Anticoagulation in COVID-19: current concepts and controversies

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- Though respiratory manifestations are the hallmark of the disease, an overwhelming amount of literature suggests that COVID-19, is associated with several coagulation abnormalities which may be responsible for thrombotic manifestations related to this disease such as venous thromboembolism (VTE) and PE.

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BRIEF REPORT

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Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia

Ning Tang[1] | Dengju Li[2] | Xiong Wang[1] | Ziyong Sun[1]

Table 2 Changes in various coagulation parameters following COVID-19 in a study by Yu *et al*

Coagulation parameter	Survivors n=162	Non-survivors n=21	Percentage difference
PT	13.6 s	15.5 s	13.97
aPTT	41.2 s	44.8 s	8.74
Fibrinogen	4.51 g/L	5.16 g/L	14.41
D-dimer	0.61 mcg/mL	2.12 mcg/mL	247.54
FDP	4 mcg/mL	7.6 mcg/mL	90.00
AT	91%	84%	−7.69

ANTICOAGULANT TYPES

- Anticoagulants have been the mainstay of prevention and treatment of thrombosis for decades.
  1)unfractionated heparin (UFH)
  2) low-molecular weight heparin (LMWH)
  3) vitamin K antagonists (warfarin)
  4) direct oral anticoagulants (DOACs)

- The preferential target of SARS-CoV-2 is respiratory epithelium where it mainly enters through the angiotensin-converting enzyme 2 (ACE2) receptor into host cells.

- Type-2 pneumocytes account for about 83% of the ACE2-expressing cells of the lung. It is also expressed in heart, vasculature, brain, gut and kidneys, which may be responsible for the pathogenesis of the extrapulmonary manifestations.

- Infection with SARS-CoV-2 causes downregulation of ACE2, thereby increasing the vulnerability to the damaging effects to angiotensin 2 (mainly by oxidative stress and inflammation).

- Exaggerated and dysregulated immune response, dysfunction of the ACE2 mediated pathways, endothelial damage with thromboinflammation and direct tissue damage by viral particles are the possible mechanisms of SARS-CoV-2 mediated extrapulmonary manifestations.

- The mechanisms of hypercoagulability in COVID-19 have yet to be fully elucidated. Characteristic hemostatic abnormalities including elevations in factor VIII, von Willebrand factor, fibrinogen andD-dimer concentration have been described.

- Endotheliopathy, due either to direct viral invasion or immune-mediated endothelial injury, may also play an important role.

Name	Identifier	Location	Type of study	Active comparator	Intervention/ treatment arm	Primary outcome
Anticoagulation in patients suffering from COVID-19 (the ANTI-CO Trial)	NCT04445935	Hamad Medical Corporation, Qatar, Doha	Triple-blinded RCT	Standard anticoagulation with LMWH/UFH	Intravenous bivalirudin according to the institutional HIT protocol.	P/F ratio (time frame: 3 days of intervention).
Anticoagulation in critically ill patients with COVID-19 (the IMPACT Trial)	NCT04406389	Weill Cornell Medicine New York, USA	Open-labelled RCT	Intermediate dose prophylaxis drug: enoxaparin, UFH, fondaparinux	Therapeutic dose anticoagulation drug: enoxaparin, UFH, fondaparinux, argatroban.	30-Day mortality.
Coagulopathy of COVID-19: a pragmatic RCT of therapeutic anticoagulation vs standard care	NCT04362085	St. Michael's Hospital, Toronto, Canada	Two arm, parallel, pragmatic, multicentre, open-label RCT	Standard Care LMWH, UFH fondaparinux at thromboprophylactic doses for acutely ill hospitalised medical patients	Therapeutic anticoagulation LMWH or UFH (high-dose nomogram) will be administered until discharged from hospital, 28 days or death.	ICU admission, non-invasive positive pressure ventilation, invasive mechanical ventilation, all-cause death (yes/no) up to 28 days.
FREEDOM COVID-19 anticoagulation strategy	NCT04512079	· Icahn School of Medicine at Mount Sinai New York, New York, USA	Prospective, multicentre, open label, randomised controlled comparative safety and effectiveness trial	1. Prophylactic enoxaparin. 2. Full-dose enoxaparin	Apixaban (5 mg every 12 hours; 2.5 mg every 12 hours for patients with at least two of three of age ≥80 years, weight ≤60 kg or serum creatinine ≥1.5 mg/dL).	Time to first events Number of in-hospita rate of BARC 3 or 5 (time frame for both: 30 days).

