# COVID-19 & venous thromboembolism

## From observations to guidelines to changing clinical practices: **Do we still know enough?**

Masterclass Series

**Key Takeaways**

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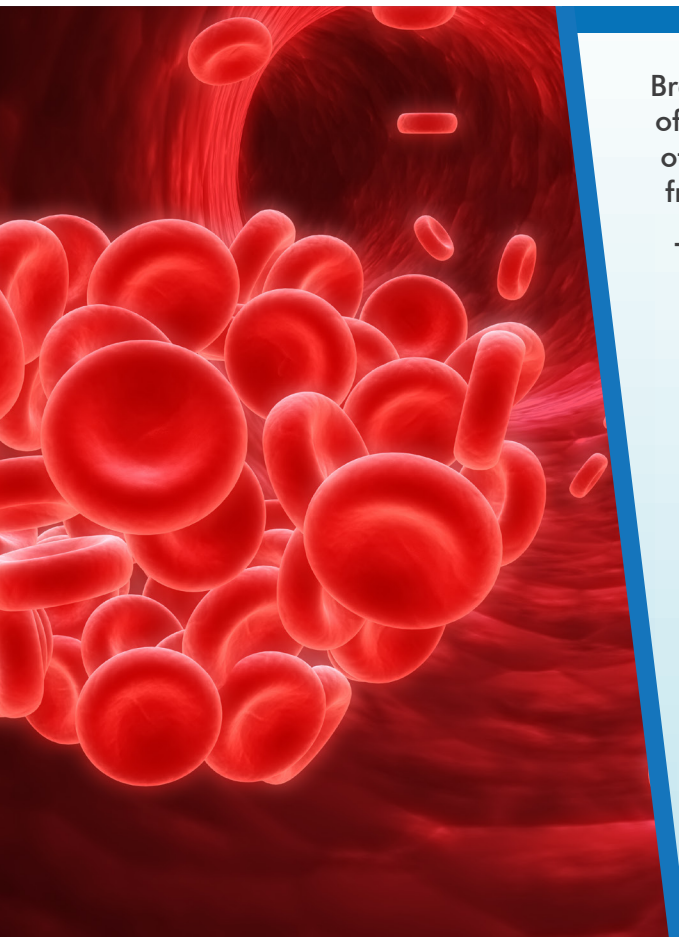


Breaking Clinical Inertia in VTE management is a continuous series of Masterclass sessions brought to us from the American College of Chest Physicians (ACCP), supported by an educational grant from Sanofi.

The first session of this series was conducted on **COVID-19 and VTE: From observations to guidelines to changing clinical practices: Do we still know enough?**

**It is accessible at: https://bcove.video/3CMi9Ij**

**Dr. N. Ramakrishnan,** senior consultant & director critical care services at Apollo hospital, Chennai, having profound experience in managing COVID-19 patients and who has also published several articles in renowned medical journals moderated this session.

**Dr. Ramakrishnan** opened the session by discussing the impact of COVID-19 and importance of management of associated comorbidities and complications, one of which is venous thromboembolism associated with coronavirus SARS-CoV-2 infection.

## CHEST® EXPERT TALK

**Dr. Lisa K. Moores** is the VTE lead at the ACCP and the principal author of VTE guidelines for coronavirus disease released in 2020 by CHEST. She has also received an award for outstanding clinical research and is an exceptional educator with special interest in VTE. She represented ACCP at this webinar, and highlighted **Coagulopathy** in **COVID-19 Pneumonia: An ever-evolving story**.

## Introduction

Understanding about COVID-19 is ever evolving and we need to change our practice as the new evidence emerges. Early in March 2020 a paper was published based on a cohort study discussing improved survival in patients who received thromboprophylaxis. This was followed by several other studies reporting DVT and/ or PE in patients with COVID-19 infection and/ or role of thromboprophylaxis. However, the thromboprophylaxis rates and regimens varied significantly across these studies.

**So, the important questions to ask are...**

1. Who did you ask?
2. What was the geographic region?
3. What was the clinical care setting (ICU patient or ward patent)?
4. Were patients routinely screened?
5. How many were on thromboprophylaxis?
6. What type of thromboprophylaxis?

