

# Venous Thromboembolism in COVID-19: Are Women Different?

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## Abstract

The epidemiological data suggests predominant male prevalence, morbidity and mortality with SARS COVID-2. Similarly, venous thromboembolic (VTE) events have a male sex predilection with variant mechanisms involving angiotensin-converting enzyme 2 (ACE-2) expression and pathways in women. COVID-19 could directly affect or it could be an indirect action of the disease via critical ailment hypoxemia, or hemostatic abnormalities might be the underlying mechanisms of VTE in a COVID-19 patient with baseline risk factor profile. VTE diagnosis in a COVID scenario has issues of a prone positioned patient, exposure of health workers and minimal therapeutic benefits in a critically ill patient with acute respiratory distress syndrome (ARDS). Anticoagulation with low-molecular weight heparin (LMWH) can be chosen over unfractionated heparin (UFH) with less monitoring requirements and thereby low exposure to healthcare workers. Variant guidelines for thromboprophylaxis (in hospital/extended postdischarge) have come up, stating anticoagulant administration, according to baseline risk profile and hemostatic biomarkers. Catheter-directed interventions should be reserved only for life-threatening situations. In women, hormonal milieu (for e.g., 17  $\beta$ -estradiol) might influence occurrence of favorable ACE 2 polymorphisms with less VTE events. The management strategies in a female patient with VTE would be more or less similar to males. Combined oral contraceptives (COC) and estrogen replacement therapies (ERT) may be curtailed in COVID-19 positive patients, given their thrombogenic potential. Pregnancy and postpartum state in COVID-19 positive patient need VTE prophylaxis all the more in the presence of risk profile favoring VTE. Also, VTE prophylaxis when indicated should be continued in women in a normal menstrual cycle. Bleeding risks specific to women (menorrhagia secondary to dysfunctional uterine bleeding [DUB], fibroids, adnexal malignancies and masses, hypothyroidism, etc.) need to be weighed while taking a decision for indicated anticoagulation regimen.

## Keywords

- ▶ COVID
- ▶ thromboembolism
- ▶ thromboprophylaxis
- ▶ venous
- ▶ women

## Introduction

The epidemiological data suggests predominant male prevalence, morbidity and mortality with SARS COVID-2.<sup>1</sup> Similarly, venous thromboembolic (VTE) events have a male sex predilection with variant mechanisms involving angiotensin-converting enzyme 2 (ACE-2) expression and pathways.<sup>2</sup> The present review aims to analyze the burden,

mechanism and management strategies studied so far in the COVID-19 pandemic. It also attempts to visualize the mechanisms and variant management strategies of VTE events in women versus men.

The COVID-19 pandemic can be responsible for VTE disease via several mechanisms. These mechanisms could be a candid action of COVID-19, an implicit effect of the disease

via critical ailment hypoxemia, or hemostatic abnormalities which might ultimately predispose the patient to disseminated intravascular coagulation (DIC). Moreover, SARS, critical illness and baseline risk factor profile might predispose a patient to developing VTE.

The novel antitherapeutic therapy of COVID-19 might interact with antiplatelets and anticoagulants in the patients with thromboembolic disease. In a retrospective analysis by Tang et al<sup>3</sup> among 183 patients with COVID-19, an overall mortality of 11.5% was observed. This era might also affect the care and management of the patients who do not have COVID-19 but have pre-existing thrombotic or thromboembolic ailments.

VTE events have a lesser predilection for fair sex. Variant biology, hormonal milieu, menstrual phases, and select bleeding risks are issues specific to women. Although the management strategies and guidelines do not differentiate between the two sexes with regard to VTE, pertinent issues need an addressal in women. After presenting the baseline data for VTE in COVID-19, this review discusses the issues different and special to women prior to conclusion.

### Hemostasis Markers

Mild thrombocytopenia and increased D-dimer values are the usual hematological parameters noticed in COVID-19 positive subjects. Besides D-dimer, prolonged prothrombin time, international normalized ratio (INR) and thrombin time have also represented the intensity of disease severity.<sup>4</sup> Cytokine storm in a patient with COVID-19 predisposes to a SARS-like condition.

