

Anticoagulation in COVID-19: current concepts and controversies

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► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/postgradmedj-2021-139923>).

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Received 8 February 2021

Revised 11 March 2021

Accepted 24 March 2021

Published Online First 13 April 2021

ABSTRACT

Rising incidence of thromboembolism secondary to COVID-19 has become a global concern, with several surveys reporting increased mortality rates. Thrombogenic potential of the SARS-CoV-2 virus has been hypothesised to originate from its ability to produce an exaggerated inflammatory response leading to endothelial dysfunction. Anticoagulants have remained the primary modality of treatment of thromboembolism for decades. However, there is no universal consensus regarding the timing, dosage and duration of anticoagulation in COVID-19 as well as need for postdischarge prophylaxis. This article seeks to review the present guidelines and recommendations as well as the ongoing trials on use of anticoagulants in COVID-19, identify discrepancies between all these, and provide a comprehensive strategy regarding usage of these drugs in the current pandemic.

INTRODUCTION

The novel beta-coronavirus, appropriately named SARS-CoV-2 by the International Committee of Taxonomy of Viruses, belongs to a family of single-stranded RNA viruses, members of which have been recognised as causative agents of the SARS-CoV and Middle East respiratory syndrome coronavirus outbreak in 2002 and 2012, respectively.^{1,2} Presently, the novel COVID-19 poses a major global health crisis, having been declared a pandemic on 11 March 2020 by the WHO.

Over the past several months, an overwhelming amount of literature suggests an increased risk of thromboembolic manifestations associated with COVID-19.² Several hypotheses have been suggested to understand the underlying pathophysiology behind development of a prothrombotic state in COVID-19 such as exaggerated inflammatory response resulting in activation of the coagulation cascade and endothelial injury.^{3,4} Usage of anticoagulants in COVID-19 remains an area of conjecture with no definite guidelines published to date highlighting the timing, dosage and duration of anticoagulation as well as the drug of choice. Most internationally published guidelines, based on consensus statements and expert opinions, recommend therapeutic doses of heparin only in patients diagnosed with or highly suspected of developing macrothrombi such as pulmonary embolism (PE) or deep vein thrombosis (DVT). However, these guidelines including those by CHEST, rarely address the requirement of postdischarge thromboprophylaxis.⁵

ANTICOAGULANT TYPES AND USES

Anticoagulants have been the mainstay of prevention and treatment of thrombosis for decades.⁶ Based on their mechanisms of action, they have been classified into broad categories.

Heparin was the first true anticoagulant. Purified heparin, including unfractionated heparin (UFH) and low-molecular weight heparin (LMWH), act by promoting formation of an intermediate protease-heparin-antithrombin complex which facilitates inhibition of thrombin and activated factor X.⁷ It is used for prevention and treatment of macrothrombi such as DVT and PE, in patients undergoing dialysis, extracorporeal circulation and cardiovascular and orthopaedic surgeries and in candidates for invasive procedures such as percutaneous coronary intervention. Bleeding is a major disadvantage of heparin as well as thrombocytopenia (in up to 30% of patients), alopecia, injection site reaction and hyperkalaemia.⁸

Historically, vitamin K antagonists such as warfarin (dicoumarol) and other coumarin derivatives were one of the earliest anticoagulants to be approved for clinical use.⁹ Warfarin is a competitive inhibitor of VKORC1, resulting in decreased hepatic synthesis of vitamin K-dependent clotting factors as well as Protein C and Protein S. Warfarin therapy requires close monitoring due to a narrow therapeutic window, drug interactions and wide dosing range needed for maintaining therapeutic international normalised ratio (INR).

Development of direct oral anticoagulants (DOACs) ensured a higher safety profile with greater efficacy requiring less frequent dose monitoring.^{10,11} These include two classes of drugs, namely direct thrombin inhibitors such as dabigatran and direct factor Xa inhibitors like apixaban, edoxaban and rivaroxaban.¹² Non-bleeding adverse effects of these drugs are rare, but include severe liver injury and gastrointestinal disorders.¹³ A major disadvantage of new oral anticoagulants lies in the present global unavailability of specific reversal agents. While idarucizumab and andexanet alfa are two such drugs approved for use in the USA as well as EU, other reversal agents are under development.¹⁴

Fondaparinux was approved for use in the USA in 2001 as an indirect inhibitor of factor Xa, which achieves anticoagulation by binding to and activating antithrombin.¹⁵ Toxicity of fondaparinux is complicated by its long half-life.