The data that was similar across all COVID-19 patients showed changes in the chemical and biochemical factors associated with COVID-19, mostly in patients with severe infection. This profile shares features with disseminated intravascular coagulation, sepsis induced coagulopathy with some important differences.

In patients with COVID-19, there is a marked decrease in platelet count with mild increase in prothrombin time and significant elevation in D-dimer levels, however, the fibrinogen level remained intact. The inflammatory biomarkers are not different except that the levels are little higher in patients with COVID-19.

Several kinds of coagulopathies including both arterial thromboembolism (ATE) and venous thromboembolism (VTE) was noted in patients suffering with COVID-19 infection, reported to be as high as 35% in ICU.

## Pathophysiology of venous thrombosis in COVID-19

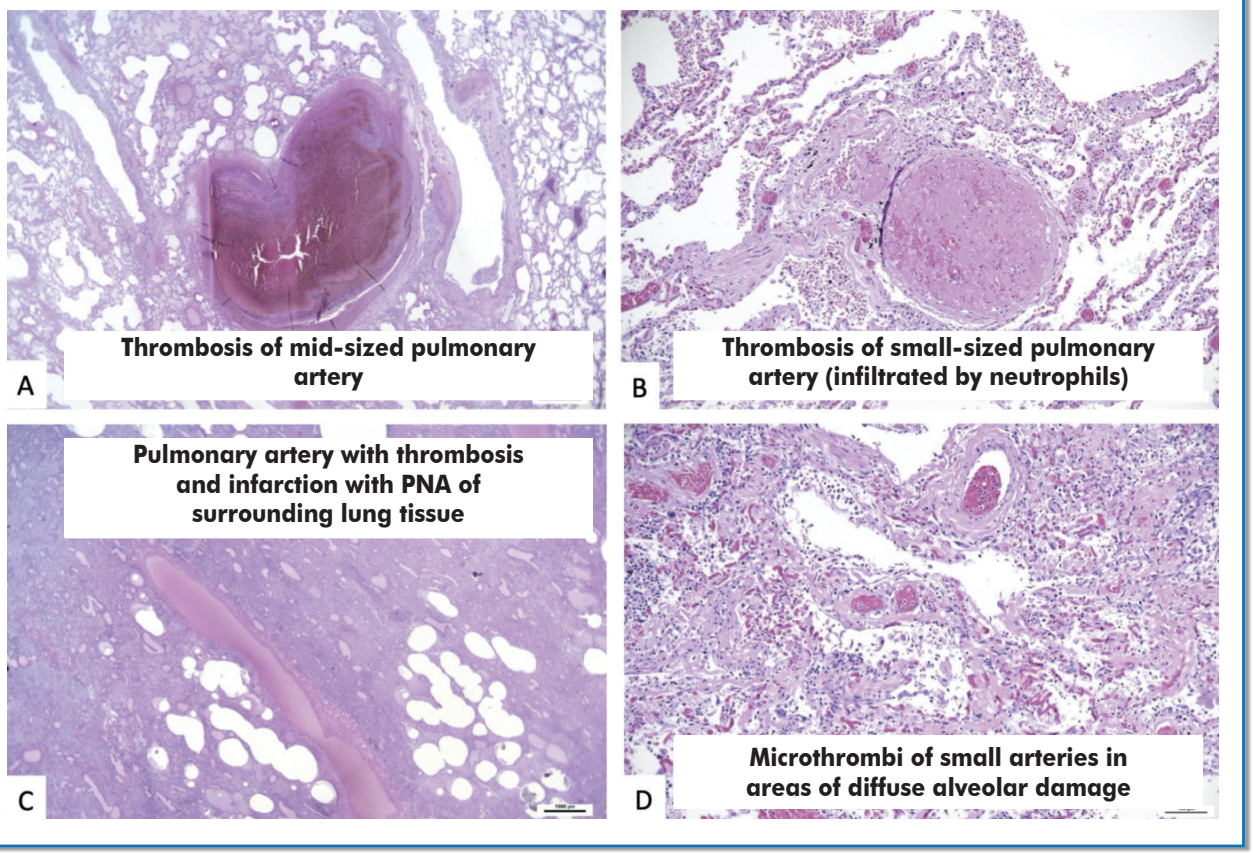
In COVID-19 patients there is thrombo-inflammatory phenotype where vascular damage or endotheliopathy is the large driving force.