Current guidelines and recommendations on use of anticoagulation in COVID-19

Guideline	Consideration of therapeutic anticoagulation	Duration of therapeutic anticoagulation	Consideration of thrombolysis	Monitoring of patients receiving therapeutic anticoagulation	Termination of anticoagulation	Mechanical thromboprophylaxis
CDC[50]	Clinically suspected thromboembolic events or high suspicion despite of normal imaging findings.	No mention	Inconclusive data. In pregnancy with acute PE and haemodynamic instability, thrombolysis may be used	As per standard care in patients without COVID-19.	Active bleeding severe thrombocytopaenia.	No mention
ISTH-IG[51]	No recommendations	No mention	No mention	No mention	Active bleeding or platelets <25 × 109/L.	No mention
ACF[52]	Clinically suspected thromboembolic events or high suspicion despite of normal imaging findings.	3 Months course for patients initiated on anticoagulation during hospitalisation (except in recent bleeding or high bleeding risk).	STEMI, acute ischaemic stroke, or high-risk massive PE with haemodynamic instability.	Monitor anti-Xa levels in UFH. Monitor anti-Xa or PTT in patients with normal baseline PTT levels and no heparin resistance (> 35 000 u heparin over 24 hours).	Active bleeding or profound thrombocytopaenia	Intermittent pneumatic compression if contraindication to pharmacological thromboprophylaxis. Both mechanical and pharmacological thromboprophylaxis in critically ill patients if no contraindication.

Guideline	Consideration of therapeutic anticoagulation	Duration of therapeutic anticoagulation	Consideration of thrombolysis	Monitoring of patients receiving therapeutic anticoagulation	Termination of anticoagulation	Mechanical thromboprophylaxis
ASH[53]	Increasing the intensity of anticoagulation regimen or change anticoagulants in patients with recurrent thrombosis of catheters and extracorporeal circuits (ie, ECMO, CRRT) on prophylactic anticoagulation regimens.	No mention	No mention	Anti-Xa monitoring of UFH.	Active bleeding and platelet count < 25 × 109/L or fibrinogen <0.5 g/L. Therapeutic anticoagulation may need to be held if platelet count <30–50 × 109/L or fibrinogen <1.0 g/L.	Mechanical thromboprophylaxis when pharmacological thromboprophylaxis is contraindicated.
SCC-ISTH[54]	Therapeutic anticoagulation not to be considered for primary prevention. Increased intensity of anticoagulation regimen can be considered in patients without confirmed VTE or PE but have deteriorating pulmonary status or ARDS.	Minimum 3 months	No mention	No specific recommendations.	No specific recommendations.	Mechanical thromboprophylaxis if pharmacological therapy contraindicated.

Guideline	Consideration of therapeutic anticoagulation	Duration of therapeutic anticoagulation	Consideration of thrombolysis	Monitoring of patients receiving therapeutic anticoagulation	Termination of anticoagulation	Mechanical thromboprophylaxis
ACC[55]	Therapeutic anticoagulation in VTE. Haemodynamically stable patients with submassive PE.	No mention	Systemic fibrinolysis is indicated for haemodynamically high-risk PE.	No mention	Suspected or confirmed DIC without overt bleeding.	Mechanical thromboprophylaxis considered in immobilised patients if pharmacological prophylaxis is contraindicated.
ACCP[5]	PE or proximal DVT	Minimum 3 months	No mention	Anti-Xa levels in all patients receiving UFH given potential of heparin resistance.	No mention	Mechanical thromboprophylaxis in critically ill patients who have a contraindication to pharmacological thromboprophylaxis.

Table 2. Definitions of target populations

Target population	Definition
Critically ill	• Patients with COVID-19 who develop respiratory or cardiovascular failure normally requiring advanced clinical support in the ICU or CCU, but could include admission to another department if the ICU/CCU was over capacity • ICU/CCU capacity and admission criteria could vary according to the specific setting
Acutely ill	• Patients with COVID-19 who require hospital admission without advanced clinical support (ie, not to the ICU/CCU), but could include treatment in other settings if the hospital was over capacity • Hospital capacity and admission criteria could vary according to the specific setting

- The American Society of Hematology (ASH) guideline panel suggests using prophylactic-intensity over intermediate-intensity or therapeutic-intensity anticoagulation for patients with coronavirus disease 2019 (COVID-19)–related critical illness who do not have suspected or confirmed venous thromboembolism (VTE).

