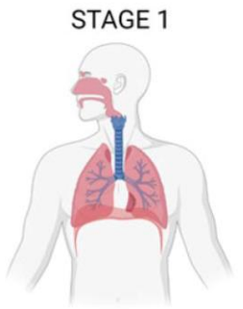
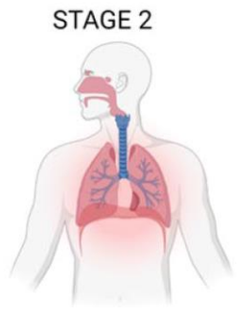
Antithrombotic Therapy in COVID-19

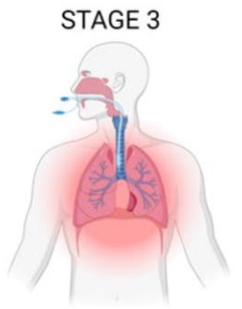
Bulent Kantarcioglu, MD.

Antithrombotic Therapy in COVID-19

- Antithrombotic therapy for non-hospitalized patients. **(Outpatients)**
- Antithrombotic therapy for non-critically ill, hospitalized patients. **(Inpatients)**
- Antithrombotic therapy for critically ill, hospitalized patients. **(ICU Patients)**
- Antithrombotic therapy for patients discharged from hospital. **(Post-discharge Patients)**

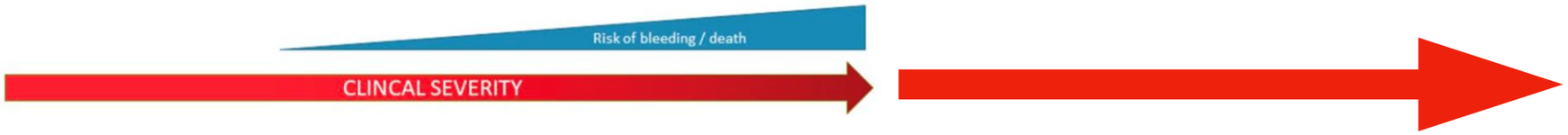






Symptoms	Mild symptoms, no need for respiratory support	More severe symptoms, need for oxygen therapy	Critical illness, mechanical ventilation and organ support
Inflammation	Mild, local	Moderate, local +/- systemic	Hyperinflammation, systemic

D-dimer	2-3 times ULN	3-6 times ULN	> 6 times ULN
Fibrinogen	Normal / increased	Normal / increased	Increased (decreased in DIC)
Platelet count	Normal	100-150 x 10^9/L	< 100-150 x 10^9/L
Prothrombin time	Normal	Normal to minimally prolonged	May be markedly prolonged
DIC	No	No	Possible



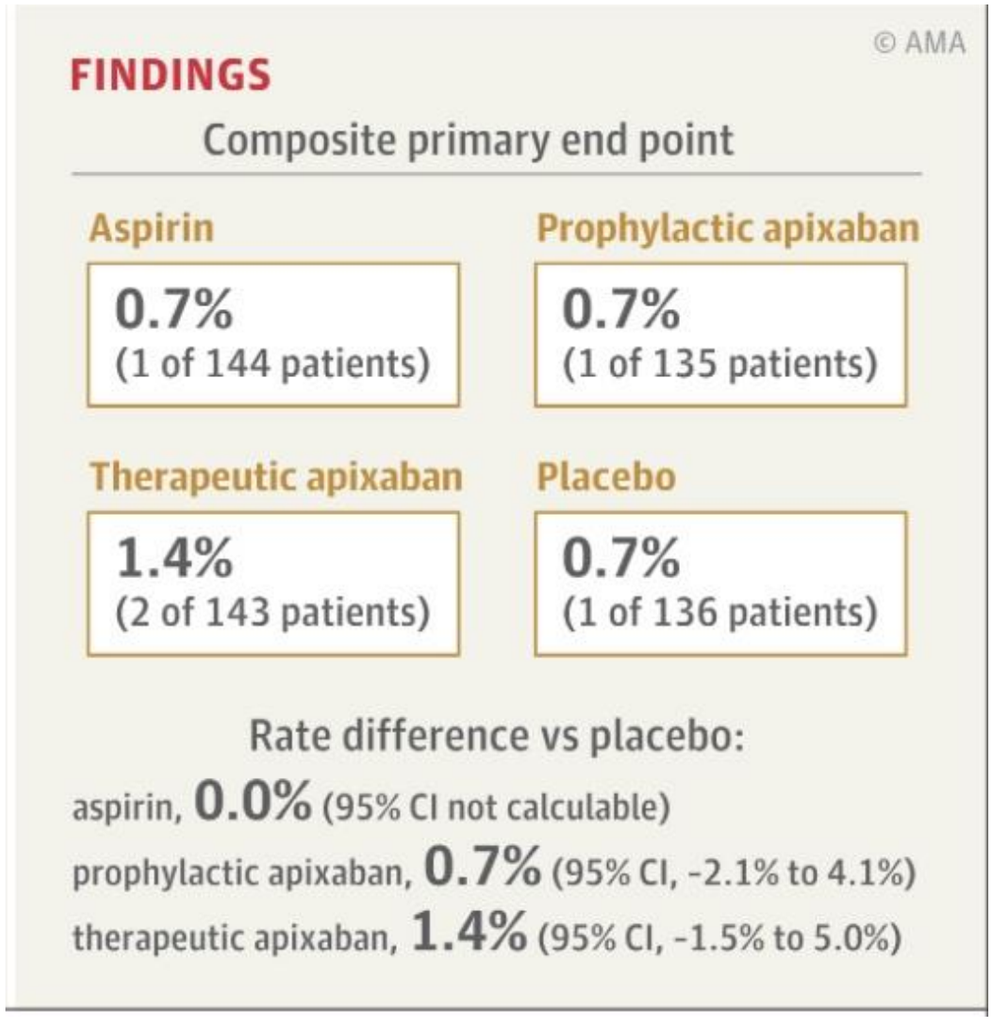
POST-DISCHARGE PERIOD

???

OUTPATIENT THERAPY

ACTIV-4B

- Randomized, double-blind, placebo-controlled trial.
- 657 symptomatic clinically stable outpatients with COVID-19, randomly allocated in a 1:1:1:1 ratio to aspirin (81 mg/day), prophylactic-dose apixaban (2.5 mg bid), therapeutic-dose apixaban (5 mg bid), or placebo (n = 164) for 45 days.
- The study were early terminated because of the lower than anticipated event rates.
- Treatment with aspirin or apixaban compared with placebo did not reduce the rate of a clinical outcomes.

