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COVID-19 and antithrombotics: what we know now for patients

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Conflicts of Interest

Scientific Ad Boards and Consulting:
- Abbott
- Anthos
- Alnylam
- Bristol-Myers Squibb
- Portola
- Takeda

Research funding to the Institution
- CSL Behring

Jean M Connors MD

COVID-19 associated coagulopathy and thrombosis

Early reports from China revealed coagulation test abnormalities

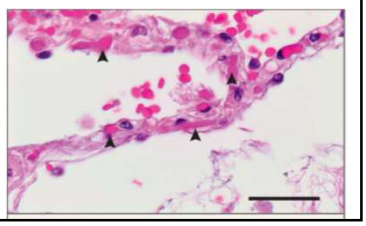
- Marked increase in D-dimer associated with disease severity and mortality
- **Thromboinflammation: driving coagulation**
  - **COVID-19 is a hypercoagulable state**

Macrovascular thrombosis

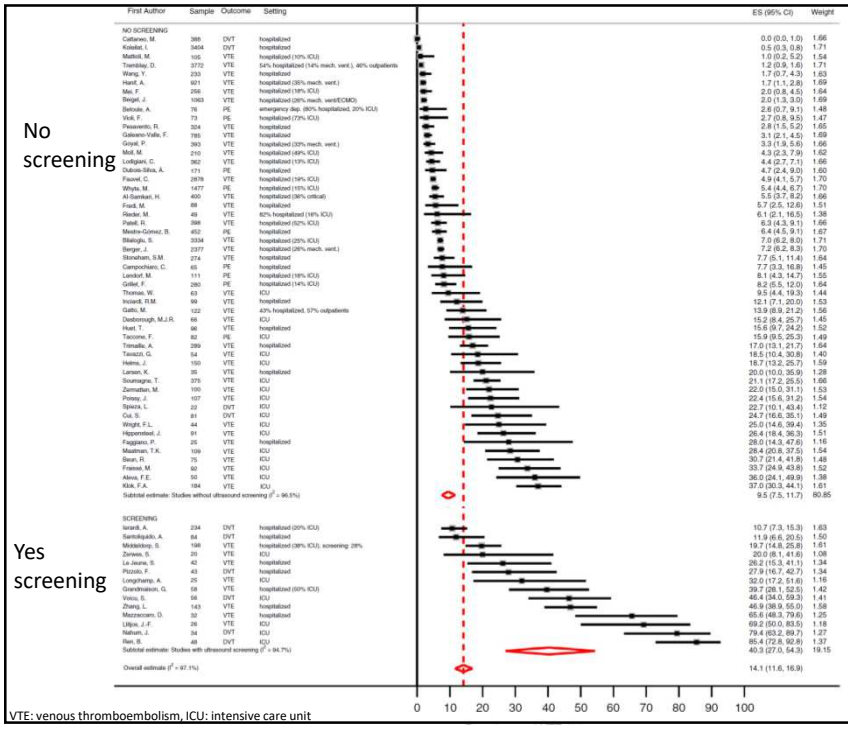
- Increased rates of VTE

Microvascular thrombosis

- Pulmonary microvascular thrombosis responsible for hypoxemia



Ackermann, NEJM 2020



VTE: venous thromboembolism, ICU: intensive care unit

VTE in COVID-19+ Meta-analysis in hospitalized patients

66 studies up to August 26, 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

Nopp, RPTH, Sep 2020

Many observational and retrospective studies on anticoagulation use in COVID-19

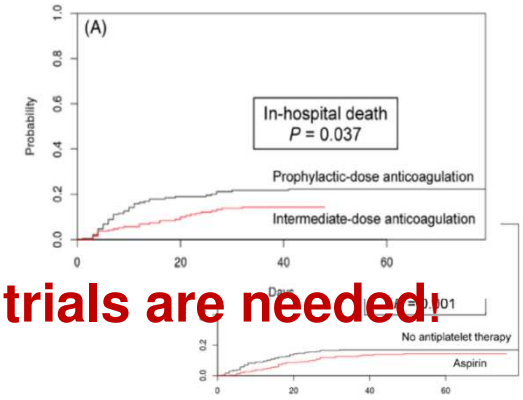
DOI: 10.1002/ajh.26102

RESEARCH ARTICLE

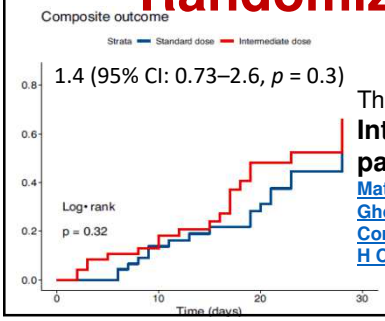
AJH WILEY

Intermediate-dose anticoagulation, aspirin, and in-hospital mortality in COVID-19: A propensity score-matched analysis

