4-5 Febbraio 2021
Giornate infettivologiche Luigi Sacco
Covid-19: la sfida di una pandemia

Aspetti clinici e terapeutici delle manifestazioni trombotiche in corso di infezione da Covid-19

Augusto B. Federici

U.O.C. di Ematologia e Medicina Trasfusionale ASST-FBF-SACCO
Università degli Studi di Milano
augusto.federici@unimi.it

Background

A systemic activation of all steps of hemostasis inducing thrombosis has been reported in several cohorts of patients not only in acute COVID-19 infection during hospitalization but also after remission from disease at home

The basic mechanisms and the true burden of such a systemic activation involving all the steps of hemostasis (vascular endothelium/sub-endothelium, circulating platelets, coagulation factors, fibrinolysis) have not been completely understood and therefore treatment of thrombosis associated with COVID-19 has been empirical in most cases

Thrombophilia in patients with Covid19

Outlines

- Incidence of Thrombosis in patients during Covid19
- Thrombotic complications and Mechanisms (DIC, MIT, SIC)
- Cardiovascular/Inflammatory biomarkers in COVID-19
- Laboratory assessment of Thrombosis in hospitalized patients
- Implications for anti-coagulation: prophylaxis versus therapy
- Chest guidelines for Prevention, diagnosis and therapy of VTE
- Risk of bleeding during anti-thrombotic agents
- Challenges in the Management of thrombosis during Covid19

Incidence of Thrombosis in COVID-19

There is a substantial evidence for an increased risk of thrombosis in patients with COVID-19. Many studies in hospitalized patients found an incidence of thrombosis in > 30% of ICU patients with COVID-19

Complications included Pulmonary Embolism (PE), Deep Vein Thrombosis (DVT), Ischemic Stroke (IS), Myocardial Infarction (MI) and Systemic Arterial Embolism (SAE). Acute PE made up as much as 83% of complication observed

Patients in ICU with COVID-19 are also more likely to develop Venous Thrombotic Embolism (VTE) than no-COVID ICU patients which suggests that the underlying cause of VTE is likely more than the immobility due to ICU treatment alone.

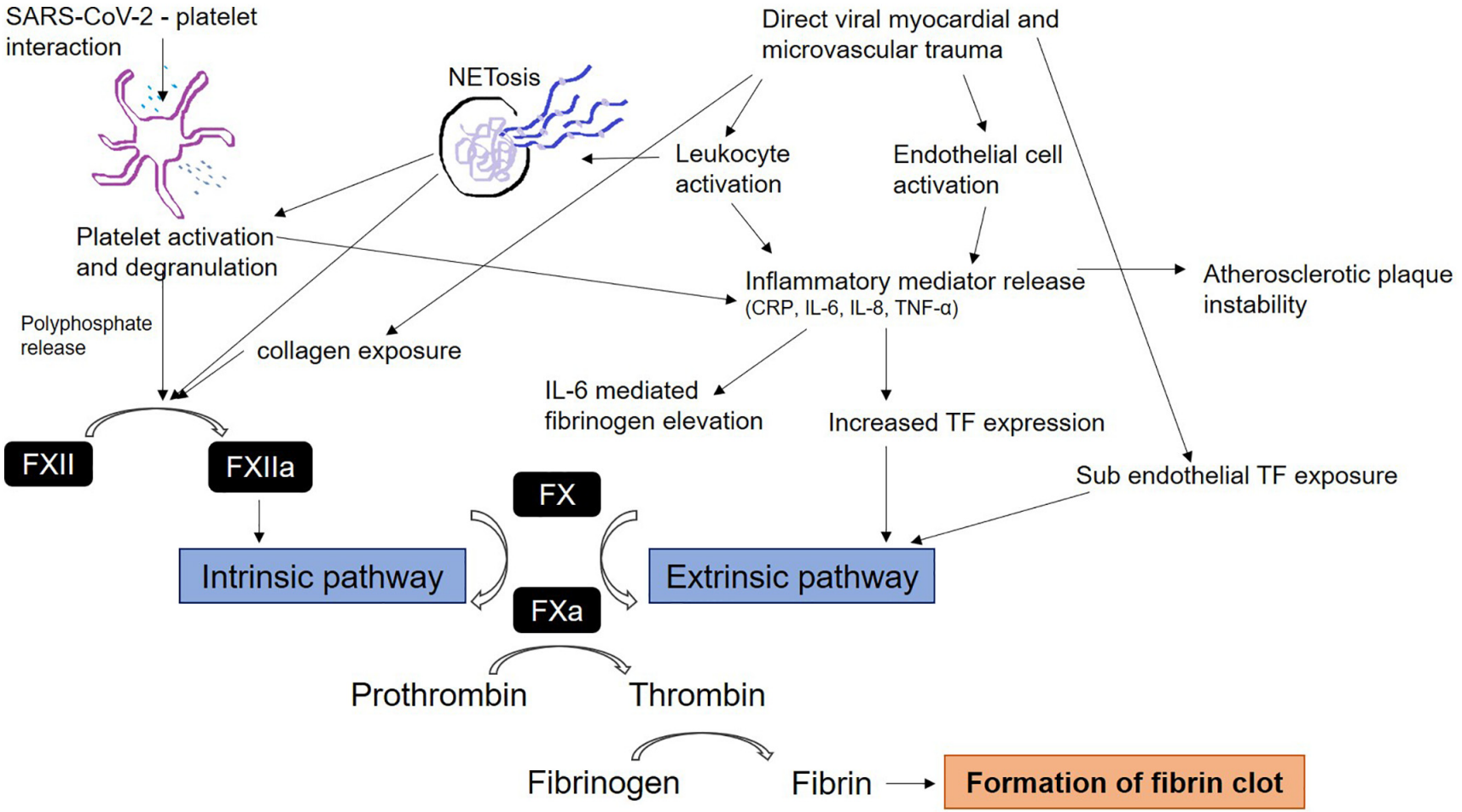
Thrombotic Mechanisms in COVID-19: DIC, MIT, SIC

The interplay between inflammation, complement activation and coagulation cascade is thought to be crucial to understanding pathophysiology of COVID-19 and is responsible for Disseminated Intravascular Coagulation (DIC).

