Internal and Emergency Medicine (2024) 19:71–79
https://doi.org/10.1007/s11739-023-03439-w

IM - ORIGINAL

Low-molecular-weight heparin for the prevention of clinical worsening in severe non-critically ill COVID-19 patients: a joint analysis of two randomized controlled trials

Maddalena Alessandra Wu[1] · Cinzia Del Giovane[2,3,4] · Riccardo Colombo[5] · Giovanni Dolci[6] · Massimo Arquati[7] · Roberto Vicini[4] · Umberto Russo[8] · Diego Ruggiero[9] · Valeria Coluccio[10] · Alba Taino[1] · Erica Franceschini[6] · Pietro Facchinetti[1] · Pasquale Mighali[11] · Lucia Trombetta[1] · Francesca Tonelli[1] · Claudia Gabiati[12] · Chiara Cogliati[1] · Roberto D'Amico[2,4] · Marco Marietta[10] · the ETHYCO Study Group

Received: 22 June 2023 / Accepted: 14 September 2023 / Published online: 4 October 2023

Abstract
Coronavirus disease 2019 (COVID-19) carries a high risk of vascular thrombosis. However, whether a specific anticoagulation intensity strategy may prevent clinical worsening in severe COVID-19 patients is still debated. We conducted a joint analysis of two randomized controlled trials, COVID-19 HD (NCT044082359) and EMOS-COVID (NCT04646655), to assess the efficacy and safety of two anticoagulant regimens in hospitalized severe COVID-19 patients. Subjects with COVID-19-associated respiratory compromise and/or coagulopathy were randomly assigned to low (4000 IU qd) or high (70 IU Kg^{-1} every 12 h) enoxaparin dose. The primary efficacy endpoint was clinical worsening within 30 days, defined as the occurrence of at least one of the following events, whichever came first: in-hospital death, evidence of arterial or venous thromboembolism, acute myocardial infarction, need for either continuous positive airway pressure (CPAP) or non-invasive ventilation (NIV) in patients receiving standard oxygen therapy or none at randomization, and need for mechanical ventilation in any patient. The safety endpoint was major bleeding. We estimated the relative risk (RR) and its 95% confidence interval (CI) for the outcomes. Among 283 patients included in the study (144 in the low-dose and 139 in the high-dose group), 118 (41.7%) were on NIV or CPAP at randomization. 23/139 (16.5%) patients in the high-dose group reached the primary endpoint compared to 33/144 (22.9%) in the low-dose group (RR 0.72, 95% CI 0.45–1.17). No major bleeding was observed. No significant differences were found in the clinical worsening of hospitalized COVID-19 patients treated with high versus low doses of enoxaparin.

Keywords Anticoagulation · Bleeding · Clinical worsening · COVID-19 · Low-molecular-weight heparin · Mortality · Thromboembolism · Thrombosis · Randomized controlled trials

Introduction

The coronavirus disease 2019 (COVID-19) carries a high risk of vascular thrombosis, including both venous thromboembolism and arterial thrombosis. The so-called immunothrombosis associated with COVID-19 is characterized by complex features that do not perfectly match any other known coagulopathy, such as sepsis-induced coagulopathy, thrombotic microangiopathy, or disseminated intravascular coagulation [1]. Given the high risk of micro- and macrothrombotic phenomena [2], anticoagulation has been considered a potentially useful treatment. However, so far, no conclusive results are available on the most appropriate therapeutic regimen. Enoxaparin has not only anticoagulant but also many anti-inflammatory, endothelial-protecting, and potentially antiviral properties [3]. It represents a promising drug for dampening the immune response and the severe hypercoagulability observed in COVID-19 patients. Its use at prophylactic doses has been shown to be associated with reduced 28-day mortality in severe COVID-19 patients with coagulopathy [4, 5]. However, no definitive evidence is

Roberto D'Amico and Marco Marietta have shared last authorship.

The members of the ETHYCO Study Group are mentioned in the Appendix section.

Extended author information available on the last page of the article

available on whether higher doses of low-molecular-weight heparin (LMWH) can improve the overall prognosis of hospitalized COVID-19 patients without significant safety issues.

The optimal approach to thromboprophylaxis in acutely ill hospitalized COVID-19 patients is still a matter of debate. It has been addressed by panel of experts worldwide and has led to shared clinical practice guidelines, which were continuously updated based on the growing body of evidence [6–9].

The guidelines from the American Society of Hematology (ASH) issued a conditional recommendation in favor of therapeutic-intensity over prophylactic-intensity anticoagulation in acutely ill COVID-19 patients without suspected or confirmed venous thromboembolism (VTE) [10]. However, the multidisciplinary panel admitted that this recommendation is based on very low certainty in the evidence, highlighting the need for data from high-quality randomized controlled trials comparing different intensities of anticoagulation in patients affected by COVID-19 pneumonia.

Most of the meta-analyses and systematic reviews suffer from marked heterogeneity of the studies included, no clear-cut distinction between moderately and severely ill patients, variability of anticoagulant regimens, timing of administration, settings of enrollment, and concomitant therapies also due to enrollment during different waves of the COVID-19 pandemic. Moreover, among the anticoagulation regimens, a wide spectrum of enoxaparin doses has been labeled as "intermediate" and variably considered as prophylactic or therapeutic [11–15].

Whether a higher dose of LMWH, intentionally designed to provide anticoagulant effects beyond prophylactic dosing while reducing the risk of bleeding, may prove beneficial in hospitalized COVID-19 patients is still an unanswered question.

