

# 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<sup>1, 2)</sup> and was finally declared a pandemic by the World Health Organization in March 2020<sup>3)</sup>. 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<sup>4, 5)</sup>. Coagulopathy in COVID-19 patients has been reported<sup>6)</sup>, which could lead to thromboembolic complications<sup>7-10)</sup>. 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 levels<sup>11</sup>.

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-2<sup>12-14</sup>), 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 protein<sup>15</sup>), and its expression on platelets was previously reported<sup>16</sup>.

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<sup>17, 18</sup>). 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<sup>19, 20</sup>). Through the disruption of vascular integrity and endothelial cell death, the thrombogenic basement membrane and activation of the clotting cascade could be induced<sup>21</sup>.

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<sup>22, 23</sup>). Several mechanisms through NET formation have been reported to cause coagulation in COVID-19 patients<sup>24</sup>), and the tissue factor expression in NETs and neutrophil-derived microparticles could directly activate the coagulation pathway<sup>25</sup>).

### 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)<sup>10</sup>). 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 protocols<sup>26</sup>).

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-19<sup>27-29</sup>), 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 patients<sup>30-32</sup>).

### 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 contraindicated<sup>33</sup>). 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 rivaroxaban<sup>34</sup>). Pharmacologically, LMWH might be a preferable anticoagulation therapy as it has not only anticoagulant effects but also putative pleiotropic anti-viral and anti-inflammatory properties<sup>35</sup>).

**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<sup>36, 37</sup>. 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-19<sup>38</sup>.

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-19<sup>33</sup>. 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 anticoagulants<sup>39</sup>. 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-19<sup>40</sup> but none among critically ill patients with COVID-19<sup>41</sup>. 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 patients<sup>42</sup>. 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 outcome<sup>43</sup>. 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 dosages<sup>34</sup>. 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<sup>31, 32, 38</sup>.

### 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 population<sup>44-46</sup>. 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 treatment<sup>47</sup>. 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 population<sup>47</sup>). 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 population<sup>48</sup>), 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 2020<sup>49</sup>). 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 hospitalization<sup>50</sup>). 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 patients<sup>51</sup>). 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%, respectively<sup>52</sup>). 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 2021<sup>53</sup>). 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 centers<sup>53</sup>). 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 admission<sup>54</sup>). 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<sup>55, 56</sup>). 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.

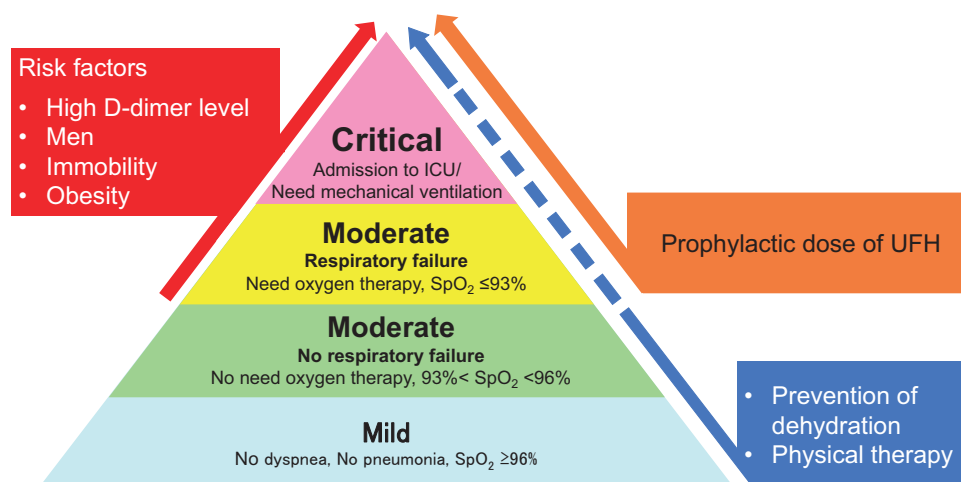
Old age was reported to be a risk factor of mortality but not necessarily of thrombosis and major bleeding<sup>57</sup>. As for sex, men were reported to have more severe COVID-19 status than women, and the risk of developing thrombosis was reported to be higher in men than in women<sup>58</sup>. A previous study demonstrated that obesity was not significantly associated with the development of thrombosis during hospitalization; however, it was associated with COVID-19 severity<sup>59</sup>. As a biomarker, higher D-dimer levels at admission were reported to be associated with a higher risk of VTE events during hospitalization<sup>60</sup>.

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 mortality<sup>61</sup>. 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 patients<sup>62</sup>.

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 associated<sup>63</sup>. 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 worldwide<sup>64</sup>.

### **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; SpO<sub>2</sub>, 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.

