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Thromboprophylaxis: balancing evidence and experience during the COVID-19 pandemic

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Abstract

A common and potent consideration has recently entered the landscape of the novel coronavirus disease of 2019 (COVID-19): venous thromboembolism (VTE). COVID-19 has been associated to a distinctive related coagulopathy that shows unique characteristics. The research community has risen to the challenges posed by this « evolving COVID-19 coagulopathy » and has made unprecedented efforts to promptly address its distinct characteristics. In such difficult time, both national and international societies of thrombosis and hemostasis released prompt and timely responses to guide recognition and management of COVID-19-related coagulopathy. However, latest guidelines released by the international Society on Thrombosis and Haemostasis (ISTH) on May 27, 2020, followed the American College of Chest Physicians (CHEST) on June 2, 2020 showed some discrepancies regarding thromboprophylaxis use. In this forum article, we would like to offer an updated focus on thromboprophylaxis with current incidence of VTE in ICU and non-ICU patients according to recent published studies; highlight the main differences regarding ISTH and CHEST guidelines; summarize and describe which are the key ongoing RCTs testing different anticoagulation strategies in patients with COVID-19; and finally set a proposal for COVID-19 coagulopathy specific risk factors and dedicated trials.

Keywords COVID-19 · Coronavirus · Thromboprophylaxis · Venous thromboembolism · Guidelines

Abbreviations

CA	Chronic therapeutic anticoagulation
BID	Twice-daily
BMI	Body mass index
COVID-19	Coronavirus disease 2019
CT	Computed tomography
DOAC	Direct oral anticoagulant
DVT	Deep vein thrombosis
ICU	Intensive care unit
IT	Thromboprophylaxis with intermediate dose of LMWH/ UFH
LMWH	Low molecular weight heparin
N/A	Not available
PE	Pulmonary embolism
RCTs	Randomized controlled trials
SD	Routine thromboprophylaxis with standard dose of UFH or LMWH
TD	Thromboprophylaxis with therapeutic dose
UFH	Unfractionated heparin
VTE	Venous thromboembolism

Highlights

- Reported incidence of venous thrombotic events in COVID-19 patients
- Major differences between ISTH and CHEST guidelines in thromboprophylaxis for patients with COVID-19
- Ongoing RCTs of different anticoagulation strategies in patients with COVID-19
- A proposal for COVID-19 coagulopathy specific risk factors and dedicated trials

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A common and potent consideration has recently entered the landscape of the novel coronavirus disease of 2019 (COVID-19): venous thromboembolism (VTE). COVID-19 has been associated to a distinctive related coagulopathy that shows unique characteristics [1]. The research community has risen to the challenges posed by this « evolving COVID-19 coagulopathy » and has made unprecedented efforts to promptly address its distinct characteristics. However, a key central question that could guide prevention, diagnosis, and treatment strategies of COVID-19 coagulopathy remains under debate: are these haemostatic changes a consequence of severe inflammation or are they a specific effect mediated by the virus? [2]. The immune response to acute SARS-CoV-2 infection and the accompanying surge of cytokines and inflammatory mediators have been accepted as a key pathway triggering thrombogenesis. In this setting, early strategies aimed at reducing inflammation might help prevent thrombosis. The alternative postulate is that the virus directly or indirectly interferes with coagulation pathways. The determinants of both hypotheses seem to stem mostly from host factors such as age, comorbidities, and the prominent role played by the extent of lung injury. Owing to these determinants, the combined use of risk scores to identify high-risk patients for adverse thrombotic events may guide individualized antithrombotic treatment of Covid-19 patients [3]. Another important insight is the recognition of

