COVID – 19

and

Thrombotic / Thromboembolic Disease

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Presenter Disclosure Information

Name: Dominick J Angiolillo

Within the past 12 months, the presenter or their spouse/partner have had a financial interest/arrangement or affiliation with the organization listed below.

Received payment as an individual for:
a) Consulting fee or honorarium from Abbott, Amgen, Aralez, AstraZeneca, Bayer, Biosensors, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, Daiichi-Sankyo, Eli Lilly, Haemonetics, Janssen, Merck, PhaseBio, PLx Pharma, Pfizer, Sanofi, and The Medicines Company.
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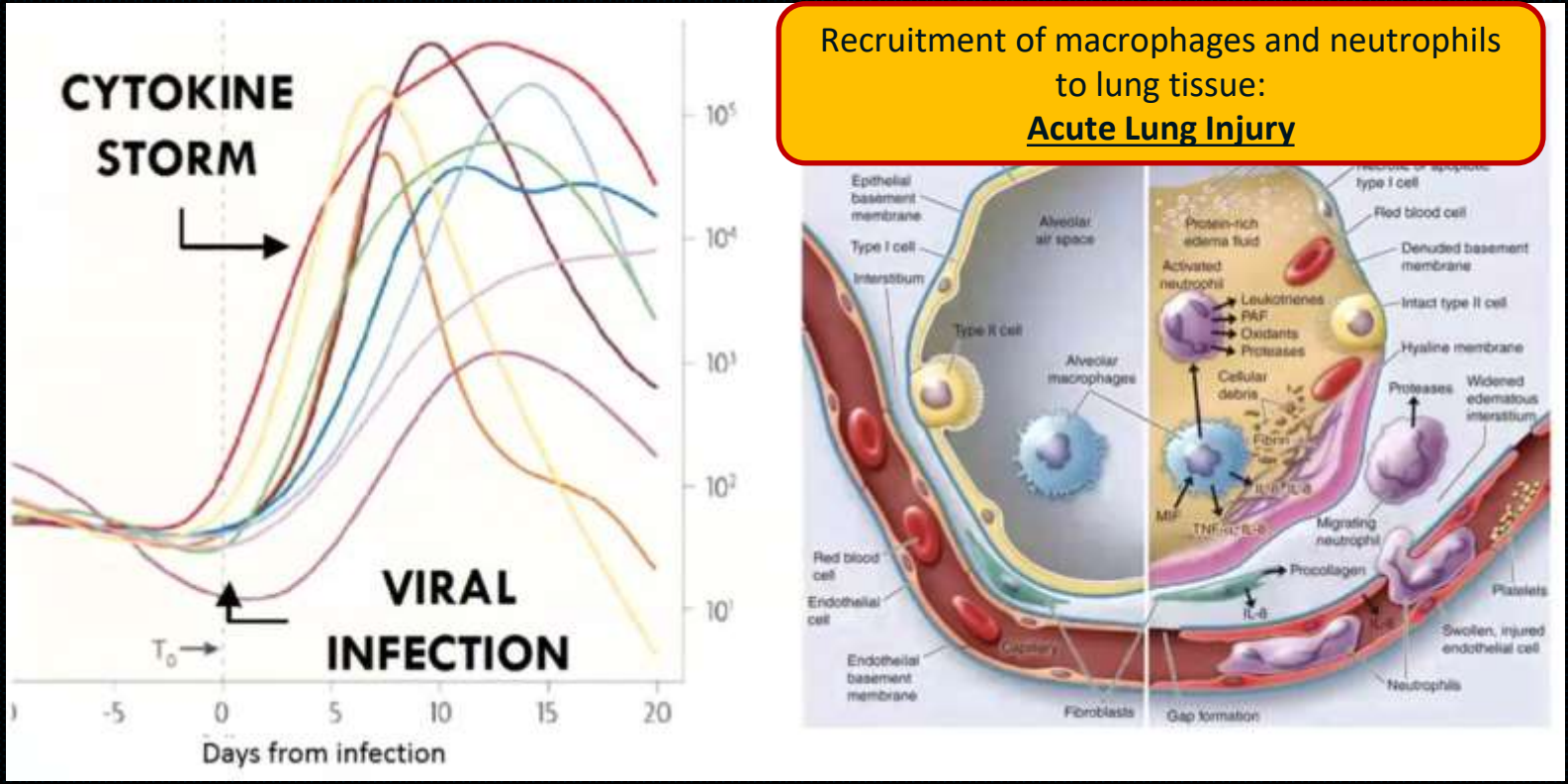
b) Grant in gift: Spartan; Scott R. MacKenzie Foundation
c) Federal agency: NIH

