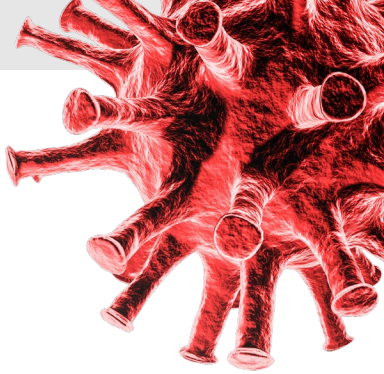

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Antithrombotics in COVID-19 patients: pre- and post-hospitalisation

Jean M Connors MD

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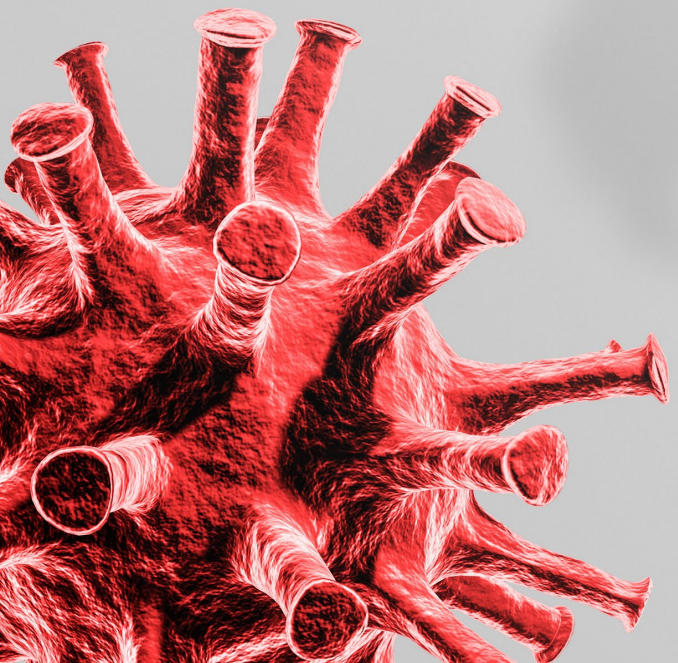
Twitter: @Connors_md



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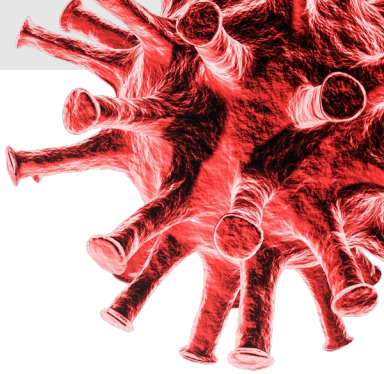

Disclosures

- Scientific advisory boards and consulting:
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  - Anthos
  - Alnylam
  - Bristol-Myers Squibb
  - Portola
  - Takeda
- Research funding to the institution
  - CSL Behring

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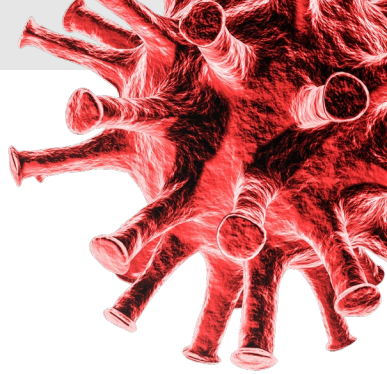
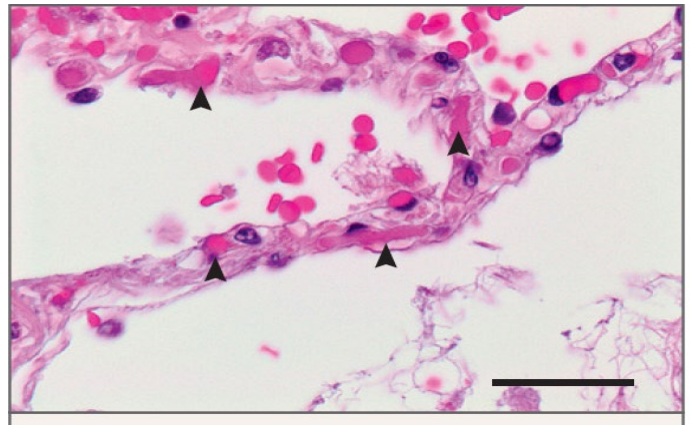
COVID-19-associated coagulopathy and thrombosis



- Early reports from China revealed coagulation test abnormalities
  - Marked increase in D-dimer associated with disease severity and mortality[1]
  - **Thromboinflammation: driving coagulation**
    - COVID-19 is a hypercoagulable state[2]

- **Macrovascular thrombosis**
  - Increased rate of VTE 1st report: **25%** in ICU patients in China[3]
  - Use of VTE prophylaxis dose heparin decreased mortality in patients with 2x ULN elevated D-dimer or high SIC score[4]

- **Microvascular thrombosis**
  - Pulmonary microvascular thrombosis responsible for hypoxemia
  - Endothelialopathy contributes to thrombosis



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ICU, intensive care unit; SIC, sepsis-induced coagulopathy; ULN, upper limits of normal; VTE, venous thromboembolism

1. Ackermann M, *et al. N Engl J Med.* 2020;382(2):120–8; 2. Abou-Ismail MY, *et al. Thromb Res.* 2020; 194:101–115 ;3. Cui S, *et al. J Thromb Haemost.* 2020;18(6):1421–4; 4. Tang N, *et al. J Thromb Haemost.* 2020;18(5):1094–9