Microvascular Immune Thrombosis (MIT) has been considered another important mechanism for thrombosis associated with COVID-19 triggered by SARS-CoV-2 platelet interactions and by the release of Neutrophil Extracellular Traps (NETs) in response to inflammation

Sepsis-Induced coagulopathy (SIC) is the term used to identify early DIC associated with sepsis. However, micro thrombus formation aligns more closely with complement-mediated TMA than DIC or SIC

Mechanism of thrombosis and cardiovascular complications in COVID-19



Page EM, Ariëns RAS. Thromb Res. 2021 Jan 18;200:1-8.

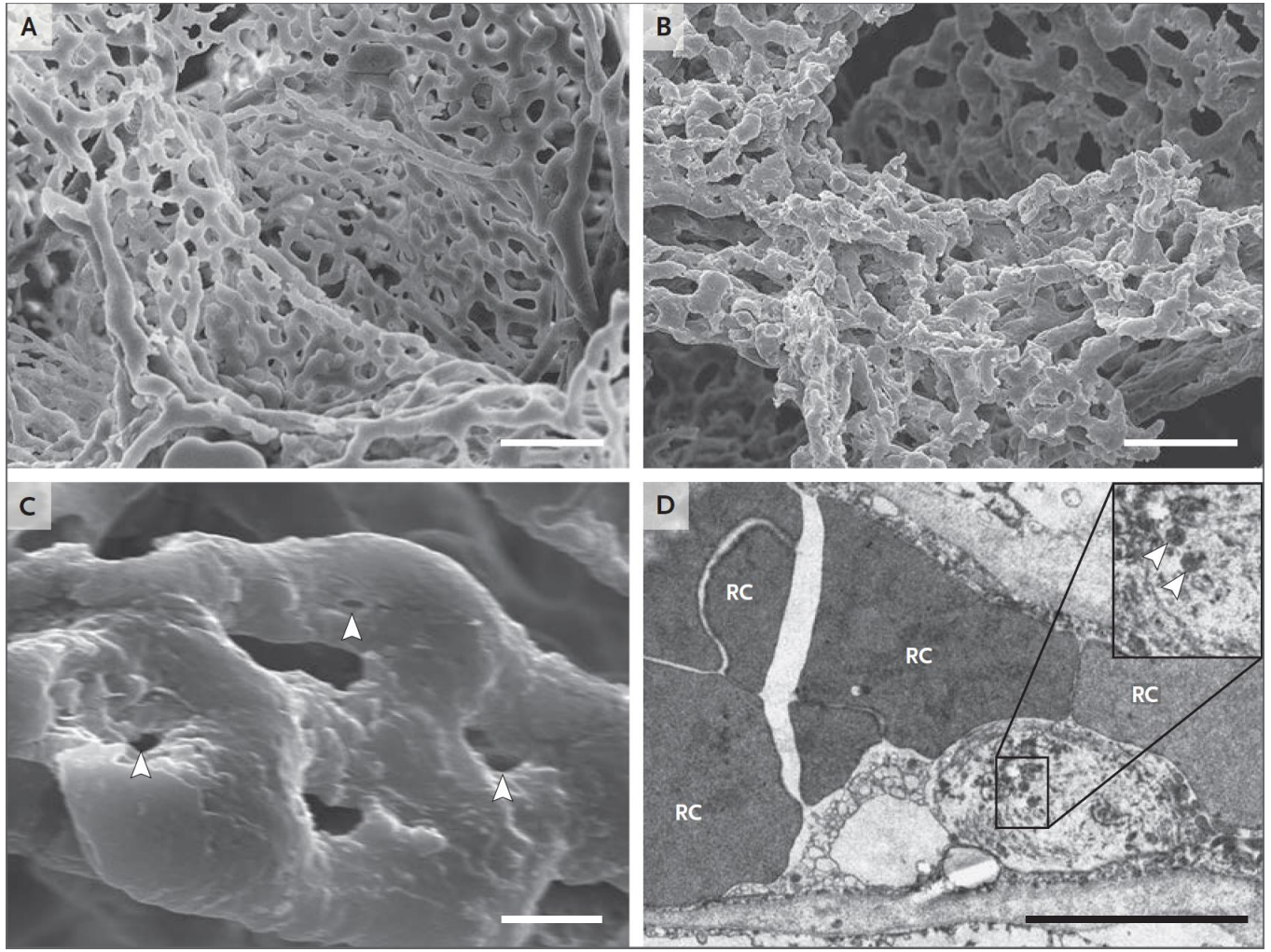
Pulmonary Micro Thrombosis (PMT) in COVID-19

In COVID-19, Pulmonary Micro Thrombosis (PMT) in the lung alveoli distinct from PE has also been reported. This PMT has been linked to the development of hypoxemia in early stage of Adult Respiratory Distress Syndrome (ARDS) usually due to a ventilation/perfusion mismatch and created by changes in microcirculatory blood flow.