Matthew L. Meizlish[1] | George Goshua[2] | Yiwen Liu[3] | Rebecca Fine[4] | Kejal Amin[5] | Eric Chang[2] | Nicholas DeFilippo[5,6] | Craig Keating[7] | Yuxin Liu[2] | Michael Mankbadi[4] | Dayna McManus[5] | Stephen Y. Wang[4] | Christina Price[8] | Robert D. Bona[2] | Cassius Iyad Ochoa Chaar[9] | Hyung J. Chun[10] | Alexander B. Pine[2] | Henry M. Rinder[2,11] | Jonathan M. Siner[12] | Donna S. Neuberg[3] | Kent A. Owusu[5,13] | Alfred Ian Lee[2]



Randomized controlled trials are needed!



Thromb Res. 2021

Intermediate versus standard dose heparin prophylaxis in COVID-19 ICU patients: A propensity score-matched analysis

Matthew Moll [1], Rebecca L Zon [2], Katelyn W Sylvester [3], Jessica Rimsans [3], Evan C Chen [4], Auyon J Ghosh [1], Eric Abston [5], Andy Kim [6], Henry Rutherford [6], Xhoi Mitre [6], Aaron Hakim [7], Nathan T Connell [8], Elisabeth Battinelli [8], Laura E Fredenburgh [9], Rebecca M Baron [9], Brian D Hobbs [1], Michael H Cho [1], Murray A Mittleman [10], Ann E Woolley [6], Jean M Connors [11]

Thromboprophylaxis Trials in COVID-19

PRE-HOSPITAL	HOSPITALIZED		CONVALESCENT
COVID+ Outpatient	COVID+ Inpatient		COVID+ Discharged
PREVENT-HD	HEP COVID	ASPEN	ACTIV-4
ETHIC	PARTISAN	ACTIV-4	COVID-PREVENT
ACTIV-4	COVID-HEP	COVID-PREVENT	NCT04508439
NCT04498273	IMPROVE	VTE-COVID	
NCT04400799	COVID-PACT*	ATTACC	
	COVAC-TP	X-COVID 19	
	COVI-DOSE	INHIXACOV19	
	RAPID-BRAZIL	ACOVACT	
	FREEDOM COVID	CORIMMUNO-COAG	
	ANTI-CO*	NCT04508439	
	IMPACT*	NCT04466670	
	INSPIRATION*	NCT04505774	
	HERO-19	NCT04360824	
	ACTION	NCT04359277	
	RAPID COVID COAG**	NCT04377997	
	TOLD	NCT04412304*	
		NCT04498273	

Trials studying available agents:

- Heparin (UFH, LMWH)
- Factor Xa inhibitor
- Direct thrombin inhibitor
- Includes antiplatelet

Novel target: extrinsic pathway

**ICU only*
***Floor status only*
ICU: intensive care unit

Inpatient RCT

RCT: Hospitalized patients with COVID-19

- RCT launched early, power calculation event rates based on early observed rates in hospitalized populations
  - Moderately ill
  - Severely ill or ICU population
- Outcomes: variable endpoints, often a combination of progression of COVID, mortality, and thrombotic events
- Trials that have been released:
  - Multiplatform—ATTACC, REMAP-CAP, ACTIV-4a
  - INSPIRATION
  - ACTION—hybrid inpatient/post-discharge
  - RAPID-COVID
  - HEP-COVID