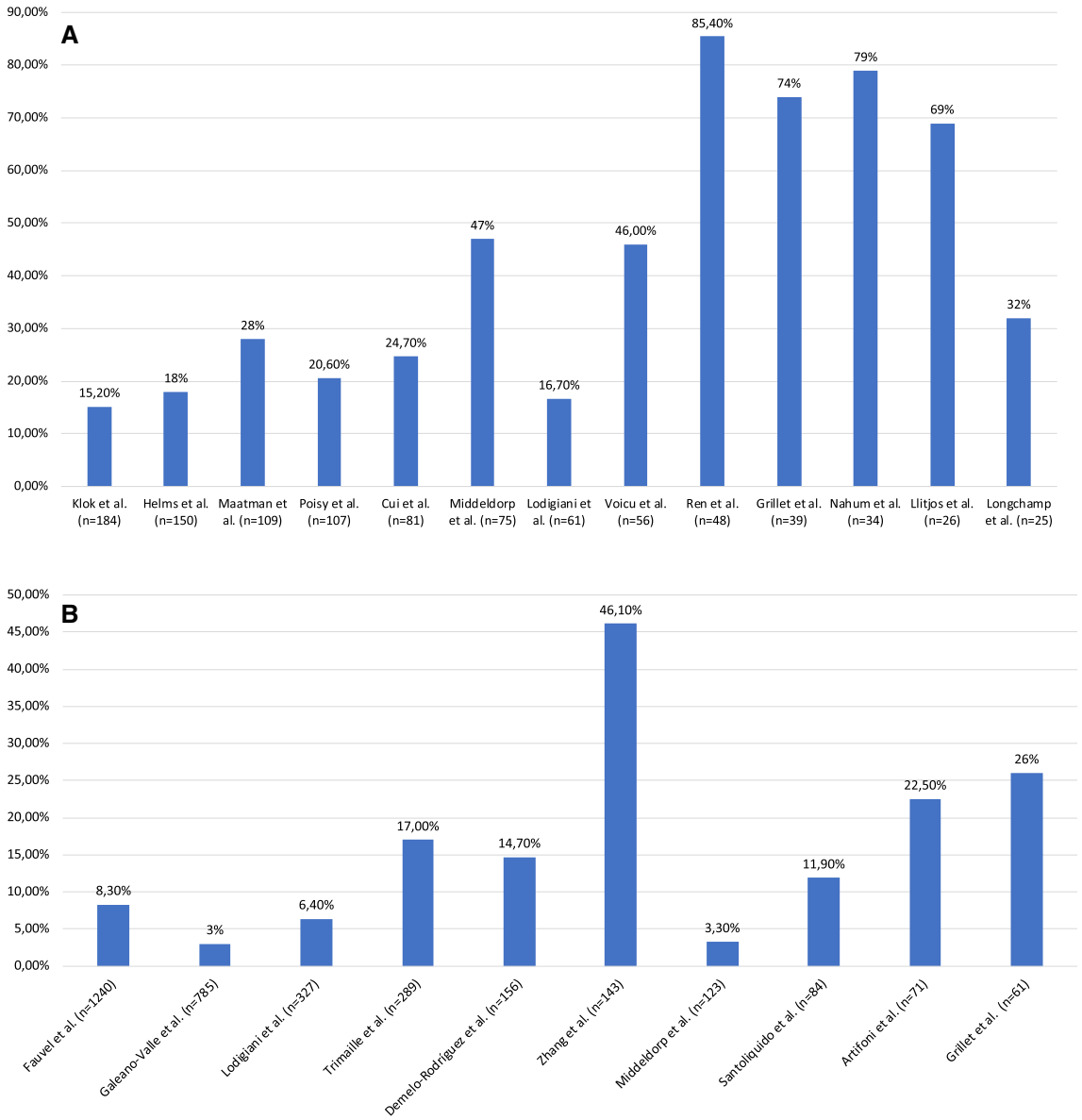

Fig. 1 Reported incidence of venous thrombotic events in COVID-19 patients hospitalized in ICU (**a**) and non-ICU (**b**). *Covid-19* coronavirus disease 201, *ICU* intensive care unit

the importance of extravascular fibrinolytic activity in the airway lumen and the alveolar compartment. Extravascular fibrin was demonstrated as a possible mechanism by which inflammatory cells can invade the lung [4]. Breakdown of fibrin as a consequence of high fibrinolytic activity would lead to a marked generation of D-dimers levels independently of thrombotic events. According to this paradigm, high D-dimers levels would not be solely considered as a marker of thrombotic propensity but should be viewed as an integrate marker of disease severity including the extent of lung damage [5].

