Clinical outcome with different doses of low-molecular-weight heparin in patients hospitalized for COVID-19

Marco G. Mennuni[1] · Giulia Renda[2,3] · Leonardo Grisafi[1,4] · Andrea Rognoni[1] · Crizia Colombo[1,4] · Veronica Lio[1,4] · Melissa Foglietta[2,3] · Ivan Petrilli[2,3] · Mario Pirisi[1,4] · Enrico Spinoni[1,4] · Danila Azzolina[4] · Eyal Hayden[1,4] · Gianluca Aimaretti[1,4] · Gian Carlo Avanzi[1,4] · Mattia Bellan[1,4] · Vincenzo Cantaluppi[1,4] · Andrea Capponi[1] · Luigi M. Castello[1,4] · Damiano D'Ardes[2,3] · Francesco Della Corte[1,4] · Sabina Gallina[2,3] · Marco Krengli[1,4] · Mario Malerba[4,5] · Sante D. Pierdomenico[2,3] · Paola Savoia[1,4] · Patrizia Zeppegno[1,4] · Pier P. Sainaghi[1,4] · Francesco Cipollone[2,3] · Giuseppe Patti[1,4] · the COVID-UPO Clinical Team

Abstract

A pro-thrombotic *milieu* and a higher risk of thrombotic events were observed in patients with CoronaVirus disease-19 (COVID-19). Accordingly, recent data suggested a beneficial role of low molecular weight heparin (LMWH), but the optimal dosage of this treatment is unknown. We evaluated the association between prophylactic vs. intermediate-to-fully anticoagulant doses of enoxaparin and in-hospital adverse events in patients with COVID-19. We retrospectively included 436 consecutive patients admitted in three Italian hospitals. Outcome according to the use of prophylactic (4000 IU) vs. higher (> 4000 IU) daily dosage of enoxaparin was evaluated. The primary end-point was in-hospital death. Secondary outcome measures were in-hospital cardiovascular death, venous thromboembolism, new-onset acute respiratory distress syndrome (ARDS) and mechanical ventilation. A total of 287 patients (65.8%) were treated with the prophylactic enoxaparin regimen and 149 (34.2%) with a higher dosing regimen. The use of prophylactic enoxaparin dose was associated with a similar incidence of all-cause mortality (25.4% vs. 26.9% with the higher dose; OR at multivariable analysis, including the propensity score: 0.847, 95% CI 0.400–0.1.792; p = 0.664). In the prophylactic dose group, a significantly lower incidence of cardiovascular death (OR 0.165), venous thromboembolism (OR 0.067), new-onset ARDS (OR 0.454) and mechanical intubation (OR 0.150) was observed. In patients hospitalized for COVID-19, the use of a prophylactic dosage of enoxaparin appears to be associated with similar in-hospital overall mortality compared to higher doses. These findings require confirmation in a randomized, controlled study.

Keywords COVID-19 · Enoxaparin doses · Mortality · Thromboprophylaxis

Highlights

- Thrombosis and inflammation have an interacting and circular relationship in COVID-19.
- In patients with COVID-19, a hypercoagulable state justifies the use of heparin as prophylaxis for future thrombotic events.
- A prophylactic dosage of enoxaparin seems to be associated with similar in-hospital mortality compared to higher doses

✉ Giuseppe Patti
giuseppe.patti@uniupo.it

1 Azienda Ospedaliero-Universitaria Maggiore della Carità, Novara, Italy

2 G. d'Annunzio University, Chieti-Pescara, Italy

3 Ospedale Santissima Annunziata of Chieti, Chieti, Italy

4 Dipartimento di Medicina Traslazionale, Università del Piemonte Orientale, UPO, Azienda Ospedaliero-Universitaria Maggiore della Carità, Via Solaroli 17, 28100 Novara, Italy

5 Sant'Andrea Hospital, Vercelli, Italy

Introduction

Coronavirus Disease-2019 (COVID-19), caused by Severe Acute Respiratory Syndrome CoronaVirus-2 (SARS-CoV-2) infection, was first described in China in December 2019; since then, it has rapidly become a global pandemic [1]. Patients hospitalized for COVID-19 usually present a respiratory syndrome, but several reports have described an increased occurrence of macrovascular thrombotic complications, with attendant higher mortality [2, 3]. Indeed, autoptic data also indicated a diffuse microvascular thrombosis in the lungs of patients who died for COVID-19 [4–6]. Thus, based on such evidence and on real-world data suggesting a clinical benefit of anticoagulant therapy [7–10], patients hospitalized for COVID-19 commonly receive early treatment with low molecular weight heparin (LMWH). Although the World Health Organization supported a strategy with LMWH at prophylactic dosage (4000 IU daily) [11], in patients admitted for COVID-19 it is common practice to use intermediate-to-therapeutic (i.e., fully anticoagulant) doses of LMWH. This is in agreement with recent reports showing a prothrombotic *milieu* in such patients [2, 12]. Thus, due to the lack of specific comparison data, the optimal dosage of LMWH in this setting is unknown and debated. In this retrospective, multicenter study, we specifically investigated the in-hospital outcome with prophylactic vs. higher dosage of LMWH in patients hospitalized for COVID-19.

