Anticoagulation Prophylaxis in COVID-19

Thursday | June 17, 2021 | 11:00am - 12:00pm EST

Presenter:

Scott Kaatz, DO, MSc

Guest Authors:

Behnood Bikdeli, MD, MS | Patrick Lawler, MD, MPH | Renato Lopes, MD, MPH, PhD

Moderator:

Tracy Minichiello, MD

Speakers

Behnood Bikdeli, MD, MS

- Clinical Fellow in Medicine, *Brigham & Woman's Hospital/Harvard Medical School*

Scott Kaatz, DO, MSc

- Clinical Professor of Medicine, *Wayne State University School of Medicine*
- Senior Staff Hospitalist, Medical Director for Professional Development and Research, *Division of Hospital Medicine, Henry Ford Hospital*

Patrick Lawler, MD, MPH

- Cardiac Critical Care Physician, *Peter Munk Cardiac Centre, Toronto General Hospital*
- Assistant Professor of Medicine, *University of Toronto*

Renato Lopes, MD, MPH, PhD

- Professor of Medicine, *Division of Cardiology, Duke University Medical Center, Duke Clinical Research Institute*

Tracy Minichiello, MD

- Professor of Medicine, *University of California San Francisco*
- Chief of Anticoagulation and Thrombosis Services, *San Francisco VA Hospital*

Disclosures & Notification of Support

Speakers have the following relevant financial relationships with commercial interests:

Behnood Bikdeli, MD, MS
- Consultant for litigation related to two specific brand models of iVC filters

Scott Kaatz, DO, MSc
- BMS/Pfizer | Osmosis Research | Janssen Pharmaceuticals | Novartis | Portola/Alexion | CSL Behring | Gilead

Patrick Lawler, MD, MPH
- None

Renato Lopes, MD, MPH, PhD

Bayer | Boehringer Ingelheim | BMS/Pfizer | Daiichi Sankyo | Glaxo Smith Kline | Medtronic | Merck

