PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	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
AUTHORS	Labbe, Vincent; Contou, Damien; heming, nicholas; Megarbane, Bruno; Ait-Oufella, Hafid; Boissier, Florence; Carreira, Serge; Robert, Alexandre; Vivier, Emmanuel; Fejjal, Mohamed; Doyen, Denis; Monchi, Mehran; Preau, Sebastien; Noel-Savina, Elise; Souweine, Bertrand; Zucman, Noémie; Picos, Santiago alberto; Dres, Martin; Juguet, William; Mariotte, Eric; Timsit, Jean-François; Turpin, Matthieu; Razazi, Keyvan; Gendreau, Ségolène; Baloul, Samia; VOIRIOT, Guillaume; Fartoukh, Muriel; Audureau, Etienne; Mekontso Dessap, Armand

VERSION 1 – REVIEW

REVIEWER	Miranda, Carlos Ribeirão Preto School of Medicine, Department of Internal Medicine
REVIEW RETURNED	17-Dec-2021

GENERAL COMMENTS	This is an exciting study design evaluating the clinical impact of high-intensity anticoagulation in microvascular thrombosis in severe COVID-19 patients. Some suggestions: 1) The authors exclude the high risk of bleeding patients (extreme weight, creatinine clearance < 30 ml/min). The elderly are another group with high bleeding risk; we suggest excluding patients with age higher than 75 years, or another option would be to correct the LMWH dose in these patients. 2) In my opinion, anticoagulation could avoid microvascular thrombosis if it was started early in the disease course. This way, the patients with respiratory failure and mechanical ventilation have an advanced disease; recent clinical trials didn't show the benefit of therapeutic anticoagulation in these patients. On the other hand, these clinical trials showed a mild clinical benefit in moderate patients without mechanical ventilation. I suggest concentrating your strength on moderate patients, according to these recent studies. The early beginning of therapeutic anticoagulation could avoid micro thrombosis in moderate patients. 3) The authors define that the patients should be included in this investigation in the first 72 hours of hospital or ICU admission. However, I considered establishing a time for symptoms duration,

	for example, less than seven days after flu-syndrome symptoms onset. 4) The authors should considerer using some imaging methods to quantify the microvascular obstruction in the CTPA.

REVIEWER	Pallarés-Carratalá, V Universitat Jaume I
REVIEW RETURNED	10-Jan-2022

GENERAL COMMENTS	I believe that this RCT can contribute to establishing decisive recommendations on the best anticoagulation strategy to limit or avoid microvascular thrombosis and its evolution in patients with severe COVID-19 without initial macrovascular thrombosis.

VERSION 1 – AUTHOR RESPONSE

REVIEWER 1

C1R1 The authors exclude the high risk of bleeding patients (extreme weight, creatinine clearance < 30 ml/min). The elderly are another group with high bleeding risk; we suggest excluding patients with age higher than 75 years, or another option would be to correct the LMWH dose in these patients.

Response
We agree with the reviewer that the elderly are at high risk of bleeding depending of their co-morbidities. However, we were careful to limit our number of exclusion criteria to allow generalization of our results to the majority of hospitalized patients with severe Covid-19.
Correcting the dose of LMWH in elderly patients independently of their renal function and weight is not recommended in France [1,2]. We therefore believe that this option is not in line with our objective to compare three strategies that are currently used in COVID-19 patients in routine care in France.

C2R2 In my opinion, anticoagulation could avoid microvascular thrombosis if it was started early in the disease course. This way, the patients with respiratory failure and mechanical ventilation have an advanced disease; recent clinical trials didn't show the benefit of therapeutic anticoagulation in these patients. On the other hand, these clinical trials showed a mild clinical benefit in moderate patients without mechanical ventilation. I suggest concentrating your strength on moderate patients, according to these recent studies. The early beginning of therapeutic anticoagulation could avoid micro thrombosis in moderate patients.

