

Ancillary study

An ancillary study will assess clinical and biological characteristics of severe COVID-19 pneumonia with or without pulmonary embolism to establish a scoring system for COVID-19-related pulmonary embolism diagnosis.

METHODS AND ANALYSIS

Trial design

This is a French multicenter, parallel-group, open-label, randomized controlled superiority trial to compare the efficacy and safety of three anticoagulation strategies (LD- PA, HD-PA, and TA) in patients with COVID-19 pneumonia. The trial protocol follows the Standard Protocol Items: Recommendations for Interventional Trial (SPIRIT) reporting guidelines.

Study setting

The study will be conducted in 31 units (23 intensive care units and 8 conventional hospital wards) in 23 hospitals in France (list of the study sites in Appendix A).

Eligibility criteria

Inclusion criteria

Adult patients (age ≥ 18 years) admitted to hospital will be eligible as soon as they meet all of the following criteria:

1. Severe COVID-19 pneumonia, defined by: i) new pulmonary parenchymal infiltrate; and ii) positive RT-PCR (either upper or lower respiratory tract) for SARS-CoV-2; and iii) WHO (World Health Organisation) ordinal scale ≥ 5 [12];
2. Provide written informed consent as per the French law (patient, next of kin, or differed consent if an emergency case).

Non-inclusion criteria

Patients presenting any of the following criteria will not be included:

1. Pregnant or breast-feeding women;
2. Postpartum (6 weeks);
3. Attaining the extremes of body weight (<40 kg or >100 kg);
4. Hospital admission of more than 72 hours (if the WHO ordinal scale is 5 at the 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);
5. Clinical need for TA;
6. Bleeding related to haemostasis disorders, acute clinically significant bleeding, presence of active gastrointestinal ulcer or any organic lesion with high risk for bleeding;

7. Platelet count < 50 G/L;
8. Within 15 days of recent surgery, within 24 hours of spinal or epidural anaesthesia;
9. Past history of intracranial haemorrhage, large acute ischemic stroke, known intracranial malformation or neoplasm, acute infectious endocarditis;
10. Severe renal failure (creatinine clearance <30 mL/min);
11. Iodine allergy;
12. Hypersensitivity to heparin or its derivatives including low molecular weight heparin;
13. Past history of type II heparin-induced thrombocytopenia;
14. Chronic oxygen supplementation;
15. Moribund patient or death expected from an underlying disease during the current admission;
16. Patient deprived of liberty and persons subject to institutional psychiatric care;
17. Patients under guardianship or curatorship;
18. Participation in another interventional research on anticoagulation.

Intervention

All patients hospitalized with a positive RT-PCR (either upper or lower respiratory tract) for COVID-19 (SARS-CoV-2) in the participating centers will be systematically screened every day looking for inclusion and non-inclusion criteria. The number of patients who do not meet the inclusion criteria will be reported prospectively in a paper register by each of the participating centers. A patient identification number as well as the reason for non-inclusion will be noted (local register of non-inclusion in each of the concerned centers).

Inclusion (D0) is performed as soon as possible, within 72 hours of hospital admission (if the WHO ordinal scale is 5 at time of inclusion, [12]) or within 72 hours of intensive care unit admission (if the WHO ordinal scale is 6 or more at time of inclusion [12]).

Chest computed tomography with pulmonary angiogram (CTPA) should be performed within 72 hours before **(**or up to 24 hours after**)** inclusion; If CTPA is performed within 7 days of inclusion and the likelihood of pulmonary artery thrombosis is deemed unchanged by the clinician, the result of that CTPA might be considered at time of inclusion (Figure 1).

- If the CTPA reveals pulmonary artery thrombosis, the patient will receive TA following current guidelines [13] and will not be randomized.
- If the CTPA does not show pulmonary artery thrombosis, the patient will be randomized to receive either LD-PA, HD-PA, or TA for 14 days (or until hospital discharge or

weaning of supplemental oxygen for 48 consecutive hours, whichever comes first). If the patient has no pulmonary artery thrombosis but presents clinical signs of deep venous thrombosis at inclusion, complete duplex ultrasound (CDUS) of the lower extremities will be performed [14]. If the CDUS demonstrates deep venous thrombosis, the patient will receive TA according to current guidelines and will not be randomized; if the CDUS is negative, the patient will be randomized.

LD-PA, HD-PA, and TA will be initiated immediately in all patients after randomization using low molecular weight heparin (LMWH), tinzaparin at a dose of 3500 IU/24h, 7000 IU/24h, or 175 IU/kg/24h, respectively. If tinzaparin is not available, enoxaparin can be used at a dose of 4000 IU/24h, 4000 IU/12h, and 100 IU/kg/12h, respectively.

In case renal failure (creatinine clearance < 30 mL/min) happens after randomization or if a patient needs invasive, high bleeding risk procedure, better replace LMWH by a continuous intravenous infusion of unfractioned heparin as follows: i) LD-PA: 100 IU/kg/24h; ii) HD-PA: 200 IU/kg/24h; iii) TA: 500 IU/kg/24h, adapted to the anti-Xa activity (target between 0.3 and 0.6 IU/ml) as per current guidelines.

After day 14, or hospital discharge, or in case TA is clinically indicated, or serious anticoagulation-related adverse event occurs, the trial anticoagulation strategy will be discontinued. Pursuing further anticoagulation treatment will be left at the discretion of the attending physicians.

In all groups, current recommendations for the management of COVID-19 pneumonia will be followed, including the use of dexamethasone [15].

Criteria and procedures of premature withdrawal of a participant from the study

In compliance with the conventional management of severe COVID-19 pneumonia, anticoagulation will be discontinued if one of the following happens:

- Major bleeding event according to the ISTH definition;
- Large acute ischemic stroke;
- Skin necrosis at the injection site;
- Type II heparin-induced thrombocytopenia;
- Allergic reaction;
- Hospital discharge prior to day 14.