- Endotheliopathy
- Hypercoagulability
- Platelet Aggregation, Coagulation Activation

There are high plasma levels of pro-inflammatory cytokines that trigger the coagulation system and complied to the fact that immobility of the patient due to isolation, hospitalization or putting in prone position can lead to thrombosis. Also, if the patient develops ARDS, a very high positive pressure is used, along with restriction of fluids, and stasis can also lead to micro thrombosis.

Thrombosis in these patients is mid-sized, small sized in the pulmonary artery and micro-thrombi significantly seen in the small arteries of diffuse alveolar damage. Some autopsy studies showed that these clots were very platelet-rich thrombi, and these findings were found in multiple organs such as lungs, heart, kidney, and liver. These clots were specific to the anatomic locations suggesting they were formed in the organs and were not embolic.

### Box 1: Thrombosis in COVID-19 patients



**Venous thrombosis in COVID-19 is a mixture of macro and micro thrombosis.**

There is a key role of complement (C3) activation in driving the platelet/neutrophil extracellular traps (NETs) in the coagulopathy axis.

**The biologic mechanisms are very complex, and listed below:**

- Coagulopathy secondary to endothelial dysfunction
- Reduced fibrinolysis
- Platelet activation
- Hypoxia and vasoconstriction
- Inflammation (cytokine/chemokine storm)
- Complement activation
- Neutrophil extracellular trap (NET) generation

## Prophylaxis for COVID-19

### Guidelines

The COVID-19 - VTE recommendations have been ever evolving as significant clinical data continues to emerge. The recommendations for ICU and ward patients have been given separately by most guidelines.

For moderate COVID-19 patients (ward patients) guidelines such American College of Chest Physicians (ACCP 2020), The American Society of Hematology (ASH) 2021, and World Health Organization (WHO) guidelines 2021 recommended conventional or low dose thromboprophylaxis except for International Society on Thrombosis and Haemostasias (ISTH) who recommended intermediate dose of LMWH.

For ICU patients, the earlier few guidelines recommended higher or intermediate doses of LMWH, however, based on the evolving clinical evidence the latest guidelines such ACCP 2020, ASH 2021, and WHO guidelines 2021, recommend a conventional low dose of thromboprophylaxis.

### CHEST expert panel views:

The rate of VTE appeared to be higher in COVID-19 patients. According to any of the risk prediction score such as Padua score or Geneva score, the risk of VTE in any hospitalized COVID-19 patients appeared to be higher.

**CHEST expert panel reported that any hospitalized COVID-19 patient should receive thromboprophylaxis.**

## Clinical Evidence

**There were two questions that needed further understanding-**

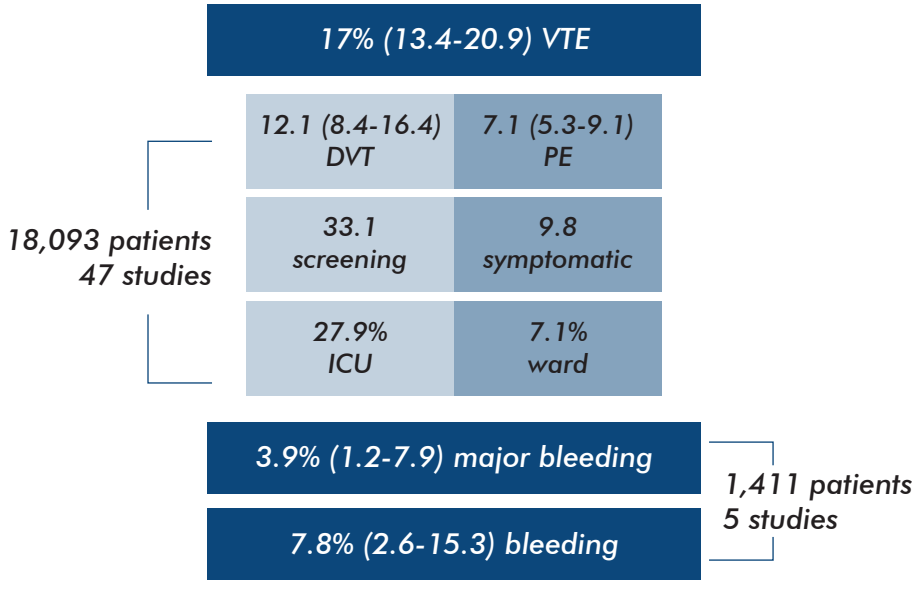
*1. Is the rate of VTE indeed higher in COVID-19 patients?*