PMT can be also triggered by the Pulmonary Angiotensin Converting Enzyme 2 (ACE2) which is mediated by endothelial injury, potential cytokine storm and development of pro-coagulant state of COVID-19

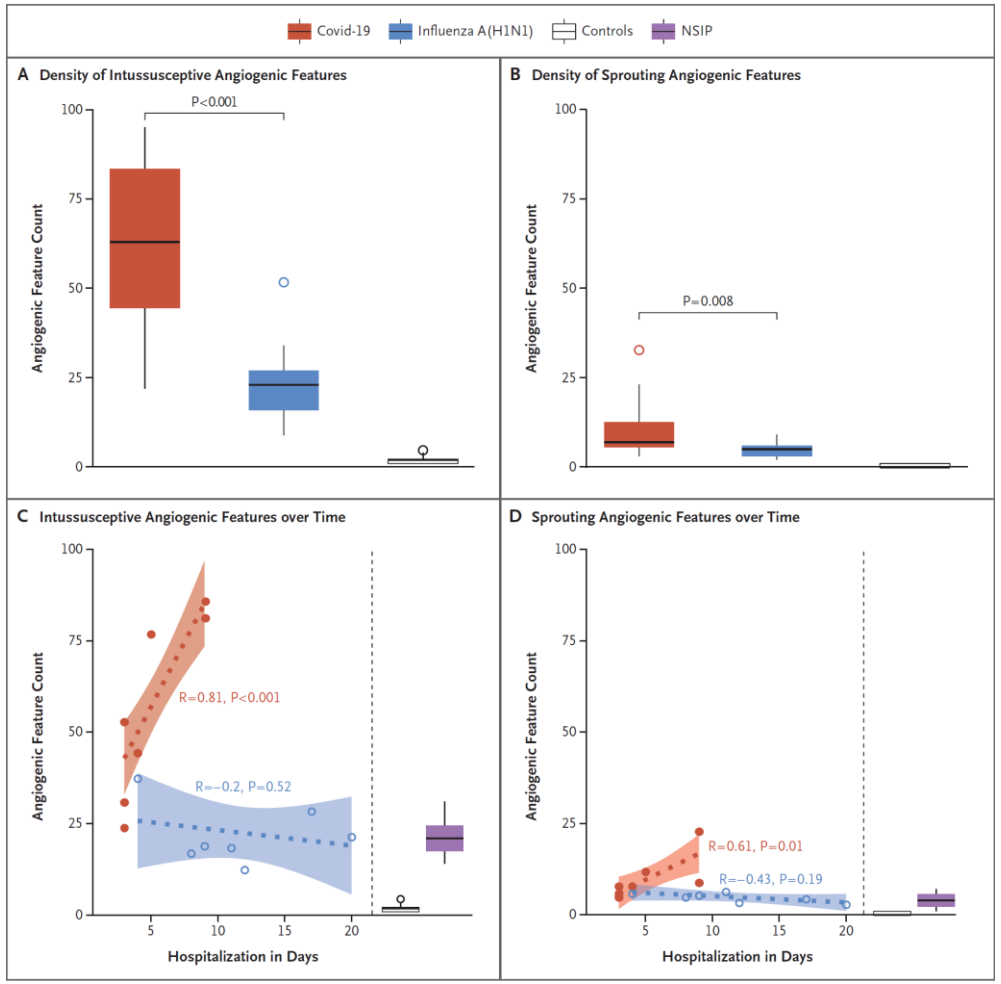
Indeed, it appears that PMT is not always preceded by DVT in COVID-19 and originates primarily from the lungs instead of PE from DVT occurring from the peripheral venous circulation

Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19



Ackermann M. et al, N Engl J Med. 2020;383:120-8.

Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19



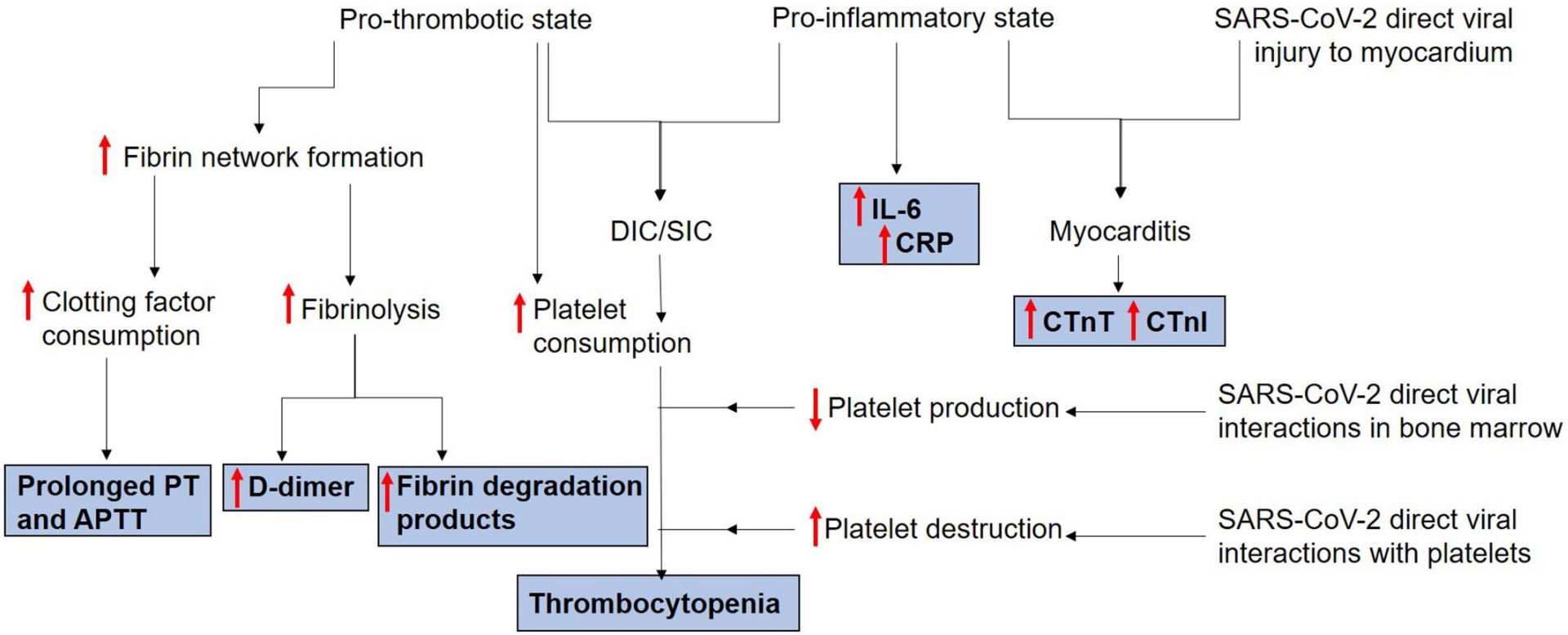
Ackermann M. et al, N Engl J Med. 2020;383:120-8.

