RAPID COMMUNICATION

Therapeutic-Dose vs. Prophylactic-Dose Anticoagulation Therapy for Critically Ill Patients With COVID-19 in a Practice-Based Observational Study

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Background: The potential benefit of therapeutic-dose anticoagulation for critically ill patients with coronavirus disease 2019 (COVID-19) is still controversial.

Methods and Results: In the CLOT-COVID study, 225 patients with severe COVID-19 on admission requiring mechanical ventilation or extracorporeal membrane oxygenation were divided into patients with therapeutic-dose anticoagulation (N=110) and those with prophylactic-dose anticoagulation (N=115). There was no significant difference in the incidence of thrombosis between the groups (9.1% vs. 7.8%, P=0.73).

Conclusions: Among a cohort of critically ill patients with COVID-19, approximately half received therapeutic-dose anticoagulation, although it did not show a potential benefit compared with prophylactic-dose anticoagulation.

Key Words: Anticoagulation; COVID-19; Critical illness; Severe illness; Thrombosis

The coronavirus disease 2019 (COVID-19) has become a pandemic respiratory infectious disease[1] that is reported to cause cardiovascular complications, including thrombosis.[2,3] COVID-19-associated thrombosis is reported to cause in-situ thrombosis in large vessels as well as small vessels of the lungs at the capillary-alveolar interface, which might contribute to the worsening of respiratory failure.[4,5] Thus, there could be potential benefit of anticoagulation therapy for prevention of thrombosis and worsening of disease severity, and several current guidelines recommend prophylactic anticoagulation therapy for all hospitalized patients with COVID-19.[6,7] Furthermore, critically ill patients with COVID-19 are reported to be especially at high risk of thrombosis despite standard-dose pharmacological thromboprophylaxis with prophylactic-dose anticoagulation therapy,[2,8] which suggests that more aggressive pharmacological thromboprophylaxis with therapeutic-dose anticoagulation therapy could be useful for these patients.[9] However, previous studies reported somewhat conflicting results for the potential benefit of therapeutic-dose anticoagulation therapy for SUCH critically ill patients.[10–12]

The uncertainty on the issue, as well as different ethnicities and medical resource availability in each country and region might lead to widely varying management strategies in daily clinical practice, including in Japan.[13,14] Thus, to
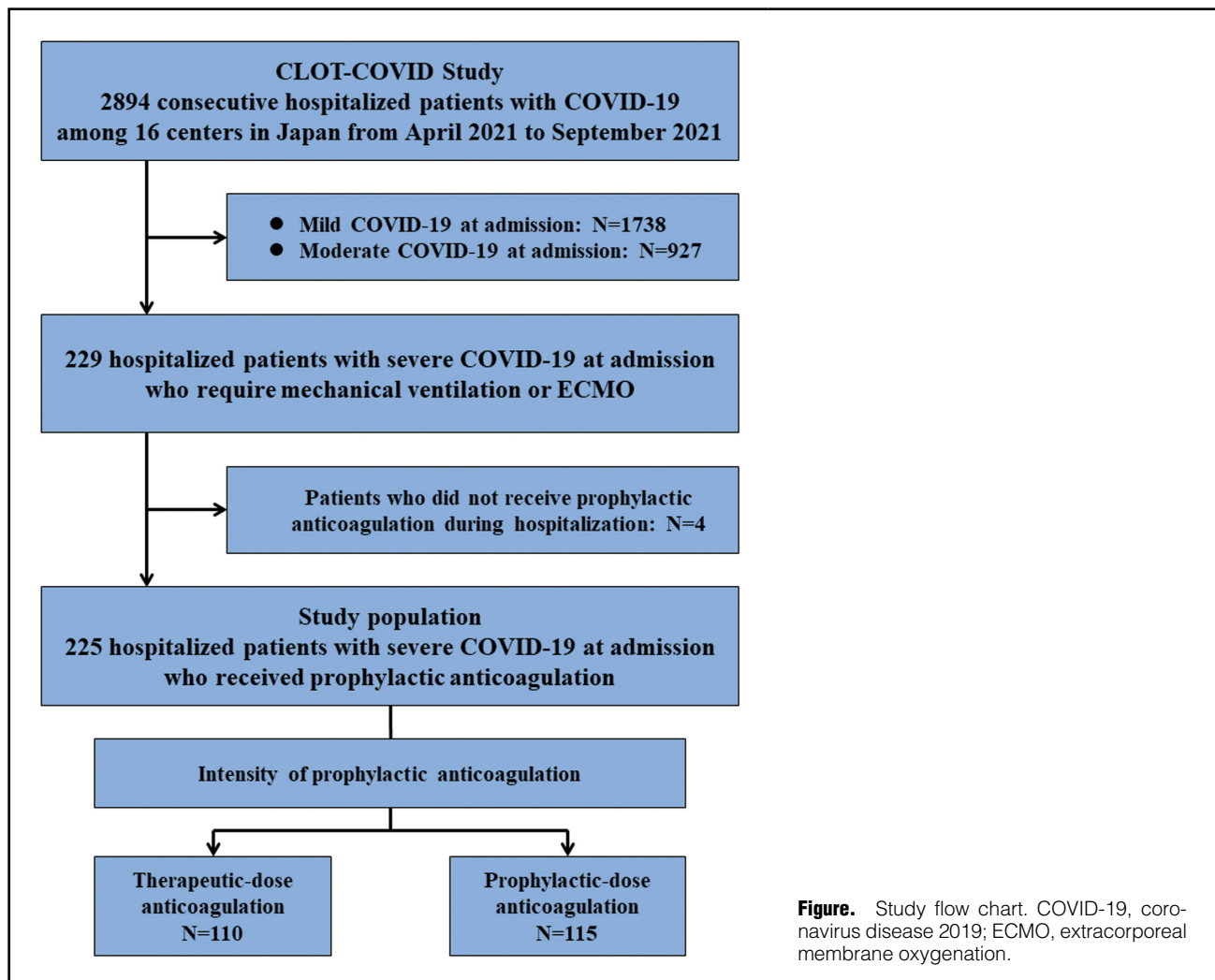
Figure. Study flow chart. COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation.

