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International Journal of Cardiology 322 (2021) 286–290

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Editorial

COVID-19 and arterial thrombosis: A potentially fatal combination

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The Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has besieged the world with its high morbidity and mortality rates, and represents the pandemic of the century, with approximately 30 million cases and over 900,000 deaths worldwide as of September 2020 [1]. Although respiratory symptoms and pneumonia generally dominate the clinical presentation, early observations later confirmed by extensive evidence accumulation made it clear that COVID-19 is a systemic disease [2]. Multi-organ involvement by SARS-CoV-2 has been linked to the pleiotropic expression of its cellular receptor, i.e. Angiotensin Converting Enzyme-2 (ACE-2), allowing for viral entry in multiple tissues, including alveolar epithelial cells, enterocytes and, most interestingly, arterial and venous endothelial cells [3,4]. Moreover, a surge in systemic inflammation has been described as a key pathogenic element in the course of COVID-19 [5]. This phenomenon, known as "cytokine storm", may further contribute to multi-organ failure [6].

In this issue of the Journal, Dr. de Roquetaillade et al. report an unusually high rate of arterial thrombosis events in a cohort of COVID-19 European patients, i.e. 24 events in 20 patients, out of a total of 209 cases managed by the Authors during the reference period [7]. While thrombotic and thrombo-embolic episodes frequently complicate the course of severe infectious diseases, this study, along with similar reports, suggests that several clinical and pathophysiological features differentiate those related to SARS-CoV-2 infection [8].

First, arterial thrombosis is generally a rare complication in infectious diseases. In the present work, however, the rate of arterial thrombotic and thromboembolic events was 9.6% [7].. This figure is even higher than the 3.7–4.4% reported in the largest previously published cohorts on COVID-19 patients [9,10].

Second, clinical profile of patients who experience these complications is in line with that emerging from similar reports, suggesting that arterial thrombosis events in SARS-CoV-2 infection more frequently involve relatively young males, and occur in large arterial vessels (e.g. the aorta and the mesenteric artery) without significant pre-existing atherosclerotic burden, suggesting a causative mechanism that may be independent of thrombotic superimposition on an unstable atherosclerotic plaque [9].

Third, hemostatic derangements in critically-ill patients usually involve a combination of coagulation pathway alteration, direct platelet consumption or activation, and inflammation-mediated pro-thrombotic state resulting in disseminated intravascular coagulation (DIC) [11]. On the contrary, laboratory test alterations typically hallmarking DIC, including low platelet count, prothrombin time prolongation, and fibrinogen consumption are often mild or lacking in COVID-19 patients experiencing thrombotic events. Indeed, in the study by Roquetaillade et al., no significant blood test abnormalities in coagulation parameters were found [7]. In addition, multiple thrombotic events were reported in 20% of patients [7] while no sign of venous or arterial embolism was found to justify these lesions, consistent with a primary, "in situ" phenomenon. Primitive, local thrombosis has also been postulated to relate with pulmonary circulation involvement in COVID-19 [12].

Proof of direct endothelial invasion and damage by SARS-CoV-2 provides a pathophysiological backbone to these observations [13]. Indeed, the delicate balance between pro-coagulant and anti-coagulant factors requires an intact endothelium. Disruption of this layer by SARS-CoV-2 infection may thus precipitate a thrombotic cascade, both by means of inflammatory damage and, more importantly, direct cellular invasion [13]. In addition, in severely-ill COVID-19 patients, the pro-inflammatory milieu may further enhance platelet activation and thrombus formation: indeed, innate-immunity factors (including IL-1, IL-6, and TNF-α) play a proven role in atherothrombosis [14].

Prevention of these potentially fatal complications remains challenging. In this study, 50% of patients were already on prophylactic anticoagulation at the time of the events [7]. Interestingly, previous reports on venous thromboembolism in severe COVID-19 pneumonia have also showed a substantial rate of thrombotic events in spite of adequate prophylactic anticoagulation [11]. Of note, this has led to many to advocate use of therapeutic anticoagulation for thromboembolic prevention in patients with severe COVID-19 pneumonia, while others proposed an "intermediate intensity" anticoagulation regimen (enoxaparin 0.5 mg/kg twice daily) [11]. Considerable disagreement on the best antithrombotic strategy still subsists: therapeutic anticoagulation and intermediate intensity anticoagulation were advocated by 5.2% and 31.6% of participants, respectively, in a recently published Delphi-method expert consensus on thrombotic complications preventions in severe COVID-19 pneumonia, with the rest supporting standard prophylactic anticoagulation [15]. A whole plethora of clinical trials have been set-up comparing either different anticoagulation approaches or different intensity of the same regimen (Table 1). Agents of interest include anti-platelets, parenteral or oral anticoagulants, and even a combination of both. Of note, whether the "in situ" nature of these arterial thrombotic events may be more sensible to anti-aggregation rather than anti-

