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## Impact of High-Dose Prophylactic Anticoagulation in Critically Ill Patients With COVID-19 Pneumonia

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**Impact of high dose prophylactic anticoagulation in critically ill patients with COVID-19 pneumonia**

Short title: High dose anticoagulation in severe COVID-19

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12

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15 Squibb/Pfizer and Sanofi.

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17 Squibb/Pfizer, CSL Behring, Octapharma, Roche, Sanofi, and Sobi

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1 **Abbreviations list**

- 2 - APTT: activated partial thromboplastin time  
3 - BMI: body mass index  
4 - COPD: chronic obstructive pulmonary disease  
5 - CRRT: continuous renal replacement therapy  
6 - DOAC: direct oral anticoagulant  
7 - ECMO: extracorporeal membrane oxygenation  
8 - HPA: high dose prophylactic anticoagulation  
9 - HR: hazard ratio  
10 - ICU: intensive care unit  
11 - INR: international normalized ratio  
12 - IPTW: inverse probability treatment weighting  
13 - LMWH: low molecular weight heparin  
14 - OR: odds ratio  
15 - TC: thrombotic complication  
16 - UFH: unfractionated heparin  
17 - VKA: vitamin K antagonist  
18 - VTE: venous thromboembolism

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**Abstract (238/300 words)**

**Background:** Due to the high risk of thrombotic complications (TC) during SARS-CoV-2 infection, several scientific societies have proposed to increase the dose of preventive anticoagulation, although arguments in favor of this strategy are inconsistent.

**Research question:** What is the incidence of TC in critically ill patients with COVID-19 and what is the relationship between the dose of anticoagulant therapy and the incidence of TC?

**Study design and methods:** All consecutive patients referred to eight French intensive care units (ICU) for COVID-19 were included in our observational study. Clinical and laboratory data were collected from ICU admission to day 14, including anticoagulation status and thrombotic and hemorrhagic events. The effect of high dose prophylactic anticoagulation (either at intermediate or equivalent to therapeutic dose), defined using a standardized protocol of classification, was assessed using a time-varying exposure model using inverse probability of treatment weight.

**Results:** Out of 538 patients included, 104 patients developed a total of 122 TC with an incidence of 22.7 % (19.2-26.3). Pulmonary embolism accounted for 52 % of the recorded TC. High dose prophylactic anticoagulation was associated with a significant reduced risk of TC (HR 0.81 [0.66-0.99]) without increasing the risk of bleeding (HR 1.11 [0.70-1.75]).

**Interpretation:** High dose prophylactic anticoagulation is associated with a reduction in thrombotic complications in critically ill COVID-19 patients without an increased risk of hemorrhage. Randomized controlled trials comparing prophylaxis with higher doses of anticoagulants are needed to confirm these results.

**Trial registration number:** NCT04405869

**Keywords:** COVID-19; thrombosis; anticoagulation; bleeding

1 **Introduction**

2

3 Patients with severe pneumonia due to SARS-CoV-2 infection, also known as coronavirus  
4 disease 2019 (COVID-19), admitted to intensive care units (ICUs) have high rates of  
5 thrombotic complications (TC), particularly pulmonary embolism. According to several  
6 studies, the proportion of hospitalized patients presenting with TC ranges from 18 to 37%,  
7 despite the use of regular prophylactic anticoagulation<sup>1</sup>. The risk of TC appears to be  
8 particularly high in critically ill patients admitted to ICUs<sup>2-5</sup>.

9 Although standard pharmacological thromboprophylaxis is recommended in hospitalized  
10 patients, several expert groups have proposed to increase anticoagulant dosing in critically ill  
11 patients with COVID-19<sup>6</sup>. In particular, the French Working Group on Perioperative  
12 Hemostasis (GIHP) and the French Study Group on Thrombosis and Hemostasis (GFHT) have  
13 proposed to progressively increase the dose of anticoagulant based on thrombotic risk  
14 factors that include obesity, high oxygen demand, need for mechanical ventilation, and  
15 biomarkers of major inflammation or hypercoagulability, despite the lack of evidence  
16 supporting this strategy<sup>7</sup>. We aimed to study the incidence of thrombotic complications and  
17 bleeding in critically ill patients with COVID-19 and examine their relationship to the dose of  
18 prophylactic anticoagulation administered.