RCT Data: multiplatform trial

- **ACTIV-4A, REMAP-CAP, ATTACC international trials**
  - 3 independent multiplatform randomized controlled trials of heparin in hospitalized COVID-19+ patients, harmonized criteria and endpoints **408 sites**
  - Low dose (prophylactic) vs full dose (therapeutic) heparin
    - **ATTACC**: Antithrombotic therapy to ameliorate complications of COVID-19
      - 58 sites in Canada, USA, Brazil, Mexico
    - **REMAP-CAP:** Randomized embedded multi-factorial, adaptive platform trial
      - 290 sites in Canada, USA, UK, Ireland, EU, Saudi Arabia, Australia, New Zealand, Nepal, India, Pakistan
    - **ACTIV-4a:** Accelerating COVID-19 therapeutic interventions and vaccines
      - 60 activated sites in USA and Spain

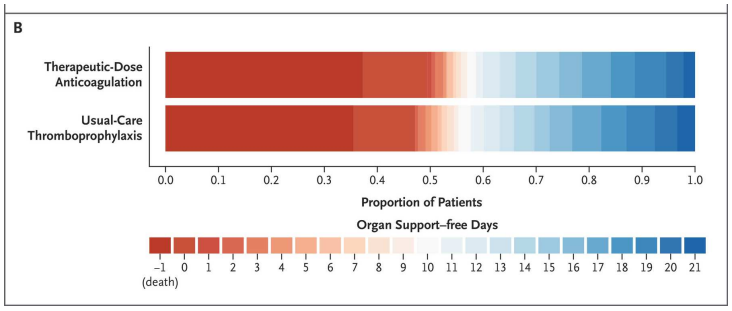
RCT Data: multiplatform trial

ACTIV-4A, REMAP-CAP, ATTACC international trials

Group	Therapeutic-Dose Anticoagulation (n with primary endpoint)	Usual-care thromboprophylaxis (n with primary endpoint)
Severe Covid-19	**534**	**564**
Moderate Covid-19 (overall)	**1171**	**1048**
D-dimer ≥2x ULN	339	291
D-dimer <2x ULN	570	505
D-dimer unknown	262	252

Severe state = ICU level care
Moderate = hospitalized not ICU
Organ support = ICU level of care and receipt of mechanical ventilation, vasopressors, ECMO, high flow nasal oxygen

Multiplatform RCT: severely ill



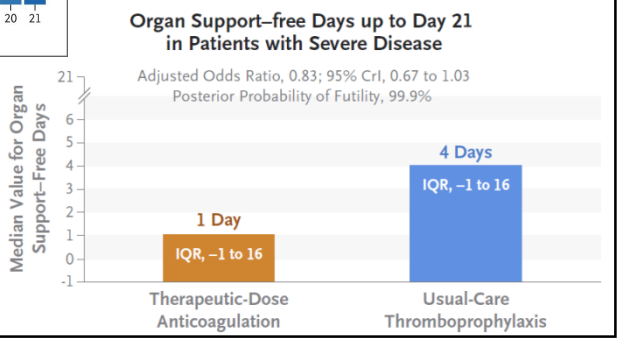
50% in usual care received intermediate dose anticoagulation

No benefit with therapeutic dose

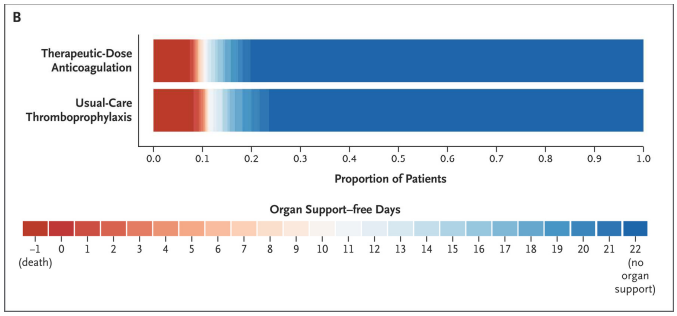
Adjusted OR 0.83 (95% CrI 0.67-1.03)