The TA strategy will be temporarily interrupted if any of the following conditions arises before terminating the treatment period (14 days from randomisation); the study drug will be resumed at least 6 hours after the resolution of the anomaly:

- Clinical indication for TA;
- Indication for lumbar puncture, spinal or epidural anaesthesia;
- Indication for surgery.

Follow-up visits

The trial clinical examination is part of the daily practice. Parameters collected in the study are those usually collected during the management of patients with severe COVID-19 pneumonia. The trial follow-up visits are at day 7, day 28, and day 90.

If the patient is still hospitalized at day 28 and day 90, data will be collected from the patient's medical records with the possible assistance of a clinical research technician (CRT). If the patient is discharged:

- the CRT will collect the medical records from the clinical departments where the patient stayed; these will be analyzed by the investigator who included the patient.
- the CRT will collect data on the patient's vital status and occurrence of serious adverse events during the follow up period:
  - ✓ (if necessary) telephone the patient (three different attempts, days, and times over 15 days);
  - ✓ (if necessary) telephone the physician in charge of the patient during the follow-up period;
  - ✓ (if necessary) telephone the patient's treating or referring physician(s);
  - ✓ (if necessary) contact the town hall of the patient's birthplace.

Endpoints

Primary endpoint

The primary endpoint is a hierarchical criterion assessed at day 28 and includes all-cause mortality followed by the time to clinical improvement. It is calculated in such a manner that death constitutes a worse outcome than delay of clinical improvement.

The time (days) to clinical improvement is defined as the time from randomization to an improvement of at least two points (from the status at randomization), using a seven-category

ordinal scale derived from the WHO recommended instrument [12], as proposed by Coa et al [16] (**table 1**). Since all included patients will at least require oxygen supplementation, live discharge from hospital will represent in itself a 2-point decrease in the 7-point scale, i.e. clinical improvement.

Secondary endpoints

Secondary endpoints will include the following:

(1) Efficacy on morbi-mortality and organ function

- Individual components of the hierarchical primary endpoint, including time to clinical improvement and all-cause death at day 28;
- All-cause death at day 90;
- Score on WHO ordinal scale and 7-point ordinal scale at day 28;
- D-dimers and Sepsis-Induced Coagulopathy Score (SCS) (see detailed definition in **Table** 2) at day 7;
- Percentage of patients needing invasive mechanical ventilation at day 28;
- Number of days alive and supplemental oxygen-free at day 28;
- Number of days alive and mechanical ventilator-free at day 28;
- Number of days alive and vasopressor-free at day 28;
- Length of intensive care unit stay at day 28 and day 90;
- Length of hospital stay at day 28 and day 90;
- Quality of life assessed using a quality-of-life questionnaire (EQ5D5L) [17] at day 90.

(2) ***Efficacy on thrombotic events***: percentage of patients with at least one thrombotic event at day 28, including ischemic stroke, non-cerebrovascular arterial thrombotic event, deep venous thrombosis, pulmonary embolism, or central venous catheter-related deep venous thrombosis;

(3) Tolerance to anticoagulation

- Percentage of patients with at least one major bleeding event (MBE) at day 28, according to the International Society on Thrombosis and Haemostasis (ISTH) definition;
- Percentage of patients with at least one life-threatening bleeding event at day 28 according to the RE-LY definition;

- Percentage of patients with any bleeding event, whether major or minor, at day 28, with minor bleedings being all non-major bleeding events;
- Percentage of patients with Heparin-Induced Thrombocytopenia (HIT) at day 28.

Classification of the severity of thrombotic and bleeding events will be carried out by an independent adjudication committee.

Sample size and its statistical justification

The required number of participants to be randomized is 300 patients (from 353 included). Estimates, derived from prior studies led in similar populations [16], showed that a sample of at least 300 patients (100 per group) suffices to achieve ≥80% power that is required to detect a statistically significant difference in the ranked composite primary endpoint. The analyses rely on 2-sided alpha of 0.017 using Bonferroni correction for multiple testing considering three pairwise comparisons between the randomized 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 LD-PA, HD-PA, and TA, respectively. We hypothesize that the rate of positive CTPA would be 15% [18,19]. For such, we aim to include 353 patients in order to randomize 300.

Sample size calculation also considered the pairwise comparisons between the groups. For each performed comparison, 5000 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 LD-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 LD-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 [16]. 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 [16], considering median [interquartile range] survival time and Kaplan Meier curves. Within each sample/pairwise comparison, an individual score is calculated by comparing each patient in one group with all patients in the second group (23). These scores are then compared between groups using Mann-Whitney/Wilcoxon test in each of the 5000 samples, and the p-value of each test is recorded. For each pairwise comparison, the percentage of tests with a p-value <0.017 is calculated, which gives an estimate of the achieved statistical power.

Recruitment

The expected duration of patients enrolment is 18 months starting from April 2021. The chronogram of the study is as follows: i) December 2020: winning industrial grant award; ii) December 2020: promotion by Assistance Publique-Hôpitaux de Paris (AP-HP); iii) March 2021: approval by an independent ethics committee; iv) April 2021-October 2022: inclusion of patients; iv) 2022-2023: end of inclusions, monitoring by the participating centres and research work by the investigators; cleaning and closure of the database; blind review to screen for protocol violation, to define intention-to-treat and per-protocol analysis populations; v) 2022-2023: data analysis, writing the manuscript, and submission for publication.