Tracy Minichiello, MD
- None

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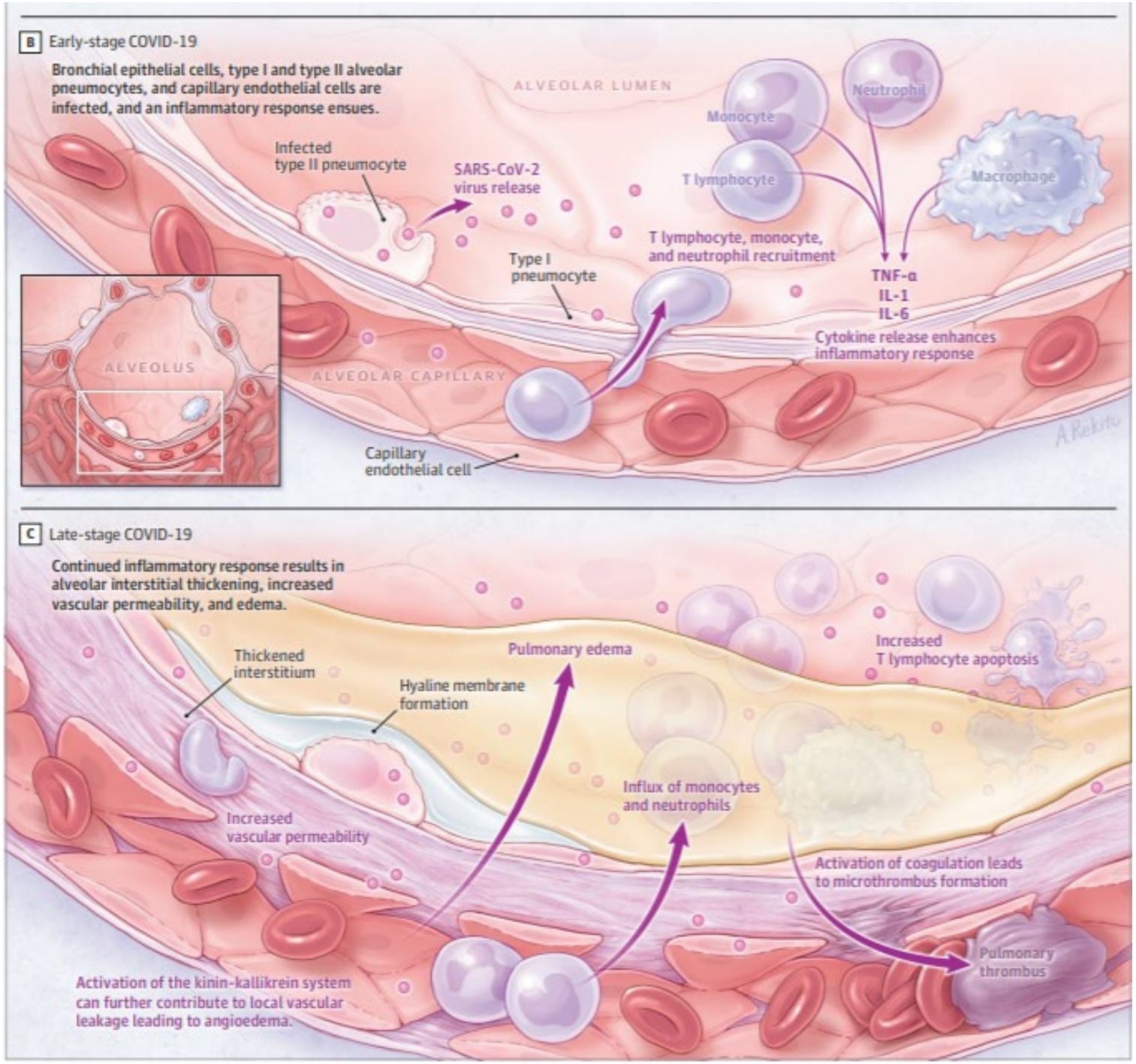