Cardiovascular/Inflammatory Biomarkers in COVID-19

Several hemostatic and inflammatory biomarkers have been explored in COVID-19 patients for possible monitoring of patients and their treatment:

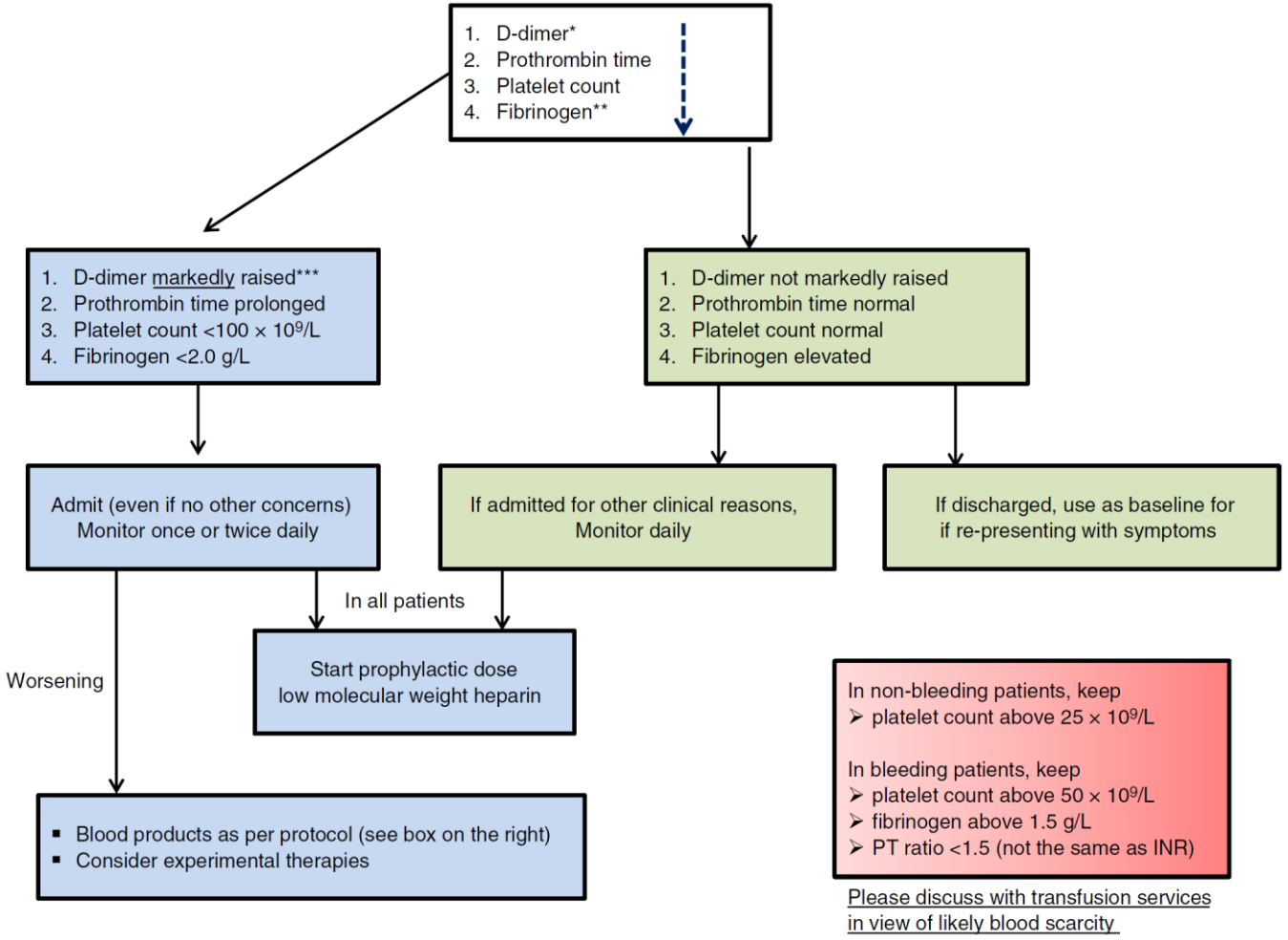
- **PT – APTT – Fibrinogen – D-DIMER**
- **Platelet Count and activity**
- **CRP – IL6 - TNF**
- **Troponin (cTnT e cTnl)**

Mechanisms of thrombosis in COVID-19 and Laboratory test assessment



Page EM, Ariëns RAS. Thromb Res. 2021 Jan 18;200:1-8.

ISTH interim guidance on recognition and management of thrombophilia in COVID-19



Thachil J. et al, J Thromb Haemost. 2020 May;18(5):1023-6.