Methods

Study population

Consecutive patients aged ≥ 18 years and admitted for COVID-19 from February 20 to May 12, 2020, in three Italian Hospitals (Maggiore della Carità Hospital of Novara; Sant'Andrea Hospital of Vercelli; Policlinico Santissima Annunziata of Chieti) were included. All patients had a nasopharyngeal swab tested positive for molecular detection of SARS-CoV-2 RNA by reverse-transcriptase–polymerase-chain-reaction assay.

A total of 637 patients with COVID-19 were admitted during the study period. For the purpose of the study, we considered those patients receiving LMWH at any time during the in-hospital stay. Two-hundred-one patients were excluded from the analysis: 157 patients because they did not receive LMWH due to clinical decision of the treating physician; 23 patients due to lack of information on the LMWH dose; 4 patients who received thromboprophylaxis with fondaparinux; 17 patients treated with oral anticoagulant agents. Thus, a total of 436 patients represent the study population. The flow diagram indicating how the final number of included patients was obtained is reported in Fig. 1 of the Online Appendix. The choice of dosing regimen of LMWH and timing of LMWH initiation was left to the physician's discretion; however, as per internal in-hospital protocols, patients deemed suitable for pharmacological prevention of thrombotic events generally received subcutaneous LMWH early after the admission, and LMWH was enoxaparin in all cases. No antiplatelet therapy or unfractionated heparin were given for thromboprophylaxis; unfractionated heparin was utilized only in patients with thrombotic complications during hospitalization. In the analysis, no patient had received both LMWH doses; switching from prophylactic to higher enoxaparin doses was performed only in the case of in-hospital thrombotic complication. Patients were included regardless of clinical features at presentation and in-hospital therapies for COVID-19. The Institutional Review Board approved the study protocol (IRB code CE 97/20), which was conducted in strict accordance with the Declaration of Helsinki principles.

Data collection

We identified patients hospitalized for COVID-19 from hospital administrative data. An electronic case report form was generated using the Research Electronic Data Capture software (REDCap, Vanderbilt University), where individual data obtained after the revision of clinical records were entered. The data entry was retrospectively performed by investigators involved in the patient's management. A unique pseudonymized code was assigned to each patient. Individual data included patients' demographic details, comorbidities, vital signs, laboratory test results, medications and in-hospital events.

Investigational regimens exposure and study end-points

Patients were divided according to the received enoxaparin dose: prophylactic (4000 IU daily) vs. higher dosage (> 4000 IU daily). The primary end-point was the incidence of all-cause death during in-hospital stay in the two groups (prophylactic vs. higher dosing regimen).

The following in-hospital secondary end-points were considered:

– Cardiovascular mortality, defined as death resulting from an acute myocardial infarction, heart failure, stroke, pulmonary embolism, or other cardiovascular causes [13].
– Venous thromboembolism, including pulmonary embolism or deep venous thrombosis

- New-onset severe acute respiratory distress syndrome (ARDS), defined according to the Berlin definition, as an acute (within a week), diffuse, inflammatory lung injury, not fully explained by cardiac failure or fluid overload, leading to increased pulmonary vascular permeability and loss of aerated lung tissue acute, with bilateral lung opacities consistent with pulmonary edema and ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO_2/FiO_2) < 100 mmHg [14].
- Need for mechanical ventilation. Criteria for mechanical ventilation were: cardiac or respiratory arrest; inability to protect the airway; coma or psychomotor agitation; unmanageable secretions or uncontrolled vomiting; life-threatening arrhythmias or electrocardiographic signs of ischemia; hemodynamic instability, defined as systolic arterial pressure less than 90 mmHg despite adequate filling or use of vasoactive agents; intolerance to all interfaces; dyspnea during noninvasive continuous positive airway pressure, a respiratory rate more than 30 breaths/min; peripheral oxygen saturation below 92% during noninvasive continuous positive airway pressure; acidosis with a pH < 7.35.
- Major bleeding and clinically relevant non-major bleeding, according to the International Society of Thrombosis and Haemostasis (ISTH) definition [15]. This analysis was performed on a subgroup of 86 consecutive patients whose bleeding complications were systematically collected and validated.

All outcome events (both primary and secondary) were counted if they occurred after the admission and after the initiation of LMWH treatment. Patients without adverse events who were still hospitalized at the time of the analysis were not included in the analysis. The length of stay was reported as days from admission to discharge.

Statistical analysis

Continuous data are reported as mean ± standard deviation if normally distributed, or as median and interquartile range if not normally distributed, and were compared by Student t-test or Mann–Whitney U test, as appropriate. Categorical variables are indicated as number (percentage), and proportions were compared by chi-squared test. Frequencies were calculated to examine the associations between LMWH doses and outcome.