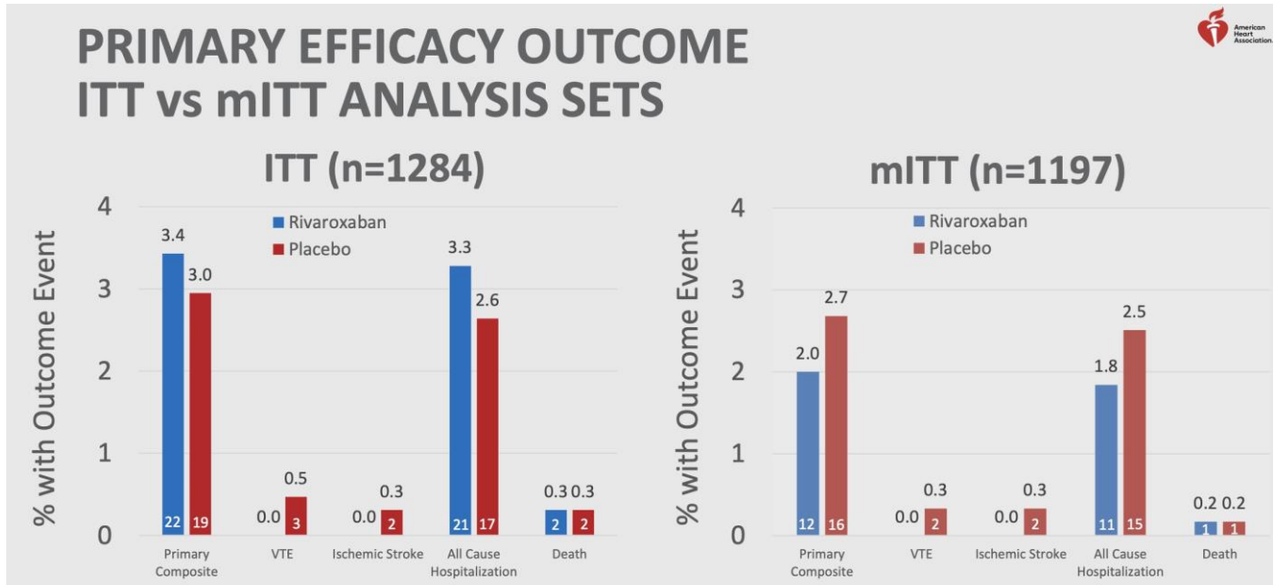


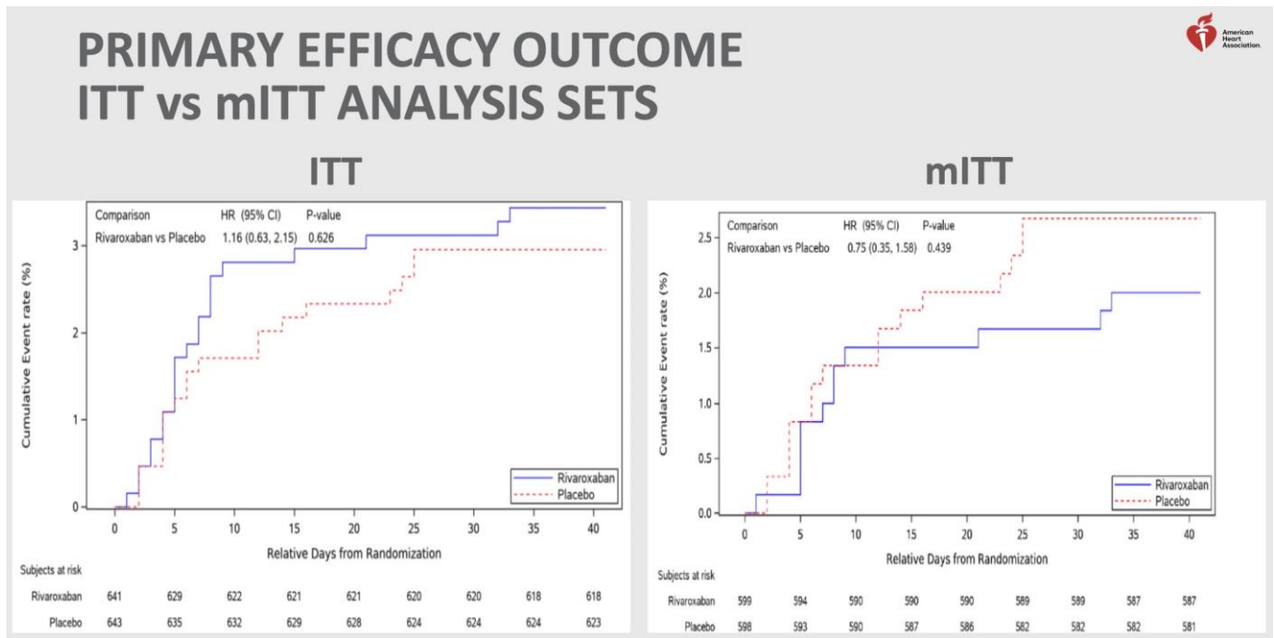
Connors JM, Brooks MM, Sciurba FC, et al. Effect of antithrombotic therapy on clinical outcomes in outpatients with clinically stable symptomatic COVID-19: the ACTIV-4B rando

OUTPATIENT THERAPY

PREVENT-HD

- Randomized, double-blind, placebo-controlled trial.
- Compared rivaroxaban 10 mg for 35 days with placebo in non-hospitalized patients.
- It was not found to reduce composite events of venous and arterial thrombotic events, hospitalization, and death.





OUTPATIENT THERAPY

Ananworanich et al.

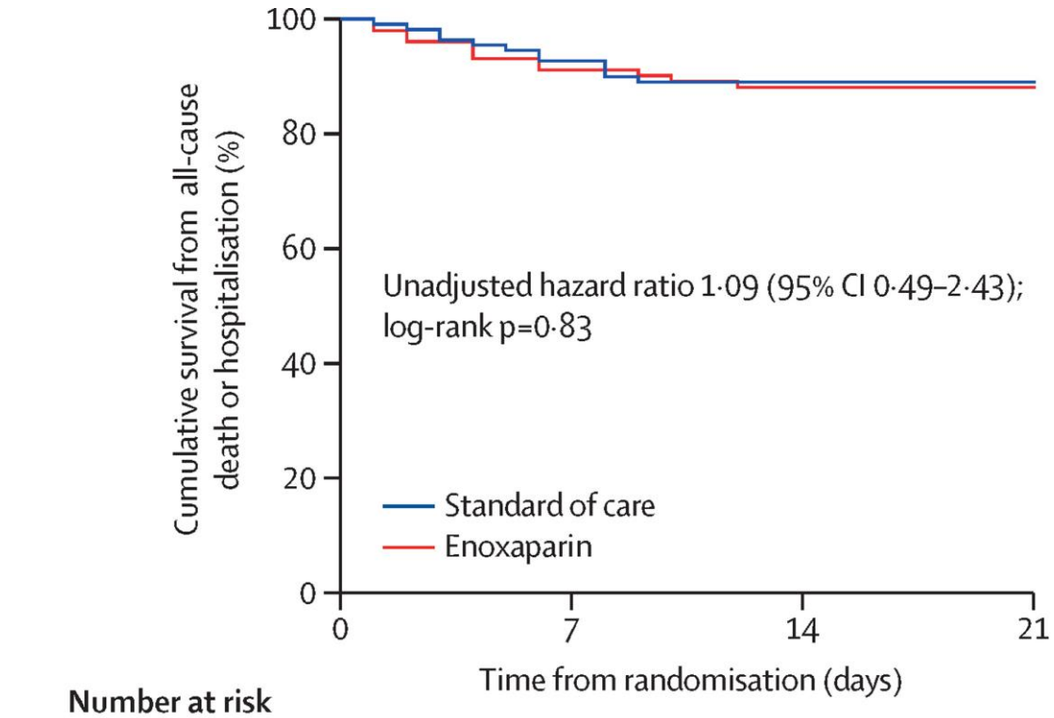
- Double-blind, placebo-controlled RCT comparing rivaroxaban 10 mg vs. placebo.
- Stopped prematurely after enrolling 497 (82%) of target sample size.
- Rivaroxaban did not reduce the disease progression in high-risk adults with mild COVID-19.

Ananworanich J, et al. Randomized Study of Rivaroxaban vs Placebo on Disease Progression and Symptoms Resolution in High-Risk Adults With Mild Coronavirus Disease 2019

OUTPATIENT THERAPY

ETHIC

- Open-label RCT of standard-intensity prophylactic anticoagulation with enoxaparin for 21 days vs. standard of care.
- Primary outcome was composite of death or hospitalization.
- Enoxaparine did not reduce the clinical outcomes.



