Anticoagulation in COVID-19

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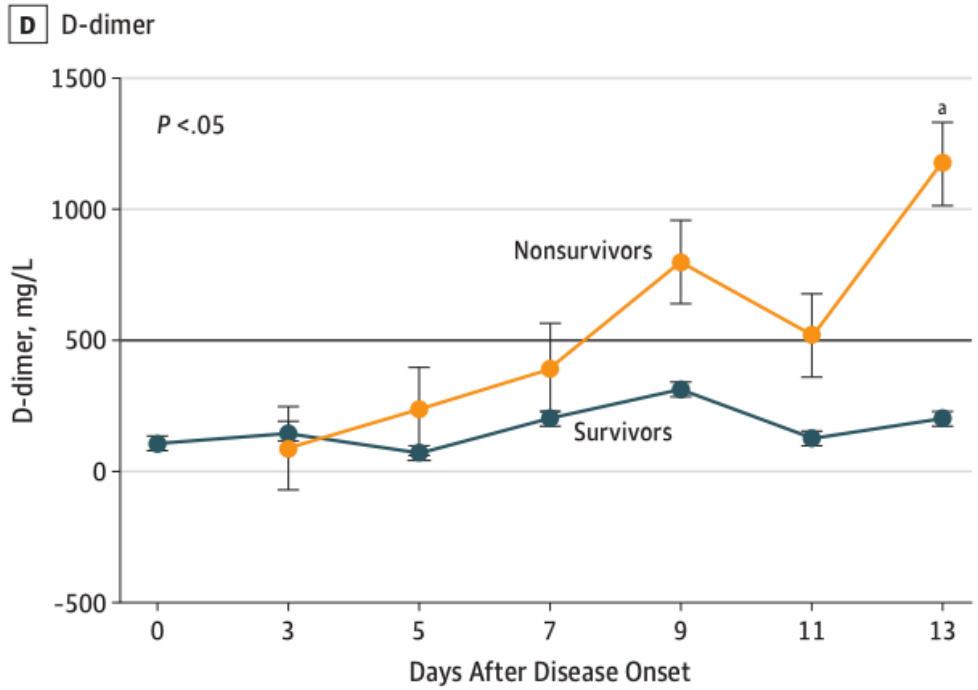
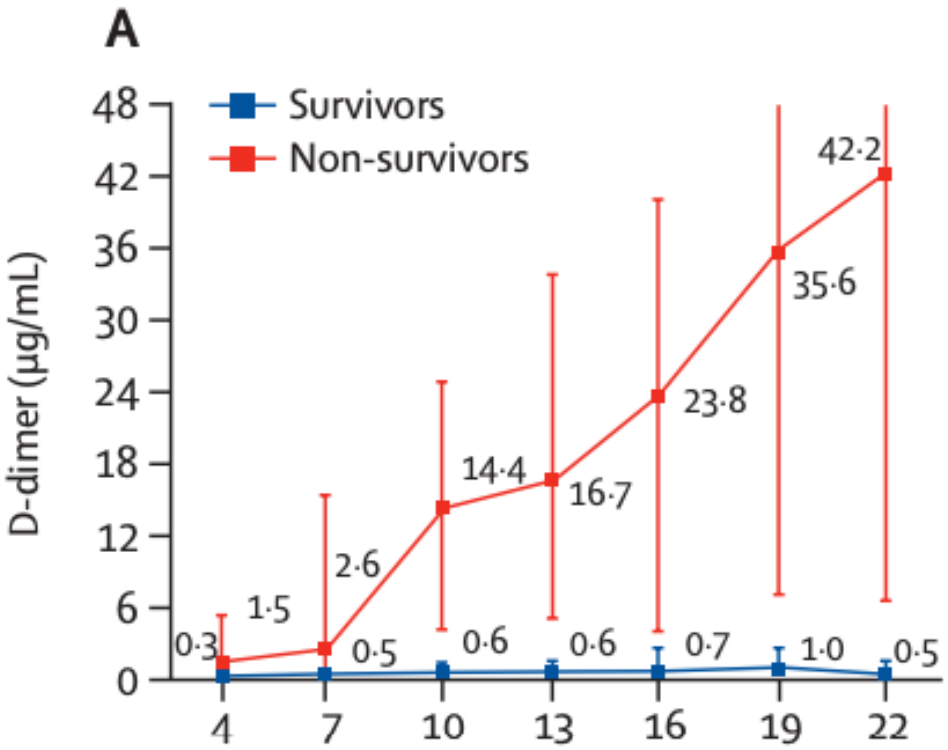
Anticoagulation in COVID-19