- The ASH guideline panel suggests using prophylactic-intensity over intermediate-intensity or therapeutic-intensity anticoagulation for patients with COVID-19–related acute illness who do not have suspected or confirmed VTE (conditional recommendation

All COVID-19 (+) patient ≥ 18 years of age admitted to the hospital ***should*** receive anticoagulant prophylaxis unless contraindicated

Critically Ill DVT Prophylaxis

High suspicion/risk for thrombosis

- Any evidence of thrombosis (including superficial veins)
- Worsening hypoxemia despite improving X-ray and good lung compliance
- D-dimer ≥ 5,000 ng/mL or rapidly ↑ D-dimer

NO → **High Dose Prophylaxis**

Enoxaparin 0.5 mg/kg SC BID (TBW)**

CrCl < 30 mL/min:
Enoxaparin 0.5 mg/kg SC once daily**
< 50 kg: Heparin 5,000 units SC every 8 hrs
≥ 50 kg: Heparin 7,500 units SC every 8 hrs

YES → **Indication for therapeutic anticoagulation**
(Including continuation of home therapy)

Enoxaparin 1 mg/kg SC BID (TBW) or **Heparin** 18 units/kg/hr IV (TBW) with standard boluses and titrations per protocol (max initial rate 2,000 units/hr)

Patients escalated to therapeutic anticoagulation based on D-dimer ≥ 5,000 ng/mL may resume "**High Dose Prophylaxis**" (see under Critically Ill) once D-dimer decreases to ≤ 2,000 ng/mL

DOACs and Warfarin
DO NOT USE for critically ill patients
May consider use in patients anticipating discharge

Non-Critically Ill DVT Prophylaxis

BMI < 40: Enoxaparin 40 mg SC once daily***
BMI ≥ 40: Enoxaparin 40 mg SC BID
BMI ≥ 50: Enoxaparin 60 mg SC BID

CrCl < 30 mL/min:
Enoxaparin 30 mg SC once daily**
Heparin 5,000 units SC every 8 hrs
≥ 100 kg: Heparin 7,500 units SC every 8 hrs

If D-dimer ≥ 2,000-3,000 ng/mL* consider Enoxaparin 40 mg SC BID or "**High Dose Prophylaxis**" (see under Critically Ill)

Avoid initiating DOACs for prophylaxis during hospitalization

Extended Thromboprophylaxis Up to 45 Days Post-Discharge
(Continued on next page)

- LMWH or UFH in hospitalized critically ill patients is preferred because of the shorter half-life and fewer drug-drug interactions compared with direct oral anticoagulants.
- LMWH or UFH remain the anticoagulants of choice in pregnancy.

- Regular warfarin users who are unable to get INR monitoring during isolation may be candidates for direct oral anticoagulant therapy, but patients with mechanical heart valves, ventricular assist devices, valvular atrial fibrillation, antiphospholipid antibody syndrome, or lactation should continue treatment with warfarin therapy.

Prophylactic*
Apixaban 2.5 mg, PO BID (with intent for VTE prophylaxis)
Bemiparin 3500 U, SC OD
Betrixaban 80 mg, PO OD
Betrixaban 160 mg, PO OD
Dabigatran 220 mg, PO OD
Dalteparin 5000 U, SC OD
Enoxaparin 30 mg (3000 U), SC OD (for GFR 15-30)
Enoxaparin 30 mg (3000 U), SC BID (for BMI $\geq$40 kg/m^2)
Enoxaparin 40 mg (4000 U), SC OD
Enoxaparin 40 mg (4000 U), SC BID (for BMI $\geq$40 kg/m^2)
Fondaparinux 2.5 mg, SC OD
Unfractionated heparin 5000 U, SC BID
Unfractionated heparin 5000 U, SC TID
Unfractionated heparin 7500 U, SC BID (for BMI $\geq$40 kg/m^2)
Nadroparin 2850 U, SC q24h (post-op general surgery)
Nadroparin 5700 U, SC q24h (high-risk medical patients $>$70 kg)
Nadroparin 3800 U, SC q24h (high-risk medical patients $\leq$70 kg or post-op hip replacement surgery)
Rivaroxaban 10 mg, PO OD
Tinzaparin 3500 U, SC OD
Tinzaparin 4500 U, SC OD
Tinzaparin 75 U/kg, SC OD