OUTPATIENT THERAPY

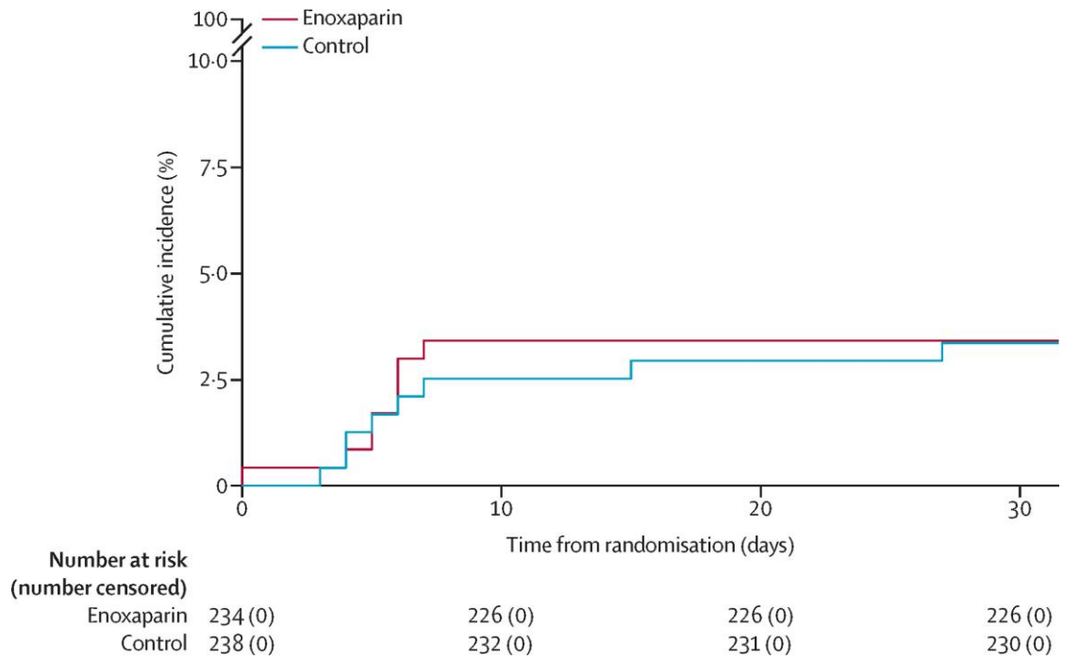
OVID Study

- Open-label RCT comparing standard intensity prophylactic anticoagulation with enoxaparin for 14 days vs. standard of care.

- Primary outcome was composite of death or hospitalization.

- Stopped prematurely after 472 (51%) of the original sample size was enrolled due to futility in interim analysis.

- Enoxaparin therapy did not reduce the adverse outcomes.

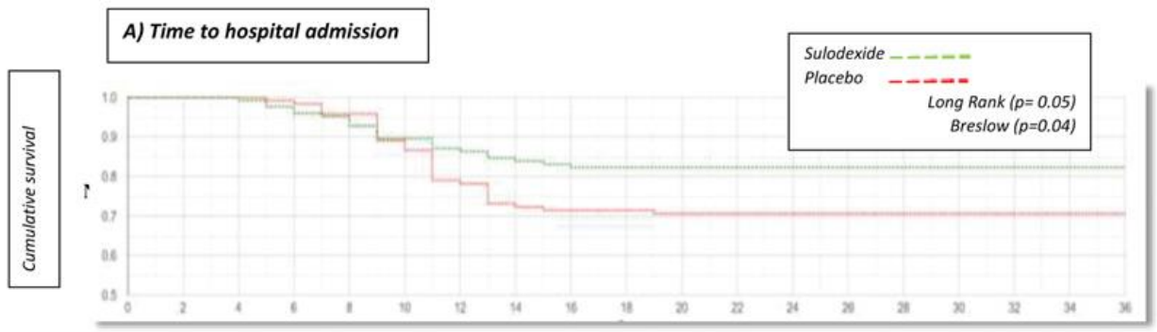


Barco S, Voci D, Held U, et al. Enoxaparin for primary thromboprophylaxis in symptomatic outpatients with COVID-19 (OVID): a randomised, open-label, parallel-group, multic

OUTPATIENT THERAPY

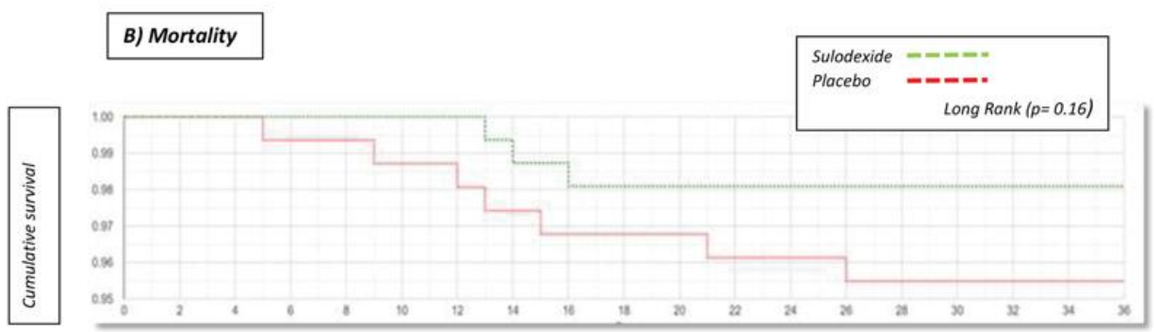
Gonzalez-Ochoa AJ et al.

- Randomized Controlled Trial evaluated Sulodexide vs. placebo.
- Primary outcome was composite of hospitalization, supplemental oxygen requirement and mortality.
- Treatment of COVID-19 patients with sulodexide, when provided within 3 days of clinical onset, improved their clinical outcomes.
- There were no between-group differences in thromboembolic events, major bleeding, or mortality.



Number at risk — Days from randomization

Sulodexide	124	123	112	104	102	102
Placebo	119	119	109	83	84	84
Day	0	5	10	15	20	26



Number at risk — Days from randomization

Sulodexide	124	124	122	122	121	121
Placebo	119	118	117	114	114	112
Day	0	5	10	15	20	26

Gonzalez-Ochoa AJ, Raffetto JD, Hernández AG, et al. Sulodexide in the Treatment of Patients with Early Stages of COVID-19: A Randomized Controlled Trial. *Thromb Haemost*. 2

INPATIENT THERAPY

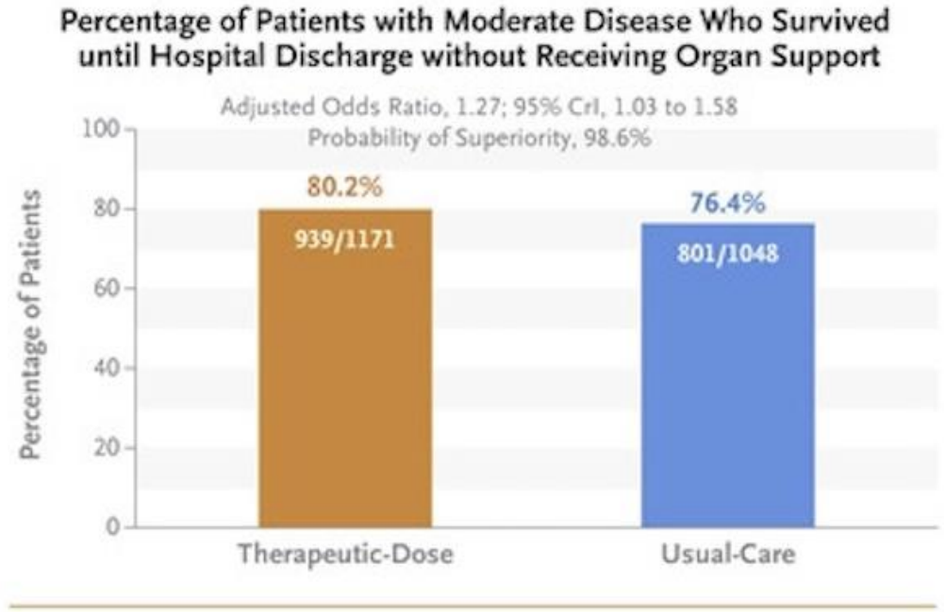
Multiplatform Trial

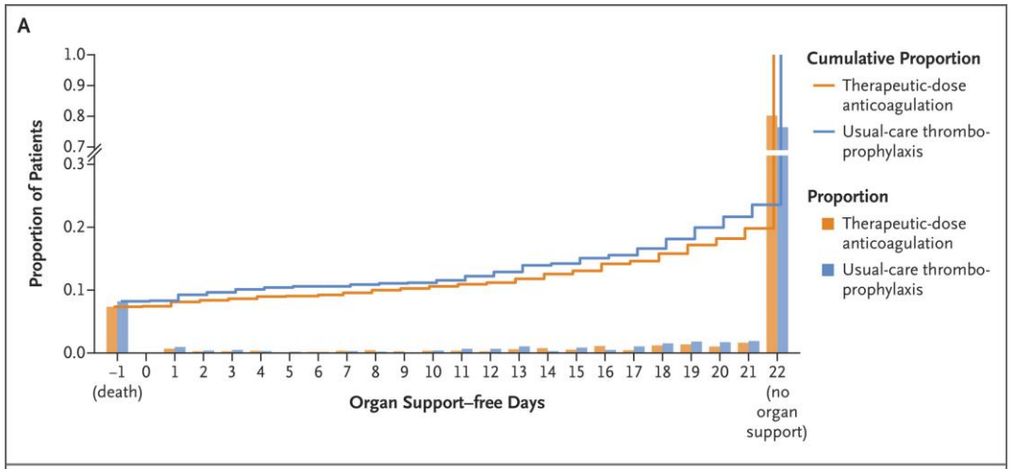
- Open-label, adaptive, multiplatform, RCT comparing full-intensity prophylactic anticoagulation vs. usual care.