Implications anti-coagulation: LMW Heparin Prophylaxis versus Therapy

Due to the increased risk of VTE in patients with COVID-19, it is currently recommended that all hospitalized patients are given routine thrombosis prophylaxis with Low Molecular Weight (LMW) Heparin if there are no additional bleeding risk

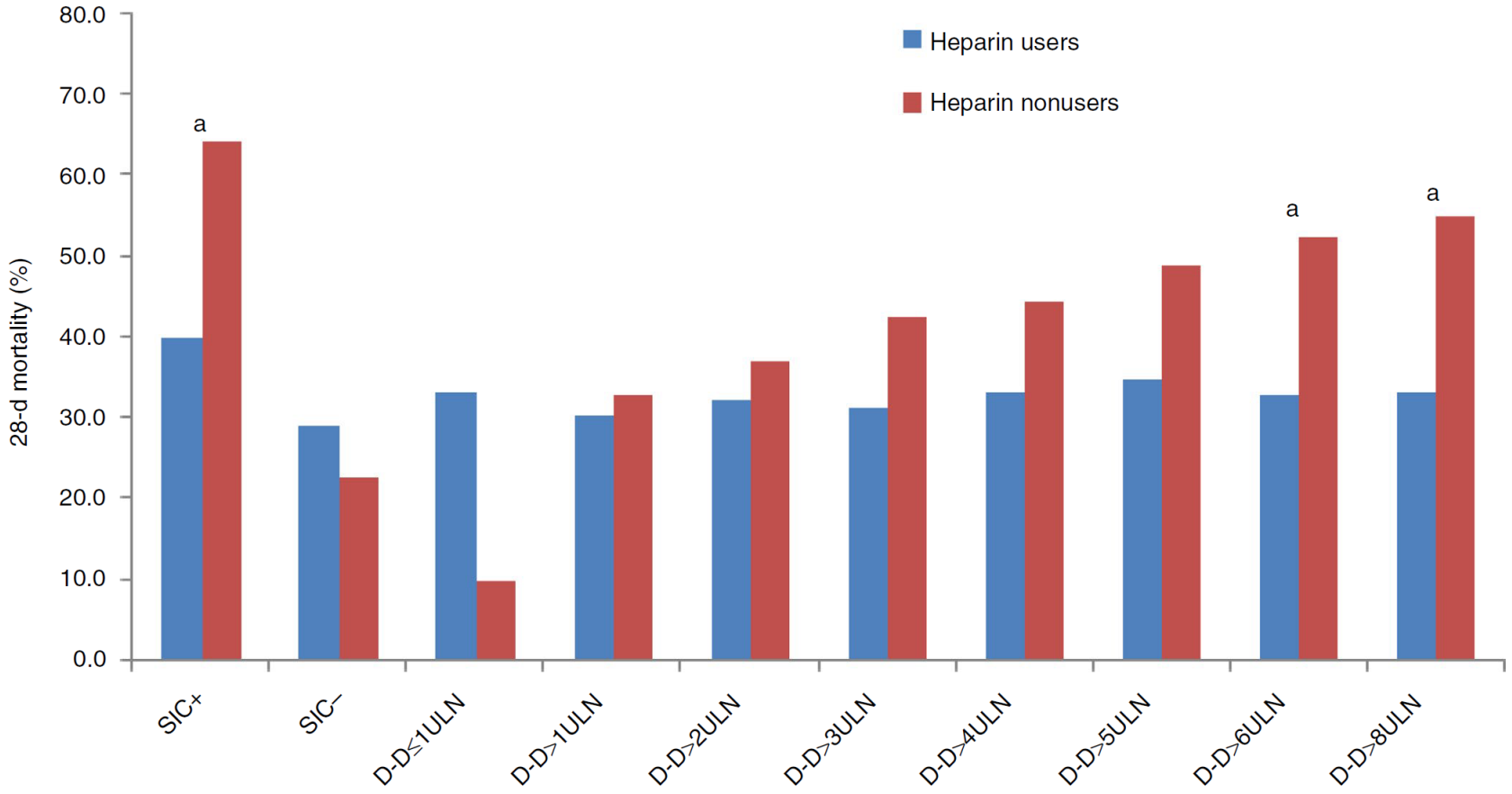
However, therapeutic heparin doses may have the additional benefits of counteracting the resistance to treatment that occurs in patients with drastically raised fibrinogen levels.

Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy

Parameters	Normal range	Total (n = 449)	Survivors (n = 315)	Nonsurvivors (n = 134)	*P* values
Age (years)		65.1 ± 12.0	63.7 ± 12.2	68.7 ± 11.4	<.001
Sex ratio (male/female)		268/181	178/137	90/44	.036
With underlying diseases		272 (60.6%)	181 (57.5%)	91 (67.9%)	.136
Receiving heparin		99 (22.0%)	69 (21.9%)	30 (22.4%)	.910
Meeting SIC criteria		97 (21.6%)	42 (13.3%)	55 (41.0%)	<.001
Coagulation parameters					
PT (s)	11.5-14.5	15.2 ± 5.0	14.6 ± 2.1	16.5 ± 8.4	<.001
Platelet count ($\times 10^9$/L)	125-350	215 ± 100	231 ± 99	178 ± 92	<.001
D-dimer (μg/mL)	<0.5	1.94 (0.90-9.44)	1.47 (0.78-4.16)	4.70 (1.42-21.00)	<.001