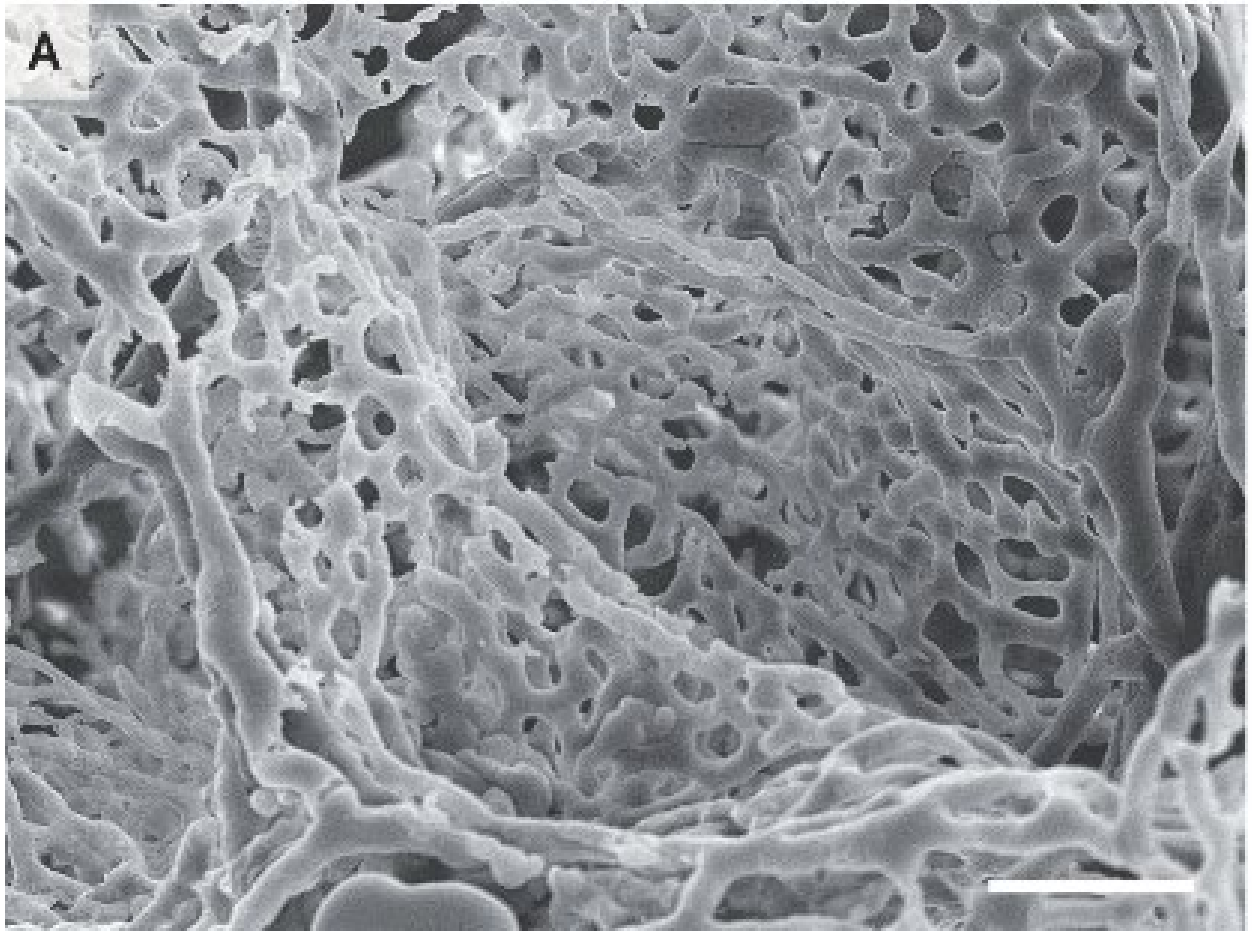
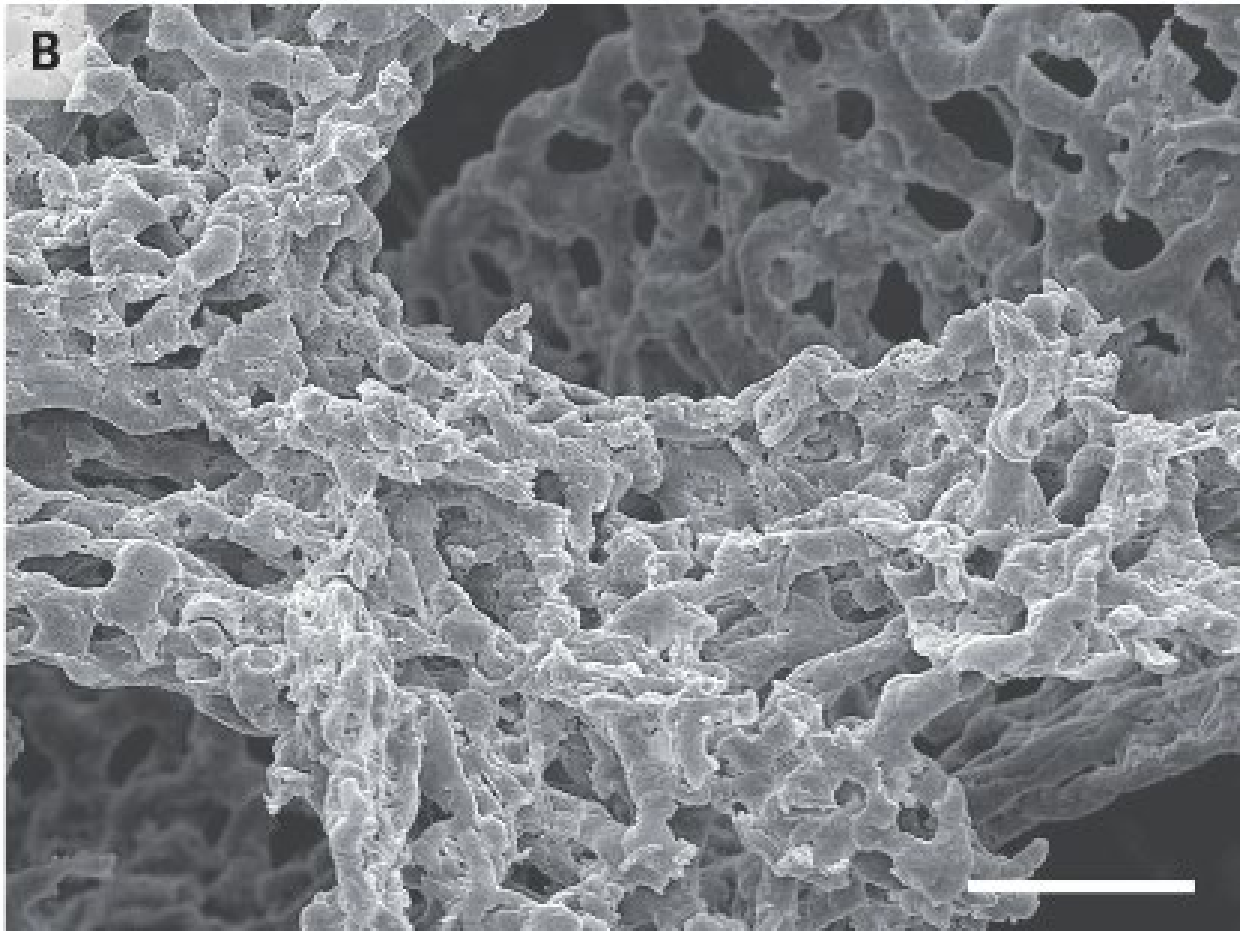
Pathophysiology of Immuno-micro Thrombosis in COVID-19