- Combined the results of 3 RCTs. (ACTIV-4A/ ATTACC/ REMAP-CAP)

- Trial stopped for superiority after enrolling 2219 participants.

- Full-intensity anticoagulation had a high probability of increasing organ-support-free days, and also reduced in-hospital mortality.





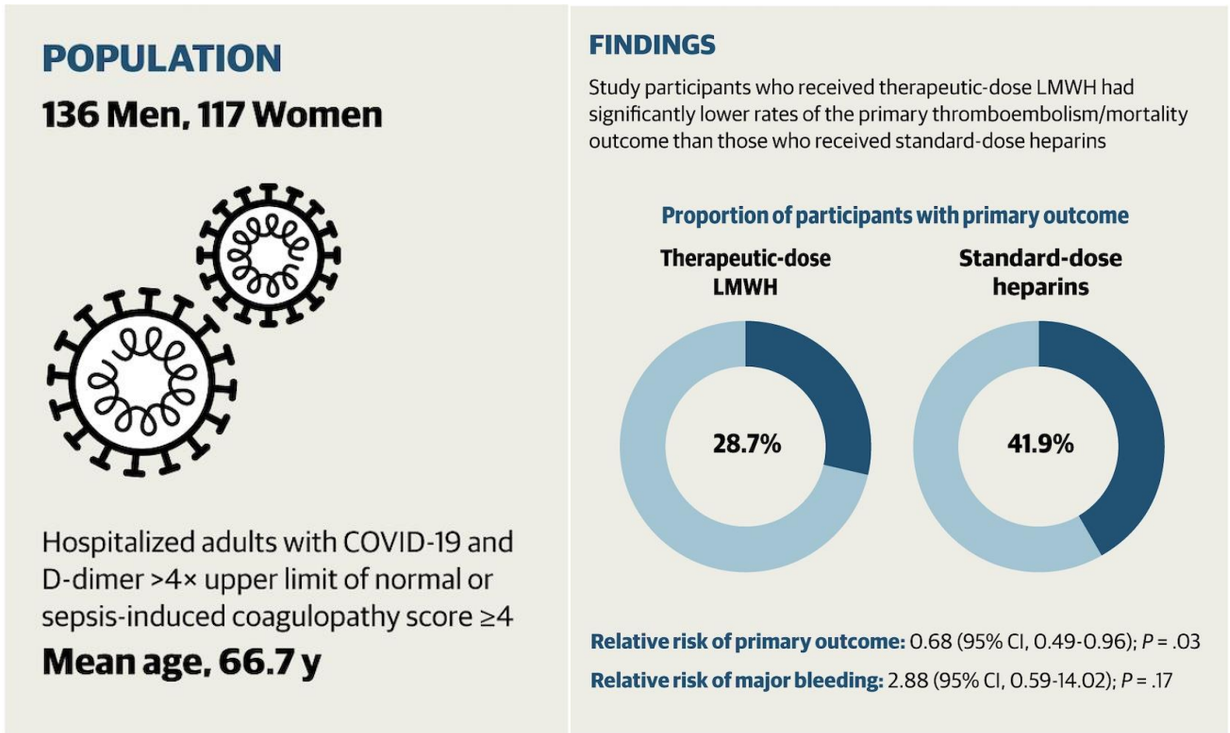
ATTACC Investigators; ACTIV-4a Investigators; REMAP-CAP Investigators, et al. Therapeutic Anticoagulation with Heparin in Noncritically Ill Patients with Covid-19. *N Engl J Me*

HEPCOVID Trial

- Multicenter randomized clinical trial recruited hospitalized adult patients with COVID-19 with D-dimer levels more than 4 times the upper limit of normal or sepsis-induced coagulopathy score of 4 or greater.

- Therapeutic dose heparins reduced the incidence of major thromboembolism or death compared to prophylactic/intermediate-dose heparins.

- This observation were not evident in the critically ill patients that were included in the study (~33%).



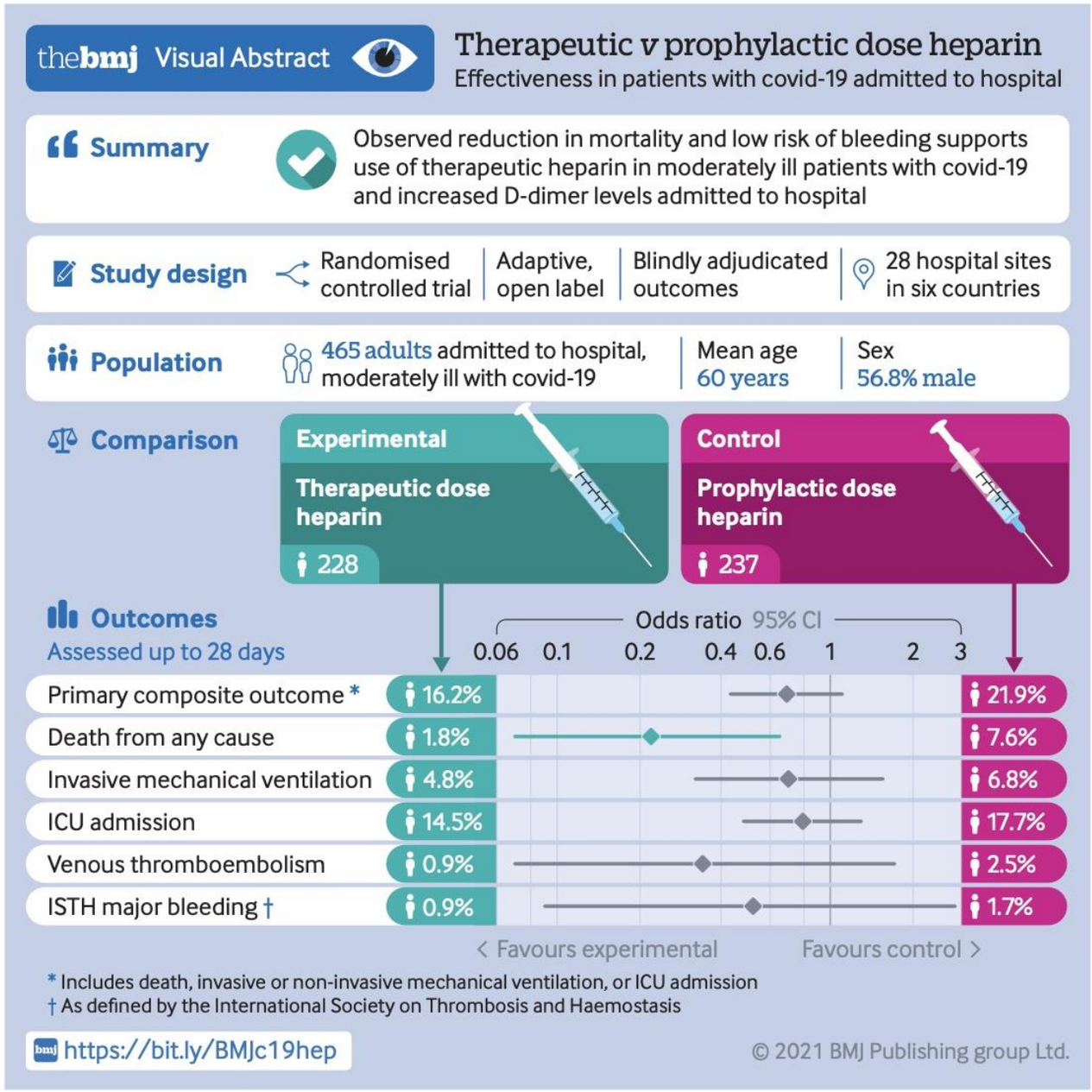
Spyropoulos AC, Goldin M, Giannis D, et al. Efficacy and Safety of Therapeutic-Dose Heparin vs Standard Prophylactic or Intermediate-Dose Heparins for Thromboprophylaxis i

RAPID Trial

- Randomised controlled, adaptive, open label clinical trial comparing therapeutic heparin with prophylactic heparin in 465 adult patients.