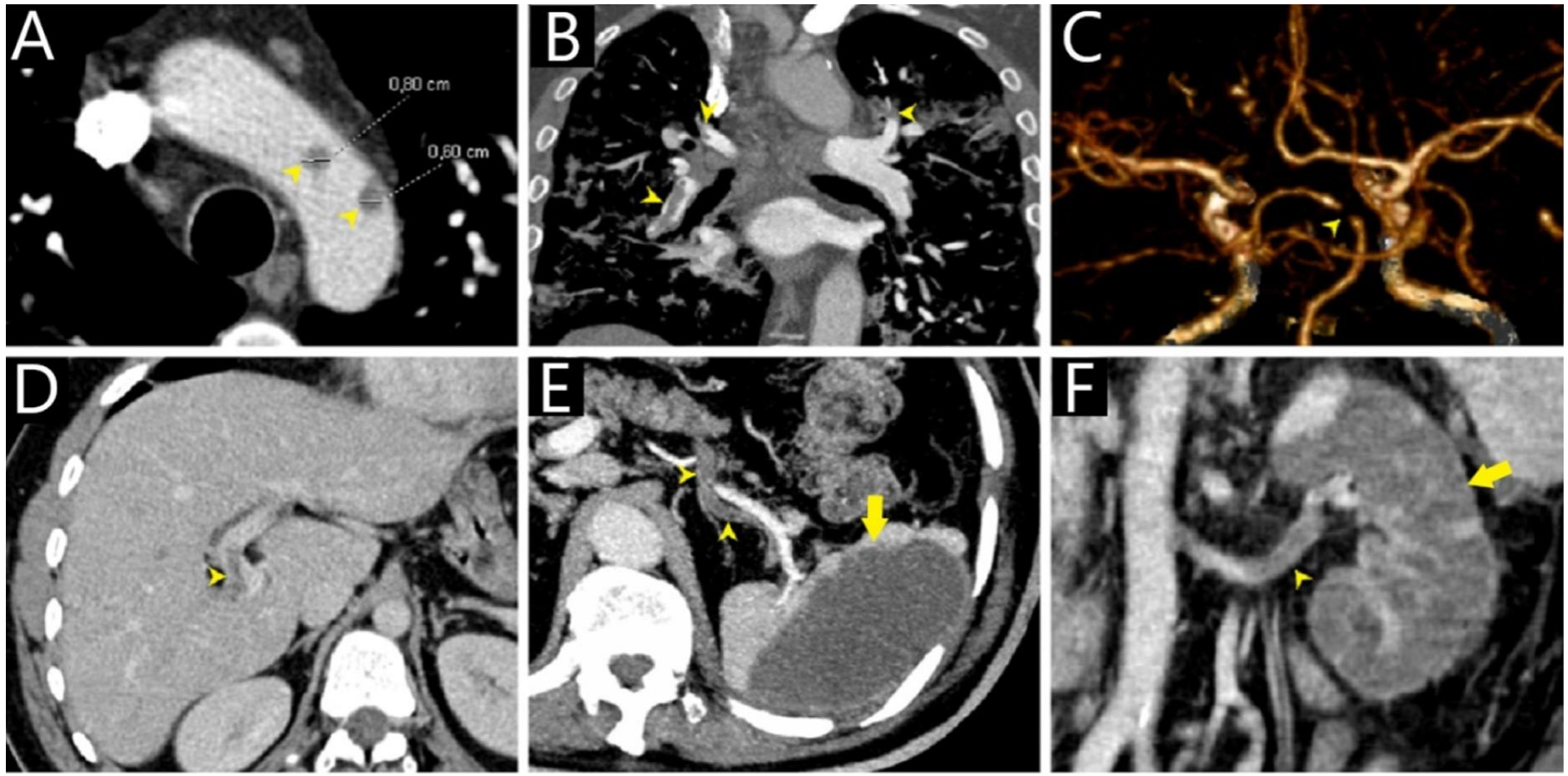
Tang N. et al, J Thromb Haemost. 2020 May;18(5):1094-9.

Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy



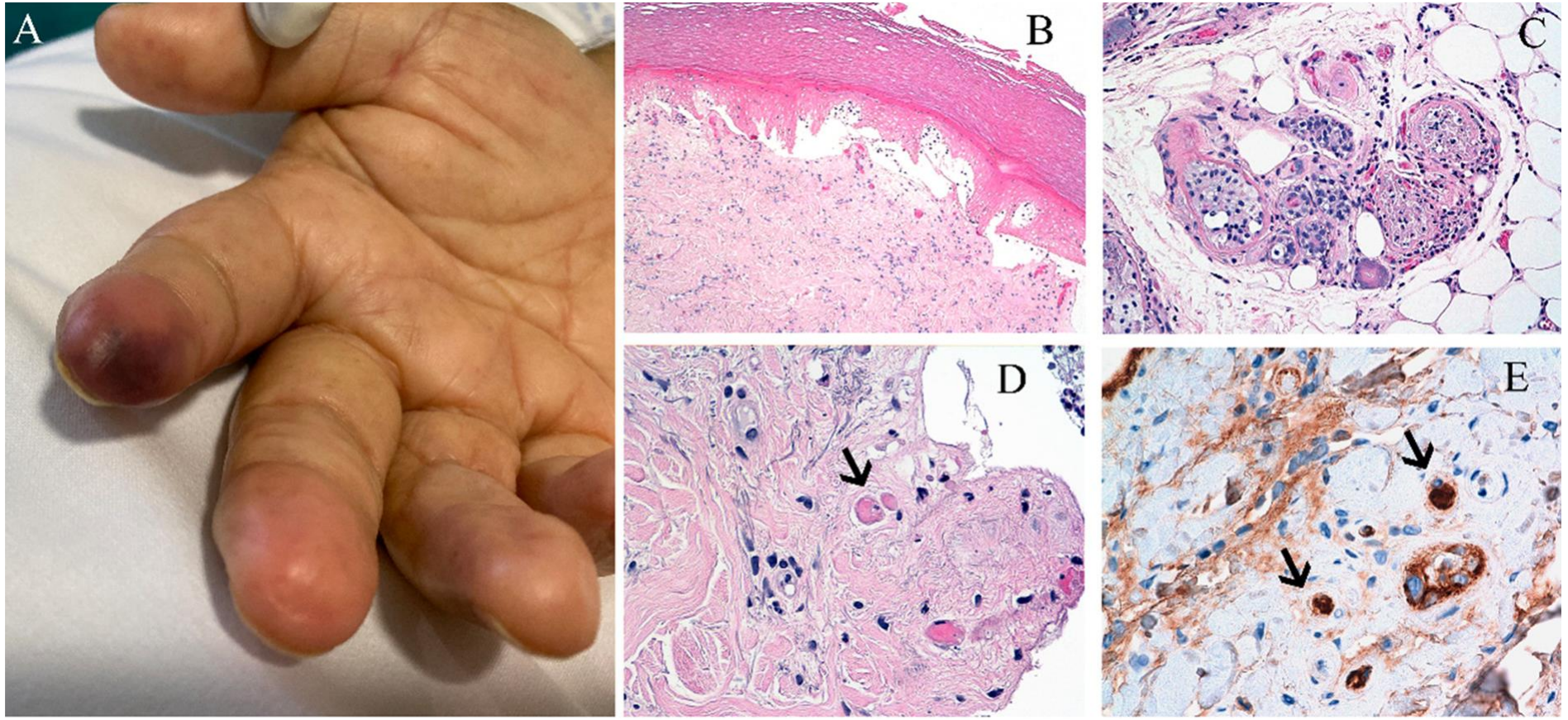
Tang N. et al, J Thromb Haemost. 2020 May;18(5):1094-9.