Raised D dimer has been linked with poor prognosis and an increased incidence of needing mechanical ventilation and ICU care and mortality in patients with COVID-19.<sup>5</sup> As much as 71.4% deaths in a study had criteria for DIC. In these patients, 3.5- and 1.94-fold rise in D-dimer and fibrin degradation products (FDP) was reported. The prothrombin time (PT) was also prolonged in the nonsurvivors by 14% ( $p$  value < 0.001).<sup>3</sup> In yet another study from Netherlands, 31% of the 184 ICU admitted critical patients had thrombotic events, most commonly VTE.<sup>4</sup>

Whether the hematological abnormalities noted in SARS-COV-2 patient are a cause or result of the cytokine storm is still being evaluated. Moreover, hepatic dysfunction in these patients might lead to changes in hemostatic parameters. The role of antiphospholipid antibodies predisposing to thrombotic events in a patient with COVID-19 is also being studied.

### Pathophysiology of VTE in COVID

The pathophysiology of VTE in a patient with SARS-COV-2 infection can be studied under the headings: base line risk profile of the patient, hematological abnormalities, and clinical manifestations.

### Baseline Risk Profile

The baseline risk profile of the patient might be inclusive of several risk factors predisposing to VTE diseases. These risk factors could include a patient admitted with acute critical

illness, a bedridden state predisposing to stasis, underlying genetic abnormalities, fever, gastroenteritis, sepsis, hepatic injury, underlying chronic kidney disease or chronic obstructive airway diseases, underlying heart failure, or malignancies predisposing to VTE. In female gender, the state of pregnancy and postpartum states are particularly noted to be hypercoagulable, especially in presence of other VTE risk factors. Moreover, women on combined oral contraceptives (COC) and estrogen replacement therapy (ERT) have aggravated risk of VTE. COC use is associated with 2 to 6 folds increase in VTE risk, while in pregnancy, the risk increases by 4 to 5 folds.

### Hematological Abnormalities

In a subject infected with SARS-COV-2, underlying risk factors might lead to activation of inflammatory mediators. Inflammatory cytokines like interleukin-6 and C-reactive protein (CRP) might further increase with a predisposition to developing superimposed infections. Endothelial dysfunction and haemostatic activation might follow this activated inflammatory response. Increase in tissue factor, Von Willebrand factor and hemostatic abnormalities like lymphopenia and thrombocytopenia might ensue. Hepatic involvement might lead to decreased coagulation and anti-thrombin formation, thereby predisposing to thrombotic abnormalities.

### Clinical Manifestations

These hemostatic abnormalities ultimately culminate into VTE events like pulmonary micro or macro thromboembolism and intravascular coagulopathy. Moreover, an elevation in cardiac biomarkers like troponins and myocardial injury also ensue. VTE risk has been reported to be maximal in patients who are critically ill and hospitalized. The risk estimates in COVID-19 outpatients are not yet available.

### VTE Prophylaxis in COVID-19

Wang et al<sup>6</sup> highlighted the importance of VTE prophylaxis in COVID-19 patients. They reported increased VTE risk in up to 40% of their hospitalized COVID-19 patients.<sup>6</sup> Administration of all scheduled doses of VTE prophylaxis should be ensured to avoid untoward events with worse clinical outcomes. A daily dosing regime of low-molecular weight heparin (LMWH) has an advantage over unfractionated heparin (UFH) with twice daily doses in COVID 19 by reducing the use of PPE and exposing the COVID-19 healthcare workers (HCWs). Daily LMWH or subcutaneous UFH has been advocated by WHO in admitted COVID-19 subjects. Mechanical VTE prophylaxis via intermittent pneumatic compression could be considered in subjects (especially in sedentary ones) with contraindications to prophylactic anticoagulation.<sup>4,7</sup>

In pregnant and postpartum patients with COVID-19, although the data is limited, it can be assumed that they are predisposed to VTE.<sup>8,9</sup> Risk assessment of a pregnant patient with COVID-19 is prudent, and pharmacological thromboprophylaxis in these pregnant patients with SARS-COV-2 should be considered all the more in the presence of baseline increased VTE risk.

