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Thrombosis and COVID-19: inpatient management

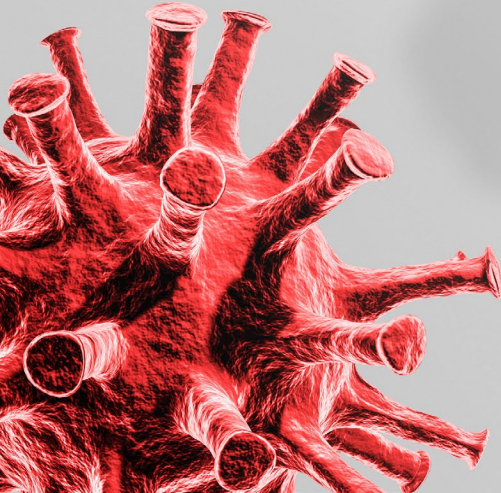
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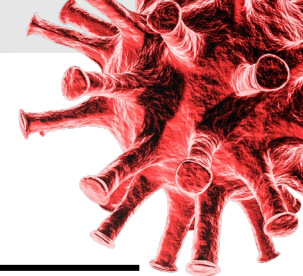
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Madrid, Spain



Disclosures

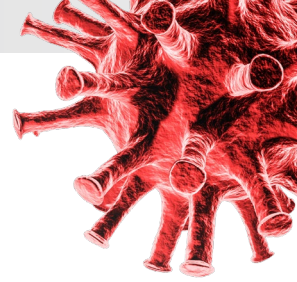


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Speaker bureau	Bayer, BMS, Sanofi
Scientific advisory board	See consultant



The problem

- What is the optimal thromboprophylaxis regimen for hospitalised patients with COVID-19?
- Is (full-dose) anticoagulation a treatment for COVID-19?



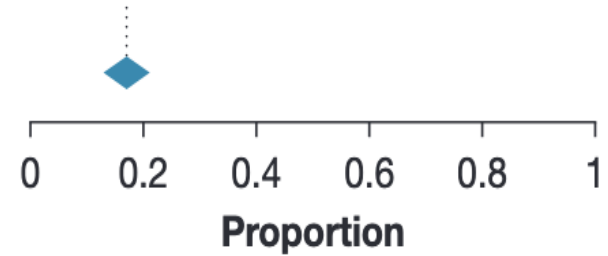
Incidence of VTE and bleeding

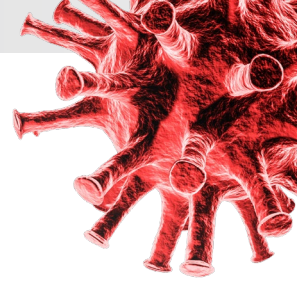
- In hospitalised patients with coronavirus disease in 2019

Incidence of VTE

Total (95% CI) 18,093 100% **0.170 [0.134–0.209]**

Heterogeneity: $\text{Tau}^2 = 0.0261$; $\chi^2 = 1,733.93$, $df = 46$ ($p=0$); $I^2 = 97\%$

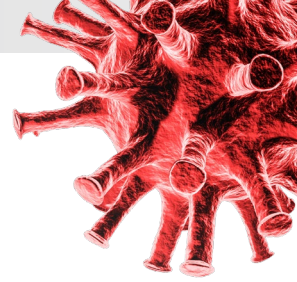




Incidence of VTE and bleeding

- In hospitalised patients with coronavirus disease in 2019

Group	Incidence (%)	Difference
VTE		
Screening	33.1	<0.0001
Clinical diagnosis	9.8	
Ward	7.1	<0.0001
ICU	27.9	
Prospective	25.5	<0.0001
Retrospective	12.4	



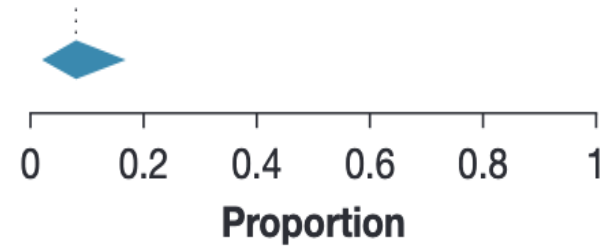
Incidence of VTE and bleeding

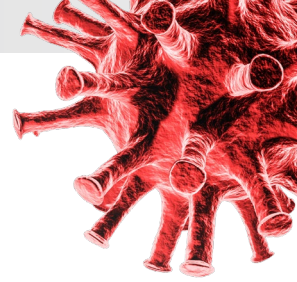
- In hospitalised patients with coronavirus disease in 2019

