Clinical Trials for Vascular Complications of COVID-19: An Overview

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Disclosures

Research grants to CPC Clinical Research from Amgen, Bayer, Janssen, Merck, and Arca Biopharma

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Overview

- **Background**
- **Clinical Trial Framework**
  - **Trial setting**
  - **Study population**
  - **Therapeutic intervention**
  - **Outcomes**
  - **Operational challenges**
- **Example trials**
- **Conclusions**

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Thrombosis plays a major role in COVID-19

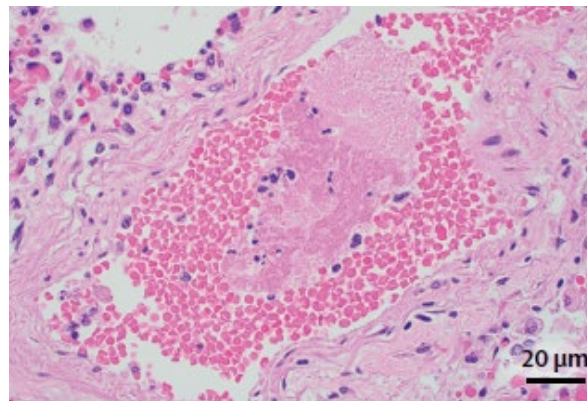**Incidence of Thrombotic Events in Hospitalized Patients with COVID-19 in a NYC Health System**

	PE	DVT	Stroke	MI	Other thromboembolism[a]	Any thrombotic event[b]	No thrombotic event
All hospitalized patients (ICU and non-ICU) (n = 3334)							
Events, No. (%)	106 (3.2)	129 (3.9)	54 (1.6)	298 (8.9)	32 (1.0)	533 (16.0)	2801 (84.0)
All-cause mortality, No. (%)[c]	40 (37.7)	36 (27.9)	20 (37)	153 (51.3)	11 (34.4)	230 (43.2)	587 (21.0)

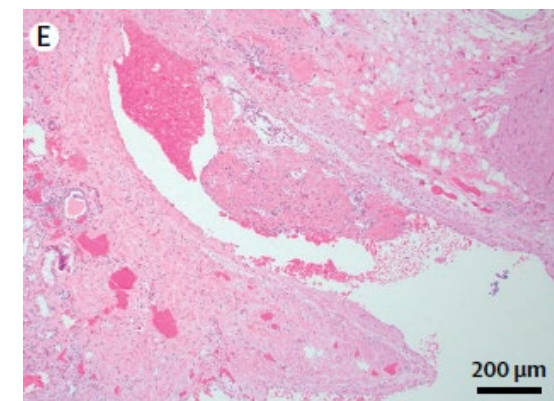**Thrombotic events detected in 31% of 184 Dutch COVID-19 ICU patients**
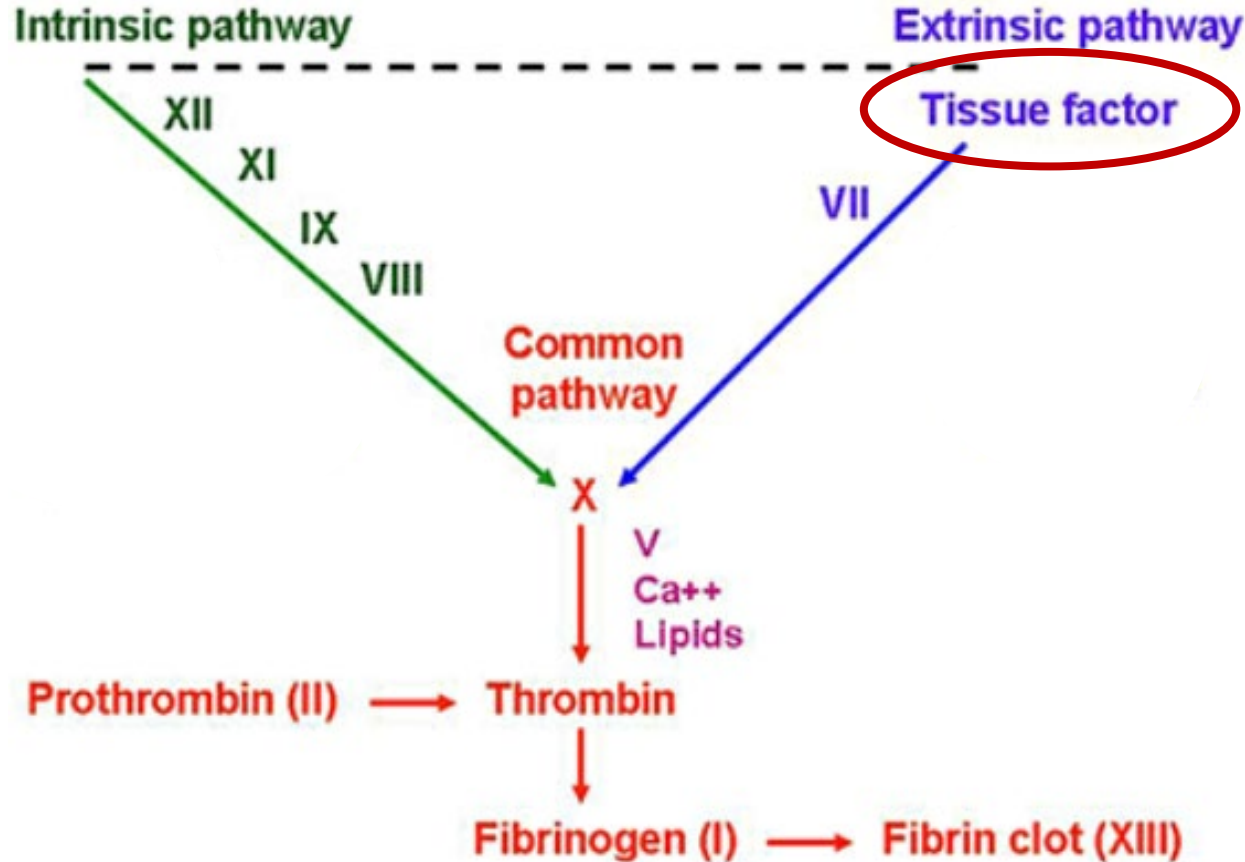
Subsegmental pulmonary embolism

Pulmonary microthrombus

Renal vein organizing thrombus

Bilaloglu S et al JAMA 2020
Klok FA, et al. Thromb Res 2020
Bradley BT, et al. Lancet 2020

Role of Tissue Factor in COVID-19

- A major activator of the coagulation cascade during viral infection

- Incorporation into viral envelope may lead to dysregulation of coagulation cascade

- Plays a central role in inflammatory signaling and dysregulated immunity related to viral infections