Selection of the ideal anticoagulant for any disease takes into account various patient-specific factors such as the underlying thromboembolic state, for example ischaemic stroke or atrial fibrillation, as



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To cite: Chandra A, Chakraborty U, Ghosh S, et al. *Postgrad Med J* 2022;**98**:395–402.

well as acceptable bleeding risk and presence of co-morbidities such as hepatic or renal disease.¹⁶

ROLE OF ANTICOAGULANTS IN PE

Acute PE has a mortality rate as high as 30% in the first month, with up to 30% survivors experiencing recurrence or chronic disabilities.^{17 18} With an annual incidence rate ranging from 0.2 to 0.8/1000, PE has been hypothesised to have multifactorial etiologies.¹⁹⁻²¹

Acute PE warrants mandatory risk stratification to determine appropriate therapeutic intervention. Models such as the Pulmonary Embolism Severity Index (PESI) and the simplified-PESI (sPESI) risk prediction scores provide a tool for identification of low-risk and high-risk patients.²² According to ESC guidelines, treatment of high-risk acute PE includes early oxygenation in the form of ventilation if required, ensuring haemodynamic stability, and management of right heart failure, including need for vasopressors and advanced life support in severe cases.²³

The CHEST guidelines provide specific recommendations regarding choice of anticoagulant with respect to phase of VTE treatment.²⁴ In the acute phase, administration of rapidly acting parenteral anticoagulant such as UFH, LMWH or fondaparinux is advocated. LMWH and fondaparinux are preferred over UFH due to a lower risk of bleeding. DOAC such as apixaban is also approved for the acute treatment of DVT and PE.²⁵

Vitamin K antagonists (VKA) with a recommended therapeutic INR range of 2 to 3 (target INR 2.5) or DOAC such as dabigatran or rivaroxaban are preferred for long term (beyond 10 days) and extended duration of treatment of PE lasting beyond 3 months.^{23 24} Several key clinical trials evaluating VKA for secondary prophylaxis conclude the following.

1. VKA treatment should be continued for a period of at least 3 months.
2. Risk of recurrence of VTE following shorter duration of prophylaxis (3–6 months) is greater compared with a longer duration of 12–24 months.

Fernandes *et al* estimated that extended anticoagulation can reduce risk of recurrence of VTE by up to 95%.²⁶ However, such a benefit is offset by an increased risk of bleeding.

DISEASE SPECTRUM OF COVID-19

The clinical manifestations of COVID-19 is associated with a broad spectrum of clinical respiratory illness, ranging from mild variety of upper respiratory tract infection to the severe form of disease such as, severe life-threatening pneumonia, acute respiratory distress syndrome (ARDS), sepsis, coagulopathy and death in a substantial proportion of patients.²⁷ Apart from the characteristic respiratory illness, it has also seen to be associated with florid extrapulmonary manifestations.²⁸ Most of the

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	13.6s	15.5s	13.97
aPTT	41.2s	44.8s	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

aPTT, activated partial thromboplastin time; AT, antithrombin; FDP, fibrin degradation products; PT, prothombin time.

severe manifestations of COVID-19 are related to an exaggerated inflammatory response.

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.²⁹ 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.²⁸ The commonly reported extrapulmonary manifestations of COVID-19 are described in [table 1](#).

COAGULATION ABNORMALITIES IN COVID-19

Though respiratory manifestations are the hallmark of the disease, over the past several months, an overwhelming amount of literature suggests that COVID-19, caused by SARS-CoV-2, is associated with several coagulation abnormalities which may be responsible for thrombotic manifestations related to this disease such as venous thromboembolism (VTE) and PE.²

Tang *et al* in a study of 183 patients of COVID-19 pneumonia presented primary data highlighting changes in coagulation parameters among survivors and non-survivors.³⁰ After secondary analysis of this data, we have noted drastic increases in prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, D-dimer and fibrin degradation products (FDP) and a sharp decline in antithrombin levels among non-survivors as compared with survivors. The changes have been formulated into a [table 2](#).

Table 1 The commonly reported extrapulmonary manifestations of COVID-19

Organ system	Manifestations
Neurologic	Anosmia, cerebrovascular accident, ageusia, encephalopathy, Guillain-Barré syndrome, acute transverse myelitis
Renal	Acute kidney injury, haematuria, proteinuria
Cardiac	Myocarditis, coronary artery disease, cardiogenic shock, acute cor pulmonale, stress cardiomyopathy
Gastrointestinal	Nausea/vomiting, diarrhoea, anorexia, hepatocellular injury
Endocrine	Hyperglycaemic, diabetic ketoacidosis
Dermatological	Urticaria, erythematous rash, petechiae, purpura fulminans
Thromboembolism	DVT, PE, catheter-related thrombosis

DVT, deep vein thrombosis; PE, pulmonary embolism.

