CPC Clinical Research

An Affiliate of:

University of Colorado Anschutz Medical Campus

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

Connie N. Hess, MD, MHS
University of Colorado School of Medicine
CPC Clinical Research

Disclosures

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

Overview

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

Overview

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

Thrombosis plays a major role in COVID-19

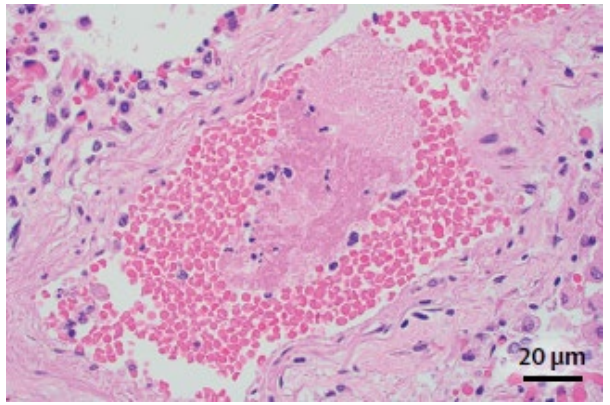
Incidence of Thrombotic Events in Hospitalized Patients with COVID-19 in a NYC Health System

	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)

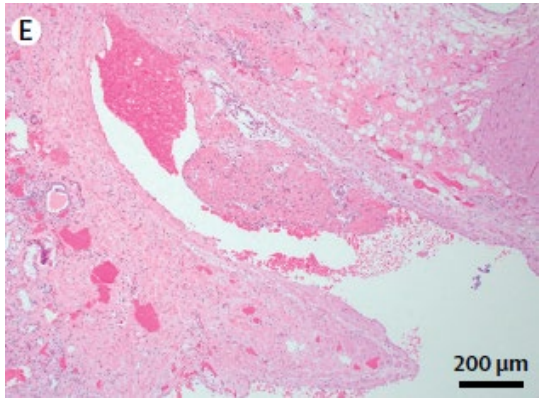
Thrombotic events detected in 31% of 184 Dutch COVID-19 ICU patients

