

Antithrombotic therapy in patients with COVID-19: indications, pharmacotherapy and controversy

David Wang,¹ Christopher Leo,² Liping Liu,^{3,4} Li Huang,⁵ Lisa Huang,⁶ Yun Lu⁷

To cite: Wang D, Leo C, Liu L, et al. Antithrombotic therapy in patients with COVID-19: indications, pharmacotherapy and controversy. *Stroke & Vascular Neurology* 2023;0. doi:10.1136/svn-2023-002321

Received 13 January 2023
Accepted 15 January 2023



© Author(s) (or their employer(s)) 2023. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

¹Department of Neurology, Petznick Stroke Center, Barrow Neurological Institute, Phoenix, Arizona, USA

²Department of Medicine/ Division of General Internal Medicine/Hospital Medicine, Duke University, Durham, North Carolina, USA

³Neurosurgical Intensive Care Unit (NICU), Beijing Tiantan Hospital, Capital Medical University, Beijing, China

⁴China National Clinical Research Center for Neurological Diseases, Beijing, China

⁵Doctors Medical Center, Modesto, California, USA

⁶Chesapeake Regional Medical Center, Chesapeake, Virginia, USA

⁷Hennepin Healthcare System and the University of Minnesota, Minneapolis, Minnesota, USA

Correspondence to

Dr David Wang;
david.wang@commonspirit.org

Hypercoagulability associated with COVID-19 infection increases risks for either venous or arterial thrombotic events (ATEs) or both.¹ For hospitalised patients with COVID-19, the incidence of venous thromboembolism (VTE) was 4.5%²; the rate among patients with critical illness was 27.9% as compared with those not critically ill (7.1%). The exact mechanism of COVID-19-related thrombotic events is unclear. However, it may partially be related to Virchow triad: alternation of blood flow (stasis), vascular endothelial injury by SARS-CoV-2 virus and alteration of the constituents of the blood including inherited or acquired hypercoagulable state. Therefore, it is a challenge to evaluate the thromboembolic risk, select an appropriate antithrombotic agent and decide on the doses and duration of therapy in these patients. Several international and American societies have published clinical guidelines that reviewed evaluation of coagulation abnormalities in patients with COVID-19.^{3–6} To balance the risk of bleeding and preventing or treating thromboembolic events, a simplified practical summarisation is needed.

STRATIFICATION OF THROMBOEMBOLIC RISK FOR PATIENTS WITH COVID-19 INFECTION

Both VTE and ATE such as myocardial infarction (MI) and ischaemic strokes (IS) have been reported in patients with COVID-19 infection. However, if they do not have significant hypoxia (less than 92%), they can be managed at home. These patients may improve within 5–7 days postinfection, and recover within 14 days. Their risk of developing a thromboembolism is relatively low. Further laboratory testing may not be necessary unless signs and symptoms of thromboembolic events are noticed.

Higher risks of thromboembolism have been observed in hospitalised patients with COVID-19 infection, especially among those on respiratory support including either CPAP,

BiPAP or mechanical ventilator. Such higher risks were also reported in the earlier phase of pandemic, mainly due to inadequate understanding of the pathogenesis of COVID-19 infection.

MONITORING OF COAGULATION PARAMETERS IN PATIENTS WITH COVID-19 INFECTION

Such monitoring will be based on the severity of COVID-19 infection. For outpatients, no routine coagulation testing is indicated unless they developed symptoms of thromboembolism. For inpatients, must-do tests should include complete blood count with platelet, prothrombin time and activated partial thromboplastin time (aPTT), fibrinogen and d-dimer on admission. Other inflammation markers including C reactive protein, ferritin, interleukin-6 may also be considered. Daily trends of these test results may be needed for patients with higher acuity. The essays for factor VIII, VWF antigen and antithrombin III, protein C and S may also be considered if thromboembolism is detected regardless of the severity of COVID-19 infection.

The Wells' criteria (table 1) have been widely used to evaluate the probability of VTE including deep vein thrombosis (DVT) and pulmonary embolism (PE).^{7,8} When the probability is low for PE or DVT, a low level of D-dimer (≤ 500 ng/mL) can rule out possible VTE events. A d-dimer level of ≥ 500 ng/mL may suggest the need for further imaging studies. Note: An 'age $\times 10$ ' cut-off should be safe for patients ≥ 50 years. For example, the cut-off for a 65-year-old person will be 650 ng/mL.⁹

Compressive ultrasonography is indicated for suspected DVT in symptomatic extremities, especially when the d-dimer is higher than the cut-off line. In patients with suspected PE, CT angiography (CTA) of pulmonary arteries are indicated. A ventilation/perfusion scan if CTA cannot be done due to impaired renal function (GFR <30), or CTA shows an