Intermediate*
Enoxaparin 0.5 mg/kg (50 U/kg), SC BID (if CrCl >30 mL/min)
Enoxaparin 0.5 mg/kg (50 U/kg), SC OD (if CrCl <30 mL/min)
Enoxaparin 30 mg (3000 U), SC BID (for BMI <40 kg/m^2)
Enoxaparin 40 mg (4000 U), SC BID (for CrCl >30 mL/min and BMI <40 kg/m^2)
Enoxaparin 60 mg (6000 U), SC BID (for CrCl >30 mL/min and BMI >40 kg/m^2)
Unfractionated heparin 7500 U, SC TID
Dalteparin 5000 U, SC BID
Therapeutic*
Acenocoumarol, PO (target INR 2.0-3.0 or greater)
Apixaban 5 mg, PO BID
Apixaban 10 mg, PO BID
Argatroban, IV to target aPTT therapeutic range as per institutional guidelines
Bemiparin 5000 U, SC OD (if weight ≤50 kg and CrCl >30 mL/min)
Bemiparin 7500 U, SC OD (if weight 50-70 kg and CrCl >30 mL/min)
Bemiparin 10000 U, SC OD (if weight 70-100 kg and CrCl >30 mL/min)
Bemiparin 115 U/kg, SC OD (if weight >100 kg and CrCl >30 mL/min)
Bivalirudin, IV to target aPTT therapeutic range as per institutional guidelines
Dabigatran 75 mg, PO BID (if CrCl 15-30 mL/min)
Dabigatran 110 mg, PO BID (AF: age ≥80 y, or >75 y and 1 or more risk factors for bleeding)
Dabigatran 150 mg, PO BID (if CrCl >30 mL/min)
Dalteparin 100 U/kg, SC BID
Dalteparin 150 U/kg, SC OD
Dalteparin 200 U/kg, SC OD
Edoxaban 30 mg, PO OD (≤60 kg, CrCl 15-50 mL/min)

JAMA | Original Investigation

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

CONCLUSIONS AND RELEVANCE Among patients admitted to the ICU with COVID-19, intermediate-dose prophylactic anticoagulation, compared with standard-dose prophylactic anticoagulation, did not result in a significant difference in the primary outcome of a composite of adjudicated venous or arterial thrombosis, treatment with extracorporeal membrane oxygenation, or mortality within 30 days. These results do not support the routine empirical use of intermediate-dose prophylactic anticoagulation in unselected patients admitted to the ICU with COVID-19.

POST DISCHARGE PROPHYLAXIS IN COVID-19

- Postdischarge thromboprophylaxis following COVID-19 remains an issue of much debate.
- Routine administration of oral anticoagulants in all patients with COVID-19 at the time of discharge is not recommended.

- The CHEST consensus statement clearly refutes it due to lack of evidence.
- NIH guidelines, as well as ISTH guidelines, BTS guidelines and SIGN (Scottish guidelines) mention post discharge thromboprophylaxis, based on expert opinion.

- Decisions regarding postdischarge prophylactic anticoagulation should be individualised.
- The patients with moderate to severe disease and fulfilling any one of the following criteria(Modified IMPROVE VTE) would be the ideal candidates for postdischarge thromboprophylaxis.

Modified IMPROVE VTE risk score

VTE risk factor	VTE risk score
Previous VTE	3
Known thrombophilia	2
Current lower limb paralysis or paresis	2
History of cancer	2
ICU/CCU stay	1
Complete immobilisation ≥1 day	1
Age ≥60 years	1

1) Modified IMPROVE VTE (MIV) score ≥4

2) MIV ≥2 with a d-dimer value >2 times the upper limit of normal range

3) Age ≥75 years

4) Age >60 years with a d-dimer value >2 times the upper limit of normal range

5) Age 40–60 years with a d-dimer value >2 times the upper limit of normal range

6) history of VTE or with diagnosed malignancy.

- This can be counter balanced against bleeding risk by the VTE BLEED or HASBLED score. If no bleeding risk is ascertained, patient can be discharged on postdischarge prophylaxis.
- There is no role of routine measurement of d-dimer during postdischarge follow-up.

Risk factor	Score
Hypertension	1
Abnormal renal/liver function	1 or 2
Stroke	1
Bleeding tendency	1
Labile INR	1
Age (eg. >65)	1
Drugs (eg. concomitant aspirin, NSAIDs, etc) or alcohol	1 or 2
Maximum score	9

Notes: A score of 0–2 indicates low risk of bleeding; a score of ≥3 indicates high risk of bleeding. Hypertension is defined as a systolic blood pressure >160 mmHg. 1 point is awarded for each of abnormal renal or liver function, and drugs or alcohol.

- DOACs do not require INR monitoring and preferred over VKAs in this regard. Preferred DOACs include rivaroxaban (10mg once a day), betrixaban (160mg on the first day followed by 80mg once a day) and apixaban (2.5mg two times per day) as per studies.

- Dexamethasone is an inducer of CYP3A4 and the extent of the drug interaction with direct oral anticoagulants is unknown.

- Sarilumab (KEVZARA) and tocilizumab (ACTEMRA) can increase cytochrome P450 enzyme activity and so they should not be used together with apixaban or rivaroxaban and may also increase the doses of warfarin required.

best regards & THANK YOU for your attention