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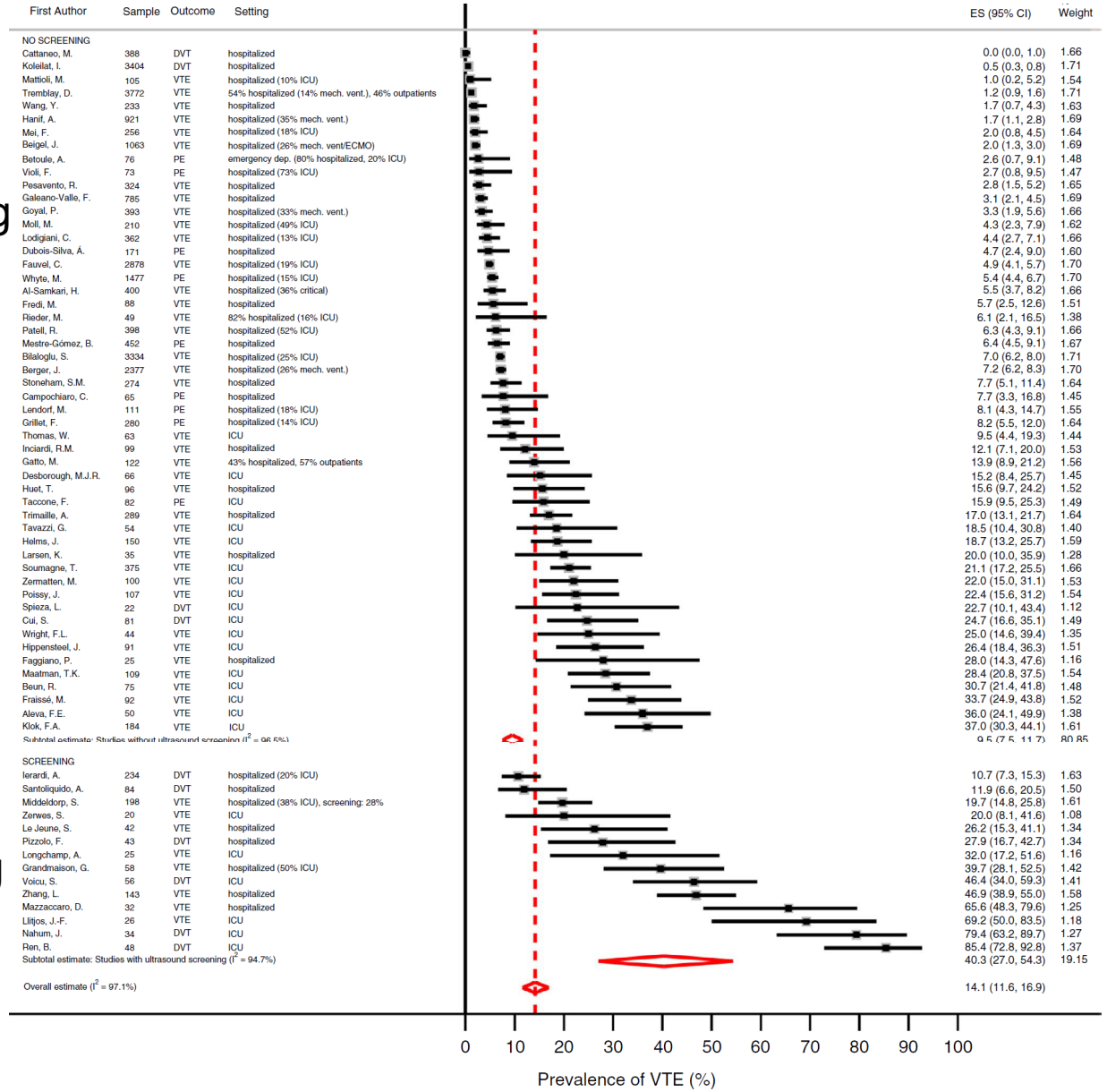
No screening

Yes screening



VTE in COVID-19+

Meta-analysis in hospitalised patients

- **66** studies up to 26 August, 2020

Overall prevalence of VTE

- **9.5%** no screening
- **40%** with screening US

ICU prevalence of VTE

- **18.7%** no screening
- **45.6%** with screening US

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ICU, intensive care unit; US, United States; VTE, venous thromboembolism

Nopp S, *et al. Res Pract Thromb Haemost.* 2020; 4(7):1178–91

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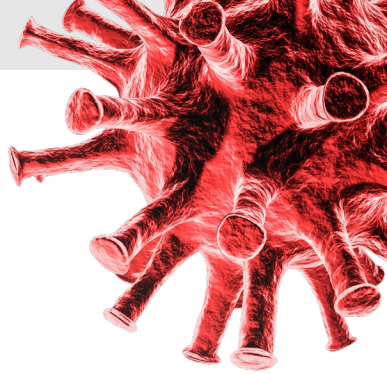

Inpatient versus outpatient data

Hospitalised patients with COVID-19

- Many observational retrospective, single-centre, multicentre and health claims database analyses available very early in the pandemic
- RCT started early, power calculation event rates based on early observed rates in hospitalised populations
- Data now emerging from RCT for inpatients

Outpatients with COVID-19

- Very limited to no data for acutely infected but not admitted to hospital or for post-discharge populations
- Concern for increased thrombosis in these populations
- RCT developed slightly later, event rates often extrapolated from other populations, patients selected based on known factors for increased thrombosis risk
- Trials underway

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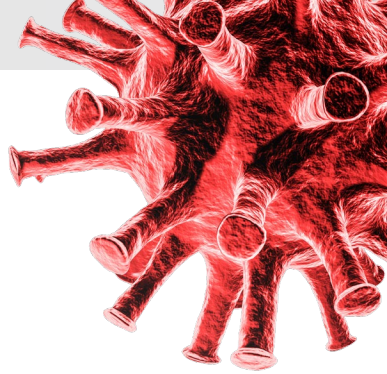
RCT, randomised controlled trial