Logistic regression models were used to estimate the independent association between LMWH dosing regimens and study end-points. Odds ratios (OR) and 95% confidence interval (CI) were calculated. The residual imbalance of adjusting covariates was addressed by a "doubly robust" method, incorporating relevant covariates in two regression models: a propensity-score model and an outcome regression

model [16]. The first model was fitted to account for the non-randomized use of different LMWH dosages. The individual propensities for receiving a prophylactic LMWH dose were estimated through a logistic regression model, including baseline demographic/clinical characteristics and comorbidities (see Tables 1 and 2). We then added the propensity score based on patients' characteristics as an additional covariate into the outcome regression model (Fig. 2 of the Online Appendix). This latter model included demographic factors (age, gender, body weight), clinical factors (comorbidities, chronic use of antiplatelet or oral anticoagulant therapy), laboratory findings (PaO_2/FiO_2) and in-hospital medications for COVID-19. In order to adjust for timing of LMWH initiation, early administration of LMWH (< 24 h from admission) was also added as a covariate.

A subgroup analysis was additionally performed to test the interaction between earlier administration of LMWH and mortality with different doses of LMWH. With the aim to keep into account differences in follow-up duration between the two study groups, a time-to-event analysis was performed for the primary end-point by using the time on LMWH treatment as a time-dependent variable. An estimation of survival at 30 days was calculated by the Kaplan–Meier method, with differences between different LMWH dosing regimens being assessed by log-rank test.

Two sensitivity analyses were conducted. We evaluated the primary outcome with different LMWH dosages stratifying by the risk of death at hospital presentation using the 4C Mortality Score; it classifies the risk of death of COVID-19 patients, based on clinical features on admission, into four groups: low, intermediate, high and very high risk [17]. Thus, we estimated the association of 4000 IU daily dose of enoxaparin vs. > 4000 IU daily dose for the primary end-point in the subgroups with low/intermediate and high/very high risk. Moreover, to test the relationship between thrombo-prophylaxis and outcome at the extreme of body weight (obesity or underweight), we performed a sensitivity analysis in the subgroup of patients in whom a precise body weight was identified on the source documents (N = 212). We classified the body weight-adjusted enoxaparin dose as prophylactic (≤ 70 IU/kg daily) or higher (> 70 IU/kg daily) and evaluated the association of the two regimens with the primary end-point. A logistic regression analysis was also performed in the two sensitivity estimations, as previously indicated for the primary assessments. Statistical analyses were performed by Stata software, version 16.0.

Results

A total of 287 patients (65.8%) received a prophylactic enoxaparin dose (4000 IU daily) and 149 (34.2%) a higher enoxaparin dose (> 4000 IU daily). The distribution of

Table 1 Baseline characteristics of patients stratified by enoxaparin dose

	Prophylactic dose N = 287	Higher dose N = 149	p value
Demographic			
Age (years)	71.2 ± 15.6	70.2 ± 13.0	0.175
Male gender	159 (55.4)	90 (60.4)	0.525
Body weight (kg)	72.6 ± 13.3	79.3 ± 13.6	< 0.001
Comorbidities			
Arterial hypertension	152 (53.0)	93 (62.4)	0.059
Diabetes mellitus	66 (23.0)	29 (19.5)	0.397
Obesity[a]	34 (14.7)	33 (27.5)	0.004
Smoking	40 (13.9)	20 (13.4)	0.882
Heart failure	41 (14.3)	27 (18.1)	0.156
Atrial fibrillation	22 (7.7)	34 (22.8)	< 0.001
Peripheral vascular disease	45 (15.7)	20 (12.4)	0.530
Chronic obstructive pulmonary disease	35 (12.2)	12 (8.1)	0.186
Chronic renal failure	51 (17.8)	17 (11.4)	0.083
History of cancer	56 (19.5)	25 (16.8)	0.486
Chronic liver disease	10 (3.5)	3 (2.0)	0.392
Clinical signs upon presentation			
Systolic blood pressure (mmHg)	129.0 ± 22.2	130.2 ± 22.1	0.591
Heart rate (bpm)	83.7 ± 14.3	87.3 ± 21.0	0.060
Body temperature (°C)	37.5 ± 1.1	37.4 ± 1.1	0.425
Severe ARDS at ED presentation	12 (4.2)	16 (10.7)	0.008
Laboratory findings			
White blood cells (n/mm^3)	7757 ± 5652	8460 ± 5245	0.113
Hemoglobin (g/dL)	12.8 ± 2.0	12.9 ± 2.1	0.601
Platelets (n/mm^3)	213,140 ± 99,410	223,030 ± 97,938	0.383
C-reactive protein (mg/dL)	23.8 ± 43.6	22.4 ± 38.7	0.336
Creatinine (mg/dL)	1.3 ± 1.3	1.0 ± 0.6	0.044
D-Dimer (µg/L)[a]	4,233 ± 10,227	5,183 ± 13,902	0.616
PaO$_2$/FiO$_2$ ratio	284.5 ± 100.2	235.4 ± 93.1	< 0.001
Risk of death upon presentation			
4C Mortality Score			0.230
Low (0–3)	12 (4.2)	2 (1.3)	
Intermediate (4–8)	90 (31.4)	46 (30.9)	
High (9–14)	168 (58.5)	96 (64.4)	
Very high (> 14)	17 (5.9)	5 (3.4)	

