Anticoagulation Prophylaxis in COVID-19

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Potential Conflict of Interest

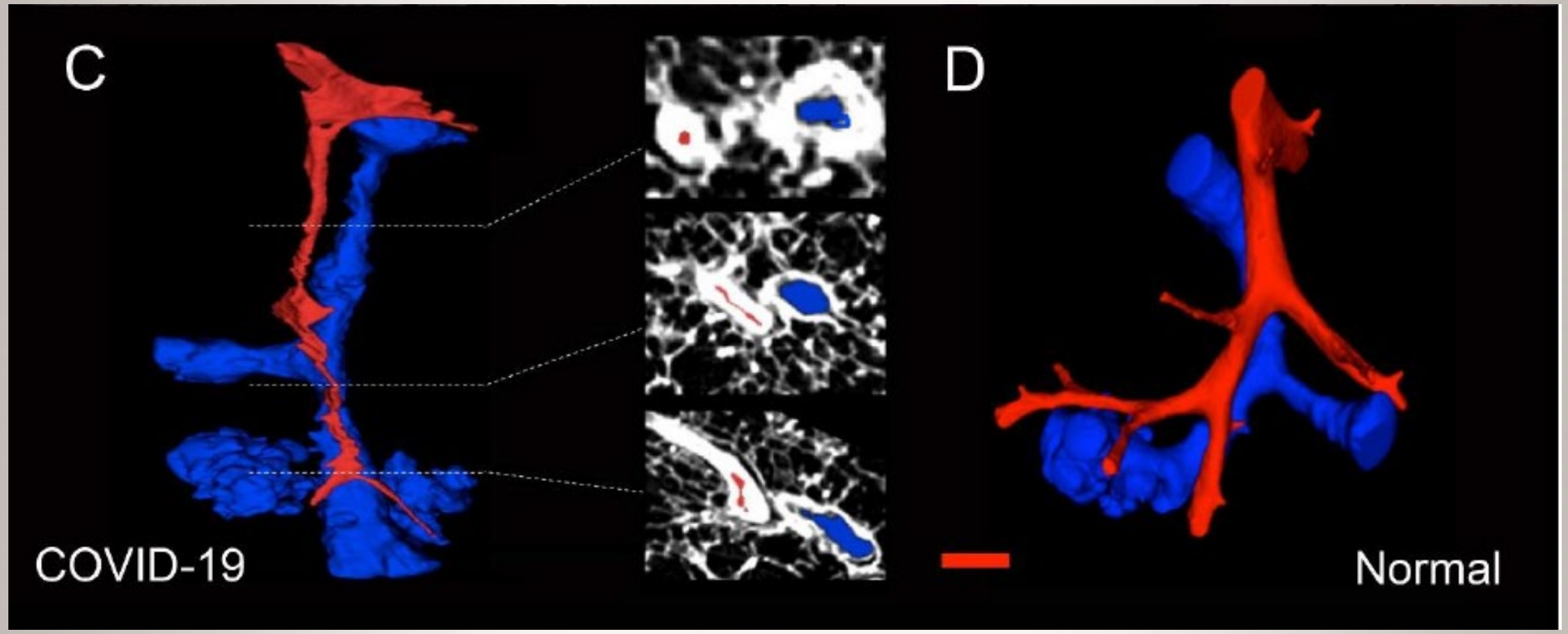
- Consultant
  - Janssen
  - Pfizer
  - Bristol Myer Squibb
  - Astra Zeneca
  - Gilead
  - Phase Bio
  - Boston Scientific

- Research funding (to institution)
  - Janssen
  - BMS
  - Osmosis research
  - NIH

- Board membership (non-profit)
  - AC Forum
  - National Blood Clot Alliance Medical and Scientific Advisory Board
  - PERT Consortium


Richard
Lee Kaatz
Amanda,
May you soar above
and watch over
us all.
With much
Love.

