COVID-19-Associated Pulmonary Embolism: Review of the Pathophysiology, Epidemiology, Prevention, Diagnosis, and Treatment

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Abstract

COVID-19 is associated with endothelial activation in the setting of a potent inflammatory reaction and a hypercoagulable state. The end result of this thromboinflammatory state is an excess in thrombotic events, in particular venous thromboembolism. Pulmonary embolism (PE) has been of special interest in patients with COVID-19 given its association with respiratory deterioration, increased risk of intensive care unit admission, and prolonged hospital stay. The pathophysiology and clinical characteristics of COVID-19-associated PE may differ from the conventional non–COVID-19-associated PE. In addition to embolic events from deep vein thrombi, in situ pulmonary thrombosis, particularly in smaller vascular beds, may be relevant in patients with COVID-19. Appropriate prevention of thrombotic events in COVID-19 has therefore become of critical interest. Several changes in viral biology, vaccination, and treatment management during the pandemic may have resulted in changes in incidence trends. This review provides an overview of the pathophysiology, epidemiology, clinical characteristics, and risk factors of COVID-19-associated PE. Furthermore, we briefly summarize the results from randomized controlled trials of preventive antithrombotic

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therapies in COVID-19, focusing on their findings related to PE. We discuss the acute treatment of COVID-19-associated PE, which is substantially similar to the management of conventional non-COVID-19 PE. Ultimately, we comment on the current knowledge gaps in the evidence and the future directions in the treatment and follow-up of COVID-19-associated PE, including long-term management, and its possible association with long-COVID.

Coronavirus disease 2019 (COVID-19) is a contagious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] Although COVID-19 is mainly associated with respiratory morbidity, patients with COVID-19 have higher D-dimer levels and an increased risk of thromboembolic events, especially venous thromboembolism (VTE).[2,3] VTE can be related to an underlying coagulopathy, endothelial activation, and interalveolar (extravascular) fibrin deposition. The risk of VTE increases with the severity of illness, and is higher among hospitalized patients, in particular the critically ill.[1,2,4] Given the relation to cardiovascular risk factors and multimorbidity, an integrated and equitable approach has been promoted to manage the COVID-19 pandemic.[5,6]

There are several potential hypotheses for the excess of thromboembolic events in COVID-19.[7] After the SARS-CoV-2 entrance through the alveolar pneumocytes, local intense endothelial activation and a subsequent proinflammatory status ensue.[8–11] The production of neutrophil extracellular traps (NETs) may lead to heightened platelet activation and aggregation, and stimulate coagulation, which clinically manifests as thromboembolic events.[1,12] Immobility, the presence of antiphospholipid antibodies, hypoxia, inflammation, and baseline comorbidities that increase the risk of thrombosis are among other potential reasons for the excess risk of thrombosis in COVID-19.[13] Added to this is the clinical and pathophysiological associations of thrombosis with some vaccines used for preventing COVID-19.[14]

Among VTE events, pulmonary embolism (PE) has been closely related to COVID-19, which has resulted in the term *COVID-19-associated PE*. Besides embolism from deep vein thrombosis (DVT) of lower extremities, another possible mechanism of PE in this setting is in situ thrombosis in pulmonary arteries, particularly affecting the distal pulmonary vasculature. This pathophysiology is supported by results from histopathological and some clinical studies.[15,16] The clinical significance of PE in patients with COVID-19 cannot be overemphasized as the excess insult on an already injured respiratory system has the potential for catastrophic consequences.[17,18] Furthermore, the long-term effects and outcomes are unknown.

In this review, we aim to provide insights into the pathophysiology, epidemiology, prevention, diagnosis, and treatment of COVID-19-associated PE. Ultimately, we will comment on the current gaps in the evidence and future research directions.

Pathophysiology

The pathogenesis of COVID-19-associated PE is still not completely understood but encompasses the effects of thromboinflammation at the alveolus, pulmonary interstitium, and pulmonary microvasculature levels.[1,2] The SARS-CoV-2 interacts with the type II pneumocytes through several membrane proteins, including the membrane-bound angiotensin-converting enzyme 2. This interaction can lead to a pneumocyte activation, production of thromboinflammatory cytokines, platelet activation, NETs formation, and coagulation stimulation, promoting an immune pulmonary intravascular coagulopathy which results in an in situ thrombosis of adjacent peripheral vasculature (►**Fig. 1**).[19,20] Furthermore, DVT and subsequent embolism can also lead to COVID-19-associated PE. In addition to immobility and venous stasis, as well as interaction between inflammation and coagulation cascade, patients with COVID-19 exhibit changes in circulating prothrombotic factors such as elevated factor VIII, fibrinogen, and hyperviscosity, which are associated with excess risk of thrombosis (►**Fig. 1**).[21] Although in situ thrombosis can be a specific mechanism in patients with COVID-19, both in situ thrombosis and embolic events can contribute to the overall COVID-19-associated PE pathogenesis.

Epidemiology

The reported incidence of COVID-19-associated PE varies significantly among the studies and meta-analyses.[22,23] Multiple reasons may explain such variability. First, the sample size and methodology of the included individual studies differ significantly, from small retrospective case series to large prospective and dedicated studies.[24] Second, the modality for diagnosis varies from underdiagnosis due to resource limitations or shortage of personal protective equipment to identification based on clinical suspicion to systematic screening of patients.[25,26] Third, the clinical status of the patients has been strongly correlated with the PE incidence. ICU patients had a higher risk of PE than non-ICU hospitalized patients; whereas non-hospitalized patients have a lower risk compared with hospitalized patients with COVID-19.[23] Furthermore, the concomitant anti-inflammatory and prophylactic antithrombotic therapy may affect the incidence.[27,28] Ultimately, most reported data were collected in 2020, before outbreaks with new variants such as delta (B.1.617.2) and omicron (B.1.1.529). Less is known about the risk of PE with these strains.[29] A small study