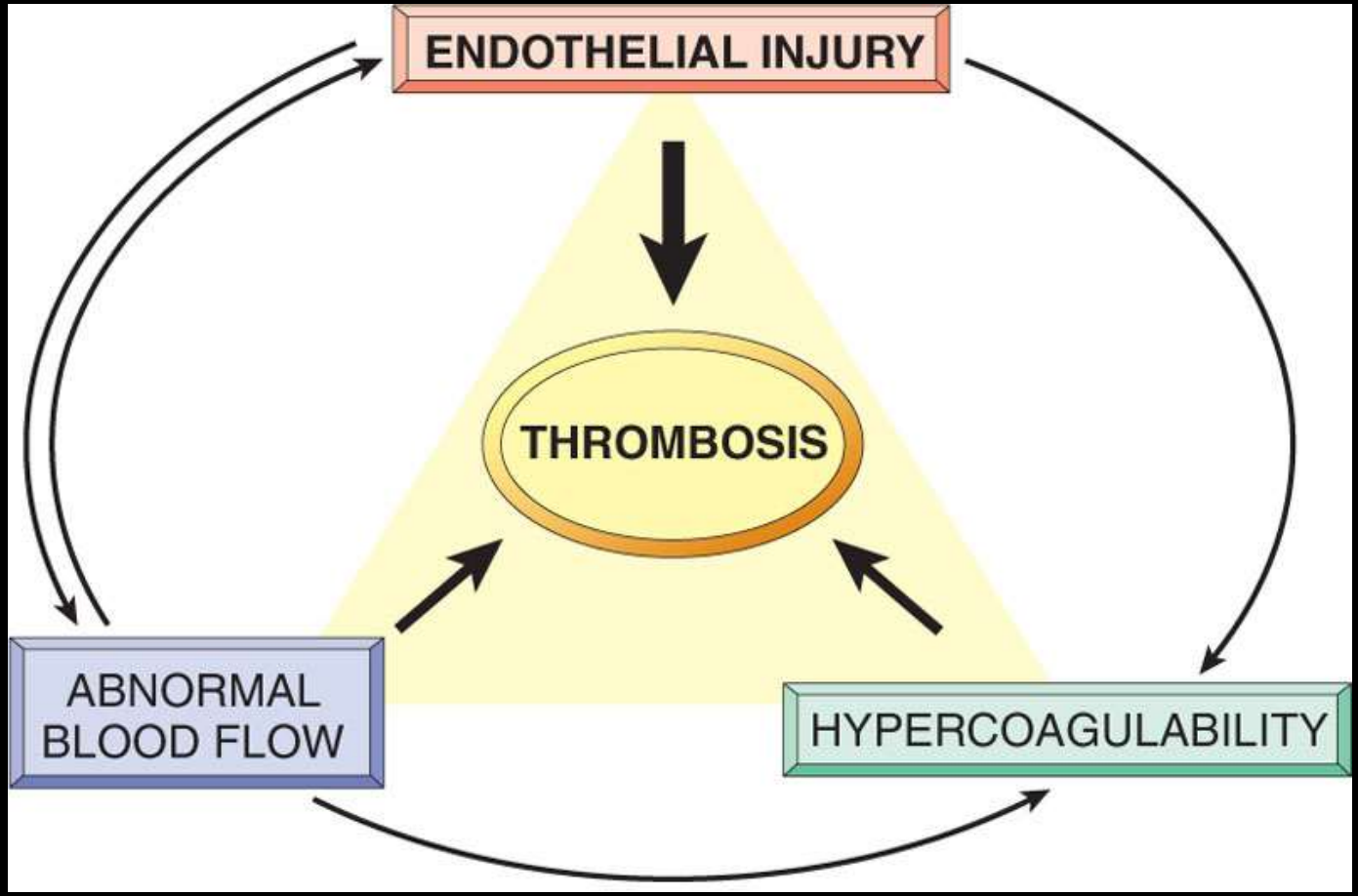
Severe COVID-19 Manifestations



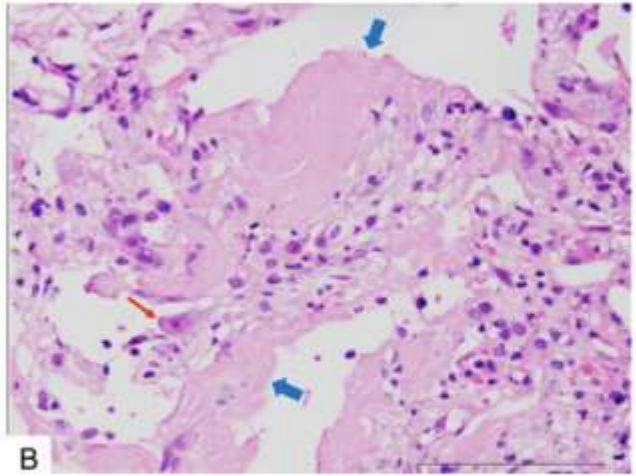
Recruitment of macrophages and neutrophils to lung tissue:
Acute Lung Injury

Occurrence of Cytokine Storm (i.e. increase in inflammatory markers, **mainly IL-6**) is a marker of progression towards severe disease.