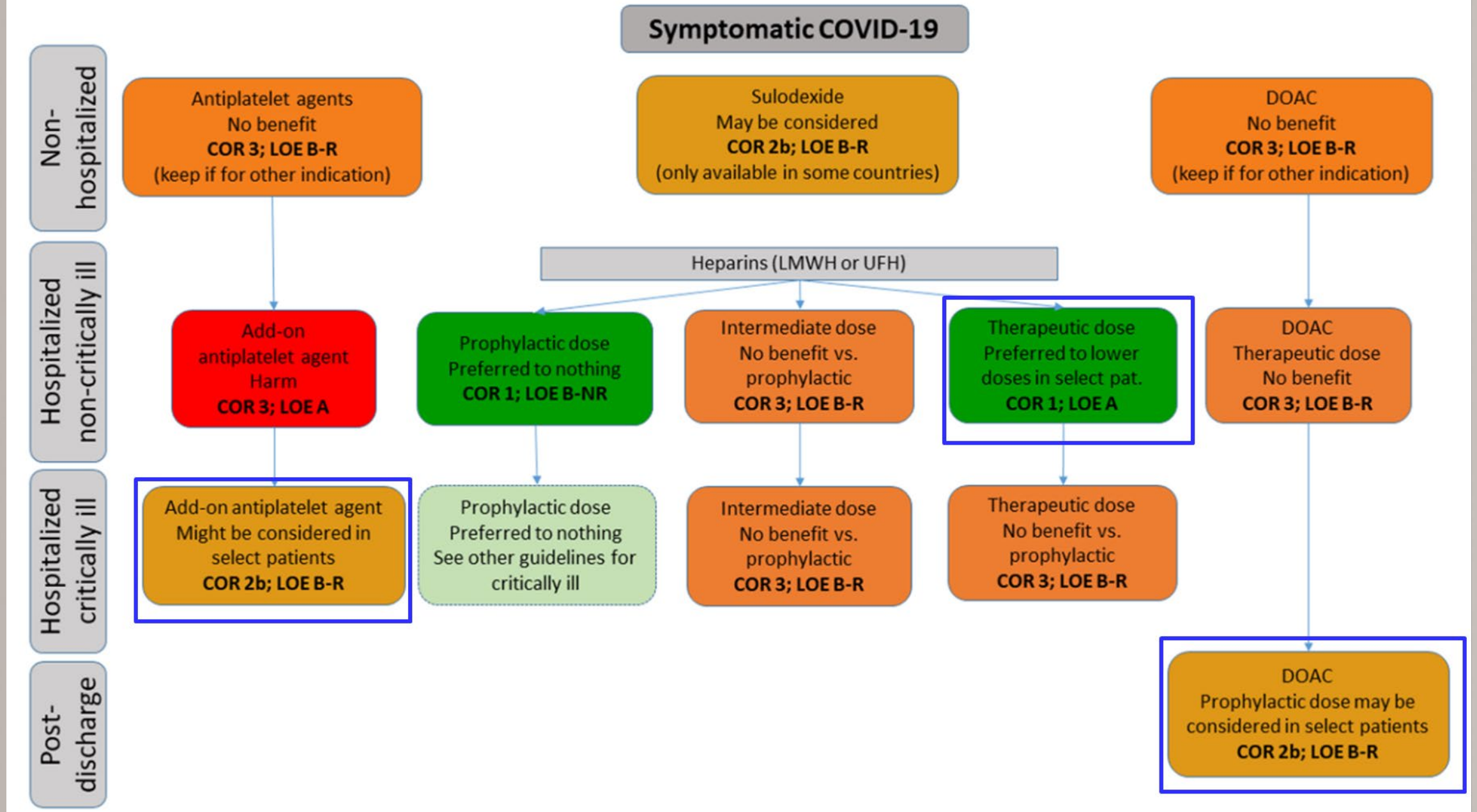
COVID-19 Immuno-micro Thrombosis
Series of 7 Autopsies



Ackermann M. N Engl J Med. 2020 May 21. PMID: 32437596.

Anticoagulation Prophylaxis in COVID-19

- Outpatient ‘pre’ hospitalization
- Inpatient on the floor
- ICU (need for organ support with high flow oxygen, mechanical ventilation or pressor/inotrope support)
- Post-hospital discharge


