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Thrombosis and Anticoagulation Strategies in Patients with COVID-19 Including Japanese Perspective

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Coronavirus disease 2019 (COVID-19) has become a major health problem worldwide since 2020. Although the main pathophysiology of COVID-19 is a respiratory infectious disease, it could also cause cardiovascular complications, including thrombosis. Thus, anticoagulation therapy has been thought to help prevent thrombosis, leading to improved survival. However, to date, several aspects of the optimal anticoagulation strategies for COVID-19 remain unclear. Considering the status of COVID-19-related thrombosis and some domestic issues in Japan, the optimal anticoagulation strategies for COVID-19 might have to be based on Japanese domestic clinical data considering racial difference. Racial disparities in terms of thromboembolic risk have been well known in the pre-COVID-19 era, and the risk of COVID-19-associated thrombosis depending on race could be an important issue. Considering a potential higher risk of bleeding with anticoagulation therapy in the Asian population, it might be important to maintain a good balance between the risks of thrombosis and bleeding. Latest evidences of COVID-19-related thrombosis and anticoagulation strategies, including some domestic issues in Japan, showed a different status of COVID-19-related thrombosis in Japan from that in Western countries, suggesting the potential benefit of different anticoagulation strategies, specifically for the Japanese population. Although these insights could be useful for the consideration of anticoagulation strategies for the Japanese population, the final decision should be based on balancing the benefits and risks of anticoagulation therapy in each patient.

Key words: COVID-19, Thrombosis, Anticoagulation, Asian: Japanese

Introduction

Coronavirus disease 2019 (COVID-19) was first reported in Wuhan, China, in December 2019^{1, 2)} and was finally declared a pandemic by the World Health Organization in March 2020³⁾. Although the main pathophysiology of COVID-19 is a respiratory infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), it could also cause cardiovascular complications^{4, 5)}. Coagulopathy in COVID-19 patients has been reported⁶⁾, which could lead to thromboembolic complications⁷⁻¹⁰⁾. Thus, COVID-19 patients have been recognized as being at a high risk for thrombosis. On the basis of the concept of the high risk for thrombosis in these

patients, anticoagulation therapy, the main therapy for preventing thrombosis in COVID-19, has been drawing attention. However, to date, the optimal anticoagulation strategies for the prevention of thrombosis in COVID-19 remains unclear despite the many previous clinical studies conducted worldwide, which is related to several issues, including SARS-CoV-2 variant, status of vaccination for SARS-CoV-2, medical resource availability, and racial difference. The present study aimed to provide an overview of the latest evidence of thrombosis and anticoagulation strategies in COVID-19 patients, and discuss some domestic issues in Japan.

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Mechanisms of COVID-19-Associated Coagulopathy

Although the exact pathophysiological mechanisms of COVID-19-associated coagulopathy are still unclear, there have been several reports on the potential mechanisms of COVID-19-associated coagulopathy, especially at the local and systemic levels¹¹.

Platelets play a significant role in thrombus formation, which could be important in COVID-19-associated coagulopathy. Although it is unclear whether platelets can interact with and internalize SARS-CoV-2¹²⁻¹⁴), several receptors on platelets have been suggested to mediate the binding and internalization of SARS-CoV-2. Angiotensin-converting enzyme-2 (ACE2) is the major receptor for the receptor binding domain of the SARS-CoV-2 spike protein¹⁵), and its expression on platelets was previously reported¹⁶.

Endothelial cells also play a pivotal role in inflammation-induced coagulation in COVID-19. The pro-inflammatory response to COVID-19 results in the release of pro-inflammatory cytokines, such as interleukin-1 beta, interleukin-6, and tumor necrosis factor, which could induce endothelial cell inflammation in COVID-19 patients^{17, 18}). ACE2 receptors are also expressed by endothelial cells, and binding of SARS-CoV-2 to ACE2 on endothelial cells impairs ACE2 activity, which could result in endothelial cell activation^{19, 20}). Through the disruption of vascular integrity and endothelial cell death, the thrombogenic basement membrane and activation of the clotting cascade could be induced²¹.

Neutrophil extracellular traps (NETs) released by circulatory or infiltrating neutrophils could also cause coagulation in COVID-19 patients. Although NETs are important for preventing pathogen invasion, activated neutrophils and NETs could also contribute to a pathological prothrombotic environment^{22, 23}). Several mechanisms through NET formation have been reported to cause coagulation in COVID-19 patients²⁴), and the tissue factor expression in NETs and neutrophil-derived microparticles could directly activate the coagulation pathway²⁵.