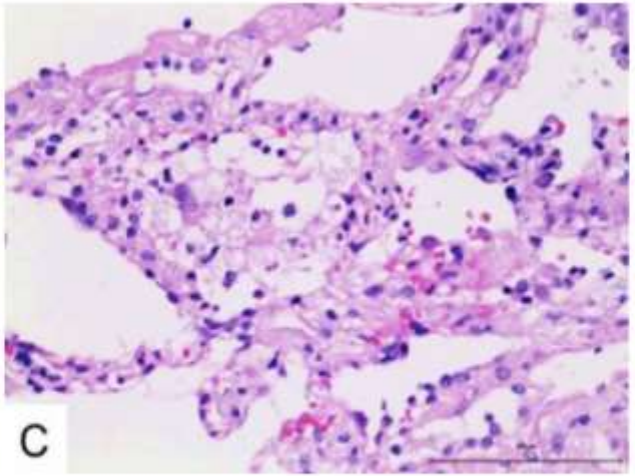
VIRCHOW'S TRIAD



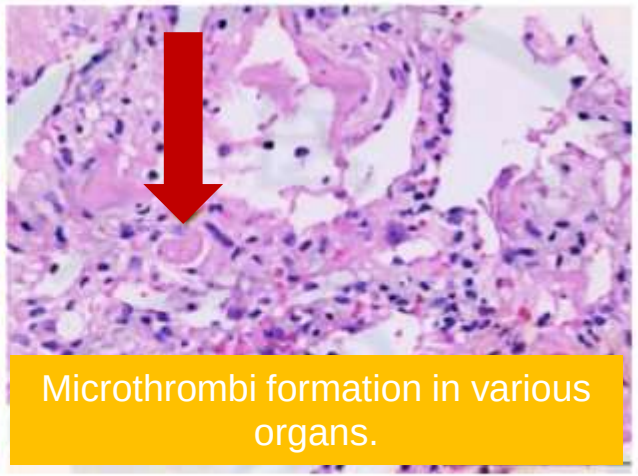
Pathogenic Changes Observed in Lungs of COVID-19 Patients



Hyaline membrane formation（blue arrow)



Interstitial mononuclear inflammatory infiltrates



Microthrombi formation in various organs.

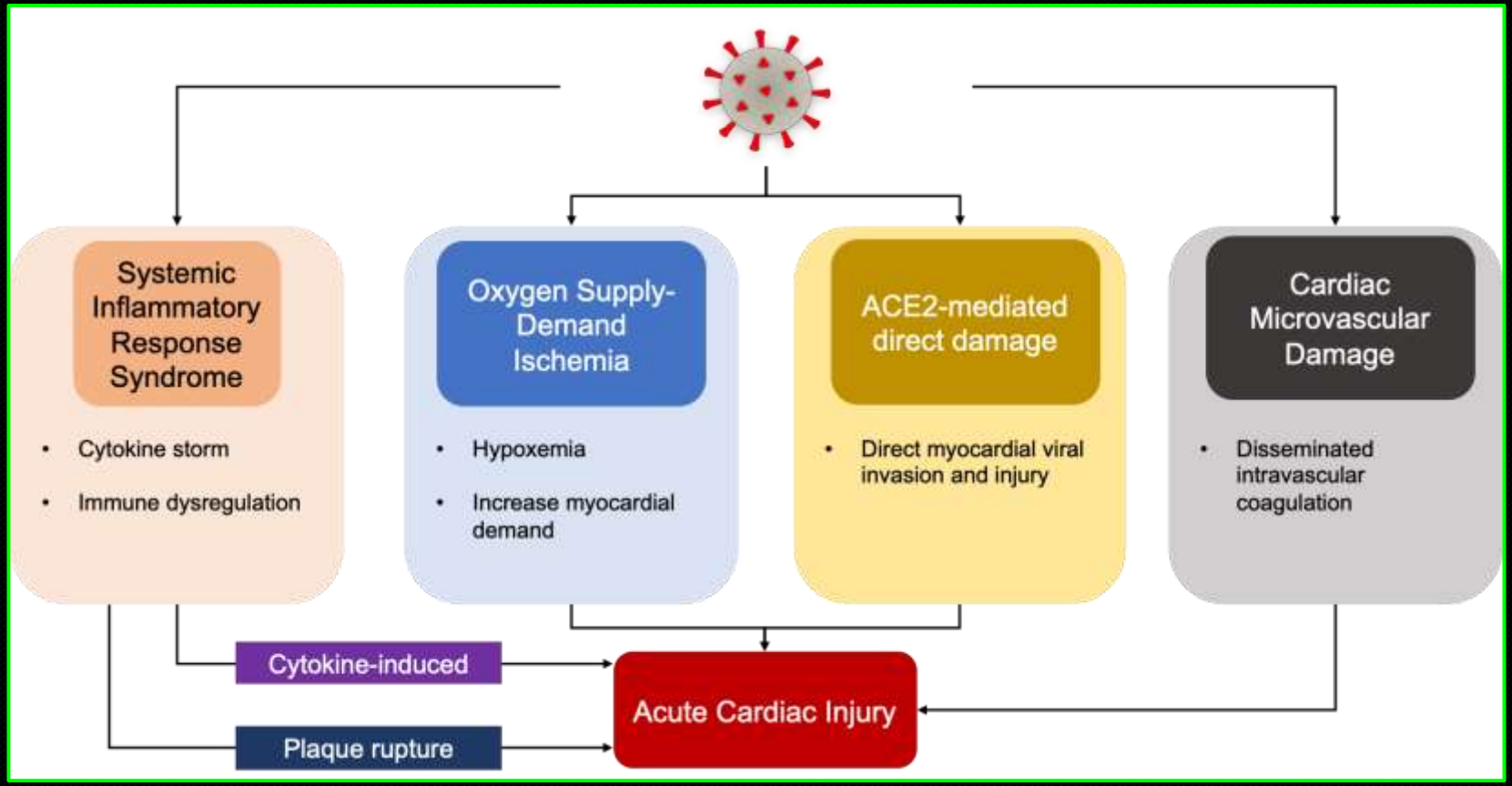
Thrombus in pulmonary arterioles (black arrow)