Initial Observations – D Dimer Levels





JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China

Dawei Wang, MD; Bo Hu, MD; Chang Hu, MD; Fangfang Zhu, MD; Xing Liu, MD; Jing Zhang, MD; Binbin Wang, MD; Hui Xiang, MD; Zhenshun Cheng, MD; Yong Xiong, MD; Yan Zhao, MD; Yirong Li, MD; Xinghuan Wang, MD; Zhiyong Peng, MD

Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study

Fei Zhou, Ting Yu*, Ronghui Du*, Guohui Fan*, Ying Liu*, Zhibo Liu*, Jie Xiang*, Yeming Wang, Bin Song, Xiaoying Gu, Lulu Guan, Yuan Wei, Hui Li, Xudong Wu, Jiuyang Xu, Shengjin Tu, Yi Zhang, Hua Chen, Bin Cao*

Initial Observations – Incidence

Contents lists available at ScienceDirect

Thrombosis Research

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

Incidence of thrombotic complications in critically ill ICU patients with COVID-19

F.A. Klok[a,*], M.J.H.A. Kruip[b], N.J.M. van der Meer[c], M.S. Arbous[d], D.A.M.P.J. Gommers[e], K.M. Kant[f], F.H.J. Kaptein[a], J. van Paassen[d], M.A.M. Stals[a], M.V. Huisman[a,1], H. Endeman[e,1]

Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: An updated analysis

F.A. Klok[a,*], M.J.H.A. Kruip[b], N.J.M. van der Meer[c,d], M.S. Arbous[e], D. Gommers[f], K.M. Kant[g], F.H.J. Kaptein[a], J. van Paassen[e], M.A.M. Stals[a], M.V. Huisman[a,1], H. Endeman[f,1]

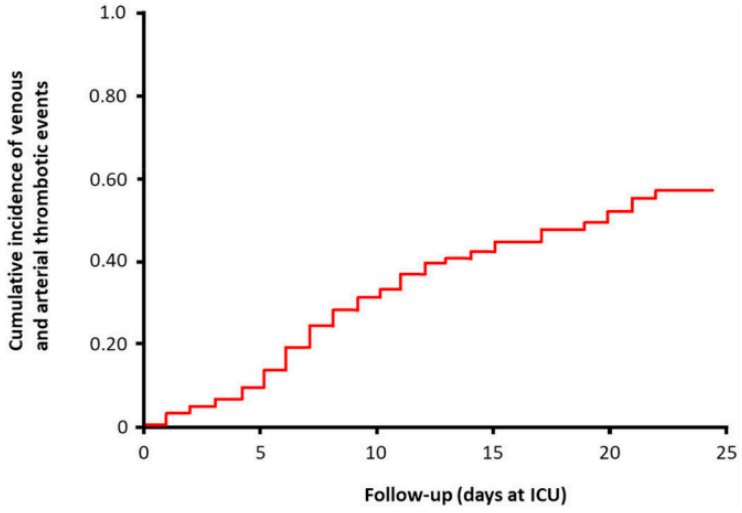
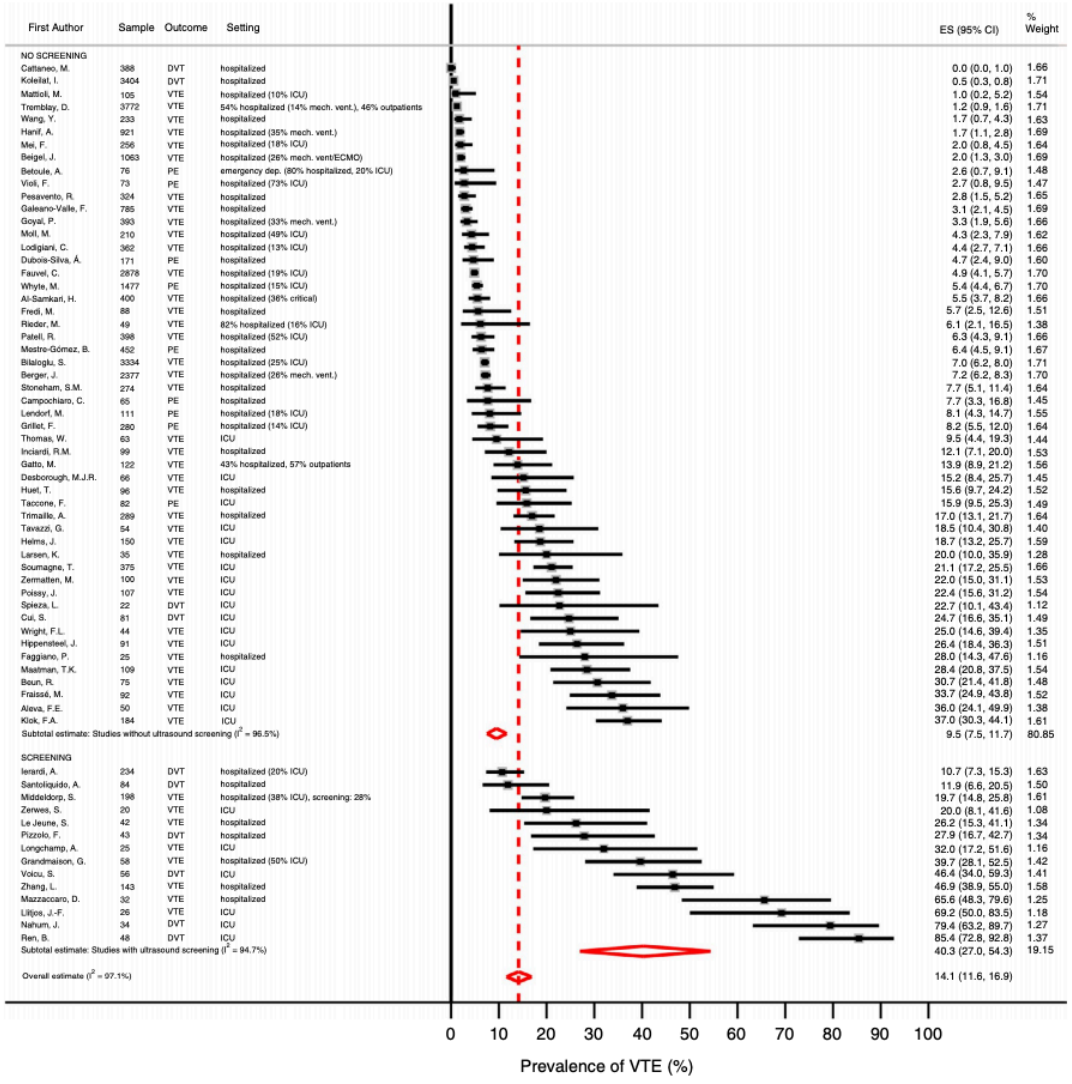