Allocation of intervention and data management

After signing the consent by the patient or their relative, all inclusion/exclusion criteria will be checked by the investigator before randomization. Centralized blocked randomization on the basis of a 1:1:1 ratio will be prepared by the Clinical Research Unit before the start of the trial. Randomization will be carried out in balanced blocks and stratified by hospital center and according to the following criteria at inclusion: need for intubation (yes or no), D-dimer levels (more or less than 3 µg/ml), and body mass index (more or less than 30 kg/m^2). Patients will be randomised electronically upon logging to the centralized electronic case report form (e-CRF) website "Cleanweb" provided by Telemedicine technologies.

Non-identifying data will be entered into the e-CRF via a web browser by a trained investigator or research assistant at each centre. The participating centers have access to electronic case report forms via a web-based data collection system (unique identification and password by user). Patients' follow-up and work schedule are detailed in the study Gantt chart **(Table 3).** The e-CRF was devised by the principal investigator and the scientific supervisor of the study in collaboration with the data manager of the clinical research unit, *Henri Mondor* Hospital AP-HP. Case report forms and data dictionary (containing variables coding

and definitions) are saved and archived in the clinical research unit - *Henri Mondor* secured servers. Paper case report forms are available in the documentation provided at each site. eCRF (CleanWeb Telemedecine) uses the secured computer servers of AP-HP. The computer files used for this research are implemented in compliance with the French (amended "*Informatique et Libertés*" law governing data protection) and European (General Data Protection Regulation – GDPR) regulations. The sponsor already obtained authorisation of CNIL (French Data Protection Agency) before implementing any data processing involving data required for this research (Ref.:MLD/MFI/AR215255 AUTORISATION)". Database quality control is undertaken by Data manager of the clinical research unit - Henri Mondor Hospital, AP-HP (missing data, range checks on quantitative values, date chronology check; R-Project computer programming) and put at the disposal of the investigation team. Data-management procedures are validated by the clinical research nit quality specialist and recorded in their secured servers and on paper.

Statistical methods

All analyses will be performed by the study statistician 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 less than 0.05 should indicate statistical significance.

In compliance with the CONSORT statement, a flow diagram will describe the progress of the three groups of patients throughout the different phases of the trial (enrolment, allocation, received interventional agents, follow-up, and data analysis). The analysis will be performed on an intention-to-treat basis. In case of premature interruption or withdrawal from the study, patients will not be substituted. Missing values will be described and, according to their nature and frequency, multiple imputation methods will be applied. A per-protocol analysis will be conducted as the trial sensitivity analysis since it excludes patients wrongly randomised or who did not receive the allocated intervention.

Comparative analysis will systematically be done with (main analysis) and without adjustment for randomisation stratification factors. There is no intention to perform interim analysis. The primary endpoint analysis will be done on the intention to treat (ITT) population whereas supportive analyses on the per protocol (PP) population. The latter aim is to investigate PP-excluded patients and their impact on ITT analysis, and eventually to check whether similar results can be obtained for a robust interpretation. All secondary endpoints

analyses will be conducted on both ITT and PP populations to assess the robustness of the results.

Descriptive analysis

Descriptive statistical analyses will be conducted on the whole study population, in particular the randomized groups to describe their general and baseline characteristics, demographics, past history, as well as numbers of premature study withdrawals. Quantitative variables will be 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 will be presented as numbers (%).

Analysis of the primary endpoint

The pre-specified primary endpoint will be a ranked composite score that incorporates death and time to clinical improvement, calculated in such a manner that death constitutes a worse outcome than delayed clinical improvement. Each patient will be 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 first will be attributed +1 and the latter −1 for that pairwise comparison. If both patients in the pairwise comparison survived, the scoring will depend on who needed more time (days) to clinically improve: fewer days mean a score of +1, and more days mean a score of −1. If both patients survived and had the same number of days to clinical improvement, or if both patients died, both will score 0 for that pairwise comparison. For each patient, scores of all pairwise comparisons will be summed to obtain a cumulative score. These cumulative scores will be ranked and compared between the three groups via non-parametric Mann-Whitney test.

Analysis of secondary endpoints

Comparisons between randomized groups at given timepoints will be conducted using Chi square or Fisher 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. Pairwise comparisons within groups (across timepoints) will be conducted using tests for paired data, i.e. McNemar test for qualitative data, and t-tests for paired data or Wilcoxon signed ranks for continuous data, as appropriate.

Individual components of the composite primary endpoint will be assessed as secondary endpoints, and those include all-cause mortality at day 28 and number of days to clinical improvement. For such, calculation of time-to-event endpoints based on follow-up censored

data will be employed, taking into account the competing risks of hospital discharge (for mortality evaluation) and death (for time to clinical improvement). Kaplan-Meier survival curves and cumulative incidence curves will be plotted for each treatment group, and Fine-Gray regression model will be used to calculate sub-hazard ratios along with their 95% confidence intervals and corresponding P-values.

Analyses of independent determinants of quantitative secondary endpoints will be performed using multivariable linear regression model adjusting for baseline characteristics. As for global longitudinal analysis, we will use generalized linear regression mixed model to test interactions between timepoints, groups, and pre-specified predictors while entering patient level as a random effect to take into consideration the hierarchical structure of repeated data.

Tolerance analysis will examine the intervention-related adverse events, according to their period of appearance and the concerned randomized group, to compare rates and time of occurrence.

Data monitoring

The trial steering committee (principal investigator, senior investigator, and methodologist) will supervise the progression and monitoring of the study. Research assistants will regularly monitor all centres on site to check protocol adherence and accuracy of the recorded data. An investigator at each centre will be responsible for daily patient screening, patient enrolment, adherence to protocol, and completion of the eCRF. Since the three treatment strategies are currently used in routine practice, no data safety monitoring board was required by the ethical committee.

Patient and public involvement

Patients and/or the public were not involved in the development of this study.