Thromboprophylaxis trials in COVID-19

PRE-HOSPITAL
COVID+ outpatient

PREVENT-HD
ETHIC
ACTIV-4
NCT04498273
NCT04400799

HOSPITALISED
COVID+ inpatient

HEP COVID
PARTISAN
COVID-HEP
IMPROVE
COVID-PACT*
COVAC-TP
COVI-DOSE
RAPID-BRAZIL
FREEDOM COVID
ANTI-CO*
IMPACT*
INSPIRATION*
HERO-19
ACTION
RAPID COVID COAG**
TOLD

ASPEN
ACTIV-4
COVID-PREVENT
VTE-COVID
ATTACC
X-COVID 19
INHIXACOV19
ACOVACT
CORIMMUNO-COAG
NCT04508439
NCT04466670
NCT04505774
NCT04360824
NCT04359277
NCT04377997
NCT04412304*
NCT04498273

CONVALESCENT
COVID+ discharged

ACTIV-4
COVID-PREVENT
NCT04508439

Trials studying available agents:
- **Heparin (UFH, LMWH)**
- **Factor Xa inhibitor**
- **Direct thrombin inhibitor**
- **Includes antiplatelet**

Novel target: **extrinsic pathway**

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*ICU only; **Floor status only
ICU, intensive care unit; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin

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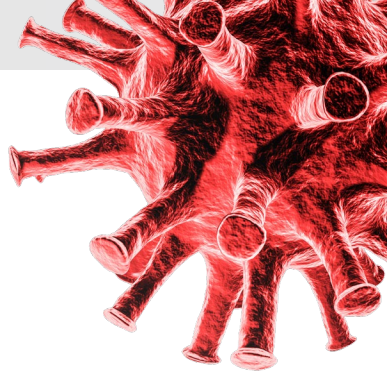

Anticoagulation use in COVID-19 patients

How should we interpret the interim results of ATTACC/ACTIV-4A/ REMAP-CAP?

Is there a **window of opportunity** to intervene with anticoagulation?

What do we expect anticoagulation to achieve?

- Mitigate thrombosis? Decrease morbidity and mortality?

- **Prevent macrovascular** venous and arterial thrombosis
  - Current data show therapeutic/full dose better than standard in ICU patients
- **Prevent** or mitigate **microvascular** thrombosis
  - No effect of therapeutic/full dose on organ support-free days in ICU patient

In those that have developed significant microvascular thrombosis, use of anticoagulants at that point may have limited effect on mortality

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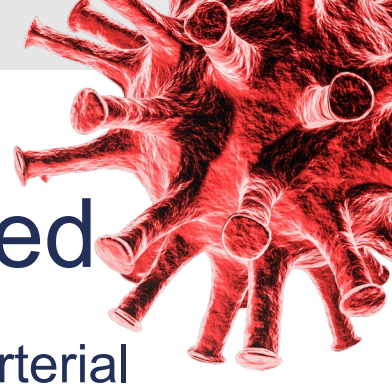
ICU, intensive care unit

Acute SARS-CoV-2 infection but not hospitalised



- COVID-19 results in a hypercoagulable state[1] with increased risk of venous and arterial thrombosis and pulmonary microvascular thrombosis[2]
- Patients newly diagnosed with COVID-19 will develop an **increased inflammatory response**, increasing their risk of thrombotic events[3]
- No data are available to guide care at time of design of the trials
  - No RCT data yet available
- Given recent results of multiplatform trials with regard to severity and timing of anticoagulant intervention, we feel the issue of thrombosis prevention in outpatient COVID-19 is even more important
- Trials for **acutely infected outpatients** that are symptomatic but not admitted to hospital are in progress

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RCT, randomised controlled trial;
SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

1. Abou-Ismail MY, *et al. Thromb Res.* 2020; 194:101–115;
2. Cui S, *et al. J Thromb Haemost.* 2020;18(6):1421–4;
3. Al-Ani F, *et al. Thromb Res.* 2020; 192:152–60

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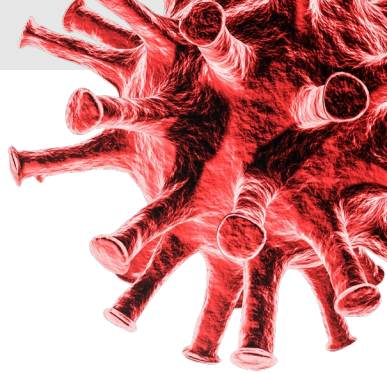
ACTIV-4b: COVID-19 outpatient thrombosis prevention trial



- A multicentre, adaptive, randomised, placebo-controlled platform trial evaluating the efficacy and safety of antithrombotic strategies in COVID-19 adults not requiring hospitalisation at time of diagnosis
- NHLBI/NIH funded trial as part of the ACTIV platform NCT04498273
- Paul Ridker, Trial Chair; Jean Connors, Trial PI

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ACTIV-4
COVID-19 Outpatient Thrombosis Prevention Study

NHLBI, NHI National Heart, Lung, and Blood Institute;
NIH, National Institutes of Health; PI, principal investigator

https://clinicaltrials.gov/ct2/show/NCT04498273 [Last accessed June 2021]

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‘Low Touch’ to ‘No Touch’ trial design

PCR or Ag positive COVID-19
Within last 14 days
Outpatient destination
Age 40–80 years

R

‘Morning Bottle’		‘Evening Bottle’
Placebo	+	Placebo
Aspirin 81 mg	+	Placebo
Apixaban 2.5 mg	+	Apixaban 2.5 mg
Apixaban 5.0 mg	+	Apixaban 5.0 mg