Futility: Prob(OR<1.2) = 99.9%

Inferiority: Prob(OR<1) = 95.0%



Multiplatform RCT: moderately ill



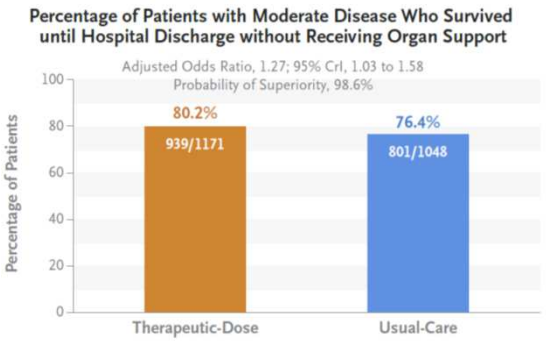
Adjusted OR 1.27 (95% CrI 1.03-1.58)

Superiority: Prob(OR>1) = 98.6%

4% adjusted difference in risk of requiring organ support or dying (20% vs. 24%)

Major bleeding: adjusted difference in risk 0.7 (-0.1 to 2.3)

Response **not** associated with D-dimer

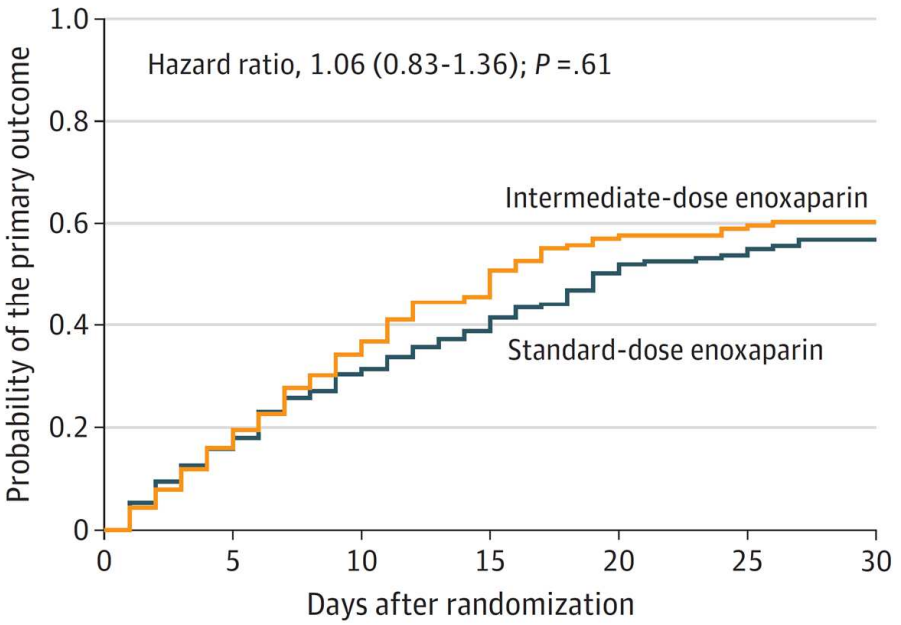


NEJM 2021

Intermediate vs Standard-Dose Prophylactic Anticoagulation in Critically-ill Patients With COVID-19: An Open Label Randomized Controlled Trial

INSPIRATION AND INSPIRATION-S

Sadeghipour P, et al,…Bikdeli B. JAMA. 2021



562 patients in mITT

Primary: Composite of venous or arterial thrombosis, or (ECMO), or mortality within 30 days

VTE events low: ? Less ill population?

Sadeghipour P, et al,…Bikdeli B. JAMA. 2021; 325: 1620-1630.

Anticoagulation in Patients Hospitalized with COVID-19

Renato Lopes, Lancet 2021

INCLUSION CRITERIA

- Patients aged ≥18 years
- Hospitalized with a confirmed diagnosis of COVID-19 and duration of symptoms related to hospitalization ≤14 days.
- Elevated D-dimer (>ULN) at admission

Randomize
N: 615 patients

MAIN EXCLUSION CRITERIA

- Indication for therapeutic anticoagulation at screening
- eCrCl <30 ml/min
- Platelets <50,000 /mm³
- Use of P2Y12 inhibitor or ASA >100 mg daily
- Very high risk of bleeding

Therapeutic anticoagulation

Stable Patients	Unstable Patients
In-hospital rivaroxaban 20 mg daily	In-hospital enoxaparin 1mg/kg twice daily

Followed by rivaroxaban through 30 days, irrespective of duration of hospitalization

Standard of care with in-hospital prophylactic dose anticoagulation

STRATEGY: Inpatient rivaroxaban 20 mg qd and after discharge for 30 days vs LMWH will inpatient only