- Enhances viral dissemination

Heparin associated with reduced mortality in severe COVID-19

Retrospective analysis of 449 patients

Tang N, et al. J Thromb Haemost 2020;18:1094-1099
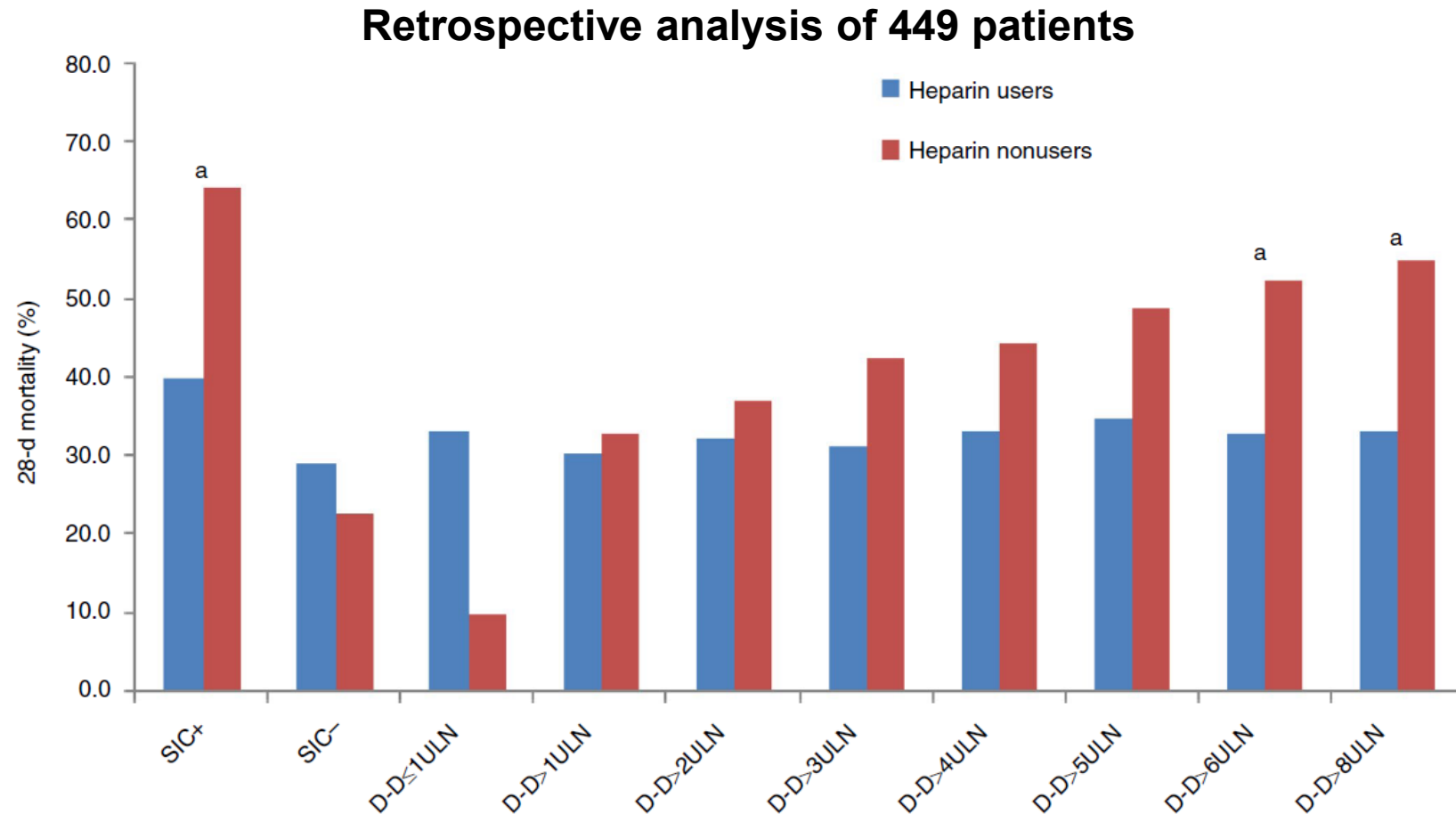
Society Thromboprophylaxis Recommendations* for Hospitalized COVID-19 Patients

Patient population	ISTH	Anticoagulation Forum	ACC	ASH
Non-ICU hospitalized COVID-19	• Prophylaxis recommended (LMWH>UFH) • Intermediate dose "can be considered" • Therapeutic AC not recommended	• Prophylaxis recommended • Therapeutic AC not recommended	• Prophylaxis recommended • Intermediate dose "can be considered" • Therapeutic AC not recommended	• Prophylaxis recommended (LMWH>UFH) • Therapeutic AC not recommended

ICU hospitalized COVID-19	• Prophylaxis recommended (LMWH>UFH)
	
	• Intermediate dose "can be considered"
	
	• Therapeutic AC not recommended
		• Intermediate dose VTE prophylaxis
		  ○ Enoxaparin 40 mg SC bid or 0.5 mg/kg SC bid
		  ○ Heparin 7500 U SC TID
		  ○ Low-intensity heparin gtt
		
		• Therapeutic AC not recommended
			• Prophylaxis recommended
			
			• Intermediate dose "can be considered"
			
			• Therapeutic AC not recommended
				• Prophylaxis recommended (LMWH>UFH)
				
				• Therapeutic AC not
				• recommended

Additional considerations		• Recommend against using biomarker thresholds (e.g. d-dimer) to trigger escalations in anticoagulation • Recommend anti-Xa assay over aPTT		• Reasonable to increase intensity of anticoagulation or to switch anticoagulants in setting of recurrent clotting of access devices despite prophylactic anticoagulation

* Recommendations based on expert survey

Spyropoulos AC, et al. J Thromb Haemost 2020
Barnes G, et al. J Thromb Thrombolysis 2020
Bikdeli B, et al. J Am Coll Cardiol 2020

CORIMMUNO-COAG
COVID-PACT
X-COVID 19
FREEDOM COVID
ATTACC
NCT04400799
NCT04508439
NCT04466670
COVI-DOSE
ACTION
IMPROVE
ANTI-CO
IMPACT
COVAC-TP
PREVENT HD
COVID-PREVENT
INSPIRATION
HEP COVID

More than 30 trials of thromboprophylaxis in COVID-19 ongoing or planned

NCT04505774
ETHIC
TOLD
ACTIV-4
ASPEN
PARTISAN
VTE-COVID
NCT04359277
NCT04498273
NCT04360824
COVID-HEP
RAPID-BRAZIL
ACOVACT
HERO-19
INHIXACOV19

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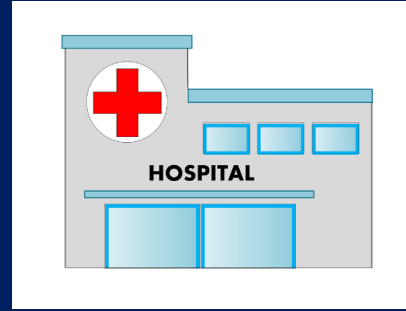- **Example trials**
- **Conclusions**

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Trial Setting

PRE-HOSPITAL	HOSPITALIZED	CONVALESCENT
COVID+ Outpatient	**COVID+** Inpatient	**COVID+** Discharged