19

## 1 **Methods**

### 2 **Study design and participants**

3 We conducted a retrospective chart review of all consecutive adult patients admitted to  
4 eight French ICUs for severe laboratory-confirmed COVID-19 pneumonia between March  
5 21<sup>st</sup> and April 10<sup>th</sup>, 2020. The protocol was approved by the University Hospital of Strasbourg  
6 Ethics Committee (reference CE-2020-76) and registered at ClinicalTrials.gov  
7 (NCT04405869). Partial data from 32 patients from the University Hospital of Strasbourg  
8 and 107 from the University Hospital of Lille were previously published<sup>5,8</sup>.

9 Demographic and relevant comorbidities were collected at admission (Day 0). Data regarding  
10 clinical management, pharmacologic thromboprophylaxis, laboratory results, and  
11 thrombotic and bleeding events were collected for each patient from ICU admission and up  
12 to 14 days of follow-up in ICU at 6 prespecified time points (day 1, day 2, day 5, day 8, day  
13 11, and day 14), defining 6 different periods of evaluation: admission to day 1, day 1 to day  
14 2, day 2 to day 5, day 5 to day 8, day 8 to day 11 and day 11 to day 14 according to the 7  
15 predefined time points. For the study purpose, we considered that a patient received  
16 pharmacologic thromboprophylaxis during one specific period of evaluation if prophylaxis  
17 was reported on the first and last day of that specific period.

18

### 19 **Thromboprophylaxis management and anticoagulation use reporting**

20 All patients received pharmacologic thromboprophylaxis for at least one period of  
21 evaluation defined as the time between two assessment points. Pharmacological  
22 thromboprophylaxis was prescribed according to national guidelines and local protocols of  
23 each ICU. Standard prophylaxis was initially recommended using either low molecular  
24 weight heparin (LMWH) or unfractionated heparin (UFH) with dosage adjustments for  
25 overweight and obese patients<sup>9</sup>. Then, after the GIHP and GFHT published their guidance  
26 document (**e-table 1**) on April 3<sup>rd</sup> 2020, doses of thromboprophylaxis were increased  
27 according to different risk factors: BMI > 30 kg/m<sup>2</sup>, known risk factor for venous  
28 thromboembolism (active cancer, recent personal history of thrombosis, ...), catheter or  
29 iterative filter coagulation, severe inflammatory syndrome (e.g. fibrinogen > 8 g/l),  
30 hypercoagulable state (e.g. D-dimer > 3.0 µg/ml), long-term anticoagulant therapy, and  
31 ECMO. The severity of COVID-19 pneumonia, defined by high flow nasal canula or invasive



1 ventilation requirement, was also a factor in increasing the anticoagulation dose. As our  
2 study period ranges from March 21<sup>st</sup> to April 10<sup>th</sup>, 2020, the doses of prophylactic  
3 anticoagulation increased during this period, according to national guidelines, allowing us to  
4 compare the two strategies.

5 We retrospectively classified the level of anticoagulation for thromboprophylaxis at each  
6 time-point into 2 groups according to the anticoagulant and the dose: standard prophylactic  
7 anticoagulation or high prophylactic anticoagulation (which included intermediate and  
8 therapeutic dose anticoagulation) (**figure 1**). For UFH, the level of anticoagulation was  
9 defined in terms of anti-Xa activity (when available), which is more accurate than the  
10 reported administered dose because the response to UFH is subject to high interpersonal  
11 variability. Cumulative treatment coverage was then expressed as the number of evaluation  
12 periods covered by anticoagulation before the occurrence of a thrombotic event.

13

#### 14 **Thrombotic and bleeding outcomes**

15 Recorded TC included pulmonary embolism, deep vein thrombosis, catheter thrombosis  
16 (within the first 24 hours after insertion or recurrent), stroke, mesenteric infarction,  
17 myocardial infarction, dialysis filter coagulation, or extracorporeal membrane oxygenation  
18 (ECMO) thrombosis. No specific screening policy was implemented. Bleeding complications  
19 were included based on ISTH guidelines and severity was classified according to the GUSTO  
20 scale<sup>10</sup>. Patients could only be reported once for each type of thrombotic or hemorrhagic  
21 event. Two different thrombotic or hemorrhagic events, e.g. pulmonary embolism and  
22 stroke, were considered to be two different types of events, and therefore several events  
23 could be reported in the same patient).

24

#### 25 **Statistical Analysis**

26 Categorical variables were described by their count and percentage and were compared  
27 using Pearson's  $\chi^2$  tests or Fisher's exact tests. Continuous variables were described by their  
28 median with their 1<sup>st</sup> and 3<sup>rd</sup> quartiles and were compared using nonparametric Wilcoxon  
29 tests.