Incidence of bleeding

Total (95% CI)	1,411	100%	0.078 [0.026–0.153]
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Heterogeneity: $\text{Tau}^2 = 0.0168$; $\chi^2 = 76.73$, $df = 4$ ($p < 0.01$); $I^2 = 95\%$





Incidence of VTE and bleeding

- In hospitalised patients with coronavirus disease in 2019

BLEEDING

Prospective	2.7	<0.001
Retrospective	9.4	
Standard dose prophylaxis	4.7	<0.001
Intermediate dose or full anticoagulation	21.4	



Trial designs

	INSPIRATION ¹	Multiplatform trials ²	ACTION ³
Population	Critically ill (562)	Non-critically ill (2,219) Critically ill (1,074)	Non-critically ill (575) Critically ill (39)
Intervention	Intermediate-dose thromboprophylaxis (LMWH)	Therapeutic anticoagulation (LMWH)	Therapeutic anticoagulation (rivaroxaban for stable and LMWH for unstable patients)
Comparator	Low-dose thromboprophylaxis	Usual care pharmacological thromboprophylaxis Low-dose: 72% Intermediate-dose: 27% Subtherapeutic: 1%	Standard of care with prophylactic dose anticoagulation
Primary outcome	Composite of adjudicated acute VTE, arterial thrombosis, undergoing ECMO or all-cause mortality	Survival to hospital discharge and days free of organ support	Hierarchical analysis of mortality, duration of hospitalisation and duration of oxygen use

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INSPIRATION trial – mITT analyses (N=562)



	Intermediate-dose thromboprophylaxis n=276	Standard-dose thromboprophylaxis n=286
Primary outcome (%) Composite of adjudicated acute VTE, arterial thrombosis, undergoing extracorporeal membrane oxygenation, or all-cause mortality	45.7	44.1
VTE (%)	3.3	3.5
Major bleeding (%)	2.5	1.4
Severe thrombocytopenia (n)	6	0

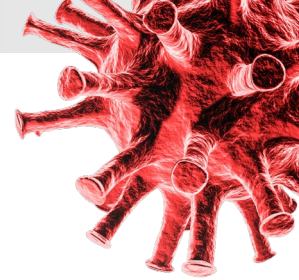
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ATTACC, REMAP-CAP and ACTIV-4a mpRCT



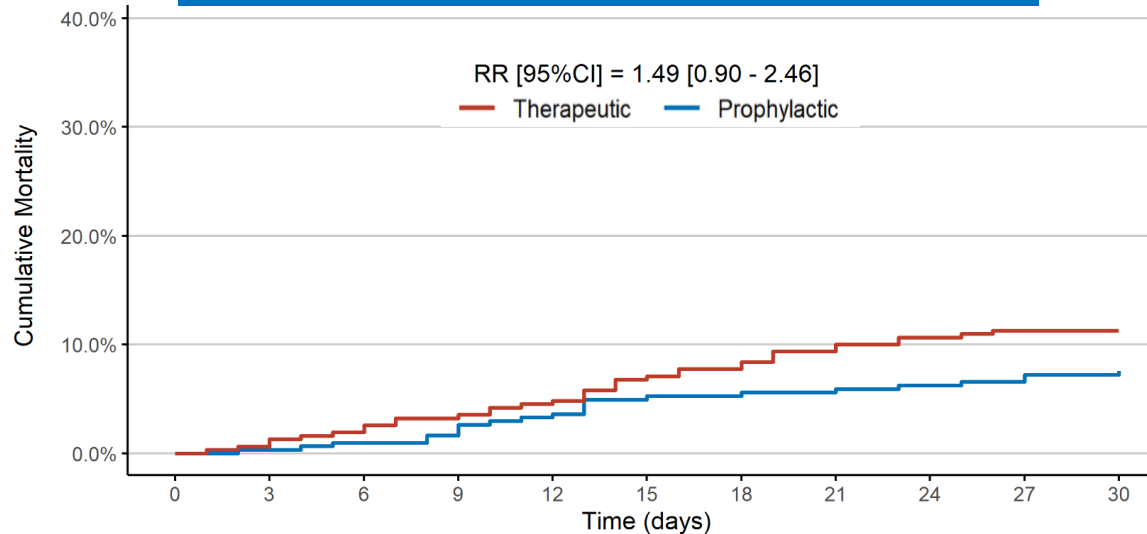
State and D-dimer strata	Proportional odds ratio Median (95% CrI)	Trial statistical conclusion
Severe state	0.76 (0.60–0.97)	Futility [Probability of OR>1.2 <0.001]