A study of 1561 patients with laboratory-confirmed COVID-19 by Yu and colleagues also showed significant elevation of coagulation parameters.³¹ The study reported a 260.00% increase in D-dimer in patients of severe disease, with levels ranging from 0.9 to 4.6 µg/mL with a median of 1.8 µg/mL. The changes in various coagulation parameters following COVID-19 in this study are described in table 2. Guan *et al* noted abnormally increased D-dimer levels in 260 (46.4%) of 560 cases with a prevalence of 43% and 60% in non-severe and critically ill intensive care unit (ICU) patients respectively.³²

The exact mechanism of coagulation dysfunction in patients with COVID-19 is unknown. The SARS-CoV-2 does not have any intrinsic procoagulant activity. Several hypotheses have been suggested to understand the underlying pathophysiology behind development of a prothrombotic state in COVID-19.³³ One possible explanation studies the effect of SARS-CoV-2 infection on the individual processes involved in the Virchow triad namely endothelial injury, stasis of blood flow and hypercoagulable state.³

The thrombogenic potential of this virus is mainly attributed to the combined effect of the profound inflammatory response along with thromboinflammation and endothelial damage. Novel coronavirus is reported to cause endothelial dysfunction by an ACE2-mediated pathway with an exaggerated inflammatory response in several patients, especially those with severe diseases.⁴ COVID-19 has also been associated with hyperviscosity. In a study by Maier *et al*, all 15 patients evaluated showed plasma viscosity greater than 95% of normal.³⁴ Inhibition of plasminogen system, platelet dysfunction and complement activation in COVID-19 are some of the other factors responsible for development of a hypercoagulable state. Use of central venous catheters and mechanical ventilation along with prolonged immobilisation in critically ill patients may act as additional risk factors for thromboembolism (TE).³⁵

A possible association between development of antiphospholipid antibodies, notably lupus anticoagulant (LAC), and COVID-19 has been identified in multiple studies, which may also contribute to hypercoagulability. Bowles *et al* found presence of LAC in 31 of 34 diagnosed patients with elevated aPTT.³⁶ Harzallah *et al* further reported 25 LAC positive cases out of 56 patients in an independent study based in Mulhouse, France.³⁷

Incidence of TE has been reported in about 20%–30% of patients in a few studies, whereas some other studies have reported this to be as high as 70%.³⁸ A study from China predicted that upto 40% of patients had a higher risk of developing DVT according to the Padua Prediction Score.³⁹ A French prospective cohort reported development of PE despite prophylactic anticoagulation in 16.7% of patients.⁴⁰ A Dutch study reported an incidence of VTE of 27% despite prophylaxis.⁴¹ An Italian study found a VTE rate of 22.2%.⁴²

The evidence of vasculopathy and thrombosis has also been seen in several reports of autopsy lung tissue in patients died of severe disease. Ackermann *et al* examined seven lung samples from patients died of severe COVID-19 and found that, apart from the diffuse alveolar damage and perivascular T-cell infiltration, there was severe endothelial damage and enhanced angiogenesis along with widespread thrombosis in pulmonary vasculature.⁴³

A weak association may also be present between current treatment modalities for COVID-19 and blood coagulation. However, evidence in this field is severely lacking. Corticosteroids have been known to result in an increased VTE risk. However, the RECOVERY trial has greatly advocated use of low-dose corticosteroids, namely dexamethasone, in combating inflammation

and ‘cytokine storm’ secondary to SARS-CoV-2 infection.⁴⁴ The possible mechanism suggested is a decrease in fibrinogen and procoagulant factors with an increase in anticoagulant factors. A few studies have also tried to evaluate procoagulant effects of remdesivir. In a study by Grein *et al*, 3 (5.66%) out of 53 patients diagnosed with COVID-19 developed DVT following administration of remdesivir.⁴⁵ However, greater understanding in this regard is warranted.

MORTALITY SECONDARY TO COAGULOPATHY IN COVID-19

The incidence of TE in COVID-19 varies widely in different published reports. The strength of association between the mortality in patients with COVID-19 and TE is also a matter of debate. The thromboembolic manifestations are seen to be related to an increased mortality and morbidity in patients with COVID-19 in several studies.