Pathological features in lungs greatly resemble those seen in SARS and MERS infection

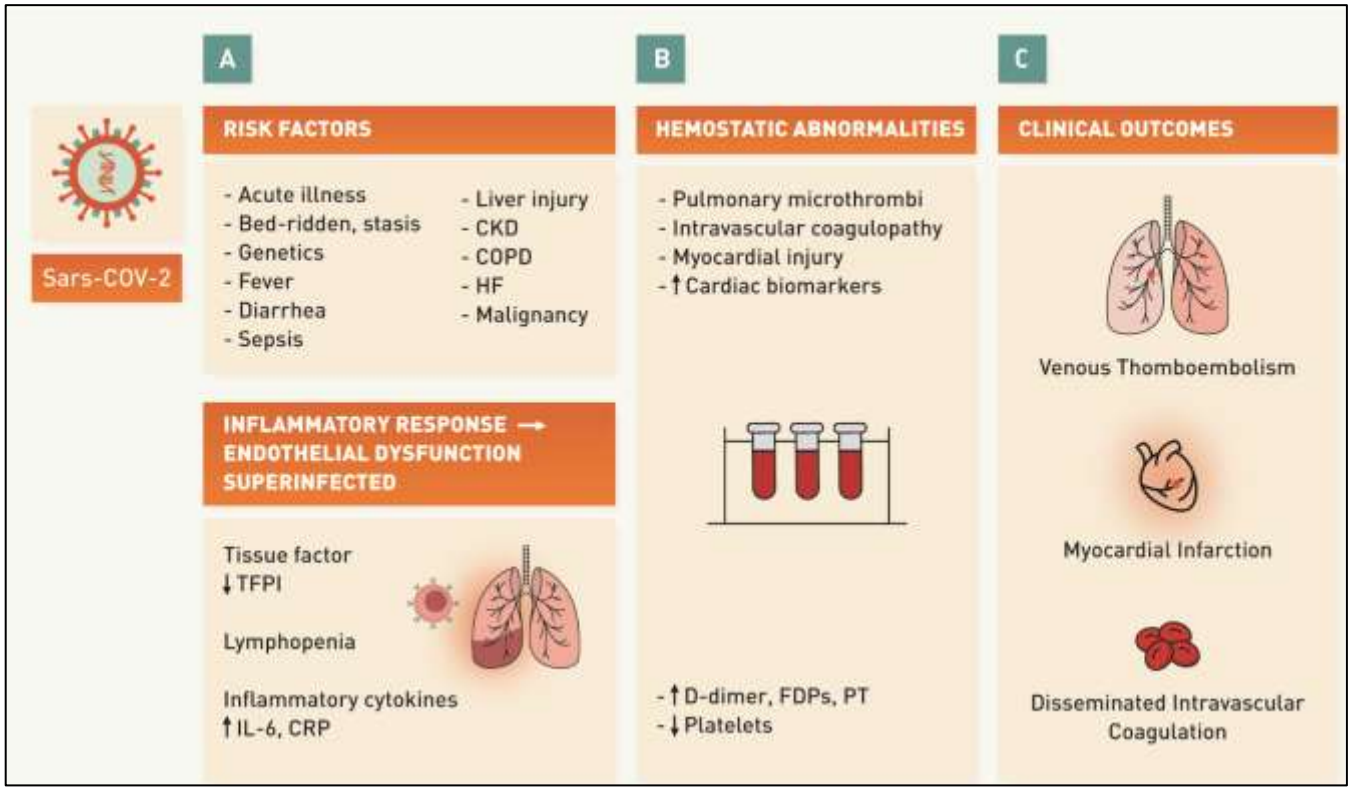
Bilateral diffuse alveolar damage with cellular fibromyxoid exudates is commonly observed

Yao et al. Chinese Journal of Pathology.2020

Mechanisms of Cardiac Injury



Mechanisms of coagulopathy in COVID-19



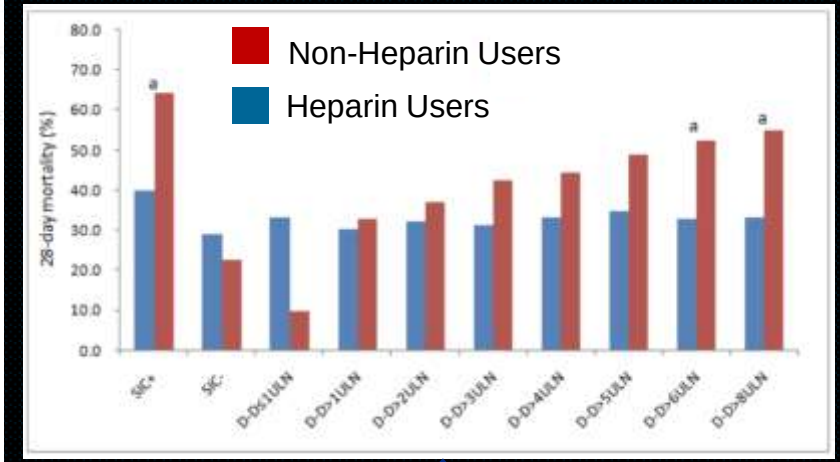
Bikdeli B, et al. J Am Coll Cardiol. 2020