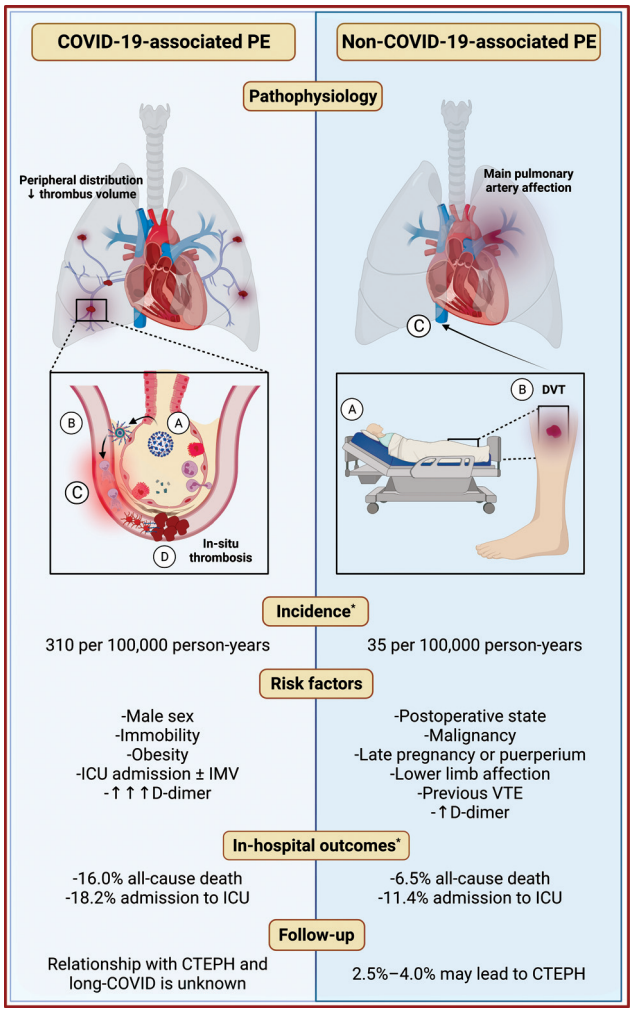

Fig. 1 Comparison of COVID-19-associated PE and non–COVID-19-associated PE. *COVID-19-associated PE*. Pathophysiology mechanism: (A) the infection by SARS-CoV-2 produces an intense endothelial activation of the pneumocytes leading to (B) an intense local inflammatory response by the inflammasome, which recruits inflammatory cells, (C) and promotes the formation of neutrophil extracellular traps (D) which induce platelet activation and aggregation with the subsequent in situ thrombosis in the peripheral vasculature. In severe cases, this phenomenon can be local and systemic. Although in situ thrombosis is a potentially frequent mechanism in COVID-19-associated PE, PE can also be produced by other mechanisms such as DVT embolization. *Non-COVID-19-associated PE* (conventional PE) is more common in (A) patients with immobility who are at risk of developing (B) lower extremity DVT with a posterior embolization to main pulmonary arterial branches. *Data extracted from a study analyzing patients treated in the emergency department before hospital admission; these rates may reflect the studied sample incidence and outcomes rather than the overall population incidence or outcomes.[44] DVT, deep vein thrombosis; IMV, invasive mechanical ventilation; VTE, venous thromboembolism; CTEPH, chronic thromboembolic pulmonary hypertension; PE, pulmonary embolism.

of patients treated in the emergency department in Utah suggested that the incidence of COVID-19-associated PE confirmed by computed tomography with pulmonary angiography (CTPA) is decreasing, possibly secondary to vaccination and the outbreak of new variants.[30] A large population study from Sweden reported that the risk of PE was highest among the first COVID-19 wave compared with the second and third, suggesting a decrease in the trends over time.[31] On the other hand, in a multicenter register in the Netherlands, mortality was reduced by 47% in the second wave. Still, the thrombotic complication rate remained high and comparable to the first wave.[32] Nevertheless, these population analyses did not biologically confirm the correlation between waves and new variants. Ultimately, dedicated large epidemiological studies involving several geographical areas are needed to determine the actual trends.

The initial reports of COVID-19 cases in China did not describe PE among the complications but did note increased levels of D-dimer and abnormal coagulation parameters in critically ill patients.[33,34] However, as the disease spread around the world, multiple cases associating COVID-19 with PE were reported.[35] These findings were subsequently confirmed by prospective studies analyzing the clinical and radiological characteristics of patients with COVID-19.[36] In these studies, COVID-19-associated PE was reported in 13.6 to 16.7% of critically ill patients and 2.2 to 8.3% of hospitalized patients who were not admitted directly to the intensive care unit (ICU).[36–39] A Cochrane systematic review pooling data from 16 studies estimated that in hospitalized patients with COVID-19, the weighted mean incidence of PE was 4.3%.[22] Another systematic review analyzing 44 studies found an incidence of 7.8% (95% confidence interval [CI], 2.6–15.3%).[23] There is greater uncertainty regarding the PE rates in outpatients and patients post-discharge with COVID-19 because of limited data. A meta-analysis assessing post-discharge rates of PE estimated an incidence of 1.5% (95% CI: 0.5–4.0%)[40] at a mean of 68 days of follow-up. However, data from placebo arms in randomized controlled trials (RCTs) of outpatients with COVID-19 have found rates of PE at approximately 1% up to 30 days of follow-up.[41,42] Results from other recently completed trials will provide further clarity on this topic.

Clinical and Radiological Characteristics

Several epidemiological and clinical differences have been observed between COVID-19-associated PE and non–COVID-19-associated PE (►**Fig. 1**). Moreover, some authors have proposed that COVID-19-associated PE exhibits a different disease phenotype than conventional non–COVID-19-associated PE.[43] In a Spanish study that included patients treated in emergency departments before hospitalization, COVID-19-associated PE had a higher incidence when compared with non–COVID-19-associated PE (310 vs. 35 per 100,000 person-years), representing an almost ninefold increase in risk.[44] Remarkably, these rates may reflect the studied sample incidence rather than the actual disease incidence in the overall population.

Conventional risk factors for PE are less frequently observed in patients with COVID-19 compared with non-COVID-19 era. In the Computerized Registry of Patients with Venous Thromboembolism (RIETE), patients who had non–COVID-associated PE (i.e., enrolled before 2018) were predominantly women aged 60 to 70 years with conventional cardiovascular risk factors,[45] whereas patients included

during the pandemic in the RIETE registry (March to May 2020) were predominantly males aged 60, with conventional cardiovascular risk factors.[46] In comparison with patients without COVID-19, patients with COVID-19 had a higher frequency of immobility (78 vs. 21%) and a lower rate of coincident surgical procedure (2 vs. 12%), malignancy (4 vs. 22%), or previous VTE events (4 vs. 15%).[45,46] Of note, more than half of patients with COVID-19-associated PE do not have concomitant DVT.[47,48] In contrast to non–COVID-19-associated PE, more patients with COVID-19-associated PE developed PE despite receiving standard-intensity thromboprophylaxis.[1] This issue has been the impetus for several other trials of intensified prophylactic antithrombotic therapies.[13,49]

The anatomical location of COVID-19-associated PE has been related to different radiological patterns compared with non–COVID-19-associated PE. COVID-19-associated PE has been particularly observed in segmental and subsegmental pulmonary arteries, whereas a smaller proportion of patients, compared with non–COVID-19-associated PE, have thrombi in the main pulmonary arteries (i.e., central vasculature).[44] These findings align with the lower frequency of DVT observed in patients with COVID-19-associated PE and in situ thrombosis in the distal pulmonary vasculature on postmortem analyses.[15,16,50,51]

Risk Stratification

In the broad population of patients with COVID-19, several risk factors have been associated with increased short-term mortality. These factors include elevated D-dimer, C-reactive protein (CRP), and cardiac troponin I.[52] Clinical characteristics including dementia, diabetes mellitus with insulin treatment, chronic obstructive pulmonary disease, peripheral arterial disease, active smoking, chronic liver disease, and rheumatologic diseases are also associated with adverse outcomes.[52,53] Over 300 prediction models have been described, but many are of limited utility.[54] The 4C Mortality Score has shown a good discrimination for mortality (C index: 0.77 [95% CI: 0.76–0.77]). It includes eight variables readily available at initial hospital assessment: age, sex, number of comorbidities, respiratory rate, peripheral oxygen saturation, level of consciousness, urea level, and CRP.[55] The model has been prospectively validated.[56]

Studies assessing risk factors for poor outcomes in patients with COVID-19-associated PE are limited. Patients with COVID-19-associated PE may have a higher risk of ICU admission, mechanical ventilation, and prolonged hospitalizations than patients without PE.[44,57] Moreover, a higher simplified Pulmonary Embolism Severity Index score and the presence of right ventricle dysfunction have been related to an increase in in-hospital mortality.[58]

Determination of the true impact of COVID-19-associated PE requires dedicated investigations that have not been conducted to date. Such analyses would need to take into account baseline comorbidities but also antithrombotic and non-antithrombotic cotreatments, as well as immortal time bias.[44,57,59,60]

Prevention

As a consequence of the limited high-quality evidence early during the pandemic, most of the recommendations were based on expert consensus documents and evidence extrapolated from the pre-COVID-19 era and mainly from noninfectious settings such as the conventional PE.[61,62] Nevertheless, an extraordinary worldwide scientific effort promoted the design of dozens of RCTs assessing the role of different drug strategies for preventing VTE in patients with COVID-19.[13,49,63,64] Currently, several of these RCTs covering different clinical settings have reported their primary results. Some were prematurely stopped due to futility, low recruitment, or logistics issues.[65] As the discussion herein primarily focuses on COVID-19-associated PE (►**Tables 1–4**), additional details for non-PE outcomes can be found in individual records of these trials and published meta-analyses of the trial results.[27,28,66]