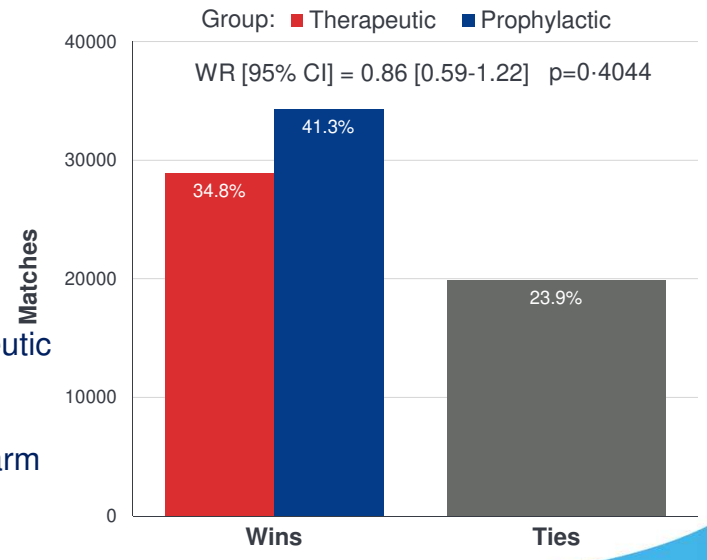
ACC.21

ACTION

Primary Outcome

Hierarchical analysis of mortality, duration of hospitalization, and duration of oxygen use through 30 days (p=0.4)

- No significant advantage for therapeutic dose rivaroxaban inpatient and extended duration outpatient
- Higher bleeding rate in therapeutic arm
  8.4% vs 2.3%



ACC.21

ACTION

Pending inpatient RCT of antithrombotics in COVID-19

- RAPID-COVID
  - therapeutic vs prophylactic dose heparin for moderately ill: small numbers, underpowered, no benefit?
- HEP-COVID
  - Treatment dose vs standard or intermediate prophylactic dose LMWH Primary outcome thrombosis—benefit?
- RECOVERY trial in UK
  - press release: no mortality benefit with aspirin

Many other trials still in progress for hospitalized patients, ambulatory, and post-discharge

Acute SARS-CoV-2 infection but not hospitalized

- COVID-19 results in a hypercoagulable state with increased risk of venous and arterial thrombosis and pulmonary microvascular thrombosis
- Patients newly diagnosed with COVID-19 will develop increased inflammatory response, increasing their risk of thrombotic events
- No data were available to guide care when trials for ambulatory patients were designed
  - some observational, registry, and health claims database analyses reported conflicting results

ACTIV-4b: COVID-19 Outpatient Thrombosis Prevention Trial

A multicenter adaptive randomized placebo-controlled platform trial evaluating the efficacy and safety of antithrombotic strategies in COVID-19 adults not requiring hospitalization at time of diagnosis

NHLBI/NIH funded trial as part of the ACTIV platform

NCT04498273

ACTIV-4
COVID-19 Outpatient Thrombosis Prevention Study

Trial Population

Key inclusion	Key exclusion	Lab evaluations **
•Ages 40-80 years •COVID-19+ in past 14 days •Never hospitalized for COVID-19	•Hospitalized •Contradiction/ other indication for anticoagulation •Need for DAPT •Pregnant or lactating	• Crcl > 30 ml/min • Platelets >100,000/ul • For analysis: D-dimer CRP

- **Platelets > 100,000 and eGFR > 30ml/min within 72 hrs of randomization, local lab or home health draw
- D-dimer and CRP levels required for analysis but not eligibility
- 45 days on treatment, then 30 day safety follow-up

"Low Touch" to "No Touch" Trial Design

ACTIV-4
COVID-19 Outpatient Thrombosis Prevention Study

ENROLLMENT

FOLLOW-UP

PCR or Ag Positive COVID-19
Within last 14 days
Platelets > 100,000
eGFR > 30 ml/min
Pregnancy Testing WOCBP
Outpatient Destination

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
- Inclusion, exclusion, bloodwork
  - Pregnancy Test as needed
  - Labs can be pending at randomization
- Central Simple Internet EDC