In the inpatient setting, the prevalence of VTE ranges from 3 to 85%, as detailed in Fig. 1 [6–25].

However, most of studies on coronavirus patients used different design (systematic screening vs D-Dimer threshold vs symptom-driven approach), different intervention (contrasting intensities of thromboprophylaxis regimens), severity (ICU vs wards) and outcome (asymptomatic vs symptomatic VTE) resulting in reduced data comparability across studies (Table 1).

Furthermore, investigations from the outpatients are warranted with high priority, as they represent the vast majority of Covid-19 cases and VTE rate in this specific subset has not been reported yet [26]. Early reports suggested a high incidence of VTE and frequent haemostasis disorders in COVID-19 patients [27, 28]. Though, it remains to be demonstrated that theses frequent «new thrombotic» features at first glance are any different from previous experience from severe viral pneumonia [29–33]. Both intrinsic and extrinsic risk factors for VTE (Fig. 2) together with large number of patients considered at high risk on the basis of current VTE risk scores [34] lead to first interim [35] followed by updated guidance on thromboprophylaxis in hospitalized patients with COVID-19 [36, 37].The first reminder of a beneficial effect of thromboprophylaxis came as early as March 27, 2020 with reduced mortality in critically ills affected by severe COVID-19 and treated with heparin [38]. Of note, only 22.0% of the population analyzed by Tang et al. received anticoagulant therapy for the prevention of VTE and this reinforced the role for routine VTE risk assessment and the initiation of adequate thromboprophylaxis [39]. A substantial 5 to 10% risk of VTE in critically ills is currently reported despite the use of prophylactic anticoagulants [40–43]. COVID-19 patients presented in later reports with unusual higher rates of VTE despite the use of prophylactic anticoagulants [6–9, 12, 21].

Latest ISTH consensus statement published on May 27, 2020 recommended routine thromboprophylaxis in non-ICU and ICU hospitalized COVID-19 patients with preferably standard-dose LMWH or UFH [37]. Due to time-sensitivity with the pandemic and in the absence of robust evidence, a "stepped therapy" approach in non-ICU patients or treatment-dose heparin in critically ills did not reach full consensus yet. With regards to the rapid deterioration reported in many COVID-19 patients requiring ICU transfer, long half-life and/or reversibility concerns, both fondaparinux and prophylactic dose DOAC were not recommended in critically ill hospitalized COVID-19 patients. Apart from body weight-adjusted dose on extremes cases (< 50 kg or > 120 kg or BMI), the ISTH expert panel recommended against the general use of intermediate dose of LMWH/UFH in non-ICU. Wisely awaiting for some strong evidences, intermediate-dose LMWH was only advocated by 30% of ISTH respondent in non-ICU and up to 50% in ICU patients (Table 2).

No more that 6 days after the ISTH guidance had been released, an American College of Chest Physicians (CHEST) panel of experts provided a conflicting set of guidelines on June 2, 2020 [44]. CHEST experts recommended (i) standard dose anticoagulant thromboprophylaxis in non-ICU and ICU patients, (ii) LMWH or fondaparinux over UFH in non-ICU patients, (iii) suggested against the addition of mechanical prophylaxis (i.e. intermittent pneumatic compression) to pharmacological thromboprophylaxis while 60% of ISTH experts pledged for it. Armed with this two set of guidelines, one being « conservative » and the other much more « liberal» on both stepped-up pharmacological and mechanical approach, how is the physician supposed to react in day use practice? Both guidelines nonetheless advocated for more evidence coming from ongoing randomized trials (Table 3), more extensive description of the « sicker » or « higher risk » patient profile likely to benefit from increased intensity anticoagulant thromboprophylaxis, and finally a call for updated evidences regarding bleeding risk in this population as they are insufficient so far. Identifying very-high-risk patients for VTE is undoubtedly the main issue of reducing both incidence and mortality risk of VTE [45]. The triad of risk seems to essentially rely on marked prothrombotic state, thromboinflammation and the extent of lung injury (Fig. 3).