## References

- 1) Guan ;WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS and China Medical Treatment Expert Group for C. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med*, 2020; 382: 1708-1720
- 2) Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J and Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*, 2020; 395: 497-506
- 3) Cucinotta D and Vanelli M. WHO Declares COVID-19 a Pandemic. *Acta Biomed*, 2020; 91: 157-160
- 4) Clerkin KJ, Fried JA, Raikhelkar J, Sayer G, Griffin JM, Masoumi A, Jain SS, Burkhoff D, Kumaraiah D, Rabbani L, Schwartz A and Uriel N. COVID-19 and Cardiovascular Disease. *Circulation*, 2020; 141: 1648-1655
- 5) Driggin E, Madhavan MV, Bikdeli B, Chuich T, Laracy J, Biondi-Zoccai G, Brown TS, Der Nigoghossian C, Zidar DA, Haythe J, Brodie D, Beckman JA, Kirtane AJ, Stone GW, Krumholz HM and Parikh SA. Cardiovascular Considerations for Patients, Health Care Workers, and Health Systems During the COVID-19 Pandemic. *J Am Coll Cardiol*, 2020; 75: 2352-2371
- 6) Zhang Y, Xiao M, Zhang S, Xia P, Cao W, Jiang W, Chen H, Ding X, Zhao H, Zhang H, Wang C, Zhao J, Sun X, Tian R, Wu W, Wu D, Ma J, Chen Y, Zhang D, Xie J, Yan X, Zhou X, Liu Z, Wang J, Du B, Qin Y, Gao P, Qin X, Xu Y, Zhang W, Li T, Zhang F, Zhao Y, Li Y and Zhang S. Coagulopathy and Antiphospholipid Antibodies in Patients with Covid-19. *N Engl J Med*, 2020; 382: e38
- 7) Tang N, Li D, Wang X and Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost*, 2020; 18: 844-847
- 8) Cui S, Chen S, Li X, Liu S and Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. *J Thromb Haemost*, 2020; 18: 1421-1424