First Video + Consent

Centralized Telemedicine Phase
- Pt receives Study Drug overnight by FedEx
- Pt followed every 7 days electronic "chatbot" or call to address adherence, compliance, and flag potential endpoints
- 24/7 Pt Call Center for safety, endpoint reporting

Second Video
Telephone Introduction to Trial

ACTIV-4b
COVID-19 Outpatient Thrombosis Prevention Study

Primary Outcome:

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

Primary Safety Endpoint: major bleeding

Stopped after 657 patients enrolled: event rate low across all arms

USZ Universitäts Spital Zürich

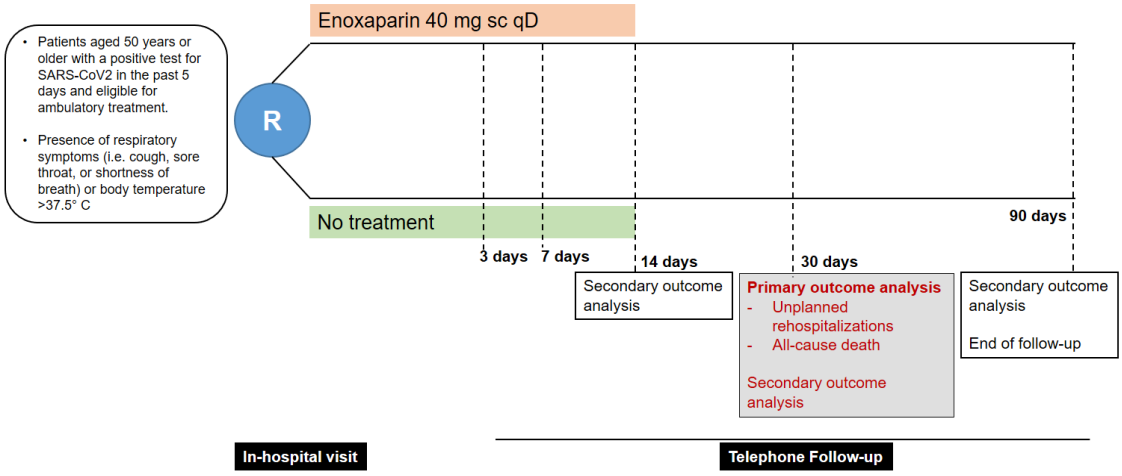
Enoxaparin for primary thromboprophylaxis in ambulatory patients with coronavirus: the multicenter randomized controlled OVID trial

NFP 78 Covid-19 – ID 198352

- **Nils Kucher, Stefano Barco, Davide Voci**
  - nils.kucher@usz.ch
  - stefano.barco@usz.ch

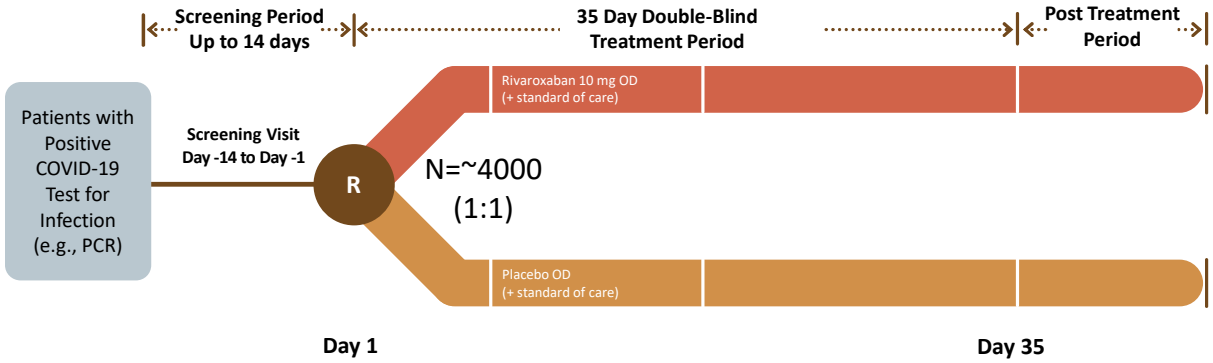
- **Zürich, 27 April 2021**

The OVID phase III trial



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

Post-hospitalization risk of thrombosis

- Patients infected with SARS-CoV2 are at increased risk for thrombotic events which contribute to overall morbidity and mortality
- Anticoagulant therapy is recommended to decrease the risk of thromboembolism in hospitalized patients with COVID-19
- Recent hospitalization is associated with an increased risk for VTE. The impact of COVID-19 on this increased risk for VTE after hospital discharge is unknown
- Trials evaluating the efficacy and safety of antithrombotic strategies COVID-19 following hospital discharge are in progress