evaluate the effectiveness and safety of therapeutic-dose anticoagulation therapy for critically ill patients in real-world clinical practice, we conducted an exploratory analysis comparing therapeutic-dose and prophylactic-dose anticoagulation therapy in critically ill patients with COVID-19, using a large-scale multicenter observational database of patients with COVID-19 in Japan.

Methods

Study Population
The CLOT-COVID study was a physician-initiated, retrospective, multicenter cohort study enrolling 2,894 consecutive patients hospitalized with COVID-19 in 16 centers in Japan from April 2021 to September 2021. The design of the study has been reported in detail.[15,16]

In the current study, we identified 229 patients with severe COVID-19 on admission who required mechanical ventilation or extracorporeal membrane oxygenation (ECMO),[14,17] after excluding 1,738 patients with mild COVID-19 on admission who did not require oxygen administration and 927 patients with moderate COVID-19 on admission who required oxygen administration (**Figure**). We further excluded 4 patients who did not receive prophylactic anticoagula-

tion during hospitalization, so the current study population consisted of 225 hospitalized patients with severe COVID-19 on admission who received prophylactic anticoagulation. The current study population was divided into 2 groups according to the intensity of prophylactic anticoagulation during hospitalization: patients with therapeutic-dose anticoagulation and those with prophylactic-dose anticoagulation, and we compared their characteristics and clinical outcomes during hospitalization.

The relevant review boards or ethics committees of all participating centers approved the research protocol. All procedures followed were in accordance with the Declaration of Helsinki. Written informed consent from each patient was waived because we used clinical information obtained in routine clinical practice. This method was concordant with the guidelines for epidemiological studies issued by the Ministry of Health, Labor, and Welfare in Japan.

Definitions of Patients' Characteristics
Prophylactic anticoagulation was evaluated as usage of any anticoagulant agents during hospitalization except for the treatment of thrombosis. Prophylactic-dose anticoagulation included unfractionated heparin at a prophylactic

Table 1. Patients' Characteristics and Management Strategies During Hospitalization