Systemic thrombosis in a large cohort of Covid-19 patients despite thromboprophylaxis: a retrospective study



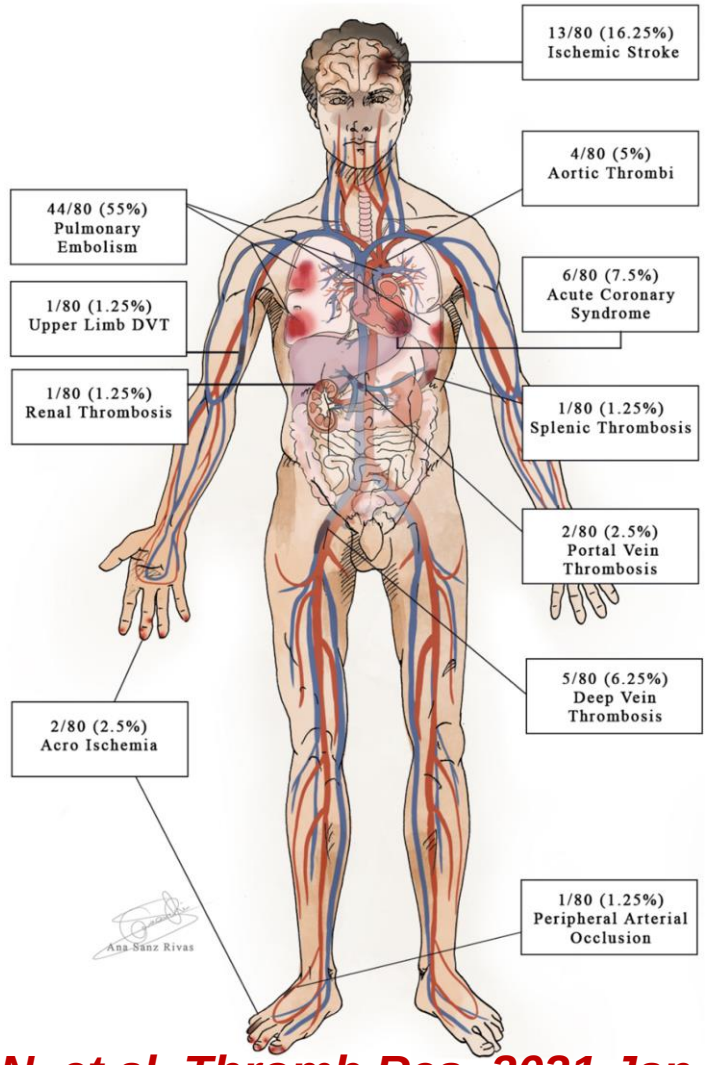
Muñoz-Rivas N. et al, Thromb Res. 2021 Jan 7;199:132-42.

Systemic thrombosis in a large cohort of Covid-19 patients despite thromboprophylaxis: a retrospective study



Muñoz-Rivas N. et al, Thromb Res. 2021 Jan 7;199:132-42.

Systemic thrombosis in a large cohort of Covid-19 patients despite thromboprophylaxis: a retrospective study



Muñoz-Rivas N. et al, Thromb Res. 2021 Jan 7;199:132-42.

Rationale for other anti-thrombotic agents

Anti-platelet agents: TICAGRELOR inhibits platelet ADP receptor P2Y12 to block platelet activation and aggregation, has been proposed as alternative thrombosis prophylaxis. **TICAGRELOR** has been shown to reduce lung injury acquired in pneumonia and prevent SIC/DIC development by reducing inflammatory mediator levels (IL6, TNF, IL8)

Fibrinolysis Agents: ACTILYSE, a tissue-type plasminogen activator (TPA), has been used in very critical cases of VTE associated with COVID-19

Prevention, diagnosis, and treatment of VTE in patients with Coronavirus Disease 2019

CHEST Guideline and Expert Panel Report

BACKGROUND: Emerging evidence shows that severe coronavirus disease 2019 (COVID-19) can be complicated by a significant coagulopathy, that likely manifests in the form of both microthrombosis and VTE. This recognition has led to the urgent need for practical guidance regarding prevention, diagnosis, and treatment of VTE.