Mortality was the main efficacy endpoint assessed by most clinical trials investigating the potential benefits of escalating thromboprophylaxis in severe COVID-19 patients. However, besides addressing per se hard outcomes such as death, use of mechanical ventilation and organ support, intensive care unit (ICU) admission, and major thrombotic and bleeding events, a meaningful endpoint is certainly the progression of respiratory failure with the need for upgrading the respiratory support (even before the use of mechanical ventilation).

In Italy, two randomized controlled trials (RCTs), COVID-19 HD and HEMOS-COVID, with similar study designs and common outcome measures have been conducted around the same time on the efficacy and safety of prophylactic vs higher dose of enoxaparin in hospitalized patients with COVID-19. Of note, the Italian Medicines Agency simultaneously authorized both studies, recommending to gather the collected data in a joint analysis at the time of interim analysis, to faster the process of collecting evidence.

Therefore, in our ETHYCO (Enoxaparin at THerapeutic or prophYlactic dose in severe COVID) Study, we performed an integrated joint analysis of the data from these two RCTs aiming at assessing the effects of two anticoagulation regimens on the clinical worsening of hospitalized severe yet non-critically ill COVID-19 patients.

Methods

COVID-19 HD was a multicenter trial conducted in eight units of three hospitals in Italy (AUO Policlinico Modena, Ospedale Sant'Agostino – Baggiovara, Ospedale Guglielmo da Saliceto – Piacenza).

EMOS-COVID was conducted at the ASST Fatebenefratelli-Sacco, University of Milan, a referral center for highly transmissible diseases in Northern Italy. A joint analysis of the two RCTs was performed.

Both studies enrolled hospitalized patients, admitted to medical wards, with COVID-19-associated respiratory compromise (as identified by respiratory rate ≥ 25 breaths min^{-1} or arterial oxygen saturation $\leq 93\%$ at rest or $PaO_2/FiO_2 \leq 300$ mmHg for COVID-19 HD and by $PaO_2/FiO_2 \leq 250$ mmHg for EMOS-COVID) and/or coagulopathy defined as D-dimer > 2000 ng ml^{-1} for both RCTs or sepsis-Induced coagulopathy (SIC) score > 4 for COVID-19 HD.

In both RCTs, patients were randomly assigned to two arms: enoxaparin at low dose (standard prophylactic dose of 4000 IU qd; in the EMOS-COVID 6000 IU qd if body weight > 100 kg) and at high dose (70 IU Kg^{-1} every 12 h). This not-fully anticoagulant dosage was chosen to reduce the risk of bleeding, by analogy with a previously published trial about the bridging therapy on AVK-treated patients [16].

In both RCTs, randomization was performed with a centralized, computer-generated allocation sequence with no stratification.

The assigned therapy was administered until hospital discharge or until a clinical indication to stop the treatment or change the dose occurred (e.g., confirmed venous thromboembolism or bleeding). In the EMOS-COVID trial, patients were treated according to the assigned arm until discharge; after discharge, all patients were treated with enoxaparin at prophylactic dose (4000 IU up to 100 kg, or 6000 IU over 100 kg) for 30 days.

Other treatments needed for COVID-19 pneumonia were administered according to the evidence available at the time of data collection, in compliance with hospital protocols, and at the discretion of the treating clinicians, with no limitations due to participation in the COVID-19 HD and EMOS-COVID trials.

Data (baseline demographic and medical information, daily clinical parameters, outcome measures) were entered into an electronic case report form by the ETHYCO investigators.

Two severity scores were calculated, the sequential organ failure assessment (SOFA) score, which evaluates organ dysfunction [17], and the sepsis-induced coagulopathy (SIC) score, which was specifically designed for sepsis-induced coagulation disturbances [18].

Details on each RCT design are provided in the Supplementary material.

The primary efficacy outcome of the joint analysis was clinical worsening, defined as the occurrence of at least one of the following events, whichever came first: in-hospital death, acute myocardial infarction, evidence of arterial or venous thromboembolism, need for either continuous positive airway pressure (CPAP) or non-invasive ventilation (NIV) in patients who were in standard oxygen therapy or none at randomization, or need for mechanical ventilation (MV) in any patient.

The primary safety outcome was major bleeding, defined according to the International Society on Thrombosis and Haemostasis [19].

The secondary efficacy outcomes were any event of the primary efficacy outcome and mortality at 30 days from randomization.

COVID-19 HD and EMOS-COVID were both approved by a central institutional review board and registered on ClinicalTrials.gov (identifiers NCT04408235 and NCT04646655, respectively). Written informed consent was obtained from participants or their legal surrogates.

Statistical analysis

We summarized data with counts and percentage for categorical data and with mean and standard deviation (SD) or median and interquartile range (IQR) for continuous data.

Each outcome was analyzed as a binary outcome. The primary outcome was also assessed as time-to-event. We estimated the relative risk (RR) and the absolute reduction for binary outcomes with the relative 95% confidence interval (CI). We estimated the hazard ratio (HR) and relative 95%CI for time-to-event data. We also calculated the Kaplan–Meier curves and compared the curves between groups using the log-rank test. All analyses for efficacy used the intention-to-treat populations from the RCTs.

A result was considered statistically significant if its p-value was less than 0.05.

For the primary efficacy outcome, we performed the following pre-specified subgroup analyses: age (≥ 70 vs < 70 years of age), sex, BMI (≥ 30 vs < 30 kg m^{-2}), D-dimer (> 2000 vs ≤ 2000 ng ml^{-1}), corticosteroid treatment, supplemental oxygen requirement at baseline (standard oxygen therapy or none vs CPAP or NIV).

The STATA version 15 (Stata Corp., College Station, TX) was used for all analyses.