The data specific to COVID-19 with regard to extended VTE prophylaxis is minimal. Hence, in patients with SARS-COV-2 infection, individualization of the treatment and weighing the risk and benefits of the tendency to developing VTE versus the hemorrhagic risk of patient needs to be done. A prolonged and extended prophylaxis for up till 45 days might be offered to COVID-19 subjects with elevated VTE risk, for example, patients with comorbidities like active cancer, patients with decreased mobility and according to expert opinion in some cases more than twice the increase in upper limit of D-dimer values with low-bleeding risk and increased body mass index (BMI) ( $\geq 30 \text{ kg/m}^2$ ).

In mild COVID-19 subjects in quarantine, the role of pharmacological prophylaxis is yet uncertain; hence mobility at home should be recommended. The pharmacological prophylaxis in these patients could be reserved for high-risk VTE subjects, for instance, in those patients who have reduced mobility, a previous history of thromboembolic event or in those who have active ongoing malignancy.<sup>4</sup>

### Diagnosis of Venous Thromboembolism (VTE)

Raised D-dimer, a marker of severity of COVID-19, might not routinely indicate an underlying VTE process.<sup>10</sup> A VTE event should be suspected in a patient of COVID-19 when the subject develops typical deep vein thrombosis (DVT) symptoms, hypoxemia which is out of proportion to the underlying respiratory pathology or development of acute unexplained right ventricular (RV) dysfunction. The diagnostic challenges in a patient with COVID-19 for VTE are as follows

1. Infection spreading to HCWs and inpatients via an unstable COVID-19 subject.
2. Prone position in a patient with severe acute respiratory distress syndrome (ARDS) limiting the imaging studies.
3. Critical ailment and prone position not permitting the required investigations for DVT.
4. Grave prognosis of the patient with COVID-19 with ARDS requiring prone position might not benefit with any other therapeutic intervention, even if underlying VTE is diagnosed.

Echocardiography might be considered to look for worsening RV dysfunction and diagnosis of RV clots/clot in transit in COVID-19 subjects.<sup>11</sup>

### Empiric Therapeutic Anticoagulation

In a single-center small sampled Chinese study, D-dimer more than 1500 g per mL was believed to have sensitivity of 85 and specificity of 88.5% for detection of VTE episodes.<sup>4</sup> Prophylactic anticoagulation is still preferred over therapeutic anticoagulation (intermediate or full dose) in subjects with yet unconfirmed VTE. The optimal anticoagulant dose has not yet been determined, although suggestions of benefit exist across some studies.

Tang et al stated a decrease mortality in patients on anticoagulant treatment with severe COVID-19 manifestations.<sup>12</sup> Incident VTE of 25% and 31% in severe COVID patients in

two studies from China and Netherlands has been reported, respectively. While the study from China noted that VTE prophylaxis was not administered to any of these patients, in the other study, all the incident VTE patients were administered prophylactic anticoagulation, although lower dosing was an observation in some subjects. Under diagnosis of VTE in severe COVID-19 subjects is possible, especially when ARDS might itself potentiate hypoxic pulmonary vasoconstriction, pulmonary arterial hypertension followed by RV dysfunction.

### Therapeutic Anticoagulation in Patients with Diagnosed Venous Thromboembolism

Once the diagnosis of VTE is confirmed, the choice of therapeutic anticoagulant would be determined by renal, hepatic, and gastrointestinal functions in a given patient as well as hematological parameters, for example, any associated thrombocytopenia and deranged haemostatic markers. UFH might be preferred by several physicians in hospital settings, given its transient effects and rare drug interactions with upcoming COVID-19 therapy. However, maintenance of therapeutic activated partial thromboplastin time (APTT) ratio with UFH requires recurrent HCW exposure to the patients; hence, LMWH could be the choice. NOACs could be preferred in these patients with their benefits of lack of need of monitoring and ability to continue at equivalent doses at times of discharge. However, drug interactions of novel oral anticoagulants (NOACs) can be an issue, for instance, apixaban and betrixaban might need doses to be adjusted in COVID-19 patients being administered lopinavir and ritonavir. Edoxaban and rivaroxaban should not be administered together with these agents due to potential interactions. Once stabilized, the patients of COVID-19 can be administered NOACs or LMWH at the discharge. This would help in limiting the need for recurrent INR monitoring and exposure of HCWs. Also, in organ dysfunction in a patient with severe COVID-19, the use of these drugs can be tedious, especially due to lack of effective reversal agents.