ETHICS AND DISSEMINATION

Ethical approval

The study has been approved by an independent ethics committee (Ethics Committee, *Ile de France* VII, Paris, France) under the registration number 2020-A03531-38. The trial is registered at ClinicalTrials.gov, NCT04808882 (registration date March 8, 2021).

Consent to participate

Patients will be included after signing a written informed consent (Appendix B). If the patient is not able to understand the information given in the consent, they can be included if a next of kin consents or helps obtain the consent. Eligible patients unable to receive information and for whom a substitute decision maker is not present, can still be included through a process of deferred consent. After recovery, the patient's agreement to stay in the trial will be sought.

Confidentiality

Data will be handled according to the French law on data protection and the European General Data Protection Regulation (GDPR). All original records will be archived at the trial sites for 15 years.

Funding and sponsorship

This study was funded by a grant from LEO Pharma. The sponsor is *Assistance Publique – Hôpitaux de Paris*, AP-HP (*Délégation à la Recherche Clinique et à l'Innovation*, DRCI).

Access to data

Investigators will make the documents and individual data required for monitoring, quality control, and audit of the study available to dedicated persons, in fulfilment with the law.

Dissemination policy

Findings will be published in peer-reviewed journals and presented at national and international meetings. Communications, reports, and publication of the results of the study will be placed under the responsibility of the principal investigator-coordinator of the study and the steering committee. Reporting will adhere to the CONSORT statement, and rules of publication will follow the international recommendations as for *The Uniform Requirements for Manuscripts* (ICMJE, April 2010) (SPIRIT checklist, appendix C).

DISCUSSION

Currently, there are no randomized controlled trials investigating the best anticoagulation strategy to manage microvascular thrombosis and to hinder the evolution of lung and multi-organ microcirculatory dysfunction in patients with COVID-19 without initial macrovascular thrombosis.

Recent trials have studied various anticoagulation strategies using heparin in COVID-19 patients [8]. In the Iranian INSPIRATION trial [20], Sadeghipour et al. compared the efficacy of standard LD-PA (40 mg enoxaparin once a day) with weight-based, higher dose-PA (1 mg/kg enoxaparin) in severe COVID-19 patients admitted to intensive care unit. Higher dose-PA did not result in a significant difference in the primary outcome (a composite of adjudicated venous or arterial thrombosis, indication for extracorporeal membrane oxygenation, or mortality within 30 days), as compared with the standard-dose PA. Additionally, the risk of bleeding was similar between the two groups. An international, multiplatform, randomized clinical trial combined data from patients who had already been enrolled in a conventional randomized trial (ACTIV-4a) and in two response-adaptive randomization trials (REMAP-CAP and ATTACC). They found that the potential benefits and risks of TA versus standard PA (at a lower or higher dose based on local practice) depended on the initial severity of patients [21,22]. In critically-ill patients, TA did not improve the primary outcome of organ support–free days at day 21 and was associated with more major bleedings (3.8% vs 2.3%) as compared with PA [22]. In non-critically-ill patients, TA appeared to increase the probability of survival to hospital discharge with reduced use of cardiovascular or respiratory organ support. However, major bleeding occurred in 1.9% of the patients receiving TA and in 0.9% of those receiving PA [21].

Our ANTICOVID study differs from these studies in several methodological and clinical aspects. The inclusion criteria differ as CTPA is systematically (ANTICOVID) vs. non-systematically (INSPIRATION, REMAPCAP, ACTIV-4, ATTACC) performed to exclude macro-thrombosis, which is de facto an indication for curative anticoagulation. By excluding macro-thrombosis before randomization, ANTICOVID will provide an answer to the specific question of micro-thrombosis. On the other hand, and in contrast to other trials, ANTICOVID explicitly excludes patients with renal failure (creatinine clearance < 30 ml/min), which has been entangled as an independent risk factor for bleeding in critically-ill patients requiring TA

[23]. Additionally, ANTICOVID excludes patients attaining the extremes of body weights, for whom LMWH dosage has not been assessed. In particular, obese patients, since they have a lower proportion of lean body mass in relation to their big total body weight. As a result, determining LMWH dosage based on total body weight could cause supra-therapeutic anticoagulation [24]. ANTICOVID will allow evaluation of anticoagulation dose escalation in a population with a minimal baseline bleeding risk. Eventually, our study is the only one to investigate in separate arms, lower and higher prophylactic doses, and compare them with curative anticoagulation. For all of the above, ANTICOVID trial is needed in order to explore the lowest effective dose (given the bleeding risk of anticoagulation) and to answer the key question of dose escalation anticoagulation in COVID-19 patients without initial macrovascular thrombosis.

Our study has several limitations. Anticoagulation assignment was open-label given the overburdened, resource-limited healthcare system during the pandemic. Time to clinical improvement, the second component of the hierarchical primary endpoint, may be too subjective, thus liable to performance bias. Detection bias could occur if potential events (especially incidental thromboses) were less likely to be investigated in patients receiving TA than in those receiving LD-PA or HD-PA. The opposite could be true for bleeding events. Reporting bias is unlikely for the primary outcome given that (i) all cause death is objective, and (ii) ICU hospitalization and type of ventilatory support determining time to clinical improvement are unambiguously supported by medical records. Nonetheless, an independent clinical events committee will blindly adjudicate all relevant outcomes. Both ICU and non-ICU patients are eligible, so our future results should not be compared directly to those of other trials limited only to critically ill patients or to non-ICU patients. We will not include obese patients and patients with renal failure, which limits the generalizability of the results to all COVID-19 inpatients. Finally, we will not take into account symptoms duration in the analysis neither quantify microvascular thrombosis on CTPA.