- In moderately ill inpatients with COVID-19 and increased D-dimer levels, therapeutic heparin was not significantly associated with a reduction in the primary outcome but the odds of death at 28 days was decreased.

- The risk of major bleeding were low in this trial.



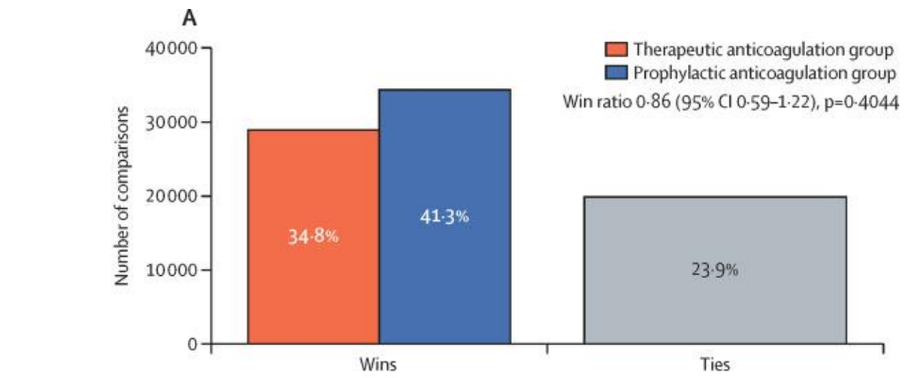
Sholzberg M, Tang GH, Rahhal H, et al. Effectiveness of therapeutic heparin versus prophylactic heparin on death, mechanical ventilation, or intensive care unit admission in mod

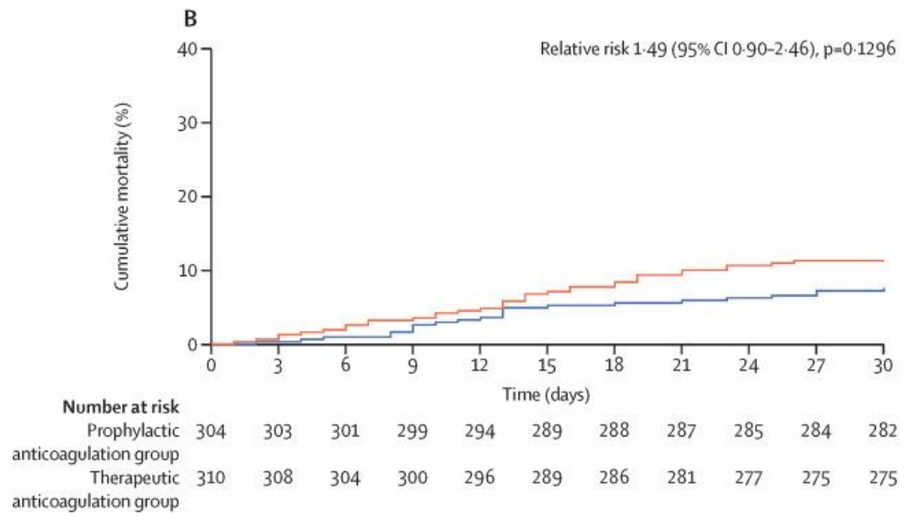
ACTION Trial

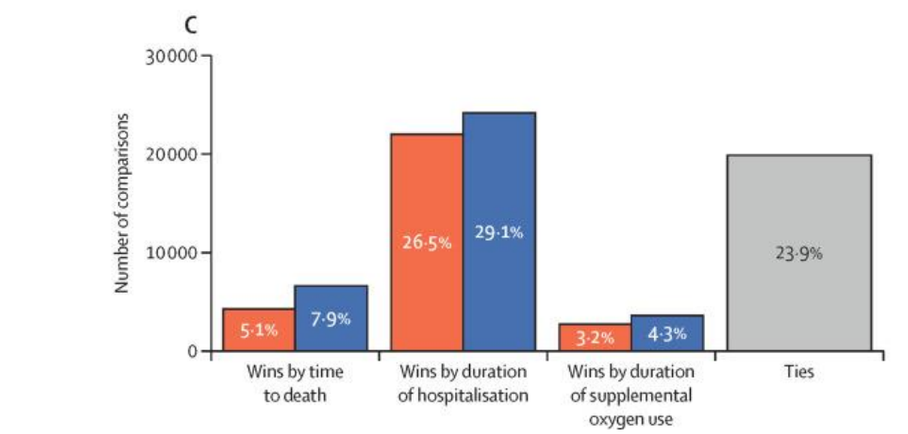
- Pragmatic, open-label (with blinded adjudication), multicentre, randomised, controlled trial, at 31 sites in Brazil.

- 615 hospitalized patients with elevated D-dimer, randomized to rivaroxaban 20mg/d (or full-intensity heparin in unstable patients followed by rivaroxaban until day 30) or standard dose prophylaxis.

- Therapeutic anticoagulation with rivaroxaban or enoxaparin followed by rivaroxaban to day 30 did not improve clinical outcomes and increased bleeding compared with prophylactic anticoagulation.