Data are expressed as n (%) or mean ± standard deviation. *ARDS* acute respiratory distress syndrome; *ED* emergency department

[a]Data were missing for obesity in 85 patients (56 in the prophylaxis and 29 in the higher dose group) and D-dimer in 267 patients (196 in the prophylaxis and 71 in the higher dose group)

baseline characteristics, clinical presentation, comorbidities, concomitant treatments and laboratory findings according to the enoxaparin dosing regimen is shown in Tables 1 and 2. A prophylactic enoxaparin dose was associated with lower body weight, reduced prevalence of atrial fibrillation and severe ARDS at Emergency Department presentation, as well as with higher creatinine values and increased PaO$_2$/FiO$_2$ at baseline. Treatment with remdesivir, lopinavir/ritonavir, steroids and tocilizumab was more frequent in patients receiving the higher enoxaparin dosage. The length of in-hospital stay was shorter in patients receiving the prophylactic dose (Table 3).

A total of 113 patients (25.9%) had a primary end-point event. Crude rates of the study end-points are reported in Table 3. Patients on prophylactic enoxaparin dose had a comparable incidence of the primary outcome measure of all-cause mortality (25.4% vs. 26.9% in those receiving the higher dose; p = 0.750). The estimated survival rates at 30 days among patients on prophylactic vs higher dosing regimen were 56.5% (95% CI 45.7–65.9%) and 61.3% (95%

Table 2 Medical treatment in patients stratified by enoxaparin dose

	Prophylactic dose N = 287	Higher dose N = 149	p value
Medical therapy			
ACE-inhibitors	58 (27.2)	40 (31.0)	0.454
Sartans	47 (22.2)	35 (27.3)	0.280
Aspirin	60 (28.0)	40 (32.0)	0.440
P_2Y_{12} inhibitors	24 (11.4)	17 (13.4)	0.583
Oral anticoagulants	15 (7.0)	32 (24.8)	<0.001
COVID-19 treatment			
Hydroxychloroquine	185 (84.9)	117 (9.7)	0.118
Daunavir	75 (35.5)	48 (39.0)	0.525
Remdesivir	0	6 (4.9)	0.001
Lopinavir	33 (15.6)	29 (23.6)	0.069
Lopinavir/Ritonavir	31 (15.2)	29 (25.2)	0.028
Azitromicin	76 (35.3)	44 (36.4)	0.852
Steroids	80 (36.7)	70 (58.8)	<0.001
Tocilizumab	19 (9.2)	25 (21.7)	0.002

Data are expressed as n (%)

ACE Angiotensin-converting enzyme, *COVID-19* CoronaVirus disease-19

CI 49.3–71.3%), respectively (log-rank $p = 0.189$; Fig. 1). Multivariate analysis, also adjusted for the propensity score, indicated a similar risk of in-hospital death in the two treatment groups (OR 0.847, 95% CI 0.400–1.792, p = 0.664) (Fig. 2). In the overall population, 68.9% of patients received enoxaparin < 24 h from Emergency Department presentation and 80.8% of patients < 48 h. There was no interaction

between earlier initiation of enoxaparin (< 24 h from admission) and different doses of enoxaparin in terms of in-hospital mortality (earlier prophylactic dose 24.8%; earlier higher dose 26.3%; late prophylactic dose 27.8%; late higher dose 25.6%; p for interaction = 0.726).

All secondary outcome measures were associated with a significantly lower risk in the prophylactic dose group (Fig. 2); in particular, adjusted OR for cardiovascular mortality was 0.165 (95% CI 0.050–0.546, p = 0.003), adjusted OR for venous thromboembolism was 0.067 (95% CI 0.011–0.388, p = 0.003), adjusted OR for new-onset severe ARDS was 0.454 (95% CI 0.227–0.910, p = 0.026) and for mechanical ventilation was 0.150 (95% CI 0.051–0.441, p = 0.010). The incidence of bleeding events was low in both groups, without significant differences (major bleeding: 1.5% with the prophylaxis regimen vs. 4.8% with the higher dose regimen; clinically relevant non-major bleeding: 3.1% vs. 4.8%).