Subsegmental pulmonary embolism

Pulmonary microthrombus

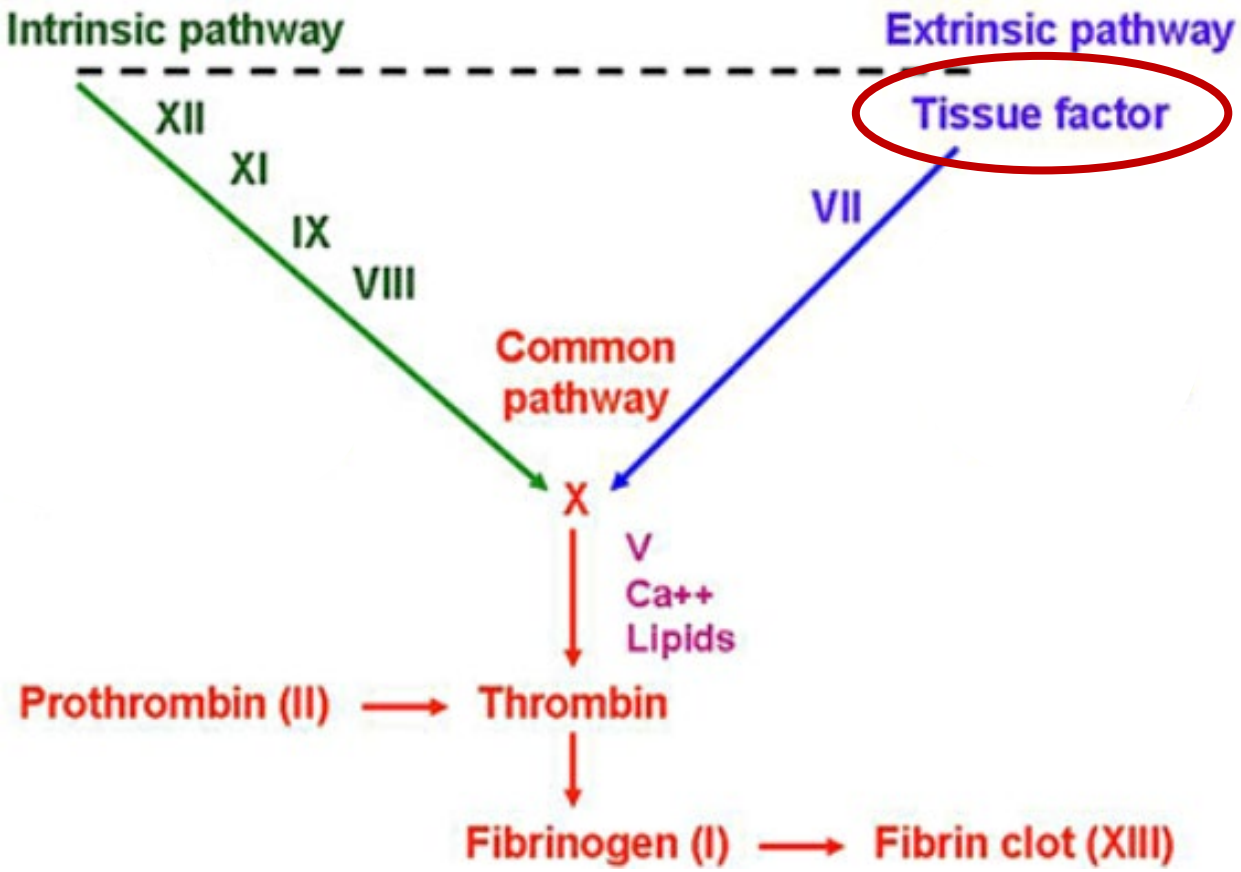


Renal vein organizing thrombus



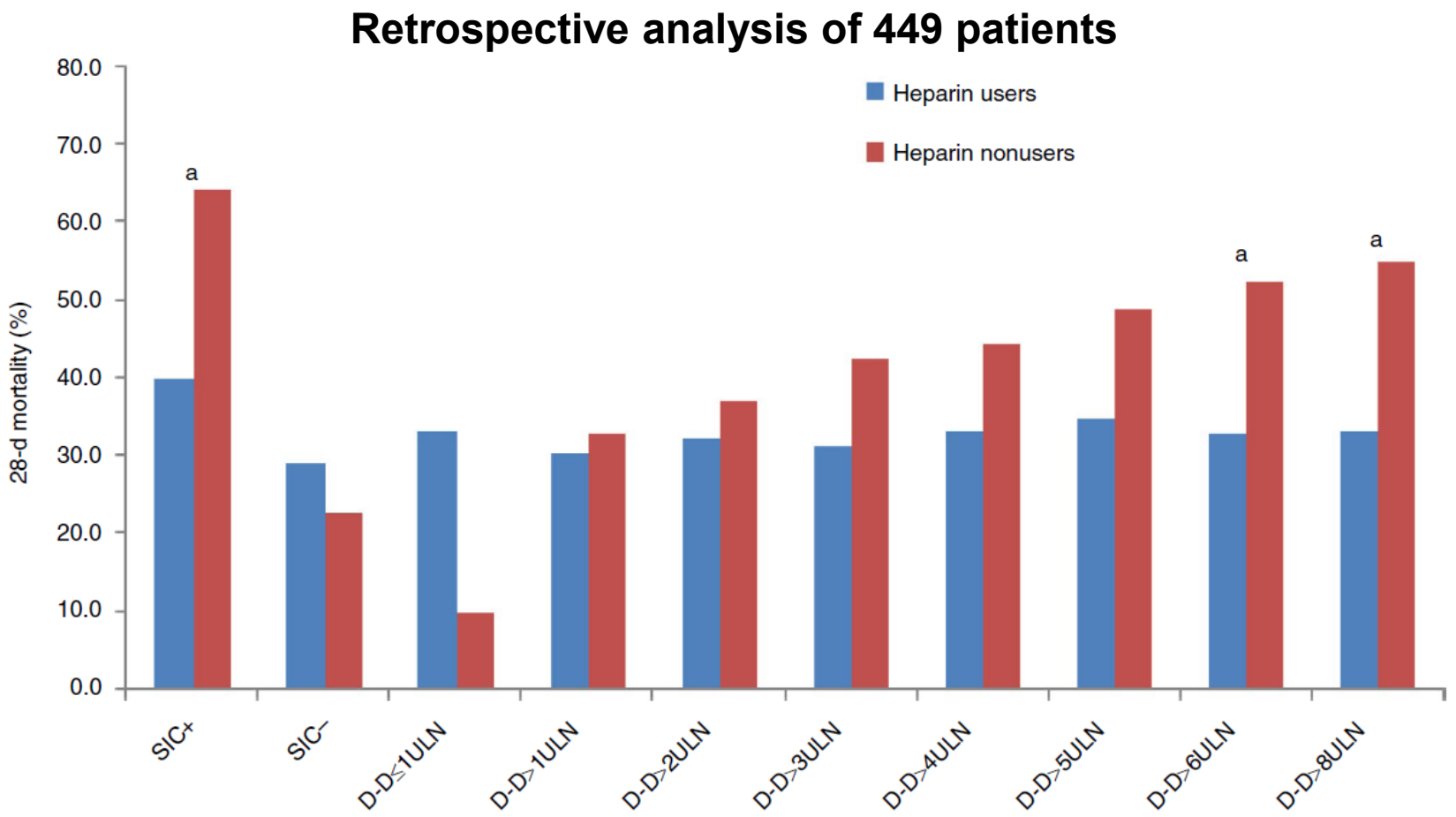
Bilaloglu S et al JAMA 2020
Klok FA, et al. Thromb Res 2020
Bradley BT, et al. Lancet 2020

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



An Affiliate of:

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 o Enoxaparin 40 mg SC bid or 0.5 mg/kg SC bid o Heparin 7500 U SC TID o 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
https://www.hematology.org/covid-19/covid-19-and-vte-anticoagulation

CORIMMUNO-COAG

COVID-PACT

X-COVID 19

ATTACC

FREEDOM COVID

NCT04400799

NCT04508439

NCT04466670

COVI-DOSE

ACTION

IMPROVE

ANTI-CO

IMPACT

COVAC-TP

PREVENT HD

COVID-PREVENT

INSPIRATION

HEP COVID

NCT04505774

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

TOLD

ACTIV-4

ETHIC

ASPEN

VTE-COVID

PARTISAN

NCT04359277

NCT04498273

NCT04360824

COVID-HEP

RAPID-BRAZIL

ACOVACT

HERO-19

INHIXACOV19

Overview

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

Trial Setting

PRE-HOSPITAL

COVID+
Outpatient

PREVENT-HD
ETHIC
ACTIV-4
NCT04498273
NCT04400799

HOSPITALIZED

COVID+
Inpatient

HEP COVID
ASPEN
PARTISAN
COVID-HEP
IMPROVE
COVID-PACT
COVAC-TP
COVI-DOSE
RAPID-BRAZIL
FREEDOM COVID
ANTI-CO
IMPACT
INSPIRATION
HERO-19

ACTIV-4
ACTION
COVID-PREVENT
VTE-COVID
TOLD
ATTACC
X-COVID 19
INHIXACOV19
ACOVACT
CORIMMUNO-COAG
NCT04508439
NCT04466670
NCT04505774
NCT04360824
NCT04359277