30 Odds-ratio and their 95 % confidence intervals were calculated using logistic regressions to  
31 evaluate risk factors for thrombotic complications. A multivariate logistic regression model  
32 was used on predictor variables selected from a stepwise model selection based on Akaike

1 information criterion. The selection of variables for the multivariate analysis was based on  
2 known risk factors for VTE and COVID-19 pneumonia severity markers.

3 To account for the non-randomized administration of high dose prophylactic anticoagulation  
4 and to reduce the effects of confounding factors, the effect of high dose prophylactic  
5 anticoagulation on thrombotic complications was analyzed with a time-varying exposure  
6 model using inverse probability of treatment weight that allows modelling intermittent  
7 treatment exposure<sup>11,12</sup>. Inverse probability treatment weighting (IPTW) was evaluated using  
8 a survival model by using age, sex, body mass index (BMI), smoking status, cardiovascular  
9 history, history of long-term anticoagulant treatment as fixed covariates and Sepsis-related  
10 Organ Failure Assessment score (SOFA score) and D-dimers as time-varying covariates. These  
11 variables were selected based on the individual propensities for receiving a high-dose  
12 prophylactic anticoagulation. IPTW was used to generate a balanced pseudo-population of  
13 patients. Cox proportional-hazards regression analysis was used on this pseudo-population  
14 to compare thrombotic complication-free survival as a function of time spent on high dose  
15 prophylactic anticoagulation. p-values < 0.05 were considered as statistically significant. All  
16 the analyses were performed using R software version 4.0.2 (The R project, Vienna, Austria.  
17 <https://www.-R-project.org>).

18

## 1 **Results**

### 2 **Description of the population**

3 A total of 538 ICU patients with confirmed COVID-19 pneumonia were included. **Table 1**  
4 summarizes patient characteristics. They were mostly men (n = 389, 72%), with a median  
5 age of 63 [55-71] years and increased body mass index (29 [26-33] kg/m<sup>2</sup>). The lowest  
6 PaO<sub>2</sub>/FiO<sub>2</sub> ratio within the ICU stay was 93 [71-126] mmHg, and 44 patients (8%) were  
7 treated with ECMO. The SOFA score at ICU admission was 4 [2-8].

8

### 9 **Laboratory results**

10 At ICU admission, patients had high fibrinogen levels of 6.9 [5.9-7.8] g/l, high D-dimer levels  
11 of 1.56 [1.00-3.37] mg/l, and high FVIII and Von Willebrand Factor antigen levels of 262  
12 UI/dL [157-299] and 395 [295-453] IU/dL, respectively. APTT ratio, INR, and platelet count  
13 were respectively 1.10 [1.01-1.26], 1.12 [1.07-1.23], and 226 [169-290] 10<sup>9</sup>.L<sup>-1</sup> on ICU  
14 admission. The evolution of coagulation parameters within the first two weeks is shown in  
15 supplementary materials (**e-Figure 1**).

16

### 17 **Thrombotic complications**

18 The overall incidence of TC was 22.7 % (19.2-26.3). During the first 2 weeks of ICU  
19 hospitalization, 104 patients experienced a total of 122 TC within a median of 6 [2.5-9] days  
20 following ICU admission. The type of TC and their respective incidence are shown in **Table 2**.  
21 The incidence of TC was particularly high in patients receiving continuous renal replacement  
22 therapy (CRRT) or supported by ECMO with an incidence of thrombotic events of 44.8%  
23 (32.4-57.5%) and 43.2% (29.2-57.7%), respectively. Conversely, the incidence of TC in  
24 patients who had neither CRRT nor ECMO was at 16.5% (13.0-20.2). Risk factors for TC are  
25 shown in **Table 3**. At ICU admission, D-dimer levels were significantly higher in patients who  
26 had TC (2.59 mg/l [1.30-7.72]) than in those without (1.5 mg/L [0.99-2.97], p<0.001) and  
27 remained significantly higher during the first 2 weeks in ICU (p<0.05 on day 2, 5, 8, 11, and  
28 14 as reported in **e-Figure 2** of the supplementary materials).

29

### 30 **Effect of prophylactic anticoagulation on thrombotic complications**

31 Cumulative exposure to higher prophylactic anticoagulation dosing was significantly  
32 associated with a reduction in the risk of TC (hazard ratio (HR) 0.79 [0.65-0.95]; p=0.014)

1 **(Table 4)**. Detail of the cumulative exposure for each period of time is shown in **e-figure 3**.  
2 This effect was unchanged after adjusting for PaO<sub>2</sub>/FiO<sub>2</sub> ratio, CRRT, and ECMO support  
3 (hazard ratio 0.80 [0.65-0.99]; p=0.040). Cumulative exposure to high dose prophylactic  
4 anticoagulation was also significantly associated with a reduction in the risk of pulmonary  
5 embolism (0.72 [0.53-0.98]; p=0.037). The evolution of the actual use of anticoagulation  
6 (UFH or LMWH) during the first two weeks of hospitalization in the ICU is shown in **e-table 2**  
7 of the supplementary materials.  
8 Cumulative exposure to higher prophylactic anticoagulation dosing was not associated with  
9 reduced mortality at day 14 (hazard ratio 1.12 [0.78-1.62]).