Sensitivity analysis showed that, as compared to the higher dosing regimen, the use of prophylactic dosage of enoxaparin was associated with comparable outcome for the primary end-point in patients (N = 286) with high/very high risk of death on admission (adjusted OR 1.373, 95% CI 0.600–3.141, p = 0.452) and an improved outcome in those (N = 150) with low/intermediate risk (adjusted OR 0.012, 95% CI 0.001–0.428, p = 0.015) (p for interaction 0.02) (Fig. 3). The analysis according to body weight-adjusted enoxaparin dose showed a similar incidence of the primary end-point in patients receiving ≤ 70 IU/Kg vs. > 70 IU/Kg daily regimen (adjusted OR 0.324, 95% CI 0.093–1.125, p = 0.076) (Fig. 3).

**Table 3** In-hospital outcome according to different enoxaparin doses

	Prophylactic dose N = 287	Higher dose N = 149	p value
Primary end-point			
All-cause death	73 (25.4)	40 (26.9)	0.750
Secondary end-points			
Cardiovascular death	11 (3.9)	19 (12.8)	0.001
Venous thromboembolism	3 (1.1)	19 (12.8)	<0.001
New-onset severe ARDS	56 (19.5)	74 (49.7)	<0.001
Need of mechanical ventilation	15 (5.2)	38 (25.5)	<0.001
Major bleeding[a]	1 (1.5)	1 (4.8)	0.431
Clinically relevant non-major bleeding[a]	2 (3.1)	1 (4.8)	0.999
In-hospital length of stay (days)[b]	13 (8–18)	17 (11–25)	<0.001

ARDS acute respiratory distress syndrome

[a]Bleeding was assessed in a subgroup including 65 consecutive patients in the prophylaxis and 21 patients in the higher dose group

[b]Expressed as median (interquartile range)
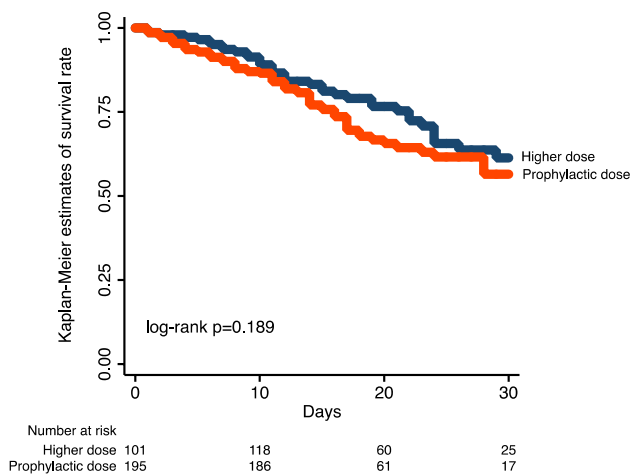
Fig. 1 Kaplan–Meier estimates of 30-day survival stratified by different doses of enoxaparin

Discussion

In this analysis, involving a multicenter cohort of patients admitted for COVID-19, the use of enoxaparin at prophylactic doses, as compared with higher doses, was associated with similar in-hospital mortality.

COVID-19 is a complex disease with both a primary involvement of the respiratory system and a pro-coagulative status [2, 3, 12]. As a matter of fact, autoptic studies on COVID-19 cadavers showed both micro-vascular lung thrombosis and macrovascular systemic or pulmonary thrombosis, regardless of antithrombotic treatment, type of anticoagulant therapy, and timing of disease course [4–6]; this suggests a pivotal role of coagulative patterns in the disease process. The indication from the World Health Organization on the use of prophylactic LMWH doses in patients with COVID-19 [11] was essentially based on preliminary evidence showing a benefit compared to no thrombo-prophylaxis, mainly in subgroups at higher risk [8, 9]; such recommendation was consistent with pre-existing guidelines for thrombo-prophylaxis in high-risk acutely ill