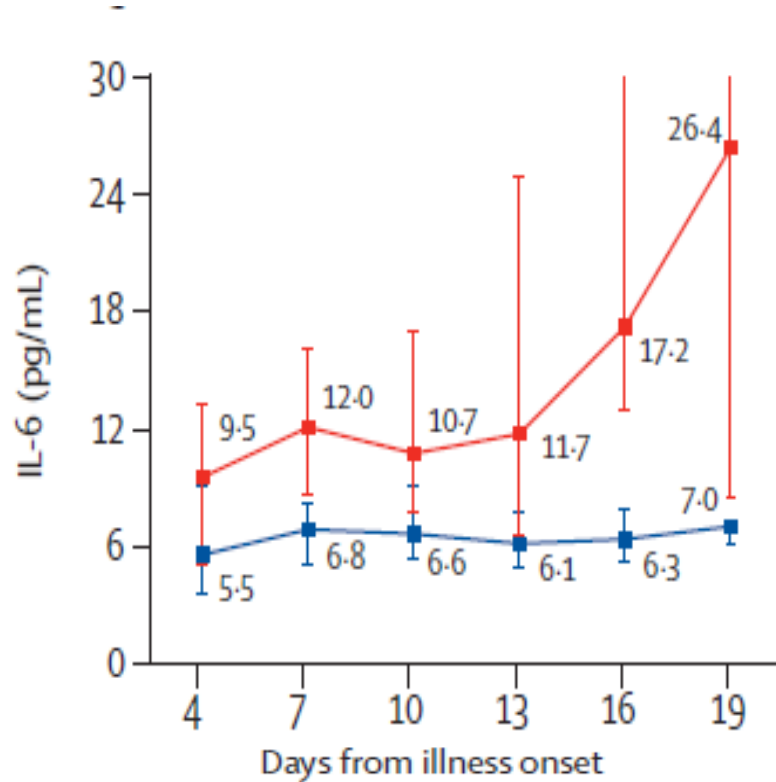| PRE-HOSPITAL	HOSPITALIZED		CONVALESCENT
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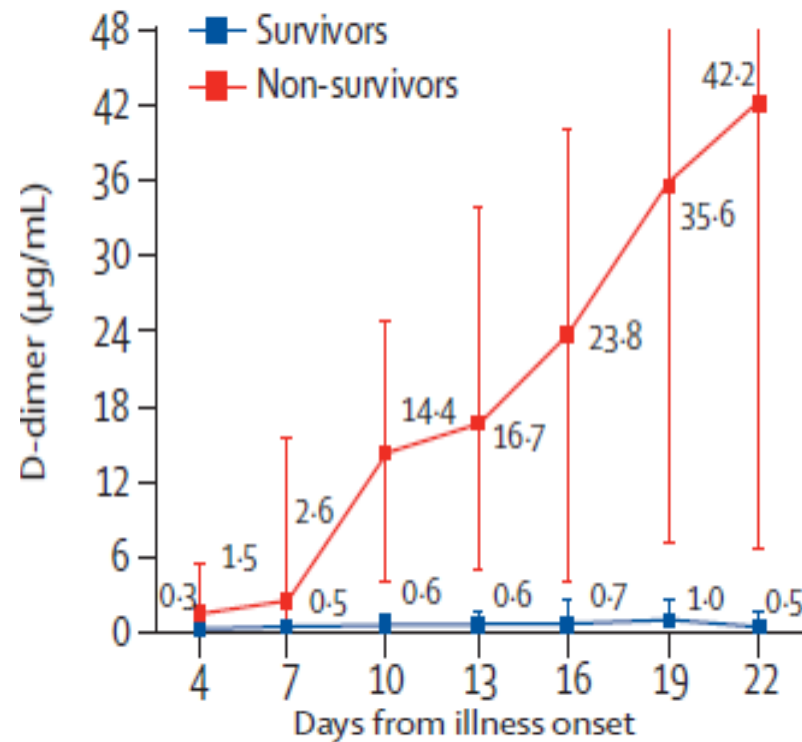- **Example trials**
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Predictors of Mortality in COVID-19

191 patients in Wuhan, China

Zhou F et al, *Lancet* 2020; 395: 1054–62
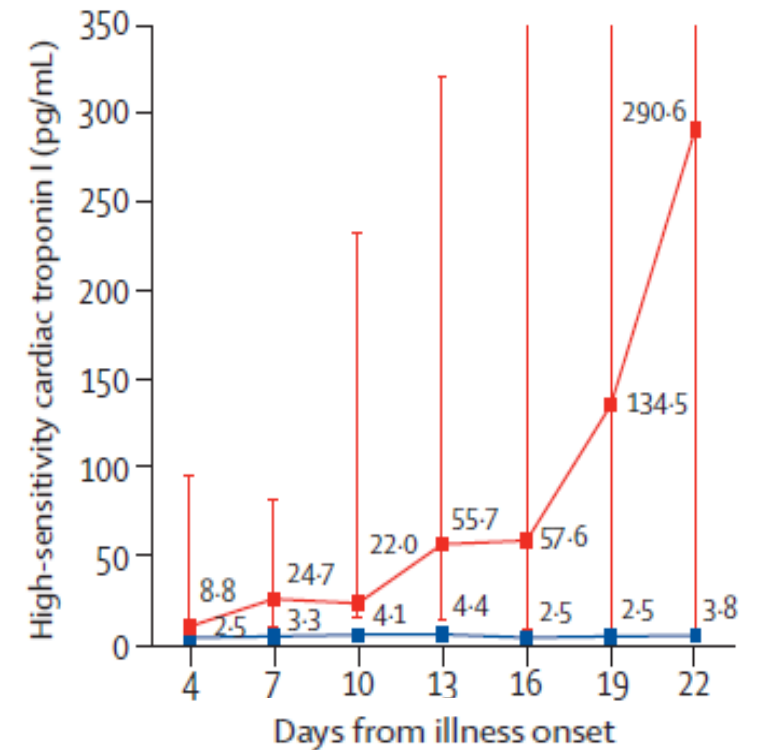
D-dimer predicts mortality in critically ill COVID-19

639 ICU COVID-19 patients in Europe

HR 2.71 (95% CI 1.56 - 4.73)