Wiersinga WJ. JAMA. 2020 Aug 25;324(8):782-793. PMID: 32648899.

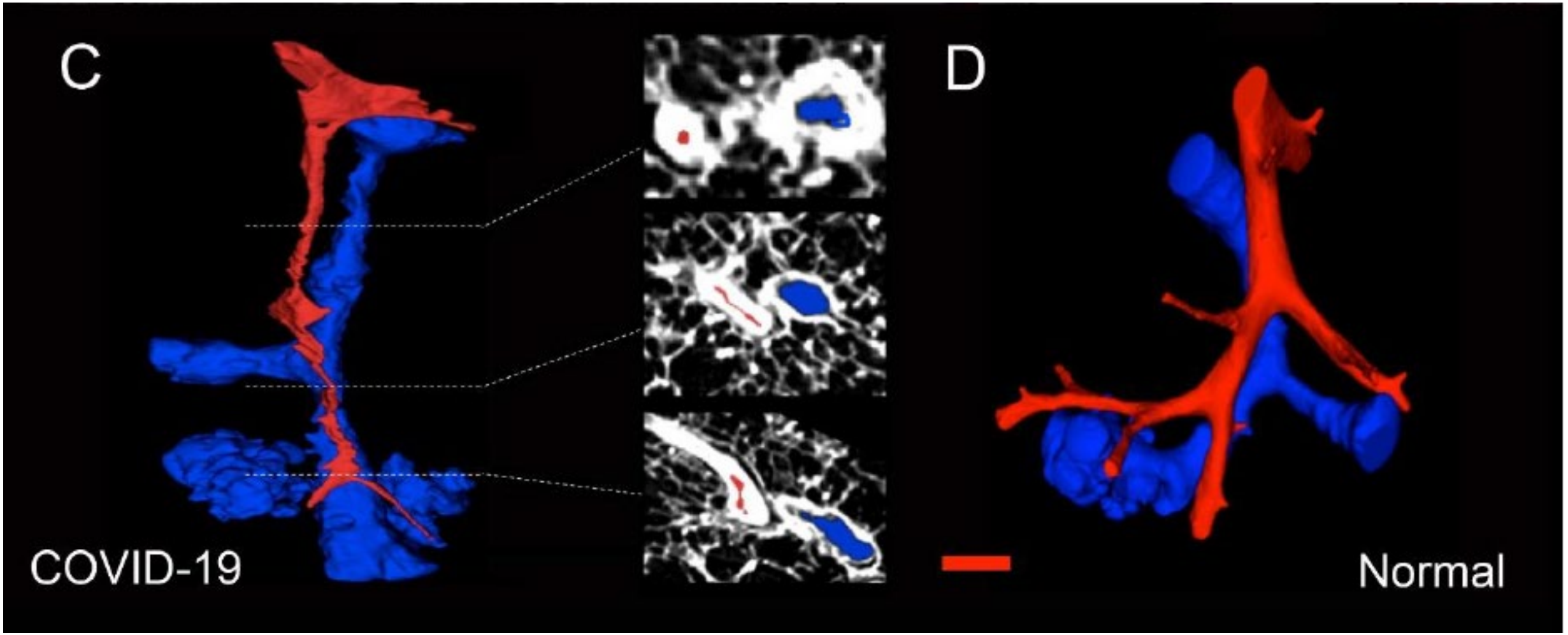
Series of 7 Autopsies





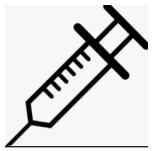
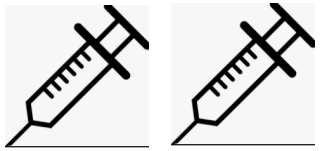
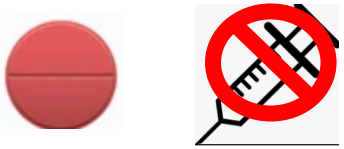
Ackermann M. N Engl J Med. 2020 May 21.. PMID: 32437596.

Series of 7 Autopsies



Ackermann M. N Engl J Med. 2020 May 21.. PMID: 32437596.

COVID-19 and Thrombosis: Searching for Evidence - Anticoagulation Thromboprophylaxis

Example Randomized Trials	Recruiting • ACTIV 4c • PREVENT	Completed • ***ATTACC*** • ***ACTIV 4a*** • ***REMAP-CAP*** • ACTION	Completed • ATTACC • ACTIV 4a • REMAP-CAP • INSPIRATION	Recruiting • ACTIV 4b
Environment of Care	 "Pre-hospitalization"	 Hospital Floor	 ICU	 Post Discharge
ASH Guidelines	 No Prophylaxis	 Prophylactic Dose	 Prophylactic Dose	 No Prophylaxis
How I Treat	 No Prophylaxis	 Therapeutic Dose	 Prophylactic Dose	 FDA approved DOAC in highly selected patients

INSPIRATION Trial

Question: Is intermediate dose anticoagulation better than prophylactic dose in COVID-19 patients admitted to the ICU?