A study by Zhang *et al* showed a higher mortality in patients with COVID-19 with TE.⁴⁶ Another study conducted by Tang *et al* revealed significantly higher levels of D-dimer and FDPs at the time of admission among the non-survivor group, thereby indicating poorer prognosis in patients with novel coronavirus pneumonia with coagulopathy.⁴⁷ A meta-analysis conducted by Malas *et al* reported an overall arterial thromboembolism (ATE) rate of 2%, VTE rate of 21%, DVT rate of 20% and PE rate of 13% among SARS-CoV-2 infected individuals. The rate of ATE, VTE, DVT and PE were 5%, 31%, 28% and 19%, respectively in case of ICU patients.³⁸ They also reported that the odds of mortality were significantly increased by TE (as high as 74%).

In contrast, a study by Hippensteel *et al* found no significant difference in mortality among the critically ill patients, though they found a higher prevalence of VTE in critically ill patients with COVID-19.⁴⁸

However, as all the patients with COVID-19 are not routinely screened for PE, therefore the reported incidence and mortality secondary to it, may differ from the reported figures.

TRIALS AND GUIDELINES

The ongoing randomised control trials (RCTs) are yet to provide concrete evidence on definitive role of anticoagulation in COVID-19, though results are promising. The ongoing RCTs have been elaborated in table 3.⁴⁹

Several international guidelines have been formulated on the use of anticoagulation in COVID-19. Some of the salient guidelines and respective recommendations have been tabulated in table 4.^{50–55}

ANTICOAGULANTS IN COVID—THE PRESENT CONSENSUS

To the best of our knowledge, no single RCT or a large dependable observational study has neither been completed nor published highlighting the timing, dosage, choice and duration of anticoagulation in patients with COVID-19. All RCTs are ongoing.⁴⁹ The guidelines, published internationally until, are based on consensus statements and expert opinions only. Some of these guidelines clearly mention the percentage of experts in the panel agreeing to a certain recommendation and the percentage recommending otherwise.^{56,57}

Thus, a current dearth of useful strategy concerning use of anticoagulants in COVID-19 exists. This grey area is still evolving and, hence, clinical judgement is necessary on case to case basis. The main limitation of available guidelines lies in recognising COVID-19 as a cause of microthrombi, leading to worsening prognosis of patients, but being unable to provide consensus statements or guidelines to appropriately address this

Table 3 Ongoing RCTs on role of anticoagulation in COVID-19

Name	Identifier	Location	Type of study	Active comparator	Intervention/ treatment arm	Primary outcome	Phase of trial
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).	4
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.	4
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.	3
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 \geq 80 years, weight \leq 60 kg or serum creatinine \geq 1.5 mg/dL).	Time to first events Number of in-hospital rate of BARC 3 or 5 (time frame for both: 30 days).	4
Intermediate or prophylactic-dose anticoagulation for venous or arterial TE in severe COVID-19	NCT04367831	Columbia University Medical Center New York, New York, USA	Single-blind parallel RCT	Prophylactic dose anticoagulation with enoxaparin, UFH.	Intermediate-dose anticoagulation with UFH infusion or enoxaparin intermediate dose.	Total number of patients with clinically relevant venous or arterial thrombotic events in ICU (time frame: discharge from ICU or 30 days).	4
Full anticoagulation vs prophylaxis in COVID-19: COALIZAO ACTION Trial	NCT04394377	Bahia, Brazil	Single-blinded parallel, multicentric RCT	Usual standard of care with prophylactic dose of enoxaparin	Rivaroxaban 20 mg/day followed by enoxaparin/UFH when needed.	Mortality, number of days alive, number of days in the hospital and number of days with oxygen therapy at the end of 30 days.	4
Tenecteplase in patients with COVID-19	NCT04505592	Mount Sinai Hospital New York, USA	Placebo-controlled, double-blind, RCT	Placebo control	Tenecteplase	Number of participants free of respiratory failure Number of occurrences of bleeding (time frame for both: 28 days).	2
Antithrombotics for adults hospitalised With COVID-19 (ACTIV-4)	NCT04505774	NYU Langone New York, New York, USA	Multicentre, adaptive, randomised controlled platform trial	Prophylactic dose anticoagulation heparin standard of care	Therapeutic dose anticoagulation increased dose of heparin above standard of care.	21-Day organ support (respiratory or vasopressor) free days.	4
Preventing COVID-19 complications with low-dose and high-dose anticoagulation	NCT04345848	Switzerland	Open-label RCT	Prophylactic doses of enoxaparin or UFH. If in intensive care augmented thromboprophylaxis	Therapeutic doses of enoxaparin or intravenous UFH, from admission until the end of hospital stay or clinical recovery.	Composite outcome of arterial or venous thrombosis, DIC and all-cause mortality (time frame: 30 days).	4
Full-dose heparin vs prophylactic or intermediate dose heparin in high-risk patients with COVID-19	NCT04401293	New York, USA	Open-label multicentre randomised active control trial	Prophylactic/intermediate dose LMWH or UFH therapy	Full-dose LMWH anticoagulation therapy.	Composite outcome of arterial thromboembolic events, VTE events and all-cause mortality at day 30 \pm 2 days.	3