Local site phase
Eligibility
Baseline labs

ENROLLMENT

45 days on treatment

Centralised telemedicine phase
Drug delivered to home

FOLLOW-UP

ACTIV-4
COVID-19 Outpatient Thrombosis Prevention Study

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Ag, antigen; PCR, polymerase chain reaction; R, randomised

https://clinicaltrials.gov/ct2/show/NCT04498273 [Last accessed June 2021]

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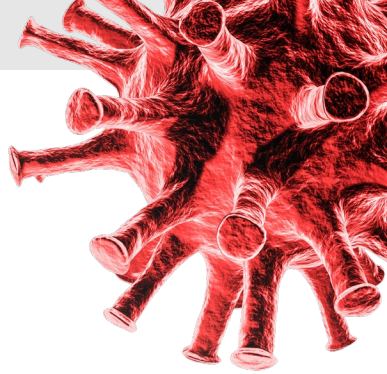

ACTIV-4b outcomes

Primary outcome:

- Composite: symptomatic DVT, PE, arterial thromboembolism, MI, ischaemic stroke, hospitalisation for cardiovascular/pulmonary events, and all-cause mortality

Primary safety endpoint:

- Major bleeding

Sample size:

- 7,000 across four arms based on event rate of 7% in placebo arm, modified intention-to-treat analysis

Will address predictive ability of D-dimer and hsCRP

ACTIV-4
COVID-19 Outpatient Thrombosis Prevention Study

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DVT, deep vein thrombosis; hsCRP, high-sensitivity C-reactive protein; MI, myocardial infarction; PE, pulmonary embolism

https://clinicaltrials.gov/ct2/show/NCT04498273 [Last accessed June 2021]

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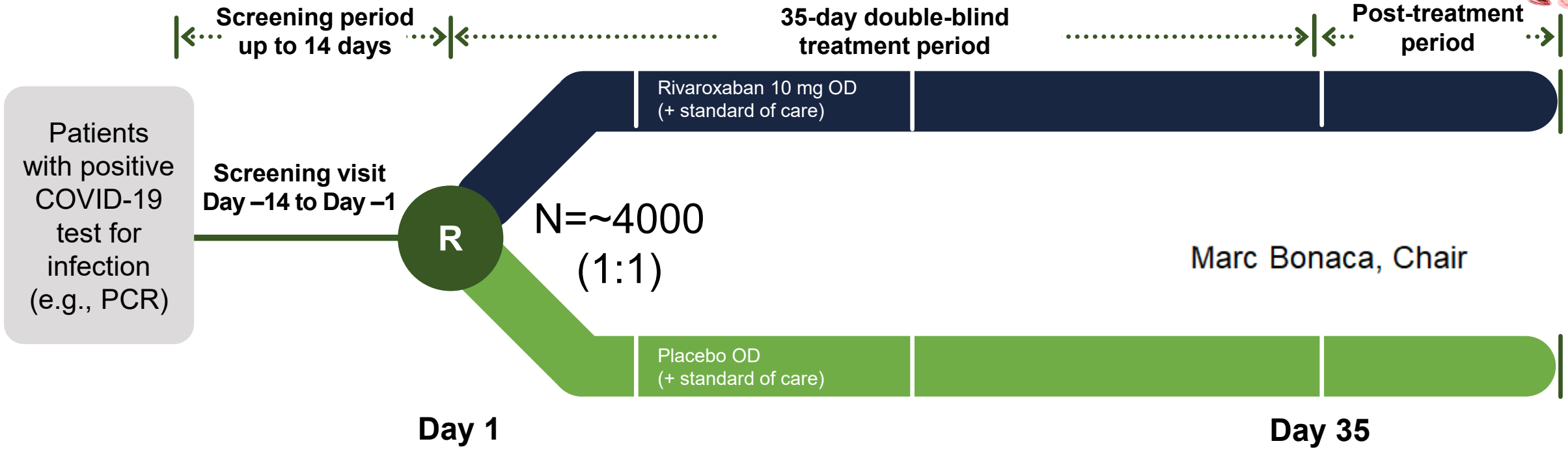
PREVENT-HD

A Study of Rivaroxaban to Reduce the Risk of Major Venous and Arterial Thrombotic Events, Hospitalisation and Death in Medically Ill Outpatients With Acute, Symptomatic COVID-19 Infection



Marc Bonaca, Chair

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At least one risk factor:

- **Age ≥60**
- **Any history of VTE**
- **History of CAD, PAD, cerebrovascular**
- **History of thrombophilia**
- **History of cancer**
- **History of diabetes**
- **History of heart failure**
- **Body mass index ≥35 kg/m^2**
- **D-dimer >ULN**

Primary efficacy endpoint: composite symptomatic VTE, MI, ischaemic stroke, acute limb ischaemia, non-CNS systemic embolism, all-cause hospitalisation, or all-cause mortality up to Day 35

Primary safety: ISTH critical site and fatal bleeding

CAD, coronary artery disease; CNS, central nervous system; ISTH, International Society on Thrombosis and Haemostasis; MI, myocardial infarction; OD, once daily; PAD, peripheral arterial disease; PCR, polymerase chain reaction; R, randomised ULN, upper limits of normal; VTE, venous thromboembolism

https://clinicaltrials.gov/ct2/show/NCT04508023 [Last accessed June 2021]

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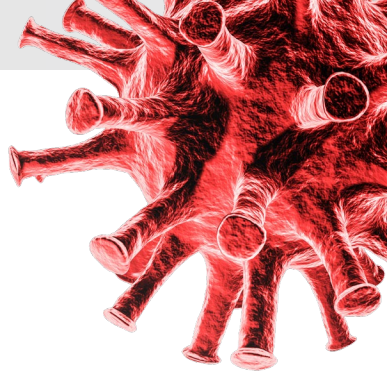