- 9) Klok FA, Kruip M, van der Meer NJM, Arbous MS, Gommers D, Kant KM, Kaptein FHJ, van Paassen J, Stals MAM, Huisman MV and Endeman H. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: An updated analysis. *Thromb Res*, 2020; 191: 148-150
- 10) Wichmann D, Sperhake JP, Lutgehetmann M, Steurer S, Edler C, Heinemann A, Heinrich F, Mushumba H, Kniep I, Schroder AS, Burdelski C, de Heer G, Nierhaus A, Frings D, Pfefferle S, Becker H, Brederke-Wiedling H, de Weerth A, Paschen HR, Sheikhzadeh-Eggers S, Stang A, Schmiedel S, Bokemeyer C, Addo MM, Aepfelbacher M, Puschel K and Kluge S. Autopsy Findings and Venous Thromboembolism in Patients With COVID-19: A Prospective Cohort Study. *Ann Intern Med*, 2020; 173: 268-277
- 11) Joly BS, Siguret V and Veyradier A. Understanding pathophysiology of hemostasis disorders in critically ill patients with COVID-19. *Intensive Care Med*, 2020; 46: 1603-1606
- 12) Zaid Y, Puhm F, Allaey I, Naya A, Oudghiri M, Khalki L, Limami Y, Zaid N, Sadki K, Ben El Haj R, Mahir W, Belayachi L, Belefquih B, Benouda A, Cheikh A, Langlois MA, Cherrah Y, Flamand L, Guessous F and Boilard E. Platelets Can Associate with SARS-CoV-2 RNA and Are Hyperactivated in COVID-19. *Circ Res*, 2020; 127: 1404-1418
- 13) Campbell RA, Boilard E and Rondina MT. Is there a role for the ACE2 receptor in SARS-CoV-2 interactions with platelets? *J Thromb Haemost*, 2021; 19: 46-50
- 14) Bury L, Camilloni B, Castronari R, Piselli E, Malvestiti M, Borghi M, KuchiBotla H, Falcinelli E, Petito E, Amato F, Paliani U, Vaudo G, Cerotto V, Gori F, Becattini C, De Robertis E, Lazzarini T, Castaldo G, Mencacci A and Gresele P. Search for SARS-CoV-2 RNA in platelets from COVID-19 patients. *Platelets*, 2021; 32: 284-287
- 15) Lan J, Ge J, Yu J, Shan S, Zhou H, Fan S, Zhang Q, Shi X, Wang Q, Zhang L and Wang X. Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor. *Nature*, 2020; 581: 215-220
- 16) Zhang S, Liu Y, Wang X, Yang L, Li H, Wang Y, Liu M, Zhao X, Xie Y, Yang Y, Zhang S, Fan Z, Dong J, Yuan Z, Ding Z, Zhang Y and Hu L. SARS-CoV-2 binds platelet ACE2 to enhance thrombosis in COVID-19. *J Hematol Oncol*, 2020; 13: 120
- 17) Pons S, Fodil S, Azoulay E and Zafrani L. The vascular endothelium: the cornerstone of organ dysfunction in severe SARS-CoV-2 infection. *Crit Care*, 2020; 24: 353
- 18) Levi M and Thachil J. Coronavirus Disease 2019 Coagulopathy: Disseminated Intravascular Coagulation and Thrombotic Microangiopathy-Either, Neither, or Both. *Semin Thromb Hemost*, 2020; 46: 781-784
- 19) Hoffmann M, Kleine-Weber H, Schroeder S, Kruger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, Muller MA, Drosten C and Pohlmann S. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell*, 2020; 181: 271-280 e8
- 20) Shaw RJ, Bradbury C, Abrams ST, Wang G and Toh CH. COVID-19 and immunothrombosis: emerging understanding and clinical management. *Br J Haematol*, 2021; 194: 518-529
- 21) Nachman RL and Rafii S. Platelets, petechiae, and preservation of the vascular wall. *N Engl J Med*, 2008; 359: 1261-1270
- 22) Martinod K and Wagner DD. Thrombosis: tangled up in NETs. *Blood*, 2014; 123: 2768-2776
- 23) Kapoor S, Opneja A and Nayak L. The role of neutrophils in thrombosis. *Thromb Res*, 2018; 170: 87-96
- 24) Busch MH, Timmermans S, Nagy M, Visser M, Huckriede J, Aendekerk JP, de Vries F, Potjewijd J, Jallah B, Yermans R, Oude Lashof AML, Breedveld PH, van de Poll MCG, van de Horst ICC, van Bussel BCT, Theunissen R, Spronk HHM, Damoiseaux J, Ten Cate H, Nicolaes GAF, Reutelingsperger CP and van Paassen P. Neutrophils and Contact Activation of Coagulation as Potential Drivers of COVID-19. *Circulation*, 2020; 142: 1787-1790
- 25) Fletcher-Sandersjoo A and Bellander BM. Is COVID-19 associated thrombosis caused by overactivation of the complement cascade? A literature review. *Thromb Res*, 2020; 194: 36-41
- 26) Kollias A, Kyriakoulis KG, Stergiou GS and Syrigos K. Heterogeneity in reporting venous thromboembolic phenotypes in COVID-19: methodological issues and clinical implications. *Br J Haematol*, 2020; 190: 529-532
- 27) Tang N, Bai H, Chen X, Gong J, Li D and Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost*, 2020; 18: 1094-1099
- 28) Paranjpe I, Fuster V, Lala A, Russak AJ, Glicksberg BS, Levin MA, Charney AW, Narula J, Fayad ZA, Bagiella E, Zhao S and Nadkarni GN. Association of Treatment Dose Anticoagulation With In-Hospital Survival Among Hospitalized Patients With COVID-19. *J Am Coll Cardiol*, 2020; 76: 122-124
- 29) Rentsch CT, Beckman JA, Tomlinson L, Gellad WF, Alcorn C, Kidwai-Khan F, Skanderson M, Brittain E, King JT, Jr., Ho YL, Eden S, Kundu S, Lann MF, Greevy RA, Jr., Ho PM, Heidenreich PA, Jacobson DA, Douglas IJ, Tate JP, Evans SJW, Atkins D, Justice AC and Freiberg MS. Early initiation of prophylactic anticoagulation for prevention of coronavirus disease 2019 mortality in patients admitted to hospital in the United States: cohort study. *BMJ*, 2021; 372: n311
- 30) Cuker A, Tseng EK, Nieuwlaat R, Angchaisuksiri P, Blair C, Dane K, Davila J, DeSancho MT, Diuguid D, Griffin DO, Kahn SR, Klok FA, Lee AI, Neumann I, Pai A, Pai M, Righini M, Sanfilippo KM, Siegal D, Skara M, Touri K, Akl EA, Bou Akl I, Boulos M, Brignardello-Petersen R, Charide R, Chan M, Dearness K, Darzi AJ, Kolb P, Colunga-Lozano LE, Mansour R, Morgano GP, Morsi RZ, Noori A, Piggott T, Qiu Y, Roldan Y, Schunemann F, Stevens A, Solo K, Ventresca M, Wiercioch W, Mustafa RA and Schunemann HJ. American Society of Hematology 2021 guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19. *Blood Adv*, 2021; 5: 872-888
- 31) Schulman S, Sholzberg M, Spyropoulos AC, Zarychanski R, Resnick HE, Bradbury CA, Broxmeyer L, Connors JM, Falanga A, Iba T, Kaatz S, Levy JH, Middeldorp S,