Fig. 2 Adjusted ORs for the study end-points with prophylactic vs. higher enoxaparin dose. *ARDS* acute respiratory distress syndrome, *CI* confidence interval, *OR* Odds ratio
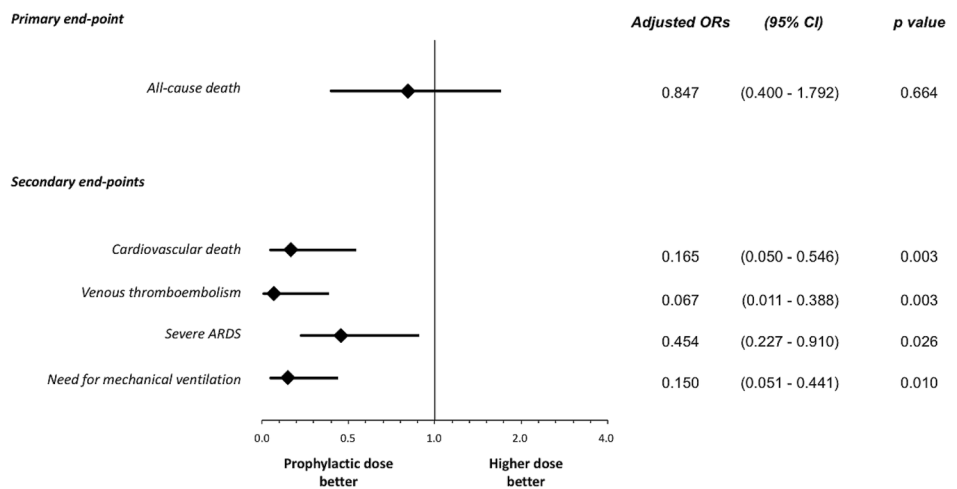
Fig. 3 Adjusted ORs for the primary end-point with: 4000 IU vs. > 4000 IU enoxaparin daily dose in the subgroups with low/intermediate and high/very high risk according to the 4C Mortality Score; ≤ 70 IU/Kg vs. > 70 IU/Kg enoxaparin daily regimen. *CI* Confidence interval; *OR* Odds ratio
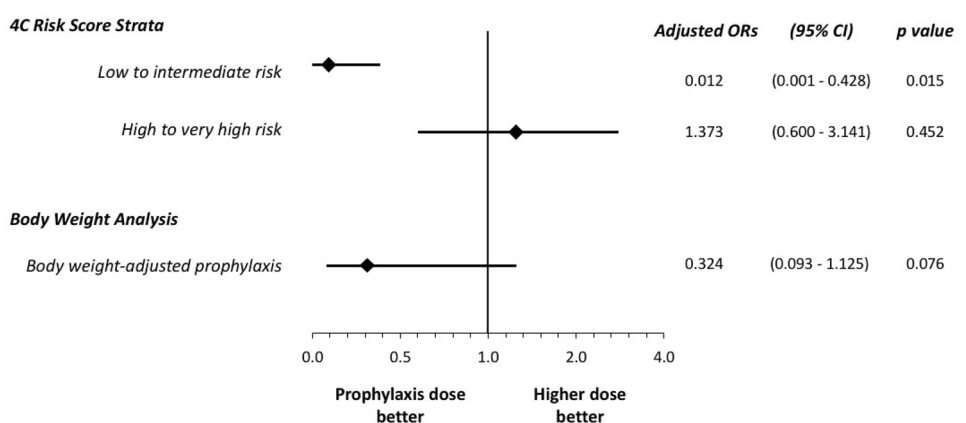
patients [18–20]. However, small observational studies demonstrated rates > 20% of thrombotic complications among critically ill patients with COVID-19, despite standard thrombo-prophylaxis [3, 9, 21]. Although flawed by the use of heterogeneous agents and variable dosages, these reports generated a source of concern and encouraged the use of intermediate or full-dose anticoagulation in this setting. Two recent investigations from the same study group showed a survival benefit of full-dose anticoagulation in patients hospitalized for COVID-19 [7], especially when initiated > 48 h from admission [22]; these results are challenging to interpret and export in clinical practice, given the mixing of oral, subcutaneous or intravenous agents and the absence of specific information on treatment indication and dosages. Thus, given the lack of direct comparisons between prophylactic and higher regimens, the optimal dosage of LMWH for preventing thrombotic events in patients with COVID-19 is uncertain and is a matter of active debate.

We explored this issue in a consecutive cohort of patients hospitalized in three Italian Hospitals, in whom a specific comparison of two dosages of enoxaparin (4000 IU vs. > 4000 IU daily) was performed. Notably, regardless of the dosing strategy, in our series enoxaparin was early given (< 48 h from admission in 81% of patients). Patients receiving the higher enoxaparin dosing regimen had higher body weight, increased frequency of atrial fibrillation, more severe hypoxemia upon admission, and received a "more aggressive" treatment for COVID-19; the length of stay was also longer. On the other hand, patients treated with the prophylaxis regimen had a higher prevalence of risk factors increasing the COVID-19-related mortality, i.e. older age, diabetes mellitus, chronic obstructive pulmonary disease, renal failure and cancer [23]. Thus, to reduce residual confounding and limit the bias from unbalanced baseline features in the study population, we performed a logistic regression analysis, where the propensity score was also added as covariate. Here the use of prophylactic and higher dose of enoxaparin resulted in a similar incidence of in-hospital mortality, even after adjustment for the timing of drug initiation. The consistency of results in the sensitivity analysis among higher risk patients strengthens the robustness of the primary analysis by further minimizing the risk of treatment bias, at least in this more critical setting. These findings lead support to the recent decision of the United States National Institutes of Health to stop the ongoing randomized trial on anticoagulants in high-risk patients with COVID-19 for futility and potential harm [24]. Notably, in our study, the use of prophylactic doses of enoxaparin in patients at low or intermediate baseline risk was associated with reduced in-hospital death, but this merits further confirmation in a larger, specific investigation.