ACTIV 4c

Post-Hospital Thrombosis Prevention Study

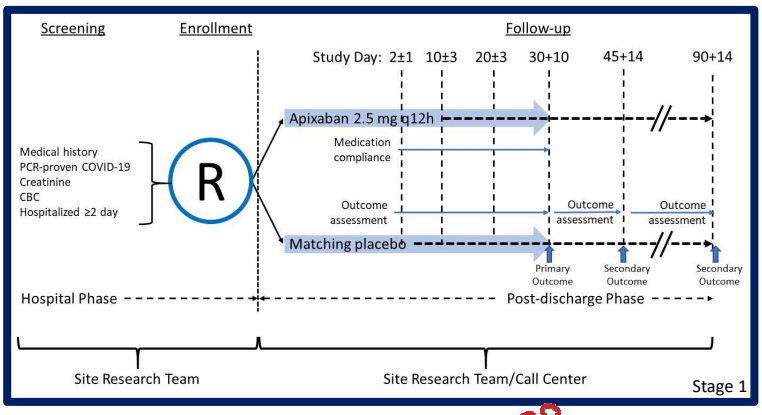
Preventing blood clots in patients discharged after being hospitalized with COVID-19

ACTIV-4
COVID-19 Post-Hospital Thrombosis Prevention Study

ACTIV 4c: Study Overview

Target Population

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



ACTIV-4
COVID-19 Post-Hospital Thrombosis Prevention Study

MEDICALLY ILL HOSPITALIZED PATIENTS FOR COVID –19 THROMBOSIS EXTENDED PROPHYLAXIS WITH RIVAROXABAN THERAPY: **THE MICHELLE TRIAL**

Eduardo Ramacciotti, **Leandro Barile Agati**, **Daniela Calderaro**, Valéria Cristina Resende Aguiar, **Alex C. Spyropoulos**, Giuliano Giova Volpiani, Caroline Candida Carvalho de Oliveira, Marcone Lima Sobreira, MD, Edwaldo Edner Joviliano, Cesar Dusilek, Kengi Itinose, Rogério Aparecido Dedivitis, André Sementilli Cortina, Suzanna Maria Viana Sanches, Nara Franzin de Moraes, Paulo Fernando Guimarães Morando Marzocchi Tierno, André Luiz Malavasi Longo de Oliveira, Adriano Tachibana, Rodrigo Caruso Chate, Marcus Vinícius Barbosa Santos, Bruno Bezerra de Menezes Cavalcante, Ricardo Cesar Rocha Moreira, Chang Chiann, **Alfonso Tafur**, **Renato D. Lopes**

On Behalf of The Michelle Trial Investigators

ESC CONGRESS 2021
THE DIGITAL EXPERIENCE

IMPROVE DD VTE

RISK SCORE

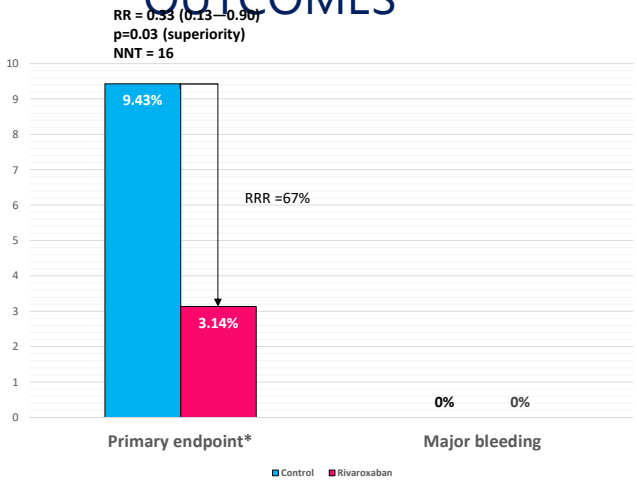
VTE RISK FACTOR	POINTS
Previous VTE	3
Known thrombophilia	2
Lower-limb paralysis	2
History of cancer (*)	2
Immobilization ≥1 day (*)	1
ICU/CCU stay	1
Age >60 years	1
D dimer≥ 2X UNL	2

(*) Modified for the MARINER clinical trial | ICU = intensive care unit; CCU = critical care unit.