COVID-19-Associated Thrombosis

COVID-19-associated coagulopathy could be presented as thrombosis in COVID-19 patients, especially venous thromboembolism (VTE), including pulmonary embolism (PE) and deep vein thrombosis (DVT)¹⁰). Notably, a significant heterogeneity in the incidence and phenotypes of thrombosis has been reported, which could be partly due to the variation in patient characteristics and hospitalization conditions as well as diagnostic and screening protocols²⁶.

Furthermore, it could be due to various influences, such as differences in practice policies at each institution and region, presence or absence of prophylactic anticoagulation therapy, and racial differences. A previous meta-analysis revealed that the overall incidence rate of VTE was 14.1%, although the incidence rates widely varied depending on the clinical status of patients: 40.3% with ultrasound screening, 9.5% without ultrasound screening, 7.9% in non-intensive care unit (ICU) patients, and 22.7% in ICU patients.

Anticoagulation Therapy for COVID-19

Considering the high risk of thrombosis in COVID-19 patients and the association between thrombosis and mortality, pharmacologic thromboprophylaxis, including anticoagulation therapy, could be a potential option for the primary prevention of thrombosis, leading to improved survival. Previous studies reported that the use of anticoagulation was associated with reduced mortality in hospitalized patients with COVID-19²⁷⁻²⁹), suggesting the potential benefit of anticoagulation for the prevention of thrombosis in COVID-19 management. In line with these reports, the current consensus statements and international practice guidelines have recommended systematic pharmacological thromboprophylaxis for all hospitalized COVID-19 patients³⁰⁻³²).

Optimal Anticoagulation Management for COVID-19

In addition to the indication of pharmacological thromboprophylaxis for COVID-19, the optimal types and intensity of anticoagulants are clinically relevant issues, which have been investigated in many previous clinical trials.

Most of the previous studies evaluated low-molecular-weight heparin (LMWH), a pharmacological thromboprophylaxis. LMWH is the commonly used anticoagulant, whereas unfractionated heparin (UFH) and fondaparinux are preferred when LMWH is contraindicated³³). As for direct oral anticoagulants (DOACs) for COVID-19 patients, a previous randomized clinical trial (RCT) evaluating the therapeutic dosage of rivaroxaban for thromboprophylaxis, an ACTION trial, demonstrated that no statistically significant difference was observed in the primary efficacy outcome of thrombosis between LMWH and rivaroxaban; however, bleeding events were more frequent in the arm administered with rivaroxaban³⁴). Pharmacologically, LMWH might be a preferable anticoagulation therapy as it has not only anticoagulant effects but also putative pleiotropic anti-viral and anti-inflammatory properties³⁵).

Thrombosis and Anticoagulation in COVID-19

Table 1. Landmark clinical trials evaluating optimal intensity of anticoagulants for hospitalized patients with COVID-19

Trial	Number of patients	Setting	Intervention	Comparator	Primary outcome	Results
INSPIRATION	562	ICU	Intermediate-dose heparin	Prophylactic-dose heparin	Thrombosis/ECMO/mortality	OR, 1.06; 95%CI, 0.76-1.48
Multiplatform (REMAP-CAP, ACTIV-4a and ATTACC) for non-critically ill	1098	ICU	Therapeutic-dose heparins	Prophylactic/intermediate-dose heparin	Organ support-free days	OR, 0.83; 95%CI, 0.67-1.03
Multiplatform (REMAP-CAP, ACTIV-4a and ATTACC) for critically ill	2219	Ward	Therapeutic-dose heparins	Prophylactic/intermediate-dose heparin	Organ support-free days	OR, 1.27; 95%CI, 1.03-1.58
HEP-COVID	257	ICU/ward	Therapeutic-dose LMWH	Prophylactic/intermediate-dose heparin	Thrombosis/mortality	RR, 0.68; 95%CI, 0.49-0.96
RAPID	465	Ward	Therapeutic-dose heparins	Prophylactic-dose heparin	Mortality/IMV/NIMV/admission to ICU	OR, 0.59; 95%CI, 0.34-1.02
ACTION	615	ICU/ward	Therapeutic rivaroxaban/enoxaparin/UFH (mainly rivaroxaban)	Prophylactic-dose heparin	Time to mortality, duration of hospitalization, duration of supplemental oxygen	Win ratio, 0.86; 95%CI, 0.59-1.22

COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation; IMV, invasive mechanical ventilation; NIMV, noninvasive mechanical ventilation; ICU, intensive care unit; OR, odds ratio; RR, relative risk; CI, confidence interval.