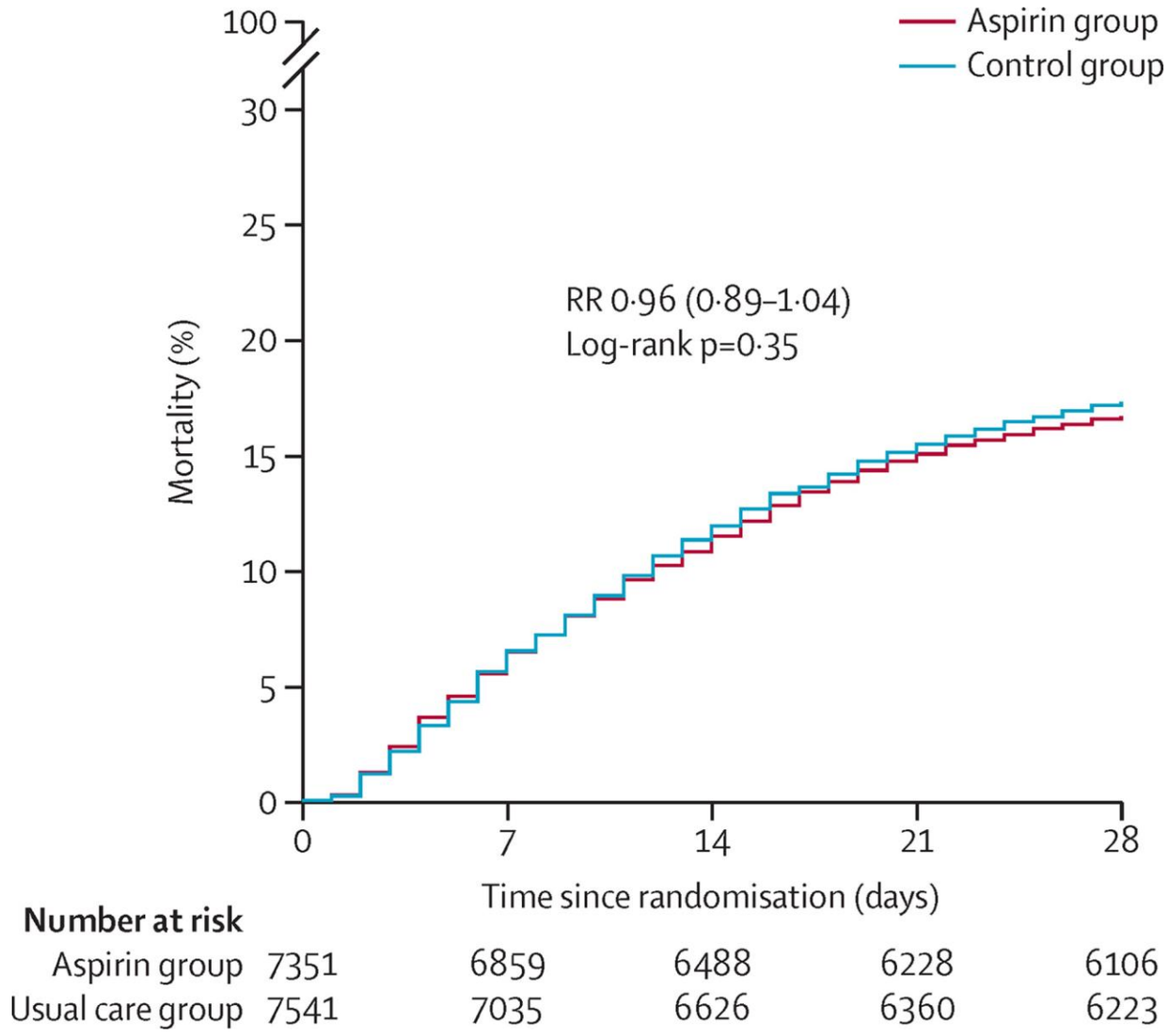


RECOVERY Trial

- Randomised, controlled, open-label, platform trial, several possible treatments were compared with usual care in patients hospitalized with COVID-19.

- Compared aspirin with usual care.

- In patients hospitalized with COVID-19, aspirin was not associated with reductions in 28 day mortality or in the risk of progressing to invasive mechanical ventilation or death, but was associated with a small increase in the rate of being discharged alive within 28 days.



RECOVERY Investigators. Aspirin in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lanc

INPATIENT THERAPY

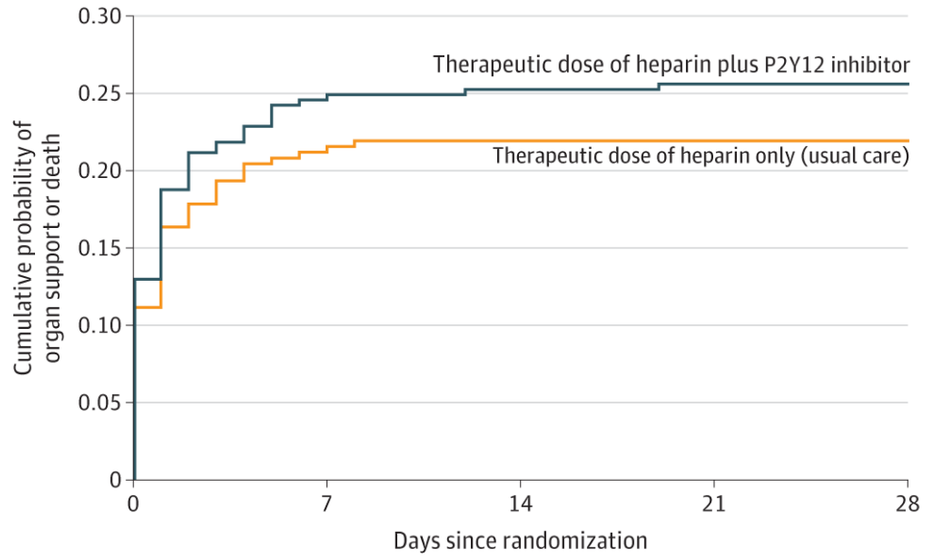
Berger JS et al.

- Open-label, bayesian, adaptive randomized clinical trial including 562 non–critically ill patients hospitalized for COVID-19.

- Compared therapeutic dose of heparin plus a P2Y12 inhibitor with therapeutic dose of heparin only.

- Ticagrelor was the preferred P2Y12 inhibitor.

- Addition of P2Y12 inhibitor to therapeutic dose of heparin did not result in an increased odds of improvement in organ support–free days within 21 days during hospitalization.



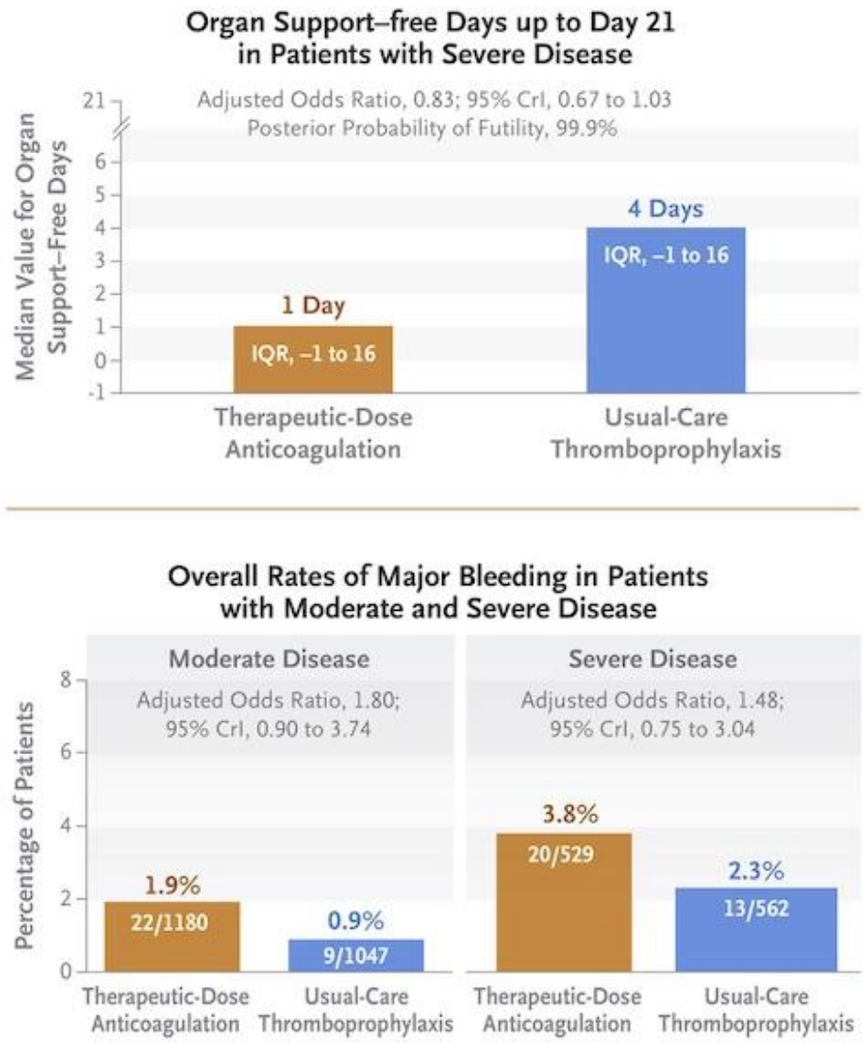
No. at risk

Heparin plus P2Y12 inhibitor	293	222	220	219	218
Heparin only	269	213	210	210	210

Berger JS, Kornblith LZ, Gong MN, et al. Effect of P2Y12 inhibitors on survival free of organ support among non-critically ill hospitalized patients with CO

Multiplatform Trial

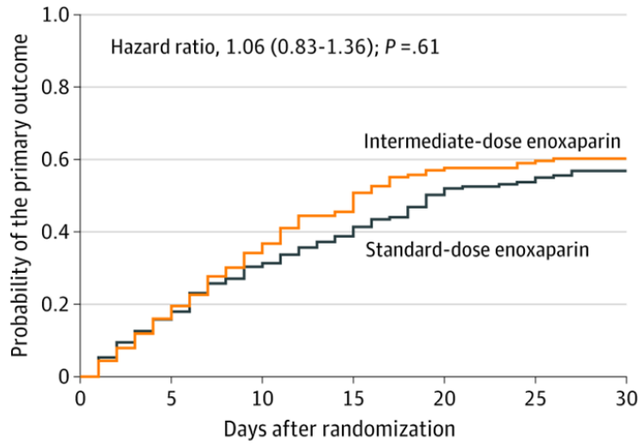
- Open-label, adaptive, multiplatform, RCT comparing full-intensity prophylactic anticoagulation vs. usual care.
- Combined the results of 3 RCTs. (ACTIV-4A/ ATTACC/ REMAP-CAP)
- 1,098 critically-ill patients with COVID-19 randomized to full-intensity heparin-based prophylactic anticoagulation vs usual care.
- Organ support–free days was the primary outcome.
- The trial was stopped when the prespecified criterion for futility was met for therapeutic-dose anticoagulation.