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ACTION trial

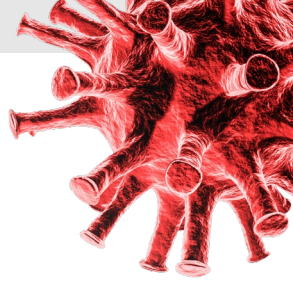
Unstable patients: 23 vs 16



Patients at risk

Prophylactic	304	303	301	299	294	289	288	287	285	284	282
Therapeutic	310	308	304	300	296	289	286	281	277	275	275

Clinical practice guidelines



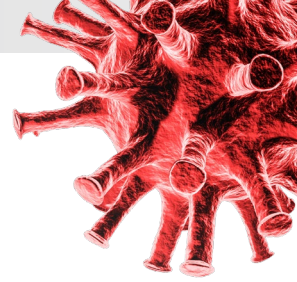
7. In critically ill patients with COVID-19, we suggest current standard dose anticoagulant thromboprophylaxis over intermediate (LMWH BID or increased weight-based dosing) or full treatment dosing, per existing guidelines.

ATTACC, REMAP-CAP and ACTIV-4a mpRCT



State and D-dimer strata	Proportional odds ratio Median (95% CrI)	Trial statistical conclusion
Moderate state, low D-dimer	1.22 (0.93–1.57)	Superiority [Probability of OR>1= 0.929]
Moderate state, high D-dimer	1.31 (1.00–1.76)	Superiority [Probability of OR>1= 0.973]
Moderate state, missing D-dimer	1.32 (1.00–1.86)	Superiority [Probability of OR>1= 0.973]

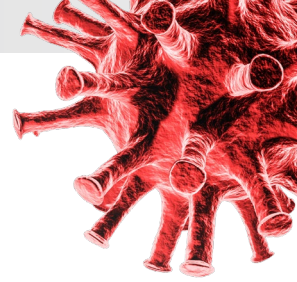
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ATTACC, REMAP-CAP and ACTIV-4a mpRCT: mortality

Therapeutic anticoagulation N=1,171	Usual care venous thromboprophylaxis N=1,048
86 (7.3%)	86 (8.2%)

**Relative risk reduction
11%**



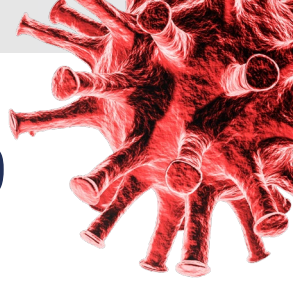
ACTION trial

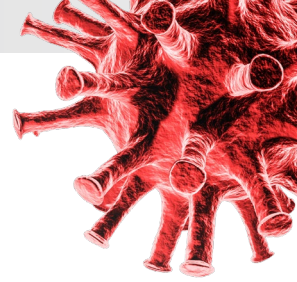
Stable patients: 288 vs 288

	Therapeutic N= 310	Prophylactic N= 304
Composite thromboembolic outcome	23 (7.4%)	30 (9.9%)
ISTH major bleeding or clinically relevant non-major bleeding	26 (8.4%)	7 (2.3%)

Anticoagulation as a treatment for COVID-19

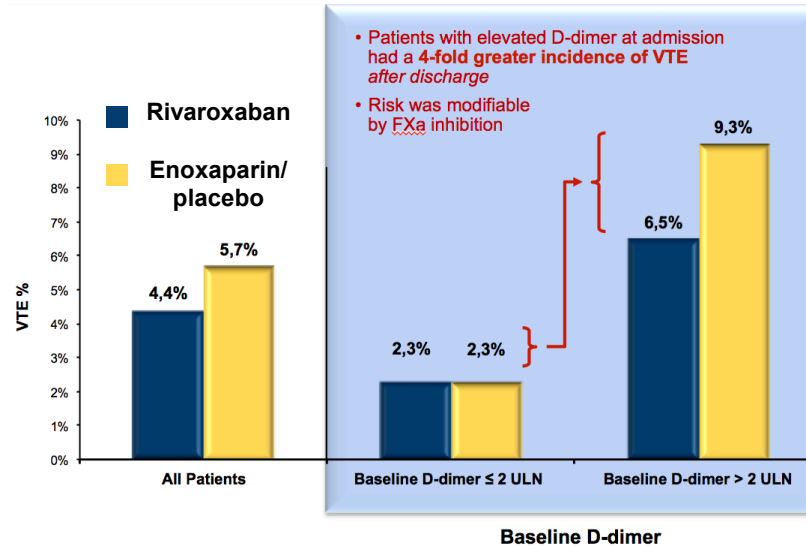
- We need to see the data in a final, peer-reviewed publication
- More questions than answers
- We also need confirmatory data