	Severe COVID-19 on admission (N=225)	Therapeutic-dose anticoagulation (N=110)	Prophylactic-dose anticoagulation (N=115)	P value
Baseline characteristics				
Age (years)	58.2±12.5	60.2±12.2	56.4±12.5	0.02
Men	171 (76%)	81 (74%)	90 (78%)	0.42
Body weight (kg)	73.6±18.2	73.1±19.1	74.2±17.4	0.64
Body mass index (kg/m²)	26.4±5.8	26.4±6.1	26.4±5.5	0.98
>30 kg/m²	49 (22%)	27 (25%)	22 (19%)	0.33
D-dimer level on admission (μg/mL) (N=211)	1.6 (1.1–3.8)	1.7 (1.2–4.9)	1.5 (1.0–2.9)	0.052
Comorbidities				
Hypertension	105 (47%)	55 (50%)	50 (43%)	0.33
Diabetes mellitus	73 (32%)	38 (35%)	35 (30%)	0.51
Heart disease	29 (13%)	18 (16%)	11 (9.6%)	0.13
Respiratory disease	36 (16%)	21 (19%)	15 (13%)	0.22
Active cancer	4 (1.8%)	1 (0.9%)	3 (2.6%)	0.33
History of major bleeding	4 (1.8%)	3 (2.7%)	1 (0.9%)	0.29
History of VTE	3 (1.3%)	2 (1.8%)	1 (0.9%)	0.54
Status of severity on admission				
Mechanical ventilation	216 (96%)	104 (95%)	112 (97%)	0.28
ECMO	9 (4.0%)	6 (5.5%)	3 (2.6%)	
Prophylactic anticoagulation during hospitalization				
Unfractionated heparin at a prophylactic dose	42 (19%)	–	42 (37%)	–
Low-molecular-weight heparin at a prophylactic dose	73 (32%)	–	73 (63%)	–
Unfractionated heparin at a therapeutic dose	78 (35%)	78 (71%)	–	–
Low-molecular-weight heparin at a therapeutic dose	0 (0%)	0 (0%)	–	–
Direct oral anticoagulants	32 (14%)	32 (29%)	–	–
Imaging examinations during hospitalization				
Contrast-enhanced CT examination	37 (16%)	20 (18%)	17 (15%)	0.49
Ultrasound examination of lower extremities	8 (3.6%)	4 (3.6%)	4 (3.5%)	0.95
Length of hospitalization (days)	15 (9–25)	21 (13–28)	12 (7–17)	<0.001

Categorical variables are presented as numbers and percentages, and continuous variables are presented as the mean and standard deviation or the median and interquartile range based on their distributions. Categorical variables were compared using the chi-squared test when appropriate; otherwise, Fisher's exact test was used. Continuous variables were compared using Student's t-test or Wilcoxon's rank sum test based on distribution. Unfractionated heparin at a therapeutic dose was defined as the administration of unfractionated heparin targeting a therapeutic range referencing the APTT. Unfractionated heparin at a prophylactic dose was defined as the administration of unfractionated heparin at a fixed dose without referencing the APTT. APTT, activated partial thromboplastin time; CT, computed tomography; COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation; VTE, venous thromboembolism.

dose and low-molecular-weight heparin at a prophylactic dose, whereas therapeutic-dose anticoagulation included unfractionated heparin at a therapeutic dose, low-molecular-weight heparin at a therapeutic dose, and direct oral anticoagulants. A therapeutic dose of unfractionated heparin was defined as the administration of unfractionated heparin targeting a therapeutic range referencing the activated partial thromboplastin time (APTT), and a prophylactic dose of unfractionated heparin was defined as the administration of a fixed dose of unfractionated heparin without a referencing the APTT.

Clinical Outcomes

The primary outcome measure was thrombosis during hospitalization, which included VTE, ischemic stroke, myocardial infarction, systemic arterial thromboembolism, and other systemic thrombosis. VTE was defined as pulmonary embolism and/or deep vein thrombosis objectively confirmed by imaging examinations (ultrasound, contrast-enhanced computed tomography, ventilation-perfusion lung scintigraphy, pulmonary angiography, or

contrast venography) or by autopsy. Ischemic stroke was defined as stroke either requiring or prolonging the hospitalization with symptoms lasting >24h. Myocardial infarction was defined in accordance with the universal myocardial infarction guidelines.[18]

The secondary outcome measures in the current study were major bleeding and all-cause death during hospitalization. Major bleeding was defined as International Society of Thrombosis and Hemostasis (ISTH) major bleeding, which consisted of a reduction in the hemoglobin level by ≥2 g/dL, transfusion of ≥2 units of blood, or symptomatic bleeding in a critical area or organ.[19]

Statistical Analysis

Categorical variables are presented as numbers and percentages. Continuous variables are presented as the mean and standard deviation or the median and interquartile range based on their distributions. Categorical variables were compared with the chi-square test when appropriate; otherwise, Fisher's exact test was used. Continuous variables were compared using Student's t-test or Wilcoxon's