All studies of haemostasis have identified a prothrombotic state in COVID-19 [46]. Thachil et al. lately proposed a new staging classification characterizing COVID-19 associated hemostatic abnormalities (CAHA) [3]. The authors proposed that the spectrum of CAHA first represents a localized phenomenon of hypercoagulability in the lung, which then becomes extensive and systemic (increased D-Dimer level, reduced platelet count and prolonged PT) if not treated adequately. We promptly confirmed a stepwise increase in VTE rates and excess mortality and/or transfer to ICU for each increment in stage of CAHA among 150 non-ICU patients with COVID-19 [47]. Hence, we proposed a CAHA threshold ≥ 2 to consider early aggressive strategies including early VTE imaging screening, "stepped-up" anticoagulant dose regimens and critical care support. VTE risk

Table 1 Prevalence of venous thrombotic events (acute pulmonary embolism and/or deep vein thrombosis) in COVID-19 patients

	Design	VTE	Thromboprophylaxis	Age	Male sex
ICU COVID-19 patients					
Klok et al. (n = 184)	Cohort study	28 (15.2%)	Thromboprophylaxis: 184 (100%). All patients received at least standard doses thromboprophylaxis, although regimens differed between hospitals and doses increased over time	64 ± 12	76%
Helms et al. (n = 150)	Cohort study	27 (18.0%)	None: 0 (0%) Standard-dose (SD): 105 (70%) Intermediate-dose (ID): 0 (0%) Therapeutic dose (TD) or chronic therapeutic anticoagulation (CA): 45 (30%)	63 (53–71)	81.3%
Maatman et al. (n = 109)	Cohort study	31 (28%)	None: 0 (0%) SD: 109 (100%) ID: 0 (0%) TD or CA: 0 (0%)	61 ± 16	57%
Poisy et al. (n = 107)	Cohort study	22(20.6%)	Among the 22 patients with pulmonary embolism None: 0 (0) SD: 20 (91%) ID: 0 (0%) TA or CA: 2 (9%)	N/A	N/A
Cui et al. (n = 81)	Systematic screening for VTE	20 (24.7%)	None: 81 (100%) SD: 0 (0%) ID: 0 (0%) TD or CA: 0 (0%)	59.9 ± 14.1	46%
Middeldorp et al. (n = 75)	Cohort study	35 (47%)	"Most ICU patients receiving routine thrombosis prophylaxis. Thrombosis prophylaxis was initiated in 167 (ICU + non-ICU) patients (84%) while 19 (9.6%) continued therapeutic anticoagulation" None: N/A SD: N/A IT: N/A TD or CA: 7 (9.3%)	62 ± 10	77%
Lodigiani et al. (n = 61)	CT cohort study	8 (16.7%)	SD: 42 (68.8%) ID: 17 (27.9%) CT or CA: 2 (3.3%)	61 (55–69)	80.3%
Voicu et al. (n = 56)	Systematic screening for DVT	26 (46%)	None: 0 (0%) SD: 49 (87%) ID: 0 (0%) TD or CA: 7 (13%)	N/A	75%
Ren et al. (n = 48)	Systematic screening for DVT	41 (85.4%)	None: 1 (2%) SD: 41 (98%) ID: 0 (0%) TD or CA: 0 (0%)	70 (62.5–80)	54.2%
Grillet et al. (n = 39)	Chest CT cohort study	17 (74%)	N/A	N/A	
Nahum et al. (n = 34)	Systematic screening for DVT	27 (79%)	« All patients received anticoagulant prophylaxis at hospital admission»	62.9 ± 7.9	74%
Llitjos et al. (n = 26)	Systematic screening for DVT	18 (69%)	None: 0 (0%) SD: 8 (31%) ID: 0 (0%) TD or CA: 18 (69%)	68 (51.5–74.5)	77%
Longchamp et al. (n = 25)	Systematic screening for DVT	8 (32%)	SD: 23 (92%) CA: 2 (8%)	68 ± 11	64%