Outpatients

In the Sulodexide in the Treatment of Early Stages of COVID-19 (SULES-COVID) trial, sulodexide (a primarily oral heparinoid with endothelial stabilizing and antithrombotic properties[67]) was not associated with a significant increase in major bleeding (risk ratio [RR]: 3.10, 95% CI: 0.10–76.0). PE event rates were not reported.[68] In the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV)-4B, apixaban 2.5 mg BID (0 vs. 0%) or 5 mg BID (0 vs. 0%) was not significantly associated with a reduction in PE compared with placebo. There were no major bleeding events in the study, but two (0.7%) clinically relevant nonmajor bleeding in patients treated with apixaban and no bleeding in the aspirin and placebo group.[41] An RCT focused on the symptoms in high-risk adults with mild COVID-19 compared the effect of rivaroxaban 10 mg with placebo for the progression and symptoms resolution. The investigators reported no PE events.[42] The Early Prophylactic Low-Molecular-Weight Heparin (LMWH) in Symptomatic COVID-19 Positive Patients (ETHIC) trial included unvaccinated patients with at least one risk factor for severe disease.[69] Standard-intensity prophylactic anticoagulation with enoxaparin for 21 days was not significantly associated with a reduction in PE compared with standard of care (RR: 0.36, 95% CI: 0.01–8.78). There were two minor bleeding in patients treated with enoxaparin and one in the standard of care group. No major bleeding was observed. The Enoxaparin for Primary Thromboprophylaxis in Ambulatory Patients With COVID-19 (OVID) trial included patients older than 50 years presenting with acute COVID-19 symptoms.[70] There was no significant reduction in the PE rate between standard-intensity prophylactic anticoagulation with enoxaparin for 14 days and standard of care (RR: 0.25, 95% CI: 0.03–2.26). No bleeding events were reported. The double-blind Study of Rivaroxaban to Reduce the Risk of Major Venous and Arterial Thrombotic Events, Hospitalization and Death in Medically Ill Outpatients With Acute, Symptomatic COVID-19 Infection (PREVENT-HD; NCT04508023) recently completed enrollment of over 1,000 symptomatic outpatients with laboratory-confirmed COVID-19 who had additional risk factors for adverse events and will compare the effect of rivaroxaban 10 mg once daily versus

Table 1 Reported RCTs assessing the role of anticoagulation on COVID-19-associated PE in outpatients

Trial	Design summary	Main findings	PE results
SULES-COVID[68]	- Single-center, placebo-controlled RCT comparing sulodexide vs. placebo - Lead researcher was not blinded to group allocation - Primary endpoint: need for hospital admission for clinical care	- 312 patients randomized; 243 patients included in the per-protocol analysis - Sulodexide significantly reduced the rate of hospitalization compared with placebo	- PE rates were not reported
ACTIV-4B[41]	- Adaptive, double-blind, placebo-controlled RCT - Random allocation in a 1:1:1:1 ratio to aspirin, low-intensity apixaban, full-intensity apixaban, or placebo for 45 d - Primary endpoint: composite of all-cause mortality, symptomatic venous or arterial thromboembolism, MI, stroke, or hospitalization for cardiovascular or pulmonary cause	- Study was stopped prematurely, 657 (9%) of the original sample size were included. Event rate was lower than expected - Aspirin or apixaban compared with placebo did not significantly reduce the rate of the composite clinical outcome	- There were no PE events
Ananworanich et al[42]	- Double-blind, placebo-controlled RCT comparing rivaroxaban 10 mg vs. placebo - Primary efficacy endpoint: proportion of participants who progressed to a moderate or severe disease category through day 28	- Study was stopped prematurely, 497 (82%) of the original sample size were included - Rivaroxaban did not significantly reduce the disease progression in high-risk adults with mild COVID-19	- There were no PE events
ETHIC[69]	- Open-label, multicenter, RCT comparing standard-intensity prophylactic anticoagulation with enoxaparin for 21 d vs. standard of care - Primary endpoint: composite of all-cause hospitalizations and all-cause mortality at 21 d - Patients were unvaccinated and had at least one risk factor for severe disease[a]	- Study was stopped prematurely, 219 (16%) of the original sample size were included - Standard-intensity prophylactic anticoagulation with enoxaparin did not significantly improve clinical outcomes compared with standard of care	- There were no significant differences in PE between standard-intensity prophylactic anticoagulation and standard of care (0 vs. 1%; RR: 0.36, 95% CI: 0.01–8.78)
OVID[70]	- Open-label, multicenter, RCT comparing standard-intensity prophylactic anticoagulation with enoxaparin for 14 d vs. standard of care - Primary endpoint: composite of any untoward hospitalizations and all-cause mortality at 30 d - Patients were 50 y or older and presented with respiratory symptoms or body temperature >37.5 °C	- Study was stopped prematurely, 472 (51%) of the original sample size were included - Standard-intensity prophylactic anticoagulation with enoxaparin did not significantly improve clinical outcomes compared with standard of care	- There were no significant differences in PE between standard-intensity prophylactic anticoagulation and standard of care (0.4 vs. 2.0%; RR: 0.25, 95% CI: 0.03–2.26)

Abbreviations: PE, pulmonary embolism; RCT, randomized controlled trial; MI, myocardial infarction; RR, risk ratio.
[a]Age ≥70 years, body mass index >25 kg/m^2, chronic obstructive pulmonary disease, diabetes mellitus, cardiovascular disease, or corticosteroid use.

placebo for a composite of symptomatic VTE, myocardial infarction, ischemic stroke, acute limb ischemia, noncentral nervous system systemic embolization, all-cause hospitalization, and all-cause mortality.[71]

Hospitalized Noncritically Ill Patients

Most data on COVID-19-associated PE come from studies of hospitalized patients.[1] In the Full Anticoagulation Versus Prophylaxis in COVID-19 (ACTION) trial, full-intensity prophylactic anticoagulation with rivaroxaban (15 or 20 mg QD) or heparin did not significantly reduce PE (RR: 0.53, 95% CI: 0.21–1.31) and was associated with a significant increase in major or clinically relevant non-major bleeding (RR: 3.64, 95% CI: 1.61–8.27) compared with standard-intensity prophylactic anticoagulation.[72] The Comparison of Two Different Doses of Bemiparin in COVID-19 (BEMICOP) and Coagulopathy of COVID-19: A Pragmatic Randomized Controlled Trial of Therapeutic Anticoagulation Versus Standard Care (RAPID) trials evaluated the effect of full-intensity prophylactic anticoagulation with LMWH or unfractionated heparin (UFH) compared with standard-intensity prophylactic heparin anticoagulation.[73,74] Full-intensity strategy was not associated with a significant difference in major bleeding in either trial (0 vs. 0%; and RR: 0.52 [95% CI: 0.09–2.85], respectively). The BEMICOP investigators did not report the PE event rate. In the RAPID trial, the full-intensity heparin strategy did not significantly reduce the rate of PE compared with the standard-intensity heparin (RR: 0.21 [95% CI: 0.02–1.77]). The Comparison of Two Doses of Enoxaparin for Thromboprophylaxis in Hospitalized COVID-19 Patients (X-COVID trial), which compared intermediate-intensity versus standard-intensity prophylactic enoxaparin, found a nonsignificant reduction in PE (RR: 0.08 [95% CI: 0.00–1.36]) without a significant effect on major bleeding (RR: 1.01 [95% CI: 0.06–15.92]).[75] The Antithrombotic Therapy to Ameliorate Complications of COVID-19 (ATTACC), ACTIV-