- A systematic meta-analysis was conducted by Jiménez D *et al*, 2021 to understand the rate of VTE in COVID-19 patients.

Study concluded -

- Rate of VTE was consistent across cohorts whether no, standard, or higher doses of anticoagulation were used.
- Rate of bleeding significantly increased with intermediate-or-full dose anticoagulation.
- When isolated distal DVT, catheter associated DVT, and isolated sub-segmental PE events were excluded, overall rate of VTE was lower than similarly ill non-COVID-19 hospitalized patients.
- With inverse variance fixed effects model, rate of VTE was 4.8%, whereas the rate of bleeding was 9.4%.

**Box 2: Rate of VTE in COVID-19 patients**




**The prevalence of VTE in hospitalized COVID-19 patients is 2-11% which is similar to that of acutely/ critically ill non- COVID-19 patients who are hospitalized.**

**CHEST guideline recommendations:**

**In acutely ill hospitalized patients with COVID-19:** Anticoagulant thromboprophylaxis with LMWH or fondaparinux over unfractionated heparin (UFH); and anticoagulant thromboprophylaxis with LMWH, fondaparinux or UFH over a direct oral anticoagulant (DOAC) is recommended.

**In critically ill patients with COVID-19:** Anticoagulant thromboprophylaxis with LMWH over UFH; and anticoagulant thromboprophylaxis with LMWH or UFH over fondaparinux or a DOAC is recommended.

Current standard dose anticoagulant thromboprophylaxis over intermediate (LMWH BID or increased weight-based dosing) or full treatment dosing, have been recommended as per CHEST 2020 guidelines.

**Extended prophylaxis:** Current guidelines recommend against routine post-discharge prophylaxis in medical patients given a net harm. Extended thromboprophylaxis would result in a net benefit only if the risk of symptomatic VTE is greater than 1.8% after the hospital discharge.

## 2. *Whether higher doses of anticoagulation are effective and safe?*

*Multiplatform COVID-19 trials*

- Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community Acquired Pneumonia (REMAP-CAP)
- Accelerating COVID-19 Therapeutic Interventions and Vaccines-4 Antithrombotics Inpatient (ACTIV-4a)
- Anti-thrombotic Therapy to Ameliorate Complications of COVID-19 (ATTACC)

*Objective of these trials:* To determine whether a pragmatic strategy of therapeutic dose anticoagulation improved survival and reduced the duration of organ support compared to usual care pharmacological thromboprophylaxis in patients with COVID-19.

*However, there were announcements from the safety boards:*

- December 19, 2020, about halting the enrolment of severe patients due to futility and potential harm.
- In January 2021: Halting the enrolment in the moderate cohort due to superiority in both D-dimer strata and no evidence of harm.

*Results of these trials-*

- Moderate state COVID-19 patients: Therapeutic dose thromboprophylaxis in ward patients decreases the risk of thrombotic events with low bleeding risk.
- Therapeutic dose is superior to usual care venous thromboprophylaxis with regard to organ support free days (OSFDs) in both high and low D-dimer subgroup. Major bleeding rate <2% on therapeutic anticoagulation.

Severe state COVID-19 patients:

- Therapeutic anticoagulation did not improve hospital survival or days free of organ support compared to usual care pharmacological thromboprophylaxis. There is numeric increase in major bleeding events and mortality.

## Extended prophylaxis

According to the reports from Roberts *et al.* 2020, the rate of symptomatic post-discharge VTE following hospitalization with COVID-19 is low.

Extended prophylaxis: ACCP 2020 guideline recommend against routine post-discharge prophylaxis in medical patients given a net harm. Only THE MICHELLE trial and small RCT suggests it may be beneficial in high-risk patients.