Fig. 1. Cumulative incidence of venous and arterial thrombotic complications during the course of intensive care unit admission of patients with proven COVID-19 pneumonia.

Risk of venous thromboembolism in patients with COVID-19: A systematic review and meta-analysis

Stephan Nopp MD[1] | Florian Moik MD[1] | Bernd Jilma MD[2] | Ingrid Pabinger MD[1] | Cihan Ay MD[1,3]



Initial Observations – Dramatic Images

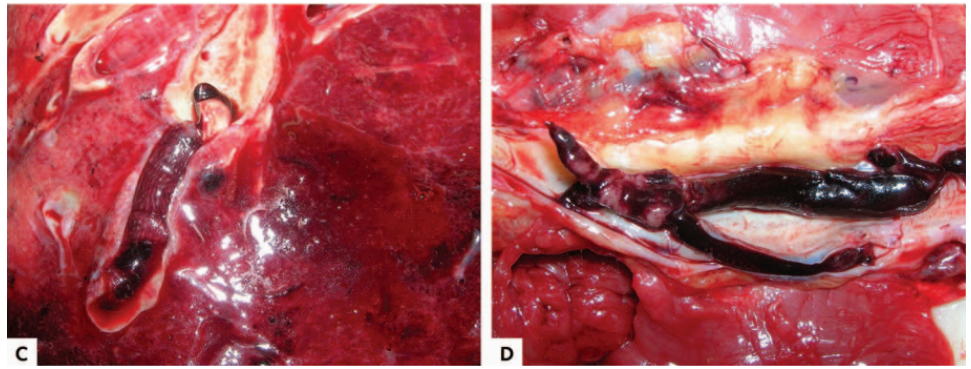
Annals of Internal Medicine

ORIGINAL RESEARCH

Autopsy Findings and Venous Thromboembolism in Patients With COVID-19

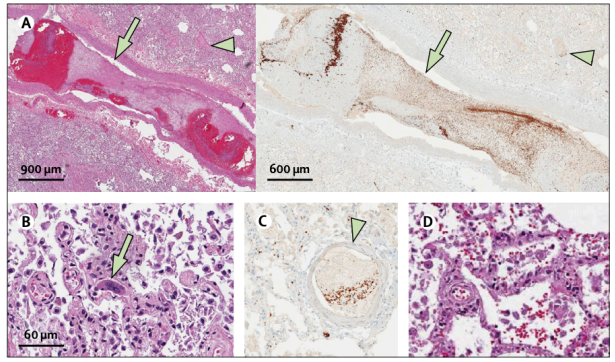
A Prospective Cohort Study

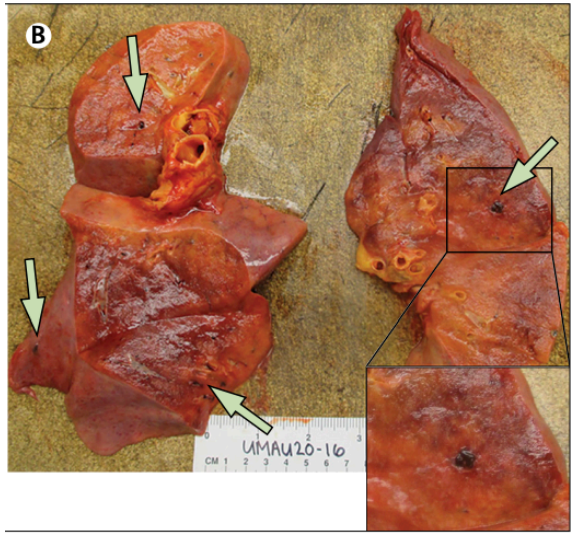
Dominic Wichmann, MD*; Jan-Peter Sperhake, MD*; Marc Lütgehetmann, MD; Stefan Steurer, MD; Carolin Edler, MD; Axel Heinemann, MD; Fabian Heinrich; Herbert Mushumba, MD; Inga Kniep, MD; Ann Sophie Schröder, MD; Christoph Burdelski, MD; Geraldine de Heer, MD; Axel Nierhaus, MD; Daniel Frings, MD; Susanne Pfefferle, MD; Heinrich Becker, MD; Hanns Bredereke-Wiedling, MD; Andreas de Weerth, MD; Hans-Richard Paschen, MD; Sara Sheikhzadeh-Eggers, MD; Axel Stang, MD; Stefan Schmiedel, MD; Carsten Bokemeyer, MD; Marylyn M. Addo, MD, PhD; Martin Aepfelbacher, MD; Klaus Püschel, MD†; and Stefan Kluge, MD†



Pulmonary and cardiac pathology in African American patients with COVID-19: an autopsy series from New Orleans

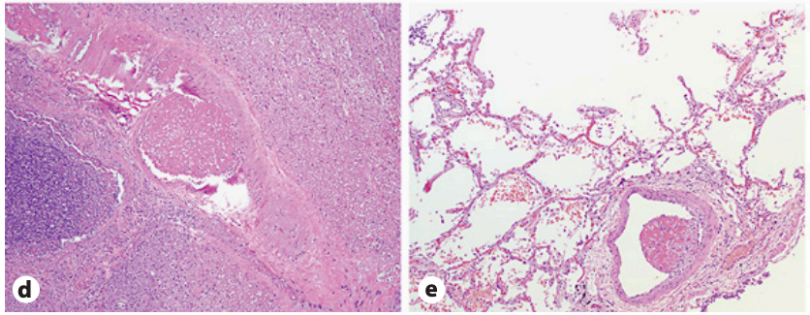
Sharon E Fox, Aibek Akmatbekov, Jack L Harbert, Guang Li, J Quincy Brown, Richard S Vander Heide





Autopsy Findings in 32 Patients with COVID-19: A Single-Institution Experience

Sarah S. Elsoukkary[a] Maria Mostyka[a] Alicia Dillard[a] Diana R. Berman[a] Lucy X. Ma[a] Amy Chadburn[b] Rhonda K. Yantiss[b] Jose Jessurun[b] Surya V. Seshan[b] Alain C. Borczuk[b] Steven P. Salvatore[b]