Table 1 (continued)

	Design	VTE	Thromboprophylaxis	Age	Male sex
Non-ICU COVID-19 patients					
Fauvel et al. (n = 1240)	Cohort study	103 (8.3%)	None: 267 (21.5%) SD: 738 (63%) ID: 99 (8.4%) TA or CA: 136 (11%)	64 ± 17.0	58.1%
Galeano-Valle et al. (n = 785)	Cohort study	24 (3%)	N/A	N/A	N/A
Lodigiani et al. (n = 327)	Cohort study	20 (6.4%)	None: 53 (16.2%) SD: 133 (40.7%) ID: 67 (20.5%) TA or CA: 74 (22.6%)	68 (55–77)	65.7%
Trimaille et al. (n = 289)	Cohort study	49 (17.0%)	None: 31 (10.7%) SD: 170 (58.8%) ID: 31 (10.7%) TD or CA: 57 (19.7%)	62.2 ± 17.0	59.2%
Demelo-Rodríguez et al. (n = 156)	Systematic screening for DVT with D-dimer > 1000 ng/ml	23 (14.7%)	None: 0 (0%) Pneumatic compression 3 (1.9%) DS: 133 (98.1%) ID: 0 (0%) TA or CA: 0(0%)	68.1 ± 14.5	65.4%
Zhang et al. (n = 143)	Systematic screening for DVT	66 (46.1%)	None: 90 (62.9%) SD: 53 (37.1%) ID: 0 (0%) TA or CA: 0 (0%)	63 ± 14	51.7%
Middeldorp et al. (n = 123)	Cohort study	4 (3.3%)	"Thromboprophylaxis was initiated in 167 (ICU + non-ICU) patients (84%) while 19 (9.6%) continued therapeutic anticoagulation" None: N/A SD and ID: N/A TA or CA: 12 (9.8%)	60 ± 10	59%
Santoliquido et al. (n = 84)	Systematic screening for DVT	10 (11.9%)	None: 0 (0%) SD: 84 (100%) ID: 0 (0%) TD or CA: 0 (0%)	67.6 ± 13.5	72.6%
Artifoni et al. (n = 71)	Systematic screening for DVT	16 (22.5%)	None: 0 (0%) SD: 71 (100%) ID: 0 (0%) TA or CA: 0 (0%)	64 (46.0–75)	60.6%
Grillet et al. (n = 61)	Chest CT cohort study	6 (26%)	N/A	N/A	N/A

CA chronic therapeutic anticoagulation, *COVID-19* coronavirus disease 2019, *CT* computed tomography, *DOAC* direct oral anticoagulant, *DVT* deep vein thrombosis, *ICU* intensive care unit, *IT* thromboprophylaxis with intermediate-dose of LMWH/UFH, *LMWH* low-molecular-weight heparin, *N/A* not available, *SD* routine thromboprophylaxis with standard-dose of UFH or LMWH, *TD* thromboprophylaxis with therapeutic dose, *UFH* unfractionated heparin, *VTE* venous thrombotic events

stratification scheme and prospective RCTs are needed to determine whether intermediate or treatment-dose anticoagulant confer both survival benefit and decreased VTE incidence according to biomarkers threshold including the use of very elevated D-dimer levels and inflammatory markers in hospitalized patients with COVID-19.

Hyperinflammation has been advocated as a key component triggering thromboinflammation and subsequent increased risk of VTE [48, 49]. The first event after inhalation of SARS coronaviruses is invasion of type II alveolar cells in the lung. Viral cell entry triggers the host's immune response and an inflammatory cascade. While viral multiplication and localized inflammation in the lung is the norm, severe COVID-19 patients will develop an overproduction of proinflammatory cytokines resulting in a cytokine storm [50]. On top of anti-inflammatory or antiviral effects, current therapeutic strategies (e.g. intravenous immunoglobulin, selective cytokine blockade etc.) [51] may have indirect antithrombotic effects and modulate the risk of VTE.