Symptomatic COVID-19
Non-hospitalized
Hospitalized non-critically ill
Hospitalized critically ill
Post-discharge
Antiplatelet agents
No benefit
COR 3; LOE B-R
(keep if for other indication)
Sulodexide
May be considered
COR 2b; LOE B-R
(only available in some countries)
DOAC
No benefit
COR 3; LOE B-R
(keep if for other indication)
Heparins (LMWH or UFH)
Add-on antiplatelet agent
Harm
COR 3; LOE A
Prophylactic dose
Preferred to nothing
COR 1; LOE B-NR
Intermediate dose
No benefit vs. prophylactic
COR 3; LOE B-R
Therapeutic dose
Preferred to lower doses in select pat.
COR 1; LOE A
DOAC
Therapeutic dose
No benefit
COR 3; LOE B-R
Add-on antiplatelet agent
Might be considered in select patients
COR 2b; LOE B-R
Prophylactic dose
Preferred to nothing
See other guidelines for critically ill
Intermediate dose
No benefit vs. prophylactic
COR 3; LOE B-R
Therapeutic dose
No benefit vs. prophylactic
COR 3; LOE B-R
DOAC
Prophylactic dose may be considered in select patients
COR 2b; LOE B-R

COR	LOE	
3: No Benefit	B-R	1. In non-hospitalized patients with symptomatic COVID-19, initiation of antiplatelet therapy is not effective to reduce risk of hospitalization, arterial or venous thrombosis, or mortality.[9]
3: No Benefit	B-R	2. In non-hospitalized patients with symptomatic COVID-19, initiation of direct oral anticoagulant (DOAC) therapy is not effective to reduce risk of hospitalization, arterial or venous thrombosis, or mortality.[9-11]
2b	B-R	3. In non-hospitalized patients with COVID-19 at higher risk of disease progression, initiation of oral sulodexide therapy within 3 days of symptom onset may be considered to reduce risk of hospitalization.[12]

Non-hospitalized

Bottom line

- No antiplatelet
- No DOAC
- No LMWH (not in the guideline)

ACTIV 4B

- Question: In clinically stable symptomatic COVID-19 patients, can anticoagulants or anti-platelets reduce major cardiopulmonary events?
- Design: RCT, double-blind, ITT, 1:1:1:1 ratio
- Patients: 558 at 52 site in the US
- Interventions
  - ASA 81 mg qd
  - Apixaban 2.5 mg bid
  - Apixaban 5 mg bid
- Comparison: Placebo
- Outcome: Composite of symptomatic deep venous thrombosis, pulmonary embolism, arterial thromboembolism, myocardial infarction, ischemic stroke, hospitalization for cardiovascular or pulmonary events, and all-cause mortality
  - Safety: Major bleeding and clinically relevant nonmajor bleeding
- Timeframe: 45 days

ACTIV 4B

	No. (%)			
	Aspirin (81 mg once daily) (n = 144)	Apixaban (2.5 mg twice daily) (n = 135)	Apixaban (5 mg twice daily) (n = 143)[a]	Placebo (n = 136)[a]
Adjudicated outcomes[d]				
Composite primary end point	0	1 (0.7)	2 (1.4)	0
Risk difference (in percentage points) vs placebo (95% CI)	0	0.7 (-2.1 to 4.1)	1.4 (-1.5 to 5.0)	
Components of primary end point				
Cardiopulmonary hospitalizations	0	1 (0.7)	2 (1.4)	0
Deep vein thrombosis or pulmonary embolism	0	0	0	0
Myocardial infarction, stroke or other arterial embolism	0	0	0	0
Death	0	0	0	0
Adjudicated hemorrhagic events[f]				
Major bleeding	0	0	0	0
Clinically relevant nonmajor bleeding	0	1 (0.7)	1 (0.7)	0

Bottom line

- Rate of venous and arterial events very low in COVID-19 outpatients
- Rate of major or clinically relevant non-major bleeding low

Anticoagulation Prophylaxis in COVID-19

- Outpatient ‘pre’ hospitalization
- **Inpatient on the floor**
- ICU (need for organ support with high flow oxygen, mechanical ventilation or pressor/inotrope support)
- Post-hospital discharge