In summary, ANTICOVID trial is an open label randomized controlled trial testing the efficacy of three routinely used anticoagulation strategies (LD-PA, HD-PA, and TA) in limiting the extension of microvascular thrombosis in severe COVID-19 patients without initial macrovascular thrombosis. The trial targets a well-selected population (notably at lower risk of bleeding), with a suitable primary objective and experimental design, to provide a robust response (lowest effective dose with respect to the bleeding risk of anticoagulation).

Therefore, this trial may help establish international recommendations with a high level of evidence for the efficacy and safety of anticoagulation dose escalation needed to improve outcomes in severe COVID-19 patients.

APPENDICES

Appendix A: List of study sites

Appendix B: Model of the consent form

Appendix C: SPIRIT Checklist

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Table 1: Seven-category ordinal scale derived from the WHO recommended instrument (proposed by Coa et al. [16])

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

Table 2: Sepsis-induced Coagulopathy Score [25]

Variable		Points
INR	≤1.2	0
	>1.2 to 1.4	1
	>1.4	2
Platelet count, x 10^9/L	≥150	0
	100 to <150	1
	<100	2
Total SOFA score [a]	0	0
	1	1
	≥2	2

[a] Summation of the SOFA respiratory, cardiovascular, hepatic, and renal score components.

Table 3: Study Gantt chart (work schedule)

Procedures and assessments (C= care; R= research)	day-0 (inclusion)	day-1 (randomization)	day-7	day-2 to day-14	day-15 to day-28 (or hospital discharge)	day-90 +/- 10 days (End of study)
Inclusion and non-inclusion criteria	R					
Enrolment						
Informed consent	R					
CTPA		C				
Intervention						
Low dose prophylactic anticoagulation strategy		C		C		
High dose prophylactic anticoagulation strategy		C		C		
Therapeutic anticoagulation		C		C		
Assessments						
Characteristics of the patient [a]	C					
Seven-category ordinal scale [b] and its components		C		C	C	
D-dimers and platelet count		C	C	C		
Sepsis coagulopathy score and its components [c]		C	C			
Adverse event		C		C	C	R
ICU stay and hospital stay					R	R
Vital status		C		C	C	R

Abbreviations: CPTA, chest computed tomography with pulmonary angiogram; ICU, intensive care unit

[a] Characteristics of patients include age, gender, height, weight, severity score indicated by the Simplified Acute Physiological Score II and the Sepsis-related Organ Failure Assessment score, pre-existing conditions (chronic cardio-vascular, respiratory, renal, liver, or gastric diseases, arterial hypertension, diabetes mellitus, thrombotic or bleeding event, stroke, neoplasia, positive serology for Human Immunodeficiency Virus, solid organ transplantation), treatments of COVID-19 at baseline, baseline organ support

[b] derived from the WHO scale [12]

[c] international normal ratio, platelet count, Sepsis-related Organ Failure Assessment score [25]

Figure 1: Experimental schema

Abbreviations: chest CT-scan: chest computed tomography scan

Administrative information

Contact for Public Queries

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Vincent Labbé, *Hôpital Tenon, 4 rue de la Chine*, 75020 Paris, France. E-mail: vincent.labbe@aphp.fr. Telephone number: + 33 (0) 156016937. Fax number: +33 (0) 156016097.

Protocol version

Version 2.0 dated 15/04/2021

Funding

This study was funded by a grant from LEO Pharma.

Sponsor

The sponsor is *Assistance Publique – Hôpitaux de Paris, AP-HP (Délégation à la Recherche Clinique et à l'Innovation, DRCI*).

Contact details: Ahmed Bacha, DRCI-Head Office project advisor, *Direction de la Recherche Clinique et de l'Innovation* - DRCI (Clinical Research and Innovation Department), *Hôpital Saint-Louis 1, avenue Claude Vellefaux*, Email: ahmed.bacha@aphp.fr .Telephone number: + 33 (0)144841749

Contributors

VL, AM-D in collaboration with all authors designed the study and wrote the manuscript together. EA provided substantial contributions to the conception and design of the study, and wrote the statistical analysis plan and estimated the sample size. VL, DC, NH, BM, HA-O; FB, SC, AR, EV, MF, DD, MM, SP, EN-S, BS, NZ, S-AP , MD, WJ, EM, J-FT, MT, KR, SG, SB, GV, MF, EA, and AM-D contributed for drafting the work, revising it critically for important intellectual content and approved the final version of the manuscript. VL, DC, NH, BM, HA-O; FB, SC, AR, EV, MF, DD, MM, SP, EN-S, BS, NZ, S-AP , MD, WJ, EM, J-FT, MT, KR, SG, SB, GV, MF, EA, and AM-D gave their agreement to be accountable for all aspects of the work, and ensure the accuracy and integrity of any part of it.

Endpoint adjudication committee

Composition: Nadia Aissaoui, MD.PhD, Department of Intensive Care, *Hôpital Cochin*, *Assistance Publique-Hôpitaux de Paris* (AP-HP), Paris, France; Matthieu Schmidt, MD.PhD Department of Intensive Care, *Hôpital Pitié-Salpêtrière*, *Assistance Publique-Hôpitaux de Paris* (AP-HP), Paris, France

Role: review and adjudicate reported thrombotic and bleeding events, as well as deaths and serious adverse events

Steering committee

Composition: principal investigator (VL), scientific supervisor (AM-D), biostatistician (EA), and the sponsor's appointed representatives of the trial: Clinical Research Associate in charge of the project and project manager URC DRCI (*URC des Hôpitaux Universitaires Henri Mondor*), and project manager of the DRCI promotion unit.

Role: Define the overall structure of the study, coordinate information, determine the initial methodology and oversee the trial.

Competing interests

AM-D reports lectures for Leo Pharma.