Results

Two hundred and eighty-three patients were enrolled in the ETHYCO Study, with 144 subjects (50.9%) randomly assigned to the low-dose arm and 139 (49.1%) to the high-dose one. Baseline characteristics of the study population were similar between the two groups (Table 1).

The clinical--biochemical parameters at baseline, together with respiratory support at screening time (none or standard oxygen therapy vs NIV), SOFA and SIC scores are summarized in Table 2. Baseline characteristics by study are shown in Table 1 and Supplementary Table 2. The main therapies (corticosteroids, immuno-modulators agents, and antiviral drugs) administered to patients enrolled in the study are summarized in Supplementary Table 3.

Primary and secondary outcomes

As Table 3 shows, among 283 participants included in the analysis of the ETHYCO Study, no significant difference in the risk of clinical worsening between high- and low- enoxaparin dose group was found (RR = 0.72; 95% CI 0.45–1.17).

Among 283 participants included in the analysis of the ETHYCO Study, 23/139 (16.5%) patients in the high-dose enoxaparin group experienced clinical worsening, compared to 33/144 (22.9%) in the low-dose enoxaparin group, representing a RR of 0.72 (95% CI 0.45–1.17) (Table 3).

Similar results were observed for the time to clinical worsening (HR 0.65 95% CI 0.37–1.15).

Figure 1 shows the Kaplan–Meier survival estimates of clinical worsening (Log-rank test p-value = 0.19). The results were consistent across the pre-specified subgroups, as shown in Supplementary Table 4.

No major bleeding was observed during the study.

In total, nine venous thromboembolic events, six in the low-dose and three in the high-dose enoxaparin group were observed (RR 0.52, 95% CI 0.13–2.03).

As highlighted in Table 3, higher enoxaparin regimens did not affect individual items of the secondary outcome. No acute myocardial infarction occurred in either group.

Discussion

The results of our joint analysis showed no significant differences in the composite primary outcome of clinical worsening in hospitalized severe non-critically ill COVID-19

Table 1 Baseline characteristics of the study population

	Low-dose enoxaparin ($n=144$)	High-dose enoxaparin ($n=139$)	Total ($n=283$)
Age			
Years, mean (SD)	60.8 (11.2)	61.4 (10.3)	61.1 (10.7)
≥ 70 years old, *n* (%)	39 (27.1)	36 (25.9)	75 (26.5)
< 70 years old, *n* (%)	105 (72.9)	103 (74.1)	208 (73.5)
Sex			
F, *n* (%)	36 (25)	40 (28.8)	76 (26.9)
M, *n* (%)	108 (75)	99 (71.2)	207 (73.1)
BMI			
Kg m^{-2}, mean (SD)	29.6 (4.4)	29.8 (5.5)	29.7 (5.0)
≥ 30, *n* (%)	66 (45.8)	59 (42.5)	125 (44.2)
< 30, *n* (%)	78 (54.2)	80 (57.5)	158 (55.8)
Comorbidities, *n* (%)			
Hypertension	47 (32.6)	49 (35.3)	96 (33.9)
Type 2 Diabetes	24 (16.7)	23 (16.5)	47 (16.6)
Coronary artery disease	6 (4.2)	7 (5.0)	13 (4.6)
Asthma	6 (4.2)	4 (2.9)	10 (3.5)
Chronic obstructive pulmonary disease	2 (1.4)	4 (2.9)	6 (2.1)
Restrictive lung diseases	0 (0)	2 (1.4)	2 (0.7)
Moderate to severe renal failure	1 (0.7)	1 (0.7)	2 (0.7)
Stroke	0 (0)	2 (1.4)	2 (0.7)
Arrhythmia	1 (0.7)	0 (0)	1 (0.4)
End-stage renal disease (Dialysis)	0 (0)	0 (0)	0 (0)

SD standard deviation, *Kg* kilogram, m^2 square meter, *F* females, *M* males

patients who were administered enoxaparin at 70 IU Kg^{-1} every 12 h compared to those who received low dose LMWH. The results were consistent across pre-defined subgroups and secondary outcomes.

Our data add some important new clues to the current knowledge on the topic. Remarkably, although most guidelines and expert consensus issued conditional recommendations against the escalation of anticoagulation in all categories of hospitalized COVID-19 patients (either moderately ill or critically ill patients), a recent meta-analysis of high-quality multicenter RCTs suggested that full-dose anticoagulation with heparin or LMWH was associated with a lower rate of all-cause mortality and major thrombotic events, with the benefits being partly offset by a modest probability of increased major bleeding in hospitalized non-critically ill COVID-19 patients [15]. However, only a few randomized clinical trials have deeply investigated the potential benefits of escalating thromboprophylaxis to a higher yet possibly safer posology (70 IU Kg^{-1} twice daily) as compared to the usual full therapeutic dose (100 IU Kg^{-1} twice daily) [11, 12]. While the enoxaparin dose chosen in our trial can be classified as "intermediate" according to the definition, which states that intermediate dose anticoagulation "refers to escalated prophylactic dosing regimen(s), with drug doses higher than standard prophylactic doses but lower than therapeutic doses of the respective anticoagulant agent"[20], the definition of "intermediate dose" per se is highly debatable. In fact, a wide spectrum of enoxaparin doses has been used in the literature (from less than 0.5–0.7 mg Kg^{-1} q12h) so that merging data from different trials with different definitions may be questionable, not only from a methodological standpoint, but also from a clinical perspective. Interestingly, different trials have included the intermediate dose in either the intervention arm [11, 12] or the control arm [13, 14]. Furthermore, the variability in the case mix under investigation (e.g., medical ward patients versus critically ill patients, and among the critically ill, those requiring only oxygen therapy versus those needing non-invasive or invasive mechanical ventilation) adds to the considerable challenge of deriving universally applicable conclusions.