- Minichiello T, Ramacciotti E, Samama CM, Thachil J, International Society on T and Haemostasis. ISTH guidelines for antithrombotic treatment in COVID-19. *J Thromb Haemost*, 2022; 20: 2214-2225
- 32) Moores LK, Tritschler T, Brosnahan S, Carrier M, Collen JF, Doerschug K, Holley AB, Iaccarino J, Jimenez D, LeGal G, Rali P and Wells P. Thromboprophylaxis in Patients With COVID-19: A Brief Update to the CHEST Guideline and Expert Panel Report. *Chest*, 2022; 162: 213-225
- 33) Kyriakoulis KG, Kollias A, Kyriakoulis IG, Kyprianou IA, Papachrysostomou C, Makaronis P, Kotronias RA, Terentes-Printzios D, Toskas I and Mikhailidis DP. Thromboprophylaxis in Patients with COVID-19: Systematic Review of National and International Clinical Guidance Reports. *Curr Vasc Pharmacol*, 2022; 20: 96-110
- 34) Lopes RD, de Barros ESPGM, Furtado RHM, Macedo AVS, Bronhara B, Damiani LP, Barbosa LM, de Aveiro Morata J, Ramacciotti E, de Aquino Martins P, de Oliveira AL, Nunes VS, Ritt LEF, Rocha AT, Tramujas L, Santos SV, Diaz DRA, Viana LS, Melro LMG, de Alcantara Chaud MS, Figueiredo EL, Neuenschwander FC, Dracoulakis MDA, Lima R, de Souza Dantas VC, Fernandes ACS, Gebara OCE, Hernandez ME, Queiroz DAR, Veiga VC, Canesim MF, de Faria LM, Feitosa-Filho GS, Gazzana MB, Liporace IL, de Oliveira Twardowska A, Maia LN, Machado FR, de Matos Soeiro A, Conceicao-Souza GE, Armaganijan L, Guimaraes PO, Rosa RG, Azevedo LCP, Alexander JH, Avezum A, Cavalcanti AB, Berwanger O and Investigators ACC-BI. Therapeutic versus prophylactic anticoagulation for patients admitted to hospital with COVID-19 and elevated D-dimer concentration (ACTION): an open-label, multicentre, randomised, controlled trial. *Lancet*, 2021; 397: 2253-2263
- 35) Drago F, Gozzo L, Li L, Stella A and Cosmi B. Use of Enoxaparin to Counteract COVID-19 Infection and Reduce Thromboembolic Venous Complications: A Review of the Current Evidence. *Front Pharmacol*, 2020; 11: 579886
- 36) Task Force for the management of C-otESoC. ESC guidance for the diagnosis and management of cardiovascular disease during the COVID-19 pandemic: part 2-care pathways, treatment, and follow-up. *Eur Heart J*, 2022; 43: 1059-1103
- 37) Ortega-Paz L, Capodanno D, Montalescot G and Angiolillo DJ. Coronavirus Disease 2019-Associated Thrombosis and Coagulopathy: Review of the Pathophysiological Characteristics and Implications for Antithrombotic Management. *J Am Heart Assoc*, 2021; 10: e019650
- 38) Spyropoulos AC, Connors JM, Douketis JD, Goldin M, Hunt BJ, Kotila TR, Lopes RD, Schulman S, International Society on T and Haemostasis. Good practice statements for antithrombotic therapy in the management of COVID-19: Guidance from the SSC of the ISTH. *J Thromb Haemost*, 2022; 20: 2226-2236