Wendel Garcia PD, et al. EclinicalMedicine 2020
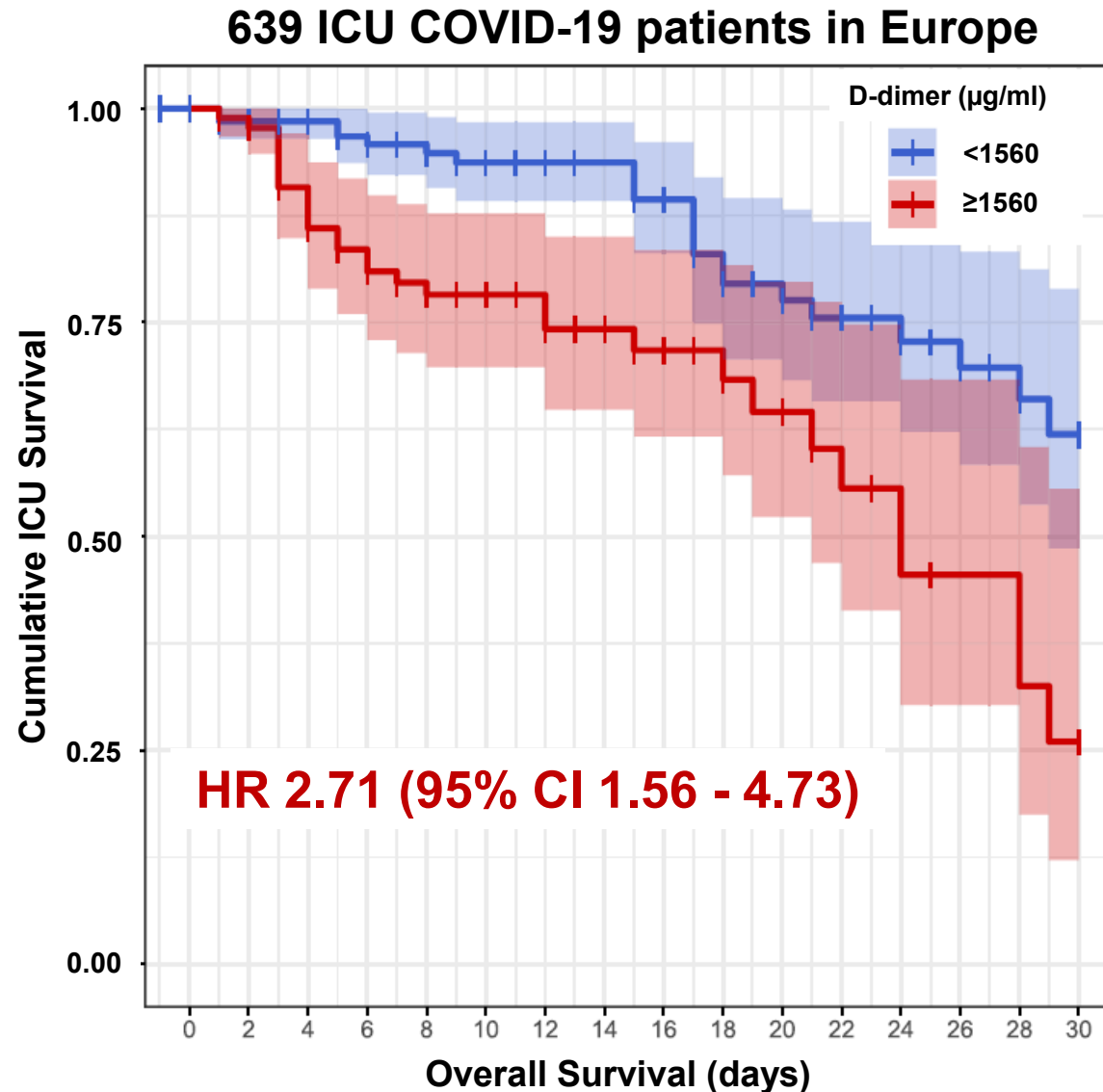
Thrombosis Risk Scores in Hospitalized Patients

Padua

Conditions	Score
Active Cancer	+3
Previous VTE (excluding superficial vein thrombosis)	+3
Reduced Mobility	+3
Already known thrombophilic condition	+3
Recent (≤1 month) trauma and/or surgery	+2
Elderly Age (≥70 years)	+1
Heart and/or respiratory failure	+1
Acute MI and/or Ischemic Stroke	+1
Acute infection and/or rheumatologic disorder	+1
Obesity (BMI ≥30)	+1
Ongoing hormonal treatment	+1

IMPROVE

Table 6—Adjusted Cox Associative Model for 3-Month VTE and Points Assigned to Each Patient Characteristic (N = 15,125)

Patient Characteristic	HR (95% CI)	χ^2	P Value	Points
Previous VTE[a]	4.7 (3.0-7.2)	48	<.001	3
Known thrombophilia	3.5 (1.1-11)	5.2	.04	2
Current lower-limb paralysis	3.0 (1.6-5.7)	11	.001	2
Current cancer	2.8 (1.9-4.2)	27	<.001	2
Immobilized ≥7 d[b]	1.9 (1.3-2.7)	11	.001	1
ICU/CCU stay	1.8 (1.1-2.9)	6.1	.01	1
Age >60 y	1.7 (1.1-2.6)	6.3	.01	1

SIC

Table 3 Scoring for the diagnosis of sepsis-induced coagulopathy

Category	Parameter	0 point	1 point	2 points
Prothrombin time	PT-INR	≤1.2	>1.2	>1.4
Coagulation	Platelet count (×10^9/L)	≥150	<150	<100
Total SOFA	SOFA four items	0	1	≥2

SOFA, Sequential Organ Failure Assessment

Barbar S et al. J Thromb and Haemost 2010
Spyropoulos AC et al. CHEST 2011
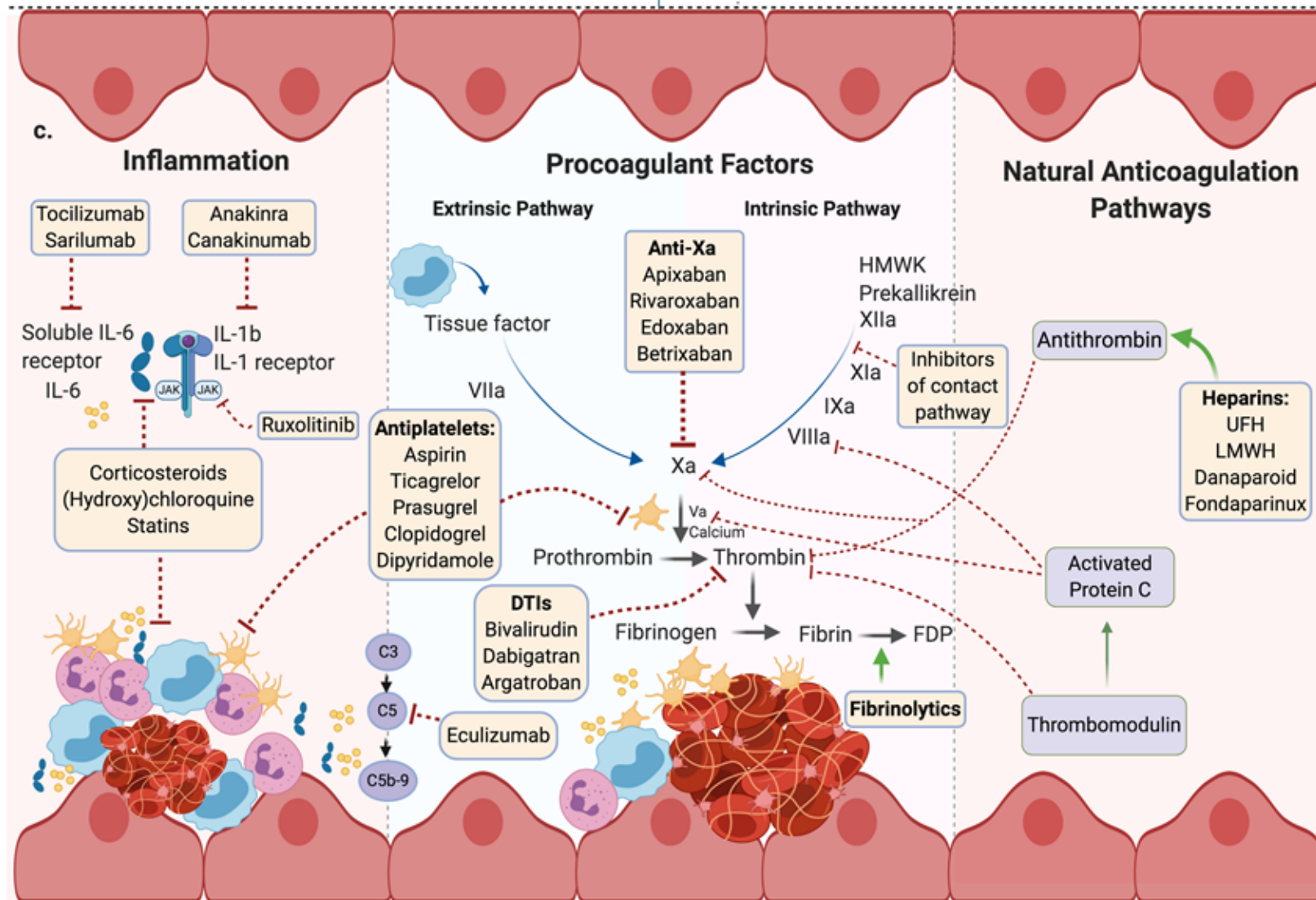Iba T et al BMJ Open 2017