Lung and pulmonary thrombosis have an intimate relationship in COVID-19. The first hint came from

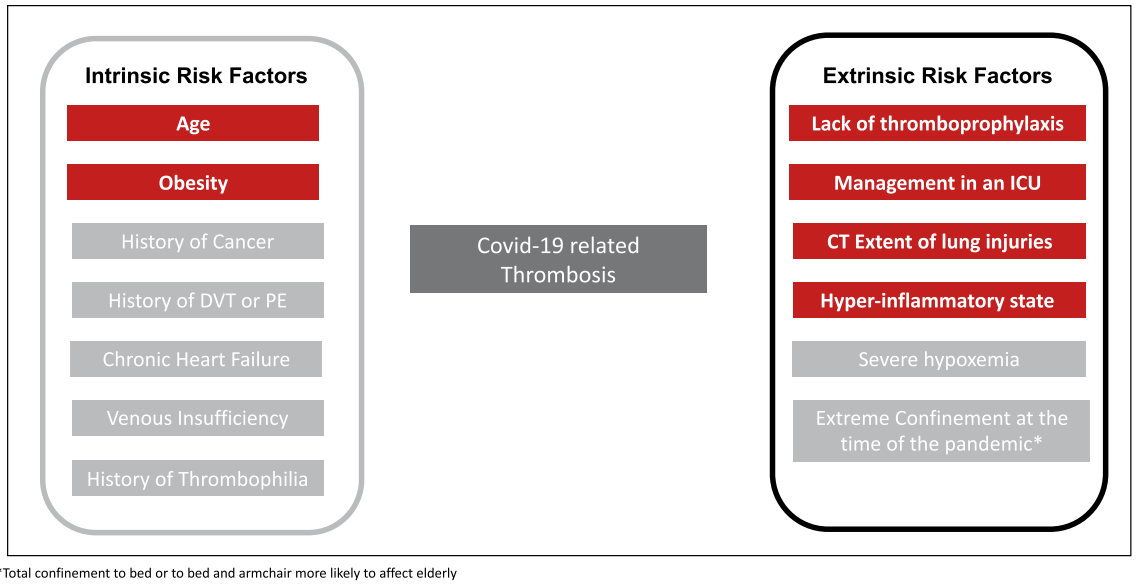

Fig. 2 Intrinsic and extrinsic risk factors for venous thromboembolism in COVID-19. *Covid-19* coronavirus disease 2019, *CT* computed tomography, *DVT* deep vein thrombosis, *ICU* intensive care unit, *PE* pulmonary embolism

Table 2 Major differences between ISTH and CHEST guidelines in thromboprophylaxis for patients with COVID-19

Major differences between ISTH and CHEST guidelines in thromboprophylaxis for patients with COVID-19	
International Society on Thrombosis and Haemostasis (ISTH)	CHEST Guideline and Expert Panel Report
VTE prophylaxis in acutely ill hospitalized patients	
Thromboprophylaxis with LMWH over UFH. Half-life and reversibility concerns regarding fondaparinux	Thromboprophylaxis with LMWH or fondaparinux over UFH. Thromboprophylaxis with LMWH, fondaparinux or UFH over a DOAC
Standard-dose anticoagulant thromboprophylaxis recommended, but intermediate-dose LMWH may also be considered (30% of responders)	Standard dose anticoagulant thromboprophylaxis over intermediate (LMWH BID or increased weight-based dosing)
VTE prophylaxis in critically ill patients	
Thromboprophylaxis with LMWH or UFH	Thromboprophylaxis with LMWH over UFH; and LMWH or UFH over fondaparinux or a DOAC
Standard-dose anticoagulant thromboprophylaxis recommended, but intermediate-dose LMWH (50% of respondents) may be considered in high risk patients	Standard dose anticoagulant thromboprophylaxis over intermediate (LMWH BID or increased weight-based dosing)
Patients with obesity as defined by actual body weight or BMI should be considered for a 50% increase in the dose of thromboprophylaxis	
Multi-modal thromboprophylaxis with mechanical methods (i.e., intermittent pneumonic compression devices) should be considered (60% of respondents)	Against the addition of mechanical prophylaxis to pharmacological thromboprophylaxis
After hospital discharge	
Extended post-discharge thromboprophylaxis should be considered for all hospitalized patients with COVID-19 that meet high VTE risk criteria. The duration of post-discharge thromboprophylaxis can be approximately 14 days at least (50% of respondents), and up to 30 days (20% of respondents)	Inpatient thromboprophylaxis only over inpatient plus extended thromboprophylaxis after hospital discharge Extended thromboprophylaxis in patients at low risk of bleeding should be considered if emerging data on the post-discharge risk of VTE and bleeding risk indicate a net benefit