CONVALESCENT

COVID+
Discharged

ACTIV-4
COVID-PREVENT
NCT04508439

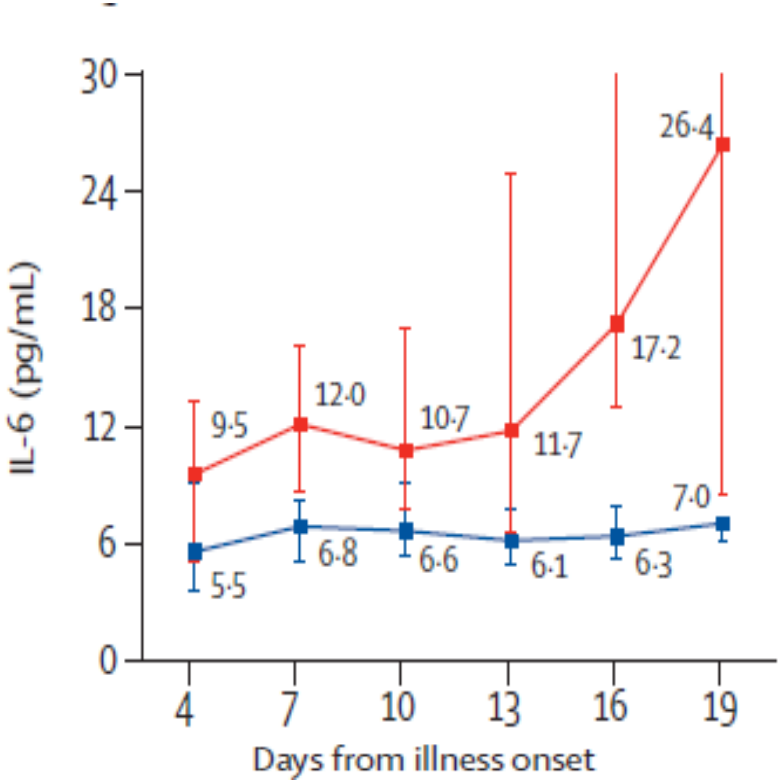
Overview

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

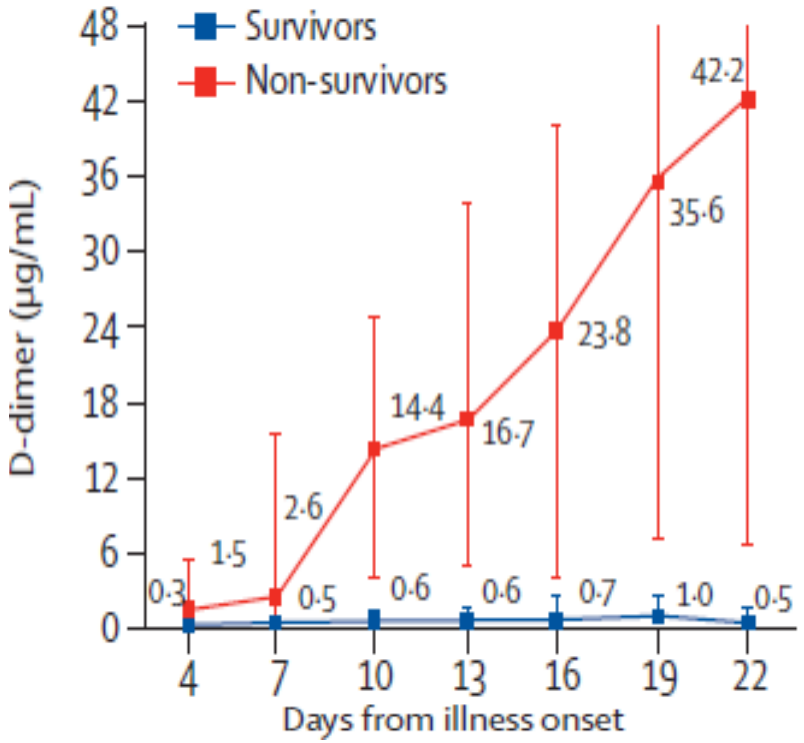
Predictors of Mortality in COVID-19

191 patients in Wuhan, China

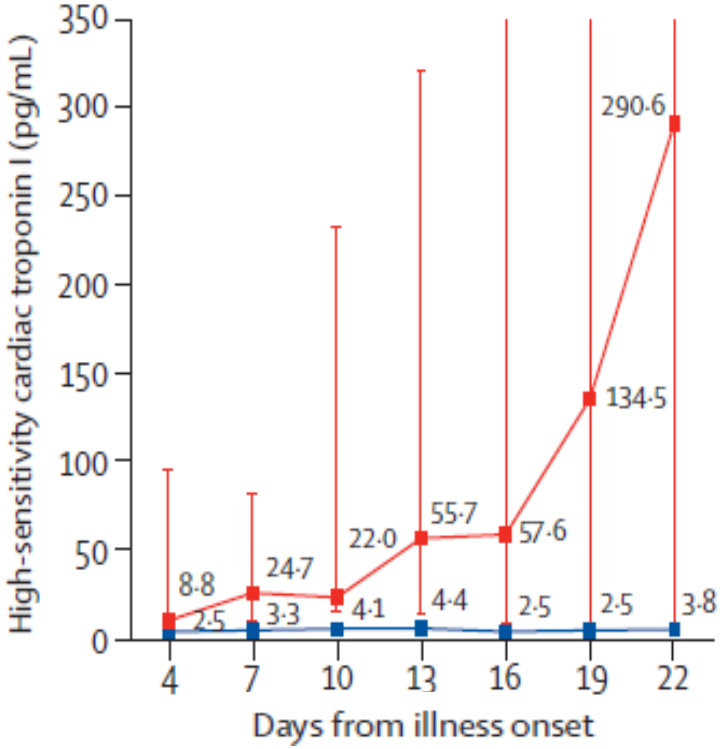
IL-6



D-dimer

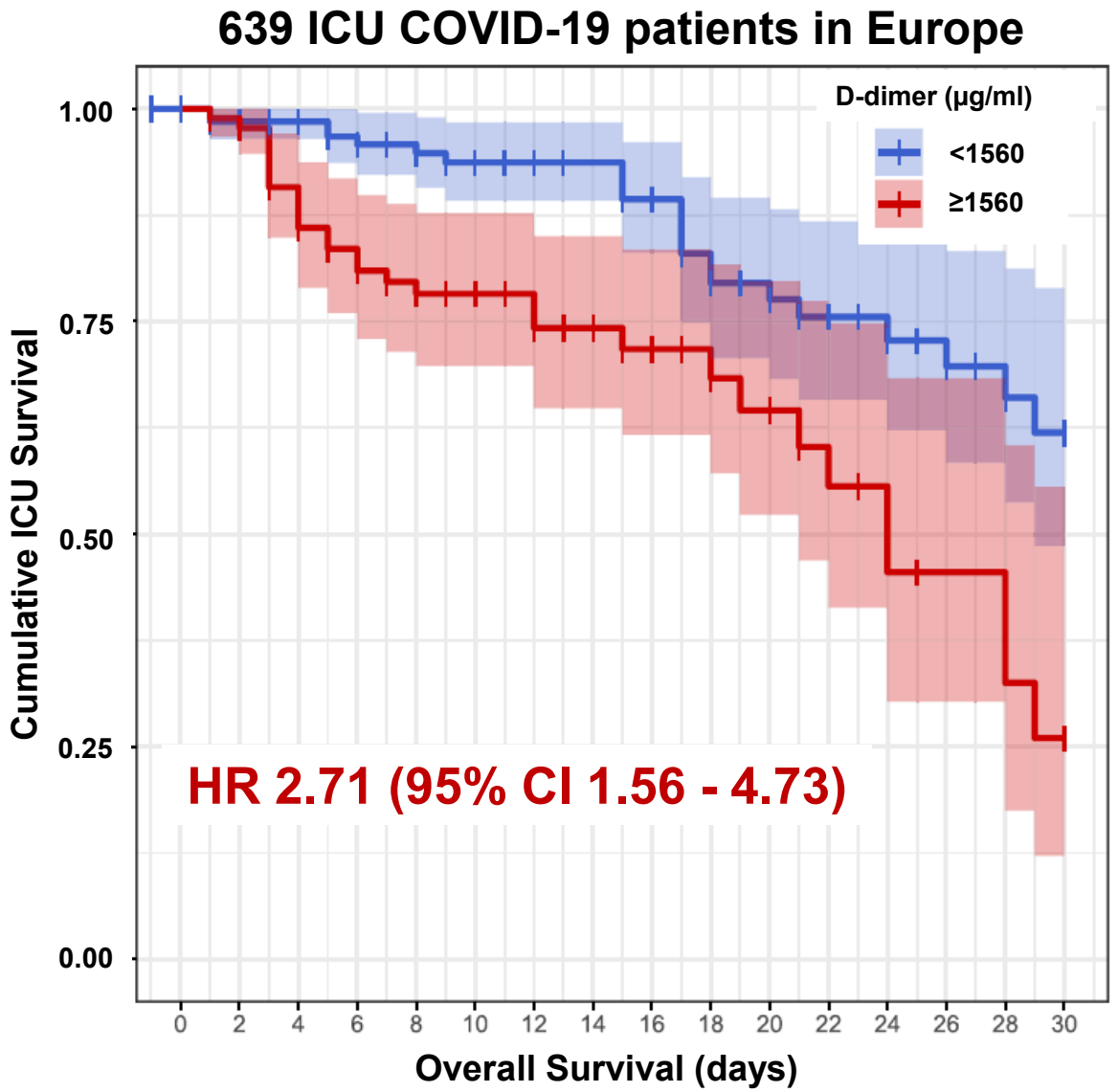


Troponin



Zhou F et al, *Lancet* 2020; 395: 1054–62

D-dimer predicts mortality in critically ill COVID-19



An Affiliate of:

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 ($\times 10^9$/L)	≧150	<150	<100
Total SOFA	SOFA four items	0	1	≧2

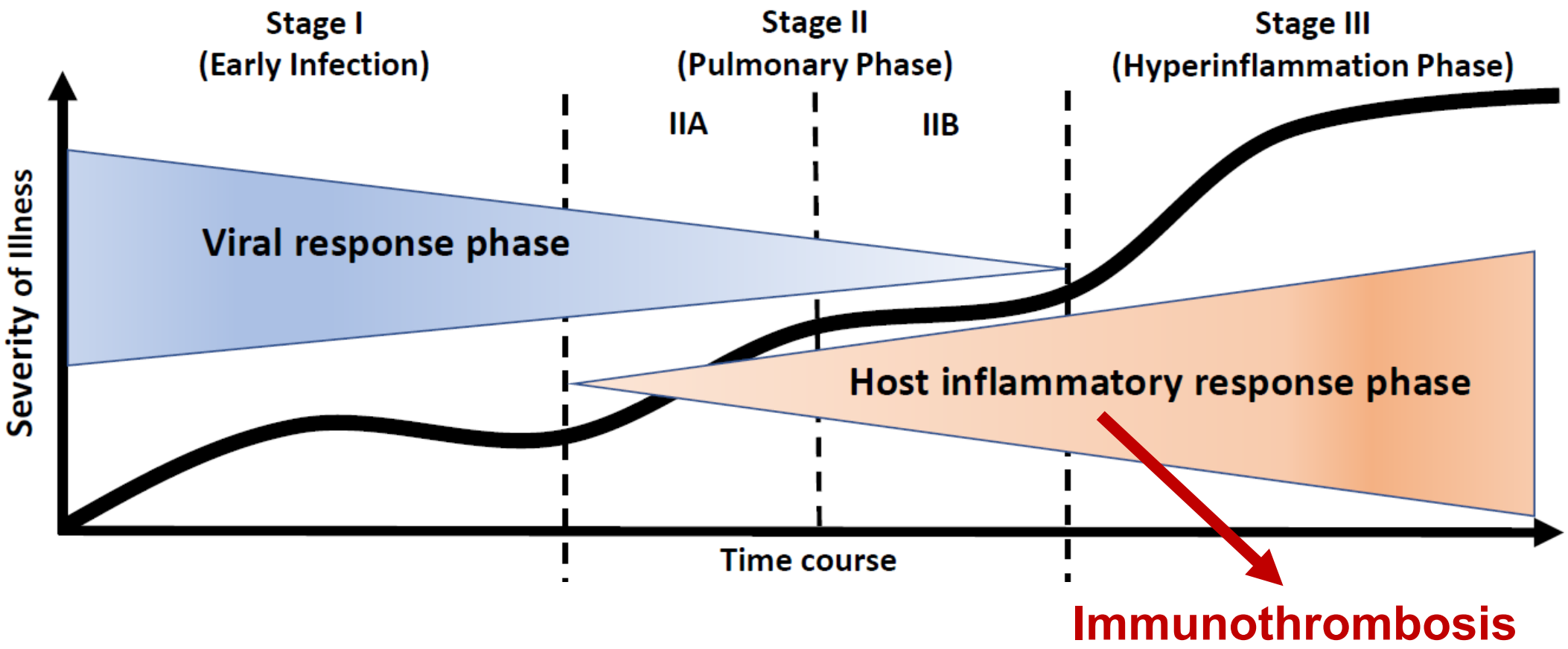
SOFA, Sequential Organ Failure Assessment

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

Overview

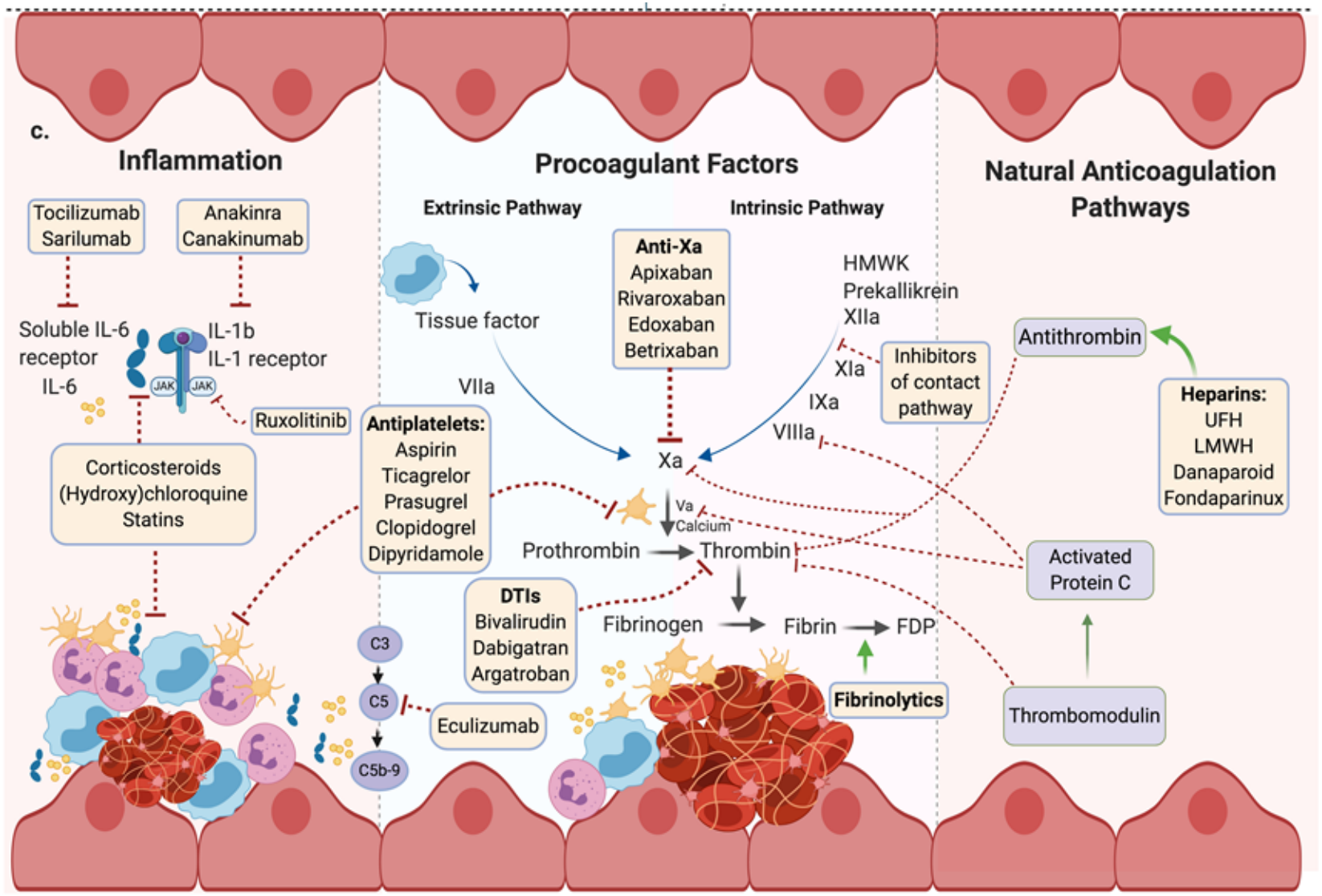
- Background
- Clinical Trial Framework
  - Trial setting
  - Study population
  - Therapeutic intervention
  - Outcomes
  - Operational challenges
- Example trials
- Conclusions