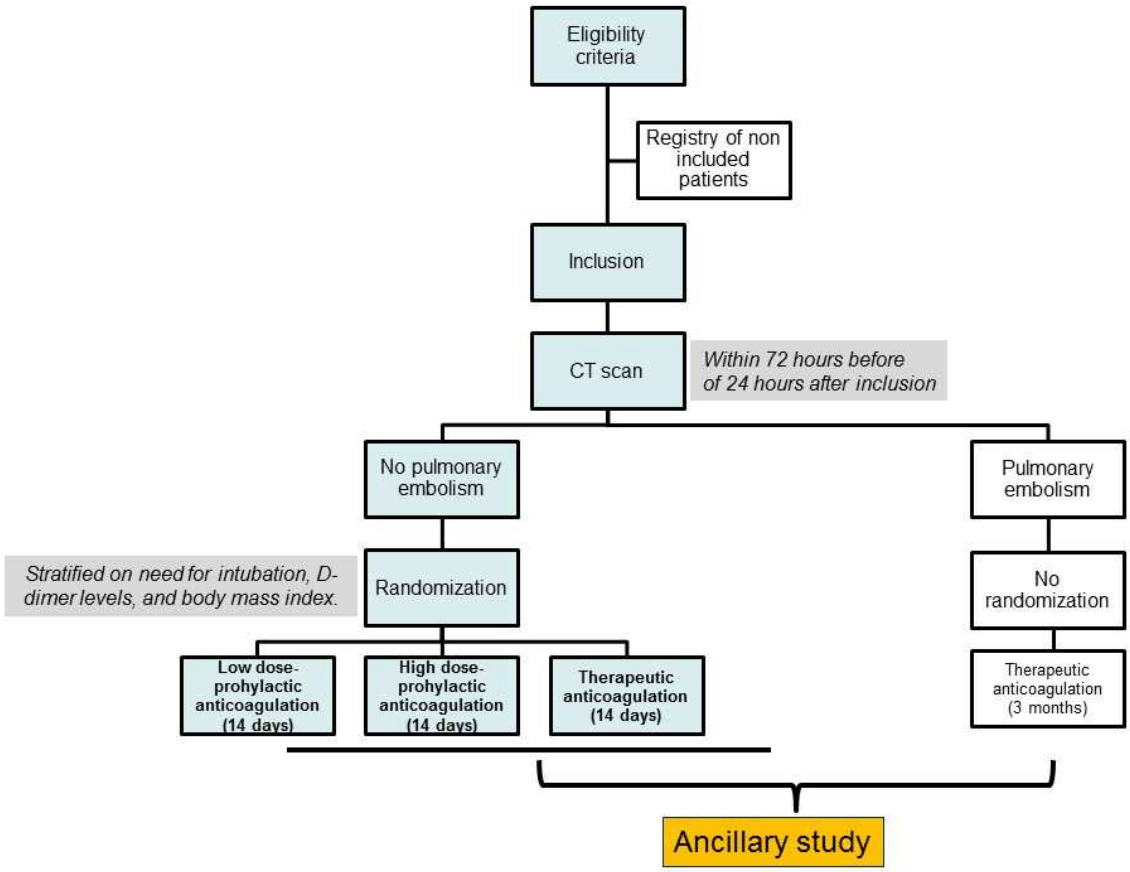
AE reports personal fees from GBT, personal fees from Hemanext, both unrelated to the present study

GV received research grant from Bio-Mérieux, SOS Oxygène, Janssen, all unrelated to the present study; and advisory board fees from BioMérieux that are unrelated to the present study.

VL receives advisory board fees from Amomed, unrelated to the present study

Provenance and peer review

Not commissioned; externally peer reviewed.



APPENDICE A: list of study sites

Service de Médecine Intensive Réanimation, Hôpital Tenon, Paris, France

Service de Maladies Infectieuses et Tropicales, Hôpital Tenon, Paris, France

Service de Réanimation Polyvalente, Centre Hospitalier Victor Dupouy, Argenteuil, France.

Service de Médecine Intensive Réanimation, Hôpital Raymond Poincaré, Garches, France.

Service de Maladies Infectieuses et Tropicales, Hôpital Raymond Poincaré, Garches, France.

Service de Réanimation Médicale et Toxicologique, Hôpital Lariboisière, Paris, France

Service de Médecine Intensive Réanimation, Hôpital Saint Antoine, Paris, France

Service de Maladies Infectieuses et Tropicales, Hôpital Saint Antoine, Paris, France.

Service de Médecine Intensive Réanimation, Centre Hospitalo-Universitaire de Poitiers, Poitiers, France.

Service d'Anesthésie-Réanimation polyvalente, Hôpital Saint Camille, Bry-sur-Marne, France

Service de Maladies Infectieuses et Tropicales, Hôpital Saint Camille, Bry-sur-Marne, France

Service de Médecine Intensive Réanimation, Hôpital Simone Veil, Centre Hospitalier de Cannes, Cannes, France

Service de Réanimation Polyvalente, Centre Hospitalier Saint Joseph-Saint Luc, Lyon, France.

Service de Médecine Intensive Réanimation, Centre Hospitalier Léon Binet, Provins, France

Service de Médecine Intensive Réanimation, Hôpital l'Archet 1, Centre Hospitalier Universitaire de Nice, Nice, France.

Service de Maladies Infectieuses et Tropicales. Hôpital l'Archet 1, Centre Hospitalier Universitaire de Nice, Nice, France.

Département de Médecine intensive, Groupe Hospitalier Sud Ile de France, Melun, France.

Service de Réanimation, Centre Hospitalo-Universitaire Lille, Lille, France

Service de pneumologie et de soins intensifs respiratoires, Hôpital Larrey, Toulouse, France

Service de Médecine Intensive Réanimation, Centre Hospitalo-Universitaire Gabriel-Montpied, Clermont-Ferrand, France.