Table 1 Wells' score and criteria for DVT and PE

Wells' score for DVT	
Clinical characteristics	Score
Active cancer receiving cancer treatment within the past 6 months or currently under palliative care	1
Paralysis, paresis or recent cast immobilisation of the lower extremities	1
Recently bedridden for >3 days, or major surgery within the past 3 months	1
Localised tenderness along the distribution of deep venous systems	1
Entire leg swelling	1
Calf swelling at 3 cm larger than that on the asymptomatic side (measure 10 cm below tibial tuberosity)	1
Pitting oedema confined to the symptomatic leg	1
Collateral superficial veins	1
Previously diagnosed DVT	1
Alternative diagnosis at least as likely as DVT	-2
Wells scoring system for DVT: -2 to 0: low probability; 1-2 points: Moderate probability; 3-8 points: high probability.	
Wells' score for PE	
Criteria	Points
Clinical signs of symptoms of VTE	3
No alternative diagnosis	3
Heart rate >100 beat/min	1.5
Immobilisation >3 days or surgery in past 4 weeks	1.5
Previous history of PE or VTE	1.5
Haemoptysis	1
Malignancy with active treatment in past 6 months or palliative care	1
Wells scoring system for PE: <2 points: low probability; 2-6 points: moderate probability; >6 points: high probability	
DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.	

indeterminate conclusion. The PE response team should be consulted if PE is confirmed.

When ATE is suspected, ECG, troponin level and coronary angiogram are indicated to evaluate for a possible MI. For IS, CT head without contrast can be performed first but microhemorrhages are often missed. Hence, MRI of the brain and MR angiography of head and neck without contrast should be considered as the first choice. Holter monitor is indicated if the infection has triggered atrial fibrillation.

PROPHYLAXIS AND TREATMENT OF THROMBOEMBOLISM IN PATIENTS WITH COVID-19

Outpatient setting

No routine thromboembolic prophylaxis is indicated according to the recommendations of all clinical guidelines.

Inpatient setting

Hospitalised patients have moderate to high risks of thromboembolic events. Prophylactic or therapeutic anticoagulants are thus recommended. Recommendations regarding the intensity of anticoagulation have been shifted over time due to less thromboembolic events

reported in the later phase of pandemic. Guidelines have also evolved.

Hospitalised non-ICU setting

Currently, therapeutic doses of anticoagulation are recommended for these patients who have developed thromboembolism. Prophylaxis dose of anticoagulation is appropriate for those hospitalised with an incidental positive COVID-19 test.

Hospitalised ICU setting

Therapeutic anticoagulation made no difference in clinical outcomes for patients in an intensive care unit (ICU). Therefore, prophylaxis dose is recommended across all the guidelines for ICU patients with COVID-19 infection. However, if a patient is already on the therapeutic doses of anticoagulation prior to admission, this regimen should continue unless contraindication is identified.

Postdischarge in an outpatient setting

One trial compared rivaroxaban 10 mg daily versus placebo for 35 days postdischarge and found a 67% relative risk reduction in their primary outcome without an increased risk of bleeding.¹⁰ However, a trial compared aspirin 81 mg daily versus apixaban 2.5 mg two times per day versus apixaban 5 mg two times per day versus placebo for 45 days and found no difference in the composite clinical outcome among four groups.¹¹ Thus extended postdischarge routine use of antiplatelet or anticoagulation therapy is not recommended unless patients are discharged with a diagnosis of VTE or ATE.

Choice of anticoagulation agent and monitoring

Low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH) are preferred unless there is a contraindication, such as severe thrombocytopenia (<50 × 100/L).

In hospitalised non-ICU COVID-19 patients without signs or symptoms of thrombosis, subcutaneous injection of LMWH such as enoxaparin 1 mg/kg two times per day to reach an antiXa level between 0.5 and 1 anti-factor Xa units/mL within 4-6 hours of starting LMWH. However, in morbidly obese patients with a body mass index ≥ 40 kg/m², or a weight ≥ 150 kg, or a severe renal insufficiency (creatinine clearance of ≤ 30 mL/min), IV UFH is preferred to reach an aPTT level of 2-3 times of the baseline. UFH molecules are distributed less to the adipose tissue than LMWH. Anticoagulation should continue for 3 months for provoked thromboembolism until clinical signs and symptoms of VTE or arterial embolism are resolved and no imaging findings of thrombus. Choices for outpatient anticoagulation include direct oral anticoagulants (DOACs) such as rivaroxaban, apixaban or dabigatran, and warfarin (international normalization of 2-3). DOACs can also be considered if drug-drug interaction of LMWH or UFH with dexamethasone and antiviral agents for treating COVID-19 is of concern.

Choice of antiplatelet agents

The usefulness of aspirin in preventing thromboembolism in patients with COVID-19 is controversial. One trial studied aspirin 150mg daily versus no aspirin and found that patients in the aspirin group had a slightly higher chance (75% vs 74%) to be discharged alive within 28 days, had less thrombotic events (4.6% vs 5.3%) but a higher chance of major bleeding events (1.6% vs 1.0%).¹² There are no data on the role of other antiplatelet agents for prophylaxis against thromboembolism in patients with COVID-19 infection.

COVID-19 INFECTION AND THROMBOEMBOLISM OF THE CENTRAL NERVOUS SYSTEM

COVID-19 infection may increase the risk of IS. The underlying causes include artery to artery emboli, cardiogenic emboli, microangiopathy due to disseminated intravascular coagulopathy and hypoxia. Early detection and timely treatment may help resolve or prevent a stroke.