### Catheter-Directed Therapy for VTE

In a given patient with COVID-19 along with acute DVT, anticoagulation with home treatment, wherever feasible, should be encouraged. Endovascular therapies with local fibrinolysis or embolectomy should be reserved in occasional cases with phlegmasia or truly refractory symptoms.

Similarly, in patients with intermediate risk hemodynamically stable pulmonary embolism (PE), anticoagulation with close monitoring should be encouraged. Rescue systemic fibrinolysis may be considered in patients with further deterioration or hemodynamically unstable high-risk patients with massive PE. Catheter-based therapies should be reserved only in the cases where systemic fibrinolysis may not be feasible in the settings where infection control is well-equipped, appropriate and equivalent. Bedside extracorporeal membrane oxygenation (ECMO) might be considered in COVID-19 positive patients rather than utilization of

interventional modalities needing cardiac catheterization laboratories or operating rooms.<sup>13</sup>

The use of inferior vena cava (IVC) filters should be minimized to cases with recurrent PE in spite of adequate anticoagulation or in those with absolute contraindication to anticoagulation.

### Approach to Non COVID-19 Patients with VTE

In patients without COVID-19 and acute VTE, outpatient management or an early discharge should be preferred. Telemedicine could be opted methodology of follow-up. With regard to pharmacotherapy, these patients could be maintained on NOACs or LMWH to avoid recurrent contact with HCWs for maintenance of INRs in patient receiving vitamin K antagonizes.

In patients already receiving vitamin K antagonizes, extending INR testing in intervals could be suggested if prior INRs have been stable. Home-based INR checks or drive through INR testing should be encouraged, although switching to a NOACs or LMWH would be the clinically appropriate strategy wherever feasible.

### Synopsis of Guidelines and Position Papers on Venous Thromboembolism

Standard dose thromboprophylaxis in hospitalized COVID-19 patients has been advocated by Chinese (CMDA),<sup>14</sup> ISTH,<sup>15</sup> and Thrombosis-UK<sup>16</sup> recommendations. However, intensified anticoagulation varying with disease severity (clinically/hematological or other biological parameters) has been recommended by CCS,<sup>17</sup> GIHP, GFHT,<sup>18</sup> NIPHN,<sup>19</sup> GTH,<sup>20</sup> SSC<sup>21</sup> and Swiss Haematology<sup>22</sup> Society.

Full-dose therapeutic anticoagulation based on inflammatory markers in oxygen-dependent patients or patients documenting rising D-dimer on prophylactic treatment has been recommended by four guidelines.

ASH guidelines,<sup>23</sup> the CMDA,<sup>14</sup> the CCS<sup>17</sup> recommendations, the GTH,<sup>24</sup> Siset,<sup>25</sup> and the ISTH/NATF/ESVM/IUA<sup>26</sup> position paper recommend extended prophylaxis postdischarge up to 45 days in high-risk VTE subjects with a low-bleeding risk.<sup>25</sup> Standard dose thromboprophylaxis is recommended in outpatient COVID-19 patients with multiple VTE risk factors by the Siset and the GTH guidelines. The ISTH/NATF/ESVM/IUA consensus paper suggests individualization of thromboprophylaxis in patients with increased VTE risk without high-bleeding risk (► **Table 1**).

Although the guidelines do not differentiate between male and female sex with regard to VTE management, issues pertinent to female sex need to be addressed. A hypercoagulable state of pregnancy and postpartum period warranting adequate thromboprophylaxis need special consideration, especially in the presence of other VTE risk factors. VTE prophylaxis when indicated should be continued in women in a normal menstrual cycle. Bleeding risks specific to women (menorrhagia secondary to dysfunctional uterine bleeding [DUB], fibroids, adnexal malignancies and masses, hypothyroidism, etc.) need to be weighed while taking a decision for indicated anticoagulation regimen.