Response
We believe that randomized trials such as ANTICOVID are still needed to study the benefits of dose-escalation anticoagulation in critically ill patients.
To the best of our knowledge, REMAP CAP is the main published trial studying the therapeutic anticoagulation in critically ill patients [3].
ANTICOVID differs from this study given the systematic screening for macro-thrombosis before randomization and exclusion of obese patients and patients with renal failure to minimize baseline bleeding risk. Moreover, our study investigate in separate arms, lower and higher prophylactic doses, as compared to curative anticoagulation 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 this setting.
In addition, the REMAP CAP trial has some limitations. First, the method of standard prophylaxis was left to the discretion of the physicians, which resulted in a mix of conventional prophylaxis doses and

intermediate doses within the treatment groups. Thus, 22.4% of those in the therapeutic-dose group did not receive a therapeutic dose, whereas 51.7% of those in the control group received an intermediate dose — a factor that may have diluted any benefit of therapeutic-dose anticoagulation [4]. Second, REMAPCAP study is a multiplatform, randomized clinical trial that combined data from patients who were enrolled in two trials that used response-adaptive randomization. Thus, the editorial of this study ends with the following sentence: “As the late Ed Salzman concluded in the early days of clinical research with LMWH: a promising innovation in antithrombotic treatment, but the jury is still out.”[4]

C3R3 The authors define that the patients should be included in this investigation in the first 72 hours of hospital or ICU admission. However, I considered establishing a time for symptoms duration, for example, less than seven days after flu-syndrome symptoms onset.

Response

To the best of our knowledge, there is no data about the risk or benefit of dose escalation of anticoagulation depending of the duration of symptoms prior to hospitalization. Moreover, we were careful to limit our number of exclusion criteria to allow generalization of our results to the majority of hospitalized patients with severe Covid-19. In practice, the day of symptom start is not always available at ICU admission.
In accordance with reviewer’s comment, we added the lack of analysis of symptoms duration as a limitation of the study in the discussion section (page 23, line 1).

C4R4 The authors should considerer using some imaging methods to quantify the microvascular obstruction in the CTPA.

Response
As the reviewer suggests, quantification of microvascular thrombosis could be of great interest. Unfortunately, the conditions for performing chest CT with pulmonary angiography in patients with severe COVID-19 rarely allows a comprehensive analysis of the micro-vascularization. Indeed, patients with severe COVID-19 are most often tachypneic and unable to maintain the apnea necessary for micro-vascularization analysis. In addition, the CTPA acquisition protocol to exclude pulmonary artery macro thrombosis requires a fast helix (to capture the injection of the contrast bolus) not dedicated to the analysis of the micro-vascularization. In accordance with reviewer’s comment, we added the lack of quantification of microvascular thrombosis as a limitation of the study in the discussion section (page 23, line 2).

REFERENCE

1. Agence nationale de sécurité du médicament et des produits de santé. Résumé des Caractéristiques du Produit Tinzaparine. agence-prd.ansm.sante.fr. Published December 24, 2019. http://agence prd.ansm.sante.fr/php/ecodex/frames.php?specid=67167017&typedoc=R&ref=R0348394.htm
2. Agence nationale de sécurité du médicament et des produits de santé. Résumé des caractéristiques du produit Enoxaparine. http://agence-prd.ansm.sante.fr/. Published November 23, 2021. http://agence-prd.ansm.sante.fr/php/ecodex/frames.php?specid=66760541&typedoc=R&ref=R0380202.htm

3. REMAP-CAP Investigators, ACTIV-4a Investigators, ATTACC Investigators, et al. Therapeutic Anticoagulation with Heparin in Critically Ill Patients with Covid-19. N Engl J Med. 2021;385(9):777-789. doi:10.1056/NEJMoa2103417
4. Ten Cate H. Surviving Covid-19 with Heparin? N Engl J Med. 2021;385(9):845-846. doi:10.1056/NEJMe2111151