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https://doi.org/10.1016/j.ijcard.2020.10.046

Table 1
Trials investigating anti-thrombotic treatments in COVID-19*.[a]

Clinical Trials Registration	Treatment Arms	Expected sample size	Starting Date	Coordinating Centre
Apixaban				
NCT04498273	-Apixaban 2.5 mg q12h -Apixaban 5 mg q12h -Aspirin 81 mg q24h -Placebo q12h	7000	August 2020	University of Pittsburgh, Pittsburgh, USA
NCT04512079 (FREEDOM COVID)	-Prophylactic enoxaparin (40 mg q24h; 30 mg q24h for CrCl <30 ml/min) -Full-dose enoxaparin (1 mg/kg q12h; 1 mg/kg q24h for CrCl <30 ml/min) -Apixaban (5 mg q12h; 2.5 mg q12h for patients with at least two of three of age ≥ 80 years, weight ≤ 60 kg or serum creatinine ≥1.5 mg/dL)	3600	September 2020	Icahn School of Medicine at Mount Sinai, New York, USA
Argatroban				
NCT04406389 (IMPACT)	*Intermediate-dose prophylaxis* -Enoxaparin 0.5 mg/kg (frequency adjusted on CrCl) -UFH 7500 U q8h (n case of AKI) -Fondaparinux 2.5 mg q24h *Therapeutic anticoagulation* -Enoxaparin 1 mg/kg -UFH (titrated on aPTT or anti-Xa level) -Argatroban (in case of HIT; according to institutional protocol) -Fondaparinux q24h (in case of HIT; weight-adjusted)	186	October 2020	Weill Medical College of Cornell University, New York, USA
Edoxaban				
NCT04516941 (CONVINCE)	-Edoxaban 60 mg q24h (or 30 mg according to CrCl and body weight) -Colchicine 0.5 mg q12h -Edoxaban 60 mg q24h (or 30 mg according to CrCl and body weight) + colchicine 0.5 mg q12h -No edoxaban and no colchicine	420	October 2020	Bern University Hospital, Bern, Switzerland
Heparins				
NCT04345848 (COVID-HEP)	-Therapeutic anticoagulation (UFH, enoxaparin) -Prophylactic anticoagulation (UFH, enoxaparin)	200	April 2020	University Hospital, Geneva, Switzerland
NCT04377997	-Therapeutic anticoagulation (UFH, enoxaparin) -Standard of care	300	May 2020	Massachusetts General Hospital, Boston, USA
NCT04409834 (COVID-PACT)	*Full-dose anticoagulation + antiplatelet therapy:* -UFH (targeting an aPTT of x 1.5–2.5) or enoxaparin 1 mg/kg q12h -Clopidogrel 300 mg LD, then 75 md q24h *Full-dose anticoagulation + no antiplatelet therapy:* - UFH (targeting an aPTT of x 1.5–2.5) or enoxaparin 1 mg/kg q12h *Prophylactic anticoagulation + antiplatelet therapy:* -UFH 5000 U q8h or enoxaparin 40 mg q24h -Clopidogrel 300 mg LD, then 75 md qd *Prophylactic anticoagulation + antiplatelet therapy:* -UFH 5000 U q8h or enoxaparin 40 mg q24h	750	August 2020	The TIMI Study Group, Boston, USA
NCT04492254 (ETHIC)	-Enoxaparin (40 mg q24h if <100 kg, 40 mg q12h if ≥100 kg) -Standard of care	1370	July 2020	Thrombosis Research Institute
NCT04367831 (IMPROVE)	*Intermediate-dose anticoagulation:* -Enoxaparin 1 mg/kg q24h or UFH 10 U/kg/h (target anti-Xa 0.1–0.3 U/ml) *Prophylactic dose anticoagulation:* -UFH 5000–7500 U q8h or enoxaparin (according to CrCl and body weight)	100	May 2020	Columbia University, New York, USA
NCT04400799	Enoxaparin 0.4 mg q24h	1000	June 2020	University of Zurich, Zurich, Switzerland
NCT04373707 (COVI-DOSE)	*Low-prophylactic dose:* -Enoxaparin 4000 U q24h (medical ward) or enoxaparin 4000 U q12h (ICU ward) *Weight-adjusted prophylactic dose:* -Enoxaparin 4000 U q12h if <50 kg -Enoxaparin 5000 U q12h if 50-70 kg -Enoxaparin 6000 U q12h if 70-100 kg -Enoxaparin 7000 U q12h if >100 kg	602	May 2020	Central Hospital, Nancy, France
NCT04401293 (HEP-COVID)	*Full-dose anticoagulation:* -Enoxaparin 1 mg/kg q12h or enoxaparin 0.5 mg/kg q12h *Prophylactic-dose anticoagulation:* -UFH 5000 U q12h/q8h or 7500 U q12h/q8h or enoxaparin 30 mg and 40 mg q24h/q12h	308	April 2020	Northwell Health, New York, USA
NCT04354155 (COVAC-TP)	Enoxaparin q12h (starting dose 0.5 mg/kg, adjusted to achieve a 4 h post-dose anti-factor Xa level of 0.20–0.49 anti-Xa U/ml)	38	June 2020	Johns Hopkins All Children's Hospital, Baltimore, USA
NCT04466670	-UFH (target anti-Xa level 0.3–0.7 U/ml) -Nebulized UFH 25000 U/5 ml inhalation q6h	310	July 2020	University of Sao Paulo General Hospital, Sao Paulo, Brazil