### COVID-19 Positive Women with Venous Thromboembolism—What's Different?

The SARS COVID-2 pandemic has so far appeared to have higher death rate in the presence of comorbidities and among men. Higher prevalence of morbidity and mortality in men raises a possibility of sex-dependent susceptibility. Males could be more susceptible to SARS COVID-19 disease due to variant involvement of ACE-2. ACE-2, when activated by the spike protein of SARS COVID-2 virus, is associated with the penetration of the same into the epithelial cells and myocardium.<sup>2</sup> 17  $\beta$  estradiol has been known to increase the expression and activity of this enzyme in adipose tissue as well as the kidneys.<sup>27</sup> Higher myocardial ACE-2 expression has been seen in the male hypertensive mice which resolves soon after orchiectomy.<sup>28</sup>

An increased mortality with VTE events has been known to be associated with COVID-19, especially in the critically sick ICU patients. The mortality, which is secondary to VTE events, is even more in the hypogonadal men on treatment with testosterone, especially in patients with greater genetic predisposition. Even further emerging are the epidemiological aspects of a variant expression of ACE-2 under the influence of sex hormones. ACE-2 is expressed in both mouse and human adult Leydig cells but in a testosterone-independent manner. ACE-2 has its role in ovarian granulosa cells with its expression rising with a rise in LH. A higher mortality has been reported in men due to higher cardiovascular and myocardial involvement secondary to the viral infection with COVID-19 via the ACE-2 pathway. Hypothesis of ACE-2 expression in the myocardium being modulated by androgen and the role of androgen receptor gene polymorphisms cannot be ruled out in the COVID-19 positive male patients.<sup>28-30</sup>

Similarly, the concern of increased VTE events in the patients receiving the testosterone is rising. A recent cross-over study with 39622 men, with 3110 having hypogonadism was done.<sup>29</sup> A higher VTE risk was found in males, with and without hypogonadism, who were on testosterone replacement therapy. The risk was all the more higher in patients with Klinefelter syndrome.<sup>30</sup> While testosterone administration needs to be halted in patients in the era of SARS COVID-2 pandemic, given its association with increased VTE events which could be lethal, there is a suggestion of considering ERT in hypogonadal and postmenopausal women. This could also suggest the involvement of polymorphisms of androgen receptor activator and repressor proteins<sup>31</sup> and the role of selective androgen receptor modulators (SERM) as therapeutic agents in men in the era of the COVID-19 pandemic.<sup>32</sup>

Barring one study by Cui et al,<sup>33</sup> in which a female predilection for VTE was found to the tune of 64% in women versus 46% men getting affected, almost all the other studies have shown a higher predilection of VTE events in the male population. Spiezia et al<sup>34</sup> and Ranucci et al<sup>35</sup> reported 91% and 94% of subjects having VTE as males, whereas most of the other studies reported 60 to 80% of their subjects with COVID-19 having VTE as men.<sup>36</sup>

The management strategies in a female patient with VTE would be more or less similar to males. However, pregnancy and postpartum state in women could be a consideration,