Furthermore, LMWH could provide the least interactions with anti-viral or other drugs used for treating COVID-19 infection compared with other anticoagulants^{36, 37}. Based on these issues, the latest practice guidance statement by the International Society on Thrombosis and Haemostasis (ISTH) have recommended LMWH as the first option for hospitalized patients with COVID-19³⁸.

The optimal intensity of anticoagulation therapy for COVID-19 has been a matter of active debate, which includes the prophylactic, intermediate, and therapeutic doses of anticoagulants. The consensus statements and international practice guidelines during the early stage of the pandemic initially favored higher doses of anticoagulants for selected patients, including those with severe COVID-19³³. So, far, a number of RCTs have investigated the issue (Table 1). The INSPIRATION trial was the first RCT that compared the intermediate versus prophylactic dosages of anticoagulants in patients with COVID-19 admitted to the ICU, which indicated that there was no benefit for the intermediate over prophylactic dosage of anticoagulants³⁹. The landmark multiplatform RCT combining REMAP-CAP, ACTIV-4a, and ATTACC demonstrated a potential benefit of the therapeutic over prophylactic dosage of anticoagulants among non-critically ill patients with COVID-19⁴⁰ but none among critically ill patients with COVID-19⁴¹. Similarly, the HEP-COVID trial demonstrated a benefit of therapeutic over prophylactic dosage of anticoagulants in selected non-ICU patients who were at a high risk for thrombosis but none in ICU patients⁴². In line with these reports,

the RAPID trial demonstrated that therapeutic heparin could have a potential benefit of decreased acute mortality among COVID-19 patients with moderate illness and increased D-dimer levels who were admitted to hospital wards, although therapeutic heparin was not significantly associated with a reduction in the primary outcome⁴³. On the other hand, the ACTION trial showed that the therapeutic doses of anticoagulants had no benefits, did not improve clinical outcomes, and increased bleeding events compared with the prophylactic dosages³⁴. Although there seems to be somewhat conflicting results regarding these issues, based on the results of previous RCTs, the latest consensus statements and international practice guidelines have recommended a therapeutic dosage of LMWH for non-critically ill (non-ICU) patients who are at a high risk of thrombosis and a prophylactic dosage for critically ill (ICU) patients^{31, 32, 38}.

Risk of Thrombosis in the Asian Population

Historically, thrombosis including VTE has been considered a relatively uncommon disease among the Asian population, including the Japanese. Some previous studies showed lower incidences of VTE in the Asian population than in the Caucasian population⁴⁴⁻⁴⁶. Furthermore, there could be a different pharmacodynamic response to antithrombotic agents including anticoagulation therapy as well as less benefit in thromboembolic event reduction and a high risk for increased bleeding events during antithrombotic treatment⁴⁷. The polygenic nature of inherited thrombophilia and the

complex interaction between genetic and epigenetic factors could lead to lower hypercoagulability, which could be a potential mechanism for the lower risk of thrombosis among the Asian population⁴⁷. Racial disparities in thromboembolic risk have been well known in the pre-COVID-19 era, and the risk of COVID-19-associated thrombosis depending on race could be an important issue. Considering a potential higher risk of bleeding with anticoagulation therapy in the Asian population⁴⁸, it is important to maintain a good balance between the risk of thrombosis and bleeding considering racial differences.

COVID-19-Related Thrombosis in Japan

Although there was a scarcity of data on COVID-19-related thrombosis at the early stage of the COVID-19 pandemic in Japan, several studies have been reported after late 2020. The first questionnaire surveillance for COVID-19 and VTE in a collaborative effort with the Japanese Society of Phlebology and Japanese Society of Pulmonary Embolism Research was reported in August 2020, which showed that the incidence rates of VTE and PE were 0.6% and 0.4%, respectively, among 1243 patients with COVID-19 from March 2020 to June 2020⁴⁹. Furthermore, each VTE case was reported in detail, which showed some clinical features of VTE patients with COVID-19 in Japan, including patients with obesity and those requiring mechanical ventilation during hospitalization⁵⁰. Another large questionnaire surveillance for COVID-19 and thrombosis conducted by a joint team of the Japanese Society of Thrombosis and Hemostasis, the Japanese Atherosclerosis Society, and the Research Study Team for Intractable Disease supported by the Ministry of Health, Labor and Welfare of Japan was reported in December 2020, which showed that the incidence rate of thrombotic events was 1.86% among 5807 COVID-19 patients⁵¹. These questionnaire surveillance suggested that the number of COVID-19 patients diagnosed with thrombosis in Japan was quite small compared with those in other countries; however, whether these results suggested the under-diagnosis of thrombosis in COVID-19 or actual lower prevalence of thrombosis in Japan remains unclear.