The concomitant reduction of new-onset severe ARDS and venous thromboembolism in patients treated with

prophylaxis regimen supports that both lung microvascular angiopathy and macrovascular venous thrombosis have a predominant role in the pathogenesis and natural history of COVID-19 [2–6]. Prevention of these thrombotic phenomena may reduce the need for mechanical ventilation and translate into a significant benefit in terms of lower cardiovascular death, as observed in the present study. According to our results, in the context of patients with COVID-19 (i.e., characterized by mounting inflammation, cytokine storm and imbalance of the hemostatic system), an approach of full anticoagulation with therapeutic doses of LMWH could not be optimal. Notably, COVID-19-related lung microvascular angiopathy shares similar pathogenetic mechanisms with complement-mediated thrombotic microangiopathy [5, 25, 26] and here full dose anticoagulation yielded unsatisfactory results [25]. Various features may explain the reason of why, in the absence of indication to therapeutic dosages for an active macrovascular thrombosis, dosing regimens of LMWH higher than prophylactic in patients with COVID-19 are associated with a poorer outcome: increased risk of heparin-induced thrombocytopenia, leading to further enhancement of the pro-thrombotic status; lower "pleiotropic" (anti-inflammatory and immunomodulant) effects [27]; increased risk of intraparenchymal bleeding and hemorrhagic infarctions in the lung, already described in COVID-19 pathology findings and possibly underestimated/undiagnosed in the COVID-19 scenario [28]. However, these hypotheses require specific evaluations in ad hoc, mechanistic studies.

We performed an additional sensitivity analysis by comparing prophylactic vs. higher body weight-adjusted enoxaparin doses (≤ 70 IU/Kg vs. > 70 IU/Kg daily). It confirmed no advantage of higher enoxaparin dosages in terms of all-cause death. Thus, our data support a standard approach of 4000 IU enoxaparin daily dose, with a strategy of body weight-adjusted dosing regimen (70 IU/Kg daily) being used in patients at the extremes of body weight. This approach is in agreement with the recommendation of the European Society of Cardiology expert consensus on LMWH dosing [29], suggesting that fixed prophylactic doses should be utilized in patients with normal weight, overweight and mild obesity; LMWH dose should be adjusted for the body weight only in patients with underweight or severe obesity. Indeed, in patients with COVID-19, a body weight-adjusted dosing appears crucial mainly in obese patients, where an additional mortality risk and a higher intrinsic risk of thromboembolic complications have been described [30, 31].

The present study confirms previous reports indicating a low incidence of hemorrhagic complications in patients with COVID-19 and reinforces the concept that the thrombotic risk rather than bleeding risk is the major concern in this setting [7]. In our investigation, the low rates of both major

bleeding and clinically relevant non-major bleeding preclude any definite conclusion on the risk of hemorrhagic events with prophylactic vs. higher enoxaparin doses.

Study limitations

The study has strengths and limitations. A multicenter cohort of consecutive patients was included, and individual data were accurately collected, with a strict source verification for the event adjudication. However, the retrospective design and the conduction of the study during a National Emergency contributed to the lack of some, although limited, data, which were not available. Given the observational nature, the study should not be used to definitely rule out either benefit or harm of different enoxaparin dosing regimens. However, the consistency of the results across multiple adjustments and analyses is reassuring for the robustness of our findings. Nevertheless, the risk of unmeasured confounding remains. Finally, our results specifically refer to enoxaparin and whether they are also generalizable to other LMWH molecules is unknown.

In conclusion, a prophylactic dose of enoxaparin in patients admitted for COVID-19 is associated with similar in-hospital mortality compared to higher dosing regimens. Our findings are hypothesis-generating and require confirmation in a randomized, controlled study.