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COVID-19 Disease Progression
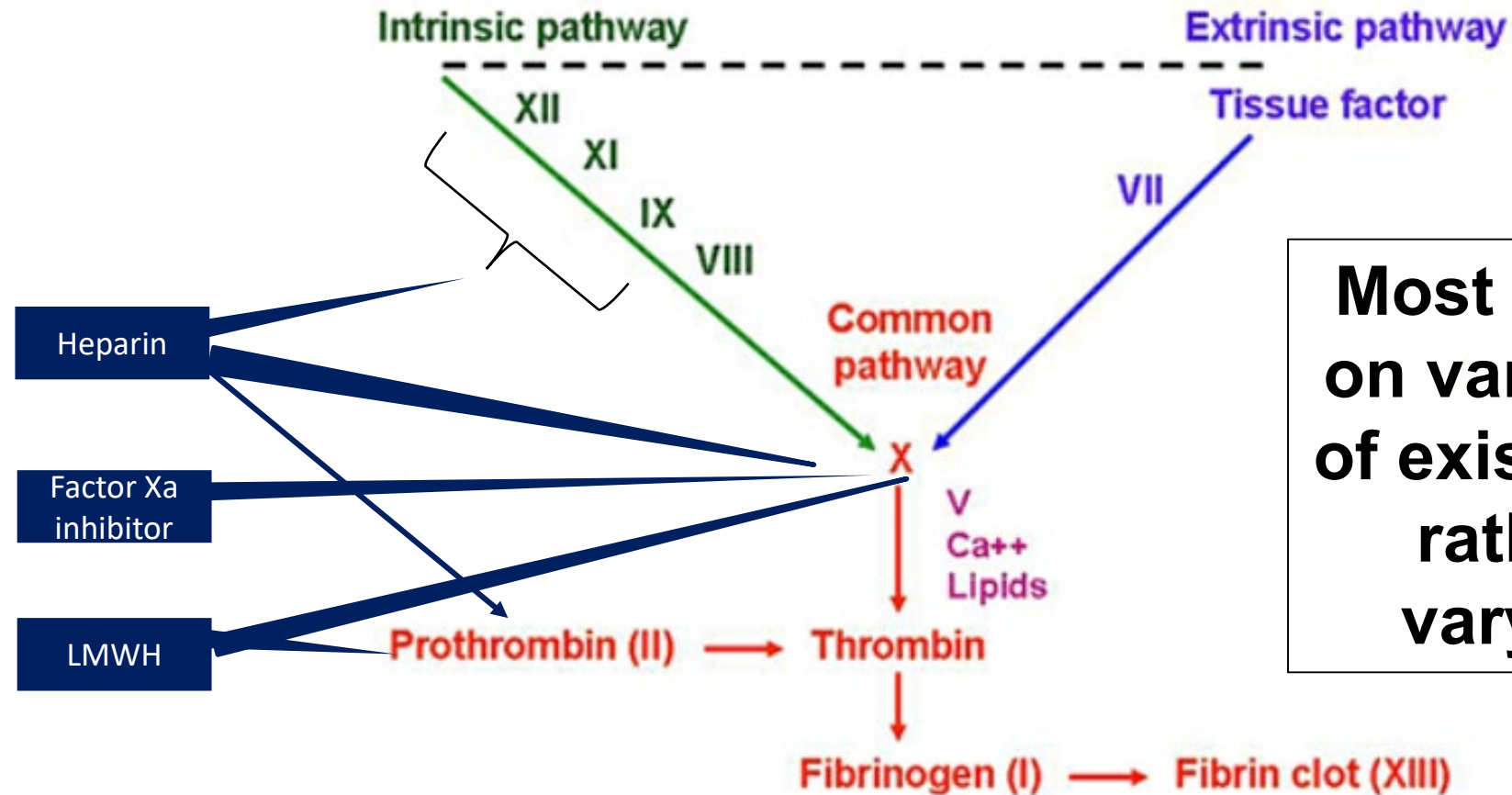

Siddiqu HK and Mehra MR. J Heart and Lung Transplant 2020
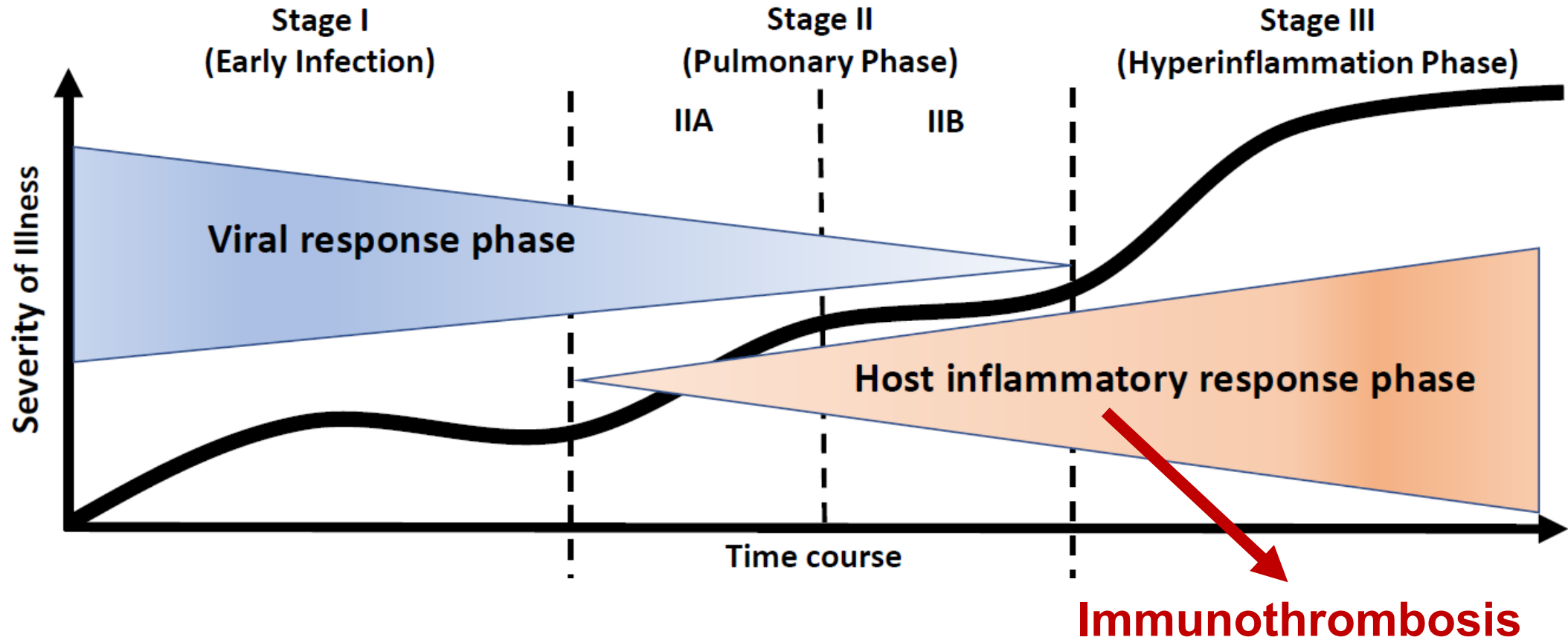
Thromboprophylaxis in COVID-19