- 39) Investigators I, Sadeghipour P, Talasaz AH, Rashidi F, Sharif-Kashani B, Beigmohammadi MT, Farrokhpour M, Sezavar SH, Payandemehr P, Dabbagh A, Moghadam KG, Jamalkhani S, Khalili H, Yadollahzadeh M, Riahi T, Rezaeifar P, Tahamtan O, Matin S, Abedini A, Lookzadeh S, Rahmani H, Zoghi E, Mohammadi K, Sadeghipour P, Abri H, Tabrizi S, Mousavian SM, Shahmirzaei S, Bakhshandeh H, Amin A, Rafiee F, Baghizadeh E, Mohebbi B, Parhizgar SE, Aliannejad R, Eslami V, Kashefzadeh A, Kakavand H, Hosseini SH, Shafaghi S, Ghazi SF, Najafi A, Jimenez D, Gupta A, Madhavan MV, Sethi SS, Parikh SA, Monreal M, Hadavand N, Hajighasemi A, Maleki M, Sadeghian S, Piazza G, Kirtane AJ, Van Tassel BW, Dobesh PP, Stone GW, Lip GYH, Krumholz HM, Goldhaber SZ and Bikdeli B. Effect of Intermediate-Dose vs Standard-Dose Prophylactic Anticoagulation on Thrombotic Events, Extracorporeal Membrane Oxygenation Treatment, or Mortality Among Patients With COVID-19 Admitted to the Intensive Care Unit: The INSPIRATION Randomized Clinical Trial. *JAMA*, 2021; 325: 1620-1630
- 40) Investigators A, Investigators AC-a, Investigators R-C, Lawler PR, Goligher EC, Berger JS, Neal MD, McVerry BJ, Nicolau JC, Gong MN, Carrier M, Rosenson RS, Reynolds HR, Turgeon AF, Escobedo J, Huang DT, Bradbury CA, Houston BL, Kornblith LZ, Kumar A, Kahn SR, Cushman M, McQuilten Z, Slutsky AS, Kim KS, Gordon AC, Kirwan BA, Brooks MM, Higgins AM, Lewis RJ, Lorenzi E, Berry SM, Berry LR, Adair AW, Al-Beidh F, Annane D, Arabi YM, Aryal D, Baumann Kreuziger L, Beane A, Bhimani Z, Bihari S, Billett HH, Bond L, Bonten M, Brunkhorst F, Buxton M, Buzgau A, Castellucci LA, Chekuri S, Chen JT, Cheng AC, Chkhikvadze T, Coiffard B, Costantini TW, de Brouwer S, Derde LPG, Detry MA, Duggal A, Dzavik V, Effron MB, Estcourt LJ, Everett BM, Fergusson DA, Fitzgerald M, Fowler RA, Galanaud JP, Galen BT, Gandotra S, Garcia-Madrona S, Girard TD, Godoy LC, Goodman AL, Goossens H, Green C, Greenstein YY, Gross PL, Hamburg NM, Haniffa R, Hanna G, Hanna N, Hegde SM, Hendrickson CM, Hite RD, Hindenburg AA, Hope AA, Horowitz JM, Horvat CM, Hudock K, Hunt BJ, Husain M, Hyzy RC, Iyer VN, Jacobson JR, Jayakumar D, Keller NM, Khan A, Kim Y, Kindzelski AL, King AJ, Knudson MM, Kornblith AE, Krishnan V, Kutcher ME, Laffan MA, Lamontagne F, Le Gal G, Leeper CM, Leifer ES, Lim G, Lima FG, Linstrum K, Litton E, Lopez-Sendon J, Lopez-Sendon Moreno JL, Lother SA, Malhotra S, Marcos M, Saud Marinez A, Marshall JC, Marten N, Matthay MA, McAuley DF, McDonald EG, McGlothlin A, McGuinness SP, Middeldorp S, Montgomery SK, Moore SC, Morillo Guerrero R, Mouncey PR, Murthy S, Nair GB, Nair R, Nichol AD, Nunez-Garcia B, Pandey A, Park PK, Parke RL, Parker JC, Parnia S, Paul JD, Perez Gonzalez YS, Pompilio M, Prekker ME, Quigley JG, Rost NS, Rowan K, Santos FO, Santos M, Olombrada Santos M, Satterwhite L, Saunders CT, Schutzgens REG, Seymour CW, Siegal DM, Silva DG, Jr., Shankar-Hari M, Sheehan JP, Singhal AB, Solvason D, Stanworth SJ, Tritschler T, Turner AM, van Bentum-Puijk W, van de Veerdonk FL, van Diepen S, Vazquez-Grande G, Wahid L, Wareham V, Wells BJ, Widmer RJ, Wilson JG, Yuriditsky E, Zampieri FG, Angus DC, McArthur CJ, Webb SA, Farkouh ME,