Design: RCT, open label (also has a statin arm in 2 x 2 design)

Patients: 562 patients in 10 Iranian academic centers' ICU from July 29, 2020, to November 19, 2020

Intervention: Enoxaparin 1 mg/kg once daily with adjustment for weight and creatinine clearance

Control: Enoxaparin 40 mg qd with adjustments

Outcome: Composite of VTE, arterial thromboembolism, ECMO or all-cause mortality

Timeframe: 30 Days

INSPIRATION Investigators, Sadeghipour P. JAMA. 2021 Apr 27;325(16):1620-1630. PMID: 33734299.

INSPIRATION Trial

Outcome	No. (%) Intermediate dose (n = 276)	Standard dose (n = 286)	Absolute difference (95% CI), %	Odds ratio (95% CI)	*P* value
Primary outcome					
Composite of adjudicated acute venous thromboembolism, arterial thrombosis, treatment with extracorporeal membrane oxygenation, or all-cause mortality[a]	126 (45.7)	126 (44.1)	1.5 (−6.6 to 9.8)	1.06 (0.76 to 1.48)	.70
Secondary outcomes					
All-cause mortality	119 (43.1)	117 (40.9)	2.2 (−5.9 to 10.3)	1.09 (0.78 to 1.53)	.50
Adjudicated venous thromboembolism	9 (3.3)	10 (3.5)	−0.2 (−3.2 to 2.7)	0.93 (0.37 to 2.32)	.87
Ventilator-free days, median (IQR)[b]	30 (3 to 30)	30 (1 to 30)	0 (0 to 0)	NA	.50[c]
Exploratory outcomes					
Objectively clinically diagnosed type I acute myocardial infarction[d]	0	0			
Objectively clinically diagnosed stroke	1 (0.4)	1 (0.3)	0.1 (−0.9 to 0.9)	1.03 (0.06 to 16.65)	.97
Objectively clinically diagnosed acute peripheral arterial thrombosis	0	0			
Safety outcomes					
Major bleeding[e]	7 (2.5)	4 (1.4)	1.1 (−1.1 to 3.4)	1.83 (0.53 to 5.93)	.33
BARC classification					
Type 3a (hemoglobin drop of 3-5 g/dL or any transfusion)	3 (1.1)	4 (1.4)	−0.3 (−2.1 to 1.5)	0.78 (0.17 to 3.49)	.73
Type 3b (hemoglobin drop >5 g/dL)	1 (0.4)	0[f]	0.3 (−0.3 to 1.0)		.30
Type 3c (intracranial hemorrhage)	1 (0.4)	0[f]	0.3 (−0.3 to 1.0)		.30
Type 5 (fatal bleeding)	2 (0.7)	0[f]	0.7 (−0.2 to 1.7)		.14
Clinically relevant nonmajor bleeding (BARC type 2)[g]	12 (4.3)	5 (1.7)	2.5 (−0.2 to 5.4)	2.55 (0.92 to 7.04)	.07
Composite of major and non-major bleeding	17 (6.2)	9 (3.1)	3.0 (−0.4 to 6.4)	2.02 (0.89 to 4.61)	.08

INSPIRATION Investigators, Sadeghipour P. JAMA. 2021 Apr 27;325(16):1620-1630. PMID: 33734299.

ACTION Trial

Question: Is therapeutic prophylactic anticoagulation primarily with rivaroxaban better than prophylactic dose in hospitalized COVID-19

Design: RCT, open label

Patients: 615 hospitalized with COVID-19 with elevated D-dimer at 31 Brazilian sites from June 24, 2020, to February 26, 2021

Intervention: Rivaroxaban 20 mg (15 mg if CrCL 30-49) for 30 days
- Initial Circle therapeutic does enoxaparin or heparin if unstable