Table 2 Reported RCTs assessing the role of anticoagulation on COVID-19-associated PE in hospitalized floor patients

Trial	Design summary	Main findings	PE results
ACTION[72]	- Open-label, multicenter, RCT comparing full-intensity prophylactic anticoagulation with rivaroxaban (enoxaparin in patient with contraindication) or standard-intensity - Primary outcome: hierarchical analysis of adjudicated time to death, duration of hospitalization, or duration of supplemental oxygen to day 30 - Only patients with elevated D-dimer were eligible	- 615 patients were included - Full-intensity prophylactic anticoagulation with rivaroxaban or enoxaparin followed by rivaroxaban up to day 30 did not significantly improve clinical outcomes compared with standard-intensity	- There were no significant differences in PE between full-intensity and standard-intensity prophylactic anticoagulation (2 vs. 4%; RR: 0.53, 95% CI: 0.21–1.31)
BEMICOP[73]	- Open-label, multicenter, RCT comparing full-intensity versus standard-intensity prophylactic anticoagulation with bemiparin - Primary outcome: composite of death, ICU admission, need of mechanical ventilation support, development of moderate/severe ARDS, and venous or arterial thrombosis within 10 d of randomization - Only patients with elevated D-dimer were eligible	- Study was stopped prematurely, 65 (39%) of the original sample size were included - Full-intensity bemiparin did not significantly improve clinical outcomes compared with standard-intensity prophylactic anticoagulation	- PE rates were not reported
RAPID[74]	- Open-label, adaptive, RCT comparing full-intensity prophylactic anticoagulation with heparin vs. standard-intensity. - Primary endpoint: composite of death, IMV, non-IMV, or admission to ICU, assessed up to 28 d - Only patients with elevated D-dimer were eligible	- 465 patients were included. - Full-intensity prophylactic anticoagulation did not significantly reduce the primary outcome compared with standard-intensity but the odds of death at 28 days was decreased	- There were no significant differences in PE between full-intensity and standard-intensity prophylactic anticoagulation (0.4 vs. 2.1%; RR: 0.21, 95% CI: 0.02–1.77)
Multiplatform trial, noncritically ill[76]	- Open-label, adaptive, multiplatform, RCT comparing full-intensity prophylactic anticoagulation vs. usual care - Primary endpoint: organ support–free days, evaluated on an ordinal scale that combined in-hospital death and the number of days free of cardiovascular or respiratory organ support up to day 21	- 2,219 patients were included - Full-intensity prophylactic anticoagulation significantly increased the probability of survival to hospital discharge with reduced use of cardiovascular or respiratory organ support (organ support–free days) compared with usual care	- There were no significant differences in PE between full-intensity prophylactic anticoagulation and usual care (0.8 vs. 1.8%; RR: 0.47, 95% CI: 0.22–1.00)
HEP-COVID[77]	- Open-label multicenter randomized active control trial comparing full-intensity prophylactic anticoagulation with enoxaparin vs. standard- or intermediate-intensity with heparin - Primary endpoint: composite of VTE, ATE, or all-cause death at 30 d - Patients underwent lower extremity compression ultrasound testing at hospital day $10 + 4$	- 257 patients were included; 32.8% were admitted to the ICU - Full-intensity prophylactic anticoagulation with enoxaparin significantly reduced major thromboembolism and death compared with standard-intensity prophylactic anticoagulation - Treatment effect was not seen in ICU stratum	- There were no significant differences in symptomatic PE between full-intensity and standard-intensity prophylactic anticoagulation (3.1 vs. 8.1%; RR: 0.38, 95% CI: 0.12–1.19)
X COVID[75]	- Open-label, multicenter, RCT comparing intermediate-intensity prophylactic anticoagulation with enoxaparin vs. standard-intensity - Primary endpoint: in-hospital incidence of VTE: asymptomatic or symptomatic proximal DVT, and/or symptomatic PE	- Study was stopped prematurely, 189 (7%) of the original sample size were included - Intermediate-intensity prophylactic anticoagulation with enoxaparin was associated with a significant reduction of VTE events compared with a standard-intensity - There were no DVT events	- Intermediate-intensity prophylactic anticoagulation with enoxaparin did not significantly reduced PE compared with standard-intensity (0.0 vs. 6.5%; RR: 0.08, 95% CI: 0.00–1.36)

Abbreviations: ARDS, acute respiratory distress syndrome; ATE, arterial thromboembolism; CI, confidence interval; DVT, deep vein thrombosis; ICU, intensive care unit; IMV, invasive mechanical ventilation; PE, pulmonary embolism; RCT, randomized controlled trial; RR, relative risk; VTE, venous thromboembolism.

Table 3 Reported RCTs assessing the role of anticoagulation on COVID-19-associated PE in hospitalized ICU patients

Trial	Design summary	Main findings	PE results
HESACOVID[79]	- Open-label, phase II study RCT comparing full-intensity prophylactic anticoagulation with enoxaparin vs. standard-intensity - Primary endpoint: gas exchange over time through the ratio of PaO_2/FiO_2	- 20 patients were included. - Full-intensity prophylactic anticoagulation with enoxaparin significantly improved gas exchange and decreased the need for mechanical ventilation in critically ill patients compared with standard-intensity	- There were no significant differences in PE between full-intensity and standard-intensity prophylactic anticoagulation (0 vs. 10.0%; RR: 0.33, 95% CI: 0.02–7.32)
INSPIRATION[80]	- Open label, multicenter RCT comparing intermediate-intensity prophylactic anticoagulation vs. standard-intensity - Primary endpoint: composite of venous or arterial thrombosis, treatment with ECMO, or mortality within 30 d	- 562 patients were included - Intermediate-intensity prophylactic anticoagulation, compared with standard-intensity, did not result in a significant difference in the primary composite outcome	- There were no significant differences in PE between intermediate-intensity prophylactic anticoagulation and standard-intensity (0.7 vs. 1.7%; RR: 0.41, 95% CI: 0.08–2.12)
Perepu et al[82]	- Open-label, multicenter RCT comparing intermediate-intensity prophylactic anticoagulation with enoxaparin vs. standard-intensity - Primary endpoint: all-cause mortality at 30 d	- 176 patients were included - Intermediate-intensity prophylactic anticoagulation with enoxaparin and standard-intensity did not differ significantly in preventing death or thrombosis at 30 d	- PE rates were not reported
Multiplatform trial, critically ill[84]	- Open-label, adaptive, multiplatform, RCT comparing full-intensity prophylactic anticoagulation with heparin vs. usual care - Primary endpoint: organ support–free days, evaluated on an ordinal scale that combined in-hospital death and the number of days free of cardiovascular or respiratory organ support up to day 21	- Trial was stopped for futility with 1,098 patients included - Full-intensity prophylactic anticoagulation with heparin did not result in a greater probability of survival to hospital discharge or a greater number of days free of cardiovascular or respiratory organ support (organ support–free days) than usual care	- Full-intensity prophylactic anticoagulation significantly reduced symptomatic PE compared with usual care (2.5 vs. 7.5%; RR: 0.33, 95% CI: 0.18–0.60)
Swiss COVID-HEP[83]	- Open-label, multicenter RCT comparing full-intensity prophylactic anticoagulation with heparin vs. usual care - Primary endpoint: all-cause death, VTE, arterial thrombosis, and disseminated intravascular coagulopathy, with screening for proximal DVT - Only patients with elevated D-dimer were eligible	- Study was stopped prematurely, 159 (79%) of the original sample size were included - In 71.7% of the patients, PE was excluded before inclusion - Full-intensity prophylactic anticoagulation with heparin was not significantly associated with a reduction in the primary endpoint compared with usual care	- One event of nonfatal PE with proximal DVT occurred in the usual-care group; there were no events in the full-intensity group (0 vs. 1.1%; RR: 0.34, 95% CI: 0.01–8.16)

Abbreviations: CI, confidence interval; ECMO, extracorporeal membrane oxygenation; PaO_2/FiO_2, pressure of arterial oxygen to fractional inspired oxygen concentration; PE, pulmonary embolism; RCT, randomized controlled trial; RR, relative risk.