Overall, our findings are in keeping with the results of other RCTs that compared intermediate to standard prophylactic LMWH doses in hospitalized non-critically ill COVID-19 patients [11–13, 21, 22].

The INSPIRATION trial compared intermediate dose of enoxaparin at 1 mg Kg^{-1} daily, which is lower than that used in the ETHYCO study, vs low-dose anticoagulant therapy in critically ill patients and found no differences in such hard outcomes as death or thromboembolic events [11]. The

Table 2 Baseline parameters: vital signs, respiratory support, main laboratory tests, severity scores

	Low-dose enoxaparin ($n=144$)	High-dose enoxaparin ($n=139$)	All patients ($n=283$)
Vital signs			
Systolic blood pressure (mmHg), mean (SD)	129.5 (15.2)	129.6 (17.7)	129.6 (16.4)
Diastolic blood pressure (mmHg), mean (SD)	75.1 (10.0)	74.2 (11.0)	74.7 (10.5)
Heart rate (beats per minute), mean (SD)	78.8 (13.7)	79.8 (15.8)	79.3 (14.8)
Respiratory rate (breaths per minute), mean (SD)	23.4 (5.2)	23.2 (6.0)	23.3 (5.6)
Saturation (SpO_2), *n* (%)	94.4 (3.9)	94.6 (3.5)	94.5 (3.7)
Temperature (°C), mean (SD)	36.5 (0.9)	36.6 (0.9)	36.6 (0.9)
Respiratory support at screening time			
None or standard oxygen therapy	85 (59.0)	80 (57.5)	165 (58.3)
CPAP or NIV	59 (41)	59 (42.5)	118 (41.7)
Laboratory tests			
WBC (10^9 L^{-1}), mean (SD)	8.3 (3.6)	8.0 (3.3)	8.2 (3.4)
PLT (10^9 L^{-1}), mean (SD)	258.9 (102.8)	255.1 (94.2)	257.0 (98.5)
Creatinine (mg dl^{-1}), mean (SD)	0.8 (0.2)	0.8 (0.2)	0.8 (0.2)
INR, mean (SD)	1.1 (0.1)	1.1 (0.1)	1.1 (0.1)
aPTT ratio, mean (SD)	1.0 (0.1)	1.1 (0.9)	1.0 (0.7)
D-Dimer (ng ml^{-1}), median (IQR)	860 (580–1246)	840 (530–1302)	852.5 (567.5–1261.5)
>2000 ng ml^{-1}, *n* (%)	14 (9.8)	18 (13.1)	32 (11.4)
≤ 2000 ng ml^{-1}, *n* (%)	129 (90.2)	119 (86.9)	248 (88.6)
Missing, *n* (%)	1 (0.7%)	2 (1.4%)	3 (0.1%)
SOFA (sequential organ failure assessment)			
Score, mean (SD)	2.7 (0.8)	2.8 (0.8)	2.8 (0.8)
≥ 2, *n* (%)	131 (91)	125 (89.9)	256 (90.5)
$=1$, *n* (%)	9 (6.3)	4 (2.9)	13 (4.6)
Missing, *n* (%)	4 (2.8)	10 (7.2)	14 (5)
SIC (Sepsis-induced coagulopathy)			
Score, mean (SD)	2.4 (0.7)	2.3 (0.6)	2.3 (0.6)

SD standard deviation, *IQR* interquartile range

Table 3 Results on primary and secondary outcomes

	Low-dose enoxaparin, Events/*n* (%)	High-dose enoxaparin, Events/*n* (%)	Relative risk (95%CI)	Absolute reduction in risk (95%CI), %
Primary outcomes				
Clinical worsening	33/144 (22.9)	23/139 (16.5)	0.72 (0.45 to 1.17)	− 6.4 (− 16.0 to 2.8)
Major bleeding	0/144 (0)	0/139 (0)	–	–
Secondary outcomes				
Death	8/144 (5.5)	7/139 (5.0)	0.91 (0.34 to 2.43)	− 0.5 (− 0.06 to 0.5)
AMI	0/144 (0)	0/139 (0)	–	–
VTE	6/144 (4.2)	3/139 (2.2)	0.52 (0.13 to 2.03)	− 2.0 (− 6.1 to 2.1)
Need for escalation of respiratory support	27/144 (18.8)	20/139 (14.4)	0.77 (0.45 to 1.30)	− 4.4 (− 13.0 to 4.3)
Need for CPAP/NIV/MV for patients in O_2 therapy at randomisation	16/85 (18.8)	12/80 (15.0)	0.80 (0.40 to 1.58)	− 3.8 (− 15.2 to 7.6)
Need for MV for patients in CPAP/NIV at randomisation	11/59 (18.6)	8/59 (13.6)	0.73 (0.32 to 1.68)	− 5.1 (− 18.3 to 8.1)
Mortality at 30 days	8/144 (5.5)	6/139 (4.3)	0.78 (0.28 to 2.18)	− 1.2 (− 6.3 to 3.8)