BARC, Bleeding Academic Research Consortium; ICU, intensive care unit; LMWH, low-molecular weight heparin; P/F ratio, PaO₂/FIO₂ ratio; RCT, randomised control trial; UFH, unfractionated heparin; VTE, venous thromboembolism.

Table 4 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 thrombocytopenia.	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 thrombocytopenia	Intermittent pneumatic compression if contraindication to pharmacological thromboprophylaxis. Both mechanical and pharmacological thromboprophylaxis in critically ill patients if no contraindication.
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.
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.

ACC, American College of Cardiology; ACCP, American College of Chest Physicians; ACF, Anticoagulation Forum; ARDS, acute respiratory distress syndrome; ASH, American Society of Hematology; CDC, Centers for Disease Control and Prevention; CRRT, continuous renal replacement therapy; DVT, deep vein thrombosis; ECMO, extracorporeal membrane oxygenation; ISTH-IG, International Society of Thrombosis and Hemostasis Interim Guidance; PE, pulmonary embolism; PTT, partial thromboplastin time; SCC-ISTH, Scientific and Standardization Committee of ISTH; STEMI, ST elevation myocardial infarction; UFH, unfractionated heparin.

issue. All the guidelines recommend heparin in therapeutic doses only in diagnosed or highly suspected macrothrombi (PE/DVT), while ignoring the issue of undiagnosable microthrombi. There is no separate scoring system to assess VTE risk on admission specific to COVID-19. Although significantly elevated levels of D-dimer are more likely to be associated with VTE, it is difficult at this point to identify the threshold that can only be used to diagnose thrombus non-invasively.⁵⁸ Rather, the decision for further diagnostic imaging should be based on overall clinical

assessment. D-dimer may be useful in investigating a possible acute VTE/PE in patients who develop new or worsening breathlessness. However, it has been universally accepted that although a high D-dimer level is a proven poor prognostic factor, it should not guide anticoagulant dosage or escalation. A single-centre randomised trial (n=20) was performed to compare the efficacy of prophylactic and therapeutic anticoagulation in critically ill ventilated patients with high D-dimer level (>1000 µg/L).⁵⁹ They showed significant improvement in the oxygenation in the

therapeutic anticoagulation group, though no difference was observed among both the arms regarding in-hospital or 28-day mortality.

Two small case series, one from All India Institute of Medical Sciences (AIIMS), Rishikesh, and another from abroad, have been successful in using recombinant tissue plasminogen activator (rTPA) in refractory hypoxaemia in ARDS (even in cases without a CT pulmonary angiography diagnosed PE).⁶⁰ However, no consensus guideline has supported this endeavour so far. RCT on use of rTPA is ongoing. Thus, there is huge scope for clinician's judgement while escalating anticoagulant dosing till more data are available.

As of now, after considering all expert opinion and consensus statements, we have come to the following conclusions:

1. Parenteral anticoagulants are indicated in any acutely ill hospitalised patients. Hence, it is indicated in moderate, severe and critical disease.
2. LMWH/fondaparinaux is preferred over UFH, due to lesser patient contact of healthcare staff and no need of aPTT monitoring (necessitating patient contacts).
3. Enoxaparin is the most preferred LMWH.
4. Dosing of anticoagulation:
 - i. Moderate disease (standard risk patient): standard weight-adjusted prophylactic dose (eg, enoxaparin 40 mg once daily for a 70 kg adult with CrCl >30 mL/min).
 - ii. Severe and critical disease (high-risk patient: requiring invasive ventilation/continuous positive airway pressure (CPAP)/non-invasive ventilation (NIV)/high-flow nasal oxygen): intermediate dose LMWH (enoxaparin 40 mg two times per day for a 70 kg adult with CrCl >30 mL/min).
 - iii. Diagnosed/highly suspected macrothrombosis (PE/DVT): therapeutic dose (enoxaparin 1 mg/kg 12 hourly subcutaneous or 1.5 mg/kg subcutaneously once daily).
 - iv. Renal insufficiency: enoxaparin with dose reduction is the preferred over other LMWH drugs/fondaparinaux. UFH with aPTT monitoring indicated at eGFR <15 mL/min.