COVID-19 Disease Progression



Siddiqu HK and Mehra MR. J Heart and Lung Transplant 2020

Thromboprophylaxis in COVID-19

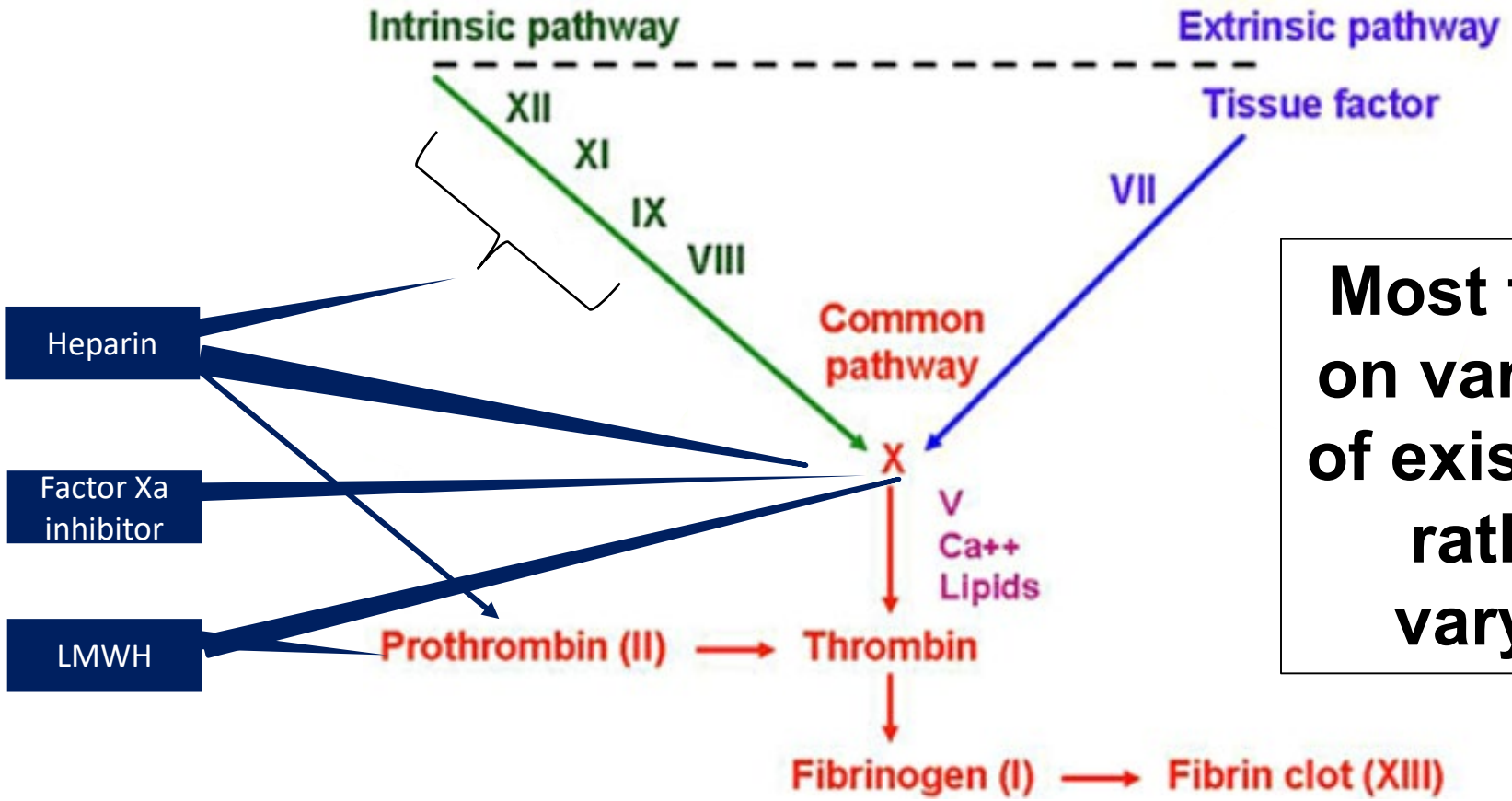


An Affiliate of:

CPC Clinical Research

Bikdeli B et al. Thromb Haemost. 2020

Study Intervention: Target vs. Intensity



Most trials focused on varying <u>intensity</u> of existing therapies rather than on varying targets

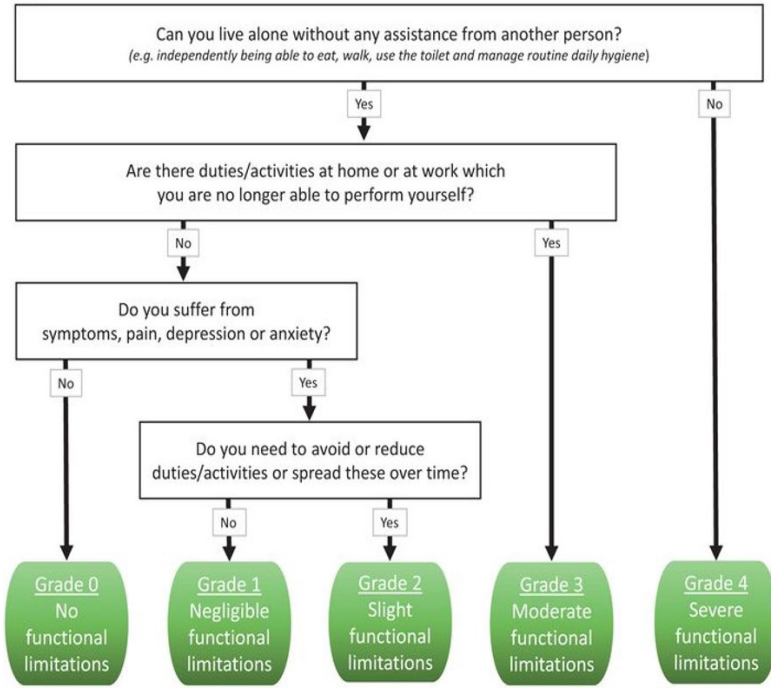
Overview

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

Outcomes

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

Post-COVID-19 Functional Status (PCFS)