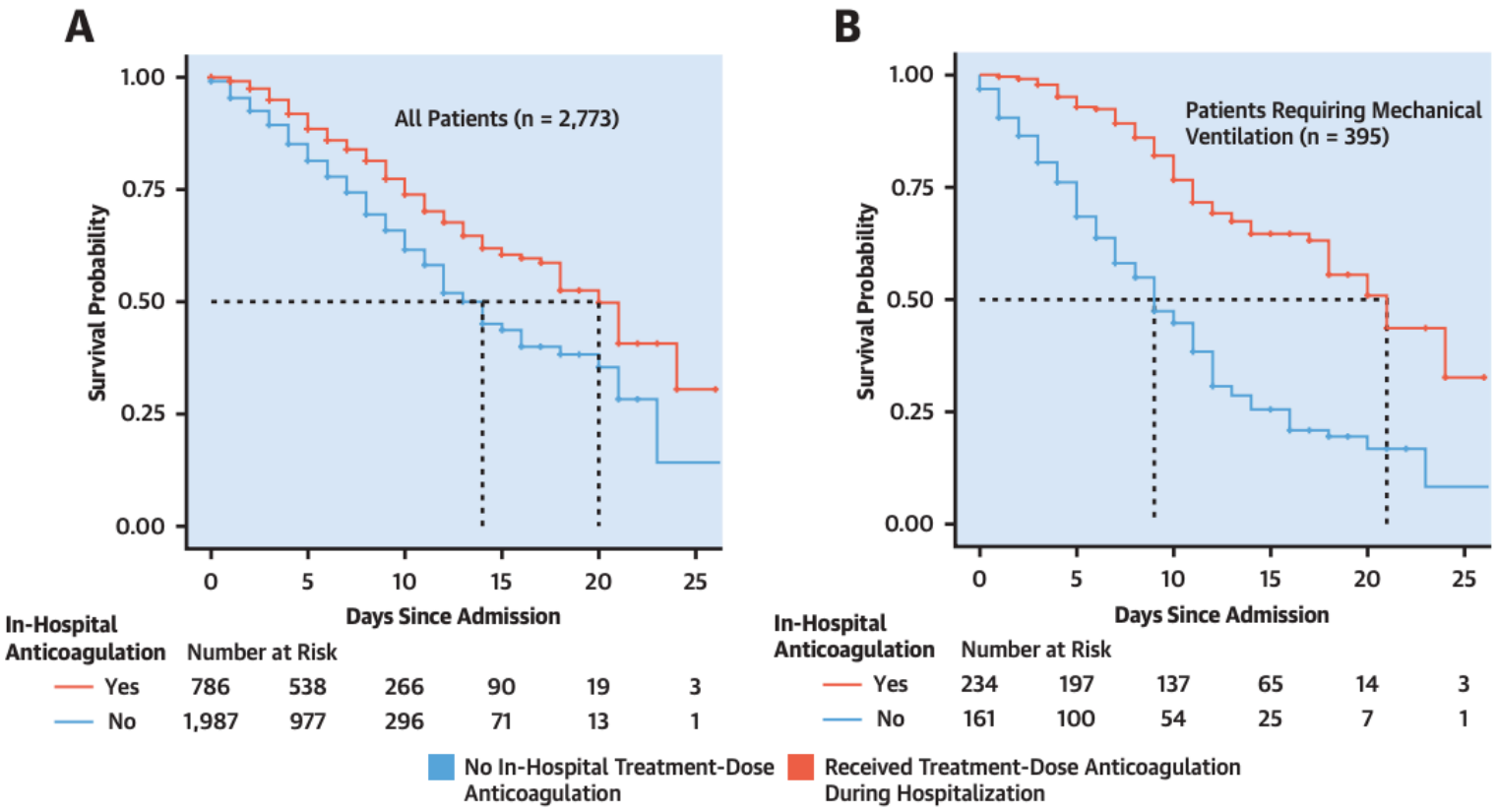
Initial Observations – Therapeutic Benefit??

Letters

Association of Treatment Dose Anticoagulation With In-Hospital Survival Among Hospitalized Patients With COVID-19

Ishan Paranjpe, BS
*Valentin Fuster, MD, PhD
Anuradha Lala, MD
Adam J. Russak, MD
Benjamin S. Glicksberg, PhD
Matthew A. Levin, MD
Alexander W. Charney, MD, PhD
Jagat Narula, MD, PhD
Zahi A. Fayad, PhD
Emilia Bagiella, PhD
Shan Zhao, MD, PhD
†Girish N. Nadkarni, MD, MPH

FIGURE 1 Kaplan-Meier Curve for Hospitalized Patients With COVID-19 and Those Mechanically Ventilated



Kaplan-Meier curve for hospitalized patients with COVID-19 **(A)** and those mechanically ventilated **(B)**. **Colors** indicate treatment-dose anticoagulation. Patients hospitalized at time of data-freeze or discharged within the study period were right-censored. COVID-19 = novel coronavirus disease-2019.

Thursday, September 10, 2020

NIH ACTIV initiative launches adaptive clinical trials of blood-clotting treatments for COVID-19

The mpRCT – ATTACC, ACTIV, and REMAPCAP

- **A**nti**T**hrombotic **T**herapy to **A**meliorate **C**omplications of **C**OVID-19
  - 58 sites in Canada, USA, Brazil, and Mexico
- **A**ccelerating **C**OVID-19 **T**herapeutic **I**nterventions and **V**accines
  - 60 sites in the USA and Spain
- A **R**andomised, **E**mbedded, **M**ulti-factorial, **A**daptive **P**latform Trial for **C**ommunity-**A**cquired **P**neumonia
  - 290 sites in Canada, USA, UK, Ireland, EU, Saudi Arabia, Australia, New Zealand, Nepal, India, Pakistan

CLINICAL DECISIONS

Anticoagulation in Hospitalized Patients with Covid-19

Jehan F. Chowdhury, D.O., Lisa K. Moores, M.D., and Jean M. Connors, M.D.

