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A novel anticoagulation treatment protocol using unfractionated heparin for coronavirus disease 2019 patients in Japan, 2022

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Abstract: Hypercoagulability, which can be induced by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) plays an important role in the pathogenesis of coronavirus disease 2019 (COVID-19). Although anticoagulation therapy is expected to decrease the incidence of thrombosis and mortality in COVID-19 patients, the optimal use of anticoagulation therapy has not been established, especially using unfractionated heparin (UFH). Herein, we suggest a new anticoagulation treatment protocol for the use of UFH in Japanese COVID-19 patients. This protocol considers the safety regarding UFH usage, to lower major bleeding events, and reflects the latest evidence and the current situation regarding anticoagulation therapy in Japan.

***Keywords*:** SARS-CoV-2, hypercoagulability, thrombosis

Introduction

Systemic and microvascular thrombosis induced by hypercoagulability are important complications of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. At the beginning of the coronavirus disease 2019 (COVID-19) pandemic, several reports showed a high prevalence of venous thromboembolism (VTE) in COVID-19 patients (*1,2*). Although some reports have suggested the indication and efficacy of anticoagulation therapy to treat COVID-19 patients (*3,4*), the optimal use of anticoagulation therapy remains unclear. Regarding drug approval in Japan, we previously reported an anticoagulation protocol using unfractionated heparin (UFH) to treat moderate-to-severe COVID-19 patients in Japan in early 2020 (*5*). Here, we report an updated anticoagulation protocol for COVID-19 patients, which reflects the latest evidence and current situation of anticoagulation therapy for COVID-19 in Japan.

Latest worldwide evidence regarding anticoagulation therapy for COVID-19 treatment

A meta-analysis showed that the prevalence of VTE in COVID-19 patients is approximately 7–8 times higher than that for other respiratory infections, and the incidence of VTE is lowered by anticoagulation therapy (*6*). Moreover, several open-label randomized controlled trials evaluated the efficacy of anticoagulation therapy in reducing mortality of COVID-19 patients. Two trials, which enrolled COVID-19 patients with elevated d-dimer level and hypoxemia showed that therapeutic-dose anticoagulation could reduce all-cause mortality (*7,8*). The most comprehensive study was a multiplatform randomized controlled trial of anticoagulation therapy for COVID-19 patients, which was conducted mainly in Western countries and Brazil. It showed that therapeutic-dose anticoagulation, compared to the usual prophylactic-dose anticoagulation, decreased in-hospital mortalities and protracted organ support-free days in patients with moderate disease. This benefit was observed regardless of the baseline D-dimer level (*9*). This trial also showed that patients with severe COVID-19 who required organ support (including high-flow nasal cannula, noninvasive or invasive mechanical ventilation, extracorporeal life support, and vasopressors or inotropes) did not benefit from therapeutic-dose anticoagulation over the prophylactic dose (*10*). Instead, patients who received therapeutic-dose anticoagulation experienced more major bleeding events than did those who received prophylactic anticoagulation therapy (*9,10*).

Consequently, the National Institutes of Health (NIH) recommends therapeutic-doses of heparin for COVID-19 patients who require low-flow oxygen and prophylactic-doses of heparin for COVID-19 patients who require intensive care unit (ICU)-level care (including high-flow

oxygen) (*11*). These recommendations are based on the results of the aforementioned open-label randomized controlled trials (*7-10*). Meanwhile, the World Health Organization has recommended prophylactic-dose anticoagulation in all hospitalized COVID-19 patients, on the grounds of low certainty of evidence (*12*).

Anticoagulation treatment strategy for COVID-19 patients in Japan

Several important points must be considered when using the latest worldwide evidence to determine anticoagulation therapy protocols for COVID-19 patients in Japan. First, in the aforementioned multiplatform randomized controlled trial, the majority of patients received anticoagulation therapy with low-molecular-weight heparin (LMWH), while UFH use is preferred in Japan, where LMWH has not been approved for thrombotic diseases. A Japanese questionnaire-based survey showed that UFH was used in 67.6% of COVID-19 patients who received anticoagulation therapy, while LMWH was used in only 12.8% of patients (*13*).