4A, and Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) is the largest reported trial assessing the role of escalated-intensity prophylactic anticoagulation and usual care with heparin in non-critically ill patients.[76] This multiplatform trial showed a non-significant reduction in PE (RR: 0.47, 95% CI: 0.22–1.00) with a non-significant increase in major bleeding (RR: 2.70 [95% CI: 1.00–4.69]). The Full Dose Heparin versus Prophylactic Or Intermediate Dose Heparin in High Risk COVID-19 Patients (HEP-COVID) trial found similar results assessing the role of enoxaparin at full-intensity versus institutional standard- or intermediate-intensity prophylactic anticoagulation in patients with a fourfold elevation of D-dimer.[77] Enoxaparin at full intensity, compared with standard or intermediate intensity, was not associated with a significant reduction in symptomatic PE (RR: 0.38, [95% CI: 0.12–1.19]) or a significant increase in major bleeding (RR: 2.88 [95% CI: 0.59–14.02]). It should be noted that none of these trials were powered for PE as the primary outcome, or for major bleeding events. Therefore, the lack of significant difference may be due to type II error. Several other RCTs are still ongoing or in the analytical phase.[13] FREEDOM COVID Anticoagulation Strategy Randomized Trial (FREEDOM COVID-19; NCT04512079) is the largest trial, including more than 3,000 patients, assessing the effect of escalated-intensity prophylactic anticoagulation with enoxaparin or apixaban, compared with standard-intensity prophylactic enoxaparin, in patients not yet requiring ICU support.[78]

Hospitalized Critically Ill Patients

Hospitalized patients admitted to the ICU are at a higher risk of PE.[23] The Therapeutic versus Prophylactic Anticoagulation for Severe COVID-19 (HESA-COVID) trial was a small pilot

Table 4 Reported RCTs assessing the role of anticoagulation on COVID-19-associated PE in post-discharge patients

Trial	Design summary	Main findings	PE results
MICHELLE[85]	- Open-label, multicenter, RCT comparing, at hospital discharge, rivaroxaban 10 mg/day or no anticoagulation for 35 d - Primary endpoint: composite of symptomatic or fatal VTE, asymptomatic VTE, symptomatic ATE, and cardiovascular death at day 35 - Only patients at increased risk for VTE were eligible - Bilateral lower limb venous Doppler ultrasound and computed tomography pulmonary angiograms were performed at 35 d	- 320 patients were included - Thromboprophylaxis with rivaroxaban 10 mg/day for 35 d reduced the risk of composite primary endpoint compared with no extended thromboprophylaxis	- There were no differences in PE between thromboprophylaxis with rivaroxaban and no extended thromboprophylaxis in symptomatic PE (0.6 vs. 1.3%; RR: 0.50, 95% CI: 0.05–5.46) or fatal PE (0.0 vs. 1.9%; RR: 0.14, 95% CI: 0.01–2.74)

Abbreviations: ATE, arterial thromboembolism; CI, confidence interval; PE, pulmonary embolism; RCT, randomized controlled trial; RR, relative risk; VTE, venous thromboembolism.

trial comparing full-intensity prophylactic enoxaparin versus standard intensity. There were no significant differences in PE (RR: 0.33 [95% CI: 0.02–7.32]) or major bleeding (0 vs. 0%; $p = \text{NS}$).[79] The Intermediate vs Standard-Dose Prophylactic Anticoagulation in Critically-ill Patients With COVID-19 (INSPIRATION) trial compared intermediate-intensity and standard-intensity prophylactic anticoagulation with heparin-based regimens. The investigator found no significant differences in PE (RR: 0.41 [95% CI: 0.08–2.12]) or major bleeding (RR: 1.81 [95% CI: 0.54–6.13]) between groups.[80,81] Perepu et al compared the effect of intermediate-intensity prophylactic enoxaparin versus standard-intensity prophylactic anticoagulation. The authors did not report PE event rates, and there was no significant increase in major bleeding (RR: 0.99 [95% CI: 0.14–6.86]).[82] The Swiss Preventing COVID-19 Complications With Low- and High-dose Anticoagulation (COVID-HEP) trial compared full-intensity prophylactic anticoagulation with heparin with lower-intensity prophylactic anticoagulation; there were no significant differences in the rate of PE (0 vs. 1.1%; RR: 0.34, 95% CI: 0.01–8.16) or major bleeding (1.4 vs. 2.5%; RR: 0.52, 95% CI: 0.05–5.61).[83] The largest trial is the ATTACC, ACTIV-4A, and REMAP-CAP including more than 1,000 critically ill patients.[84] Full-intensity prophylactic anticoagulation was associated with a significant reduction in PE (RR: 0.33 [95% CI: 0.18–0.60) without a significant increase in major bleeding (RR: 1.63; 95% CI: 0.82–3.25]) compared with usual care. Nevertheless, this multiplatform RCT did not reach its primary endpoint (see original trial report and summary in ►**Table 3**).[84]

Meta-Analyses and Systematic Reviews

One systematic review and meta-analysis, including six RCTs of hospitalized floor patients and four RCTs of ICU patients, found a significant reduction in the COVID-19-associated PE in patients treated with escalated-intensity prophylactic anticoagulation compared with standard-intensity (RR: 0.39, 95% CI: 0.26–0.58). However, escalated-intensity was associated with a significant increase in major bleeding (RR: 1.73, 95% CI: 1.15–2.60) and did not significantly decrease all-cause death (RR: 0.96, 95% CI: 0.78–1.18) compared with standard-intensity. The results were consistent regardless of the patient clinical status (floor vs. no floor).[27,28] An interesting observation is that in contrast to conventional PE, in COVID-19-associated PE, escalated-intensity prophylaxis anticoagulation was not associated with a risk reduction in DVT (RR: 1.03, 95% CI: 0.60–1.75), raising the hypothesis that the underlying thromboinflammatory mechanism might differ between these two entities.[27,28] Another systematic review and meta-analysis analyzing six trials of therapeutic heparin (three on moderately ill and three on critically ill) found a significant interaction between heparin treatment intensity and severity of the disease (moderately vs. critically ill) ($P_{\text{Interaction}} = 0.034$). In moderately ill patients, there was no significant reduction in all-cause death between heparin-based full-intensity prophylactic anticoagulation and standard-intensity (odds ratio [OR]: 0.76, 95% CI: 0.57–1.02), but significant reductions in the composite of death or invasive mechanical ventilation (OR: 0.77, 95% CI: 0.60–0.98), and death or any thrombotic event (OR: 0.58, 95% CI: 0.45–0.77) were observed, without a significant increase in bleeding events. However, in severely ill patients, there was no benefit of heparin-based full-intensity prophylactic anticoagulation over standard-intensity.[66]

Post-Discharge Patients

In the post-discharge patients setting, the Medically Ill hospitalized Patients for COVID - THrombosis Extended ProphyLaxis with rivaroxaban ThErapy (MICHELLE) trial evaluated the role of extended thromboprophylaxis with rivaroxaban 10 mg compared with the standard of care in patients with an increased risk of VTE and D-dimer.[85] At 1-month follow-up, extended thromboprophylaxis was not associated with a significant reduction in symptomatic pulmonary PE (RR: 0.50, 95% CI: 0.05–5.46) or fatal PE (RR: 0.14, 95% CI: 0.01–2.74), without a significant increase in clinically relevant non-major bleeding (RR: 1.00, 95% CI: 0.14–7.01). The ongoing ACTIV-4C trial (NCT04650087) will provide

valuable data on the role of extended thromboprophylaxis with apixaban 2.5 mg compared with placebo 30 days after discharge.