(continued on next page)

Table 1 (*continued*)

Clinical Trials Registration	Treatment Arms	Expected sample size	Starting Date	Coordinating Centre
	-Acetylsalicylic acid 100 mg q24h -Enoxaparin 1 mg/kg q12h			
NCT04359277	*Higher-dose anticoagulation:* -Enoxaparin if CrCl >30 or UFH (target anti-Xa level 0.3–0.5 unit/ml) -Enoxaparin 1 mg/kg q12h if 50–150 kg -Enoxaparin 0.75 mg/kg q12h if >150 kg or BMI >40 *Lower-dose prophylactic anticoagulation:* -UFH 5000 U q12h/q8h or 7500 U q12h/q8h if BMI > 40 or weight > 150 kg -Enoxaparin 40 mg q24h or 30 mg q12h/q24h (if CrCl <30 ml/min) or enoxaparin 40 mg q12h for weight > 150 kg or BMI >40–50 -Enoxaparin 60 mg q12h for BMI >50	77	April 2020	NYU Langone Health, New York, USA
NCT04406389 (IMPACT)	*Intermediate-dose prophylaxis* -Enoxaparin 0.5 mg/kg (frequency adjusted on CrCl) -UFH 7500 U q8h (n case of AKI) -Fondaparinux 2.5 mg q24h *Therapeutic anticoagulation* -Enoxaparin 1 mg/kg -UFH (titrated on aPTT or anti-Xa level) -Argatroban (in case of HIT; according to institutional protocol) -Fondaparinux q24h (in case of HIT; weight-adjusted)	186	October 2020	Weill Medical College of Cornell University, New York, USA
NCT04366960 (X-Covid 19)	-Enoxaparin 40 mg q12h -Enoxaparin 40 mg q24h	2712	May 2020	Niguarda Hospital, Milan, Italy
NCT04372589 (ATTA CC)	-Enoxaparin 1.5 mg/kg q24h or 1 mg/kg q12h or UFH (target aPTT x 1.5–2.5) -No intervention	3000	May 2020	University of Manitoba, Manitoba, Canada
NCT04528888 (STAUNCH-19)	*LMWH group:* -Enoxaparin 4000 U q24h, 6000 U q24h if >90 kg *LMWH + steroids group:* -Enoxaparin 4000 U q24h, 6000 U q24h if >90 kg + methylprednisolone *UFH + steroid group:* -UFH 18 U/kg/h (target aPTT x 1.5–2.0)	210	September 2020	University of Modena and Reggio Emilia, Modena, Italy
NCT04512079 (FREEDOM COVID)	-Prophylactic enoxaparin (40 mg q24h; 30 mg q24h for CrCl <30 ml/min) -Full-dose enoxaparin (1 mg/kg q12h; 1 mg/kg q24h for CrCl <30 ml/min) -Apixaban (5 mg q12h; 2.5 mg q12h for patients with at least two of three of age ≥ 80 years, weight ≤ 60 kg or serum creatinine ≥1.5 mg/dl)	3600	September 2020	Icahn School of Medicine at Mount Sinai, New York, USA