UFH mainly inhibits thrombin and factor Xa, while LMWH inhibits factor Xa more specifically than UFH (*14*). Because the biological half-life of UFH is 45-60 minutes with usual intravenous doses, intravenous infusion is necessary to maintain the therapeutic range (*15*). Since the bioavailability of UFH is unstable, which is because UFH also binds endothelial cells, platelet factor 4, and platelets, frequent monitoring of the activated partial thromboplastin time (aPTT) is necessary (*14*). In contrast, the biological half-life of LMWH is 2 hours for intravenous infusion and 4 hours for subcutaneous infusion, and the bioavailability of LMWH is 90-100% after subcutaneous infusion. Therefore, the therapeutic range can be easily maintained with subcutaneous infusion of fixed dose LMWH. Dose adjustment of LMWH is necessary when creatinine clearance is less than 30mL/min, while UFH is not affected by renal function. LMWH is associated with a lower risk of heparin induced thrombocytopenia and bleeding complications compared to UFH (*15*). Additionally, a systematic review using the Cochrane database revealed that prophylactic-dose LMWH is more effective than UFH in reducing the risk of deep vein thrombosis in acutely ill medical patients, also exhibiting a lower bleeding risk (*16*). For these reasons, there is a concern that therapeutic-dose anticoagulation therapy with UFH may increase the incidence of major bleeding events compared with LMWH.

Second, whether ethnic differences affect the incidence of thrombosis in COVID-19 patients should be considered. The reported prevalence of thromboembolic events in COVID-19 patients in Japan is 1.9-2.9% among all hospitalized patients, and 7.5-13.5% among patients who require ICU-level care (*13,17*). A systematic review of the incidence of VTE in COVID-19 patients, which included 17 studies from Europe and the USA and three studies from China, showed that the pooled incidence of VTE was 21% among all hospitalized patients and 27% among ICU patients (*18*). Even though systematic screening of VTE was not routinely performed in Japanese studies, the prevalence of VTE in COVID-19 patients may possibly be lower in Japan than in Western countries. Indeed, induced endothelial dysfunction and hypercoagulability may differ generally according to ethnicity; however, a firm conclusion has not been attained due to insufficient data. Besides, Asian populations are considered to be more prone to bleeding complication due to anticoagulation therapy than other ethnicities. Although, the data for ethnic disparity of bleeding complications with UFH and LMWH is insufficient so far (*19*).

For these reasons, considering the therapeutic-dose of UFH for all COVID-19 patients requiring low-flow oxygen – based on the NIH recommendation – may not be reasonable in the Japanese population when considering the bleeding risk and expected benefit.

Suggestion for a new anticoagulation protocol, using UFH for COVID-19 treatment in Japan

We suggest a new anticoagulation protocol for COVID-19 treatment that reflects the latest evidence and considers the concerns regarding anticoagulation therapy for COVID-19 treatment in Japan (Figure 1). In this new anticoagulation protocol, we recommend a prophylactic-dose of UFH for patients who need oxygenation regardless of the method of administration (from nasal cannula to mechanical ventilation), unless there is a contraindication for UFH. If thrombosis is clinically suspected, we recommend diagnostic imaging before initiating therapeutic-dose UFH. If the diagnosis of thrombosis is confirmed or the imaging test is unavailable, but clinicians strongly suspect thrombosis, therapeutic-dose UFH should be initiated. To minimize the risk of bleeding, aPTT should be routinely monitored. Protamine can be administered for neutralizing UFH when excessive prolongation of aPTT or major bleeding events occur. Because of rapid drug clearance, the advantage of UFH for LMWH is flexibility of discontinuation when clinically indicated. Moreover, UFH can be neutralized by protamine more effectively than LMWH (*15*).