How much are you currently affected in your everyday life by COVID-19? Please indicate which one of the following statements applies to you most.	Corresponding PCFS scale grade
I have no limitations in my everyday life and no symptoms, pain, depression or anxiety related to the infection.	0
I have negligible limitations in my everyday life as I can perform all usual duties/activities, although I still have persistent symptoms, pain, depression or anxiety.	1
I suffer from limitations in my everyday life as I occasionally need to avoid or reduce usual duties/activities or need to spread these over time due to symptoms, pain, depression or anxiety. I am, however, able to perform all activities without any assistance.	2
I suffer from limitations in my everyday life as I am not able to perform all usual duties/activities due to symptoms, pain, depression or anxiety. I am, however, able to take care of myself without any assistance.	3
I suffer from severe limitations in my everyday life: I am not able to take care of myself and therefore I am dependent on nursing care and/or assistance from another person due to symptoms, pain, depression or anxiety.	4

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**

Beigel JH et al. NEJM 2020
Klok FA et al. Eur Respir J 2020

Overview

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

Operational Challenges for COVID-19 Trials

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

Overview

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

Trial Setting

PRE-HOSPITAL

COVID+
Outpatient

PREVENT-HD
ETHIC
ACTIV-4
NCT04498273
NCT04400799

HOSPITALIZED

COVID+
Inpatient

HEP COVID
ASPEN
PARTISAN
COVID-HEP
IMPROVE
COVID-PACT
COVAC-TP
COVI-DOSE
RAPID-BRAZIL
FREEDOM COVID
ANTI-CO
IMPACT
INSPIRATION
HERO-19

ACTIV-4
ACTION
COVID-PREVENT
VTE-COVID
TOLD
ATTACC
X-COVID 19
INHIXACOV19
ACOVACT
CORIMMUNO-COAG
NCT04508439
NCT04466670
NCT04505774
NCT04360824
NCT04359277

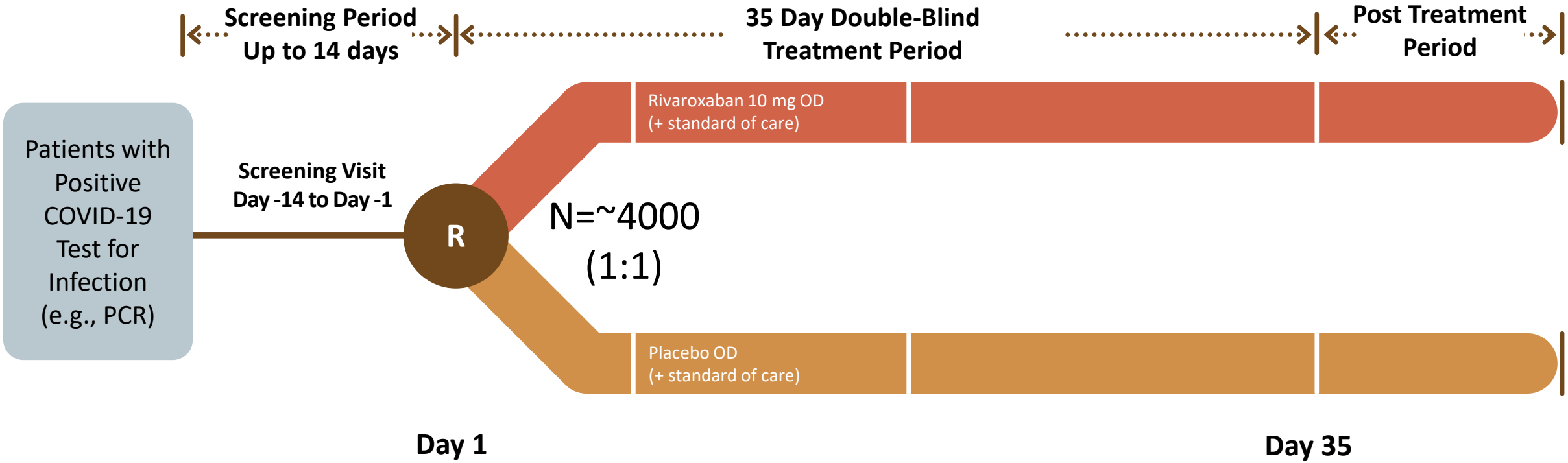
CONVALESCENT

COVID+
Discharged

ACTIV-4
COVID-PREVENT
NCT04508439

PREVENT-HD

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



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

PRE-HOSPITAL

COVID+
Outpatient

PREVENT-HD
ETHIC
ACTIV-4
NCT04498273
NCT04400799

HOSPITALIZED

COVID+
Inpatient

HEP COVID
ASPEN
PARTISAN
COVID-HEP
IMPROVE
COVID-PACT
COVAC-TP
COVI-DOSE
RAPID-BRAZIL
FREEDOM COVID
ANTI-CO
IMPACT
INSPIRATION
HERO-19

ACTIV-4
ACTION
COVID-PREVENT
VTE-COVID
TOLD
ATTACC
X-COVID 19
INHIXACOV19
ACOVACT
CORIMMUNO-COAG
NCT04508439
NCT04466670
NCT04505774
NCT04360824
NCT04359277