COR	LOE	
1	B-NR	4. In non-critically ill patients hospitalized for COVID-19, low (prophylactic) dose LMWH or UFH is recommended in preference to no LMWH or UFH to reduce risk of thromboembolism and possibly death.[20-26]
1	A	5. In select non-critically ill patients hospitalized for COVID-19, therapeutic-dose LMWH or UFH is beneficial in preference to low (prophylactic) or intermediate dose LMWH or UFH to reduce risk of thromboembolism and end organ failure.[27-30]
3: No Benefit	B-R	6. In non-critically ill patients hospitalized for COVID-19, intermediate-dose LMWH or UFH is not recommended in preference to low (prophylactic) dose LMWH or UFH to reduce risk of thromboembolism and other adverse outcomes.[20,31-34]
3: Harm	A	7. In non-critically ill patients hospitalized for COVID-19, add-on treatment with an antiplatelet agent is potentially harmful and should not be used.[35,36]
3: No Benefit	B-R	8. In non-critically ill patients hospitalized for COVID-19, therapeutic-dose DOAC is not effective to reduce risk of thromboembolism and other adverse outcomes.[37]

Hospitalized Non-critically Ill

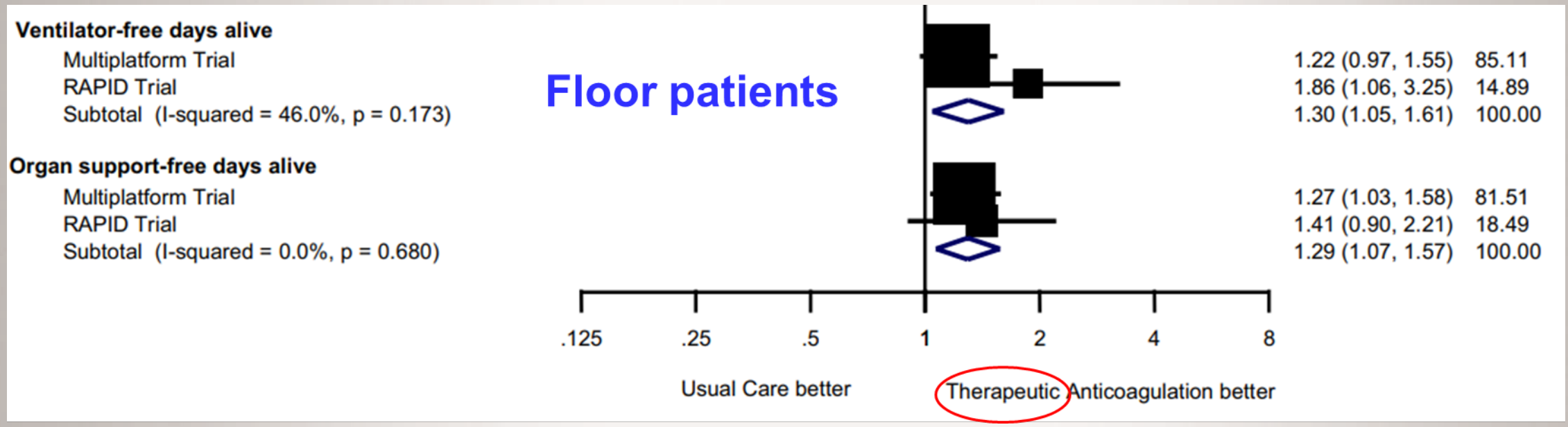
Bottom line

- Prophylactic LMWH at least in almost all patient
- Select patients, therapeutic LMWH
- Don’t use intermediate dose
- Don’t add antiplatelets
- Don’t use DOAC for prophylaxis

Schulman S. J Thromb Haemost. 2022 Jul 8:10.1111/jth.15808. PMID: 35906716

Henry Ford Health System

Systematic Review of 4 COVID-19 RCTs on LMWH/Heparin Anticoagulation Dosing



- In the mpRCT
  - Absolute risk reduction of 4% (NNT = 25) for alive without ICU care
  - Absolute increase in major bleeding of 0.9% (NNH = 111)
- Bottom line: Therapeutic LMWH (heparin for renal failure) in low bleed risk

ACTION trial – therapeutic rivaroxaban in COVID-19 patients mostly on the floor

- Question: Is therapeutic anticoagulation primarily with rivaroxaban better than prophylactic dose in hospitalized COVID-19?
- Design: RCT, open label
- Patients: 615 hospitalized with COVID-19 with elevated D-dimer at 31 Brazilian sites from June 24, 2020, to February 26, 2021
  - Approximately 90% moderately ill
- Intervention: Rivaroxaban 20 mg (15 mg if CrCL 30-49) for 30 days
  - initial therapeutic does enoxaparin or heparin if unstable
- Comparison: Prophylactic dose enoxaparin or heparin while in hospital and provider discretion for extended prophylaxis
- Outcome: Hierarchical composite of time to death, duration of hospitalization or duration of oxygen
- Timeframe: 30 Days