Extended thromboprophylaxis would result in a net benefit only if the risk of symptomatic VTE is above 1.8% after hospital discharge.

## Vaccine-induced immune thrombocytopenia and thrombosis (VITT)

VITT is caused by antibodies that recognize platelet factor 4 bound to platelets. VITT is a prothrombotic syndrome observed in a small number of individuals. It strongly resembles spontaneous heparin-induced thrombocytopenia. It is also referred by several other names in the literature such as vaccine-induced immune thrombotic thrombocytopenia, thrombosis with thrombocytopenia syndrome (TTS), and vaccine-induced prothrombotic immune thrombocytopenia (VIPIT).

**VITT have typical clinical presentations such as:**

- Thrombosis and thrombocytopenia 6-24 days after vaccination
- Often multiple thromboses, in atypical/unusual sites, particularly cerebral venous sinus thrombosis (CVST) and portal vein thrombosis
- Arterial events have been described in 10% of patients. Mortality ranges from 30%-60%
- More likely to suffer cerebral hemorrhage than non-vaccine associated CVST

**VITT management includes:**

- CBC, coagulation studies (PT, aPTT, fibrinogen, D-dimer); PF4 antibody (ELISA)
- Anticoagulation (DOAC, fondaparinux, argatroban, bivalirudin)
- IVIg (1 gm/kg for two days); do not wait for PF4 testing if high suspicion (modified VITT 4T score can be used)
- Plasma exchange for refractory cases
- Minimize platelet transfusions

**Summary of Dr. Lisa K. Moores' talk -**

- VTE is a common complication of patients with COVID-19.
- The rate of VTE is similar to other infections that cause a prothrombotic state [may be slightly higher in intensive care unit (ICU) patients]
- The prevalence of VTE in COVID-19 patients compared with similarly ill non-COVID-19 patients is about the same.
- All patients hospitalized with COVID-19 should receive thromboprophylaxis.
- High risk patients may benefit from post-discharge prophylaxis.
- VITT is a rare, but well documented complication of the adenoviral vector-based vaccines.

## INDIAN EXPERT TALK

**Dr. Suresh Ramasubban**, senior consultant pulmonary & critical care medicine at Apollo hospital, Kolkata who has been bestowed with many awards, such as ACCP Research Award, Best Research Award, Residency Program, was the Indian expert who presented the case-based discussion on hospitalized COVID-19 patients.

The speaker discussed a couple of cases on hospitalized COVID-19 patients, the risk of VTE, and its management.

Majority of the ICU patients along with reduced mobility will have some of the risk factors such as heart failure or respiratory failure, rheumatologic disease, acute myocardial infection, ischemic stroke or infection/sepsis, and obesity. According to the Padua risk score, an ICU patient with reduced mobility and any one of the above-mentioned risk factors is at high risk of VTE and needs prophylaxis. **And the question that comes here is whom not to give prophylaxis if hospitalized in intensive care unit.** Guidelines recommend anticoagulant thromboprophylaxis over no thromboprophylaxis in acutely/critically ill hospitalized COVID-19 patients unless contraindicated. Hospitalized COVID-19 patients should receive VTE prophylaxis unless contraindicated.