BID twice-daily, *BMI* body mass index, *Covid-19* coronavirus disease 2019, *DOAC* direct oral anticoagulant, *ICU* intensive care unit, *LMWH* low-molecular-weight heparin, *UFH* unfractionated heparin, *VTE* venous thromboembolism

Table 3 Ongoing RCTs of different anticoagulation strategies in patients with COVID-19

Ongoing RCTs of different anticoagulation strategies in patients with COVID-19			
RCT	Estimated sample size	Interventions	Estimated completion date
ICU			
NCT04362085	462	Therapeutic (LMWH or UFH) vs. Prophylactic-Dose (LMWH, UFH or fondaparinux)	December 2020
NCT04367831	100	Intermediate vs. Prophylactic-Dose with LMWH or UFH	April 2021
Acute Respiratory Distress Syndrome (ARDS)			
NCT04445935	100	Bivalirudin Injection vs. Standard treatment in COVID-19 ARDS	March 2021
NCT04357730	60	Fibrinolytic Therapy (Alteplase) to Treat ARDS	November 2020
ICU and non-ICU			
NCT04359277	1000	Intermediate vs. Prophylactic-Dose with Enoxaparin with LMWH or UFH	April 2021
NCT04344756	808	Therapeutic (Tinzaparin or UFH) vs. Prophylactic-Dose (Enoxaparin, Tinzaparin, dalteparin or UFH)	September 2020
NCT04373707	602	Low Prophylactic vs. Weight-Adjusted Prophylactic Dose of LWMH	October 2020
NCT04394377	600	Therapeutic (Rivaroxaban 20 mg/ daily or enoxaparin or UFH) vs. Prophylactic-Dose (Enoxaparin)	December 2020
NCT04351724	500	Rivaroxaban 5 mg BID vs. Prophylactic-Dose of LMWH	December 2020
NCT04416048	400	Rivaroxaban vs. LMWH or UFH at prophylactic doses	May 2021
NCT04401293	308	Therapeutic (LMWH) vs. Prophylactic/Intermediate Dose (LMWH or UFH) in high risk COVID-19 patients (SIC score > 4 OR D-dimer > 4.0 X ULN)	April 2021
NCT04377997	300	Therapeutic vs. Prophylactic-Dose with Enoxaparin or UFH and D-dimer > 1.5 g/mL	January 2022
NCT04345848	200	Therapeutic vs. Prophylactic-Dose with Enoxaparin	November 2020
NCT04406389	186	Therapeutic vs. intermediate dose with LMWH or UFH or fondaparinux	June 2021
Non-ICU			
NCT04366960	2712	Intermediate vs. Prophylactic-Dose with Enoxaparin	November 2020
NCT04444700	462	Therapeutic Enoxaparin vs. Prophylactic-Dose with Enoxaparin or UFH	December 2020
NCT04360824	170	Intermediate vs. Prophylactic-Dose with Enoxaparin	April 2021
Ambulatory patients			
NCT04400799	1000	Prophylactic dose of Enoxaparin 4000 IU antiXa activity vs. control	April 2021
Children			
NCT04354155	38	Safety, dose-requirements, and exploratory efficacy of enoxaparin BID	October 2022