- No difference in primary outcome
- No difference in VTE
- No difference in death

- More major or clinically relevant non-major bleeding

- Bottom line
  - Use primarily LMWH or heparin and not a DOAC

Anticoagulation Prophylaxis in COVID-19

- Outpatient ‘pre’ hospitalization
- Inpatient on the floor
- **ICU (need for organ support with high flow oxygen, mechanical ventilation or pressor/inotrope support)**
- Post-hospital discharge

Hospitalized Critically Ill

COR	LOE	
3: No Benefit	B-R	9. In critically ill patients hospitalized for COVID-19, intermediate dose LMWH/UFH is not recommended over prophylactic dose LMWH/UFH to reduce risk of adverse events, including mortality and thromboembolism.[45-47]
3: No Benefit	B-R	10. In critically ill patients hospitalized for COVID-19, therapeutic dose LMWH/UFH is not recommended over usual-care or prophylactic dose LMWH/UFHs.[28,48,49]*
2b	B-R	11. In select critically ill patients hospitalized for COVID-19, add on treatment with an antiplatelet agent to prophylactic dose LMWH/UFH is not well established but might be considered to reduce mortality.[36,50]

Bottom line

- Prophylactic LMWH in most
- Intermediate dose LMWH/UFH not recommended
- Therapeutic dose LMWH/UFH not recommended
- Might consider adding antiplatelet agent

Schulman S. J Thromb Haemost. 2022 Jul 8:10.1111/jth.15808. PMID: 35906716
Spyropoulos AC. J Thromb Haemost. 2022 Jul 7:10.1111/jth.15809. PMID: 35906715.

Critically Ill COVID-19
mpRCTs – ATTACC, ACTIV-4a and REMAP-CAP

- Question: Will therapeutic LMWH/heparin decrease the need for organ support in critically ill COVID-19?
- Design: RCT, open label
- Patients: 1098 critically ill patients from 9 countries from April 2020 to December 2020
- Intervention: Therapeutic dose LMWH/heparin (89% LMWH)
- Comparison: Usual care, 40% low, remainder intermediate or higher dose
- Outcome: Survival to 21 days and organ support free days
  - High flow oxygen, mechanical ventilation (with or without intubation) vasopressor/inotrope support

Critically Ill COVID-19 mpRCTs – ATTACC, ACTIV-4a and REMAP-CAP

Table 2. Primary and Secondary Outcomes.

Outcome	Therapeutic-Dose Anticoagulation (N = 536)	Usual-Care Thromboprophylaxis (N = 567)	Adjusted Difference in Risk (95% Credible Interval)	Adjusted Odds Ratio (95% Credible Interval)*	Probability of Superiority	Probability of Futility	Probability of Inferiority
	median no. (IQR)		*percentage points*		%	%	%
Organ support–free days up to day 21†‡	1 (–1 to 16)	4 (–1 to 16)	—	0.83 (0.67 to 1.03)	5.0	99.9	95.0
	no. of patients/total no. (%)						
Survival to hospital discharge‡	335/534 (62.7)	364/564 (64.5)	–4.1 (–10.7 to 2.4)	0.84 (0.64 to 1.11)	10.8	99.6	89.2
Major thrombotic events or death§	213/531 (40.1)	230/560 (41.1)	1.0 (–5.6 to 7.4)	1.04 (0.79 to 1.35)	40.3	—	59.7
Major thrombotic events¶	34/530 (6.4)	58/559 (10.4)	—	—	—	—	—
Death in hospital	199/534 (37.3)	200/564 (35.5)	—	—	—	—	—
Any thrombotic events or death§	217/531 (40.9)	232/560 (41.4)	1.5 (–4.9 to 8.0)	1.06 (0.81 to 1.38)	33.4	—	66.6
Any thrombotic events‖	38/530 (7.2)	62/559 (11.1)	—	—	—	—	—
Death in hospital	199/534 (37.3)	200/564 (35.5)	—	—	—	—	—
Major bleeding§	20/529 (3.8)	13/562 (2.3)	1.1 (–0.6 to 4.4)	1.48 (0.75 to 3.04)	12.8	—	87.2