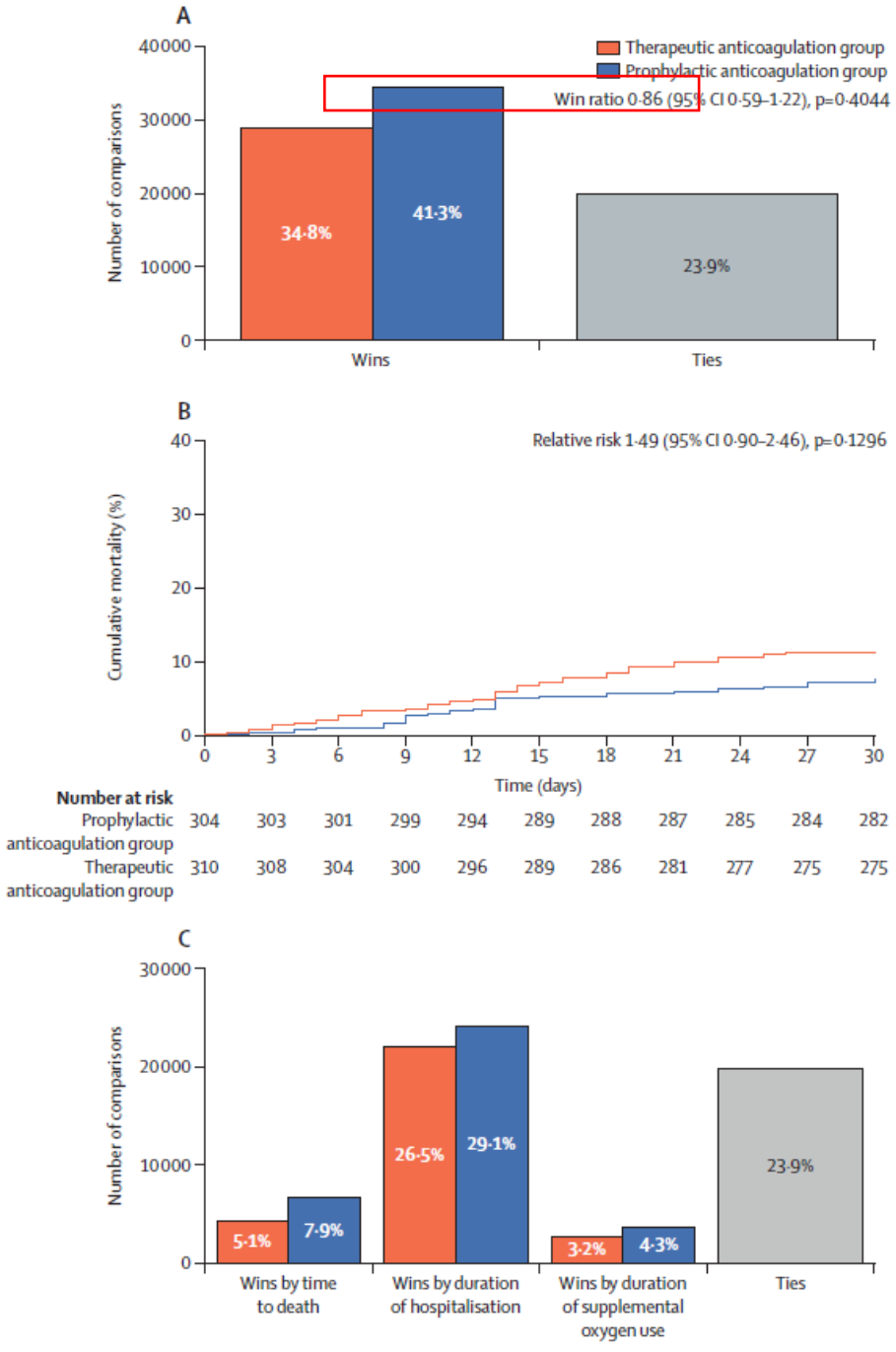
Comparison: Prophylactic dose enoxaparin or heparin while in hospital and provider discretion for extended prophylaxis

Outcome: Hierarchical composite of time to death, duration of hospitalization or duration of oxygen

Timeframe: 30 Days

ACTION Investigators; Lopes R.D., et al. Lancet. 2021 Jun 4:S0140-6736(21)01203-4.PMID: 34097856.

ACTION Trial



ACTION Investigators; Lopes R.D., et al. Lancet. 2021 Jun 4:S0140-6736(21)01203-4.PMID: 34097856.

ACTION Trial

	Therapeutic anticoagulation group (n=310)	Prophylactic anticoagulation group (n=304)	Effect (95% CI)	p value
Efficacy outcomes				
Composite thrombotic outcome*	23 (7%)	30 (10%)	RR 0·75 (0·45–1·26)	0·32
Venous thromboembolism†	11 (4%)	18 (6%)	RR 0·60 (0·29–1·25)	0·19
Deep vein thrombosis	5 (2%)	5 (2%)	RR 0·98 (0·29–3·35)	1·00
Pulmonary embolism	7 (2%)	13 (4%)	RR 0·53 (0·21–1·31)	0·18
Myocardial infarction	13 (4%)	14 (5%)	RR 0·91 (0·44–1·91)	0·85
Stroke	1 (<1%)	0	..	..
Major adverse limb event	0	1 (<1%)	..	..
Composite thrombotic outcome* and all-cause death	46 (15%)	44 (14%)	RR 1·03 (0·70–1·50)	0·91
Death	35 (11%)	23 (8%)	RR 1·49 (0·90–2·46)	0·13
Safety outcomes				
Major bleeding or clinically relevant non-major bleeding (ISTH definitions)	26 (8%)	7 (2%)	RR 3·64 (1·61–8·27)	0·0010

ACTION Investigators; Lopes R.D., et al. Lancet. 2021 Jun 4:S0140-6736(21)01203-4.PMID: 34097856.