Study Intervention: Target vs. Intensity

Most trials focused on varying **intensity** of existing therapies rather than on varying **targets**
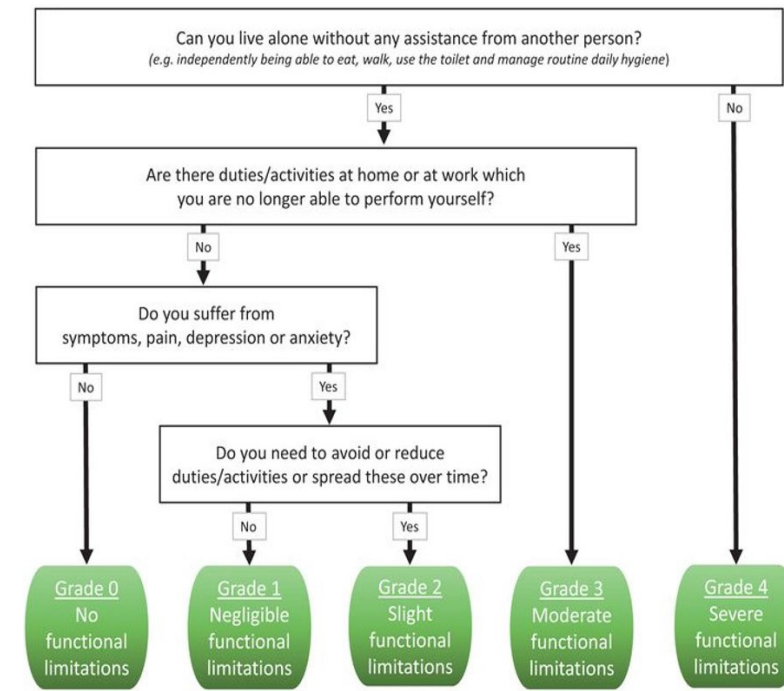
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Outcomes

- **Efficacy**
  - **Clinical endpoints**
  - **Novel endpoints**
- **Safety**

Post-COVID-19 Functional Status (PCFS)

Adaptive COVID-19 Treatment Trial (ACTT) Scale

1. Death
2. Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation
3. Hospitalized, on non-invasive ventilation or high flow oxygen devices
4. Hospitalized, requiring supplemental oxygen
5. Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care
6. Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care
7. Not hospitalized, limitation on activities and/or requiring home oxygen
8. Not hospitalized, no limitations on activities

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Operational Challenges for COVID-19 Trials

- **Informed consent**
- **Drug manufacturing and delivery**
- **Monitoring**
- **Endpoint identification and adjudication**
- **Timelines**
- **Competing studies**

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PREVENT-HD

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

Screening Period Up to 14 days

35 Day Double-Blind Treatment Period

Post Treatment Period

Patients with Positive COVID-19 Test for Infection (e.g., PCR)

Screening Visit Day -14 to Day -1

R

N=~4000 (1:1)

Rivaroxaban 10 mg OD (+ standard of care)

Placebo OD (+ standard of care)

Day 1

Day 35
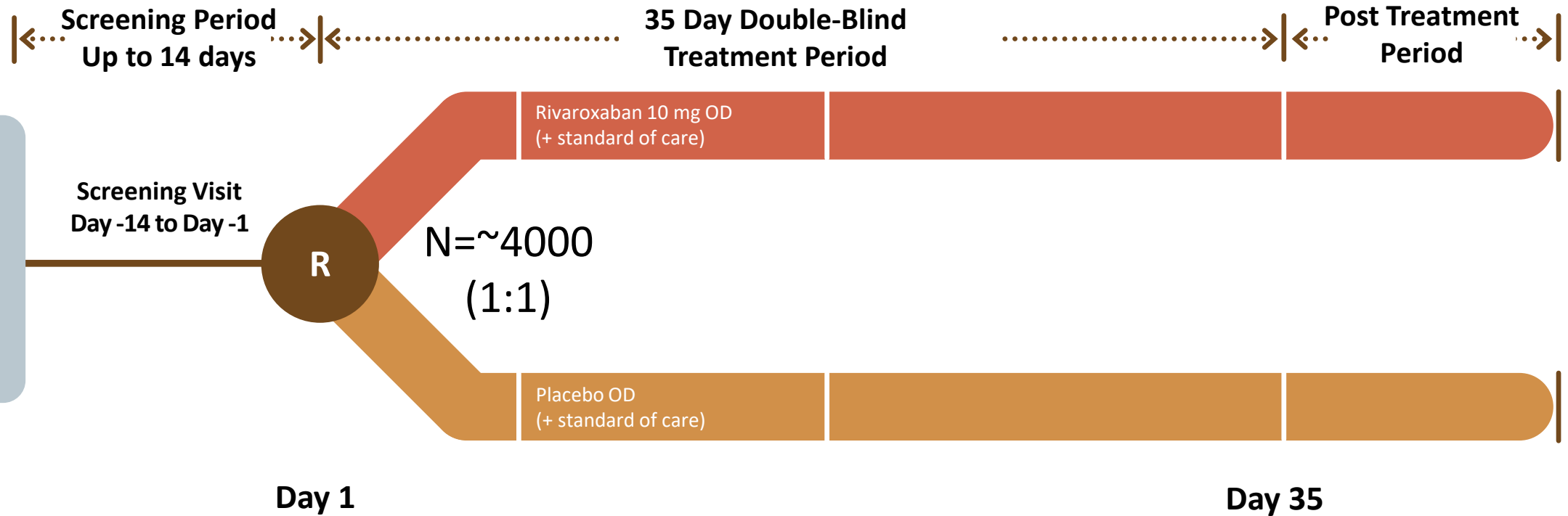
At least one risk factor:

- **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/m2**
- **D-dimer > ULN**