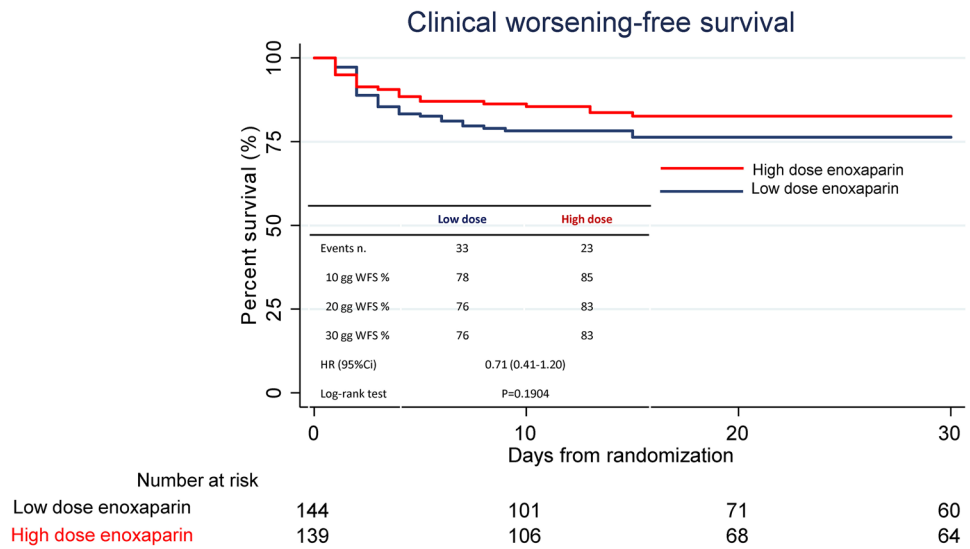

Fig. 1 Kaplan-Meier survival estimates for clinical worsening-free survival in high- and low-enoxaparin dose group

recent ANTICOVID trial [22] showed that escalating anticoagulation dose did not improve survival or disease resolution in patients hospitalized with hypoxemic COVID-19 pneumonia. However, intermediate dose anticoagulation (almost comparable to the high-dose of the ETHYCO study) was associated with the best net benefit, driven by a four-fold reduction in de novo thrombosis (mainly pulmonary artery) with a good safety profile. In contrast, no additional advantage of fully therapeutic anticoagulation was observed. We found a similar trend with a lower, although not significant, occurrence of venous thromboembolism in the high-dose group.

Growing knowledge during the course of the pandemic and concurrent treatments may have influenced the outcomes assessed in our study. Many studies on anticoagulation in COVID-19 have been conducted during the first pandemic wave, when corticosteroids had still not become the standard of care. Therefore, the net effect of the anticoagulant treatment on the clinical course of hospitalized COVID-19 patients may have been blunted in the ETHYCO study, since 93% patients were on corticosteroid treatment at randomization, as compared to much lower proportions in other large trials [23].

We speculate that, overall, these results suggest the need for an individualized assessment of risk of thrombosis and bleeding, a thorough evaluation of associated morbidity and mortality as well as the impact on quality of life to perform tailored treatment decisions. Although the subgroup analysis did not highlight specific sub-populations that may benefit from high-dose anticoagulation, the question whether such a categorization may have failed to reflect the complexity of the clinical scenario is still open. Higher intensity-anticoagulation strategies in higher-risk hospitalized patients may still need to be considered on a case-by-case basis. The National Institutes of Health currently recommends therapeutic-dose anticoagulation for hospitalized COVID-19 patients with increased D-dimer levels requiring low-flow oxygen [24]. This indication may appear debatable, but it probably stems from the need to consider more than one parameter to individualize treatment.

A multimodal evaluation considering clinical--biochemical-imaging data (e.g., advanced age, history of cancer or VTE, elevated D-dimer, radiological pattern of ARDS), possibly with their dynamic changes over time, is necessary. Whether a specific COVID-19 risk score may be useful, as advocated by some Authors [23], or no tool can truly capture what may be understood only through complex clinical judgment, remains to be investigated.

The most appropriate timing of administration of anticoagulation strategies is also an issue of pivotal importance. Our results seem to confirm that once the multiple underlying pathophysiological mechanisms (inflammation, endothelial injury and immunothrombosis) are activated, the complex clinical course of COVID-19 patients with respiratory compromise cannot be favorably influenced even by very early administration of high intensity anticoagulation [25].

Some important limitations of our trial must be acknowledged. The most relevant limitation is the quite small sample size, which might have limited the possibility to detect even small differences between the study groups not only on such an hard outcome as mortality, but also on endpoints as the need for advanced respiratory support on which previous trials have shown that anticoagulation might be of benefit [14].

The high-dose group was administered 70 IU Kg^{-1} bid of enoxaparin. While this dose significantly exceeds much lower doses referred to as "intermediate" in the literature, it remains lower than the full therapeutic dose. Consequently, our findings are not universally generalizable and should be interpreted as a component within the complex mosaic of a patient-tailored anticoagulation strategy for severe

SARS-CoV-2 disease. It is crucial to emphasize that our chosen dosage choice inherently limits any inferences concerning a direct comparison between a full therapeutic dose and a prophylactic dose.

Moreover, we enrolled predominantly white patients; therefore, the results might not be generalizable to patients of other ethnicities.

Our study's strengths encompass a uniform patient population (severe COVID-19 cases meeting similar criteria, consistent care in comparable hospital units excluding ICU), and a consistent trial design. Notably, our therapeutic arm featured a singular, specified treatment choice (LMWH at 70 IU Kg-1 every 12 h), setting it apart from larger randomized trials that explored various therapeutic-dose groups, including LMWH, unfractionated heparin, and even direct-acting oral anticoagulants.

We speculate that the issue of the most appropriate anticoagulation strategy in COVID-19 patients should be interpreted in the wider context of the appropriateness of anticoagulant drug prescriptions for VTE prophylaxis in hospitalized (often multimorbid) medical patients, which is certainly an ever-evolving and debated topic [26, 27].