Hypercoagulability in COVID-19 Patients

Table 3 Multivariate correlative factors of 28-day mortality in severe COVID-19

	Multivariate analysis	
	Odds ratio (95% CI)	*P* value
Age	1.033 (1.013-1.055)	0.002
Sex ratio	0.677 (0.425-1.078)	0.100
With underlying diseases	0.861 (0.538-1.379)	0.534
Treating with heparin	1.647 (0.929-2.921)	0.088
Prothrombin time	1.107 (1.008-1.215)	0.033
Platelet count	0.996 (0.993-0.998)	0.001
D-dimer	1.058 (1.028-1.090)	<0.001

28-day Mortality



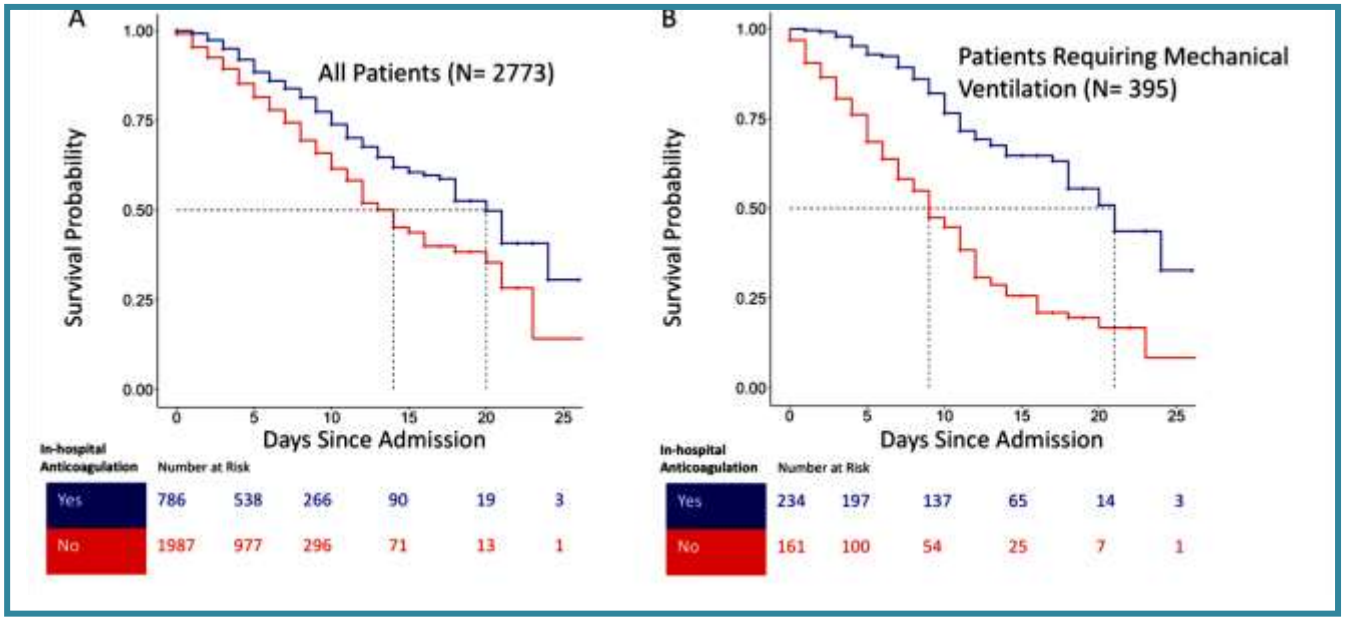
Coagulation Abnormalities Associated with **28-day Mortality** in COVID-19 patients.

Prophylactic Anticoagulation Helpful in Patients with Abnormal Parameters?