10

### 11 **Bleeding complications**

12 During the same period, 39 patients (7.2%) presented a total of 53 bleeding complications  
13 within a median of 9 [5-12] days after ICU admission. Among these bleeding complications  
14 12 (22.6 %) were considered as severe according to the GUSTO scale (e-Table 3). Data on the  
15 level of anticoagulation at the onset of bleeding was unavailable in 38.5 % of bleeding  
16 events. Nineteen bleeding events occurred in patients under ECMO (n=13 patients). Body  
17 mass index (BMI) (OR 0.87 [0.78-0.97] p=0.02) and ECMO support (OR 6.26 [2.31-17.01]  
18 p<0.001) were significantly associated with a higher bleeding risk. Exposure to higher  
19 prophylactic dosing within the 24 hours before the event was not associated with an  
20 increased bleeding risk compared to standard dosing (hazard ratio 0.63 [0.28-1.44]), neither  
21 was the cumulative exposure to higher dosing (hazard ratio 1.11 [0.70-1.75]). The type of  
22 bleeding and anticoagulation status during or just prior to the bleeding are shown in  
23 supplementary materials (**e-table 3**).

24

25

26

1 **Discussion**

2 To our knowledge, this is one of the biggest studies evaluating the effect of higher dosing  
3 prophylactic anticoagulation on TC in critically ill patients with COVID-19. Our results indicate  
4 that exposure to higher dosing was significantly associated with a reduced risk of TC.

5 In our study, 22.7 % of patients had at least one TC in the first two weeks of ICU  
6 hospitalization that were clinically relevant and primarily pulmonary embolism in 52% of the  
7 patients with TC. This high incidence of pulmonary embolism is consistent with previous  
8 reports, including a French prospective cohort of ICU patients diagnosing TC in 42.7 % of  
9 patients, of which 16.7 % had pulmonary embolism. These TCs occurred despite the routine  
10 use of prophylactic anticoagulation, even at therapeutic doses for 30 % of the patients<sup>5</sup>. In  
11 Europe, Klok et al. reported a cumulative incidence of TC of 31 % in the ICU, despite routine  
12 pharmacological thromboprophylaxis<sup>2</sup>. Middeldorp et al. found a cumulative incidence of  
13 venous thromboembolic events (VTE) of 48 % after 14 days in ICU patients with a systematic  
14 screening approach<sup>4</sup>.

15 Thromboses are important in influencing patient outcomes with COVID-19. Indeed,  
16 Middeldorp and al. found that the occurrence of VTE in COVID-19 was significantly  
17 associated with death (adjusted HR 2.9, 95% CI 1.02-8.0)<sup>4</sup>. Similar results were observed in a  
18 retrospective study of 3334 patients hospitalized in New York City for COVID-19 where  
19 thrombosis was independently associated with death (HR 1.82; 95% CI, 1.54-2.15)<sup>13</sup>.

20 To address the high thrombotic risk, many experts and national societies have empirically  
21 intensified prophylaxis to high prophylactic doses, particularly in obese and critically ill  
22 patients. For example, Dutch intensivists have increased their anticoagulation dosing with a  
23 double dose of LMWH (Nadroparin)<sup>2,4</sup>. In France, on April 3<sup>rd</sup>, the GIHP and the GFHT  
24 published a guidance document defining 4 levels of thromboembolic risk based on clinical  
25 criteria, biomarkers, and VTE risk factors. As a result, they suggested to administer heparin  
26 at standard doses in non-critically ill patients without risk factors for thrombosis, or at high  
27 dose for critically ill patients (intermediate or therapeutic doses)<sup>7</sup>. In our study, patients  
28 from March 21<sup>st</sup> to April 10<sup>th</sup> 2020, were evaluated, so the anticoagulation level gradually  
29 increased during this period, allowing us to compare the two strategies.