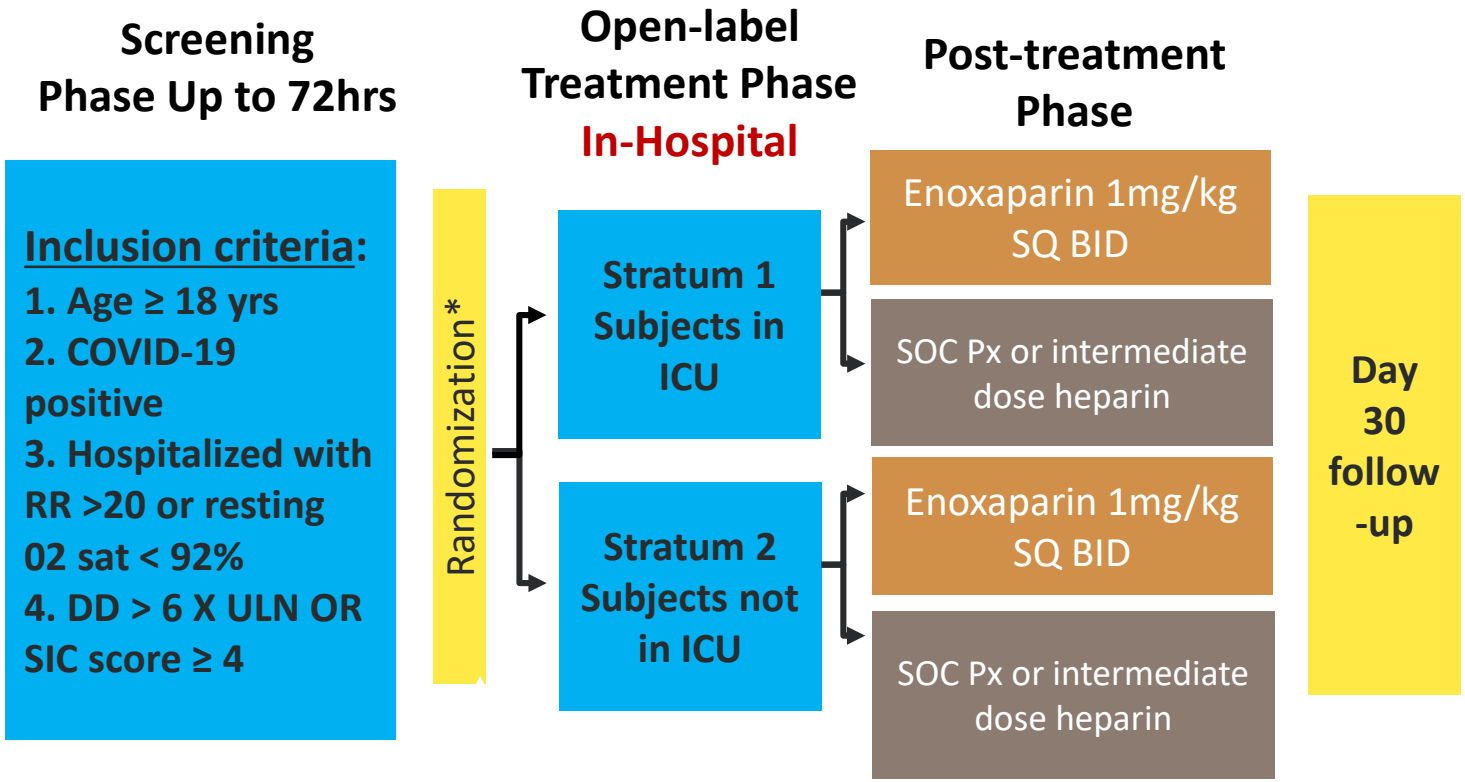
CONVALESCENT

COVID+
Discharged

ACTIV-4
COVID-PREVENT
NCT04508439

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



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%

Trial Setting

PRE-HOSPITAL

COVID+
Outpatient

PREVENT-HD
ETHIC
ACTIV-4
NCT04498273
NCT04400799

HOSPITALIZED

COVID+
Inpatient

HEP COVID
ASPEN
PARTISAN
COVID-HEP
IMPROVE
COVID-PACT
COVAC-TP
COVI-DOSE
RAPID-BRAZIL
FREEDOM COVID
ANTI-CO
IMPACT
INSPIRATION
HERO-19

ACTIV-4
ACTION
COVID-PREVENT
VTE-COVID
TOLD
ATTACC
X-COVID 19
INHIXACOV19
ACOVACT
CORIMMUNO-COAG
NCT04508439
NCT04466670
NCT04505774
NCT04360824
NCT04359277