Primary efficacy endpoint: Composite symptomatic VTE, MI, ischemic stroke, acute limb ischemia, non-CNS systemic embolism, all-cause hospitalization, or all-cause mortality up to Day 35

Primary safety: ISTH critical site and fatal bleeding

Trial Setting

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HEP-COVID Trial

Systemic Anticoagulation With Full Dose Low Molecular Weight Heparin (LMWH) vs. Prophylactic or Intermediate Dose LMWH in High Risk COVID-19 Patients

Screening Phase Up to 72hrs

Open-label Treatment Phase
In-Hospital

Post-treatment Phase

Inclusion criteria:
1. Age ≥ 18 yrs
2. COVID-19 positive
3. Hospitalized with RR >20 or resting O2 sat < 92%
4. DD > 6 X ULN OR SIC score ≥ 4

Randomization*

Stratum 1 Subjects in ICU
→ Enoxaparin 1mg/kg SQ BID
→ SOC Px or intermediate dose heparin

Stratum 2 Subjects not in ICU
→ Enoxaparin 1mg/kg SQ BID
→ SOC Px or intermediate dose heparin

Day 30 follow-up

Primary Efficacy Endpoint: Composite of total venous thromboembolism, arterial thromboembolism, all-cause mortality on Day 30 ± 2

Key Secondary Efficacy Endpoint: Primary efficacy endpoint at Day 10 + 4

Other Secondary Efficacy Endpoints: Progression to ARDS, need for intubation, rehospitalization on Day 30 ± 2

Principal Safety Endpoint: Major Bleeding (ISTH Definition) on Day 30 ± 2

Sample size: 308 with event rate in control of 42%, RRR of 40%, power of 80% and 2-sided alpha 5%

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Recombinant Nematode Anticoagulant Protein c2 (rNAPc2)

- **Small recombinant protein cloned from hookworm**

- **Potent, long-acting inhibitor of tissue factor**

- **Anticoagulant activity, safety, and PK established from clinical trials in 700+ patients**
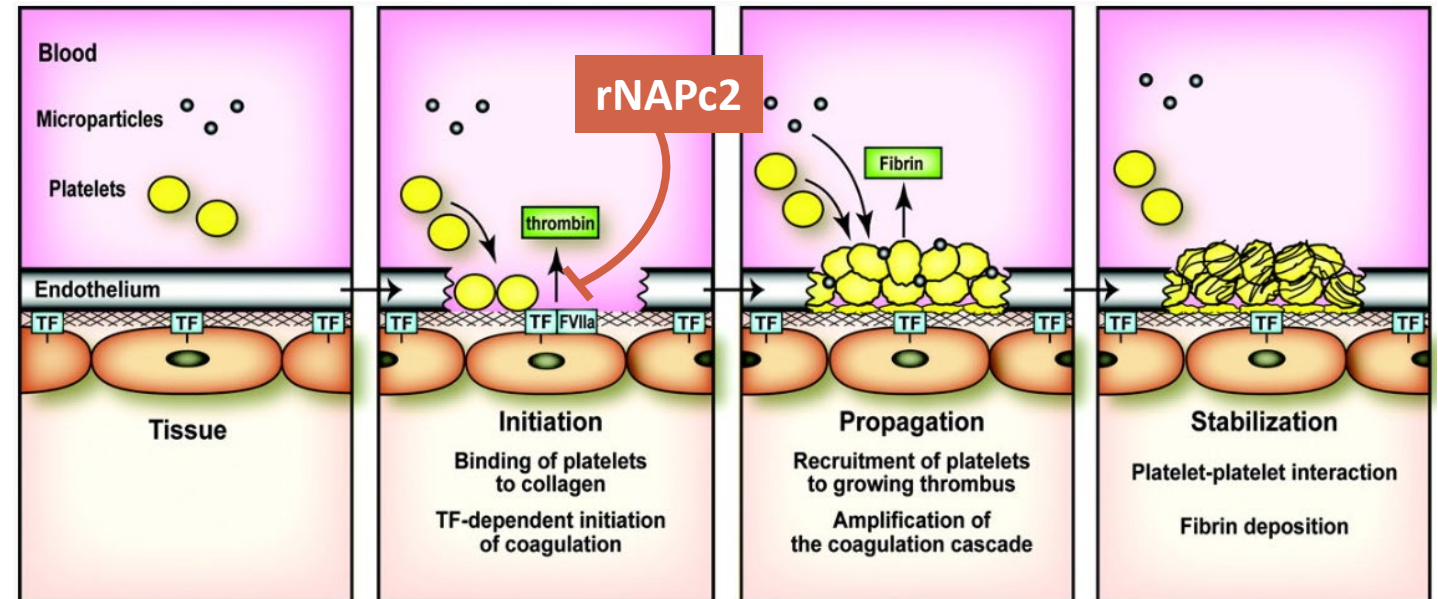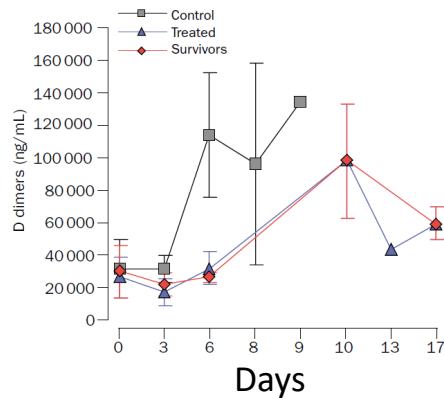

rNAPc2 inhibits Tissue Factor at the initiation phase of coagulation
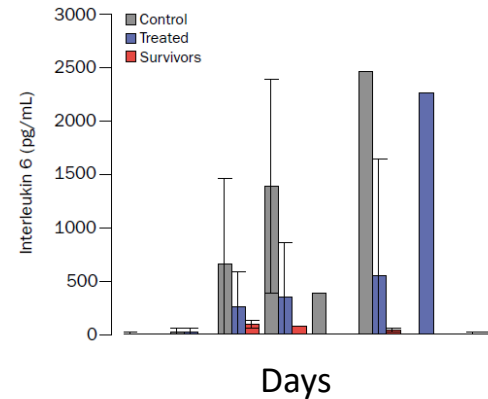
rNAPc2 Targets More Than Coagulation

rNAPc2 lowers D-dimer and inflammation and improves survival in Ebola-infected non-human primates

