

Anticoagulation for Covid-19 pneumonia

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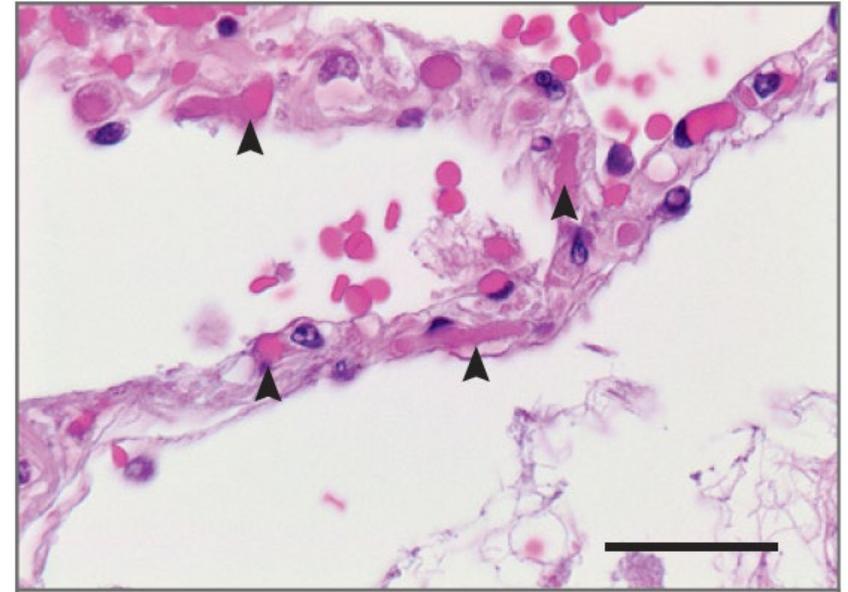
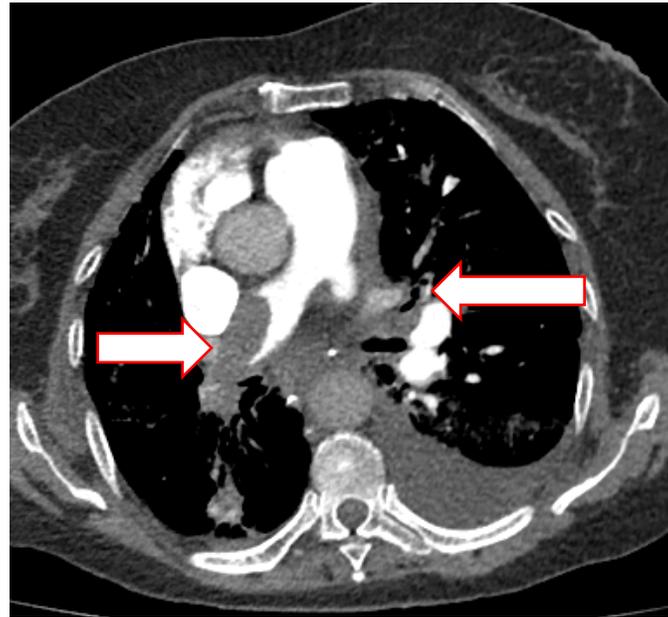
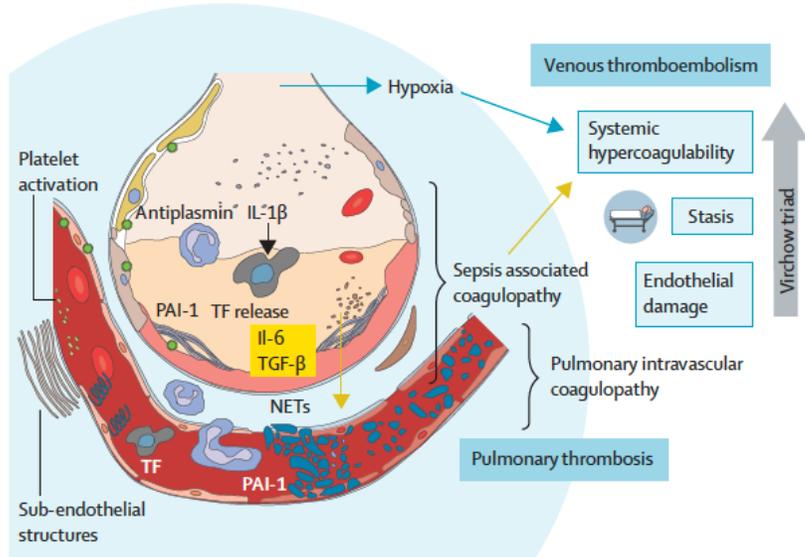