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 American College of Chest Physicians guidelines published in CHEST as well as the American College of Cardiology guidelines published in the Journal of the American College of Cardiology (JACC) do not elucidate on postdischarge thromboprophylaxis.^{5 55}

The CHEST consensus statement clearly refutes it due to lack of evidence. However, NIH guidelines, updated on 11 February, as well as ISTH guidelines, BTS guidelines and SIGN (Scottish guidelines) mention post discharge thromboprophylaxis, based on expert opinion.^{50 51 61 62}

Decisions regarding postdischarge prophylactic anticoagulation should be individualised. Based on present recommendations as well as past and ongoing trials regarding usage of anticoagulants, we can conclude that patients with moderate to severe disease and fulfilling any one of the following criteria would be the ideal candidates for postdischarge thromboprophylaxis⁵⁰:

1. Modified IMPROVE VTE (MIV) score (table 5) ≥ 4
2. MIV ≥ 2 with a D-dimer value >2 times the upper limit of normal range
3. Age ≥ 75 years

Table 5 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

CCU, critical care units; ICU, intensive care unit; IMPROVE, International Medical Prevention Registry on Venous Thromboembolism; VTE, venous thromboembolism.

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 and history of VTE or with diagnosed malignancy

Candidates, thus, selected should be assessed for VTE risk using the MIV score.⁶³ 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. DOACs do not require INR monitoring and, hence, are preferred over VKAs in this regard. Preferred DOACs include rivaroxaban (10 mg once a day), betrixaban (160 mg on the first day followed by 80 mg once a day) and apixaban (2.5 mg two times per day) as per studies.^{63 64}

In renal insufficiency, warfarin is preferred over DOACs with INR monitoring. However, at eGFR 30–15 mL/min, apixaban 2.5 mg two times per day may be used. At eGFR <15 mL/min and patients with ESRD on dialysis, it is preferably better to avoid DOACs. The FDA has approved apixaban 2.5 mg two times per day at eGFR <15 mL/min and 5 mg two times per day in patients with ESRD on dialysis since it is partially dialysable. However, as European guidelines negate usage of DOACs at

Main messages

- ▶ VTE secondary to COVID-19 has resulted in higher mortality.
- ▶ A vast majority of patients present with undiagnosed thromboembolism following COVID-19.
- ▶ Anticoagulation in moderate to severe and critical cases of COVID-19 is advisable.
- ▶ Enoxaparin is the preferred low-molecular weight heparin for anticoagulation in acute phase of venous thromboembolism.
- ▶ Postdischarge prophylaxis may be considered in patients with high risk of thromboembolic events after assessing the bleeding risk.
- ▶ Rivaroxaban and apixaban are preferred for post discharge prophylaxis.

Current research questions

- ▶ Should postdischarge prophylaxis with anticoagulants be recommended in all hospitalised patients of COVID-19?
- ▶ If yes, what should be the duration of such prophylaxis?
- ▶ Should direct oral anticoagulants be used in patients of COVID-19 with renal insufficiency?

Key references

- ▶ Miesbach W, Makris M. COVID-19: coagulopathy, risk of thrombosis, and the rationale for anticoagulation. *Clin Appl Thromb Hemost* 2020;26:1076029620938149.
- ▶ Kearon C, Akl EA, Comerota AJ, et al. Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141(2 Suppl):e419S–96S.
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Self assessment questions

1. Which of the following are extrapulmonary manifestations of COVID-19?
 - a. Myocarditis
 - b. Acute kidney injury
 - c. Endocarditis
 - d. Encephalopathy
 - e. Hypoglycaemic
2. COVID-19 contributes to coagulopathy by all of the following mechanisms except?
 - a. Inflammation producing endothelial damage
 - b. Platelet dysfunction
 - c. Activation of Factor X
 - d. Complement activation
3. Which of the following anticoagulants are preferred in patients with COVID-19 with renal insufficiency?
 - a. UFH
 - b. Fondaparinux
 - c. Enoxaparin
 - d. Warfarin
 - e. Rivaroxaban
4. Which of the following anticoagulants are preferred for postdischarge prophylaxis of COVID-19 patients?
 - a. Fondaparinux
 - b. Enoxaparin
 - c. Warfarin
 - d. Rivaroxaban
 - e. Apixaban
5. Which factors should be considered before prescribing postdischarge prophylaxis in patients with COVID-19?
 - a. Previous VTE
 - b. Known thrombophilia
 - c. Immobilisation
 - d. D-dimer level
 - e. Presence of secondary bacterial infection

eGFR <15 mL/min, avoiding administration of these drugs in such a clinical scenario may be wise.