- Hochman JS and Zarychanski R. Therapeutic Anticoagulation with Heparin in Noncritically Ill Patients with Covid-19. *N Engl J Med*, 2021; 385: 790-802
- 41) Investigators R-C, Investigators AC-a, Investigators A, Goligher EC, Bradbury CA, McVerry BJ, Lawler PR, Berger JS, Gong MN, Carrier M, Reynolds HR, Kumar A, Turgeon AF, Kornblith LZ, Kahn SR, Marshall JC, Kim KS, Houston BL, Derde LPG, Cushman M, Tritschler T, Angus DC, Godoy LC, McQuilten Z, Kirwan BA, Farkouh ME, Brooks MM, Lewis RJ, Berry LR, Lorenzi E, Gordon AC, Ahuja T, Al-Beidh F, Annane D, Arabi YM, Aryal D, Baumann Kreuziger L, Beane A, Bhimani Z, Bihari S, Billett HH, Bond L, Bonten M, Brunkhorst F, Buxton M, Buzgau A, Castellucci LA, Chekuri S, Chen JT, Cheng AC, Chkhikvadze T, Coiffard B, Contreras A, Costantini TW, de Brouwer S, Detry MA, Duggal A, Dzavik V, Effron MB, Eng HF, Escobedo J, Estcourt LJ, Everett BM, Fergusson DA, Fitzgerald M, Fowler RA, Froess JD, Fu Z, Galanaud JP, Galen BT, Gandotra S, Girard TD, Goodman AL, Goossens H, Green C, Greenstein YY, Gross PL, Haniffa R, Hegde SM, Hendrickson CM, Higgins AM, Hindenburg AA, Hope AA, Horowitz JM, Horvat CM, Huang DT, Hudock K, Hunt BJ, Husain M, Hyzy RC, Jacobson JR, Jayakumar D, Keller NM, Khan A, Kim Y, Kindzelski A, King AJ, Knudson MM, Kornblith AE, Kutcher ME, Laffan MA, Lamontagne F, Le Gal G, Leeper CM, Leifer ES, Lim G, Gallego Lima F, Linstrum K, Litton E, Lopez-Sendon J, Lother SA, Marten N, Saud Marinez A, Martinez M, Mateos Garcia E, Mavromichalis S, McAuley DF, McDonald EG, McGlothlin A, McGuinness SP, Middeldorp S, Montgomery SK, Mouncey PR, Murthy S, Nair GB, Nair R, Nichol AD, Nicolau JC, Nunez-Garcia B, Park JJ, Park PK, Parke RL, Parker JC, Parnia S, Paul JD, Pompilio M, Quigley JG, Rosenson RS, Rost NS, Rowan K, Santos FO, Santos M, Santos MO, Satterwhite L, Saunders CT, Schreiber J, Schutgens REG, Seymour CW, Siegal DM, Silva DG, Jr., Singhal AB, Slutsky AS, Solvason D, Stanworth SJ, Turner AM, van Bentum-Puijk W, van de Veerdonk FL, van Diepen S, Vazquez-Grande G, Wahid L, Wareham V, Widmer RJ, Wilson JG, Yuriditsky E, Zhong Y, Berry SM, McArthur CJ, Neal MD, Hochman JS, Webb SA and Zarychanski R. Therapeutic Anticoagulation with Heparin in Critically Ill Patients with Covid-19. *N Engl J Med*, 2021; 385: 777-789
  - 42) Spyropoulos AC, Goldin M, Giannis D, Diab W, Wang J, Khanijo S, Mignatti A, Gianos E, Cohen M, Sharifova G, Lund JM, Tafur A, Lewis PA, Cohoon KP, Rahman H, Sison CP, Lesser ML, Ochani K, Agrawal N, Hsia J, Anderson VE, Bonaca M, Halperin JL, Weitz JI and Investigators H-C. Efficacy and Safety of Therapeutic-Dose Heparin vs Standard Prophylactic or Intermediate-Dose Heparins for Thromboprophylaxis in High-risk Hospitalized Patients With COVID-19: The HEP-COVID Randomized Clinical Trial. *JAMA Intern Med*, 2021; 181: 1612-1620