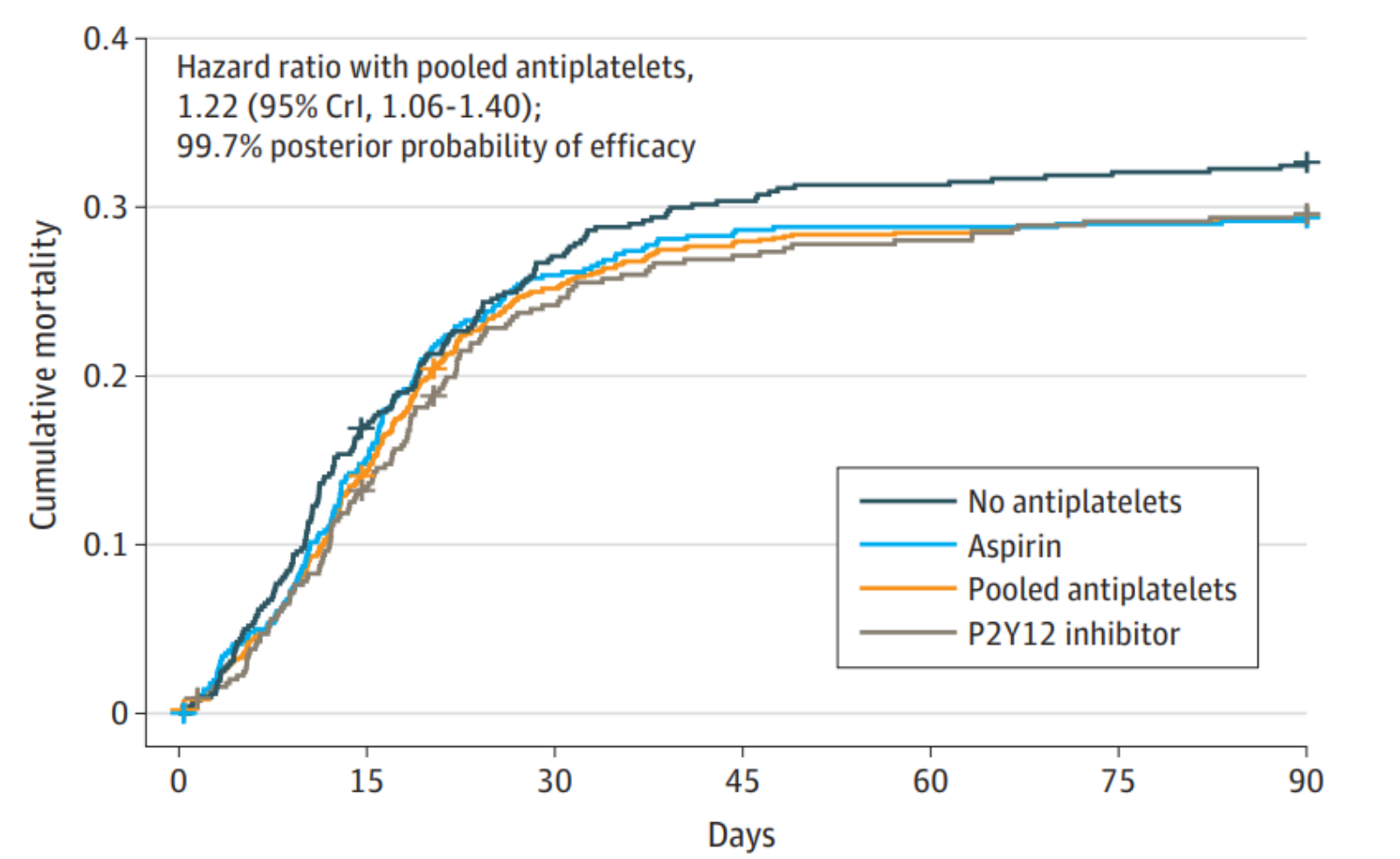
REMAP-CAP Investigators; ACTIV-4a Investigators; ATTACC Investigators, Goligher EC, N Engl J Med. 2021 Aug 26;385(9):777-789. PMID: 34351722