Covid-19 coronavirus disease 2019, *ICU* intensive care unit, *LMWH* low-molecular-weight heparin, *RCTs* randomized controlled trials; *VTE* venous thromboembolism

accumulating evidence of published necropsy series with the prominence of clot, widespread micro-thrombi and occlusion of alveolar capillaries [26, 52–54]. More evidence followed with proof of pulmonary endotheliitis in the time course of SARS-CoV-2 infection [55]. A distinctive pattern of pulmonary intravascular coagulopathy has finally been proposed [56, 57]. The current consensus puts the lungs as the epicenter for the hemostatic and inflammatory issues in COVID-19. Desborough et al. nicely addressed this issue providing evidence that many of the acute pulmonary embolism are indeed described on CT pulmonary angiograms as segmental or subsegmental and that these thromboses may be immunothromboses due to local inflammation, rather than thromboembolic disease

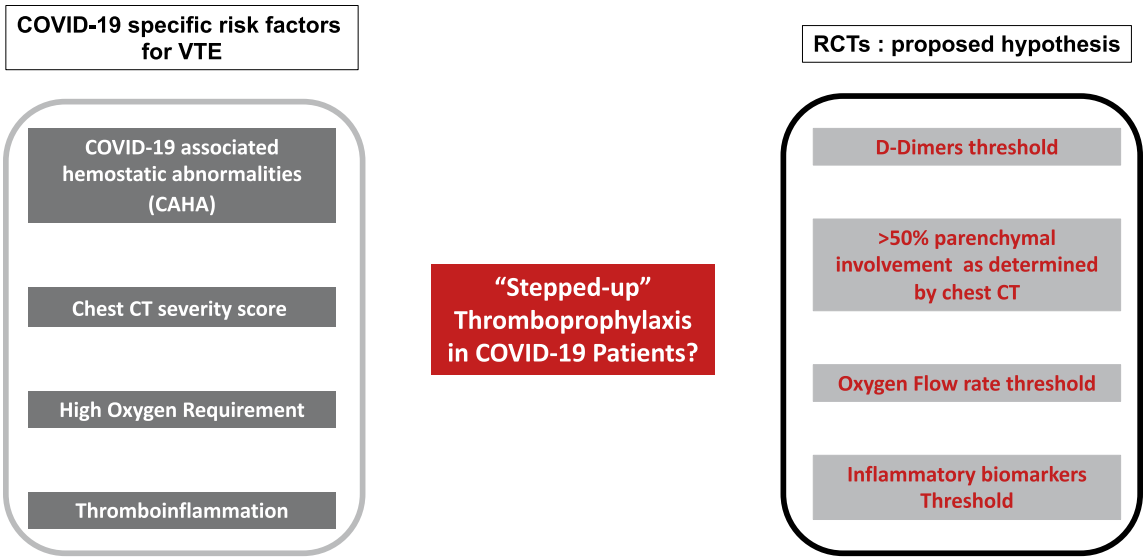

Fig. 3 A proposal for COVID-19 coagulopathy specific risk factors and dedicated trials. *Covid-19* coronavirus disease 2019, *CT* computed tomography, *ICU* intensive care unit, *RCTs* randomized controlled trials, *VTE* venous thromboembolic events

[58]. First localized to the lung, then extensive and finally systemic if not treated, the phenomenon of pulmonary intravascular coagulopathy in COVID-19 pneumonia translates in clinical practice with higher oxygen requirement and extensive lung injuries assessed by chest CT [18, 47, 59].

Several anticoagulant regimens are been currently investigated in patients with COVID-19. Systematic screening for marked prothrombotic state, hyperinflammation and the extent of lung injury as determined by chest CT could be helpful to guide individualized thromboprophylaxis in COVID-19 patients.

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Informed Consent All the authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation. All authors have read and approved submission of the manuscript.

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