Service de Médecine Intensive Réanimation, Hôpital Louis Mourier, Colombes, France.

Service de Médecine Intensive Réanimation, Centre Hospitalier La Dracenie De Draguignan, Draguignan, France

Service de Médecine intensive Réanimation, Hôpital Pitie Salpêtrière, Paris, France

Service de Réanimation Médico-Chirurgicale, Hôpital Avicenne, Bobigny, France

Service de Maladies Infectieuses et Tropicales, Hôpital Avicenne, Bobigny, France

Service de Médecine Intensive-Réanimation, Hôpital Saint-Louis, Paris, France

Service de Médecine Intensive et Réanimation Infectieuse, Hôpital Bichat, Paris, France

Service de Médecine Intensive-Réanimation, Centre Hospitalier Sud Francilien, Corbeil-Essonnes, France

Service de Médecine Intensive Réanimation, Hôpitaux Universitaires Henri Mondor-Albert Chenevier, Créteil, France

Service du Département d'Aval des Urgences, Hôpitaux Universitaires Henri Mondor-Albert Chenevier, Créteil, France

Service de Maladies Infectieuses et Tropicales, Hôpitaux Universitaires Henri Mondor-Albert Chenevier, Créteil, France

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

Title of the research:
Anticoagulation in Patients with Severe COVID-19: a Multicenter, Parallel-group, Open-label, Randomized Controlled Trial
(ANTICOVID)

This research is promoted by *Assistance Publique - Hôpitaux de Paris*
Represented by the Director of
***Direction de la Recherche Clinique et de l'Innovation* (DRCI)**
1 avenue Claude Vellefaux
75010 Paris

PARTICIPATION INVITATION

Dear Madam, dear Sir

Dr./Pr. (delete as appropriate)..... (First name, Surname), working at …….. Hospital, invites you to participate in a research study conducted to examine your disease.
We highly encourage you to read this document carefully before making any decision. Do not hesitate to ask for further information.
If you agree to participate in this research, you will be asked to sign a written consent.

1) What is the objective of this research?

You are admitted to hospital to be treated for COVID-19. The study you are asked to take part in assesses the different approaches used to prevent blood clotting (anticoagulation) in patients with COVID-19, either with high dose (therapeutic), low dose (standard prophylactic) or intermediate dose (intermediate prophylactic) anticoagulation. The three options are currently employed in the management of COVID-19.
To perform this research study, we intend to include 353 of the COVID-19 patients who are admitted to French hospitals.

2) What does the research consist in?

COVID-19 may trigger excessive coagulation leading to the development of blood clots in the lung vessels (pulmonary thrombosis). Some middle and big-size clots can be seen via an imaging technique called chest Computed Tomography with Pulmonary Angiogram (CTPA), but not the small clots.
If you agree to participate in this study, we will do CTPA since it is a standard investigation tool to look for pulmonary thrombosis in COVID-19 patients.
If your CTPA is positive, you will receive anticoagulant treatment at a therapeutic dose for three months, as recommended.
If your CTPA is negative, you will receive anticoagulant treatment, either at standard prophylactic (low) dose, intermediate prophylactic (intermediate) dose, or therapeutic (high) dose. The anticoagulant dose will be randomly selected (this random selection is called randomization). Except in particular conditions, the anticoagulant is tinzaparin, of which you will take one subcutaneous injection a day for 14 days.
In all cases, you will also receive the recommended treatment for COVID-19 throughout your hospitalization.

3) What is the work schedule of the research?

The research is expected to take 6 months and your participation 90 days (3 months). After signing your consent form at the first visit, your participation in the study will start. If you did not undergo CTPA within the three days prior to inclusion, new CTPA would be performed within 24 hours of your inclusion in this study. If your CTPA is negative for thrombosis, the dose of anticoagulant therapy will be randomized within 24 hours of CTPA. This randomization is performed at the first day of the study (D1).

You will receive the randomized strategy for 14 days, from D1 to D14. Your monitoring data (routine clinical examinations and blood tests) will be daily collected during your hospitalization. For a better assessment of your health status, your follow-up in this study will take three months. The evolution of your condition (vital status, oxygen support, and other complications) will be evaluated at D28 (or at discharge if it occurs before D28). You will receive a telephone call at month 3 of follow up to assess your quality of life. The follow-up will be identical for all patients included in the study, whether randomized or not.

4) What are the benefits of your participation?

By participating in this research, you will benefit from regular medical follow-up at no additional cost. Intermediate prophylactic and therapeutic anticoagulation strategies could decrease the duration of COVID-19 as well as its mortality. In addition, your participation will help us deepen our knowledge about COVID-19 treatment.

5) What are the anticipated risks and constraints added by the research?

Anticoagulation can induce bleeding (major bleeding is exceptional). The study approaches are already part of the routine medical treatment of COVID-19 patients. Therefore, there is no risk specifically related to this research. Close monitoring, as is the standard protocol in patients hospitalized for COVID-19, will be performed during hospitalization.
If you agree to participate, you should respect the following point: not to participate in another research project without your doctor's approval, in order to protect yourself from any health problems that could result, for example, from possible incompatibilities between the studied drugs or from other exposures.

6) What are the potential medical alternatives?

If you choose not to participate in this research, you will receive appropriate healthcare according to your condition, in compliance with standard clinical practice.

7) What kind of medical care to have after participation?

The follow-up is not specific for this study. You will continue to receive the care adapted to your health condition whether it concerns the usual management in case of premature interruption of the research or the care to receive at the end of your participation.
Your doctor may decide at any time to stop your participation and should explain the reasons to you.

8) If you participate, how will your collected data be used in the research?

Within the framework of the research you are invited to participate in, the treatment of your personal data will be carried out by AP-HP, the research promoter in charge of data management, to analyze the results.