Therapeutic Anticoagulation in Critically Ill Hospitalized Patients with Covid-19

Preliminary Report

Multiplatform RCT

A collaboration between 3 international trial platforms

ATTACC · REMAP-CAP · ACTIV-4 Acute Inpatient Anti-Thrombotic Study

SEVERELY ILL HOSPITALIZED COVID-19

- High flow nasal oxygen
- Mechanical ventilation
- ECMO
- Vasopressor or inotrope support

R

N=1074
(987 from REMAP-CAP)

	MEDIAN ORGAN SUPPORT-FREE DAYS		MAJOR BLEEDING
Therapeutic anticoagulation	**3 days** (-1, 16)	AOR 0.87 (0.70-1.08)	**3.1%** (15/482)
Usual Care pharmacological thromboprophylaxis 41% prophylactic 51% intermediate	**5 days** (-1,16)		**2.4%** (12/495)

Probability of inferiority = 89%

99.8% Posterior probability of futility

CONCLUSIONS: In patients with severe Covid-19, therapeutic anticoagulation did not improve hospital survival or days free of organ support compared to usual care pharmacological thromboprophylaxis.

Zarychanski R. et al. medRxiv. https://doi.org/10.1101/2021.03.10.21252749

Multi-Platform Trials – Non-Critically Ill COVID-19

Question: Is therapeutic anticoagulation better than usual care in non-critically ill hospitalized COVID -19?

Design: RCT, open label, 3 multi-platform RCTs

Patients: 2219 in 129 global sites hospitalized without need for ICU-level care of high flow oxygen, mechanical ventilation (invasive and non-invasive), vasopressors or inotropes within 72 hours-ish of admission from April 21, 2020, to January 22, 2021,

- with high, low or unknown D-dimer

Intervention: Therapeutic anticoagulation with LMWH (94.7%) or heparin

Comparison: Usual care with 71.7% low-dose and 26.5% intermediate dose anticoagulation

Outcome: Organ-support-free days

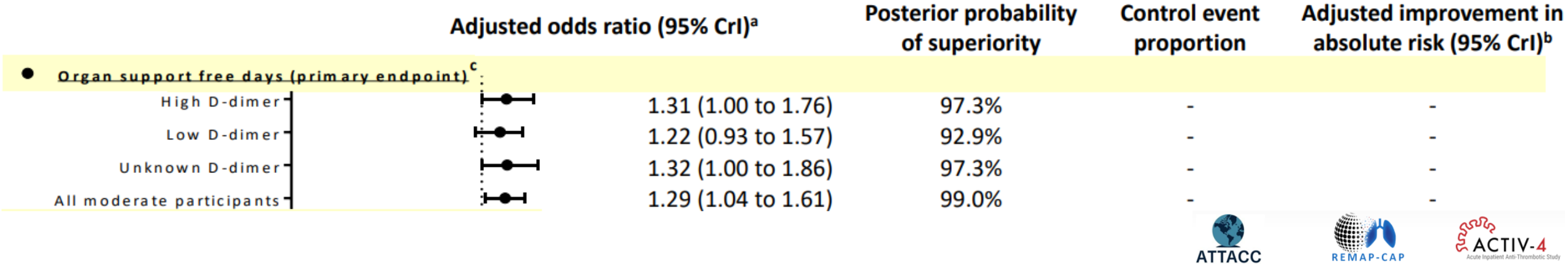
Timeframe: 21 days for organ support and 90 days for death

ATTACC REMAP-CAP ACTIV-4 Acute Inpatient Anti-Thrombotic Study

Lawler, P.R. et al. medRxiv 2021.05.13.21256846; doi: https://doi.org/10.1101/2021.05.13.21256846

Multi-Platform Trials – Non-Critically Ill COVID-19

- The proportion of participants in the thromboprophylaxis arm surviving to hospital discharge without receipt of organ support during the first 21 days (control event frequency) was
  - 76.4% (247/1048).
- The median adjusted absolute improvement in this proportion with therapeutic-dose anticoagulation was
  - 4.6% (95% CrI 0.7 to 8.1).