## VTE prophylaxis in critically ill hospitalized COVID-19 patients

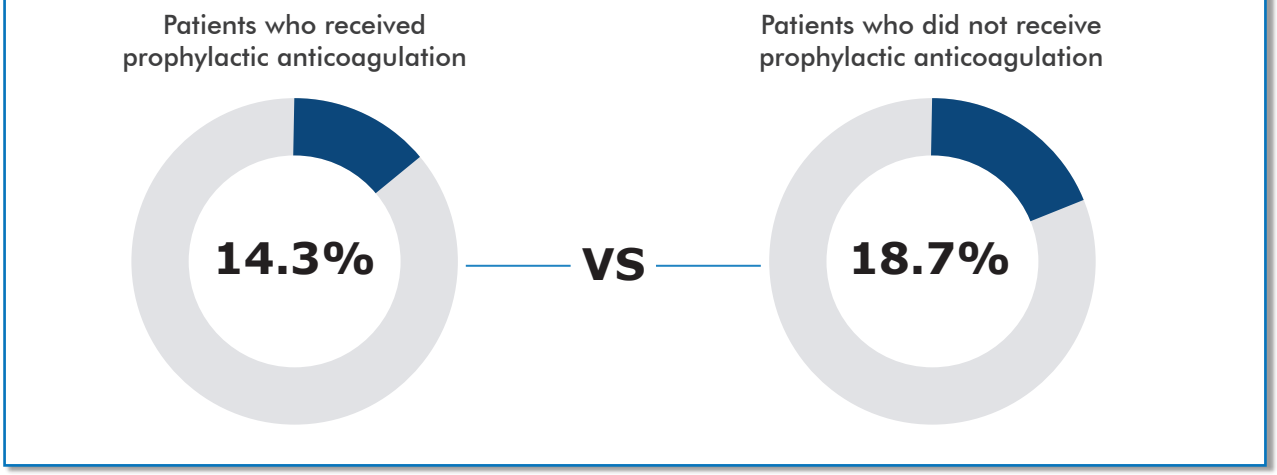
- **ASH 2021:** The guideline recommends prophylactic-intensity over intermediate-intensity or therapeutic-intensity anticoagulation for patients with COVID-19–related acute illness who do not have suspected or confirmed VTE. LMWH is recommended over UFH to reduce contact.

- **NICE 2021:** Consider a standard prophylactic dose of LMWH as soon as possible and within 14 hours of admission to young people and adults with COVID-19 who need low-flow or high-flow oxygen, continuous positive airway pressure, non-invasive ventilation, or invasive mechanical ventilation and who do not have an increased bleeding risk. Treatment should be continued for a minimum of 7 days, including after discharge.

## Early use of prophylactic LMWHs

Prophylactic anticoagulation within 24 hours in hospitalized COVID-19 patients associated with decreased risk of 30 - day mortality and no increased serious bleeding risk.

Box 3: Rate of VTE in patient receiving vs not receiving prophylactic anticoagulation

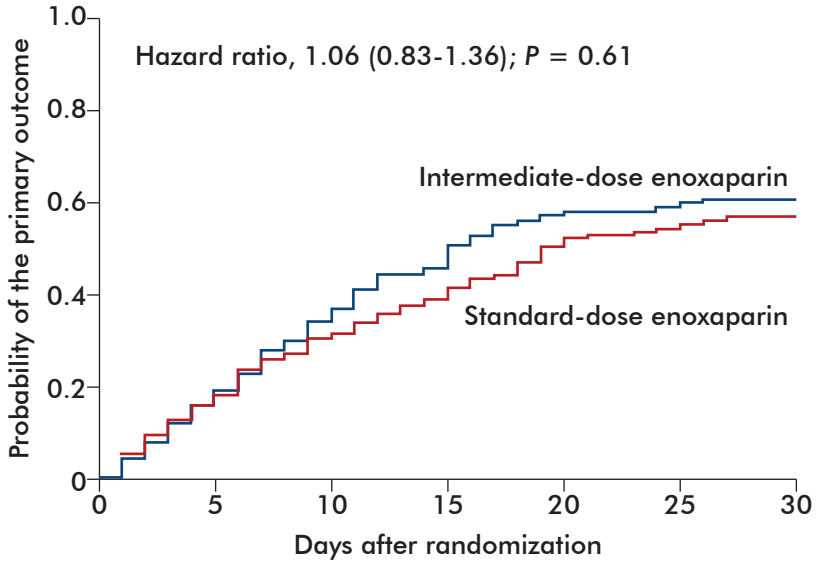



## Intermediate vs standard prophylactic anticoagulant dose

According to the INSPIRATION randomized clinical trial, intermediate-dose prophylactic anticoagulation compared to standard-dose prophylactic anticoagulation in patients with COVID-19 admitted to the ICU did not result in a significant difference in the primary outcome of a composite of venous or arterial thrombosis, treatment with extracorporeal membrane oxygenation, or mortality within 30 days.