30

1 At least 2 other studies support the use of an increased dose of anticoagulant for  
2 prophylaxis. In an American retrospective study of 2,773 hospitalized patients with COVID-  
3 19, Paranjpe et al. suggested that systemic treatment-dose anticoagulation could improve  
4 outcomes<sup>14</sup>. A more recent study comparing an intermediate dosage of LMWH to a standard  
5 prophylactic dosage of LMWH reported that intermediate dosage was associated with a  
6 reduction of in-hospital mortality (5.8% vs. 18.8%,  $p = 0.02$ ). However, this study did not  
7 focus on critically ill patients, and groups were not strictly comparable<sup>15</sup>. Thus, there is a lack  
8 of evidence to recommend a high dose anticoagulant strategy. We found that cumulative  
9 exposure to higher dosing prophylactic anticoagulation was significantly associated with  
10 reduced risk of TC, with a hazard ratio of 0.80 [0.65-0.99], which underscores the potential  
11 beneficial impact of a higher dosing strategy in critically ill COVID-19 patients.

12 In our study, laboratory data suggested an initial procoagulant profile with  
13 hyperinflammation, characterized by increased levels of D-dimer, fibrinogen, FVIII, and von  
14 Willebrand Factor antigen. Interestingly, evolution of biomarkers was biphasic, with an initial  
15 increase, then a slight decrease. TC mainly occurred during the first phase, whereas bleeding  
16 complications were mainly reported during the second phase (**Figure S1**). Therefore,  
17 prophylactic anticoagulation might be adjusted according to the evolution of inflammation.

18 Our study highlights that TC risk factors in the COVID-19 context do not include traditional  
19 thromboembolic risk factors but rather severity of COVID-19 pneumonia. Severe hypoxemia,  
20 defined according to  $\text{PaO}_2/\text{FiO}_2$  ratio (and ECMO requirement) as well as inflammation and  
21 hypercoagulability, characterized by high levels of D-dimers, were independent risk factors  
22 for TC. Zhang et al. also found that an elevated pneumonia severity score (CURB-65), and a  
23 D-dimer  $>1 \mu\text{g/mL}$  were independently associated with an increased risk of thrombosis<sup>16</sup>.  
24 Similarly, Bilaloglu et al. identified higher D-dimer levels at hospital presentation as a risk  
25 factor for arterial or venous thrombosis<sup>13</sup>. Although obesity has been described as a risk  
26 factor for severe SARS-CoV-2 infection<sup>17</sup>, our results did not show an increased risk of TC in  
27 obese patients, suggesting that high-dose prophylactic anticoagulation was effective in  
28 preventing TC in this high-risk population.

29

30 We also found that 7% of our patients had bleeding complications. Most complications were  
31 minor, although 4 patients presented with intracranial hemorrhage, and 1 patient died from

1 hemorrhage. These results are consistent with another French study where only 2.7% of  
2 patients had bleeding complications, while 30% of patients were receiving therapeutic  
3 anticoagulation<sup>5</sup>. Paranjpe et al. also did not observe increased risk of bleeding by increasing  
4 the dose of prophylactic anticoagulation in hospitalized patients for COVID-19<sup>14</sup>. Similarly,  
5 we reported no association between cumulative exposure to higher prophylactic  
6 anticoagulation and a bleeding complication. However, the anticoagulant status was  
7 unknown in 38.5% of patients as the date of the bleeding event was unavailable, and  
8 statistical analysis might be underpowered.

9 Contrary to recently published studies<sup>18,19</sup>, the mortality rate was not influenced by high-  
10 dose prophylactic anticoagulation in our study. We only recorded the mortality rate on Day  
11 14, which in our study was 11.9%, whereas the ICU mortality rate described in these studies  
12 ranged from 29.6 to 48.3%. In addition, unlike these studies which only included therapeutic  
13 anticoagulation, we also included intermediate-dose anticoagulation in our analysis which  
14 may not have been sufficient to influence mortality.

15 Our study has several limitations. First, data collection was limited to the first 14 days. The  
16 follow-up period was limited to minimize the contribution of long-term unspecific ICU  
17 complications. Indeed, according to pathophysiology of COVID-19 induced thrombosis,  
18 hypercoagulability is high within this early period then decreases, and thrombotic events  
19 were reported at a median of 6 [1-13] days after admission to the ICU<sup>20</sup>. Nevertheless, as  
20 bleeding events appear to occur later, at a median of 15 [6-25] days after ICU admission<sup>21</sup>,  
21 we might have underestimated the incidence of bleeding events.

22 Second, because of the retrospective design of the study, some data were missing, especially  
23 those of patients who were transferred to other ICUs as part of the reorganization of the  
24 national healthcare system during the pandemic.

25 The anticoagulation strategy was not standardized among centers, and none of the ICU used  
26 a systematic venous thromboembolism screening policy. However, data were sufficiently  
27 robust to classify the anticoagulation status of most patients.