When a patient's mental and neurological status cannot be adequately assessed, such as in those on life support, a screening brain imaging should be performed. Intravenous thrombolysis is controversial for patients with COVID-19 who have an acute IS due to possible higher percentage of symptomatic intracranial haemorrhage. Otherwise, antiplatelet medications are indicated for secondary stroke prevention.¹³

Cerebral venous sinus thrombosis (CVST) is a life-threatening condition that has been seen in patients with COVID-19 infection.^{14 15} When a COVID-19 patient has signs and symptoms related to the elevated intracranial pressure such as severe headache, visual disturbances and/or decrease level of consciousness, CT venography, MR venography or digital subtraction venography of the brain can help diagnosing a CVST. Although with no clear guidelines, therapeutic anticoagulation is indicated but with caution since brain parenchymal petechiae or haemorrhage or thrombocytopenia are often present with a COVID-19 infection. Close monitoring of coagulation profiles and routine use of CT of head or MRI may be indicated when anticoagulation therapy is in-progress. The duration of anticoagulation for CVST is inconclusive. Full anticoagulation may need to be continued until COVID-19 has been treated and there are no neuroimaging signs of CVST.

CONCLUSION

For outpatients with COVID-19 infection, no routine prophylactic anticoagulation is needed. Once they are hospitalised, therapeutic anticoagulation for non-ICU patients may shorten the days requiring organ support but with higher risk of bleeding. For ICU patients, prophylactic anticoagulation should be considered in those with

no VTE, not on anticoagulant prior to admission and no arterial thromboembolism. Postdischarge, these patients do not require extended antithrombotic therapy unless they have a confirmed diagnosis of VTE or ATEs.

Funding This study was funded by Chinese Stroke Association

Competing interests None declared.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; internally peer reviewed.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

REFERENCES

- Malas MB, Naazie IN, Elsayed N, *et al*. Thromboembolism risk of COVID-19 is high and associated with a higher risk of mortality: a systematic review and meta-analysis. *EClinicalMedicine* 2020;29:100639.
- Tong X, Yang Q, Asaithambi G, *et al*. Venous thromboembolism among medicare acute ischaemic stroke patients with and without COVID-19. *Stroke Vasc Neurol* 2022;svn-2022-001814.
- Schulman S, Sholzberg M, Spyropoulos AC. International society on thrombosis and haemostasis. ISTH guidelines for antithrombotic treatment in COVID-19. *J Thromb Haemost* 2022;22:14–25.
- Cuker A, Tseng EK, Nieuwlaar R, *et al*. American Society of hematology 2021 guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19. *Blood Adv* 2021;5:872–88.
- Cuker A, Tseng EK, Nieuwlaar R, *et al*. American society of hematology living guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19: january 2022 update on the use of therapeutic-intensity anticoagulation in acutely ill patients. *Blood Adv* 2022;6:4915–23.
- Barnes GD, Burnett A, Allen A, *et al*. Thromboembolic prevention and anticoagulant therapy during the COVID-19 pandemic: updated clinical guidance from the anticoagulation forum. *J Thromb Thrombolysis* 2022;54:197–210.
- Modi S, Deisler R, Gozel K, *et al*. Wells criteria for DVT is a reliable clinical tool to assess the risk of deep venous thrombosis in trauma patients. *World J Emerg Surg* 2016;11:24.
- Wolf SJ, McCubbin TR, Feldhaus KM, *et al*. Prospective validation of wells criteria in the evaluation of patients with suspected pulmonary embolism. *Ann Emerg Med* 2004;44:503–10.
- Righini M, Van Es J, Den Exter PL, *et al*. Age-Adjusted D-dimer cutoff levels to rule out pulmonary embolism: the ADJUST-PE study. *JAMA* 2014;311:1117–24.
- Ramacciotti E, Barile Agati L, Calderaro D, *et al*. Rivaroxaban versus no anticoagulation for post-discharge thromboprophylaxis after hospitalisation for COVID-19 (MICHELLE): an open-label, multicentre, randomised, controlled trial. *Lancet* 2022;399:50–9.
- Connors JM, Brooks MM, Sciruba FC, *et al*. Effect of antithrombotic therapy on clinical outcomes in outpatients with clinically stable symptomatic COVID-19: the ACTIV-4B randomized clinical trial. *JAMA* 2021;326:1703–12.
- RECOVERY Collaborative Group. Aspirin in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* 2022;399:143–51.
- Nannoni S, de Groot R, Bell S, *et al*. Stroke in COVID-19: a systematic review and meta-analysis. *Int J Stroke* 2021;16:137–49.
- Dakay K, Cooper J, Bloomfield J, *et al*. Cerebral venous sinus thrombosis in COVID-19 infection: a case series and review of the literature. *J Stroke Cerebrovasc Dis* 2021;30:105434.
- Ikenberg B, Demleitner AF, Thiele T, *et al*. Cerebral venous sinus thrombosis after chadox1 ncov-19 vaccination with a misleading first cerebral MRI scan. *Stroke Vasc Neurol* 2021;6:668–70.