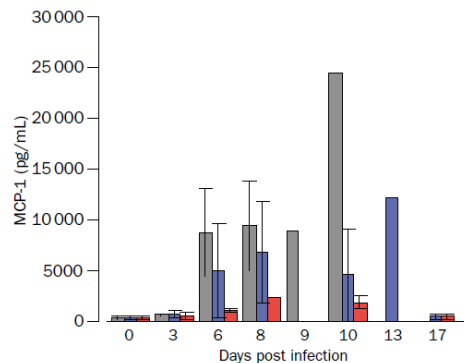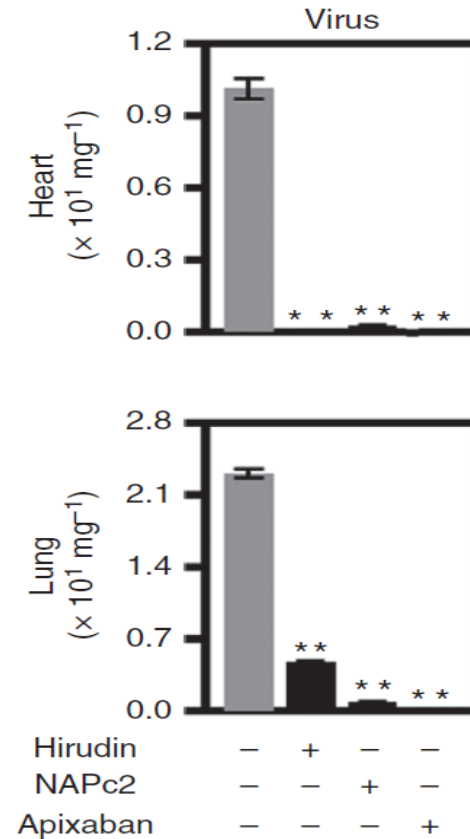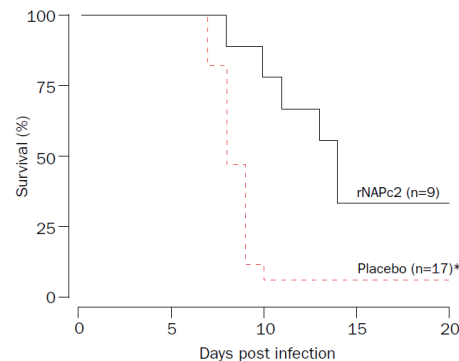**rNAPc2 reduces viral load in mice inoculated with HSV1**

rNAPc2
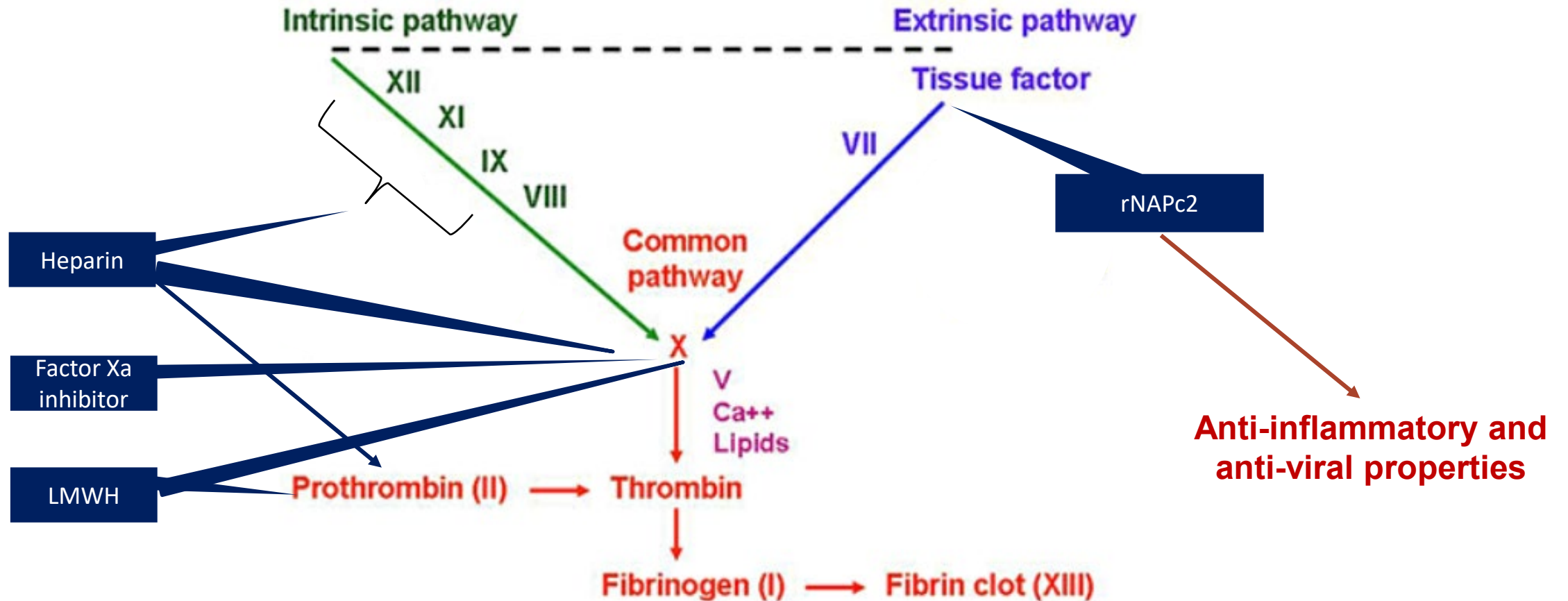
ASPEN-COVID-19
Assessing Safety and Efficacy of rNAPc2 in COVID-19

Phase 2b

Screening up to 7d

Inclusion
Inclusion • SARS-CoV-2 positive • D-dimer > ULN

R

rNAPc2 lower dose, n=25

rNAPc2 higher dose, n=25

Heparin SOC, n=50

30d follow up

Endpoints
1° efficacy: ΔD-dimer (baseline to day 8)
2° efficacy: coagulation and inflammatory biomarkers
Other exploratory EPs
1° safety: clinically relevant bleeding
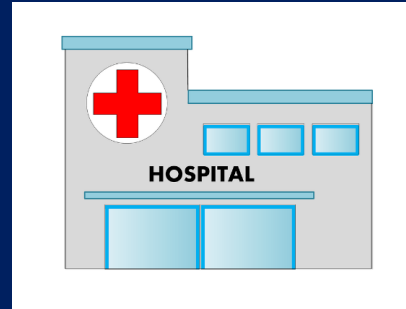
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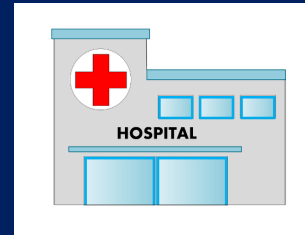| PRE-HOSPITAL	HOSPITALIZED		CONVALESCENT
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ACTIV-4 Antithrombotics
Accelerating COVID-19 Therapeutic Interventions and Vaccines

	PRE-HOSPITAL	HOSPITALIZED	CONVALESCENT
Setting/Population	Elevated D-dimer and CRP	Hospitalized for COVID-19	Discharged after COVID-19 hospitalization
Intervention	Apixaban 5 mg Apixaban 2.5 mg Aspirin 81 mg Placebo	Therapeutic heparin Prophylactic heparin	Antithrombotic therapy
Outcome	Hospitalization for CV/pulm events, arterial or venous thrombosis, all-cause mortality up to 45 days	21-day organ support	Arterial or venous thrombosis, death within 45 days

Conclusions

- **Thrombosis is a significant vascular complication in COVID-19**

- **Many COVID-19 thromboprophylaxis trials ongoing or planned**
  - **Varying intensities of existing therapies**
  - **Novel therapeutic targets**

- **Operational considerations remain a challenge**

- **Collaborative and innovative efforts to expedite scientific discovery and improve treatment for COVID-19 patients**

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