NCT04508439	-Enoxaparin 1 mg/kg q12h -Enoxaparin 1 mg/kg q24h	130	June 2020	Hospital Regional de Alta especialidad de Ixtapaluca, Ixtapaluca, Mexico
NCT04360824	-Prophylactic dose enoxaparin (40 mg q24h if BMI <30 and 30 mg q12h or 40 mg q12h if BMI ≥30) -Intermediate-dose enoxaparin (1 mg/kg q24h if BMI < 30 or 0.5 mg/kg q12h if BMI ≥ 30)	170	May 2020	University of Iowa, Iowa City, USA
NCT04344756 (CORIMMUNO-COAG)	-Tinzaparin or UFH 175 IU/kg/24 h for 14 days if CrCl ≥20 ml/min, or UFH (target anti-Xa target 0.5–0.7 U/ml) for 14 days -Standard of care	808	April 2020	Assistance Publique - Hôpitaux de Paris, Paris, France
NCT04359212 (VTE-COVID)	LMWH or fondaparinux in medical ward vs ICU patients	90	May 2020	University of Padua, Padua, Italy
NCT04444700 (RAPID-BRAZIL)	*Therapeutic anticoagulation* -Enoxaparin 1 mg/kg q12h *Standard of care* -Enoxaparin 40 mg q24h, enoxaparin 60 mg q24h, UFH 5000 q12h, UFH 5000 U q8h (BMI <40) or enoxaparin 40 mg q12h, UFH 7500 U q8h (BMI ≥40)	463	July 2020	University of Sao Paulo General Hospital, Sao Paulo, Brazil
Fondaparinux				
NCT04368377 (PIC-19)	Tirofiban 25 μg/kg bolus + a rate of 0,15 μg/kg/min for 48 h and clopidogrel 300 mg LD + 75 mg q24h for 30 days and acetylsalicylic acid 250 mg iv LD + 75 mg q24h for 30 days and fondaparinux 2.5 mg q24h	5	April 2020	University of Milan, Milan, Italy
NCT04359212 (VTE-COVID)	LMWH or fondaparinux in medical ward vs ICU patients	90	May 2020	University of Padua, Padua, Italy
NCT04406389 (IMPACT)	*Intermediate-dose prophylaxis* -Enoxaparin 0.5 mg/kg (frequency adjusted on CrCl) -UFH 7500 U q8h (n case of AKI) -Fondaparinux 2.5 mg q24h *Therapeutic anticoagulation* -Enoxaparin 1 mg/kg -UFH (titrated on aPTT or anti-Xa level) -Argatroban (in case of HIT; according to institutional protocol) -Fondaparinux q24h (in case of HIT; weight-adjusted)	186	October 2020	Weill Medical College of Cornell University, New York, USA
Rivaroxaban				
NCT04416048 (COVID-PREVENT)	-Rivaroxaban 20 mg q24h (15 mg for subjects with an eGFR ≥30 ml/min/1.73m^2 and < 50 ml/min/1.73m^2) for at least 7 days -Standard of care	400	August 2020	Charite University of Berlin, Berlin, Germany

Table 1 (*continued*)