Table 2. Clinical Outcomes During Hospitalization			
	Severe COVID-19 on admission (N=225)	Therapeutic-dose anticoagulation (N=110)	Prophylactic-dose anticoagulation (N=115)	P value
Thrombosis	19 (8.4% [5.4–12.9%])	10 (9.1% [4.8–16.1%])	9 (7.8% [4.0–14.4%])	0.73
Type of thrombosis				
VTE	17 (7.6% [4.7–11.8%])	9 (8.2% [4.2–15.0%])	8 (7.0% [3.4–13.3%])	–
Arterial thrombotic event	4 (1.8% [0.5–4.6%])	2 (1.8% [0.1–6.8%])	2 (1.7% [0.1–6.5%])	–
Ischemic stroke	4/4 (100%)	2/2 (100%)	2/2 (100%)	–
Myocardial infarction	0/4 (0%)	0/2 (0%)	0/2 (0%)	–
Systemic arterial thromboembolism	0/4 (0%)	0/2 (0%)	0/2 (0%)	–
Other thrombosis	1 (0.4% [0.0–2.7%])	1 (0.9% [0.0–5.5%])	0 (0.0% [0.0–3.9%])	–
Major bleeding	27 (12.0% [8.3–16.9%])	21 (19.1% [12.8–27.5%])	6 (5.2% [2.2–11.1%])	0.001
Site of bleeding				
Intracranial	4/27 (15%)	3/21 (14%)	1/6 (17%)	–
Gastrointestinal	10/27 (37%)	9/21 (43%)	1/6 (17%)	–
Urinary	1/27 (3.7%)	0/21 (0%)	1/6 (17%)	–
Surgery-related/iatrogenic	7/27 (26%)	7/21 (33%)	0/6 (0%)	–
Subcutaneous	1/27 (3.7%)	1/21 (4.8%)	0/6 (0%)	–
Other	4/27 (15%)	1/21 (4.8%)	3/6 (50%)	–
All-cause death	57 (25.3% [20.1–31.4%])	36 (32.7% [24.7–42.0%])	21 (18.3% [12.2–26.4%])	0.01

Clinical outcomes are presented as numbers of events and percentages with the 95% confidence intervals, which were compared by chi-squared test when appropriate; otherwise, Fisher's exact test was used. COVID-19, coronavirus disease 2019; VTE, venous thromboembolism.

rank sum test based on their distributions. The clinical outcomes are presented as numbers of events and percentages with the 95% confidence intervals (CI), which were compared using the chi-squared test when appropriate; otherwise, Fisher's exact test was used. All statistical analyses were performed with JMP version 14.0.0 software (SAS Institute Inc., Cary, NC, USA). All reported P values were 2-tailed, and P<0.05 was considered statistically significant.

Results

Patients' Characteristics
Among the 225 patients with severe COVID-19 on admission, 110 (49%) received therapeutic-dose anticoagulation, and 115 (51%) received prophylactic-dose anticoagulation (**Figure**). Patients given therapeutic-dose anticoagulation were older (60.2 vs. 56.4 years, P=0.02), but there were no significant differences in sex, body weight or body mass index between the groups (**Table 1**). The median D-dimer level on admission trended higher in patients given therapeutic-dose anticoagulation than in those given prophylactic-dose anticoagulation, although not statistically significant (1.7 vs. 1.5 μg/mL, P=0.052). There were no significant differences in the prevalence of comorbidities between the groups.

As for the status of disease severity on admission, 216 patients (96%) needed mechanical ventilation, and 9 patients (4.0%) needed ECMO. Patients given therapeutic-dose anticoagulation included 78 patients (71%) given unfractionated heparin at a therapeutic dose and 32 patients (29%) given direct oral anticoagulants; patients given prophylactic-dose anticoagulation included 42 patients (37%) given unfractionated heparin at a prophylactic dose and 73 patients (63%) given low-molecular-weight heparin at a prophylactic dose (**Table 1**).

Clinical Outcomes During Hospitalization
During hospitalization, 19 patients (8.4% [95% CI, 5.4–12.9%]) developed thrombosis; there was no significant difference in the incidence of thrombosis between the groups (9.1% [95% CI, 4.8–16.1%] vs. 7.8% [95% CI, 4.0–14.4%], P=0.73) (**Table 2**).

During hospitalization, 27 patients (12.0% [95% CI, 8.3–16.9%]) developed major bleeding, and patients given therapeutic-dose anticoagulation more often developed major bleeding than those given prophylactic-dose anticoagulation (19.1% [95% CI, 12.8–27.5%] vs. 5.2% [95% CI, 2.2–11.1%], P=0.001) (**Table 2**). The most frequent type of bleeding was gastrointestinal bleeding (37%), followed by surgery-related/iatrogenic bleeding (26%). During hospitalization, 57 patients (25.3% [95% CI, 20.1–31.4%]) died, and patients given therapeutic-dose anticoagulation more often died than those given prophylactic-dose anticoagulation (32.7% [95% CI, 24.7–42.0%] vs. 18.3% [95% CI, 12.2–26.4%], P=0.01).