Goligher EC, Bradbury CA, McVerry BJ, et al. Therapeutic anticoagulation with heparin in critically ill patients with Covid-19. N Engl J Med. 2021; 385: 777-89.

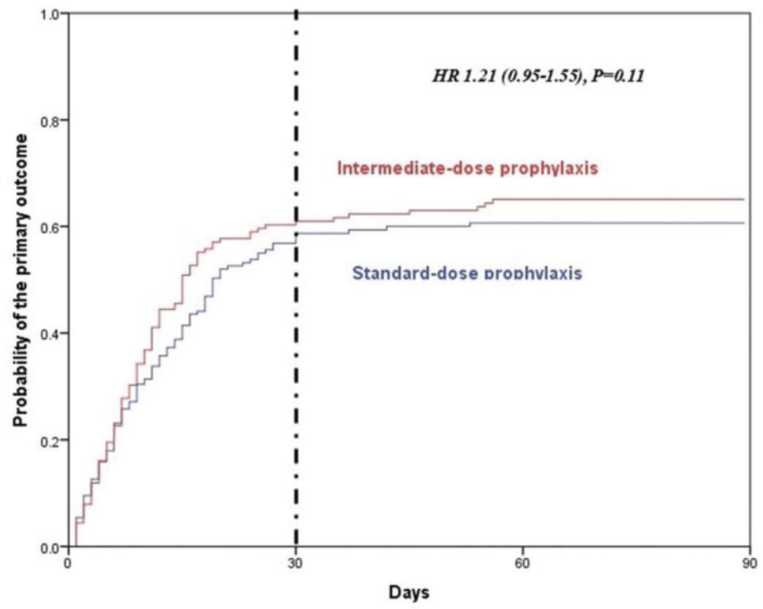
INSPIRATION Trial

- An open label randomized controlled trial (INSPIRATION) study.
- Patients with COVID-19 admitted to intensive care were randomized to intermediate-dose versus standard-dose prophylactic anticoagulation for 30 days.
- Intermediate-dose compared with standard-dose prophylactic anticoagulation did not reduce a composite of death, treatment with ECMO, or venous or arterial thrombosis at 30-days and 90-day follow-up.



No. of patients at risk

Intermediate dose							
Total	276	235	196	175	156	154	150
Primary outcome	0	41	39	21	19	2	4
All-cause mortality	0	37	41[a]	20	16	2	2
VTE	0	4	1	1	2	0	0
Ischemic stroke	0	0	0	0	1	0	0
Standard dose							
Total	286	244	211	194	173	167	160
Primary outcome	0	42	33	17	21	6	7
All-cause mortality	0	38	29	17[a]	21[a]	6	6
VTE	0	3	4	1	2[b]	0	1
Ischemic stroke	0	1	0	0	0	0	0



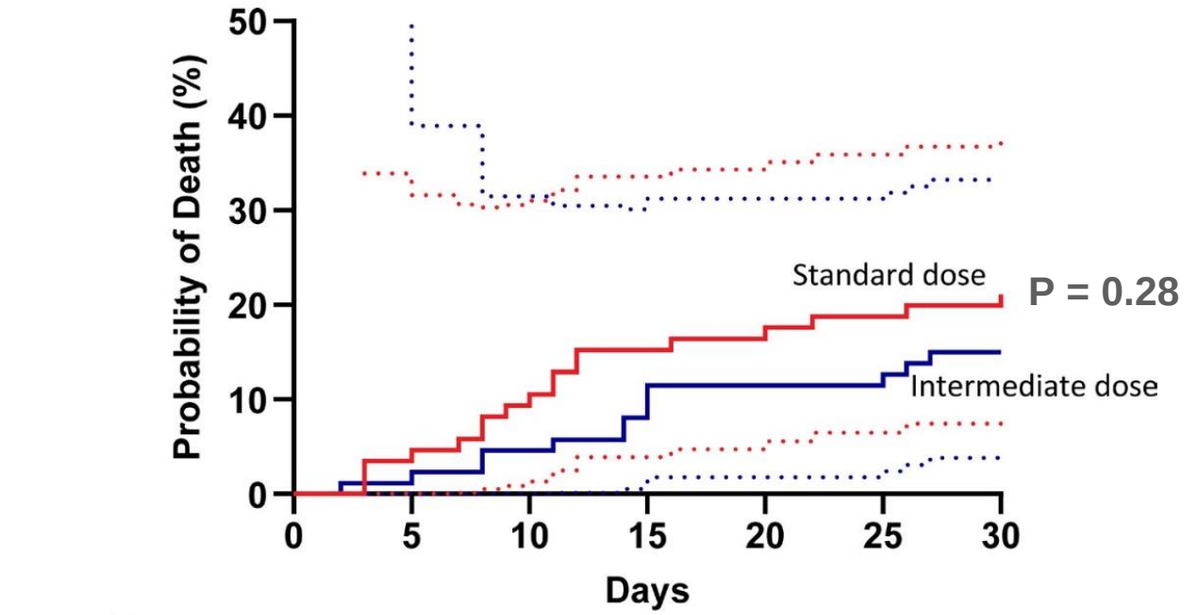
No. at risk				
Intermediate-dose	276	150	144	144
Standard-dose	286	160	156	156

Sadeghipour P, Talasaz AH, Rashidi F, et al. Effect of intermediate-dose vs standard-dose prophylactic anticoagulation on thrombotic events, extracorporeal membrane oxygenation treatment, or mortality among patients with COVID-19 admitted to the intensive care unit: the INSPIRATION randomized clinical trial. JAMA. 2021; 325: 1620-30.

Bikdeli B, Talasaz AH, Rashidi F, et al. Intermediate-dose versus standard-dose prophylactic anticoagulation in patients with COVID-19 admitted to the iIntensive care unit: 90-day results from the INSPIRATION randomized trial. Thromb Haemost. 2021; 122: 131-41.

Perepu et al.

- Multi-center, open-label, randomized controlled trial.
- Compared standard prophylactic dose versus intermediate dose enoxaparin.
- In hospitalized adults with severe COVID-19, standard prophylactic dose and intermediate dose enoxaparin did not differ significantly in preventing death or thrombosis at 30 days.