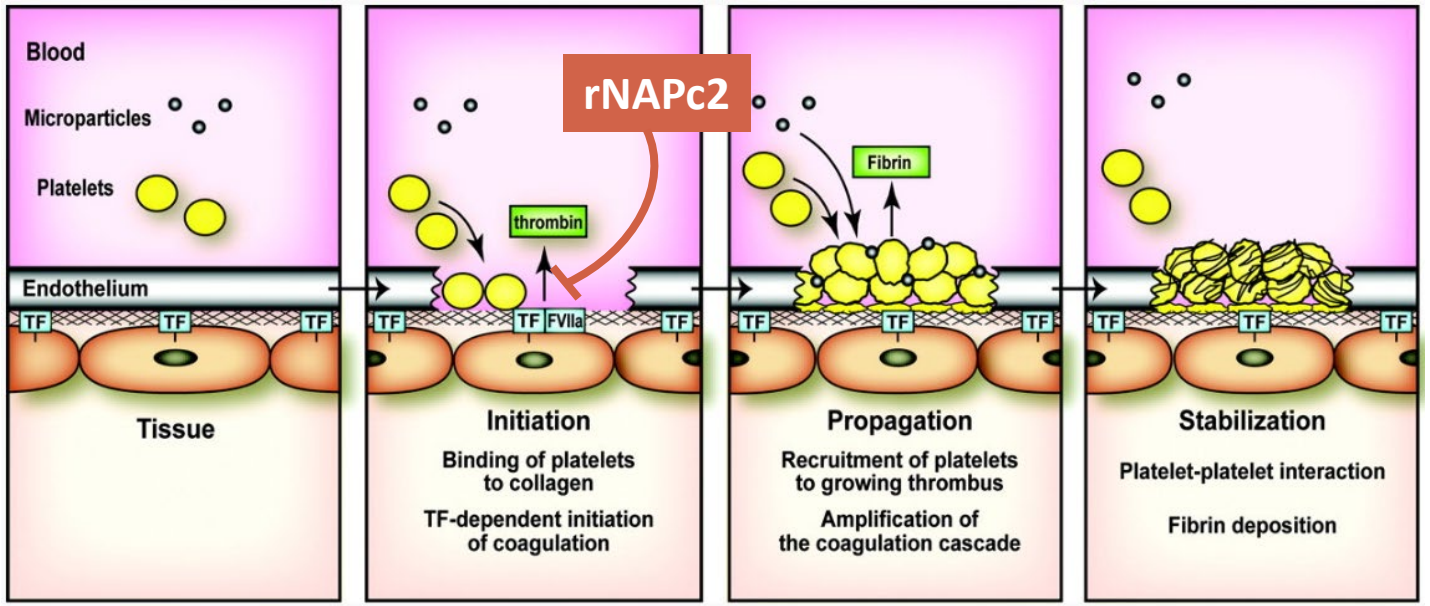
CONVALESCENT

COVID+
Discharged

ACTIV-4
COVID-PREVENT
NCT04508439

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

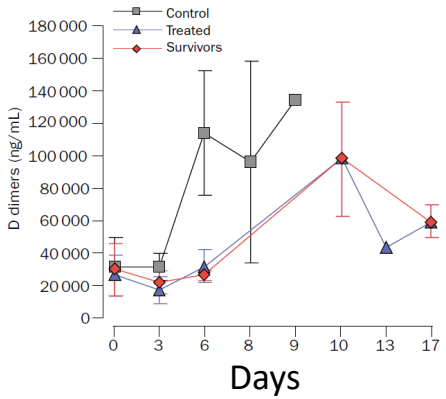


rNAPc2 inhibits Tissue Factor at the initiation phase of coagulation

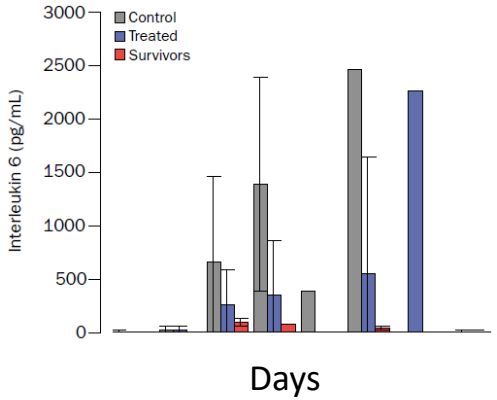
rNAPc2 Targets More Than Coagulation

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

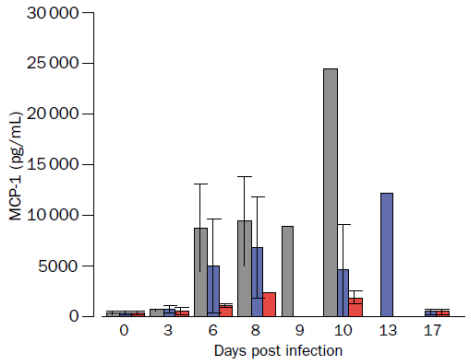
D-dimer



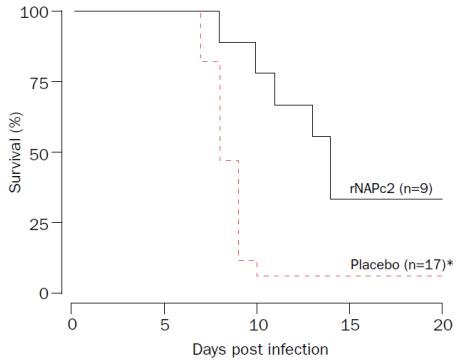
IL-6



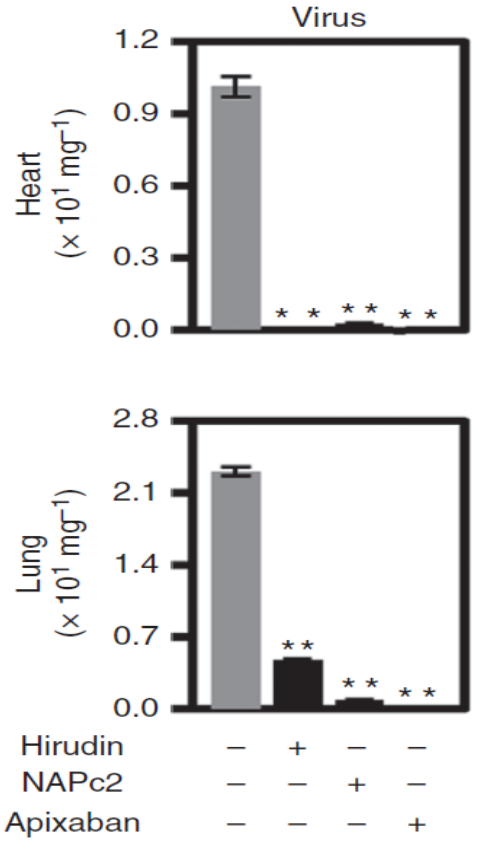
MCP-1



Survival



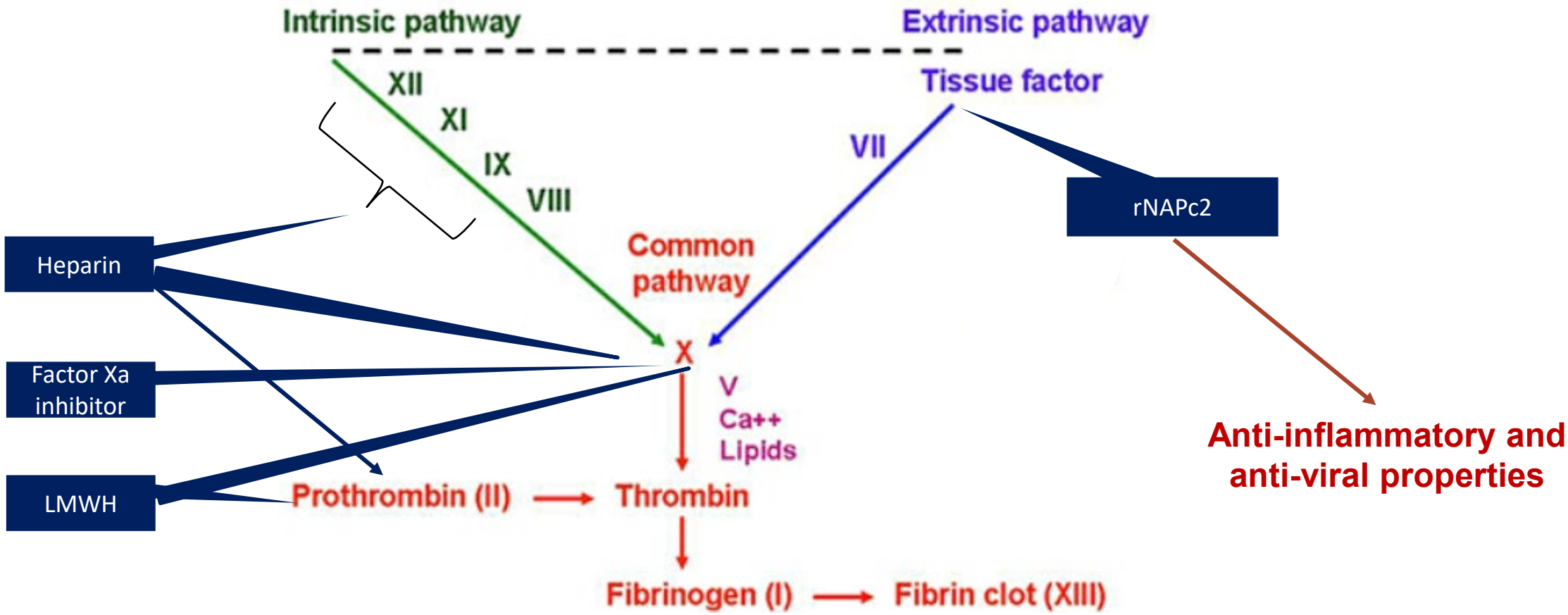
rNAPc2 reduces viral load in mice inoculated with HSV1



An Affiliate of:

Lancet 2003;362:1953
J Thromb Haemost 2019;17:482

rNAPc2


Intrinsic pathway
Extrinsic pathway
XII
XI
IX
VIII
Tissue factor
VII
rNAPc2
Heparin
Common pathway
X
Factor Xa inhibitor
V
Ca++
Lipids
LMWH
Prothrombin (II)
Thrombin
Fibrinogen (I)
Fibrin clot (XIII)
Anti-inflammatory and anti-viral properties

ASPEN-COVID-19

Assessing Safety and Efficacy of rNAPc2 in COVID-19

Phase 2b

Screening up to 7d

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

An Affiliate of:

Trial Setting

PRE-HOSPITAL

COVID+
Outpatient

PREVENT-HD
ETHIC
ACTIV-4
NCT04498273
NCT04400799

HOSPITALIZED

COVID+
Inpatient

HEP COVID
ASPEN
PARTISAN
COVID-HEP
IMPROVE
COVID-PACT
COVAC-TP
COVI-DOSE
RAPID-BRAZIL
FREEDOM COVID
ANTI-CO
IMPACT
INSPIRATION
HERO-19

ACTIV-4
ACTION
COVID-PREVENT
VTE-COVID
TOLD
ATTACC
X-COVID 19
INHIXACOV19
ACOVACT
CORIMMUNO-COAG
NCT04508439
NCT04466670
NCT04505774
NCT04360824
NCT04359277

CONVALESCENT

COVID+
Discharged

ACTIV-4
COVID-PREVENT
NCT04508439

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