  - 43) Sholzberg M, Tang GH, Rahhal H, AlHamzah M, Kreuziger LB, Ainle FN, Alomran F, Alayed K, Alsheef M, AlSumait F, Pompilio CE, Sperlich C, Tangri S, Tang T, Jaksa P, Suryanarayan D, Almarshoodi M, Castellucci LA, James PD, Lillcrap D, Carrier M, Beckett A, Colovos C, Jayakar J, Arsenault MP, Wu C, Doyon K, Andreou ER, Dounaevskaia V, Tseng EK, Lim G, Fralick M, Middeldorp S, Lee AYY, Zuo F, da Costa BR, Thorpe KE, Negri EM, Cushman M, Juni P and investigators Rt. Effectiveness of therapeutic heparin versus prophylactic heparin on death, mechanical ventilation, or intensive care unit admission in moderately ill patients with covid-19 admitted to hospital: RAPID randomised clinical trial. *BMJ*, 2021; 375: n2400
  - 44) Liao S, Woulfe T, Hyder S, Merriman E, Simpson D and Chunilal S. Incidence of venous thromboembolism in different ethnic groups: a regional direct comparison study. *J Thromb Haemost*, 2014; 12: 214-219
  - 45) White RH, Zhou H, Murin S and Harvey D. Effect of ethnicity and gender on the incidence of venous thromboembolism in a diverse population in California in 1996. *Thromb Haemost*, 2005; 93: 298-305
  - 46) Stein PD, Kayali F, Olson RE and Milford CE. Pulmonary thromboembolism in Asians/Pacific Islanders in the United States: analysis of data from the National Hospital Discharge Survey and the United States Bureau of the Census. *Am J Med*, 2004; 116: 435-442
  - 47) Kim HK, Tantry US, Smith SC, Jr., Jeong MH, Park SJ, Kim MH, Lim DS, Shin ES, Park DW, Huo Y, Chen SL, Bo Z, Goto S, Kimura T, Yasuda S, Chen WJ, Chan M, Aradi D, Geisler T, Gorog DA, Sibbing D, Lip GYH, Angiolillo DJ, Gurbel PA and Jeong YH. The East Asian Paradox: An Updated Position Statement on the Challenges to the Current Antithrombotic Strategy in Patients with Cardiovascular Disease. *Thromb Haemost*, 2021; 121: 422-432
  - 48) Chiang CE, Wang KL and Lip GY. Stroke prevention in atrial fibrillation: an Asian perspective. *Thromb Haemost*, 2014; 111: 789-797
  - 49) Literature Commentary. *J Neuroophthalmol*, 2021; 41: 553-559
  - 50) Yamashita Y, Hara N, Obana M, Ikeda S, Furuichi M, Ishiguro S, Iwai T, Kobayashi T, Mo M and Yamada N. Clinical Features of Venous Thromboembolism in Patients With Coronavirus Disease 2019 (COVID-19) in Japan - A Case Series Study. *Circ J*, 2021; 85: 309-313
  - 51) Horiuchi H, Morishita E, Urano T, Yokoyama K and Questionnaire-survey Joint Team on the C-rt. COVID-19-Related Thrombosis in Japan: Final Report of a Questionnaire-Based Survey in 2020. *J Atheroscler Thromb*, 2021; 28: 406-416
  - 52) Yamashita Y, Maruyama Y, Satokawa H, Nishimoto Y, Tsujino I, Sakashita H, Nakata H, Okuno Y, Ogihara Y, Yachi S, Toya N, Shingaki M, Ikeda S, Yamamoto N, Aikawa S, Ikeda N, Hayashi H, Ishiguro S, Iwata E, Umetsu M, Kondo A, Iwai T, Kobayashi T, Mo M, Yamada N, Taskforce of VTE and Study C-ij. Incidence and Clinical Features of Venous Thromboembolism in Hospitalized Patients With Coronavirus Disease 2019 (COVID-19) in Japan. *Circ J*, 2021; 85: 2208-2214
  - 53) Nishimoto Y, Yachi S, Takeyama M, Tsujino I, Nakamura J, Yamamoto N, Nakata H, Ikeda S, Umetsu M, Aikawa S, Hayashi H, Satokawa H, Okuno Y, Iwata E, Ogihara Y, Ikeda N, Kondo A, Iwai T, Yamada N, Ogawa T, Kobayashi T, Mo M, Yamashita Y and Investigators C-CS.