Tang et al.; J Thromb Haemost, 2020

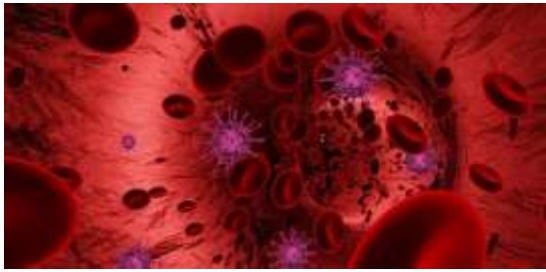
Anticoagulation and survival

2,773 patients hospitalized with laboratory confirmed COVID-19

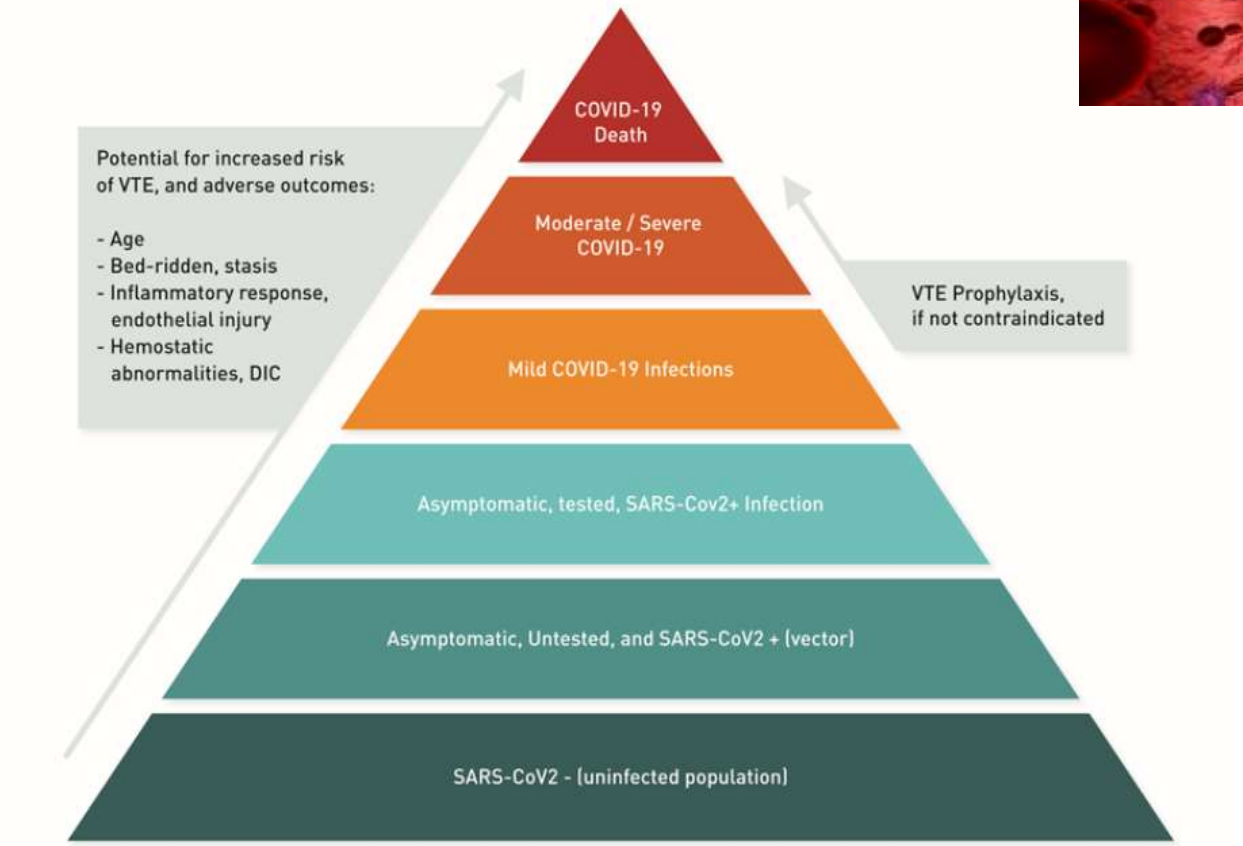


Paranjpe I, et al. JACC. 2020 [Epub ahead of print]

Anticoagulation Guidance for COVID-19



If thrombosis is the major reason for multiorgan failure, then anticoagulation is important.



COVID-19 & Anticoagulation

- **When to start?** **Early**
- **Which drug?** **LMWH**
- **Which dose?** **Prophylaxis (early)**
- **How long?** **2 weeks post discharge (NOAC)**

Oral Anticoagulant Therapies and Drug-drug interaction: Considerations in COVID-19 Patients

Table 4. Potential Drug Interactions Between Anticoagulants* and Investigational Therapies for COVID-19