REMAP-CAP Antiplatelet

- Question: Does antiplatelet therapy improve outcomes in critically ill COVID-19?
- Design: 3 arm open label adaptive platform RCT
- Patients: 1557 critically ill COVID-19, October 30, 2020 – June 23, 2021
- Interventions: While in hospital up to 14 days, pooled compared to control
  - ASA (n = 565) 75-100 mg
  - P2Y12 inhibitor with clopidogrel, ticagrelor or prasugrel
- Control: No anti-platelet
- Outcome:
  - Primary efficacy: organ support-free days within 21 days
  - Key secondary: survival at 90 days
  - Primary safety: major bleeding at 14 days

REMAP-CAP Writing Committee for the REMAP-CAP Investigators, Bradbury CA.. JAMA. 2022 Apr 5;327(13):1247-1259. PMID: 35315874.

REMAP-CAP Antiplatelet



- No difference in primary outcome
- 5% decrease mortality at 90 days
- Increased major bleeding by absolute 0.8%
- Gastric protection encouraged

REMAP-CAP Writing Committee for the REMAP-CAP Investigators, Bradbury CA.. JAMA. 2022 Apr 5;327(13):1247-1259. PMID: 35315874.

RECOVERY trial

- Question: What is the efficacy and safety of aspirin in hospitalized patients with COVID-19?
- Design: Open label, ITT, platform RCT from Nov 1, 2020, to March 21, 2021
- Patients: 22,560 primarily in UK
- Intervention: Aspirin 150 mg
- Comparison: Usual care
- Outcome: Mortality at 28 days

RECOVERY Collaborative Group. Lancet. 2022 Jan 8;399(10320):143-151. PMID: 34800427.

RECOVERY trial

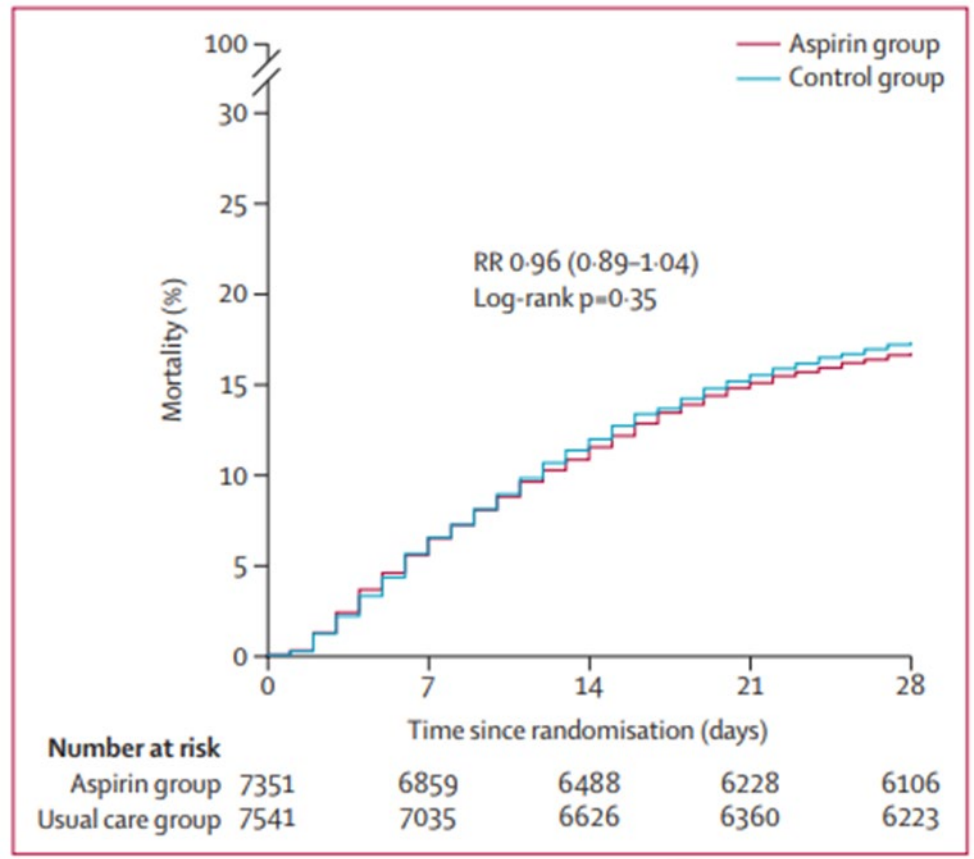


Figure 2: **Effect of allocation to aspirin on 28 day mortality**
RR=rate ratio.