October 22, 2020
N Engl J Med 2020; 383:1675-1678
DOI: 10.1056/NEJMclde2028217

14 References 7 Citing Articles 25 Comments Poll

Poll

Which option would you choose?

Continue prophylactic anticoagulation during hospitalization and discontinue at hospital discharge.	41%
Switch to intermediate-dose anticoagulation and continue anticoagulation after hospital discharge.	58%

You've already voted

7196 Total Responses

This open poll should not be interpreted as a scientifically valid physician survey.

What to do clinically?

Tuesday, December 22, 2020

NIH ACTIV Trial of blood thinners pauses enrollment of critically ill COVID-19 patients

Friday, January 22, 2021

Full-dose blood thinners decreased need for life support and improved outcome in hospitalized COVID-19 patients

ATTACC, REMAP-CAP, and ACTIV IV-4a mpRCT

Primary outcome

State & D-dimer Strata	Proportional Odds Ratio Median (95% CrI)	Trial Statistical Conclusion
Moderate state, low D-dimer	1.57 (1.14 - 2.19)	**Superiority** [Probability of OR>1 = 0.997]
Moderate state, high D-dimer	1.53 (1.09 - 2.17)	**Superiority** [Probability of OR>1 = 0.991]
Moderate state, missing D-dimer	1.51 (1.06 – 2.15)	n/a⏃
Severe state	0.76 (0.60 – 0.97)	**Futility*** [Probability of OR>1.2 < 0.001]

* Posterior probability of **inferiority** [Probability of OR<1 = 0.985]

⏃ Not evaluated for stopping at interim

OR >1 represents benefit. A higher OR occurs when either mortality is improved and/or if those who survive have reduced requirement for organ support

Release date: January 28, 2021

Pre-publication interim data, not from a locked database and not peer reviewed

Organ support-free days

INTERIM

Approx. proportion requiring organ support

~25%

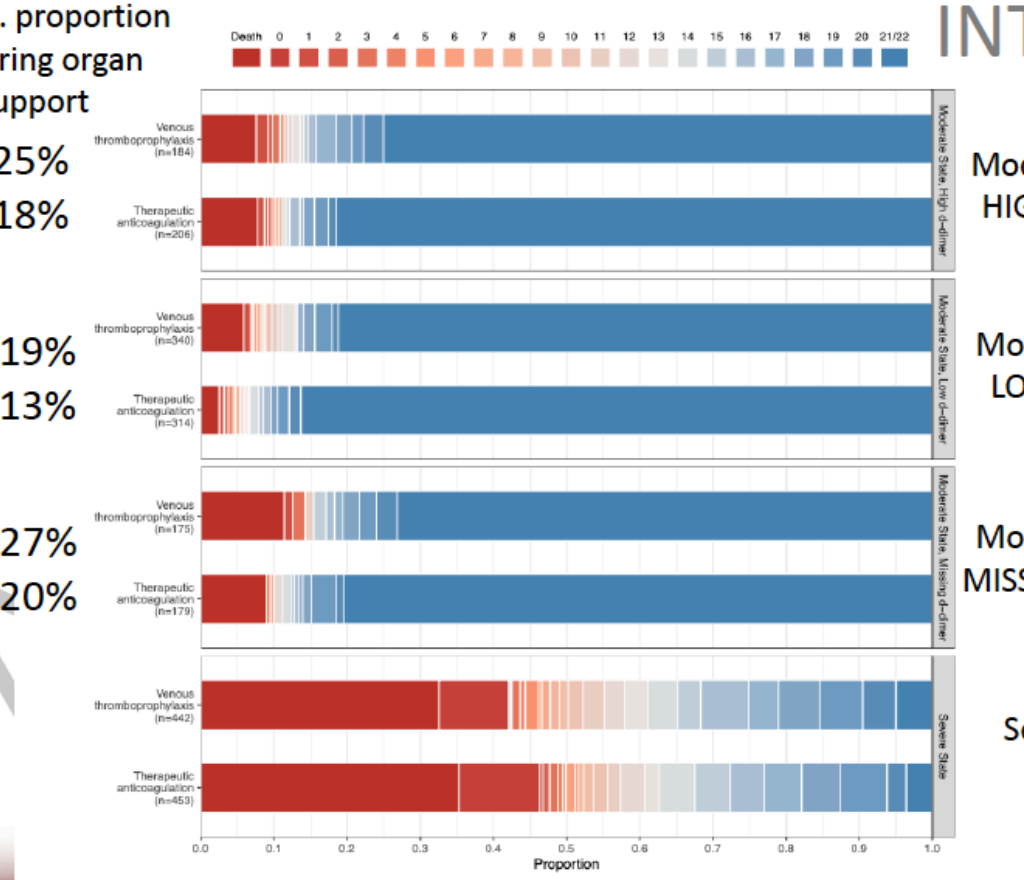
~18%

~19%

~13%

~27%

~20%



Moderate state; HIGH D-dimer

Moderate state; LOW D-dimer

Moderate state; MISSING D-dimer

Severe state

Overall moderate state:

Requirement for organ support
Prophylactic anticoagulation – **~23%**
Therapeutic anticoagulation – **~16%**

Proportion requiring organ support represents a post-hoc analysis and is included to enhance clinical interpretation

Release date: January 28, 2021

Pre-publication interim data, not from a locked database and not peer reviewed

ATTACC, REMAP-CAP, and ACTIV-4a mpRCT

Mortality – not primary outcome (part of OSFDs)

	Moderate State		Severe State	
INTERIM	Therapeutic anticoagulation N = 699	Usual Care venous thromboprophylaxis N = 699	Therapeutic anticoagulation N = 453	Usual Care venous thromboprophylaxis N = 442
Mortality	40 (5.7%)	54 (7.7%)	160 (35.3%)	144 (32.6%)

Release date: January 28, 2021

Pre-publication interim data, not from a locked database and not peer reviewed

ATTACC, REMAP-CAP, and ACTIV-4a mpRCT

Major Bleeding

	Moderate State		Severe State	
INTERIM	Therapeutic anticoagulation N = 853	Usual Care venous thromboprophylaxis N = 742	Therapeutic anticoagulation N = 460	Usual Care venous thromboprophylaxis N = 448
Major Bleeding[Φ]	14 (1.6%)	7 (0.9%)	17 (3.7%)	8 (1.8%)

[Φ]Events reported are preliminary, unadjudicated, and potentially subject to reporting bias

Small differences in denominators when compared to mortality/OSFD exist due to variation in the days efficacy and safety outcome were forwarded by each platform to individual DSMBs and to the Statistical Analysis Committee.

Release date: January 28, 2021

Pre-publication interim data, not from a locked database and not peer reviewed

ATTACC, REMAP-CAP, and ACTIV-4a mpRCT

Thrombotic events

	Moderate State		Severe State	
INTERIM	Therapeutic anticoagulation N = 853	Usual Care venous thromboprophylaxis N = 742	Therapeutic anticoagulation N = 460	Usual Care venous thromboprophylaxis N = 448
Thrombotic events*Φ	16 (1.9%)	24 (3.2%)	31 (6.7%)	53 (11.8%)

*Defined as Deep Vein Thrombosis, Pulmonary Embolism, Myocardial infarction, Ischemic Stroke, Other thrombotic event

ΦEvents reported are preliminary, unadjudicated, and potentially subject to reporting bias

Small differences in denominators when compared to mortality/OSFD exist due to variation in the days efficacy and safety outcome were forwarded by each platform to individual DSMBs and to the Statistical Analysis Committee.

Release date: January 28, 2021

Why might this effect be seen in non critically ill?