Enoxaparin for primary thromboprophylaxis in ambulatory patients with coronavirus: the multicentre randomised controlled OVID trial

NFP 78 Covid-19 – ID 198352
NCT04400799

Nils Kucher, Stefano Barco, Davide Voci

Zürich, 27 April 2021

MAT-GLB-2101945/(V1.0) June 2021

https://clinicaltrials.gov/ct2/show/NCT04400799 [Last accessed June 2021]

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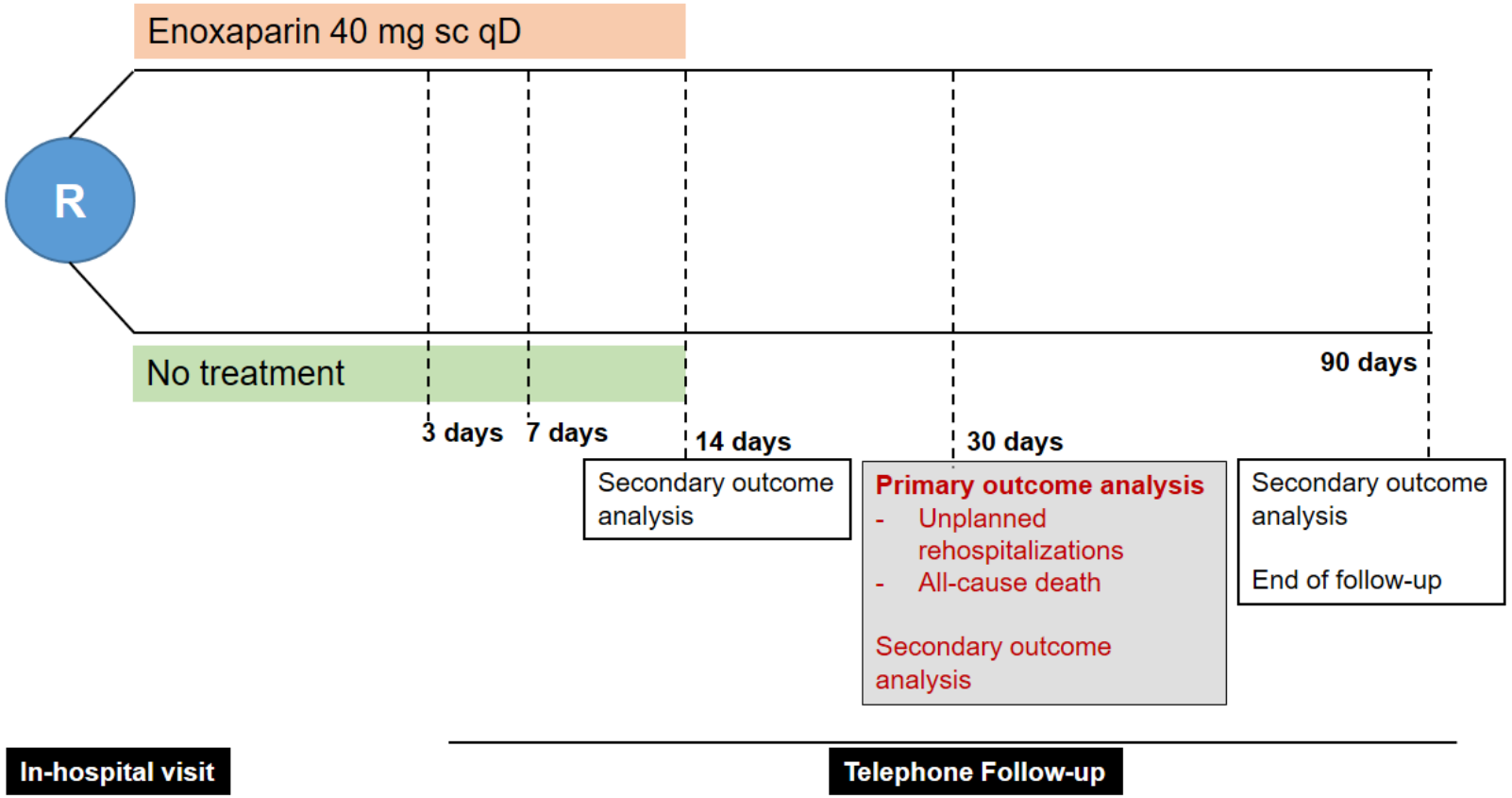
The OVID Phase III trial



N=1,000, expected event rate in placebo group 15%, treatment group 9%

qD, once a day; R, randomized; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; sc, subcutaneous

Kucher N, *et al.* https://clinicaltrials.gov/ct2/show/NCT04400799 [Last accessed June 2021]

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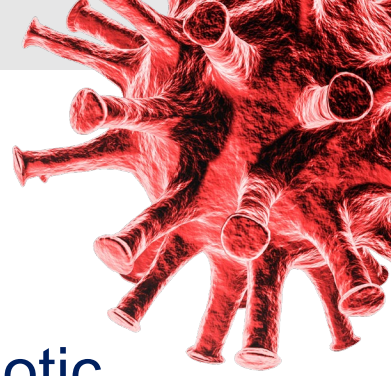

Post-hospitalisation risk of thrombosis

- Inpatients infected with SARS-CoV2 are at increased risk for thrombotic events, which contribute to overall morbidity and mortality[1]
- Anticoagulant therapy is recommended to decrease the risk of thromboembolism in hospitalised patients with COVID-19[2]
- Recent hospitalisation is associated with an increased risk for VTE.[3] The impact of COVID-19 on this increased risk for VTE **after hospital discharge** was unknown at time of trial design
  - No RCT data yet available
- RCTs evaluating the efficacy and safety of antithrombotic strategies COVID-19 following hospital discharge are in progress