In conclusion, our joint analysis of two RCTs showed that among hospitalized severe non-critically ill COVID-19 patients, the escalation of LMWH to a dose higher than prophylactic, yet below fully therapeutic levels, did not significantly impact the progression of clinical worsening.

Appendix

Complete list of the participants to the ETHYCO (Enoxaparin at THerapeutic or prophYlactic dose in severe COVID) Study Group: III Division of Infectious Diseases, ASST Fatebenefratelli Sacco, Luigi Sacco Hospital, Milan, Italy: Spinello Antinori; Department of Biomedical and Clinical Sciences, University of Milan, Italy: Spinello Antinori, Antonio Brucato, Manuela Nebuloni, Pierachille Santus; Columbus Center Clinic, Milan, Italy: Massimo Arquati; U.O.SD Cardiologia Riabilitativa, Hospital of Piacenza, Piacenza, Italy: Daniela Aschieri; Division of Internal Medicine, ASST Fatebenefratelli Sacco, Fatebenefratelli Hospital, Milan, Italy: Antonio Brucato; Medicina Interna d'Urgenza e Area Critica, Azienda Ospedaliero-Universitaria di Modena, Modena, Italy: Lucio Brugioni, Luca Sarti; Respiratory Disease Unit, Azienda Ospedaliero-Universitaria di Modena, Modena, Italy: Enrico Clini; Infectious Disease Unit, Hospital of Piacenza, Piacenza, Italy: Mauro Codeluppi; Division of Anesthesiology and Intensive Care, ASST Fatebenefratelli Sacco, Luigi Sacco Hospital, University of Milan, Milan, Italy: Riccardo Colombo; Hematology Unit, Azienda Ospedaliero-Universitaria, Modena, Italy: Valeria Coluccio; Division of Internal Medicine, ASST Fatebenefratelli Sacco, Luigi Sacco Hospital, Milan, Italy: Chiara Cogliati, Elena Condorelli, Pietro Facchinetti, Alba Taino, Francesca Tonelli, Maddalena Alessandra Wu; Department of Medical and Surgical Sciences for Children and Adults, University-Hospital of Modena and Reggio Emilia, Modena, Italy: Roberto D'Amico, Cinzia Del Giovane; Institute of Primary Health Care (BIHAM), University of Bern, Bern, Switzerland: Cinzia Del Giovane; UOC Pneumologia e UTIR, AUSL Piacenza, Piacenza, Italy: Silvia Di Stasi, Cosimo Franco; Infectious Diseases Unit, University of Modena and Reggio Emilia, Modena, Italy: Giovanni Dolci, Erica Franceschini, Marianna Meschiari, Cristina Mussini; Division of Haematology, ASST Fatebenefratelli Sacco, Luigi Sacco Hospital, University of Milan, Milan, Italy: Augusto B. Federici; Division of Anesthesiology and Intensive Care, ASST Fatebenefratelli Sacco, Fatebenefratelli Hospital, Milan, Italy: Marco Gemma; Servizio Formazione, Ricerca e Innovazione, Azienda Ospedaliero-Universitaria di Modena, Modena, Italy: Annita Gozzi, Pasquale Mighali, Paola Vandelli; Internal Medicine Unit, Medical Department, Hospital of Piacenza, Piacenza, Italy: Davide Imberti; U.O.C. Pronto Soccorso/ Obi/ Medicina D'Urgenza, Hospital of Piacenza, Piacenza, Italy: Andrea Magnacavallo; Pathology Unit, ASST Fatebenefratelli Sacco, Luigi Sacco Hospital, University of Milan, Milan, Italy: Manuela Nebuloni; Medicina Interna, Azienda Ospedaliero-Universitaria di Modena, Modena, Italy: Antonello Pietrangelo; I Division of Infectious Diseases, ASST Fatebenefratelli Sacco, Luigi Sacco Hospital, Milan, Italy: Giuliano Rizzardini; Division of Cardiology, ASST Fatebenefratelli Sacco, Luigi Sacco Hospital, University of Milan, Milan, Italy: Diego Ruggiero; Division of Respiratory Diseases, ASST Fatebenefratelli Sacco, Luigi Sacco Hospital, University of Milan, Milan, Italy: Pierachille Santus; U.O.SD Medicina D'Urgenza, Hospital of Piacenza, Piacenza, Italy: Matteo Silva; Unità di Supporto Statistico Metodologico per la Ricerca Clinica Azienda Ospedaliero-Universitaria di Modena, Modena, Italy: Roberto Vicini.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11739-023-03439-w.

Author contributions Conception of the work: MAW, MA, UR, MM, VC, RV, RD, PM; Methodology and data curation: MAW, CDG, RC, GD, MA, DR, RV, RD, URo; Data acquisition/investigation: MAW, GD, RC, AT, EF, PF, LT, FT, LB, GC, EC, DA, MC, EC, SDS, EF, CF, MG, AG, AI, DI, AM, DR, MMi, CM, C. Picchi, AP, GP, GR, LS, MS, PV, AT, CG, FT; Formal analysis: CDG, RD and RV; Supervision: MM, SA, CC, ABF, MN, GR, P.S; Project administration: MAW, MM, MA, RD; Writing—original draft: MAW; Writing—review and editing: MAW, CDG, RC, GD, MA, DR, RV, RD, UR, MM. The present study is based on an analysis of data of two trials. Underlying data were verified by the authors of the original studies. All authors contributed to interpretation of the results, critically revised the manuscript, and approved its final version.