To elucidate the detailed status of thrombosis, including VTE, in Japan, a multicenter retrospective cohort study was conducted to investigate the incidence and clinical features of VTE among hospitalized COVID-19 patients who underwent contrast-enhanced computed tomography (CECT) during hospitalization at 22 centers in Japan between March 2020 and October 2020. This study demonstrated that among 1236 COVID-19 patients,

only 45 (3.6%) underwent CECT for evaluation; moreover, VTE events occurred in 10 patients (22.2%), and the incidence rates of VTE in mild, moderate, and severe COVID-19 patients were 0%, 11.8%, and 40.0%, respectively⁵². The study suggested that patients with least severe COVID-19, such as those who do not require oxygen, were at a lower risk of VTE among non-ICU hospitalized patients in Japan. On the other hand, considering the high risk for VTE among patients with severe COVID-19, clinicians might have to conduct an appropriate imaging examination on these patients when they are suspected to have VTE during the course of COVID-19 treatment to avoid under-diagnosis of VTE.

Recently, a large-scale observational study evaluating the detailed status of patients in the fourth and fifth waves of the COVID-19 in Japan, the CLOT-COVID Study, was conducted, which enrolled 2894 consecutive hospitalized patients with COVID-19 from 16 centers from April 2021 to September 2021⁵³. The primary report from the CLOT-COVID-19 study indicated that 55 patients (1.9%) developed thrombosis during hospitalization, mostly VTE (71%), and the incidence of thrombosis increased according to the COVID-19 severity in 0.2% with mild COVID-19, 1.4% with moderate COVID-19, and 9.5% with severe COVID-19.

Anticoagulation Strategies in Japan

The CLOT-COVID-19 study also investigated the real-world anticoagulation strategies for COVID-19 patients in Japan, which demonstrated that 43% of hospitalized patients with COVID-19 underwent pharmacological thromboprophylaxis, and the proportion of pharmacological thromboprophylaxis increased according to COVID-19 severity in 9.8% with mild COVID-19, 61% with moderate COVID-19, and 97% with severe COVID-19; moreover, the types and doses of anticoagulants widely varied across the participating centers⁵³. Pharmacological thromboprophylaxis, using anticoagulants at therapeutic doses, was reported to be selectively implemented in COVID-19 patients with comorbidities and severe COVID-19 status at admission⁵⁴. The proportion of hospitalized patients with COVID-19 who underwent pharmacological thromboprophylaxis was substantially higher in this study than in the previous ones from the first and second waves of COVID-19 in Japan^{55, 56}. However, not all hospitalized patients with COVID-19 underwent pharmacological thromboprophylaxis, as recommended by latest international guidelines. Furthermore, the widely varying types and doses of

anticoagulants across the participating centers indicated that the management strategies might have been based on individual decisions and the distinct resource availability at each institution.

Another important issue is that LMWH is recommended as a preferable anticoagulant for COVID-19-related thrombosis in the latest international guidelines. However, LMWH is not covered by Japanese national insurance, except for specific conditions such as primary prevention of VTE after surgery, and UFH is commonly used in Japan. Considering the status of COVID-19-related thrombosis and some domestic issues in Japan, the optimal anticoagulation strategies for COVID-19 might have to be based on Japanese domestic clinical data considering racial difference.

Clinical Evidences of Thrombosis and Anticoagulation Strategies for COVID-19 in Japan

Recently, a number of clinical evidences of thrombosis and anticoagulation strategies for COVID-19 in Japan have been reported, which could be useful for clinicians when considering the optimal anticoagulation strategies for individual patient.

Old age was reported to be a risk factor of mortality but not necessarily of thrombosis and major bleeding⁵⁷. As for sex, men were reported to have more severe COVID-19 status than women, and the risk of developing thrombosis was reported to be higher in men than in women⁵⁸. A previous study demonstrated that obesity was not significantly associated with the development of thrombosis during hospitalization; however, it was associated with COVID-19 severity⁵⁹. As a biomarker, higher D-dimer levels at admission were reported to be associated with a higher risk of VTE events during hospitalization⁶⁰.

Other clinical outcomes aside from thrombosis could also be important when considering anticoagulation therapy. A previous study showed that the incidence of major bleeding was not uncommon, especially in patients with severe COVID-19, and independent risk factors for major bleeding included history of major bleeding, COVID-19 severity, and anticoagulant use, which could be associated with poor clinical outcomes, including higher mortality⁶¹. Another previous study reported several independent risk factors for mortality in hospitalized patients with COVID-19, such as age >70 years, high D-dimer values on admission, heart disease, active cancer, higher COVID-19 severity on admission, and development of major bleeding during hospitalization, which could facilitate appropriate risk stratification of COVID-19 patients⁶².