In conclusion, because the efficacy and safety of UFH for COVID-19 treatment is uncertain, we developed a new protocol for its safe usage and to reduce the risk of major bleeding events. A multiplatform randomized controlled trial showed that therapeutic-doses of LMWH lowers the mortality and number of organ support-free days in COVID-19 patients requiring low-flow oxygen. Although there are limited data of the usefulness of UFH use in Japanese patients with COVID-19, for example,

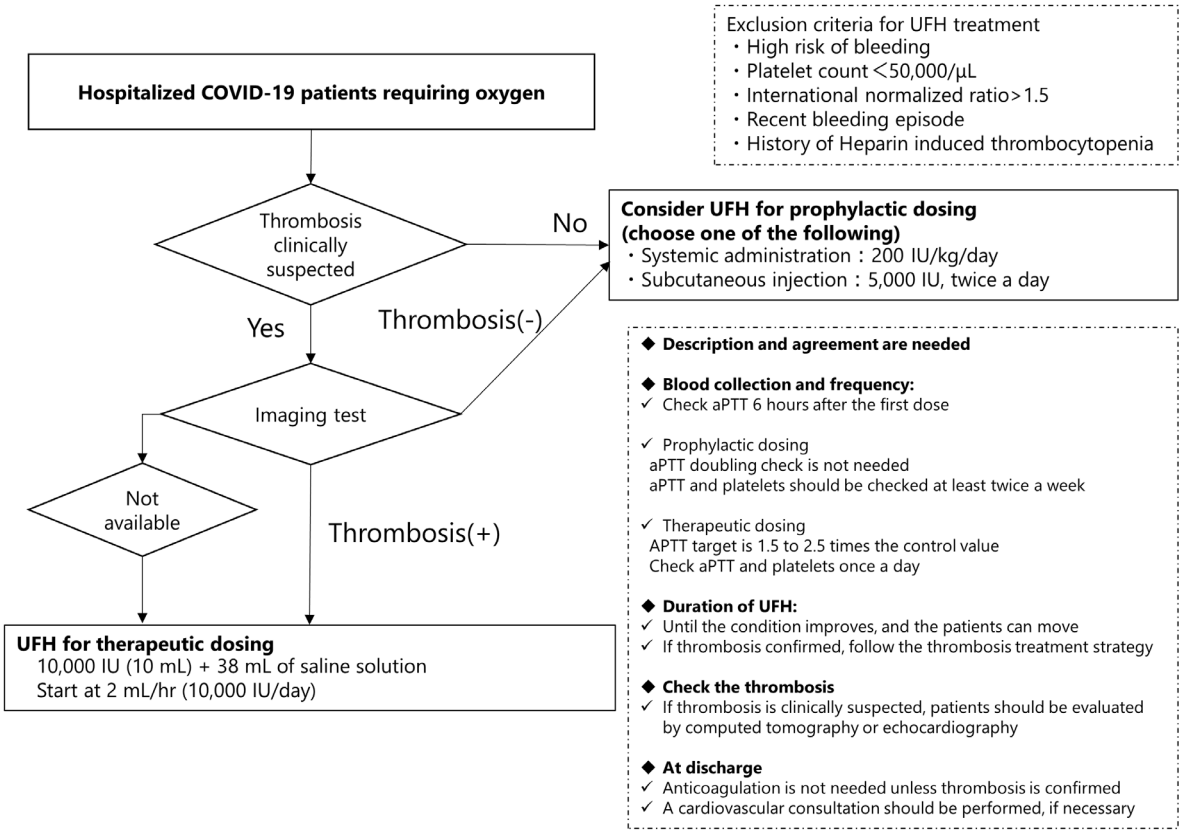

Figure 1. New anticoagulation protocol for the use of unfractionated heparin (UFH) in coronavirus disease 2019 (COVID-19) patients in Japan. This figure shows the new anticoagulation treatment protocol for the use of UFH in COVID-19 patients who require oxygen support.

in young patients without underlying diseases, the risk of bleeding is low, and therefore, UFH with a therapeutic dose may be acceptable. UFH may be considered for therapeutic doses if new studies clarify that UFH has a low risk of bleeding if used appropriately. Thus, it will be necessary to further investigate the usefulness of UFH use in Japanese patients with COVID-19 based on the latest evidence and the situation in Japan when new evidence emerges.

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

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