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SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; RCT, randomised controlled trial; VTE, venous thromboembolism

1. Malas MB, *et al. EClinicalMedicine.* 2020: doi: 10.1016/j.eclinm.2020.100639 [Epub ahead of print]; 2. Cuker A, *et al. Blood Adv.* 2021; 5(3):872–88; 3. Al-Ani F, *et al. Thromb Res.* 2020;192:152–60

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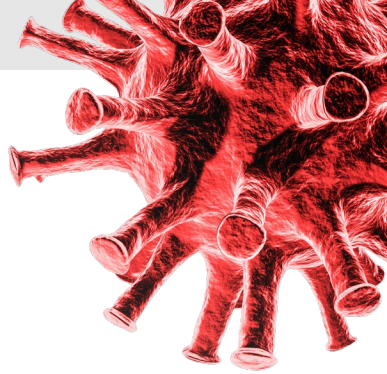
ACTIV 4c: Post-Hospital Thrombosis Prevention Study



Preventing blood clots in patients discharged after being hospitalised with COVID-19

- Thomas L Ortel, Chair
- Alison Morris, Co-chair
- Tracy Y Wang, PI

ClinicalTrials.gov NCT04650087

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ACTIV-4
COVID-19 Outpatient Thrombosis Prevention Study

PI, principal investigator

https://clinicaltrials.gov/ct2/show/NCT04650087 [Last accessed June 2021]

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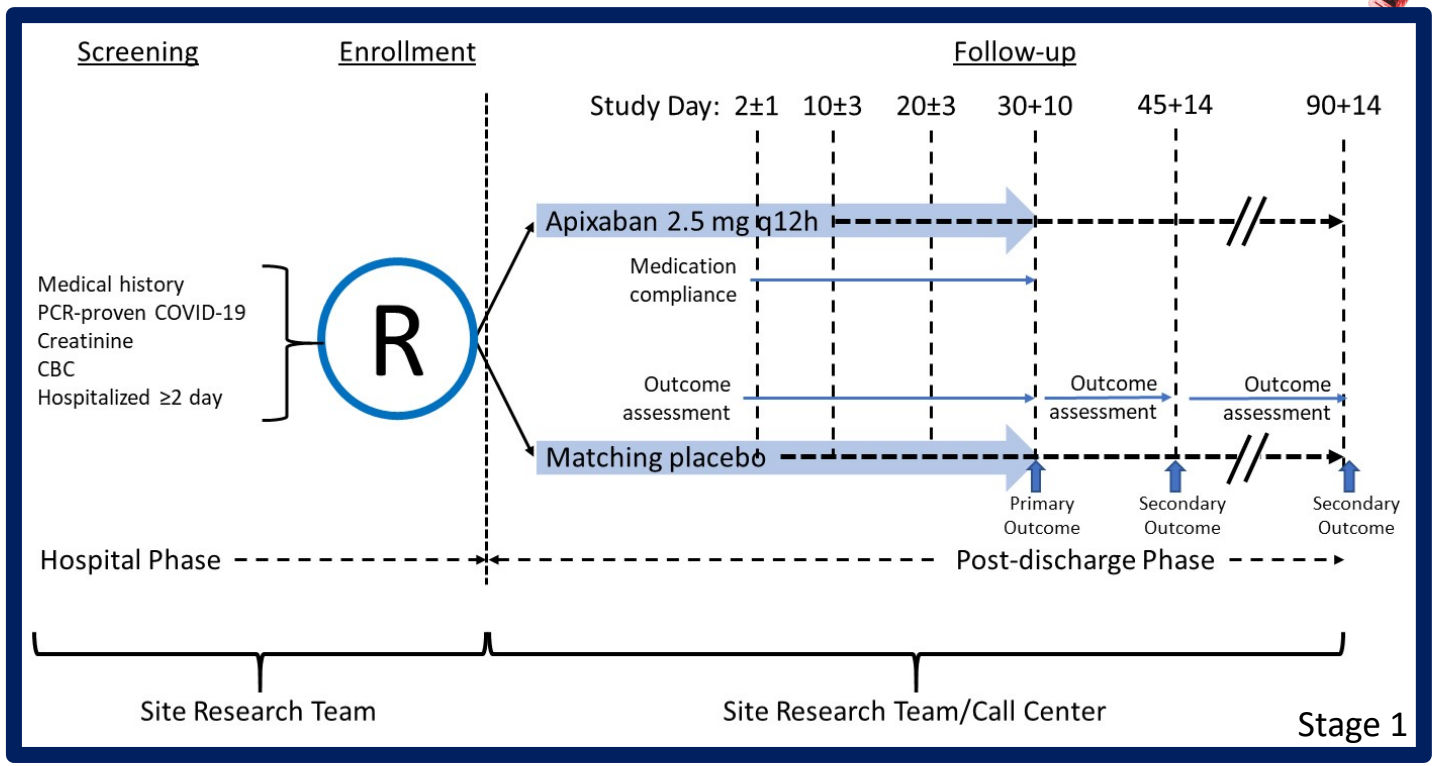
ACTIV 4c: study overview

Target population:

- Adults aged ≥18 with PCR-positive COVID-19 infection
- Hospitalised for at least 2 days
- Exclusions include a **requirement for**, or **contraindication to**, anticoagulation



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ACTIV-4
COVID-19 Outpatient Thrombosis Prevention Study

CBC, complete blood count; PCR, polymerase chain reaction; q12h, every 12 hours; R, randomised

https://clinicaltrials.gov/ct2/show/NCT04650087 [Last accessed June 2021]