**Table 1** VTE patient characteristics across several studies

Study	Study Population	VTE diagnostic criteria	N	Age (median or mean)	Men	Women	Percentage of patients on thromboprophylaxis	Percentage of patients with PE	Percentage of patients with DVT
Cui et al <sup>33</sup>	ICU in patients with COVID-19	Objective imaging of DVT; no PE	81	60 years	46%	64%	0%	N/A	24.6%
Grein <sup>43</sup>	In patients treated for severe COVID-19 infections and hypoxemia	DVT; no PE	53	64 years	75%	25%	n/a	N/A	5.66%
Grillet <sup>44</sup>	In patients with COVID-19	PE on performed angio-CT; no DVT	280	n/a	N/A	N/A	n/a	23/280 8.21%	n/a
Helms et al <sup>20</sup>	ICU in patients with COVID-19 ARDS	Objective imaging of PE and unclear diagnosis for DVT	150	63 years	81%	19%	100% (30% therapeutic)	25/150 16.6%	2%
Klok <sup>38,39</sup>	ICU in patients with COVID-19	Objective imaging (PE and DVT)	184	64 years	76%	24%	100%	65/184 35.3%	1.63%
Litjos <sup>40</sup>	ICU in patients with COVID-19	Objective imaging (+ TEE for PE)	26	68 years	77%	23%	100% (69% therapeutic)	6/26 23.07%	53.8%
Lodigiani <sup>45</sup>	In patients with COVID-19	Objective imaging (PE and DVT)	388	66 years	68%	32%	79% (29% therapeutic)	10/362 2.76%	1.65%
Poissy <sup>41</sup>	ICU in patients with COVID-19	Objective imaging of PE and DVT	107	57 years	59%	41%	100% (9% therapeutic)	22/107 20.5%	4.67%
Spiezia et al <sup>34</sup>	ICU in patients with COVID-19, without cancer	DVT	22	67 years	91%	9%	100%	Not stat-ed	22.7%
Ranucci et al <sup>35</sup>	ICU in patients with COVID-19, with mechanical ventilation	Not stated	16	61 years	94%	6%	100%	0/16 0	0
Thomas <sup>42</sup>	ICU in patients with COVID-19	Objective imaging of PE and/or DVT	62 <sup>‡</sup>	59	N/A	N/A	100%	5/62 8.06%	1.61%

Abbreviations: ARDS; acute respiratory distress syndrome; DVT, deep vein thrombosis; ICU, intensive care unit; PCR, polymerase chain reaction; PE, pulmonary embolism; RT-PCR, real-time PCR.

**Table 2** Guideline recommendations for VTE management

Body of guidelines	Recommendations of thromboprophylaxis in absence of bleeding risk)	Choice of anticoagulant	Weight adjustment	Consideration of disease severity	Biomarker consideration	Extended thromboprophylaxis
American Society of Hematology	Recommended in standard dose; in all hospitalized patients with COVID-19	LMWH or fondaparinux over UFH to reduce contact	Dose adjustment for obesity may be used per institutional guidance	No	N/A	Consider extended thromboprophylaxis after discharge after a regulatory-approved regimen
Chinese Consensus Statement	Recommended in standard dose in severe or critically ill patients and according to RAM for mild or moderate patients; yes, in ambulatory patients according to RAM for medical inpatients	LMWH or UFH	Yes, in severely or critically ill patients only; enoxaparin 6000 IU od. for weight 90–130 kg and 4000 IU bid if > 130 kg	No (except in obese patients).	D-dimers may be part of the assessment of VTE risk and promote in-creasing the dose of anticoagulant	Yes, if perceived to have persistent risk for VTE
Chinese Medical Doctor Association	Recommended in standard dose, according to risk assessment	LMWH or UFH	N/A	No	No	Consider extended thromboprophylaxis after discharge according to VTE risk
GHP/GFHT	Recommended in standard dose	LMWH or UFH or fondaparinux	Yes, if BMI > 30 kg/m <sup>2</sup> , intermediate dose: enoxaparin 40 mg b.i.d. < 120 kg and 60 mg b.i.d. > 120 kg; therapeutic dose if additional risk factors (active cancer, past history of VTE in the past 2 years) and high-flow oxygen/ mechanical ventilation	Yes, if high flow oxygen therapy or mechanical ventilation, intermediate dose; therapeutic dose if additional risk factors (active cancer, past history of VTE in the past 2 years); therapeutic dose if ECMO	Yes (fibrinogen > 8 g/L or D-dimers > 3000 ng/m or rapidly increasing D-dimer levels), therapeutic dose	n/a
Society of Thrombosis and Haemostasis	Recommended in all hospitalized patients and in ambulatory patients with D-dimer ≥1.5–2.0 mg/L; standard dose	LMWH	Yes, if BMI > 30 kg/m <sup>2</sup> , intermediate dose	Yes, in ICU patients; intermediate dose	Yes, if rapid in-crease of D-dimers; intermediate dose	Yes, if persistent inflammation or immobilization or BMI >30 kg/m <sup>2</sup> or previous history of VTE or active cancer
International Society on Thrombosis and Hemostasis (ISTH)	Recommended in no particular dose mentioned; in all inpatients	LMWH	N/A	N/A	No	N/A