Funding None.

Data availability Data collected and analyzed for the current study are available upon reasonable request and approval of the ETHYCO investigators and of the Ethics Committee.

Declarations

Conflict of interest The authors have no conflicts of interest to disclose.

References

1. Iba T, Levy JH, Connors JM, Warkentin TE, Thachil J, Levi M (2020) The unique characteristics of COVID-19 coagulopathy. Crit Care 24:360. https://doi.org/10.1186/s13054-020-03077-0
2. Connors JM, Levy JH (2020) Thromboinflammation and the hypercoagulability of COVID-19. J Thromb Haemost 18:1559–1561. https://doi.org/10.1111/jth.14849
3. Thachil J (2020) The versatile heparin in COVID-19. J Thromb Haemost 18:1020–1022. https://doi.org/10.1111/jth.14821
4. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B et al (2020) A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 382:727–733. https://doi.org/10.1056/NEJMoa2001017
5. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z (2020) Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost 18(5):1094–1099. https://doi.org/10.1111/jth.14817
6. Moores LK, Tritschler T, Brosnahan S, Carrier M, Collen JF, Doerschug K, Holley AB, Iaccarino J et al (2022) Thromboprophylaxis in patients with COVID-19: a brief update to the CHEST guideline and expert panel report. Chest 162:213–225. https://doi.org/10.1016/j.chest.2022.02.006
7. Schulman S, Sholzberg M, Spyropoulos AC, Zarychanski R, Resnick HE, Bradbury CA, Broxmeyer L, Connors JM et al (2022) ISTH guidelines for antithrombotic treatment in COVID-19. J Thromb Haemost 20:2214–2225. https://doi.org/10.1111/jth.15808
8. Baumann Kreuziger L, Sholzberg M, Cushman M (2022) Anticoagulation in hospitalized patients with COVID-19. Blood 140:809–814. https://doi.org/10.1182/blood.2021014527
9. Cuker A, Tseng EK, Schunemann HJ, Angchaisuksiri P, Blair C, Dane K, DeSancho MT, Diuguid D et al (2022) American Society of Hematology living guidelines on the use of anticoagulation for thromboprophylaxis for patients with COVID-19: March 2022 update on the use of anticoagulation in critically ill patients. Blood Adv 6:4975–4982. https://doi.org/10.1182/bloodadvances.2022007940
10. Cuker A, Tseng EK, Nieuwlaat R, Angchaisuksiri P, Blair C, Dane K, DeSancho MT, Diuguid D et al (2022) American Society of Hematology living guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19: January 2022 update on the use of therapeutic-intensity anticoagulation in acutely ill patients. Blood Adv 6:4915–4923. https://doi.org/10.1182/bloodadvances.2022007561
11. Investigators INSPIRATION, Sadeghipour P, Talasaz AH, Rashidi F, Sharif-Kashani B, Beigmohammadi MT, Farrokhpour M, Sezavar SH et al (2021) Effect of intermediate-dose vs standard-dose prophylactic anticoagulation on thrombotic events, extracorporeal membrane oxygenation treatment, or mortality among patients with COVID-19 admitted to the intensive care unit: the INSPIRATION randomized clinical trial. JAMA 325:1620–1630. https://doi.org/10.1001/jama.2021.4152
12. Perepu US, Chambers I, Wahab A, Ten Eyck P, Wu C, Dayal S, Sutamtewagul G, Bailey SR et al (2021) Standard prophylactic versus intermediate dose enoxaparin in adults with severe COVID-19: a multi-center, open-label, randomized controlled trial. J Thromb Haemost 19:2225–2234. https://doi.org/10.1111/jth.15450
13. Spyropoulos AC, Goldin M, Giannis D, Diab W, Wang J, Khanijo S, Mignatti A, Gianos E et al (2021) Efficacy and safety of therapeutic-dose heparin vs standard prophylactic or intermediate-dose heparins for thromboprophylaxis in high-risk hospitalized patients with COVID-19: the HEP-COVID randomized clinical trial. JAMA Intern Med 181:1612–1620. https://doi.org/10.1001/jamainternmed.2021.6203
14. Lawler PR, Goligher EC, Berger JS, Neal MD, McVerry BJ, ATT ACC Investigators, ACTIV-4a Investigators et al (2021) Therapeutic anticoagulation with heparin in noncritically ill patients with Covid-19. N Engl J Med 385:790–802. https://doi.org/10.1056/NEJMoa2105911
15. Pilia E, Belletti A, Fresilli S, Lee TC, Zangrillo A, Finco G, Landoni G (2023) The effect of heparin full-dose anticoagulation on survival of hospitalized, non-critically ill COVID-19 patients: a meta-analysis of high quality studies. Lung 201(2):135–147. https://doi.org/10.1007/s00408-023-00599-6
16. Pengo V, Cucchini U, Denas G, Erba N, Guazzaloca G, La Rosa L, De Micheli V, Testa S et al (2009) Standardized low-molecular-weight heparin bridging regimen in outpatients on oral anticoagulants undergoing invasive procedure or surgery: an inception cohort management study. Circulation 119:2920–2927. https://doi.org/10.1161/CIRCULATIONAHA.108.823211
17. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, Machado FR, McIntyre L et al (2021) Surviving sepsis campaign: International Guidelines for Management of Sepsis and Septic Shock 2021. Crit Care Med 49:e1063–e1143. https://doi.org/10.1097/CCM.0000000000005337
18. Iba T, Nisio MD, Levy JH, Kitamura N, Thachil J (2017) New criteria for sepsis-induced coagulopathy (SIC) following the revised sepsis definition: a retrospective analysis of a nationwide survey. BMJ Open 7:e017046. https://doi.org/10.1136/bmjopen-2017-017046
19. Schulman S, Kearon C, Subcommittee on Control of Anticoagulation of the S, Standardization Committee of the International Society on T, Haemostasis (2005) Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 3:692–694. https://doi.org/10.1111/j.1538-7836.2005.01204.x
20. Potpara T, Angiolillo DJ, Bikdeli B, Capodanno D, Cole O, Yataco AC, Dan GA, Harrison S et al (2023) Antithrombotic therapy in arterial thrombosis and thromboembolism in COVID-19: an American College of Chest Physicians Expert Panel Report. Chest. https://doi.org/10.1016/j.chest.2023.06.032
21. Zuily S, Lefevre B, Sanchez O, Empis de Vendin O, de Ciancio G, Arlet JB, Khider L, Terriat B et al (2023) Effect of weight-adjusted intermediate-dose versus fixed-dose prophylactic anticoagulation with low-molecular-weight heparin on venous thromboembolism among noncritically and critically ill patients with COVID-19: the COVI-DOSE trial, a multicenter, randomised, open-label, phase 4 trial. EClinicalMedicine 60:102031. https://doi.org/10.1016/j.eclinm.2023.102031
22. Labbe V, Contou D, Heming N, Megarbane B, Razazi K, Boissier F, Ait-Oufella H, Turpin M et al (2023) Effects of standard-dose prophylactic, high-dose prophylactic, and therapeutic anticoagulation in patients with hypoxemic COVID-19 pneumonia: the ANTICOVID randomized clinical trial. JAMA Intern Med