In another study by Lopes *et al*. 2021, reported in patients hospitalised with COVID-19 and elevated D-dimer concentration, in-hospital therapeutic anticoagulation with rivaroxaban or enoxaparin followed by rivaroxaban to day 30 did not improve clinical outcomes and increased bleeding compared with prophylactic anticoagulation. Therefore, use of therapeutic-dose rivaroxaban, and other direct oral anticoagulants, should be avoided in these patients in the absence of an evidence-based indication for oral anticoagulation.

## Box 4: Intermediate dose vs standard dose prophylactic among patients with COVID-19 admitted to ICU




| No. of patients at risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| Intermediate dose | | | | | | | |
| Total | 276 | 235 | 196 | 175 | 156 | 154 | 150 |
| Primary outcomes | 0 | 41 | 39 | 21 | 19 | 2 | 4 |
| All-cause mortality | 0 | 37 | 41 | 20 | 16 | 2 | 2 |
| VTE | 0 | 4 | 1 | 1 | 2 | 0 | 0 |
| Ischemic stroke | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Standard dose | | | | | | | |
| Total | 286 | 244 | 211 | 194 | 173 | 167 | 160 |
| Primary outcomes | 0 | 42 | 33 | 17 | 21 | 6 | 7 |
| All-cause mortality | 0 | 38 | 29 | 17 | 21 | 6 | 6 |
| VTE | 0 | 3 | 4 | 1 | 2 | 0 | 1 |
| Ischemic stroke | 0 | 1 | 0 | 0 | 0 | 0 | 0 |

**In critically ill COVID-19 patients, pharmacological VTE prophylaxis is recommended over mechanical prophylaxis. LMWH (enoxaparin) dose appropriately adjusted for renal function and/or weight, is the preferred agent for thromboprophylaxis in hospitalized COVID-19 patients. No thromboprophylaxis is currently recommended after hospital discharge in patients with COVID-19.**

## Box 5: VTE prophylaxis for all hospitalized highly suspected or confirmed COVID-19 patients

| CrCl | ≥30 mL/min | 29–10 mL/min | <10 mL/min |
|---|---|---|---|
| | Enoxaparin | | Heparin |
| BMI less than 40 | 40 QD | 30 QD | 5000 U q8h |
| BMI 40 or greater | 40 BID | 40 QD | 7500 U q8h |

*For patients <50 kg and age >80 YO, dose adjustment to Heparin 5000 units SubQ q12 hour
If pharmacologic prophylaxis contraindicated (active bleeding, PLT <25-30K): SCDs

**MONITORING:**
**CrCl and CBC: Daily for critically ill, or every 2-3 days for other hospitalized**
**PTT, PT/INR, D-dimer, fibrinogen: Every 2-3 days**

## Box 6: Preferred treatment regimens for highly suspected or confirmed VTE cases

| CrCl | |
|---|---|
| CrCl >30 mL/min | Enoxaparin 1 mg/kg SubQ q12h |
| CrCl 29–10 mL/min | Enoxaparin 1 mg/kg SubQ q24 |
| CrCl <10 mL/min | Heparin infusion for venous thromboembolism |

THERAPEUTIC ANTICOAGULATION MONITORING
**DAILY: CrCl and CBC**
Every 2-3 days: PTT, INR/PT, D-dimer, fibrinogen

## COVID-19 patient diagnosed with VTE

**ACCP (2020) recommendations in proximal DVT or PE**

**VTE treatment in acutely ill hospitalized COVID-19 patients**

- Initial parenteral anticoagulation with therapeutic weight adjusted LMWH or IV UFH.
- Initial oral anticoagulation with apixaban or rivaroxaban recommended in patients without any drug-to-drug interactions. Dabigatran and edoxaban can be used after initial parenteral anticoagulation. Vitamin K antagonists can be used after overlap with initial parenteral anticoagulation.
- Systemically administered thrombolytics recommended in both acute, objectively confirmed PE and hypotension or signs of obstructive shock due to PE, and without high risk of bleeding.

- Against use of systemic thrombolysis, catheter-directed thrombolysis or thrombectomy for most patients without objectively confirmed VTE.