Spyropoulos AC et al Chest 2011; 140:706-14

Rivaroxaban is not approved for patients admitted or discharged for an acute medical illness by EMEA

PRIMARY EFFICACY/SAFETY OUTCOMES



*Composite of composite of symptomatic VTE, VTE-related death, asymptomatic VTE (Doppler and AngioCT scan) and symptomatic ATE, MI, non-hemorrhagic stroke, (MALE), and cardiovascular death at day 35.

Anticoagulation use in COVID-19 patients

What do we expect anticoagulation to achieve?

- Prevent macrovascular venous and arterial thrombosis
- Prevent or mitigate microvascular thrombosis
  - Progression of COVID-19 represented by need for cardiac or pulmonary "organ support" or admission to ICU or need for ECMO
  - Decreased mortality

COVID-19 thrombosis and inpatient anticoagulation

Benefit of increased or therapeutic doses of anticoagulants not clear

Guidelines vary:

- all currently suggest prophylactic dose heparin in ICU patients
- NICE UK guidelines
  - prophylactic dose for ICU patients
  - Consider treatment dose for adults requiring low flow 02 and no bleeding risk
- Ontario Science Advisory Table
  - Therapeutic dose anticoagulation may be considered over prophylactic dose anticoagulation in moderately ill patients who are felt to be at low risk of bleeding. All other patients should receive prophylactic dose anticoagulation.
- Waiting for ASH, ISTH, and others

COVID-19 inpatient anticoagulation and mortality

Benefit of anticoagulation on **mortality?**

- Too late for ICU patients to prevent mortality due to COVID-19
  - What does it mean that approximately 50% got intermediate dose?
  - Decreased arterial and venous thrombosis with therapeutic dose?
- mpRCT moderately ill: 4% difference in composite outcome with 0.7% major bleeding
  - Roughly 3% difference in organ support free days with many questions about data
  - No difference in survival to discharge
- mpRCT investigators assessing patient characteristics to determine what subsets of moderately ill truly benefit

Summary: what to do today

All hospitalized patients should get at least standard VTE prophylactic dose anticoagulation if no contraindications

ICU—standard prophylaxis dose, adjusted for weight and renal function

Moderately ill—carefully consider therapeutic dose if increased VTE risks and no risk of bleeding, more data on which patients benefit coming soon

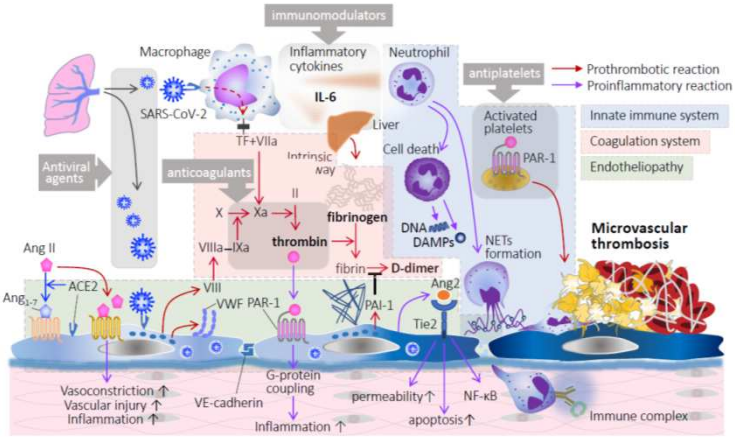
Ambulatory newly diagnosed: no need for antithrombotic treatment

Post-discharge: consider using for those with known increased VTE risk as with any post-discharge patients

Anticoagulation and COVID-19

Anticoagulation alone does not appear to be sufficient to ameliorate the thromboinflammation associated with COVID-19

Multiple pathways require multiple strategies



Connors, Iba, Gandhi, *Clinical Infectious Diseases*, 2021