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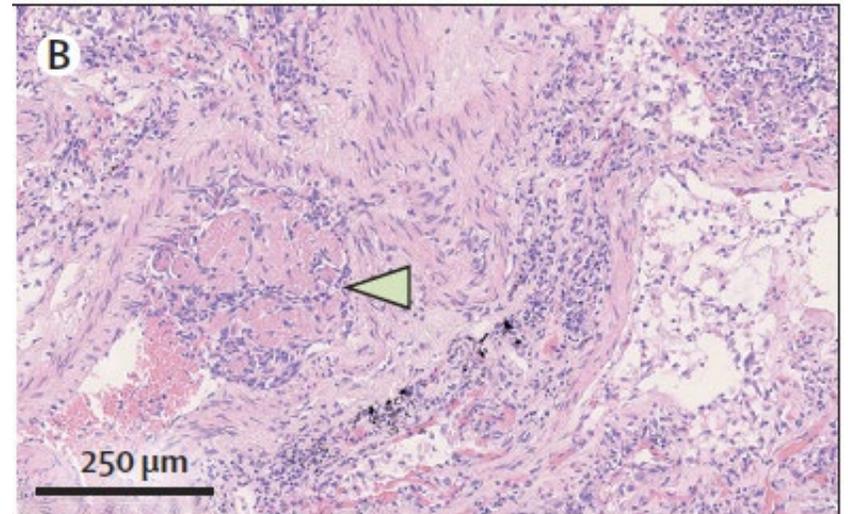
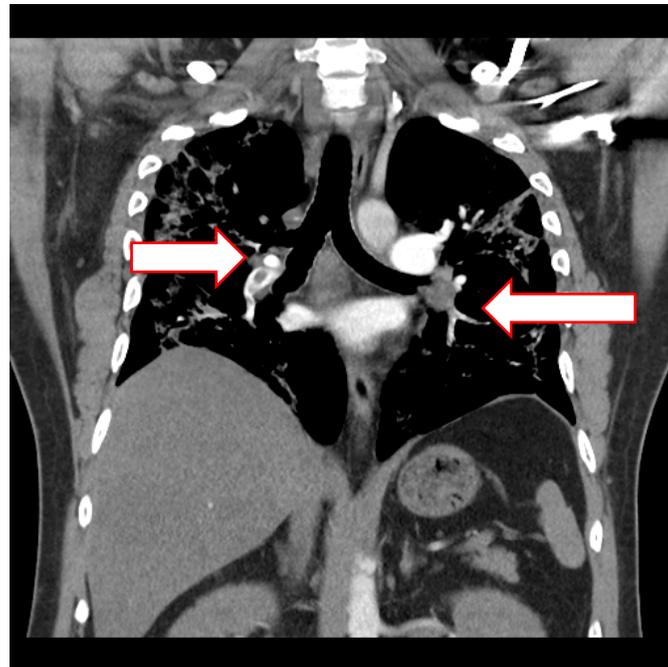
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Thromboinflammation is a feature of Covid