28

29 In conclusion, we showed that high dose prophylactic anticoagulation therapy is associated  
30 with reduced TC in critically ill COVID-19 patients, without increasing the risk of bleeding.

- 1 Randomized controlled trials comparing prophylactic and higher doses of anticoagulants are
- 2 needed to further confirm these results.
- 3



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2

3 **Guarantor:** CT is the guarantor of the content of the manuscript, including the data and  
4 analysis

5

6 **Authors' contribution**

7 **CT, AM, AIG** contributed substantially to the conception and design of the study, to the  
8 acquisition of data, to the analysis and interpretation of the data, drafted the article and  
9 provided final approval of the version submitted for publication

10 **JG, JHL** contributed substantially to the analysis and interpretation of the data, provided  
11 critical revision of the article and provided final approval of the version submitted for  
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1 **Take Home Point:** The incidence of thrombotic complications is high in critically ill patients  
2 with COVID-19. The use of high dose prophylactic anticoagulation is associated with a  
3 reduction in thrombotic risk without increasing the risk of bleeding.

4

	Overall	No TC	TC	p-value
n	538	417	121	
Age	63 [55-71]	63 [55-71]	62 [56-71]	0.47
Sex male	389 (72.4)	303 (72.7)	86 (71.1)	0.73
BMI	29.0 [26.0-33.0]	29.0 [25.0-33.0]	29.0 [26.0-33.0]	0.52
<b>Medical history</b>				
Hypertension	275 (51.1)	215 (51.6)	60 (49.6)	0.76
Diabetes	139 (25.8)	104 (24.9)	35 (28.9)	0.41
Smoking	29 (5.4)	22 (5.3)	7 (5.8)	0.82
Alcohol	11 (2.0)	7 (1.7)	4 (3.3)	0.48
COPD	18 (5.0)	13 (3.1)	5 (4.1)	0.79
Heart failure	40 (7.4)	35 (8.4)	5 (4.1)	0.17
Coronary artery disease	67 (12.5)	57 (13.7)	10 (8.3)	0.12
Atrial fibrillation	25 (4.6)	23 (5.5)	2 (1.6)	0.05
Peripheral arterial disease	27 (5.0)	25 (6.0)	2 (1.6)	0.06
Stroke	24 (4.5)	20 (4.8)	4 (3.3)	0.62
Chronic kidney disease	37 (6.9)	30 (7.2)	7 (5.8)	0.69
Venous thromboembolism	16 (3.0)	12 (2.9)	4 (3.3)	1.00
Active cancer	36 (6.7)	29 (7.0)	7 (5.8)	0.84
Cirrhosis	5 (0.9)	2 (0.5)	3 (2.5)	0.08
Autoimmune disease	22 (4.1)	16 (3.8)	6 (5.0)	0.60
Thrombophilia	2 (0.4)	1 (0.2)	1 (0.8)	0.40
<b>Chronic medications</b>				
Aspirin	96 (17.8)	78 (18.7)	18 (14.9)	0.42
Clopidogrel	15 (2.8)	15 (3.6)	0 (0.0)	0.03
VKA	12 (2.2)	9 (2.2)	3 (2.5)	0.74
DOAC	28 (5.2)	24 (5.8)	4 (3.3)	0.36
<b>ICU management</b>				
Delay first clinical signs / ICU admission	8 [6-10]	8 [6-11]	8 [6-10]	0.24
SOFA score at ICU admission	4 [2-8]	4 [2-8]	5 [3-9]	0.01
PaO <sub>2</sub> /FiO <sub>2</sub> ratio <sup>a</sup>	93 [71-126]	95 [75-133]	85 [64-110]	<0.01
ECMO	44 (8.2)	25 (6.0)	19 (15.7)	<0.01
RRT	58 (10.8)	32 (7.7)	26 (21.5)	<0.01
Duration of mechanical ventilation over 14 days	236 (43.9)	155 (37.2)	81 (66.9)	<0.01
<b>Outcome</b>				
Patients alive at Day 14	430 (88.1)	331 (89)	99 (85.3)	0.37

2 **Table 1:** Characteristics of the study population

3 Data are described as median and inter-quartile range (median [IQR]) or counts and proportion (n (%))  
4 TC: thrombotic complication within the first 2 weeks of hospitalization in intensive care unit (ICU). No TC: no  
5 thrombotic complications diagnosed in the first two weeks of ICU hospitalization.