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ACTIV 4c: outcomes, endpoints and sample size

- **Primary outcome:** composite endpoint of symptomatic VTE, ischaemic stroke, MI, peripheral arterial thromboembolism and all-cause mortality
- **Primary study endpoint:** incidence of the primary outcome by 30 days after discharge from the hospital
- **Primary safety endpoint:** ISTH-defined major bleeding
- **Sample size:** 5,320 patients, intention-to-treat analysis

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ACTIV-4
COVID-19 Outpatient Thrombosis Prevention Study

ISTH, International Society on Thrombosis and Haemostasis;
MI, myocardial infarction;VTE, venous thromboembolism

https://clinicaltrials.gov/ct2/show/NCT04650087 [Last accessed June 2021]

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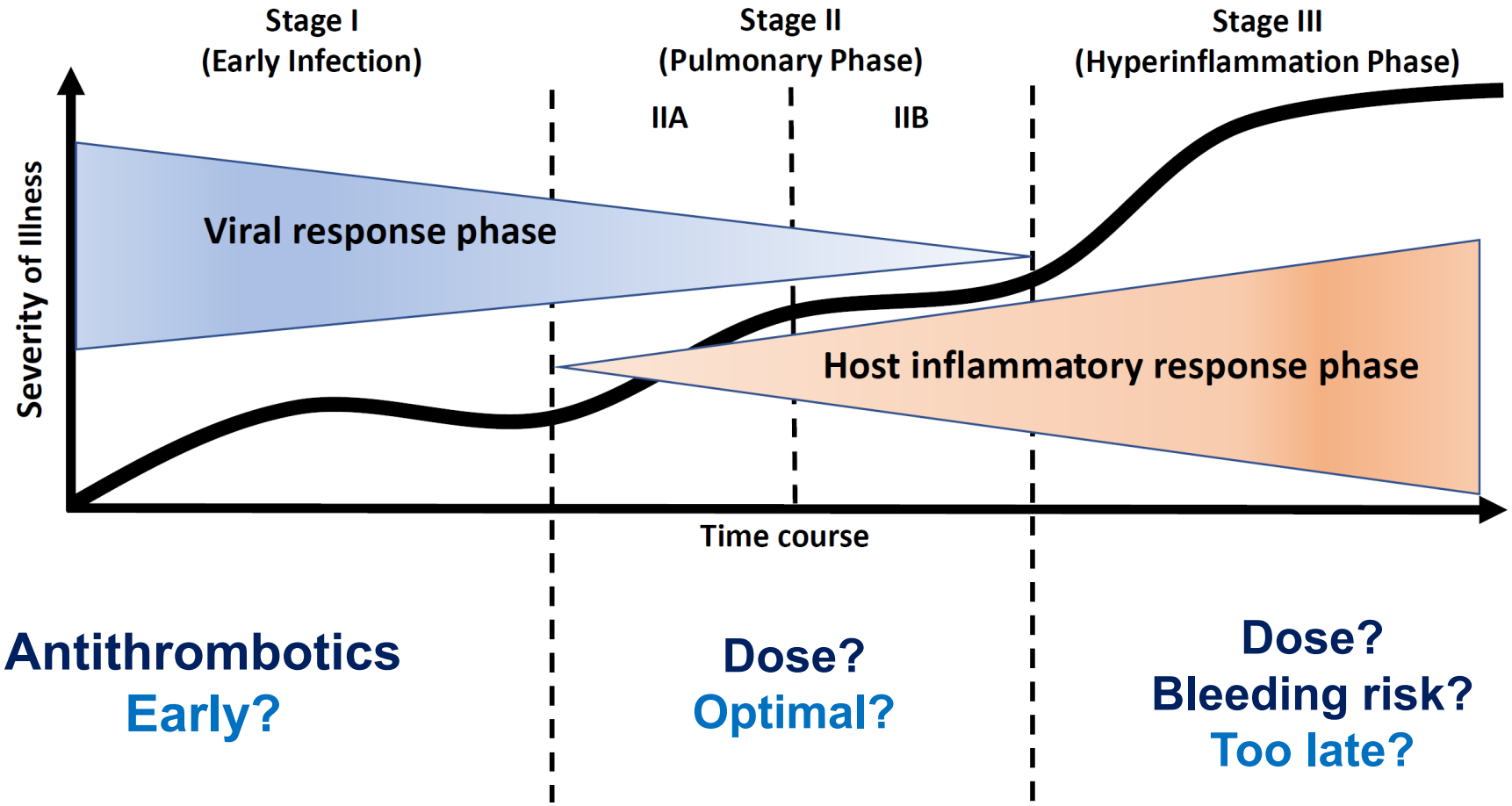
Antithrombotics in relation to stage of COVID-19



Post-hospitalisation

- Increased thrombosis risk
- d/c early
- Continued inflammatory state
- Persistent prothrombotic state

Antithrombotics
Early?

Dose?
Optimal?

Dose?
Bleeding risk?
Too late?

Prevent post-discharge VTE?