Table 2 (Continued)

Body of guidelines	Recommendations of thromboprophylaxis in absence of bleeding risk)	Choice of anticoagulant	Weight adjustment	Consideration of disease severity	Biomarker consideration	Extended thromboprophylaxis
ISTH- North American Thrombosis Forum European Society of Vascular Medicine - International Union of Angiology	Recommended in following a risk stratification rule for inpatients, standard dose (majority of panel members); considered for outpatients at high-VTE risk	LMWH or UFH	N/A	N/A	N/A	Yes, up to 45 days, for patients with elevated risk of VTE (reduced mobility, active cancer, ± elevated D-dimers) and with low risk of bleeding
National Institute for Public Health of the Netherlands	Recommended in all hospitalized patients, standard dose	N/A	N/A	N/A	Consider therapeutic anticoagulation if D-dimers at admission > 1000 ng/mL and increase during follow-up and imaging for VTE or PE not feasible	N/A
Italian Society for Thrombosis and Haemostasis	Recommended in all inpatients and in ambulatory patients with pre-existing risk factors (i.e., reduced mobility, BMI > 30, previous VTE, active cancer, etc.), standard dose	LMWH or UFH or fondaparinux	Yes (BMI > 30 kg/m <sup>2</sup> ), intermediate dose (enoxaparin 40 mg b.i.d.)	N/A	No	Yes, 7–14 days in cases of pre-existing or persisting VTE risk factors (i.e., reduced mobility, BMI > 30 kg/m <sup>2</sup> , previous VTE, active cancer, etc.).
Spanish Society of Cardiology	Recommended in all hospitalized patients; standard dose	LMWH or UFH	Yes, if BMI > 35 kg/m <sup>2</sup> : "increase dosage"	Yes, if severe respiratory insufficiency; intermediate dose (enoxaparin 1 mg/kg od.). Therapeutic dose if additional biological factors	Yes, if D-dimers > 6 × "normal" or > 2 of the following: CRP > 15, D-dimers > 3 × "normal," IL-6 > 40, ferritin > 1000, lymphopenia < 800; intermediate dose. Therapeutic dose if associated severe respiratory insufficiency	Yes, standard dose 7–10 days
Thrombosis–UK	Recommended in high risk patients (according to NICE/ASH stratification guidelines), standard dose	LMWH or UFH or fondaparinux	N/A	N/A	N/A	N/A
Swiss Society of Hematology	Recommended in all hospitalized patients; standard dose	LMWH or UFH	Yes (> 100 kg), no details	Yes (signs of hepatic or renal dysfunction or imminent respiratory failure), intermediate or therapeutic dose; therapeutic dose if ECMO.	Yes (large increase in D-dimers, severe inflammation), intermediate or therapeutic dose.	N/A

Abbreviations: BMI, body mass index; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IL, interleukin; LMWH, low-molecular weight heparin; n/a, not available; RAM, risk assessment models; UFH, unfractionated heparin; VTE, venous thromboembolism.

assuming an increased predilection for developing VTE when they are COVID-19 positive. Hence, considering thromboprophylaxis in this subset of female patients, especially when they have other associated VTE risk factors, is advisable.

► **Table 2** shows the percentage of women with VTE events in the variant COVID-19 studies as of now. In a recent study from Italy<sup>37</sup> published in mid July, persistent gender gap in occurrence VTE events was further emphasized. However, they believed an increased male predilection to be a representation of in-hospital population. Hence, occurrence of VTE in COVID-19 patients has a tendency to involve more men than women. Notwithstanding this gender gap, women deserve to be treated adequately for their VTE events with thromboprophylaxis as well as institute anticoagulant therapy when they get diseased by these events. Pregnancy and postpartum state in a COVID-19 positive patient deserve special attention, especially when they have other VTE risk factors.

#### Conflicts of Interest

None declared.

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