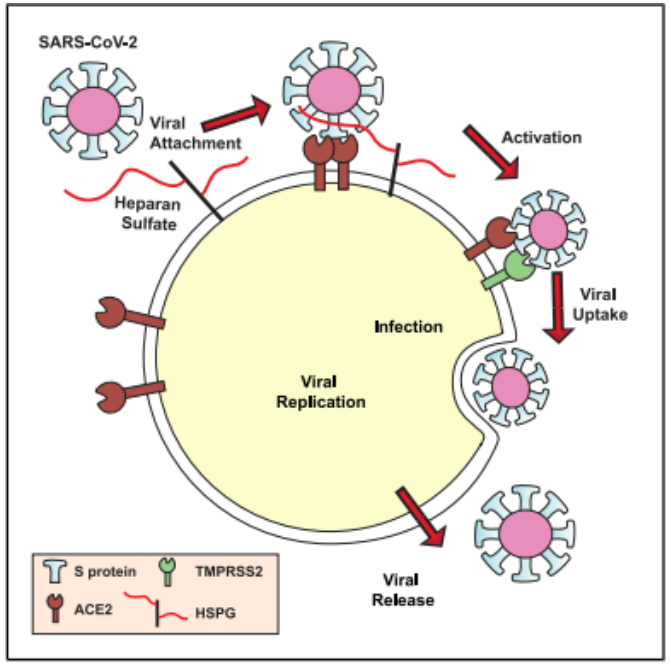
Cell

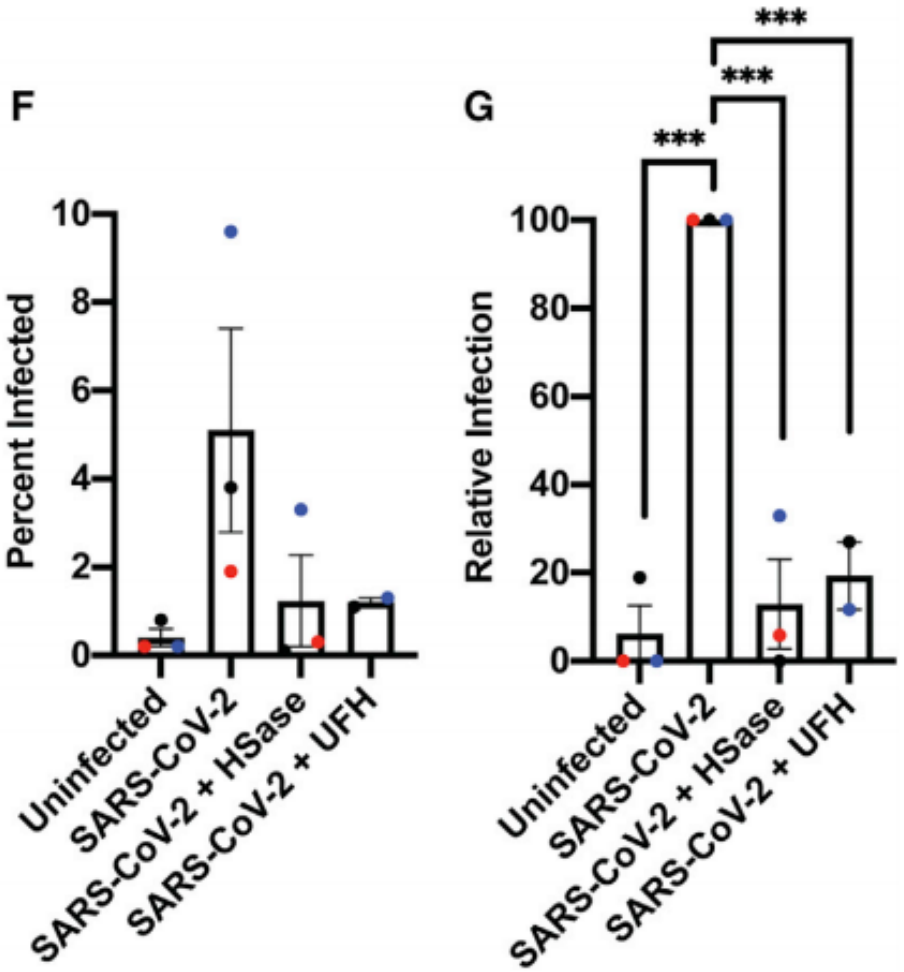
CellPress

Article

SARS-CoV-2 Infection Depends on Cellular Heparan Sulfate and ACE2

Thomas Mandel Clausen,[1,2,18,19,20,*] Daniel R. Sandoval,[1,19] Charlotte B. Spliid,[1,2,18] Jessica Pihl,[1,2,18] Hailee R. Perrett,[3] Chelsea D. Painter,[1,4] Anoop Narayanan,[5] Sydney A. Majowicz,[5] Elizabeth M. Kwong,[6] Rachael N. McVicar,[6] Bryan E. Thacker,[7] Charles A. Glass,[7] Zhang Yang,[8] Jonathan L. Torres,[3] Gregory J. Golden,[1,4] Phillip L. Bartels,[1,17] Ryan N. Porell,[9] Aaron F. Garretson,[10] Logan Laubach,[9] Jared Feldman,[11] Xin Yin,[12] Yuan Pu,[12] Blake M. Hauser,[11] Timothy M. Caradonna,[11] Benjamin P. Kellman,[13,14,15] Cameron Martino,[13,14] Philip L.S.M. Gordts,[10,17] Sumit K. Chanda,[12] Aaron G. Schmidt,[11,16] Kamil Godula,[9,17] Sandra L. Leibel,[14] Joyce Jose,[5] Kevin D. Corbett,[1] Andrew B. Ward,[3] Aaron F. Carlin,[10] and Jeffrey D. Esko[1,17,*]





Where do we go from here?

- Honestly, I don’t know…
- VTE Prophylaxis has a strong evidence-base for critically ill patients and we should continue to use it as we always have
- Despite the above findings, *no* major professional society has changed their recommendations to include therapeutic anticoagulation for non-critically ill hospitalized patients
- If inflammatory markers are climbing and your patient is worsening, it may be reasonable to initiate intermediate dose anticoagulation
- Stay tuned for data about antiplatelet agents, anticoagulation in patients at home, and continuation of anticoagulation upon hospital discharge in ACTIV-4b, 4c, and beyond…