Non-Anticoagulant Trials

Some RCTs evaluating drugs targeting thromboinflammatory pathways have also assessed the effects on COVID-19-associated PE. The Randomized Evaluation of COVID-19 Therapy (RECOVERY) and ACTIV-4B trials evaluated the effect of aspirin in hospitalized patients and outpatients, respectively. There were no significant differences in PE rates between patients allocated to antiplatelet versus standard therapy in both trials.[41,86] The REMAP-CAP trial assessed the effect of aspirin and $P2Y_{12}$ inhibitors (mostly clopidogrel) in critically ill patients with COVID-19 and there were no significant differences in the study groups in the incidence of COVID-19-associated PE.[87] Furthermore, trials assessing the role of anti-inflammatory, lipid-lowering, or antiviral drugs such as baricitinib, colchicine, canakinumab, atorvastatin, and remdesivir did not find a significant effect of these drugs on PE rates compared with standard of care or placebo in hospitalized patients.[88–92]

Clinical Guidelines

Professional and scientific organizations have integrated the current evidence and published clinical guidelines for the management of antithrombotic therapy in patients with COVID-19.[93–96] These recommendations extend beyond PE, per se, and include the risk of venous or arterial thrombosis, organ support, mortality, and bleeding. The recommendations are divided according to the severity of the disease and outpatient or inpatient settings. In outpatients, the consensus is against routine antithrombotic therapy to prevent PE or other thrombotic events and against routine continuation of VTE prophylaxis in unselected patients after hospital discharge. However, extending thromboprophylaxis can be considered in patients at high risk for VTE and low risk of bleeding, similar to patients without COVID-19. Among inpatients, the recommendations are stratified according to the need for ICU and oxygen flow requirements. In patients who require ICU-level care, including those receiving high-flow oxygen, standard-intensity prophylactic anticoagulation is recommended by most guideline documents. In contrast, full-intensity prophylactic anticoagulation for VTE is considered in carefully selected non-ICU patients. These include floor patients who require low-flow oxygen, elevated D-dimer, and without increased bleeding risk. Among patients who do not meet these criteria, the recommendation is to use standard-intensity prophylactic anticoagulation with heparin regimens.

Diagnosis

Evaluation of COVID-19-associated PE may be challenging because PE symptoms can overlap with inherent COVID-19 symptoms, and imaging studies may not be feasible in all cases, especially those who are critically ill. Nevertheless, clinicians should be vigilant about the risk of PE in patients with COVID-19. Conventional predictive models such as Padua, International Medical Prevention Registry on Venous Thromboembolism (IMPROVE), or Caprini can be used to assess the risk of VTE, particularly in hospitalized patients.[1] It should be highlighted that based on these models, a high proportion of patients with COVID-19 qualify as a high risk for VTE due to acute infection, immobilization, respiratory failure, and elevated D-dimer. However, in an external validation study, the IMPROVE-DD demonstrated very good discrimination in identifying hospitalized patients with COVID-19 at risk of VTE.[97] In patients with a low or moderate pretest probability of PE, a normal D-dimer may be sufficient to exclude the diagnosis of PE. Similar to pre-COVID-19 era, the positive predictive value of D-dimer level elevation, alone, is not sufficiently high to diagnose PE.[94] CTPA is the preferred test to confirm or exclude the diagnosis. Implementing bedside ultrasound (i.e., to evaluate for right ventricular strain, clot in transit in the heart, or DVT of extremities) can be helpful in patients who cannot be transferred for CTPA (i.e., hemodynamically unstable, prone position, etc.).[2] Currently, there is no strong evidence to support routine screening for PE regardless of their coagulation markers.[93] However, retrospective studies have found that ultra-high D-dimer levels (i.e., >10–20 times fold the upper limit of normal) in patients with COVID-19 have been closely associated with COVID-19-associated PE and increased mortality.[98,99] The optimal screening strategy in patients with COVID-19 and ultra-high D-dimer levels is unknown.[100] Several studies have evaluated the utility of current PE diagnosis prediction models (i.e., Wells, YEARS, Geneva, etc.) in patients with COVID-19.[101,102] Overall, the current models have shown a limited discrimination ability to identify patients with COVID-19-associated PE. The CHOD (CRP, heart rate, oxygen saturation, D-dimer) score exhibited the best performance among the current models.[102] Furthermore, the number of patients who can be managed without CTPA is lower than in patients without COVID-19, and the failure rate (proportion of PE cases in the group of patients with low probability) is higher than in patients without COVID-19.[100] Of note, developing and validating prediction tools for patients with COVID-19 that consider specific variables such as disease stage, need for ICU stay, and anticoagulation prophylaxis is needed in future. In hospitalized patients who experience rapid deterioration of pulmonary, cardiac, or neurological function or sudden, localized loss of peripheral perfusion, evaluation of thromboembolic disease should be performed.

Treatment

The management considerations for COVID-19-associated PE are summarized in ►**Fig. 2**. Overall, acute treatment does not differ from the non-COVID-19 patients.[103] Therapeutic anticoagulation is appropriate for COVID-19-associated PE, similar to individuals without COVID-19. Moreover, therapeutic anticoagulation might be considered in select cases with a high index of suspicion until further diagnostic tests can be performed.[93] Potential drug–drug interactions