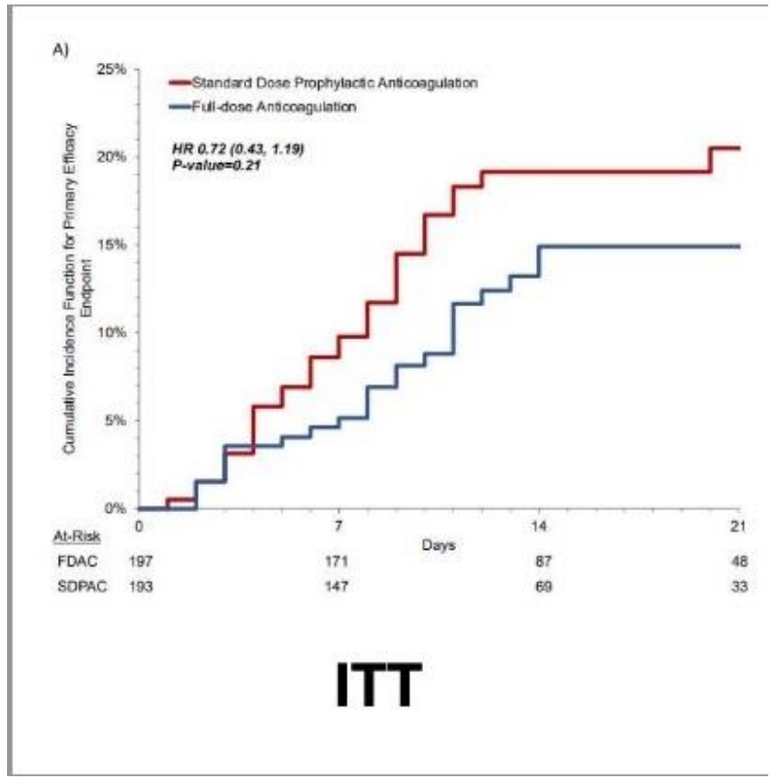
No. at Risk

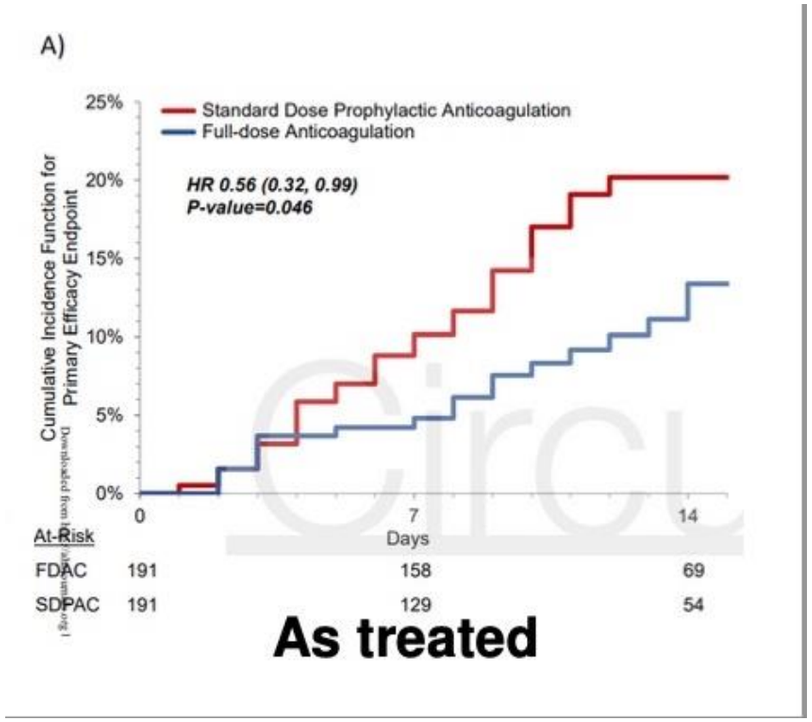
Standard dose	86	83	77	72	71	69	68
Intermediate dose	87	86	83	80	77	76	72

Perepu US, Chambers I, Wahab A, et al. Standard prophylactic versus intermediate dose enoxaparin in adults with severe COVID-19: A multi-center, open-label, randomized controlled tri

COVID-PACT Trial

- ICU patients with COVID-19
- Randomized to full-intensity vs standard-dose prophylactic anticoagulation.
- Also randomized to clopidogrel vs no P2Y12 inhibition.
- In critically ill patients with COVID-19, full-dose anticoagulation, but not clopidogrel, reduced thrombotic complications with an increase in bleeding, driven primarily by transfusions in hemodynamically stable patients, and no apparent excess in mortality.



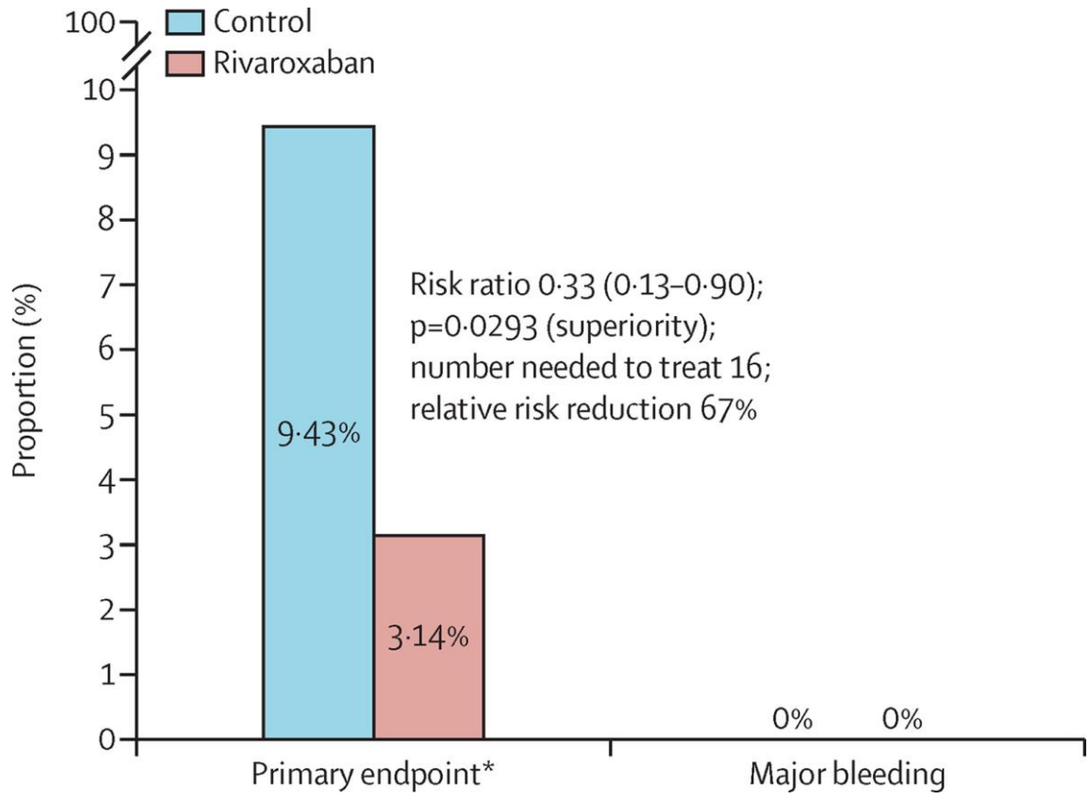


Bohula EA, Berg DD, Lopes MS, et al. Anticoagulation and Antiplatelet Therapy for Prevention of Venous and Arterial Thrombotic Events in Critically Ill Patients With COVID-19: COVID-P

POST-DISCHARGE PATIENTS

MICHELE Trial

- 320 post-discharge patients with COVID-19 randomized to rivaroxaban 10 mg/day or no anticoagulation for 35 days.
- High risk patients discharged after hospitalisation due to COVID-19, thromboprophylaxis with rivaroxaban 10 mg/day for 35 days improved clinical outcomes compared with no extended thromboprophylaxis.



Ramacciotti E, Barile Agati L, Calderaro D, et al. Rivaroxaban versus no anticoagulation for post-discharge thromboprophylaxis after hospitalisation for COVID-19 (MICHELLE): an open-la

Antithrombotic Therapy in COVID-19

Summary

OUTPATIENT THERAPY	INPATIENT THERAPY	THERAPY OF ICU PATIENTS	POST-DISCHARGE
✅SULODEXIDE • Gonzalez-Ochoa AJ et al.	✅PROPHYLACTIC DOSE HEPARIN BASED ANTICOAGULATION • Observational Studies and indirect evidence from RCTs.	✅PROPHYLACTI DOSE HEPARIN BASED ANTICOAGULATION • Observational Studies and indirect evidence from RCTs.	✅RIVAROXABAN • MICHELLE
❌RIVAROXABAN • PREVENT-HD • Ananworanich et al.	✅THERAPEUTIC DOSE HEPARIN BASED ANTICOAGULATION • Multiplatform Trial • HEP-COVID • RAPID	❌THERAPEUTIC DOSE HEPARIN BASED ANTICOAGULATION • Multiplatform Trial	
❌ ASPIRIN/APIXABAN • ACTIV-4B	❌RIVAROXABAN • ACTION	❌INTERMEDIATE-DOSE HEPARIN BASED ANTICOAGULATION • INSPIRATION • Perepu et al.	
❌ENOXAPARIN • ETHIC • OVID	❌ASPIRIN • RECOVERY	❌P2Y12 INHIBITORS • COVID-PACT	
	❌P2Y12 INHIBITORS • Berger JS et al.		