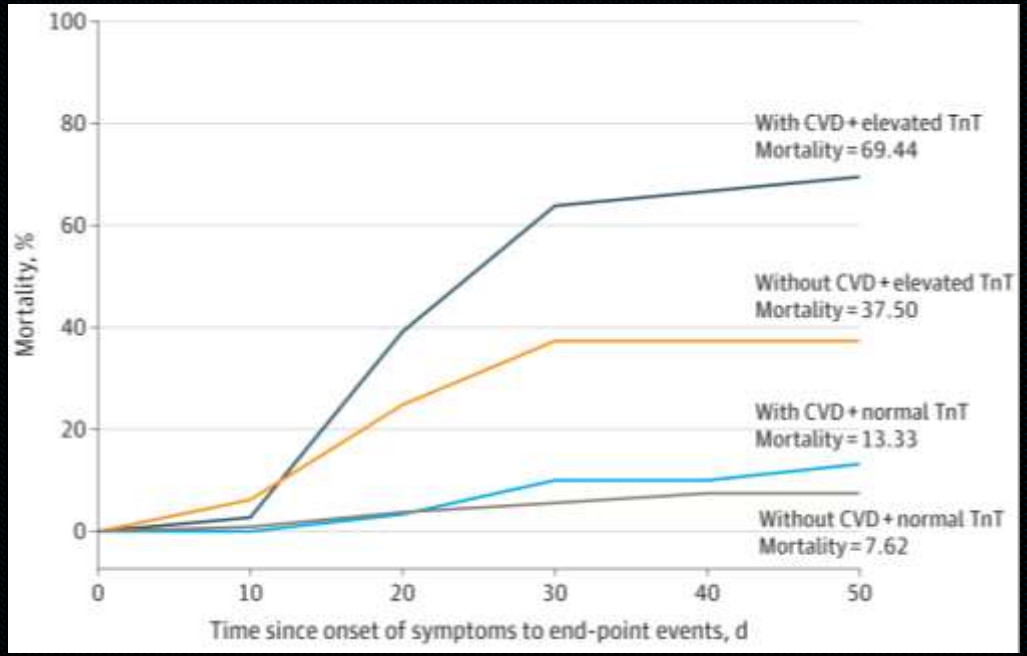
	Oral Anticoagulants					
Investigational COVID-19 Therapies	Vitamin K antagonists	Dabigatran	Apixaban	Betrixaban	Edoxaban	Rivaroxaban
Lopinavir/Ritonavir	**CYP2C9 induction:** May decrease plasma concentration. Adjust dose based on INR	**P-gp inhibition:** May increase plasma concentration. No dose adjustment recommended	**CYP3A4 and P-gp inhibition:** Administer at 50% of dose (do not administer if initial dose is 2.5 mg twice daily)†	**P-gp and ABCB1 inhibition:** Decrease dose to 80 mg once followed by 40 mg once daily	**P-gp inhibition:** Do not co-administer	**CYP3A4 and P-gp inhibition:** Do not co-administer
Tocilizumab	-	-	**Reported increase in expression of 3A4 (major pathway):** No dose adjustment recommended	-	-	**Reported increase in expression of 3A4 (major pathway):** No dose adjustment recommended
Interferon‡	**Unknown mechanism:** Decreased dose may be needed	-	-	-	-	-
Ribavirin	**Mechanism not well known:** Possibly decreased absorption of warfarin in the presence of ribavirin.(166) Increased dose may be needed	-	-	-	-	-
Methylprednisolone	**Unknown mechanism:** Decreased dose may be needed	-	-	-	-	-
Sarilumab§			**Reported increase in expression of CYP3A4 (major pathway):** No dose adjustment recommended			**Reported increase in expression of CYP3A4 (major pathway):** No dose adjustment recommended
Azithromycin	**Unknown mechanism:** Decreased dose may be needed	**P-gp inhibition:** May increase plasma concentration. No dose adjustment recommended		**P-gp inhibition:** Decrease dose to 80 mg once followed by 40 mg daily	**P-gp inhibition:** VTE: Limit dose to 30 mg daily. Non-valvular AF: No dose recommendation	
Hydroxychloroquine and Chloroquine	-	-	-	-	-	-

Other drugs being studied to treat COVID-19 include bevacizumab, chloroquine/hydroxychloroquine, eculizumab, fingolimod, losartan, and pirfenidone. Drug-drug interactions between these medications and oral anticoagulants have yet to be identified. Bevacizumab has been reported to cause deep vein thrombosis (9%), arterial thrombosis (5%) and pulmonary embolism (1%). It is also reported to cause thrombocytopenia (58%).*Parenteral anticoagulants (including unfractionated or low-molecular weight heparins, bivalirudin, argatroban, and fondaparinux) are non CYP metabolized and don't interact with any of the investigational agents ‡Reported with interferon alpha. †These recommendations are based on the U.S. package insert. The Canadian package insert considers the combination of these agents to be contraindicated. ‡Interferon has been reported to cause pulmonary embolism (<5%), thrombosis (<5%), decreased platelet count (1-15% with Alfa-2b formulation), and ischemic stroke (<5%). §Sarilumab has been reported to cause decreased platelet count, with decreases to less than 100,000 mm^3 in 1% an 0.7% of patients on 200 mg and 150 mg doses, respectively. CYP: Cytochrome P system.

Bikdeli et al. JACC 2020

Mortality of Patients with COVID-19 +/- CVD

- Myocardial injury is significantly associated with fatal outcome of COVID-19
- The prognosis of patients with underlying CVD but without myocardial injury is relatively favorable.
- Inflammation may be a potential mechanism for myocardial injury.



It is reasonable to triage patients with COVID-19 according to the presence of underlying CVD and evidence of myocardial injury for prioritized treatment and even more aggressive strategies.

Guo et al., JAMA, 2020

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Troponin and BNP Use in COVID-19

Mar 18, 2020

- Clinicians are advised to only measure troponin if the diagnosis of acute MI is being considered on clinical grounds and an abnormal troponin should not be considered evidence for an acute MI without corroborating evidence

- Use of echocardiography or coronary angiography for COVID-19 patients with myocardial injury or elevated natriuretic peptide should be restricted to those patients in whom these procedures would be expected to meaningfully affect outcome.

- No data exist to suggest benefit from anti-platelet or anticoagulant therapy for those with acute myocardial injury with the exception of those with Type 1 MI.