Clinical Trials Registration	Treatment Arms	Expected sample size	Starting Date	Coordinating Centre
NCT04508023 (PREVENT-HD)	-Rivaroxaban 10 mg q24h -Placebo q24h	4000	August 2020	Janssen Research & Development, LLC, Raritan, NJ, USA
Aspirin				
NCT04363840 (LEAD COVID-19)	-No intervention -Aspirin 81 mg q24h -Aspirin 81 mg q24h + Vitamin D 50000 U once weekly	1080	May 2020	Louisiana State University Health Sciences Center in New Orleans, New Orleans, USA
NCT04498273	-Apixaban 2.5 mg q12h -Apixaban 5 mg q12h -Aspirin 81 mg q24h -Placebo q12h	7000	August 2020	University of Pittsburgh, Pittsburgh, USA
NCT04466670	-UFH (target anti-Xa level 0.3–0.7 U/ml) -Nebulized UFH 25000 U/5 ml inhalation q6h -Acetylsalicylic acid 100 mg q24h -Enoxaparin 1 mg/kg q12h	310	July 2020	University of Sao Paulo General Hospital, Sao Paulo, Brazil
NCT04368377 (PIC-19)	Tirofiban 25 μg/kg bolus + a rate of 0,15 μg/kg/min for 48 h and clopidogrel 300 mg LD + 75 mg q24h for 30 days and acetylsalicylic acid 250 mg iv LD + 75 mg q24h for 30 days and fondaparinux 2.5 mg q24h	5	April 2020	University of Milan, Milan, Italy
Clopidogrel				
NCT04409834 (COVID-PACT)	*Full-dose anticoagulation + antiplatelet therapy:* -UFH (targeting an aPTT of x 1.5–2.5) or enoxaparin 1 mg/kg q12h -Clopidogrel 300 mg LD, then 75 md q24h *Full-dose anticoagulation + no antiplatelet therapy:* - UFH (targeting an aPTT of x 1.5–2.5) or enoxaparin 1 mg/kg q12h *Prophylactic anticoagulation + antiplatelet therapy:* -UFH 5000 U q8h or enoxaparin 40 mg q24h -Clopidogrel 300 mg LD, then 75 md qd *Prophylactic anticoagulation + antiplatelet therapy:* -UFH 5000 U q8h or enoxaparin 40 mg q24h	750	August 2020	The TIMI Study Group, Boston, USA
NCT04368377 (PIC-19)	Tirofiban 25 μg/kg bolus + a rate of 0,15 μg/kg/min for 48 h and clopidogrel 300 mg LD + 75 mg q24h for 30 days and acetylsalicylic acid 250 mg iv LD + 75 mg q24h for 30 days and fondaparinux 2.5 mg q24h	5	April 2020	University of Milan, Milan, Italy
Dipyridamole				
NCT04391179 (DICER)	-Dipyridamole 100 mg q6h -Placebo	80	May 2020	University of Michigan, Ann Arbor, USA
Prasugrel				
NCT04445623 (PARTISAN)	-Prasugrel 60 mg LD + 10 mg q24h -Placebo	128	July 2020	Azienda Ospedaliera Universitaria Integrata Verona, Verona, Italy
Tirofiban				
NCT04368377 (PIC-19)	Tirofiban 25 μg/kg bolus + a rate of 0,15 μg/kg/min for 48 h and clopidogrel 300 mg LD + 75 mg q24h for 30 days and acetylsalicylic acid 250 mg iv LD + 75 mg q24h for 30 days and fondaparinux 2.5 mg q24h	5	April 2020	University of Milan, Milan, Italy
Fibrinolysis activators				
NCT04453371 (AtTAC)	-tPA 25 mg iv over 2 h, followed by a 25 mg tPA over the subsequent 22 h. Then UFH starting from 10 U/kg/h (target aPTT 40–50″) -Ringer solution	50	October 2020	Negovsky Reanimatology Research Institute, Moscow, Russia
NCT04530604	Defibrotide 25 mg/kg q24h, given in 4 divided doses	12	July 2020	University of Michigan, Ann Arbor, USA
Therapeutic Plasma Exchange (TPE)				
NCT04441996	-TPE with frozen plasma replacement on 2 sequential days -Standard of care	20	October 2020	Emory University, Atlanta, Georgia, USA

[a] Search updated at 10th October 2020.

coagulation in unknown. A number of trials exploring the efficacy of aspirin, clopidogrel, dipyridamole, prasugrel and tirofiban may provide precious results to this end.

In conclusion, data from the study from de Roquetaillade et al., stirs our attention on the profound impact that SARS-CoV-2 exerts on the hemostatic axis. Once more, the (probably) pivotal role of endothelial damage leaps out, linking a seemingly primary respiratory disorder to a profound systemic illness: thus, collaboration between infective diseases specialists, intensivists and cardiovascular specialists may be key to success in treating this challenging disease.

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