More questions than answers

- No benefit for the most severe patients
- Benefit for moderate patients with low D-dimer



ATTACC, REMAP-CAP and ACTIV-4a mpRCT



	Therapeutic anticoagulation N= 1,180	Usual care venous thromboprophylaxis N= 1,046
Venous thrombotic events	16 (1.4%)	26 (2.5%) MEDEXOX trial 5.5%
Major bleeding	22 (1.9%)	9 (0.9%) MEDEXOX trial 2.0%

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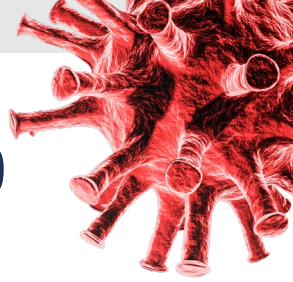


More questions than answers

Intervention	Population	Mortality RRR (%)
Dexamethasone ¹	6,425 patients hospitalised with COVID-19	17
Remdesivir ²	1,062 patients hospitalised with COVID-19	25
Tocilizumab ³	389 patients hospitalised with COVID-19 who were not receiving mechanical ventilation	21
Full-dose anticoagulation ⁴	1,398 moderate patients with COVID-19	25

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Anticoagulation as a treatment for COVID-19



- We also need confirmatory data

ORIGINAL ARTICLE

Tocilizumab in Hospitalized Patients with Severe Covid-19 Pneumonia¹

COVACTA study

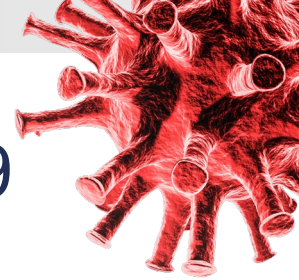
Double-blind, placebo-controlled trial
Negative for mortality

ORIGINAL ARTICLE

Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19²

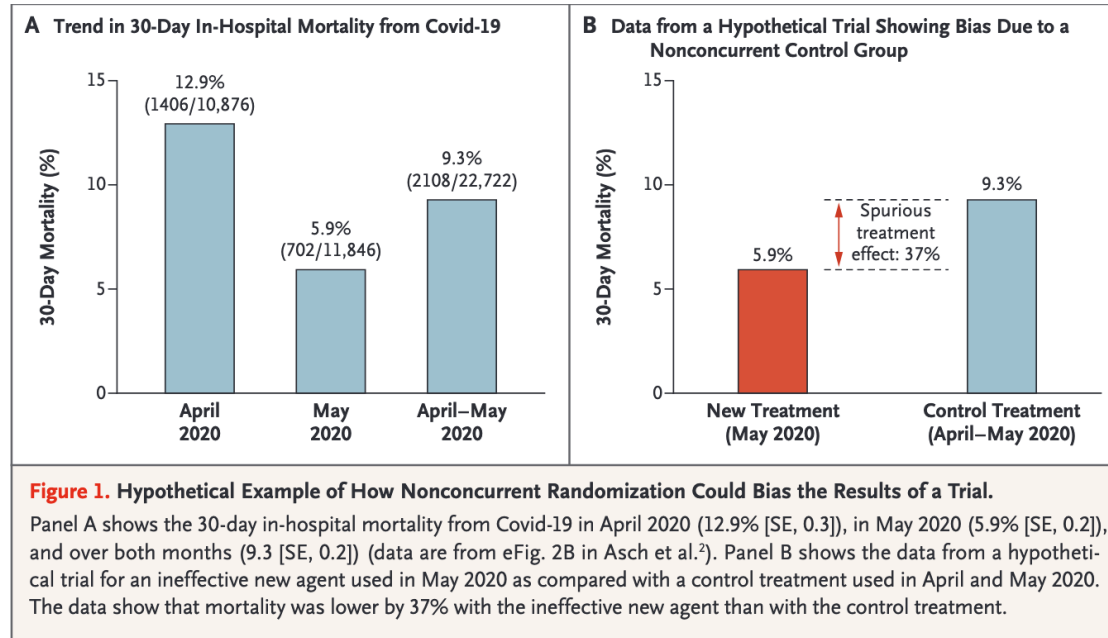
REMAP-CAP study

Open-label trial
Positive for mortality



Anticoagulation as a treatment for COVID-19

- Methodological issues with multiplatform trials



Conclusions

- I still use standard-dose thromboprophylaxis for the vast majority of patients hospitalised with COVID-19
- Peer-reviewed data from RCTs will dictate whether anticoagulation is a treatment for COVID-19, and hopefully will identify patient subgroups who benefit most from this therapy