Journal of the American College of Cardiology
March 2020
DOI: 10.1016/j.jacc.2020.03.021

PDF Article

CARDIOVASCULAR MEDICINE AND SOCIETY

Just Accepted

Catheterization Laboratory Considerations During the Coronavirus (COVID-19) Pandemic: From ACC's Interventional Council and SCAI

Frederick G.P. Welt, Pinak B. Shah, Herbert D. Aronow, Anna E. Bortnick, Timothy D. Henry, Matthew W. Sherwood, Michael N. Young, Laura J. Davidson, Sabeeda Kadavath, Ehtisham Mahmud, Ajay J. Kirtane and American College of Cardiology's (ACC) Interventional Council and the Society of Cardiovascular Angiography and Intervention (SCAI)

- Deferral of all elective coronary, structural and vascular diagnostic/interventional procedure among stable patients with non-lifethreatening conditions
- In NSTEMI, efforts should be made in differentiating type 1 vs. type 2 MI.
- In NSTEMI, medical management should be considered appropriate except in unstable pts (ongoing chest pain, hemodynamic or electrical instability secondary to the ACS).
- Fibrinolysis to be considered an option in low-risk STEMI patients with confirmed COVID-19
- If primary PCI for STEMI and unknown COVID19 status, personnel should wear appropriate PPE during the case.

Oral Antiplatelet Therapies and Drug-drug interaction: Considerations in COVID-19 Patients

Table 3. Potential Drug Interactions Between Antiplatelet Agents* and Investigational Therapies for COVID-19

		$P2Y_{12}$ Platelet Receptor Inhibitors			Phosphodiesterase III Inhibitor
Investigational COVID-19 Therapies	**Mechanism of Action of COVID-19 Therapy**	Clopidogrel [1,2]	Prasugrel [2]	Ticagrelor [3,4]	Cilostazol
Lopinavir/ Ritonavir	Lopinavir is a protease inhibitor; Ritonavir inhibits CYP3A4 metabolism increasing lopinavir levels	**CYP 3A4 Inhibition (minor pathway):** Reduction in clopidogrel active metabolite. Do not co-administer or if available utilize $P2Y_{12}$ platelet function assays for monitoring.† With limited clinical data, prasugrel may be considered as alternative, if no contraindications	**CYP3A4 Inhibition:** Decreased active metabolite but maintained platelet inhibition. Can administer with caution.	**CYP3A4 Inhibition:** Increased effects of ticagrelor. Do not co-administer or if available utilize $P2Y_{12}$ monitoring or consider dose-reduced ticagrelor*	**CYP3A4 Inhibition:** Recommend decreasing dose to maximum of 50 mg BID.
Remdesivir	Nucleotide-analog inhibitor of RNA-dependent RNA polymerases	**Reported inducer of CYP3A4 (minor pathway):** No dose adjustment recommended.	**Reported inducer of CYP3A4 (major pathway):** No dose adjustment recommended.	**Reported inducer of CYP3A4 (major pathway):** No dose adjustment recommended.	**Reported inducer of CYP3A4 (major pathway):** No dose adjustment recommended.
Tocilizumab	Inhibits IL-6 receptor: may potentially mitigate cytokine release syndrome symptoms in severely ill patients	**Reported increase in expression of 2C19 (major pathway) and 1A2, 2B6, and 3A4 (minor pathways:** No dose adjustment recommended.	**Reported increase in expression of 3A4 (major pathway) and 2C9 and 2C19 (minor pathway):** No dose adjustment recommended.	**Reported increase in expression of 3A4 (major pathway):** No dose adjustment recommended.	**Reported increase in expression of 3A4 (major pathway):** No dose adjustment recommended.
Sarilumab	Binds specifically to both soluble and membrane-bound IL-6Rs (sIL-6Rα and mIL-6Rα) and has been shown to inhibit IL-6-mediated signaling: may potentially mitigate cytokine release syndrome symptoms in severely ill patients	**Reported increase in expression of 3A4 (minor pathways:** No dose adjustment recommended.	**Reported increase in expression of 3A4 (major pathway):** No dose adjustment recommended.	**Reported increase in expression of CYP3A4(major pathway):** No dose adjustment recommended.	**Reported increase in expression of 3A4 (major pathway):** No dose adjustment recommended.

Other drugs being studied to treat COVID-19 include azithromycin, bevacizumab, chloroquine/hydroxychloroquine, eculizumab, fingolimod, interferon, losartan, methylprednisolone, pirfenidone, and ribavirin. Drug-drug interactions between these medications and antiplatelet agents have yet to be identified. *Cangrelor, aspirin, dipyridamole, and glycoprotein IIb/IIIa inhibitors (eptifibatide, tirofiban, abciximab) are not known to interact with investigational therapies for COVID-19.
†Monitoring of P2Y12 levels can be assessed through the VerifyNow assay, or others. Evaluation of effect of protease inhibitors on P2Y12 inhibitors has not been extensively studied. Dose reduction recommendations for $P2Y_{12}$ inhibitors or P2Y12 platelet function assay monitoring is not commonly practiced.

Bikdeli et al. JACC 2020

Don’t forget….

- Most COVID-19 patients are asymptomatic/mild symptoms.
- Patients with cardiovascular disease and with cardiovascular risk factors (i.e., HTN) more commonly affected.
- Many of these patients already on antiplatelet therapy.
- Don’t switch therapy if patient is asymptomatic/mild symptoms!