Regarding duration, the FDA recommends use of rivaroxaban (10 mg daily) for 31 to 39 days and betrixaban (160 mg on the first day followed by 80 mg once a day) for 35 to 42 days.⁵⁰ ACC suggested extended thromboprophylaxis with LMWH or DOACs for a maximum period of 45 days in case of high risk for VTE such as, D-dimer level of more than two times the upper limit of normal or presence of active cancer.⁵⁵ The SCC-ISTH suggests duration of 14–30 days for thromboprophylaxis.⁵⁴

CONCLUSION

Increased mortality secondary to COVID-19 has necessitated need for definitive guidelines addressing timing, choice, duration and dosage of anticoagulation in patients diagnosed with the novel coronavirus. As most RCTs as well as observational studies are ongoing with multiple conflicting guidelines, a concrete strategy is yet to be devised. Most clinicians have resorted to individual bias in treatment of patients with anticoagulants, with decisions varying case to case as per individual patient profile. After thorough research of existing protocols, current knowledge and ongoing trials, we have identified areas of information deficiency pertaining to usage of anticoagulants in management of COVID-19 and attempted to condense all available strategies to formulate a single guideline to direct anticoagulation treatment. We recommend anticoagulation with enoxaparin in moderate to severe cases of COVID-19 along with postdischarge prophylaxis to prevent possible undiagnosed microthrombi with DOACs such as rivaroxaban and apixaban. We encourage further research on the aforementioned conclusions drawn and recommendations made by us to help in the better treatment of mankind during this pandemic.

Contributors AC, UC and SG prepared the manuscript with adequate planning and execution. SD contributed to review of literature, critical revision of content and final approval of manuscript. All authors are in agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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Answers

1. a. True b. True c. False d. True e. False
2. a. False b. False c. True d. False
3. a. False b. False c. True d. True e. False
4. a. False b. False c. False d. True e. True
5. a. True b. True c. True d. True e. False

Associate Editor and Reviewer: 1		
Reviewer comments	Authors' response	Changes made
This paper is of interest to the PGMJ but please could you resubmit with attention to the points of the reviewers. The review article summarizes available data on the mechanisms, prophylaxis and therapy of COVID-19 associated venous thromboembolism, which is a hot topic of paramount clinical importance during the pandemic.	We would like to thank the reviewer for appreciating the potential significance of this review article. We did our best to revise the manuscript in a more organized way as suggested by the reviewer.	We have incorporated the changes as suggested by the reviewer in the revised manuscript.
The first part presenting the anticoagulant agents and guidelines for the management of VTE contains several imprecise data and mistakes listed below.	We are extremely thankful to the reviewer for pointing out those important issues regarding the revision of our article.	We have thoroughly revised our manuscript as advised by the reviewer.
Regarding the key issues of this review, tables 3 and 4 are of great value and are well designed.	We would like to thank the reviewer for appreciating the potential significance of table 3 and 4.	-----
The authors need to clarify the recommended doses of LMWH. They claimed that " Weight and Renal function based intermediate dose (e.g. 1mg/kg Enoxaparin SC 12hrly in a 70 kg adult with normal renal function)." and then "Therapeutic dose (Enoxaparin 1mg/kg 12hrly SC" According all guidelines and product characteristics, a prophylactic dose of enoxaparin is 40 mg SC or 0.5 mg/ kg body weight. The same daily dose 1 mg/kg enoxaparin bid cannot be both intermediate and therapeutic dose; it is a therapeutic dose.	Agreed. We have modified our statement regarding the prophylactic, intermediate and therapeutic dosing of enoxaparin. We have mentioned the recommended doses of LMWH in accordance to the BTS Guidance on Venous Thromboembolic Disease in patients with COVID-19. (Updated 8 th February, 2021) and the product information available at https://www.medicines.org.uk/emc/medicine/10054 .	The changes have been incorporated in the revised manuscript and highlighted in yellow. (Page 17 and 18-marked copy)