183(6):520–531. https://doi.org/10.1001/jamainternmed.2023.0456
23. Stone GW, Farkouh ME, Lala A, Tinuoye E, Dressler O, Moreno PR, Palacios IF, Goodman SG et al (2023) Anticoagulation strategies in non-critically ill patients hospitalized with COVID-19: a randomized clinical trial. J Am Coll Cardiol 81(18):1747–1762. https://doi.org/10.1016/j.jacc.2023.02.041
24. National Institutes of Health (2023) Antithrombotic Therapy in Patients With COVID-19. In: COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. Available at: https://www.covid19treatmentguidelines.nih.gov/therapies/antithrombotic-therapy/. Accessed 22 Aug 2023
25. Becker RC, Ortel TL (2023) Anticoagulation in patients with COVID-19 pneumonia-what is the optimal intensity? JAMA Intern Med 183(6):532–533. https://doi.org/10.1001/jamainternmed.2023.0625
26. Spyropoulos AC (2022) To prophylax or not, and how much and how long? Controversies in VTE prevention for medical inpatients, including COVID-19 inpatients. Hematol Am Soc Hematol Educ Progr 2022:506–514. https://doi.org/10.1182/hematology.2022000403
27. Rossio R, Mandelli S, Ardoino I, Nobili A, Peyvandi F, Mannucci PM, Franchi C et al (2023) Prescription appropriateness of anticoagulant drugs for prophylaxis of venous thromboembolism in hospitalized multimorbid older patients. Intern Emerg Med 18:97–104. https://doi.org/10.1007/s11739-022-03121-7

Authors and Affiliations

Maddalena Alessandra Wu[1] · Cinzia Del Giovane[2,3,4] · Riccardo Colombo[5] · Giovanni Dolci[6] · Massimo Arquati[7] · Roberto Vicini[4] · Umberto Russo[8] · Diego Ruggiero[9] · Valeria Coluccio[10] · Alba Taino[1] · Erica Franceschini[6] · Pietro Facchinetti[1] · Pasquale Mighali[11] · Lucia Trombetta[1] · Francesca Tonelli[1] · Claudia Gabiati[12] · Chiara Cogliati[1] · Roberto D'Amico[2,4] · Marco Marietta[10] · the ETHYCO Study Group

✉ Maddalena Alessandra Wu
maddalena.ale.wu@gmail.com; maddalena.wu@unimi.it

1 Division of Internal Medicine, Department of Biomedical and Clinical Sciences, ASST Fatebenefratelli Sacco, Luigi Sacco Hospital, University of Milan, Milan, Italy

2 Department of Medical and Surgical Sciences for Children and Adults, University-Hospital of Modena and Reggio Emilia, Modena, Italy

3 Institute of Primary Health Care (BIHAM), University of Bern, Bern, Switzerland

4 Unità di Supporto Statistico Metodologico per la Ricerca Clinica Azienda Ospedaliero-Universitaria di Modena, Modena, Italy

5 Division of Anesthesiology and Intensive Care, ASST Fatebenefratelli Sacco, Luigi Sacco Hospital, University of Milan, Milan, Italy

6 Infectious Diseases Unit, University of Modena and Reggio Emilia, Modena, Italy

7 Columbus Center Clinic, Milan, Italy

8 Division of Haematology, ASST Fatebenefratelli Sacco, Luigi Sacco Hospital, University of Milan, Milan, Italy

9 Division of Cardiology, ASST Fatebenefratelli Sacco, Luigi Sacco Hospital, University of Milan, Milan, Italy

10 Hematology Unit, Azienda Ospedaliero-Universitaria, Modena, Italy

11 Servizio Formazione, Ricerca e Innovazione, Azienda Ospedaliero-Universitaria di Modena, Ospedale Policlinico, Modena, Italy

12 Division of Internal Medicine, Department of Biomedical and Clinical Sciences, ASST Fatebenefratelli Sacco, Fatebenefratelli Hospital, University of Milan, Milan, Italy