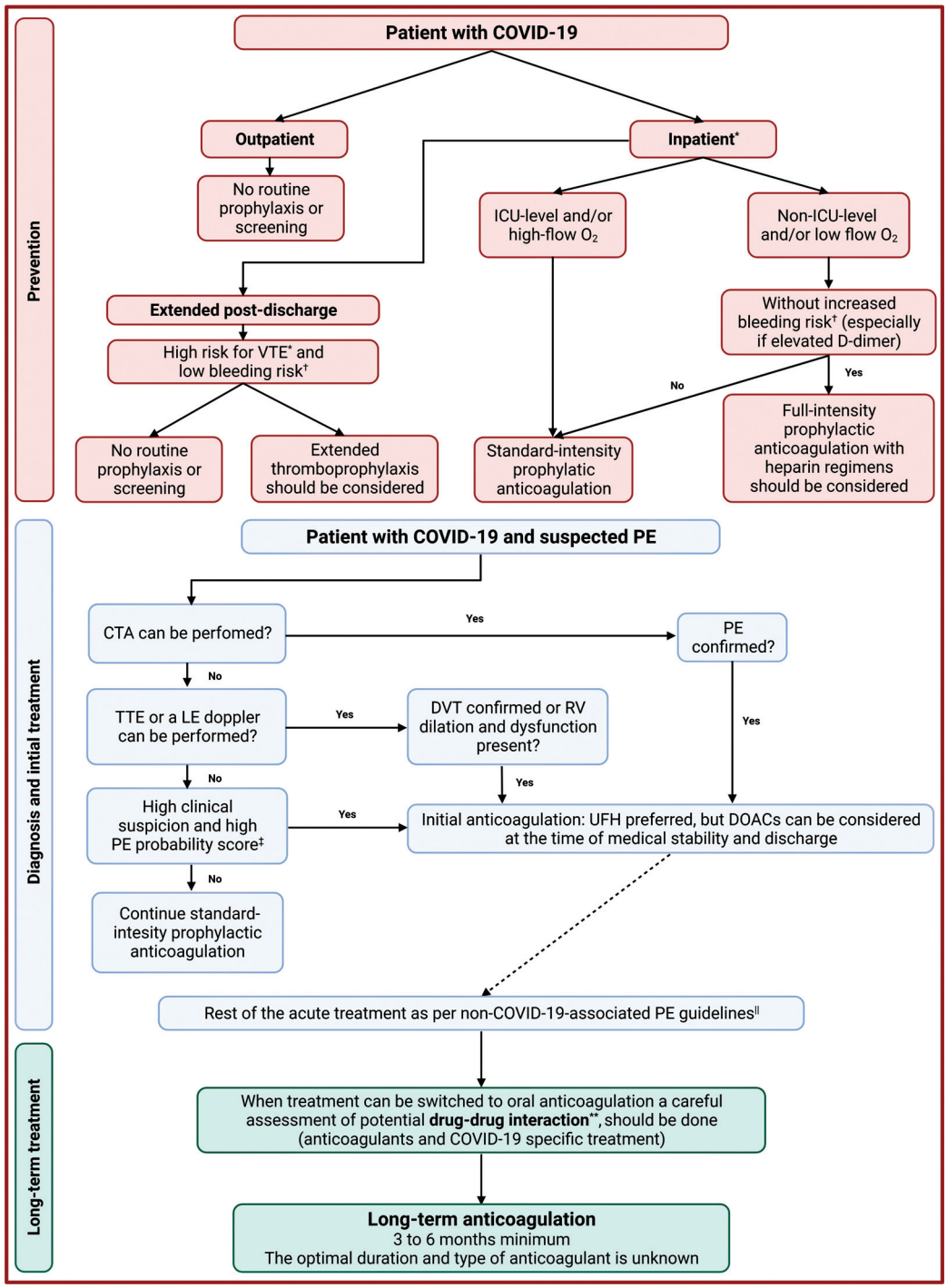

Fig. 2 Algorithms for prevention, diagnosis and initial treatment, and long-term treatment of COVID-19-associated PE. *Prevention.* The algorithm is based on the NIH (National Institutes of Health) COVID-19 treatment guidelines. *Details about drug and regimen selection and VTE risk assessment are defined according to the NIH guidelines.[93] *Diagnosis and initial treatment*. The algorithm differs from the non–COVID-19-associated PE in the feasibility of performing a CTA as the standard gold diagnosis.[103] If the patient can't be transferred from a CTA assessment test such as TTE or LE, Doppler can provide bedside evaluation for guiding the decision-making process. In patients in whom any test can be performed, with a high suspicion or pre-test probability, the current recommendation is to initiate therapeutic anticoagulation. †Criteria suggesting high bleeding risk as per NIH guidelines are a platelet count $<50 \times 109$/L, hemoglobin <8 g/dL, the need for dual antiplatelet therapy, bleeding within the past 30 days that required an emergency department visit or hospitalization, history of a bleeding disorder, or an inherited or active acquired bleeding disorder.[93] ‡PE probability scores to consider are Wells criteria, Geneva score, and Pulmonary Embolism Rule-out Criteria. ||Currently available guidelines include 2019 European Society of Cardiology guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society[105] and Executive Summary: Antithrombotic Therapy for VTE Disease: Second Update of the CHEST Guideline and Expert Panel Report.[132] *Long-term treatment*. When the treatment can be switched to oral, a careful assessment of the potential drug–drug interactions between anticoagulants and COVID-19-specific treatment should be done. **A complete list of drug–drug interaction has been previously reported.[7] PE, pulmonary embolism; CTA, CT angiography; TTE, transthoracic echocardiogram; LE, lower extremity; DVT, deep vein thrombosis; UFH, unfractionated heparin; DOACs, direct oral anticoagulants.

between COVID-19 therapies and oral anticoagulants should be assessed when considering initiating oral anticoagulation.[1,7] The treatment with systemic thrombolysis in selected high-risk patients has been reported in case series using recombinant tissue plasminogen activator without any major bleeding event but a mortality rate of more than 40% (3/7 patients).[104] Any treatment with systemic thrombolysis should be considered in line with the current clinical guidelines.[105] In a pilot RCT, low-dose, systemic thrombolytic therapy with recombinant tissue plasminogen activator did not improve gas exchange outcomes or organ failure scores compared with standard-intensity versus full-intensity prophylactic anticoagulation regimens in critically ill patients.[106]

COVID-19 is considered a provoking factor for PE. Whether the prothrombotic effect of COVID-19 is enduring remains unknown. Therefore, the ideal duration of anticoagulation after COVID-19-associated PE is uncertain. In a small prospective study of 48 patients, after 6 months of oral anticoagulation, mostly with direct oral anticoagulants, there were no recurrent PE events or major bleeding events, while 3 minor bleeding events were identified.[107] In contrast, another study suggested that patients who had COVID-19 could be at risk of PE even at 6 months of follow-up regardless of initial COVID-19 severity.[31] Therefore, it is unknown if the conventional PE treatment duration can be extrapolated to COVID-19 patients. Additional analyses from large registries, including RIETE, are ongoing. To the best of our knowledge, there are no dedicated randomized trials assessing the optimal duration of anticoagulation in COVID-19-associated PE. However, we consider that the duration of anticoagulation should be as per the standard of care for patients without COVID-19, or 3 to 6 months (►**Fig. 2**). In selected patients with persistent risk factors and/or high thrombotic burden, indefinite anticoagulation may be considered.

The Unknown: Areas of Uncertainty and Knowledge Gaps

Although there has been an exponential growth in published data, there remain several areas of uncertainty, in particular in the treatment and follow-up of patients with COVID-19-associated PE. ►**Table 5** summarizes the current gaps in the evidence and future research directions.

Incidence and Screening

The new SARS-CoV-2 variants (B.1.1.529 and BA.2) have been associated with higher rates of mild and asymptomatic disease than previous variants (B.1.617).[108] However, it is unknown if this difference correlates with a decreased risk of COVID-19-associated PE. Given the higher virulence and transmissibility of newer variants, a higher number of overall infected people may lead to a higher number of COVID-19-associated PE cases, despite a lower individual risk.

The introduction of COVID-19 vaccines was a point of inflection during the pandemic resulting in a significant decrease in adverse outcomes.[109] However, regarding PE, the effect of vaccination on non–vaccine-related PE rates is uncertain.[110] Preliminary data from the United Kingdom Biobank have suggested that in patients who develop COVID-19, a history of full vaccination may be associated with a significantly lower 30-day risk of COVID-19-associated VTE (hazard ratio [HR]: 0.13, 95% CI: 0.06–0.28) compared with unvaccinated patients. The vaccination status did not affect the risk of non–COVID-19-associated VTE.[111]

The current guideline documents recommend against routine screening for VTE in patients with COVID-19.[93] It remains to be determined whether periodic screening in carefully selected individuals is of clinical utility.

Pathophysiology

The underlying pathophysiological mechanisms of thrombosis in COVID-19 have not been completely elucidated. Acquired antiphospholipid syndrome (APS), via molecular mimicry and endothelial dysfunction, could plausibly explain thrombogenesis in COVID-19.[112,113] The exact biological role of antiphospholipid antibodies in PE events and whether they persist over time remain unknown. Furthermore, the role of antibodies related to heparin-induced thrombocytopenia in the COVID-19 thrombosis mechanism and the development of thrombosis with thrombocytopenia syndrome in association with adenoviral vector-based vaccines are poorly understood. It is similarly unknown whether NETs, high circulating von Willebrand factor, and factor VIII are causally implicated in COVID-19 thrombosis. Further research is needed to determine whether targeting NETs formation with anti-inflammatory therapies (i.e., anti-cytokine therapy against interleukin-1β, glucocorticoids, or colchicine) or targeting NETs formation or clearance may improve patient outcomes.

Prevention

Mechanical thromboprophylaxis is a therapeutic modality widely used in ICU patients, especially those in whom anticoagulation is contraindicated.[114] Some scientific societies have recommended mechanical thromboprophylaxis in ICU COVID-19 patients, but these recommendations are based on expert opinion and evidence from non-COVID-19 patients.[115] The safety and efficacy of mechanical thromboprophylaxis with or without pharmacological thromboprophylaxis should be a topic of further research.