The comparisons between patients with and without major bleeding showed no significant difference in the baseline characteristics and comorbidities except for a higher prevalence of history of major bleeding in patients with major bleeding (7.4% vs. 1.0%, P=0.02). Patients with major bleeding more often received anticoagulation at therapeutic doses (78% vs. 45%, P=0.001).

Discussion

The main findings of the current study were as follows: (1) among critically ill patients with COVID-19 on admission who required mechanical ventilation or ECMO, approximately half received therapeutic-dose anticoagulation therapy; (2) there was no significant difference in the incidence of thrombosis between therapeutic-dose and prophylactic-dose anticoagulation therapy; and (3) patients

given therapeutic-dose anticoagulation may have a higher risk of major bleeding than those given prophylactic-dose anticoagulation.

COVID-19-associated thrombosis has been reported as a common complication in patients with COVID-19, and there has been thought to be a potential benefit of prophylactic anticoagulation for patients with COVID-19.[6,7,13] Furthermore, previous observational studies reported a potential benefit of therapeutic-dose anticoagulation rather than prophylactic-dose anticoagulation.[9,20] Although the effectiveness and safety of more intensive anticoagulation for patients with COVID-19 is still controversial, clinicians may think that more intensive anticoagulation is a reasonable option, especially for critically ill patients, based on a high risk of thrombosis in these patients. The current study showed that approximately half of the critically ill patients received therapeutic-dose anticoagulation therapy, suggesting that it is not a rare option for critically ill patients in real-world clinical practice.

Although a previous small randomized clinical trial reported a benefit of therapeutic-dose anticoagulation compared with prophylactic-dose anticoagulation for patients with severe COVID-19 requiring mechanical ventilation,[12] recent landmark randomized clinical trials have not shown a benefit of intermediate-dose or therapeutic-dose anticoagulation for critically ill patients admitted to intensive care units.[10,11] In line with these recent studies, the current study did not show a potential benefit of therapeutic-dose anticoagulation for critically ill patients requiring mechanical ventilation or ECMO in terms of thrombosis. Because more aggressive anticoagulation therapy could increase the risk of bleeding, that should be taken into consideration when deciding the intensity of anticoagulation therapy. In fact, previous studies reported a higher risk of major bleeding with more intensive anticoagulation therapy.[10,11] Consistent with previous reports, the current study also showed that patients given therapeutic-dose anticoagulation could have a higher risk of major bleeding than those given prophylactic-dose anticoagulation.

The current exploratory analysis evaluated different treatment strategies in an observational study, and thus, the current results should be interpreted very cautiously due to selection bias. However, the current study seemed not to show a potential benefit of therapeutic-dose anticoagulation, including a lower risk of thrombosis, a lower risk of all-cause death, and a comparable risk of bleeding. Considering that randomized clinical trials are not currently available in Japan, it might be reasonable at this moment not to recommend therapeutic-dose anticoagulation over prophylactic-dose anticoagulation for critically ill patients requiring mechanical ventilation or ECMO in Japan. Further randomized clinical trials are warranted to investigate the potential benefit and harm of therapeutic-dose anticoagulation for critically ill patients with COVID-19 in Japan.

Study Limitations
First and most importantly, the current study was observational and thus can only show association, not causality. In particular, a causal relationship between the intensity of prophylactic anticoagulation and the development of thrombosis was unclear. Prophylactic anticoagulation was left to the discretion of the attending physicians, which could influenced the clinical outcomes. Second, the current study evaluated only clinical outcomes during hospitaliza-

tion. Thus, we could not discuss the risk of thrombosis after discharge. Third, the current study did not evaluate the exact APTT values in each patient during their clinical course. The intensity of heparin as measured by APTT in each group could have influenced the clinical outcomes. Fourth, anticoagulation therapy could be influenced by renal and liver functions, which were not evaluated in the current study. Fifth, the detailed status of coagulation abnormalities was not evaluated in the current study, which could have influenced the clinical outcomes.

Conclusions
Among critically ill patients with COVID-19 on admission who required mechanical ventilation or ECMO, approximately half received therapeutic-dose anticoagulation in real-world Japanese clinical practice, but therapeutic-dose anticoagulation did not show a potential benefit compared with prophylactic-dose anticoagulation.

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