This data processing is necessary to carry out research of public health interest, which comes in alignment with the missions of AP-HP as a public university hospital.

For this purpose, your medical and lifestyle data will be transmitted to the Promoter or to persons or partners working on its behalf, in France or abroad. Such data will be identified by a registration number. As well, such data could be transmitted to French or foreign health authorities, under conditions that guarantee their confidentiality.

It is also possible that your medical data, which could be documented in reports by competent authorities interested in the strategies evaluated in this research, be transmitted to an industrial company in order to allow a greater number of patients to benefit from the results of this research. This transmission will be done under conditions that guarantee confidentiality.

Your data could be used in further research work or complementary analysis in collaboration with private or public partners, in France or abroad, under conditions that guarantee their confidentiality and the same level of protection as stated by the European legislation.
You can object to any further analysis of your data at any time by informing the doctor who is following you in this research.

Your data will only be kept for as long as is strictly necessary and warranted by the research purpose. It will be stored in the information systems of the data manager for two years after the last publication of the research results. Your data will then be archived in fulfilment with the regulations in force.

The database used in this research is established in compliance with the French (modified "*Informatique et Libertés*" law) and European (*Règlement Général sur la Protection des Données* - RGPD) laws. You have the right to access, modify, restrict, and object to the processing of data which are covered by professional secrecy and used in the framework of this research.

If you decide to stop your participation, the data collected prior to this decision will be used in accordance with the regulations and exclusively for the purposes of this research. Deleting them would compromise the validity of the research results. However, from that date on your data will not be further used in this research or in other works.

If you have a problem concerning your rights, you can contact the AP-HP's data protection officer at the following address: protection.donnees.dsi@aphp.fr, who will be able to explain to you the possible channels available for you at the CNIL. You can also use your right to complain directly to the CNIL (for further information on this subject, visit www.cnil.fr).

9) How is this research supervised?

AP-HP has taken all the measures to carry out this research in compliance with the Public Health Regulations applicable to research involving human volunteers.

AP-HP has taken out an insurance policy (number …….) that guarantees its civil liability and that of all those involved with HDI-GERLING company through its insurance broker BIOMEDICINSURE whose address is *Parc d'Innovation, Bretagne Sud C.P.142 56038 Vannes Cedex*.

AP-HP obtained approval from the ethics committee [indicate the name of the CPP] on [indicate the date of the meeting in dd/mm/yyyy format].

10) What are your rights?

Your participation in this research is free and voluntary. Your decision will not compromise the quality of care and treatment you are expected to receive.

Throughout the study period and at any given time, you can ask your investigating doctor for further information about your health as well as explanations of the research process.

You may withdraw from the research at any time without explanation, without any consequences for your treatment or the quality of care you receive, and without any consequences for your relationship with your doctor. After this withdrawal, you may be followed by the same medical team. In this case, the data collected until the withdrawal will be used for the analysis of the research results.

Your medical file will remain confidential and can only be consulted under the responsibility of the doctor in charge of your treatment as well as by the health authorities and by persons who are authorised by AP-HP for research and are subjected to professional confidentiality.

At the end of the study and its data analysis, you can have access to the overall results by asking the doctor who is treating you in the study.

You can also access all your medical data directly or through a doctor of your choice in fulfillment with Article L 1111-7 of the Public Health Regulations.

If you agree to participate in the research after you have read all this information, discussed it with your doctor and had time to think about it, you will be asked to sign and date the informed consent form at the end of this document.

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

CONSENT FORM

I, the undersigned, Ms., Mr. [delete as appropriate] (First name, Surname) ..... voluntarily agree to participate in the study entitled

"Anticoagulation in Patients with Severe COVID-19: a Multicenter, Parallel-group, Open-label, Randomized Controlled Trial"

promoted by *Assistance Publique - Hôpitaux de Paris* and I was informed about by Dr./Pr. (name, surname, telephone)....., investigator of this research.

- I have read the participation invitation version 1.0 of 18/12/2020 (3 pages), which explains the purpose of this trial, how it will be conducted, and what my participation will consist of;
- I will keep a copy of the participation invitation and the consent form:
- I have received appropriate answers to all my questions;
- I have had sufficient time to make my decision;
- I have understood that my participation is free and that I can stop my participation at any time, without any liability and without prejudices to the quality of care I will receive;
- I have been informed that the data collected in the research may be used for other studies, and that I can object to that at any time;
- I am aware that my participation can also be interrupted whenever necessary by the doctor who should then explain the reasons;
- I have been informed that my participation in this research will last three months during which I cannot consider participation in another research without informing the investigating doctor in charge of my case in this trial,
- My consent in no way releases the doctor who is following me in the research nor AP-HP from all their responsibilities, and I retain all rights guaranteed to me by the law.

Signature of the participating person		**Signature of the doctor**	
First name, Surname:		Fist name, Surname:	
Date:	Signature:	Date:	Signature:

This document must be produced in three copies: one copy must be kept by the investigator for 15 years, the second given to the consenting person, and the third sent to AP-HP in a sealed envelope at the end of the study.

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Repored on page NO
Administrative information			**27-28-29**
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	27,28
Protocol version	3	Date and version identifier	27
Funding	4	Sources and types of financial, material, and other support	28
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,2,3,428
	5b	Name and contact information for the trial sponsor	28
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	12, 17, 28
Introduction			6

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6
	6b	Explanation for choice of comparators	6
Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8,9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9,10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	10
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	n/a
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11,12
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13,14
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	n/a
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	14
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	14
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	14
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a

	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11,14,15,17
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11,17
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	14,15
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15,16,17
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15,16
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	17

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11,14,17
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	17
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	n/a
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	17,18
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	18
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	18
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	18
	31b	Authorship eligibility guidelines and any intended use of professional writers	18
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	22
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.