6 COPD: chronic obstructive pulmonary disease; VKA: vitamin K antagonist; DOAC: direct oral anticoagulant  
7 therapy; ECMO: extracorporeal membrane oxygenation; RRT: renal replacement therapy.

8 <sup>a</sup> lower value during ICU stay

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1

Type of thrombosis	N (%)	Cumulative incidence
All thrombosis	122 (100)	22.7 (19.2-26.3) <sup>a</sup>
Pulmonary embolism	64 (52)	12.0 (9.2-14.7) <sup>a</sup>
Deep vein thrombosis	18 (15)	5.0 (2.7-7.3) <sup>b</sup>
Catheter thrombosis	14 (11)	3.9 (1.9-5.9) <sup>b</sup>
Stroke	4 (3)	1.1 (0.1-2.2) <sup>b</sup>
Other thrombosis	2 (2)	0.5 (0.0-1.3) <sup>b</sup>
Mesenteric infarction	1 (2)	0.2 (0.0-1.0) <sup>b</sup>
Myocardial infarction	1 (1)	0.2 (0.0-0.8) <sup>b</sup>
RRT filter clotting	13 (11)	22.8 (11.8-33.7) <sup>b,c</sup>
ECMO clotting	5 (4)	11.6 (1.9-21.3) <sup>b,d</sup>

2 **Table 2:** Thrombotic complications and their respective cumulative incidence within the first  
3 2 weeks of hospitalization in ICU.

4 Incidences are expressed as percentage (95 % confidence interval) of having a TC within the first 2 weeks of  
5 hospitalization in ICU. Incidences were estimated considering discharge from ICU or transfer and death as  
6 competing risks.

7 <sup>a</sup>These incidences were calculated on the global population (538 patients)

8 <sup>b</sup> These incidences were calculated on 360 patients because 1 center did not record these complications

9 <sup>c</sup> This incidence was calculated on patients receiving renal replacement therapy (RRT)

10 <sup>d</sup> This incidence was calculated on patients supporting by extracorporeal membrane oxygenation (ECMO)

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	Univariate analysis		Multivariate analysis	
	Odds ratio	p	Odds ratio	p
Age	0.99 [0.97-1.01]	0.38	-	
Body mass index	1.00 [0.97-1.03]	0.99	-	
History of VTE	1.05 [0.29-3.16]	0.94	-	
Active cancer	1.06 [0.29-3.05]	0.93	-	
Antiplatelet therapy	0.65 [0.36-1.10]	0.12	-	
Oral anticoagulant	0.71 [0.28-1.56]	0.42	-	
D-dimers level at ICU admission	1.62 [1.27-2.06]	<0.01	1.45 [1.10-1.91]	0.01
Fibrinogen level at ICU admission	0.93 [0.81-1.08]	0.35	-	
PaO <sub>2</sub> /FiO <sub>2</sub> ratio <sup>a</sup>	0.99 [0.98-0.99]	<0.01	0.99 [0.98-0.99]	0.04
RRT	3.37 [1.90-5.95]	<0.01	-	
ECMO	2.88 [1.50-5.46]	<0.01	2.35 [0.99-5.57]	<0.05

3 **Table 3:** Risk factors for thrombotic complications in critically ill COVID-19 patients  
4 VTE: venous thromboembolism; ECMO: extracorporeal membrane oxygenation; RRT: renal replacement  
5 therapy  
6 <sup>a</sup> lower value during ICU stay