Compliance with ethical standards

References

1. Huang C, Wang Y, Li X et al (2020) Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 395:497–506. https://doi.org/10.1016/S0140-6736(20)30183-5
2. Tang N, Li D, Wang X, Sun Z (2020) Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost 18:844–847. https://doi.org/10.1111/jth.14768
3. Klok FA, Kruip MJHA, van der Meer NJM et al (2020) Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res 191:145–147. https://doi.org/10.1016/j.thromres.2020.04.013
4. Carsana L, Sonzogni A, Nasr A et al (2020) Pulmonary post-mortem findings in a series of COVID-19 cases from northern Italy: a two-centre descriptive study. Lancet Infect Dis. https://doi.org/10.1016/S1473-3099(20)30434-5
5. Ackermann M, Verleden SE, Kuehnel M et al (2020) Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. N Engl J Med. https://doi.org/10.1056/NEJMoa2015432
6. Rapkiewicz AV, Mai X, Carsons SE et al (2020) Megakaryocytes and platelet-fibrin thrombi characterize multi-organ thrombosis at autopsy in COVID-19: A case series. EClinicalMedicine. https://doi.org/10.1016/j.eclinm.2020.100434
7. Paranjpe I, Fuster V, Lala A et al (2020) Association of treatment dose anticoagulation with in-hospital survival among hospitalized patients with COVID-19. J Am Coll Cardiol. https://doi.org/10.1016/j.jacc.2020.05.001
8. Bikdeli B, Madhavan MV, Jimenez D et al (2020) COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up. J Am Coll Cardiol. https://doi.org/10.1016/j.jacc.2020.04.031
9. Tang N, Bai H, Chen X et al (2020) Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost. https://doi.org/10.1111/jth.14817
10. Ayerbe L, Risco C, Ayis S (2020) The association between treatment with heparin and survival in patients with Covid-19. medRxiv. https://doi.org/10.1101/2020.05.27.20114694
11. Clinical management of COVID-19. https://www.who.int/publications-detail-redirect/clinical-management-of-covid-19. Accessed 27 Jun 2020
12. Thachil J, Tang N, Gando S et al (2020) ISTH interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haemost 18:1023–1026. https://doi.org/10.1111/jth.14810
13. Hicks KA, Mahaffey KW, Roxana M et al (2018) 2017 Cardiovascular and stroke endpoint definitions for clinical trials. Circulation 137:961–972. https://doi.org/10.1161/CIRCULATIONAHA.117.033502
14. Definition Task Force ARDS, Ranieri VM, Rubenfeld GD et al (2012) Acute respiratory distress syndrome: the Berlin definition. JAMA 307:2526–2533. https://doi.org/10.1001/jama.2012.5669
15. Kaatz S, Ahmad D, Spyropoulos AC, Schulman S (2015) Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH. J Thromb Haemost 13:2119–2126. https://doi.org/10.1111/jth.13140
16. Elze MC, Gregson J, Baber U et al (2017) Comparison of propensity score methods and covariate adjustment: evaluation in 4 cardiovascular studies. J Am Coll Cardiol 69:345–357. https://doi.org/10.1016/j.jacc.2016.10.060

17. Knight SR, Ho A, Pius R et al (2020) Risk stratification of patients admitted to hospital with covid-19 using the ISARIC WHO clinical characterisation protocol: development and validation of the 4C mortality score. BMJ. https://doi.org/10.1136/bmj.m3339

18. Konstantinides SV, Meyer G, Becattini C et al (2020) 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J 41:543–603. https://doi.org/10.1093/eurheartj/ehz405

19. Kahn SR, Lim W, Dunn AS et al (2012) Prevention of VTE in nonsurgical patients. Chest 141:e195S-e226S. https://doi.org/10.1378/chest.11-2296

20. Schünemann HJ, Cushman M, Burnett AE et al (2018) American Society of Hematology 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalized and non-hospitalized medical patients. Blood Adv 2:3198–3225. https://doi.org/10.1182/bloodadvances.2018022954

21. Julien P, Julien G, Morgan C et al (2020) Pulmonary embolism in COVID-19 patients: awareness of an increased prevalence. Circulation. https://doi.org/10.1161/CIRCULATIONAHA.120.047430

22. Nadkarni GN, Lala A, Bagiella E et al (2020) Anticoagulation, mortality, bleeding and pathology among patients hospitalized with COVID-19: a Single Health System Study. J Am Coll Cardiol. https://doi.org/10.1016/j.jacc.2020.08.041

23. Zhou F, Yu T, Du R et al (2020) Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 395:1054–1062. https://doi.org/10.1016/S0140-6736(20)30566-3

24. (2020) NIH ACTIV Trial of blood thinners pauses enrollment of critically ill COVID-19 patients. In: National Institutes of Health (NIH). https://www.nih.gov/news-events/news-releases/nih-activ-trial-blood-thinners-pauses-enrollment-critically-ill-covid-19-patients. Accessed 6 Jan 2021

25. Masias C, Vasu S, Cataland SR (2017) None of the above: thrombotic microangiopathy beyond TTP and HUS. Blood 129:2857–2863. https://doi.org/10.1182/blood-2016-11-743104

26. Gavriilaki E, Brodsky RA (2020) Severe COVID-19 infection and thrombotic microangiopathy: success does not come easily. Br J Haematol 189:e227–e230. https://doi.org/10.1111/bjh.16783

27. Poterucha TJ, Libby P, Goldhaber SZ (2017) More than an anticoagulant: do heparins have direct anti-inflammatory effects? Thromb Haemost 117:437–444. https://doi.org/10.1160/TH16-08-0620

28. Fox SE, Akmatbekov A, Harbert JL et al (2020) Pulmonary and cardiac pathology in Covid-19: the first autopsy series from New Orleans. Pathol 8:681–686

29. Rocca B, Fox KAA, Ajjan RA et al (2018) Antithrombotic therapy and body mass: an expert position paper of the ESC Working Group on Thrombosis. Eur Heart J 39:1672–1686f. https://doi.org/10.1093/eurheartj/ehy066

30. Petrilli CM, Jones SA, Yang J et al (2020) Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. BMJ 369:m1966. https://doi.org/10.1136/bmj.m1966

31. Patti G, Pecen L, Manu MC et al (2020) Thromboembolic and bleeding risk in obese patients with atrial fibrillation according to different anticoagulation strategies. Int J Cardiol. https://doi.org/10.1016/j.ijcard.2020.06.010