Multiple microthrombi in alveolar capillaries with extravasated RBCs



Organising microthrombus

- Micro- and macrovascular thrombosis is common
- Elevated D-dimer associated with worse outcomes and may be predictive of VTE
- Survival benefit from AC in observational studies
- **Is thrombosis a marker of severe illness or an independent contributor to mortality (does it require prevention/treatment)?**

REMAP-CAP, ACTIV-4a, and ATTACC trials



- Multiplatform, open-label, adaptive Bayesian trial (UK, US, Canada, Brazil)
- Randomised to therapeutic anticoagulation with heparin vs prophylaxis for 14 days
- Primary outcome
 - Ordinal scale combining in-hospital mortality (assigned -1) and days free of organ support to day 21
 - Higher value = better outcome
- Key secondary outcomes: major bleeding, major thrombotic event, death

Severe/Critically ill patients

Severe Covid-19: **HFNO**, non-invasive ventilation, IMV, vasopressors, or inotropes

Moderately ill patients

Hospitalised but not initially requiring ICU or organ support

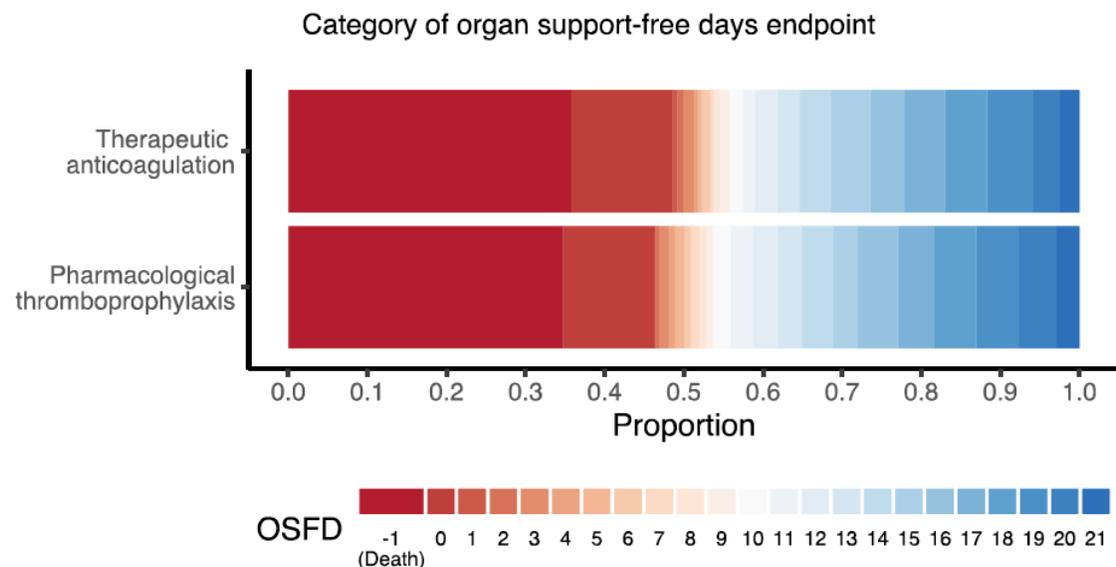
D-dimer strata

- High: $\geq 2x$ ULN
- Low: $< 2x$ ULN
- Unknown

4 groups independently analysed

Severe/Critically ill patients: harm likely

	Therapeutic AC (n = 529)	Usual care (n = 545)
Median organ support-free days to day 21	3 (-1, 16)	5 (-1, 16)
Adjusted proportional odds ratio	0.87 (0.70-1.08)	Ref
Probability of futility	99.8%	
Probability of inferiority	89.4%	
Survival to hospital discharge	340/529 (64.3%)	356/545 (65.3%)



Fewer major thrombotic events with AC:

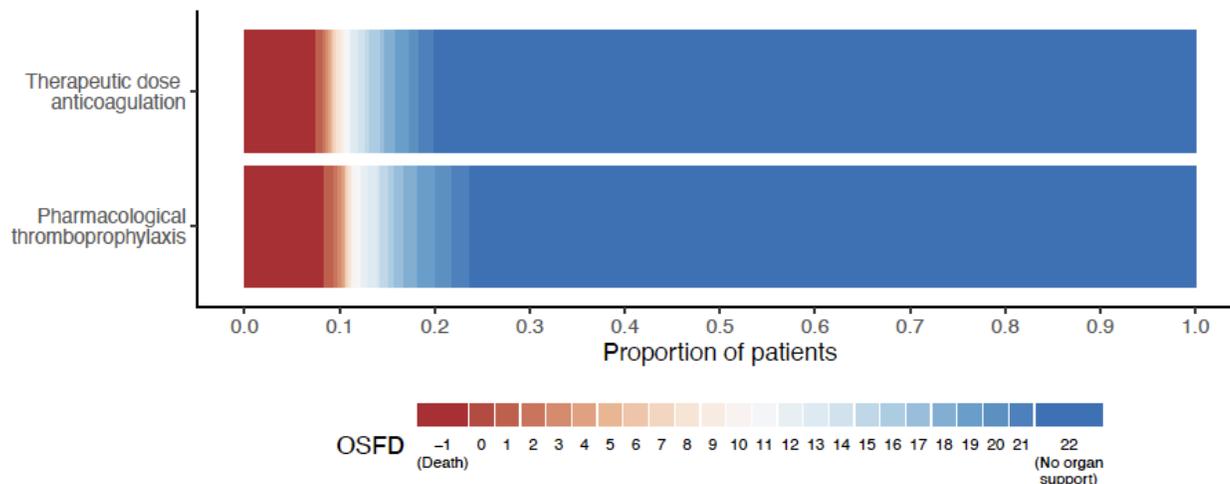
- AC 5.7% vs. SOC 10.3%

Major bleeding:

- AC 3.1% vs. SOC 2.4%

Moderately ill patients: benefit possible in certain subgroups

	Therapeutic AC (n = 1181)	Usual care (n = 1050)
Adjusted proportional odds ratio for primary outcome	1.29 (1.04 to 1.61)	Ref
Probability of superiority	99.9%	
<ul style="list-style-type: none"> • High D-dimer • Low D-dimer 	1.31 (1.00 to 1.76) 1.22 (0.93 to 1.57)	
Survival to hospital discharge	1085/1171 (92.7%)	962/1048 (91.8%)
Adjusted odds ratio (95% CrI)	1.21 (0.87 to 1.68)	Ref