<p>Little attention has been paid on a predictive value of elevated D-dimer, though this issue has been mentioned.</p>	<p>Agreed. We have discussed this issue in a more detail in our revised manuscript under the heading ‘Anticoagulants in COVID-The present consensus’. We have mentioned the importance of D-dimer in investigating a possible acute VTE/PE. We have also highlighted that, although a high D-dimer level is a proven poor prognostic factor, it should not guide anticoagulant dosage or escalation.</p>	<p>The changes have been incorporated in the revised manuscript. (Page 16 and 17- marked copy)</p>
<p>Please state clearly whether or not any scoring systems implemented in routine hospital practice to assess VTE risk on admission should be used in hospitalized COVID-19 patients.</p>	<p>We are again grateful to the reviewer for mentioning this point. There is no separate scoring system to assess VTE risk on admission specific to COVID-19. But all patients hospitalized with COVID-19 should be thoroughly assessed for VTE risk as in other hospitalized patients.</p>	<p>We have mentioned this information under the heading ‘Anticoagulants in COVID-The present consensus’. (Page 16-marked copy)</p>
<p>Regarding duration of thromboprophylaxis following discharge, how long should it be administered? In several centers at least 2 weeks of prophylaxis is recommended in high-risk patients post-discharge given increased risk of VTE within the first month. The authors provided suggestions regarding the identification of such patients however, they should address the issue of duration; should D-dimer levels be measured after 2 weeks?, if further elevated e.g. 1500 ng/ml, should LMWH be continued or not?</p>	<p>We are extremely grateful to the reviewer for pointing out this issue. In fact, at least 2 weeks of prophylaxis is recommended in high-risk patients post-discharge given increased risk of VTE within the first month in several centers. We have discussed the issue of duration of thromboprophylaxis in a more detail in our revised manuscript. There is no mention of routine measurement of D-dimer during post-discharge follow-up in any of the guidelines.</p>	<p>We have added those information under the heading ‘Post discharge prophylaxis in covid-19’ of our revised manuscript. (Page 18, 19, 20- marked copy).</p>

	ACC suggested extended thromboprophylaxis with LMWH or DOACs for a maximum period of 45 in case of high risk for VTE such as, D-dimer level of more than 2 times ULN.	
Minor comments p. 4 l. 18-22 The statement "Purified heparin, including unfractionated heparin (UFH) and low molecular weight heparin (LMWH), inactivate thrombin by binding to antithrombin and producing a surface change." requires modification; LMWH are indirect inhibitors of FXa (2-4:11) as compared to inhibition of thrombin and heparins increase the antithrombin mediated inhibition of those proteins.	Agreed	We have modified our statement as-‘Purified heparin, including unfractionated heparin (UFH) and low molecular weight heparin (LMWH), act by promoting formation of an intermediate protease-heparin-antithrombin complex which facilitates inhibition of thrombin and activated factor X.’ We have also replaced the previous reference with a new one [Ref no-7] in support of our statement.
p. 4 l. 35 VKA were the first oral anticoagulants; heparins are also anticoagulant agents!	We are extremely grateful to the reviewer for pointing out this issue as well.	We have modified our statement as-‘Historically, Vitamin K antagonists such as warfarin (dicoumarol) and other coumarin derivatives were one of the earliest anticoagulants to be approved for clinical use.’

p. 5. l. 1 idarucizumab and andexanet alfa are approved in the European Union, and the first one is widely available in Europe and used as shown in several observational studies. Please correct the sentence.	Agreed.	We have modified our statement as-‘While Idarucizumab and andexanet alfa are two such drugs approved for use in the US as well as EU, other reversal agents are under development.’
p. 5 l. 9 the current guidelines recommend using the term antithrombin, not antithrombin III (there are no antithrombin I, II or IV).	Agreed.	We have made changes in the revised manuscript as suggested by the reviewer.
p. 5 l. 27 the term multivariate etiologies should be replaced by multifactorial.	Agreed.	The term ‘multivariate etiologies’ has been replaced by ‘multifactorial etiologies’.
p. 5 ref 24 the comment on the 2019 ESC guidelines refers solely to high-risk acute PE (5% of all PE cases); this statement must be rephrased or removed. The key issue is clinical risk assessment (3 main categories).	We would like to thank the reviewer again for pointing out the issue.	We have revised our statement as suggested by the reviewer.
p. 5 l. 52 apixaban is also approved and used in acute PE.	Agreed	We have revised our statement as suggested by the reviewer.
While presenting studies, ie ref 30 the authors should use the name of the first author followed by et al or and co-workers.	Agreed.	We have made necessary changes as suggested by the reviewer.

Table 2, units must be provided for each parameter. In this table percentage difference not change has been shown.	We would like to thank the reviewer again for pointing out the issue.	We have made changes as suggested in the revised manuscript.
p. 16 l. 27 randomized controlled trial, not control	Agreed.	Correction has been made.
Other changes	Reference no 7, 25, 58 and 59 have been replaced with four new references to better explain our statements.	

The changes incorporated in the revised manuscript have been highlighted in yellow.