The optimal intensity of anticoagulation therapy for COVID-19 according to its severity might also be a big issue in Japan, although it has been investigated in a number of previous clinical trials, mainly in the Caucasian population. As for the anticoagulation therapy for moderately ill patients with COVID-19, a previous study showed that approximately 20% of patients with moderate COVID-19 experienced worsened severity during hospitalization with which increased age, diabetes, D-dimer levels >1.0 µg/mL on admission, and the development of thrombosis during hospitalization were significantly associated⁶³. These results indicated that a more aggressive pharmacological thromboprophylaxis might be helpful for the prevention of worsening COVID-19 severity among high-risk patients. As for the therapeutic-dose anticoagulation for critically ill patients with COVID-19, another previous study reported that approximately half of critically ill patients with COVID-19 received therapeutic-dose anticoagulation, although it did not show a potential benefit compared with prophylactic-dose anticoagulation, which seemed to be consistent with the results of RCTs worldwide⁶⁴.

Potential Optimal Anticoagulation Strategies in Japan

Considering the different risks of COVID-19-related thrombosis between the Japanese and Western populations, Japanese clinicians need to determine whether the results obtained outside Japan and some recommendations by international guidelines could directly apply to Japanese clinical practice. Based on the latest evidences in Japan, the clinical guideline for thromboprophylaxis and anticoagulation strategies for COVID-19 has been published as a collaborative effort between the Japanese Society of Phlebology, Japanese Society of Pulmonary Embolism Research, Japanese Society of Vascular Surgery, Japanese College of Angiology, and Japanese Circulation Society. This guideline, unlike international guidelines, does not recommend anticoagulation therapy for all hospitalized patients with COVID-19 but recommends it for moderately ill patients requiring oxygen therapy or critically ill patients; moreover, considering the domestic issue in Japan, this guideline recommends anticoagulation therapy using a prophylactic dose of UFH (Fig. 1). Although these recommendations could be potentially useful when considering anticoagulation strategies, the final decision should be based on balancing the benefits and risks of anticoagulation therapy in individual patients.

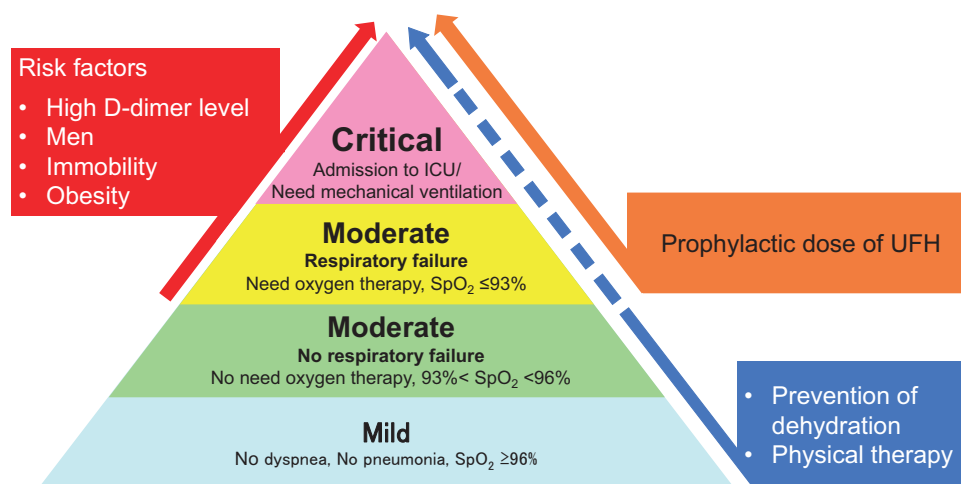


Fig. 1. Flow chart of the recommended anticoagulation strategies for COVID-19 in Japan

The original Japanese version was created by Dr. Nobutaka Ikeda and Dr. Hiroya Hayashi.

COVID-19, coronavirus disease 2019; ICU, intensive care unit; UFH, unfractionated heparin; SpO₂, saturation of percutaneous oxygen.

Conclusions

In the current overviews of the latest evidences of COVID-19-related thrombosis and anticoagulation strategies, including some domestic issues in Japan, there could be somewhat a different status of COVID-19-related thrombosis in Japan from that in Western countries, suggesting a potential benefit of different anticoagulation strategies, specifically for the Japanese population.

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Conflicts of Interest

All authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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