- The current status of thrombosis and anticoagulation therapy in patients with COVID-19 in Japan: From the CLOT-COVID study. *J Cardiol*, 2022; 80: 285-291
- 54) Hayashi H, Izumiya Y, Fukuda D, Wakita F, Mizobata Y, Fujii H, Yachi S, Takeyama M, Nishimoto Y, Tsujino I, Nakamura J, Yamamoto N, Nakata H, Ikeda S, Umetsu M, Aikawa S, Satokawa H, Okuno Y, Iwata E, Ogihara Y, Ikeda N, Kondo A, Iwai T, Yamada N, Ogawa T, Kobayashi T, Mo M, Yamashita Y and Investigators C-CS. Real-World Management of Pharmacological Thromboprophylactic Strategies for COVID-19 Patients in Japan: From the CLOT-COVID Study. *JACC Asia*, 2022; 2: 897-907
- 55) Fujiwara S, Nakajima M, Kaszynski RH, Fukushima K, Tanaka M, Yajima K, Kobayashi T, Sekiya N, Yamamoto Y, Miwa M, Ishihata A, Yamauchi Y, Yamamoto K, Goto H and Imamura A. Prevalence of thromboembolic events and status of prophylactic anticoagulant therapy in hospitalized patients with COVID-19 in Japan. *J Infect Chemother*, 2021; 27: 869-875
- 56) Oba S, Hosoya T, Amamiya M, Mitsumura T, Kawata D, Sasaki H, Kamiya M, Yamamoto A, Ando T, Shimada S, Shirai T, Okamoto T, Tateishi T, Endo A, Aiboshi J, Nosaka N, Yamanouchi H, Ugawa T, Nagaoka E, Oi K, Tao S, Maejima Y, Tanaka Y, Tanimoto K, Takeuchi H, Tohda S, Hirakawa A, Sasano T, Arai H, Otomo Y, Miyazaki Y and Yasuda S. Arterial and Venous Thrombosis Complicated in COVID-19: A Retrospective Single Center Analysis in Japan. *Front Cardiovasc Med*, 2021; 8: 767074
- 57) Yamashita Y, Yachi S, Takeyama M, Nishimoto Y, Tsujino I, Nakamura J, Yamamoto N, Nakata H, Ikeda S, Umetsu M, Aikawa S, Hayashi H, Satokawa H, Okuno Y, Iwata E, Ogihara Y, Ikeda N, Kondo A, Iwai T, Yamada N, Ogawa T, Kobayashi T, Mo M and Investigators C-CS. Significant Impact of Age on Mortality and Non-significant Impact of Age on Thrombosis and Major Bleeding in Patients with COVID-19: From the CLOT-COVID Study. *J Atheroscler Thromb*, 2022; in press. doi: <https://doi.org/10.5551/jat.63702>
- 58) Yamashita Y, Yachi S, Takeyama M, Nishimoto Y, Tsujino I, Nakamura J, Yamamoto N, Nakata H, Ikeda S, Umetsu M, Aikawa S, Hayashi H, Satokawa H, Okuno Y, Iwata E, Ogihara Y, Ikeda N, Kondo A, Iwai T, Yamada N, Ogawa T, Kobayashi T, Mo M and Investigators C-CS. Influence of sex on development of thrombosis in patients with COVID-19: From the CLOT-COVID study. *Thromb Res*, 2022; 213: 173-178
- 59) Ogihara Y, Yachi S, Takeyama M, Nishimoto Y, Tsujino I, Nakamura J, Yamamoto N, Nakata H, Ikeda S, Umetsu M, Aikawa S, Hayashi H, Satokawa H, Okuno Y, Iwata E, Ikeda N, Kondo A, Iwai T, Yamada N, Ogawa T, Kobayashi T, Mo M, Yamashita Y and Investigators C-CS. Influence of obesity on incidence of thrombosis and disease severity in patients with COVID-19: From the CLOT-COVID study. *J Cardiol*, 2023; 81: 105-110
- 60) Ikeda N, Yachi S, Takeyama M, Nishimoto Y, Tsujino I, Nakamura J, Yamamoto N, Nakata H, Ikeda S, Umetsu M, Aikawa S, Hayashi H, Satokawa H, Okuno Y, Iwata E, Ogihara Y, Kondo A, Iwai T, Yamada N, Ogawa T, Kobayashi T, Mo M, Yamashita Y and Investigators C-CS. D-Dimer Values and Venous Thromboembolism in Patients With COVID-19 in Japan - From the CLOT-COVID Study. *Circ Rep*, 2022; 4: 215-221
- 61) Nakamura J, Tsujino I, Yachi S, Takeyama M, Nishimoto Y, Konno S, Yamamoto N, Nakata H, Ikeda S, Umetsu M, Aikawa S, Hayashi H, Satokawa H, Okuno Y, Iwata E, Ogihara Y, Ikeda N, Kondo A, Iwai T, Yamada N, Ogawa T, Kobayashi T, Mo M, Yamashita Y and Investigators C-CS. Incidence, risk factors, and clinical impact of major bleeding in hospitalized patients with COVID-19: a sub-analysis of the CLOT-COVID Study. *Thromb J*, 2022; 20: 53
- 62) Takeyama M, Yachi S, Nishimoto Y, Tsujino I, Nakamura J, Yamamoto N, Nakata H, Ikeda S, Umetsu M, Aikawa S, Hayashi H, Satokawa H, Okuno Y, Iwata E, Ikeda N, Kondo A, Iwai T, Yamada N, Ogawa T, Kobayashi T, Mo M and Yamashita Y. Mortality-Associated Risk Factors in Hospitalized COVID-19 Patients in Japan: Findings of the CLOT-COVID Study. *J Epidemiol*, 2022
- 63) Ikeda S, Ueno Y, Maemura K, Yachi S, Takeyama M, Nishimoto Y, Tsujino I, Nakamura J, Yamamoto N, Nakata H, Umetsu M, Aikawa S, Hayashi H, Satokawa H, Okuno Y, Iwata E, Ogihara Y, Ikeda N, Kondo A, Iwai T, Yamada N, Ogawa T, Kobayashi T, Mo M, Yamashita Y and Investigators C-CS. Association Between the Development of Thrombosis and Worsening of Disease Severity in Patients With Moderate COVID-19 on Admission - From the CLOT-COVID Study. *Circ J*, 2022
- 64) Yamashita Y, Yachi S, Takeyama M, Nishimoto Y, Tsujino I, Nakamura J, Yamamoto N, Nakata H, Ikeda S, Umetsu M, Aikawa S, Hayashi H, Satokawa H, Okuno Y, Iwata E, Ogihara Y, Ikeda N, Kondo A, Iwai T, Yamada N, Ogawa T, Kobayashi T and Mo M. Therapeutic-Dose vs. Prophylactic-Dose Anticoagulation Therapy for Critically Ill Patients With COVID-19 in a Practice-Based Observational Study. *Circ J*, 2022; 86: 1137-1142