Several trial-level meta-analyses of RCTs of escalated-intensity versus standard-intensity prophylactic anticoagulation have been reported.[27,28,66] Nevertheless, some trials are still ongoing or unreported, and comprehensive analyses of these trials using published and unpublished data are underway by the World Health Organization (WHO). Furthermore, ongoing independent patient data meta-analysis can produce more reliable results.[116]

Treatment

Some clinicians and investigators recommend the measurement of anti-activated factor X (anti-Xa) instead of activated partial thromboplastin time (aPTT) for titration of the intensity of heparin-based anticoagulation in COVID-19. However, data from the pre-COVID-19 era have not yet supported the

Table 5 Current gaps in the evidence of COVID-19-associated PE

	Gap	Comments
Incidence and screening	Temporal trends in COVID-19-associated PE	- Rates of PE events with new viral variants are unknown - Role of vaccination for the development of COVID-19-associated PE in patients developing breakthrough infection is uncertain - Potential effect of non-antithrombotic therapies (such as antiviral agents and anti-inflammatory agents) on PE event rates is unknown
	Role of "screening" among high-risk patients	- Efficacy and cost-effectiveness of routine PE screening (e.g., by CTPA), either at the time of admission or routine periodic screening in ICU patients is unknown
Pathophysiology	Role of antiphospholipid antibodies in PE pathophysiology and prognosis	- Biological role of antiphospholipid antibodies in COVID-19-associated hypercoagulability, whether the antibodies persist, and their potential effects on PE remain unknown
	Role of NETs, vWF, and FVIII in PE pathophysiology and prognosis	- Determine if NETs, vWF, and FVIII are causally implicated in the pathophysiology - Determine if pharmacological interventions targeting NETs may reduce COVID-19-associated PE
Risk stratification	Effect of COVID-19-associated PE on in-hospital mortality and long-term outcomes	- Data related to potential effect of COVID-19-associated PE on mortality are low quality and uncertain - Short- and long-term effects of COVID-19-associated PE on mortality remain unknown
Prevention	Efficacy of mechanical thromboprophylaxis	- Safety and efficacy of mechanical thromboprophylaxis as an add-on to pharmacoprophylaxis are unknown
	- Pooled treatment effect is uncertain - Specific treatment effects within subgroups is uncertain (i.e., sex, age group, or severity of the disease) - Specific treatment effects for comparative effectiveness of detailed treatment regimens are uncertain (i.e., all possible comparisons of different drugs and doses)	- Study-level meta-analysis from the WHO working group (CRD42020213461) is ongoing - Ongoing independent patient data meta-analysis will provide more reliable data
Treatment	How to monitor parenteral anticoagulant therapy	- Determine the comparative utility of anti-FXa vs. aPTT, and optimal algorithms for titrating them
	Role of catheter-direct thrombolysis	- Determine the optimal patient selection and efficacy
Follow-up	Optimal method for follow-up, and the ideal duration of treatment of COVID-19-associated PE	- Optimal duration of treatment is unknown
	Relationship of COVID-19-associated PE with long COVID	- Role of COVID-19-associated PE in the development of CTEPH and long-COVID is unknown - Ongoing trials are assessing the role of anticoagulants, statins, and other agents for improving Long COVID-19 symptoms: HEAL-COVID (NCT04801940), PROVID-LD (NCT05080244), SOLIDARITY (NCT05220280), NCT04900961, and NCT04978259

Abbreviations: Anti-FXa, anti-activated factor X; aPTT, activated partial thromboplastin time; CTEPH, chronic thromboembolic pulmonary hypertension; CTPA, computed tomography with pulmonary angiography; FVIII, factor VIII; ICU, intensive care unit; NET, neutrophil extracellular traps; PE, pulmonary embolism; US, ultrasound; vWF, von Willebrand factor; WHO, World Health Organization.

superiority of anti-Xa testing.[117] Nevertheless, the nonspecific binding of UFH in a high inflammatory setting and the unreliability of the aPTT due to high FVIII and fibrinogen in patients with COVID-19 are facts against the use of aPTT testing.[1,118] In the case of measuring the effect of LMWH or UFH, anti-Xa testing seems to be a preferable strategy, although it requires further validation in prospective studies.

Currently, dexamethasone, interleukin-6 inhibitors (i.e., sarilumab and tocilizumab), and Janus kinase inhibitors (i.e., baricitinib and tofacitinib) are anti-inflammatory therapies with proven or potential efficacy for treating hospitalized patients with COVID-19. It is uncertain if these drugs can affect PE occurrence by modulating thromboinflammation. In the main trials assessing the role of dexamethasone,

tocilizumab, sarilumab, and tofacitinib, the rates of PE were not reported.[119–122] It is probable that at the beginning of the pandemic, there was limited awareness of the need for including PE or VTE among the potential outcomes interest. However, the available analyses are underpowered for PE endpoints, underscoring the need for further research in this area.

Catheter-directed thrombolysis (CDT) has been reported in highly selected patients with high-risk COVID-19-associated PE.[123] CDT can be an interesting strategy in patients with high bleeding risk and comorbidities in whom systemic thrombolysis and surgical embolectomy are contraindicated.[123] The full-treatment tradeoffs of CDT in patients with intermediate-risk PE, outside of COVID-19, are currently under intense investigations.[124]

Follow-up

The long-term effects of COVID-19 are not entirely understood and are the topic of ongoing research.[125–127] Furthermore, the optimal follow-up for COVID-19-associated PE is unknown. In particular, there are limited data on the timing, dedicated workup, optimal method in terms of imaging, and type and duration of the antithrombotic therapy after the diagnosis of COVID-19-associated PE.

The WHO defines long COVID as a condition in individuals with a history of probable or confirmed COVID-19, usually at least 3 months after infection onset, with symptoms that last for at least 2 months and cannot be explained by an alternative disease.[128] Its estimated prevalence varies with the age group, disease severity, and type of persistent symptom but can range from 10 to 71%.[12,129,130] Among its more common symptoms, there are several respiratory symptoms such as fatigue (58%), dyspnea (24%), polypnea (21%), and cough (19%). It is unclear how the micro- and macrothrombotic pulmonary events could be related to the long COVID-19 symptoms. However, the fact that the COVID-19-associated PE entails a severe vascular condition in addition to the parenchymal viral affection could explain the presence of the multiple respiratory manifestations of long COVID. Moreover, the relative frequency of chronic thromboembolic pulmonary hypertension (CTEPH) and its association with long COVID remains to be determined in patients with COVID-19-associated PE.[131]

Patients who survive COVID-19 have an increased 1-year risk of cardiovascular adverse events, regardless of the disease severity.[127] Therefore, developing models to stratify patients at high risk of adverse events during follow-up would help select patients in whom a comprehensive workup can be cost-effective. Moreover, determining the effect of COVID-19-associated PE on long-term clinical outcomes such as mortality, long COVID, CTEPH, and other adverse events warrants further attention.

Conclusions

COVID-19-associated PE has some specific clinical characteristics compared with conventional non–COVID-19-associated PE, suggesting it can include a different disease phenotype. Further research is needed to clarify its true prognostic significance on fatal and nonfatal outcomes. Major scientific organizations provide conditional recommendations in favor of full-intensity over standard-intensity prophylactic anticoagulation in noncritically ill hospitalized patients with COVID-19 who have a low risk of bleeding. Although treatment of acute COVID-19-associated PE is generally similar to pre-COVID-19 management, careful attention must be given to potential drug–drug interactions between COVID-19 therapies and oral anticoagulants. The optimal type and duration of anticoagulation, long-term effects of COVID-19-associated PE on mortality or CTEPH, and the relationship with long COVID will require future investigation.

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