No real difference in major thrombotic events:

- AC 8% vs. SOC 9.9%
- Adjusted risk difference: 2.6% (0.2, 4.4)

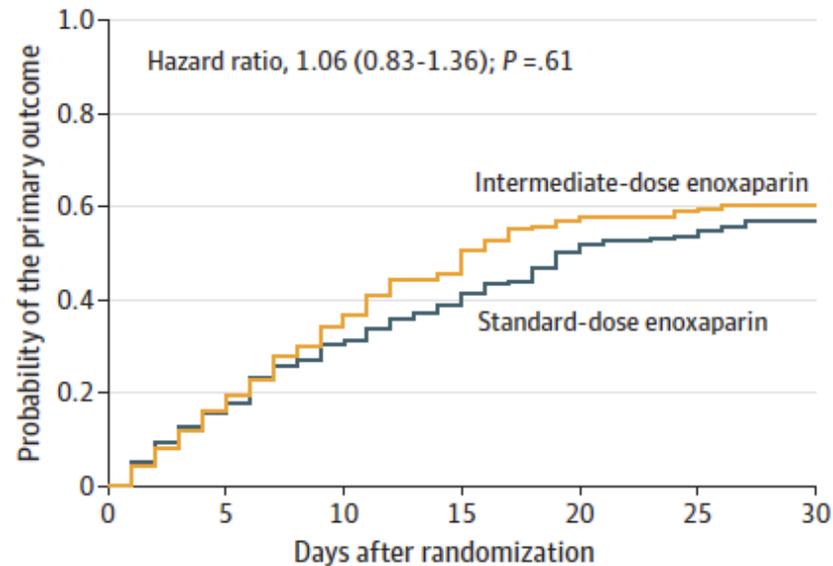
Double the risk of major bleeding:

- AC 1.9% vs. SOC 0.9%

Two other trials support lack of effect

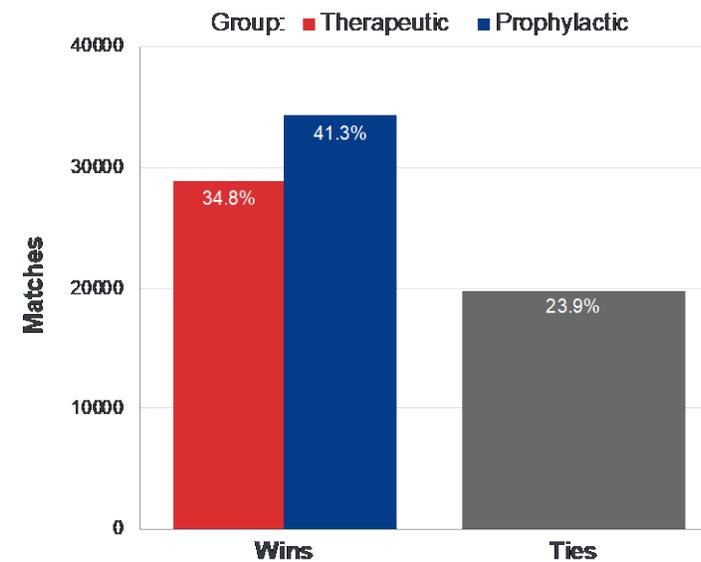
INSPIRATION trial

- n = 562; Iran; **Covid pneumonia in ICU**
- Intermediate- vs standard-dose prophylactic AC
- Primary outcome:
 - Venous/arterial thrombosis, ECMO, or death
- **No difference: 126 patients (45.7%) vs. 126 (44.1%)**
- Major bleeding: 2.5% vs. 1.4%



ACTION trial

- n = 615; Brazil; **inpatients with Covid pneumonia and elevated D-dimer (60% FMO2; HFNO/IMV ~15%)**
- Randomised to: rivaroxaban 20 mg daily (stable) or enoxaparin 1 mg/kg BD (unstable)
- Primary outcome: Mortality, hospitalisation and oxygen use duration



No improvement in clinical outcomes

More major bleeding (3.2% vs. 1.3%)

Higher mortality 11.3% vs. 7.6%
RR 1.49 (0.90–2.46)

Conclusions from trials

Severe Covid pneumonia (ICU/HFNO)

NIH trials and INSPIRATION

- No benefit
- Possible harm

Moderate Covid pneumonia (FMO2)

NIH trials

- Small effect on reducing need for organ support if D-dimer $> 2x$ ULN
- No impact on mortality; more bleeding

ACTION and INSPIRATION (40% FMO2)

- Clinical outcomes not improved
- Suggestion of harm

Suggested practice