RESULTS: The systematic review and critical analysis of the literature based on 13 Population, Intervention, Comparator, Outcome questions resulted in 22 statements. Very little evidence exists in the COVID-19 population. The panel thus used expert consensus and existing evidence-based guidelines to craft the guidance statements.

CONCLUSIONS: The evidence on the optimal strategies to prevent, diagnose, and treat VTE in patients with COVID-19 is sparse but rapidly evolving.

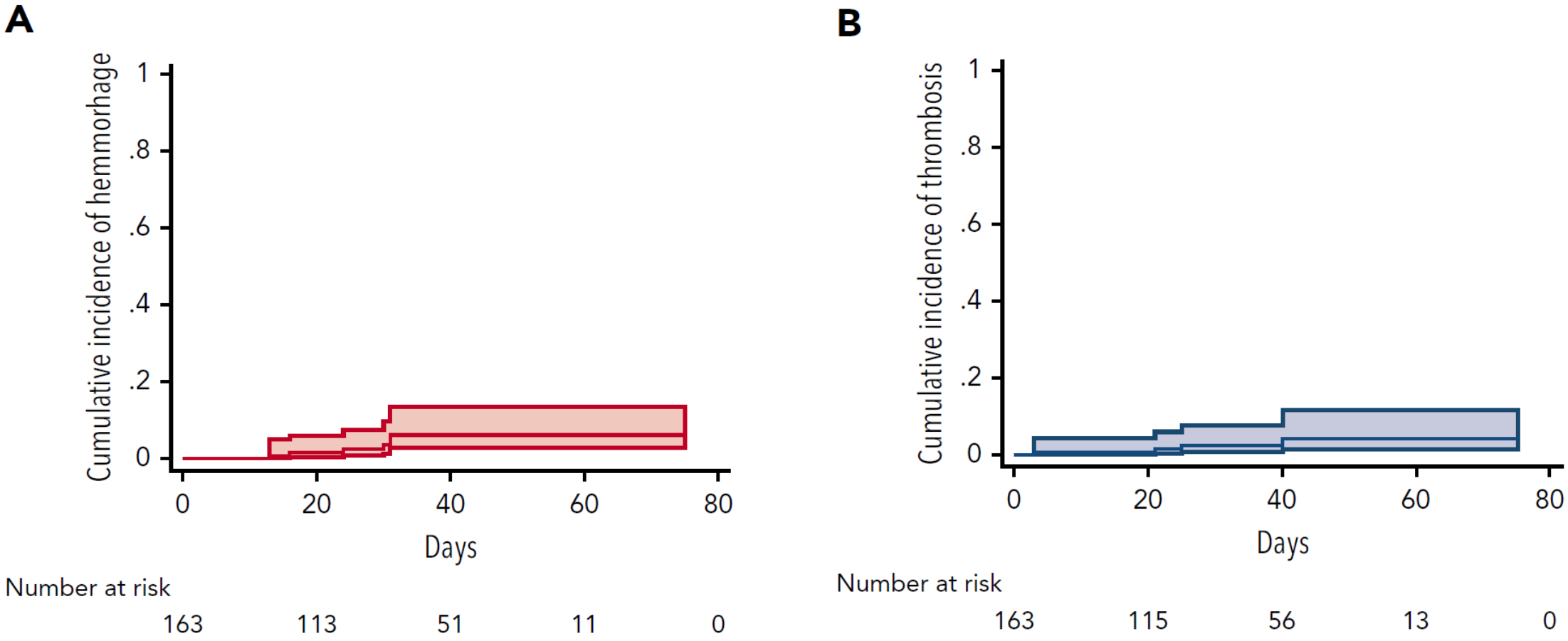
Moores LK. et al, CHEST. 2020 Sep;158(3):1143-63.

Risk of Bleeding during anti-thrombotic agents

In patients with thrombosis associated with COVID-19, anti-thrombotic agents including anti-coagulants such LMW heparins have been associated with risks of bleeding which should be weighed against the clinical anti-thrombotic benefit

This risk should be considered on a patient-by-patient basis, taking into account potential coagulation activation or defects as well as renal insufficiency

Postdischarge thrombosis and hemorrhage in patients with COVID-19



Patell R. et al, Blood. 2020 Sep 10;136(11):1342-6.

Incidence of VTE and bleeding among hospitalized patients with Coronavirus Disease 2019

A Systematic Review and Meta-analysis

BACKGROUND: Individual studies have reported widely variable rates for VTE and bleeding among hospitalized patients with coronavirus disease 2019 (COVID-19).

RESEARCH QUESTION: What is the incidence of VTE and bleeding among hospitalized patients with COVID-19?

INTERPRETATION: Among hospitalized patients with COVID-19, the overall estimated pooled incidence of VTE was 17.0%, with higher rates with routine screening, inclusion of distal DVT, and subsegmental PE, in critically ill patients and in prospective studies. Bleeding events were observed in 7.8% of patients and were sensitive to use of escalated doses of anticoagulants and nature of data collection. Additional studies are required to ascertain the significance of various thrombotic events and to identify strategies to improve patient outcomes.

Jeménez D. et al, CHEST. 2020 Nov 17;S0012-3692(20)35146-1.

Management of Thrombosis in COVID-19 patients

The **interplay between the inflammatory, coagulation and complement systems in COVID-19** requires further research, to establish their mechanistic contributions to the pathophysiology of thrombosis associated with COVID-19. ***STIMA-COVID19*** can cover these issues.

Understanding the **balance of these systems** is therefore essential for optimal management of pulmonary micro thrombosis versus PE and DIC/SIC versus complement mediated micro thrombus formation

Randomized control trials are urgently needed to determine the safety of proposed **anti-thrombotic drugs** such as anticoagulants and anti-platelet agents used therapy of patients with COVID-19. A randomized clinical trial ***(EMOS-COVID)*** is currently approaching these issues