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Population	Model	Factor	Coef (se)	HR [CI <sub>95%</sub> ]	p-value
TC all thrombosis (n <sub>events</sub> = 53, 1104 observations, 245 patients)					
	Univariate Cox model				
		HPA	-0.243 (0.112)	0.785 [0.646 - 0.952]	0.01
	Adjusted Cox model				
		HPA	-0.208 (0.115)	0.813 [0.663 - 0.996]	0.05
		RRT	0.687 (0.308)	1.988 [1.083 - 3.648]	0.03
		ECMO	0.254 (0.401)	1.290 [0.577 - 2.881]	0.54
		PaO <sub>2</sub> /FiO <sub>2</sub> ratio	-0.002 (0.004)	0.998 [0.989 - 1.007]	0.69
	Weighted Cox model				
		HPA	-0.332 (0.152)	0.718 [0.532 - 0.967]	0.03
	Weighted and Adjusted Cox model				
		HPA	-0.217 (0.112)	0.804 [0.653 - 0.990]	0.04
		RRT	0.671 (0.308)	1.957 [1.056 - 3.627]	0.03
		ECMO	0.173 (0.405)	1.189 [0.514 - 2.751]	0.69
		PaO <sub>2</sub> /FiO <sub>2</sub> ratio	-0.002 (0.004)	0.998 [0.989 - 1.007]	0.64
All TC excluding RRT- filter clotting or ECMO circuit clotting (n <sub>events</sub> = 45, 1086 observations, 245 patients)					
	Univariate Cox model				
		HPA	-0.234 (0.118)	0.791 [0.628 - 0.997]	0.04
	Adjusted Cox model				
		HPA	-0.220 (0.139)	0.801 [0.632 - 1.017]	0.07
		RRT	0.301 (0.378)	1.352 [0.644 - 2.839]	0.43
		ECMO	0.048 (0.516)	1.049 [0.381 - 2.885]	0.93
		PaO <sub>2</sub> /FiO <sub>2</sub> ratio	-0.001 (0.005)	0.999 [0.989 - 1.010]	0.87
	Weighted Cox model				
		HPA	-0.256 (0.125)	0.774 [0.612 - 0.980]	0.03
	Weighted and Adjusted Cox model				
		HPA	-0.245 (0.127)	0.783 [0.614 - 0.997]	0.04
		RRT	0.313 (0.360)	1.367 [0.648 - 2.886]	0.41
		ECMO	-0.039 (0.497)	0.961 [0.341 - 2.714]	0.94
		PaO <sub>2</sub> /FiO <sub>2</sub> ratio	-0.001 (0.004)	0.999 [0.990 - 1.008]	0.85
Pulmonary embolism or venous thrombo-embolism (n <sub>event</sub> = 35, 1086 observations, 245 patients)					
	Univariate Cox model				
		HPA	-0.298 (0.144)	0.742 [0.568 - 0.969]	0.03
	Adjusted Cox model				
		HPA	-0.286 (0.139)	0.751 [0.572 - 0.987]	0.04
		RRT	0.333 (0.424)	1.395 [0.607 - 3.207]	0.43
		ECMO	0.062 (0.583)	1.064 [0.340 - 3.333]	0.92
		PaO <sub>2</sub> /FiO <sub>2</sub> ratio	0.001 (0.005)	1.001 [0.991 - 1.011]	0.90
	Weighted Cox model				
		HPA	-0.312 (0.139)	0.732 [0.560 - 0.957]	0.02
	Weighted and Adjusted Cox model				
		HPA	-0.303 (0.141)	0.739 [0.561 - 0.973]	0.03
		RRT	0.365 (0.400)	1.441 [0.624 - 3.327]	0.39
		ECMO	-0.036 (0.551)	0.964 [0.300 - 3.107]	0.95
		PaO <sub>2</sub> /FiO <sub>2</sub> ratio	0.001 (0.005)	1.001 [0.991 - 1.010]	0.91
Pulmonary embolism (n <sub>event</sub> = 30, 1086 observations, 245 patients)					
	Univariate Cox model				
		HPA	-0.311 (0.158)	0.733 [0.544 - 0.987]	0.04
	Adjusted Cox model				
		HPA	-0.300 (0.161)	0.740 [0.546 - 1.003]	0.05
		RRT	0.315 (0.442)	1.371 [0.553 - 3.398]	0.50
		ECMO	-0.223 (0.631)	0.799 [0.221 - 2.889]	0.73
		PaO <sub>2</sub> /FiO <sub>2</sub> ratio	-0.005 (0.006)	0.995 [0.984 - 1.005]	0.30
	Weighted Cox model				
		HPA	-0.332 (0.153)	0.717 [0.532 - 0.967]	0.03
	Weighted and Adjusted Cox model				
		HPA	-0.325 (0.155)	0.722 [0.531 - 0.981]	0.04
		RRT	0.356 (0.425)	1.427 [0.572 - 3.563]	0.47
		ECMO	-0.312 (0.632)	0.731 [0.196 - 2.735]	0.64
		PaO <sub>2</sub> /FiO <sub>2</sub> ratio	-0.004 (0.006)	0.995 [0.985 - 1.006]	0.39



1 **Table 4:** Summary table of Cox model for the effect of high dose prophylactic  
2 anticoagulation on thrombotic complications.  
3 HPA: high dose prophylactic anticoagulation; RRT: renal replacement therapy; ECMO; extracorporeal  
4 membrane oxygenation; HR: hazard ratio. Coef (se): standard error of the coefficient  
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**Figure 1:** Retrospective classification of the level of anticoagulation for thromboprophylaxis

LWMH: Low molecular weight heparin; UFH: unfractionated heparin

This algorithm was used at each time point to classify the patient into either standard or high-dose prophylaxis. A patient could change category between two time points several times during the study period.