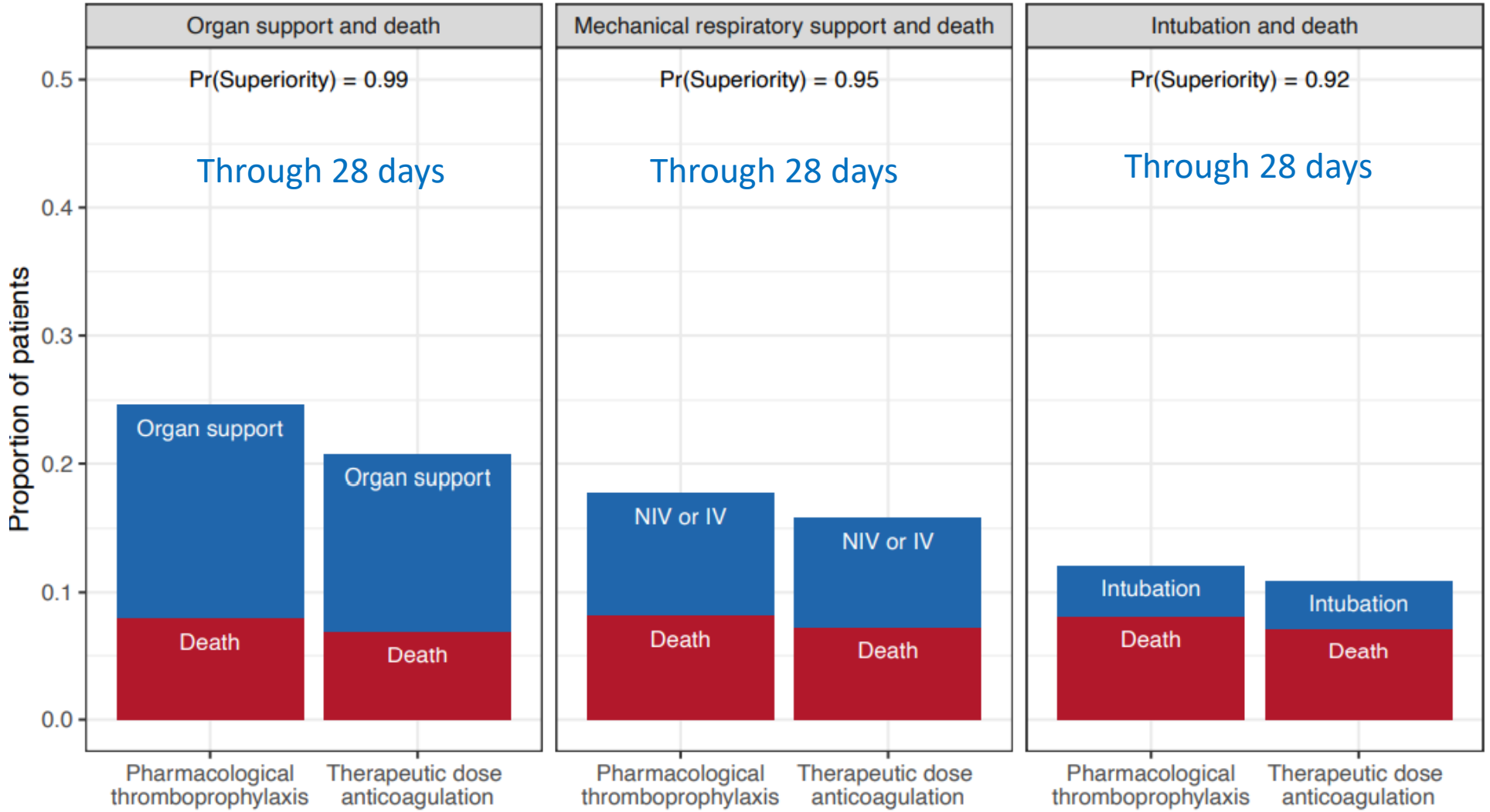


	Adjusted odds ratio (95% CrI)[a]	Posterior probability of superiority	Control event proportion	Adjusted improvement in absolute risk (95% CrI)[b]
Organ support free days (primary endpoint)[c]				
High D-dimer	1.31 (1.00 to 1.76)	97.3%	-	-
Low D-dimer	1.22 (0.93 to 1.57)	92.9%	-	-
Unknown D-dimer	1.32 (1.00 to 1.86)	97.3%	-	-
All moderate participants	1.29 (1.04 to 1.61)	99.0%	-	-

ATTACC
REMAP-CAP
ACTIV-4
Acute Inpatient Anti-Thrombotic Study

Lawler, P.R. et al. medRxiv 2021.05.13.21256846; doi: https://doi.org/10.1101/2021.05.13.21256846

Multi-Platform Trials – Non-Critically Ill COVID-19



ATTACC REMAP-CAP ACTIV-4 Acute Inpatient Anti-Thrombotic Study

Lawler, P.R. et al. medRxiv 2021.05.13.21256846; doi: https://doi.org/10.1101/2021.05.13.21256846

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