**VTE treatment in critically ill hospitalized COVID-19 patients**

- Parenteral (LMWH or fondaparinux over UFH) over oral anticoagulant therapy.
- In patients with COVID-19 and acute PE with cardiopulmonary deterioration due to PE after initiation of anticoagulant therapy who have not yet developed hypotension and who have low risk of bleeding, systemic thrombolytic therapy over no such therapy is recommended.
- Switching to therapeutic weight-adjusted LMWH recommended in COVID-19 and recurrent VTE despite anticoagulation with apixaban, dabigatran, rivaroxaban or edoxaban, or vitamin K antagonists (in therapeutic range).

**Summary of Indian expert talk:**

- All hospitalized COVID-19 patients should receive VTE prophylaxis unless contraindicated.
- LMWH is recommended over UFH as thromboprophylaxis for critically ill COVID-19 patients.
- LMWH, fondaparinux or UFH is recommended over DOAC as thromboprophylaxis for acutely ill hospitalized COVID-19 patients.
- No thromboprophylaxis after hospital discharge is recommended in COVID-19 patients.
- For patients with COVID-19 and confirmed VTE, consider LMWHs, fondaparinux, UFHs or DOACs for VTE treatment and should be continued for a minimum duration of 3 months

## Question and answer session

**Q1 Many a times the creatinine is high especially in the second wave of COVID-19. Can we use UFH or others instead? Do we then use aPTT and at what range?**

Ans The decision needs to be taken on the degree of dysfunction. If the renal function is rapidly declining, switch should be made to UFH. If UFH is used for prophylaxis at prophylactic dose, there is no need to monitor aPTT.

**Q2 Is thrombolysis not considered due to different type of fibrinogen or risk of bleeding?**

Ans There is a complex mechanism involved in the thrombolysis in COVID-19 patients, involving tissue factor and TPA. Recommendation for indications for thromboprophylaxis should be the same as in non-COVID patient. In case of life-threatening pulmonary embolism, sustained hypertension, or cardiac syncope, use the same approach as these patients are at higher risk of bleeding. In most severe cases of ARDS, the degree of pulmonary hemorrhage is significant, and we may worsen that with bleeding. Until we have better prospective data, the approach should be same as non-COVID patient.

**Q3 Will clinical deterioration be an appropriate reason to increase from OD to BD enoxaparin?**

Ans Patient with ARDS, who is stable radiologically or can't make out what's really happening or deteriorating as far as oxygenation is concerned. So, the risk of PE is raised especially in patients with high D-dimer levels. So, considering the D-dimer levels and CT angiography, a joint decision by all stakeholders such as by intensivist, family should be taken whether to increase the dose to therapeutic level.

**Q4 Some post COVID-19 patients have been complaining of stiff lung symptoms even after 2-3 months of recovery. Do they require OAC therapy?**

Ans There is no data in these group patients. The stiff lung symptoms can be due to the diffuse alveolar damage. OAC can be considered if the patient has other indications and is immobile even after 2-3 months of recovery.

**Q5 Should we add clopidogrel to the management if the platelets are hyperactive?**

Ans Multiplatform trials are ongoing, where anti-platelet is tested in hospital and post-discharge along with heparin. There is no conclusive evidence yet.

**Q6 Is development of VITT a result of the vaccine or host response to vaccine?**

Ans Yes, VITT is thought to be due to the vaccine itself, as it is observed in a subset of people receiving ADENOVIRAL vector-based vaccine. This effect is not seen in other group of population receiving other vaccine. There is a debate going on, if these people survive of VITT, whether the second dose of vaccine should be given.

**Q7 Patients with COVID-19 in second wave with D-dimer more than 4000 and on ventilator, which anticoagulant, and dose is recommended?**

Ans Heparin based anticoagulant can be used either enoxaparin or UFH. Use standard dose prophylaxis eg. 40 mg enoxaparin OD. Some consideration can be given depending on the weight.

**Dr. Ramakrishnan summarized the session:**

- VTE is real phenomenon in most hospitalized patients with COVID-19 similar to hospitalized patients for other conditions/infections.
- Both venous and arterial thrombosis is observed in post COVID-19 patients.
- VTE prophylaxis with LMWH or heparin is absolutely essential. Giving additional or therapeutic doses are currently not recommended on routine basis.
- D-dimer has been followed for various patients, but we don't know what those numbers really mean and to base the decision on anticoagulating on full dose is not scientifically justified.

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