- 34% higher dose LMWH
- In non-ICU patients, no difference in progression to ICU care
- 0.6% reduction in VTE
- 0.6% increase in major bleeding

RECOVERY Collaborative Group. Lancet. 2022 Jan 8;399(10320):143-151. PMID: 34800427.

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Post Discharge

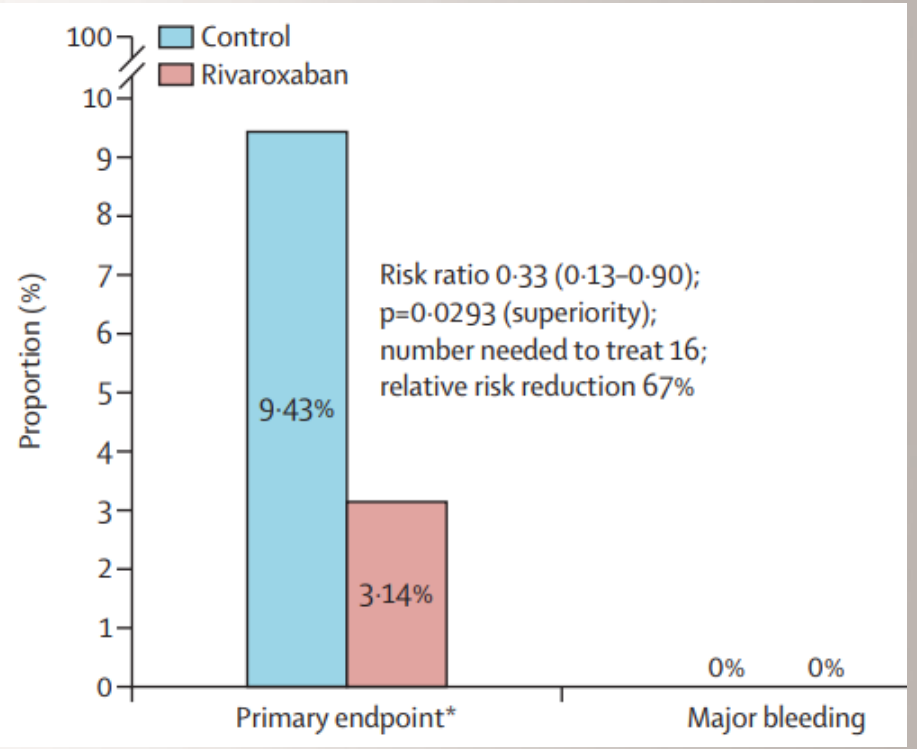
COR	LOE	
2b	B-R	12. In select patients who have been hospitalized for COVID-19, post-discharge treatment with prophylactic dose rivaroxaban for approximately 30 days may be considered to reduce risk of VTE.[55,56]

Bottom line

- Consider rivaroxaban 10 mg daily for 30 days if
  - Low bleeding risk
  - High VTE risk based on IMPROVE DD score

MICHELLE trial

- Question: Does prophylactic dose rivaroxaban prevent major adverse vascular events after discharge for COVID-19?
- Design: RCT, open label
- Patients: 320 patients in 14 hospitals in Brazil from Oct 8, 2020, to June 29, 2021; hospitalized for at least 3 days and receiving standard dose thromboprophylaxis
  - IMPROVE score of 2 or 3 and D-dimer > 500 (62%) or
  - IMPROVE score of ≥ 4 (38%)
- Intervention: Rivaroxaban 10 mg qd (prophylactic dose)
- Comparison: No anticoagulants
- Outcome: Composite of
  - Efficacy composite outcome
    - symptomatic or fatal VTE,
    - **VTE detected at bilateral lower limbs venous duplex scan and computed tomography pulmonary angiogram**
    - symptomatic arterial thromboembolism (MI, non-hemorrhagic stroke, major adverse limb event
    - cardiovascular (CV) death
  - Safety outcome: Major bleeding (ISTH)
- Timeframe: 35 days



- Symptomatic and fatal VTE
  - Rivaroxaban: 0.63%
  - Control: 5.03%
  - P = 0.0148

Anticoagulation Prophylaxis in COVID-19

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Thank you.

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