Adjust anticoagulation to degree of inflammation and thrombotic risk

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d/c, discontinued; VTE, venous thromboembolism

Siddiqi HK and Mehra MR. *J Heart Lung Transplant.* 2020;39(5):405–7

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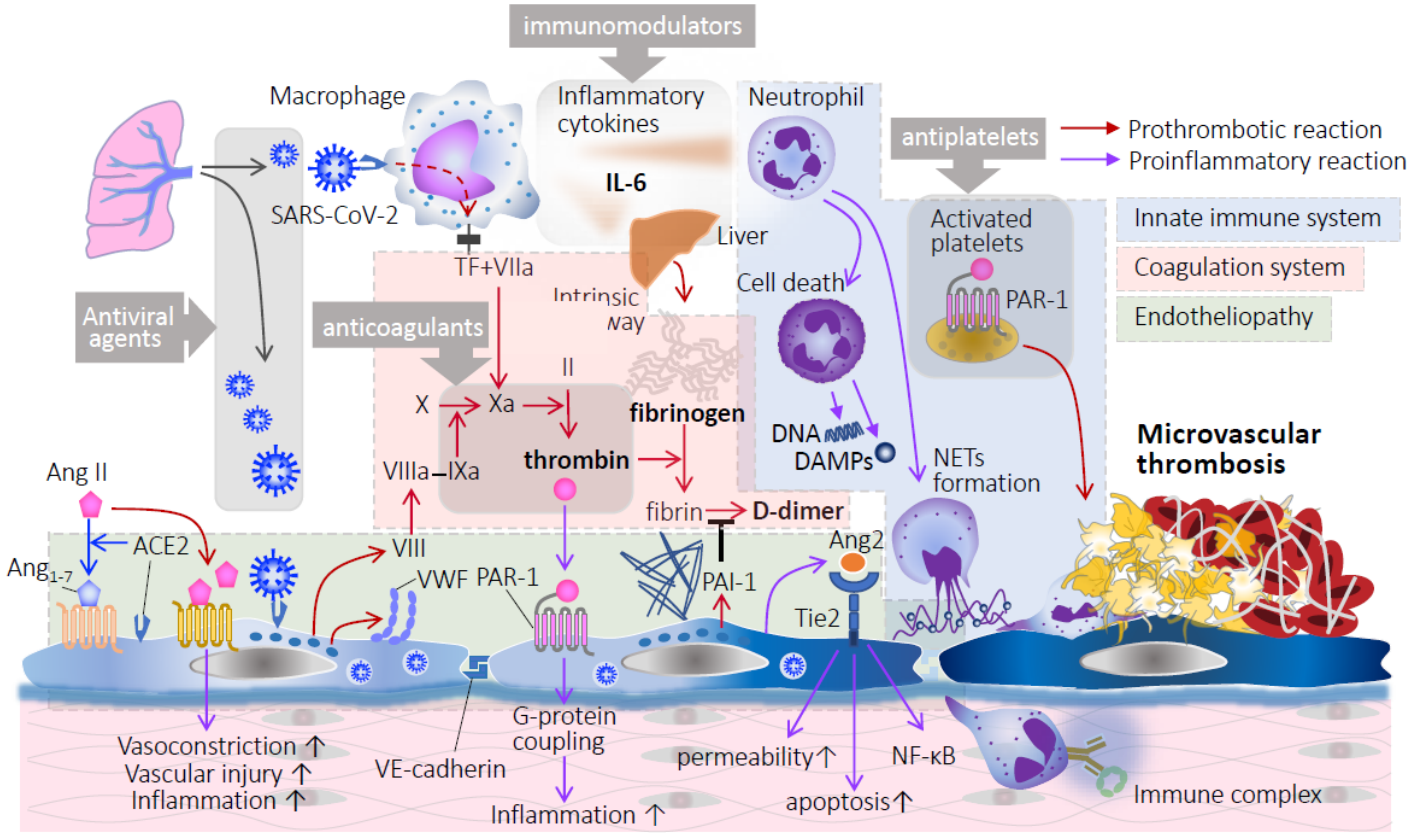
1 year later – more questions?

- Are thrombotic rates lower now with improved COVID-19 care?

- What is the thrombotic risk with COVID-19 variants?

- What is the role of antiplatelet therapy?

- Anticoagulation **alone** may not ameliorate the thromboinflammation that results from COVID-19



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ACE2, angiotensin-converting enzyme 2; Ang II, angiotensin II; Ang2, angiopoietin 2; DAMP, damage-associated molecular pattern; IL-6, interleukin 6; NET, neutrophil extracellular trap; PAR-1, protease-activated receptor 1; TF, transcription factor; VWF, von Willebrand factor

Connors JM, *et al. Clin Infect Dis.* 2021; doi: 10.1093/cid/ciab096 [Epub ahead of print]

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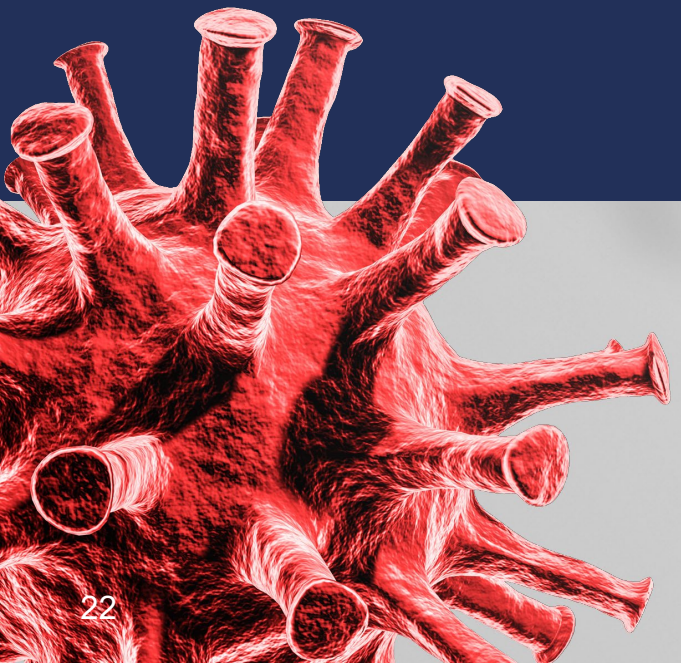
BRIGHAM HEALTH

BWH BRIGHAM AND WOMEN'S HOSPITAL

Thank you



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